

Review

Sensory thalamus function, plasticity and neuromodulation in health and disease

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ABSTRACT

For each of the many sensory channels through which animals perceive the world, sensory thalamus is an important processing station whose role lies between faithful stimulus encoding and cognitive interpretation. Located deep in the brain, sensory thalamus neurons must receive and transmit peripheral information reliably, while modulating it based on valence, internal states and memory from previous experience. It has to speak to the neocortex with the appropriate volume, and in an orderly way, to prioritize attention to what matters most in each circumstance. In this review, we recapitulate classic and recent findings on the sensory thalamus, and how its plasticity and modulation allow it to provide a basis not only for perception, but also memory and cognition. Finally, we discuss how alterations in sensory thalamus may underlie pathogenesis or contribute to specific symptoms of cognitive and neuropsychiatric disorders.

1. Introduction

First named by Galen (129 – 216 AD), the thalamus is believed to owe its name to the ancient Greek word “thalamos” (transliterated to English from θάλαμος), which refers to the innermost part of Greek houses usually the bed or bridal room (García-Cabezas et al., 2021; Serra et al., 2019; Cassel and Pereira de Vasconcelos, 2021). The thalamus is a grey matter structure located deep in the brain as part of the diencephalon. It is highly connected with many cortical and subcortical areas (Hwang et al., 2017). Due to its location and extensive connectivity, it was classically understood as a relay center that communicates with many different areas - the cortex connection being thought of as the one with the most sophisticated computations (Jones, 1991). However, over the last decades many studies expanded this role and support that the thalamus may act as an integrative hub, combining inputs from multiple sources and participating in brain-wide information processing and cognitive control (Halassa and Kastner, 2017; Shine et al., 2023).

2. Two-stage signal transmission in sensory thalamus

All sensory pathways, with the exception of the olfactory system (Courtillot and Wilson, 2015), transmit their information to cerebral

cortex via dedicated sensory nuclei in the thalamus. The so-called first-order (or lemniscal) (Ahissar et al., 2000) sensory thalamic nuclei are the first to receive these sensory inputs, which are excitatory and also inhibitory (Winer et al., 1996a); Peruzzi et al., 1997; Mellott et al., 2014; Beebe et al., 2018; Whyland et al., 2020) and send it to sensory cortices (Fig. 1a). These nuclei respond to sensory stimuli (Sumser et al., 2025; Taylor et al., 2021; El-Boustani et al., 2020), are necessary for perception (Hasegawa et al., 2024; Leva et al., 2024) and include the lateral geniculate nucleus (LGN, for vision) (Le Gros Clark and Penman, 1934; Bishop et al., 1962), the ventral portion of the medial geniculate body (MGBv, for audition) (Adrian et al., 1966; Rouiller et al., 1979), the parvocellular portion of the ventral posterior medial nucleus (VPMpc, gustatory) (Ogawa and Nomura, 1988), the ventral posterior medial (VPM, somatosensory) (El-Boustani et al., 2020; Pierret et al., 2000; Wimmer et al., 2010; Diamond et al., 2008), the ventral posterior lateral (VPL, somatosensory) (Zhang et al., 2006; Vázquez et al., 2013), the posterior ventral medial (VMpo, in primates, somatosensory) (Craig et al., 1994) and its rodent homolog posterior triangular (PoT, in rodents, somatosensory) (Leva et al., 2024; Gauriau and Bernard, 2004; Bokinić et al., 2018). Occasionally, VPM and VPL are investigated together and named ventrobasal complex (VB) (Koyama et al., 1998). First-order sensory thalamic nuclei receive modulatory feedback

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from deep cortical layers (typically L6), forming the so-called cortico-thalamic loops (Sherman and Guillery, 1996).

The so called higher-order thalamic (or paralemniscal) (Ahissar et al., 2000) nuclei also respond to sensory stimuli (Sumser et al., 2025; Taylor et al., 2021; Petty and Bruno, 2024; Odegaard et al., 2025) and play a role in perception (Taylor et al., 2021; La Terra et al., 2022), yet a large fraction of their input arrives as feedback from sensory cortical areas – primarily layer 5/6 pyramidal neurons – as well as directly from the periphery (El-Boustani et al., 2020). These nuclei are also part of the cortico-thalamic loops (Diamond et al., 1992), but they receive more contextual information from layer 6 neurons than first-order nuclei (Kirchgeßner et al., 2020) and exclusive cortical input from layer 5 (Sherman, 2016). They receive more processed inputs including global, multisensory information. These nuclei include the pulvinar (LP, visual) (Petty and Bruno, 2024; Petty et al., 2021; Kurzwski et al., 2022), the dorsal and medial portions of MGB (MGBd and MGBm, auditory) (Wepsic, 1966; Love and Scott, 1969; Edeline and Weinberger, 1991a; Anderson and Linden, 2011), as well as posterior medial (POm, somatosensory) (El-Boustani et al., 2020; Wimmer et al., 2010; Petty and Bruno, 2024; Diamond et al., 1992; Petty et al., 2021) and mediodorsal thalamus (MD or MDT, mainly linked to non-sensory, higher-order functions but also encodes olfactory and gustatory stimuli) (Courtillot and Wilson, 2015; Fredericksen and Samuelsen, 2022).

Both first and higher-order sensory thalamic nuclei are mainly composed of excitatory neurons. The presence of local interneurons is limited and nucleus-specific in rodent thalamus, particularly mouse (Seabrook et al., 2013; Jager et al., 2021; Simko and Markram, 2021a; Gorin et al., 2023), yet interneurons in sensory thalamus are more frequent in primates (Butler, 2008). Ferrets (Sanchez-Vives et al., 1996), cats (Huang et al., 1999) and guinea pigs (Spreafico et al., 1994) also exhibit local interneurons in sensory thalamic nuclei.

As expected, based on their connectivity, first-order and higher-order sensory thalamus display functional differences. Higher-order thalamus responses to sensory stimuli are strongly driven by sensory cortex, whereas those in first-order do not, and are present upon cortical inactivation (Diamond et al., 1992). First and higher-order thalamus also show different mechanisms to encode stimulus features. For example,

first-order auditory thalamic cells vary their response amplitudes to sounds of different frequencies, whereas higher-order auditory thalamus change instead their response latencies (Ahissar et al., 2000). Higher-order sensory thalamus has been shown to respond to multi-modal stimulation (Wepsic, 1966; Love and Scott, 1969), behavioral state (e.g., active sensing) (Petty et al., 2021) and arousal (Wang et al., 2023). Furthermore, higher order neurons show greater bursting, and less spontaneous activity, than first-order cells (Ramcharan et al., 2005), and project to both sensory and motor cortical areas (Casas-Torremocha et al., 2017, 2019).

Both first and higher-order thalamus are under tight inhibitory control by GABAergic projections from the thalamic reticular nucleus (TRN) (Wimmer et al., 2015; Liu et al., 1995; Pinault, 2004; Li et al., 2020). However, higher-order nuclei appear to receive a greater GABAergic inhibition from other sources, such as the anterior pretectal nucleus (Bokor et al., 2005), and the zona incerta (Barthó et al., 2002) (Fig. 1b). Moreover, higher-order nuclei project to areas beyond the neocortex, like the high-order auditory thalamus projections to amygdala (Taylor et al., 2021; Li et al., 1995), or the high-order visual thalamus terminals in the brainstem (Vega-Zuniga et al., 2025).

In summary, both first and higher-order thalamic nuclei show robust, replicable and time-locked neuronal responses to sensory stimuli, and specific inactivation of either first and higher-order sensory thalamus leads to strong deficits in perceptual acuity. First-order nuclei receive sensory information at a pre-cortical stage and are specialized in stimulus feature encoding, whereas higher-order thalamus receive extensive cortical input and is linked to broader stimulus modalities and cognitive context (Sherman, 2016; Wolff et al., 2021).

3. Beyond the relay

Despite this classical separation of sensory thalamic functions in first and higher-order nuclei, first-order thalamus can carry higher-order information. For instance, first-order visual thalamus has been shown to respond to visual stimulation in either eye, performing binocular integration, a process that was believed to arise only in cortex (Howarth et al., 2014). LGN and MGB also encode sensory features kept in working

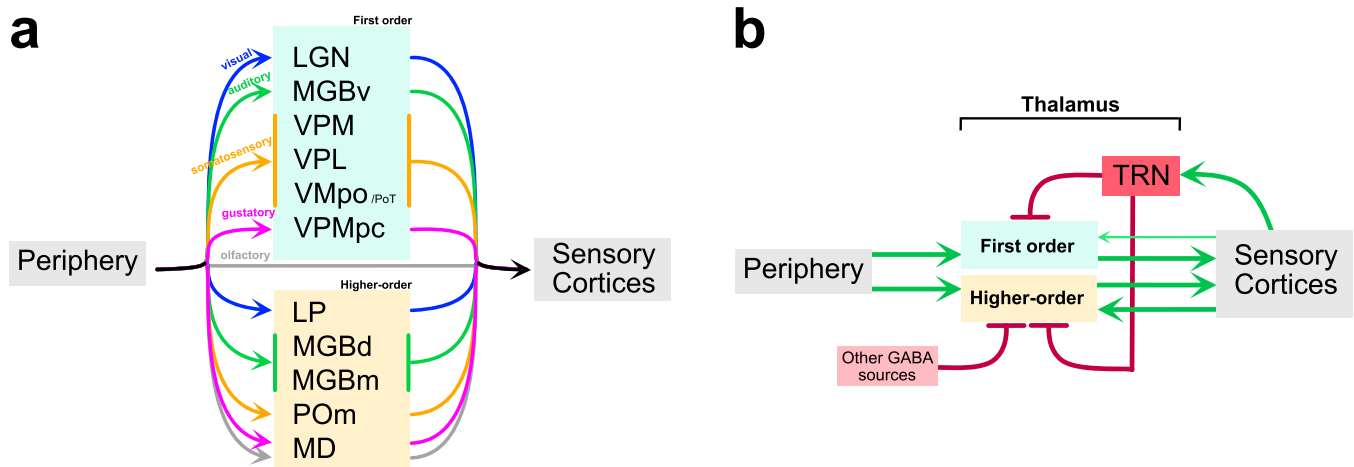


Fig. 1. Sensory nuclei of the thalamus in a first and higher-order classification. **a.** Diagram of the functional division between first order and higher-order nuclei of sensory thalamus. LGN, MGBv, VPM, VPL, VMpo (or PoT, in mice) and VPMpc are first order thalamic nuclei, whereas LP, MGBd, MGBm, POm and MD are higher-order thalamic nuclei. Both types get sensory input from the periphery, segregated by sensory modality, and both send projections to sensory cortices (and to other regions, not depicted here). Olfactory information reaches cortex without a first order thalamic nucleus. MD is typically not regarded as a sensory nucleus, but rather a high-order site involved in cognitive functions. However, it is included here due to recently identified olfactory and gustatory sensory information encoding. **b.** Summary of the major excitatory inputs and outputs of sensory thalamic nuclei. Peripheral information, mainly excitatory, travels to first and higher-order sensory thalamic nuclei, which in turn send projections to sensory cortices. Cortex sends feedback to thalamus, in the so-called thalamo-cortico-thalamic loops. Higher-order nuclei get particularly rich excitatory input from cortex. On the other hand, sensory cortices activate TRN, which in turn inhibits both kinds of sensory thalamic nuclei. Finally, higher-order nuclei also receive inhibitory input from other GABAergic structures (anterior pretectal nucleus and zona incerta). Overall, first order sensory thalamus is mainly driven by the peripheral input, whereas higher-order thalamic nuclei receive more innervation from either cortex or other sources, making them richer in multimodal and cognitive information.

memory (Hasegawa et al., 2024; Rahmati et al., 2023), just like the higher-order MD (Peräkylä et al., 2017). In somatosensory thalamus, both first and higher-order nuclei integrate highly complex whisker and head kinematics (Oram et al., 2024). Moreover, first-order thalamic nuclei exhibit response plasticity to stimuli upon learning (Edeline and Weinberger, 1991b), which was classically attributed to higher-order nuclei (Edeline and Weinberger, 1991a). In sensory goal-oriented tasks in mice, sensory thalamus additionally encodes choice (Gilad et al., 2020). Furthermore, cochlear lesions trigger tonotopic reorganization in first-order auditory thalamus that is very similar to that observed in primary auditory cortex, suggesting its participation in cortical plasticity (Kamke et al., 2003). Conversely, subsets of cells in higher-order thalamus also encode stimulus features reliably (Anderson and Linden, 2011).

Recently, the presence of neural ensembles has been reported in sensory thalamus, similar to cortex (Hu et al., 2024). Cells that fire synchronously are physically closer to each other and have similar tuning properties. Synchrony in these thalamic neural ensembles is seen under stimulus-driven firing but also spontaneously (Hu et al., 2024). It is believed that ensembles refine the encoding of information, such as stimulus features, which would be more poorly transmitted by individual neurons. Coordinated neural activity is more likely to trigger neural responses in downstream targets (Zandvakili and Kohn, 2015).

Finally, communication between sensory thalamus and cortex in thalamo-cortical loops plays an important role in perception. A recent study inhibited feedback projections from sensory cortex back to higher-order thalamus, which suppressed perception in mice as well as sensory stimulus feature encoding in primary sensory cortex (Mo et al., 2024). These findings support the notion that sensory systems do not rely solely on bottom-up feature encoding to generate percepts. Instead, perception may arise from an integration of feature encoding with top-down contextual influence. This framework is commonly described as Bayesian or predictive coding (Knill and Pouget, 2004; Kanai et al., 2015; Furutachi et al., 2024; Keller and Msršic-Flogel, 2018). This view is supported by animal studies demonstrating that internal states shape stimulus encoding in sensory thalamus (Taylor et al., 2021; Hasegawa et al., 2024; Petty and Bruno, 2024) and sensory cortex (Furutachi et al., 2024; English et al., 2023). In line with this, human studies have shown that expectations can modulate sensory responses both in the auditory cortex (SanMiguel et al., 2013) and in the auditory thalamus (Tabas et al., 2020; Cacciaglia et al., 2015).

Together, these findings suggest that the roles of first and higher-order thalamic nuclei are more diffuse and diverse than traditionally suggested. Sensory thalamus performs high-level sensory processing and is involved in cognitive processing and behavioral adaptation and is referred to as an integrative hub for brain networks (Hwang et al., 2017).

4. Sensing under the watch of the thalamic reticular nucleus

TRN projections are the main form of inhibitory control over sensory thalamus, both first and higher-order nuclei. Because TRN neurons are, in turn, driven by prefrontal (Cornwall et al., 1990; Nakajima et al., 2019) and primary sensory cortices (Pinault, 2004), as well as other structures like basolateral amygdala (BLA) (Aizenberg et al., 2019), thalamic responses can be modulated quickly on a context and attentional basis. This is important because the relevance of a sensory modality depends on the specific contexts (e.g., an animal may first rely on audition to assess predator sounds outside a safe location or may attend to vision to find a specific food source). Studies have shown that sensory thalamic nuclei modulate their activity by suppression or enhancing the encoding of a given modality according to task demands (Wimmer et al., 2015; Williamson et al., 2015). TRN mediates this control by specifically modulating thalamic nuclei that are less relevant in a given context (Wimmer et al., 2015; McAlonan et al., 2006) and thus TRN has been referred to as a “searchlight” (Crick, 1984) that provides an additional

dimension to sensory thalamus coding during cognition.

5. Sensory thalamus plasticity

Activity in the thalamic circuit has the ability to change with time. Plasticity in the sensory thalamus has been identified in two forms: First, lesions or sensory deprivation were shown to trigger changes in thalamic receptive fields or responsiveness. Such modifications may allow sensory systems to be adaptable and optimize the neural encoding of stimuli in every circumstance, similar to synapses being refined or brain areas taking over functions upon sensory loss (Bedny et al., 2011; von Melchner et al., 2000; Diniz CRAF, 2023). Second, plastic changes in sensory thalamus can also occur in a cognitive context, such as identifying a previously known stimulus (Disterhoft and Olds, 1972; O'Connor et al., 1997; Halverson et al., 2010), assigning a valence (Taylor et al., 2021; Buchwald et al., 1966), or responding according to internal state (Gilad et al., 2020; Peelman and Haider, 2024).

Several lines of research studied thalamic plasticity upon sensory deprivation. For example, skin lidocaine anesthesia reversibly rearranges receptive fields in somatosensory VPM (Nicoletis et al., 1993). This fast thalamic plasticity depends, at least in part, on primary sensory cortex (Krupa et al., 1999). In the visual system, monocular deprivation triggers synaptic boutons to shift their responsiveness between monocular and binocular tuning, and vice versa. This effect is reversible and independent of cortico-thalamic feedback (Jaepel et al., 2017). Synaptic inhibition is necessary for ocular dominance thalamic plasticity (Sommeijer et al., 2017; Qin et al., 2023). In humans, short-term visual deprivation with an eye patch elicits plasticity in the higher-order visual thalamus, as measured by monocular stimulation responses in the ventral pulvinar nucleus, with the deprived eye responses being enhanced (Kurzawski et al., 2022). This form of plasticity has also been observed in the first-order auditory thalamus, MGBv (Kamke et al., 2003). Altogether, these data show that sensory thalamic nuclei adapt to injury or sensory deprivation to optimally harvest the neural resources available for perception. This sort of plasticity can also occur at pre-thalamic stages, and first-order sensory thalamus itself can receive new connections upon injury (Takeuchi et al., 2012).

On the other hand, sensory thalamus plastically modulates its responses upon associative learning. Studies on fear conditioning have shown that auditory thalamus has enhanced responses to a tone that is coupled to an aversive outcome (Disterhoft and Olds, 1972; O'Connor et al., 1997; Halverson et al., 2010; Buchwald et al., 1966). This has been shown in cats (Buchwald et al., 1966; Ryugo and Weinberger, 1978), rabbits (O'Connor et al., 1997), rats (Disterhoft and Olds, 1972; Halverson et al., 2010) and mice (Barsy et al., 2020; Pardi et al., 2020; Taylor et al., 2021). Enhanced thalamic responses to conditioned stimuli also weaken upon extinction learning of the association (Taylor et al., 2021; Buchwald et al., 1966), and reversal training experiments show that neurons can re-tune to stimuli if they become more relevant (Hasegawa et al., 2024; Gabriel et al., 1975). Mechanistic experiments show that inactivating sensory thalamus projections to amygdala impairs fear learning (Barsy et al., 2020; Pardi et al., 2020; Taylor et al., 2021). Furthermore, thalamic plasticity is complex, with cells being able to up- or downregulate their responses to many elements, such as conditioned stimuli, safe stimuli, and expected or unexpected outcomes (Taylor et al., 2021; Hasegawa et al., 2024; Ryugo and Weinberger, 1978; Supple and Kapp, 1989). While it has been shown that plasticity occurs in higher-order thalamic nuclei (e.g., during fear learning, Barsy et al., 2020; Pardi et al., 2020), first-order sensory thalamus neurons are also plastic upon learning (Fig. 2a).

Recently, behavioral studies demonstrated that sensory thalamus also shows plasticity upon goal-oriented, appetitive learning. Upon learning an association between a stimulus and reward, sensory thalamic cells re-tune, while the coding of the reward-predicting stimulus gets enhanced (Hasegawa et al., 2024; Petty and Bruno, 2024; Gilad et al., 2020). Moreover, internal states, motor features and behavioral

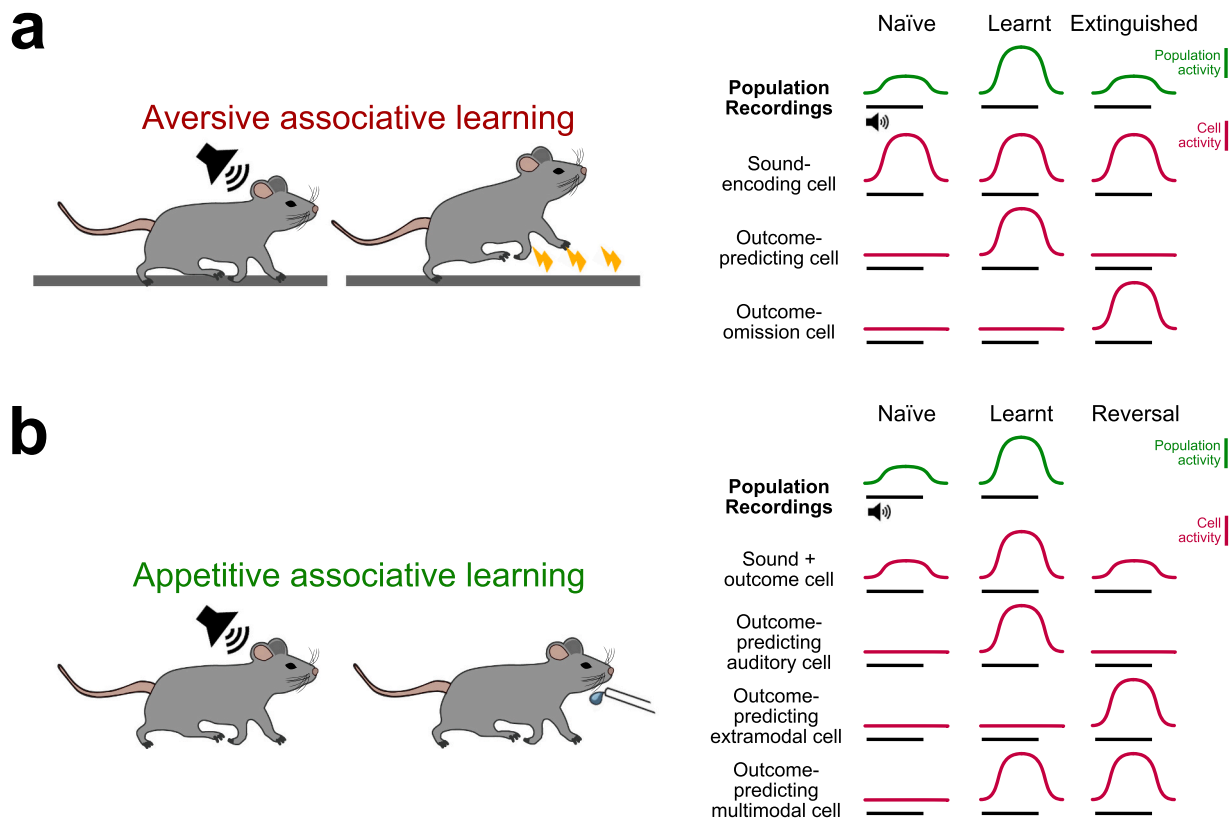


Fig. 2. Sensory thalamus shows plastic responses upon learning and cognitive variables. **A.** Left: Example of an aversive associative learning task in mice. In fear conditioning, mice learn to associate an auditory stimulus with an unpleasant outcome, in this case a mild electrical foot shock on the floor. Right: Sensory thalamus response examples over learning stages reveal that some cells stably encode the stimulus ("sound-encoding cells"), but others show plastic changes over learning ("outcome-predicting cells", which respond to the tone for as long as it is predictive of the aversive outcome, and "outcome-omission cells", which respond to the tone only after the animal has learnt that it no longer predicts the shock). Traces in red represent illustrative cell activity, and the stimulus presentation window is depicted with a black line. These plots summarize some findings of [Ryugo and Weinberger, 1978](#), [Halverson et al., \(2010\)](#) (population data) and [Taylor et al., \(2021\)](#) (single cell data). **B.** Left: Example of an appetitive associative learning task. In Go/No-Go sensory tasks, animals associate a sensory stimulus to a positive outcome, such as the delivery of a soymilk reward droplet, and they need to report the stimulus prior to obtaining the reward. In some tasks, experimenters use reversal training, where a new cue predicts the reward, and the original stimulus is no longer predictive of it. Right: Example responses of sensory thalamus cells during these behaviors. Some cells that respond to the sensory cue prior to the learning change their responses once the cue is predictive of the reward ("sound+outcome cells"). On the other hand, there are cells in sensory thalamus that respond to the stimulus only when it is predictive of reward ("outcome-predicting cells"), and even when the cue is of a different sensory modality ("outcome-predicting extramodal cell"). Stable cells are also present in these datasets, but are only shown in A. These data summarize some of the findings of [Gilad et al., \(2020\)](#) (population data), [Hasegawa et al., \(2024\)](#), [Petty and Bruno, 2024](#) and other unpublished findings (single cell data, Paricio-Montesinos & Gründemann, in preparation). Some cells respond by enhancing their firing rate, and some by lowering it. Here we show all changes in activity as increased activity for clarity purposes.

choice to respond to a stimulus are encoded in sensory thalamic cells ([Gilad et al., 2020](#); [Peelman and Haider, 2024](#)), and sensory nuclei from one sensory modality can become tuned to respond to stimuli of a different modality, if it is predictive of reward ([Hasegawa et al., 2024](#); [Petty and Bruno, 2024](#)) (Fig. 2b).

6. Sources of plasticity in thalamus

Sensory thalamus has minimal connectivity between neighboring neurons ([Halassa and Sherman, 2019](#)) as well as a very small number of local interneurons ([Halassa and Acsády, 2016](#); [Simko and Markram, 2021b](#)), which makes it structurally distinct from cortical areas. As such, plasticity in sensory thalamus is most likely mediated by changes in intrinsic excitability and plastic synaptic inputs or changes in presynaptic activity from external sources, rather than through local circuit dynamics.

Non-synaptic plasticity, particularly changes in intrinsic excitability, have been suggested to occur in sensory thalamus ([Apergis-Schoute et al., 2005](#)). These changes may occur in the context of sensory exposure and learning, and are supported by evidence of transcriptional regulation in auditory thalamus upon sensory exposure and learning

([Ran et al., 2003](#); [Han et al., 2008](#); [Brauth et al., 2007](#)). Such modifications can influence the responsiveness of thalamic neurons to incoming signals without altering synaptic strength.

On the other hand, synaptic plasticity in sensory thalamus may arise from several input sources: i) pre-thalamic sensory nuclei (such as the superior and inferior colliculi, dorsal column nuclei or the trigemino-thalamic tract) ([Lee and Sherman, 2011](#); [Winer et al., 1996b](#); [Xue et al., 1994](#); [Lund and Webster, 1967](#)), ii) sensory cortex feedback from layer 6 neurons ([Sherman and Guillery, 1996](#)), iii) primary and higher-order sensory cortex layer 5 neurons driving predominantly higher-order nuclei ([Lee and Sherman, 2010](#); [Miller-Hansen and Sherman, 2022](#)), and iv) TRN ([Halassa and Acsády, 2016](#); [Zikopoulos and Barbas, 2012](#)). Additionally, sensory thalamus receives neuromodulatory input from other sources, which will be discussed in the next section.

While the pre-thalamic nuclei that feed sensory information to thalamus (found at the midbrain and brainstem) have been observed to exhibit plasticity, it is limited to adaptations following functional loss. For example, alterations in the peripheral sensory pathways can lead to adaptations in the superior and inferior colliculi ([Gold and Knudsen, 2000, 1999](#); [Rauschecker and Harris, 1983](#)). In contrast, sensory thalamic nuclei display a broader repertoire of plasticity, encompassing

not only responses to injury or sensory deprivation but also processes such as encoding associative learning, with individual neurons finely tuned to cognitively-relevant features (Taylor et al., 2021; Hasegawa et al., 2024). This processing is likely mediated instead by projections from the cerebral cortex and the inhibitory control exerted by TRN. For instance, layer 6 corticothalamic projections modulate the gain and temporal dynamics of sensory thalamic responses to sensory stimuli (Mease et al., 2014). These projections can directly excite sensory thalamic cells or inhibit them indirectly by driving TRN activity, depending on the context (Crandall et al., 2015). Additionally, higher-order sensory thalamic nuclei receive “driver” inputs from multiple cortical areas, allowing them to integrate information from diverse sources (Sampathkumar et al., 2021), and some of these nuclei have shown plasticity across sensory learning (Audette et al., 2019). Furthermore, the amygdala and prefrontal cortex also target TRN, positioning it as a hub for emotional and cognitive convergence that subsequently regulates sensory thalamus activity (Zikopoulos and Barbas, 2012). Together, these cortical and TRN inputs are likely candidates to mediate plasticity in sensory thalamic nuclei.

Regarding the cellular mechanisms of sensory thalamic plasticity, there are various identified sources. In retinogeniculate synapses, trains of stimulation cause short-term depression of AMPA receptor-mediated currents (Chen et al., 2002), which requires and is mediated by the protein CKAMP44 (Chen et al., 2018). Cortico-thalamic feedback synapses onto sensory thalamus show reversible, NMDA-independent long-term potentiation (Castro-Alamancos and Calcagnotto, 1999). In TRN cells, repetitive stimulation of glutamatergic cortico-reticular synapses results in an increase in excitability via GluN2C-NMDA receptors (Fernandez et al., 2017). Together, these mechanisms of plasticity influence the responsiveness and synaptic transmission in sensory thalamus.

Altogether, the studies above show that thalamic nuclei are able to modify their connectivity and responsiveness upon sensory deprivation and learning. The fact that sensory thalamic nuclei can quickly and reversibly update their tuning according to behavioral demands postulates sensory thalamus as a key cognitive structure in the brain.

7. Neuromodulation of sensory thalamus

Neural networks change their function and plasticity through neuromodulation (Bazzari and Parri, 2019; Brzosko et al., 2019; Varela, 2014). Here, we will briefly discuss the main neuromodulators of sensory thalamus: acetylcholine (ACh), serotonin (5-HT), histamine, noradrenaline and dopamine.

Cholinergic input to the sensory thalamus originates mostly from the Pontomesencephalic tegmentum (PMT) in the brainstem (Schofield et al., 2011), while inputs from basal forebrain are less prominent (Heckers et al., 1992; Hallanger et al., 1987). The PMT is subdivided in two nuclei: the Pedunculo-pontine nucleus (PPN) and the Laterodorsal Tegmental nucleus (LDT) (Schofield et al., 2011). First and higher-order thalamic nuclei exhibit distinct cholinergic modulation. Electrophysiological data in auditory thalamus indicate that, in the first-order MGBv, ACh muscarinic receptor activation triggers depolarization and tonic firing, whereas cholinergic modulation in higher-order MGBd is more diverse, and many cells exhibit hyperpolarization by ACh (Mooney et al., 2004). This suggests that ACh may elicit specific modulation in first and higher-order auditory thalamus. VPM increases its spontaneous firing upon activation of ACh receptors, possibly thereby increasing noise levels (Hirata et al., 2006). Cholinergic modulation is most likely brain state-dependent, as cells in the PMT, the main source of cholinergic input to auditory thalamus (Schofield et al., 2011), show sleep-waking cycle-dependent activity, with peaks during wakefulness (Boucetta et al., 2014). PMT also sends extensive cholinergic modulation to visual thalamus (Billet et al., 1999) and TRN (Jourdain et al., 1989; Beierlein, 2014). In TRN, ACh triggers both direct action potentials via activation of nicotinic acetylcholine receptors (nAChRs), but also changes the

ability of TRN neurons to respond to presynaptic stimuli via muscarinic receptors (mAChRs), both expressed in TRN (Sun et al., 2013). Local administration of carbachol, which activates both receptor types, results in a decrease in spontaneous firing of TRN cells (Hirata et al., 2006). However, recent *in vivo* experiments found that optogenetic activation of cholinergic inputs onto TRN enhanced the activity of TRN cells and even promoted sleep (Ni et al., 2016). Finally, cholinergic cells from the PMT also target sensory areas beyond sensory thalamus, such as the inferior colliculus or the cochlear nucleus, underlining global cholinergic effects on sensory pathways (Schofield et al., 2011).

Therefore, cholinergic input appears to exert complex control over sensory thalamus. Both directly, possibly eliciting different effects in first and higher-order sensory nuclei, as well as by modulating its inhibition indirectly through TRN neuron control and other stages of the sensory pathway. Overall, cholinergic modulation in thalamus plays a role in sleep and arousal, attention and state-dependent sensory processing.

Serotonergic afferents to the sensory thalamus arise from the median (Gonzalo-Ruiz et al., 1995; Vertes et al., 1999) and dorsal (Vertes, 1991; Kirifides et al., 2001) raphe nuclei in the brainstem. Direct application of 5-HT elicits depolarization in most neurons of first-order sensory thalamic nuclei (Varela and Sherman, 2009) and, in higher-order nuclei, it depolarizes many but not all; it also hyperpolarizes a significant subset (~15 %) (Varela and Sherman, 2009; Monckton and McCormick, 2002). On the other hand, 5-HT has been reported to act on the retinal, presynaptic terminals that target visual thalamus, decreasing calcium activity and vesicle release onto thalamic cells (Reggiani et al., 2023). In TRN, there is expression of serotonin receptors with opposing net effects on GABAergic release (Goitia et al., 2016). The dorsal raphe nucleus has also been identified as an important modulator of pain perception (Wang and Nakai, 1994). Overall, serotonin appears to exert a nuanced control over sensory thalamus, supporting sensory gating. Moreover, 5-HT may be of particular importance during development, where it plays a role in the plasticity of thalamocortical axons (Sinclair-Wilson et al., 2023).

Histamine signaling in the central nervous system arises exclusively from the tuberomammillary nucleus of the posterior hypothalamus and it innervates, among other brain regions, sensory thalamus (Yoshikawa et al., 2021; Panula and Nuutinen, 2013; Scammell et al., 2019). Sensory thalamic nuclei, but not TRN, express receptors for histamine (Jin et al., 2002). This suggests that histaminergic influence over sensory thalamus is local. Histaminergic activation of first-order visual thalamus has been shown to depolarize cells via suppression of K⁺ currents (McCormick and Williamson, 1991), and has been suggested to mediate sensory arousal (Uhlrich et al., 1993). The expression of histaminergic receptors appears similar between first and higher-order sensory thalamic nuclei (Jin et al., 2005), suggesting that this neuromodulator may affect both in similar ways. Histamine signaling in general has also been extensively linked to wakefulness and arousal (Yoshikawa et al., 2021; Panula and Nuutinen, 2013).

Noradrenaline is an additional modulator of sensory thalamus. Noradrenergic projections that target sensory thalamus originate in locus coeruleus of the brainstem (Rogawski and Aghajanian, 1980a; Pérez-Santos et al., 2021; Rico and Cavada, 1998; Simpson et al., 1997). Neurons in sensory thalamic nuclei can be activated by noradrenaline *in vitro*, through alpha-adrenergic receptors (Rogawski and Aghajanian, 1980a, 1980b). However, the picture is more complex *in vivo*, where both enhancement and suppression of thalamic firing were found upon locus coeruleus stimulation (Moxon et al., 2007; Devilbiss and Waterhouse, 2011). The direct effects of noradrenaline on higher-order thalamus are unknown. Because the receptor alpha1/alpha2 ratio of expression differs between some first and higher-order nuclei, there may be specific outcomes for noradrenergic release depending on the region (Pérez-Santos et al., 2021). In a neural circuit context, cortical loop input to sensory thalamus is suppressed in the presence of noradrenaline (Nersisyan et al., 2021). Moreover, norepinephrine activates TRN

neurons and, therefore, indirectly reduces spontaneous firing of sensory thalamus, enhancing the signal-to-noise ratio in sensory thalamic cells (Hirata et al., 2006; Castro-Alamancos and Calcagnotto, 2001). Together, evidence suggests that noradrenaline modulates sensory thalamus in sensory processing and arousal.

Dopamine in the primate thalamus has various sources. Retrograde tracing of dopaminergic axons from the thalamus shows that these arise from the hypothalamus, ventral mesencephalon, periaqueductal gray (PAG) and the lateral parabrachial nucleus (LPbN) (Sánchez-González et al., 2005). While primate thalamus is densely innervated with dopamine, especially higher-order nuclei, its dopaminergic input in rodents is much scarcer (Sánchez-González et al., 2005). However, some dopaminergic axons can still be found in rodent sensory thalamus (Papadopoulos and Parnavelas, 1990). In slices, the direct effect of dopamine on sensory thalamus neurons depends on D1 and D2 receptors and it seems to be overall excitatory in both first and higher-order nuclei (Govindaiah and Cox, 2005; Govindaiah et al., 2010a; Lavin and Grace, 1998). However, dopamine may also inhibit the presynaptic terminals that target sensory thalamus (Govindaiah and Cox, 2006). The neuro-modulating effects of dopamine in sensory thalamus *in vivo* have been reported to be dose-dependent: while small amounts of dopamine result in sensory facilitation, larger amounts appear to reduce sensory responses (Zhao et al., 2002, 2001). The high dose inhibition, however, is most likely an indirect effect mediated by the action of dopamine on GABAergic inhibition (Zhao et al., 2002; Albrecht et al., 1996). In TRN, dopamine signaling appears to increase activity. On one hand, local dopamine application elicits an increase in spontaneous firing in reticular cells (Barrientos et al., 2019). On the other hand, local dopamine release acts on presynaptic GABAergic terminals from globus pallidus that target TRN, inhibiting their GABA release. This results in a disinhibition of TRN cells and a tighter silencing of sensory nuclei (Govindaiah et al., 2010b; Gasca-Martínez et al., 2010). Altogether, dopaminergic input to sensory thalamus and TRN modulates sensory processing and gating.

Overall, research has shown that sensory thalamus receives extensive neuromodulation (Table 1). Acetylcholine and serotonin are mainly activating but also inactivate a subset of higher-order cells. Histamine and noradrenaline are excitatory too; however, noradrenaline also activates TRN – which may result in a net silencing effect in sensory thalamus. Finally, dopamine appears to exert opposing, complex modulation in sensory thalamus, and an increase in TRN activity.

8. The sensory thalamus in disease states

Sensory thalamic function has been linked to either the pathogenesis or the symptomatology of some neuropsychiatric disorders. It appears to be a key structure involved in schizophrenia, autism, and may also underlie some of the symptoms of Alzheimer’s disease and other illnesses (Fig. 3).

8.1. Schizophrenia

Schizophrenia is a neuropsychiatric disorder characterized by impairments in reality testing, with delusions, hallucinations, formal thought disorder and disorganized behavior (World Health Organization, 2024). Schizophrenic patients may also show anhedonia, deficits in attention, problem solving and speech (among other symptoms) (Orsolini et al., 2022). In schizophrenia, the size of the thalamus is reduced and its function is impaired (Buchsbaum et al., 1996). Despite differing findings (Selemon and Begović, 2007; Dorph-Petersen et al., 2009), evidence suggests that both first (i.e., LGN, MGB) and higher-order (i.e., MD, LP) sensory thalamic nuclei – as well as other non-sensory nuclei – are of smaller volume in schizophrenia patients than in healthy individuals (Adriano et al., 2010; Perez-Rando et al., 2022; Mørch-Johnsen et al., 2023). In addition, the thalamus of schizophrenic patients has abnormally high levels of dopamine (Oke

Table 1
Summary of neuromodulatory input onto sensory thalamus. Acetylcholine, serotonin, histamine, noradrenaline and dopamine innervate first and higher-order sensory thalamic nuclei in different ways, triggering different outcomes in the cells they target. The source, innervation, effects and main references are summarized here.

	Source	Innervation & effect	References
Acetylcholine (ACh)	Pontomesencephalic tegmentum & Basal forebrain	1 st order: depolarization Higher-order: depolarization & hyperpolarization (subset) TRN: depolarization	Mooney et al., (2004) Mooney et al., (2004) Sun et al., (2013), Ni et al., (2016)
Serotonin	Median & Dorsal Raphe nuclei	1 st order: depolarization Higher-order: depolarization & hyperpolarization (subset) TRN: depolarization & hyperpolarization	Varela and Sherman, (2009) Monckton and McCormick, (2002), Varela and Sherman, (2009) Goitia et al., (2016)
Histamine	Tuberomammillary nucleus of Posterior Hypothalamus	1 st order: depolarization Higher-order: unknown (similar receptors to 1 st order) TRN: no local receptors	McCormick and Williamson, (1991) Jin et al., (2005) Jin et al., (2002)
Noradrenaline (NA)	Locus coeruleus	1 st order: <i>in vitro</i> depolarization, <i>in vivo</i> mixed Higher-order: unknown (nuclei-specific $\alpha 1/\alpha 2$ expression) TRN: depolarization	Rogawski and Aghajanian, (1980a), (1980b), Moxon et al., (2007) Pérez-Santos et al., (2021) Hirata et al., (2006)
Dopamine	Hypothalamus, Ventral Mesencephalon, Periaqueductal Gray, Lateral Parabrachial nucleus	1 st order: <i>in vitro</i> activity increase, <i>in vivo</i> mixed Higher-order: hyperpolarization but increase in excitability TRN: activity increase	Papadopoulos and Parnavelas, (1990), Govindaiah et al., 2010 Lavin and Grace, (1998) Barrientos et al., (2019), Gasca-Martínez et al., 2010

et al., 1988), which has classically been linked to schizophrenia pathogenesis (Lau et al., 2013; Brisch et al., 2014). Lower thalamic D2/D3 dopamine receptor binding has also been reported (Talvik et al., 2003; Yasuno et al., 2004).

Schizophrenia patients suffer from sensory hallucinations (i.e., experience of percepts in absence of external stimuli, therefore self-generated), which are linked to activity in thalamic nuclei, striatum, hippocampus, cingulate gyrus and orbitofrontal cortex (Silbersweig et al., 1995). Alterations in thalamocortical connectivity are also reported in schizophrenia patients (Marengo et al., 2012).

The link between sensory thalamic function and schizophrenia may partially have genetic roots. In humans, a specific deletion of the chromosome 22 (22q11.2) causes a number of signs and symptoms, one of them being a proneness to develop auditory hallucinations and schizophrenia (Mancini et al., 2020). Patients with the 22q11.2 deletion syndrome also have a smaller sensory thalamus and abnormal hyperconnectivity between MGB and auditory cortex (Mancini et al., 2020). A mouse model lacking

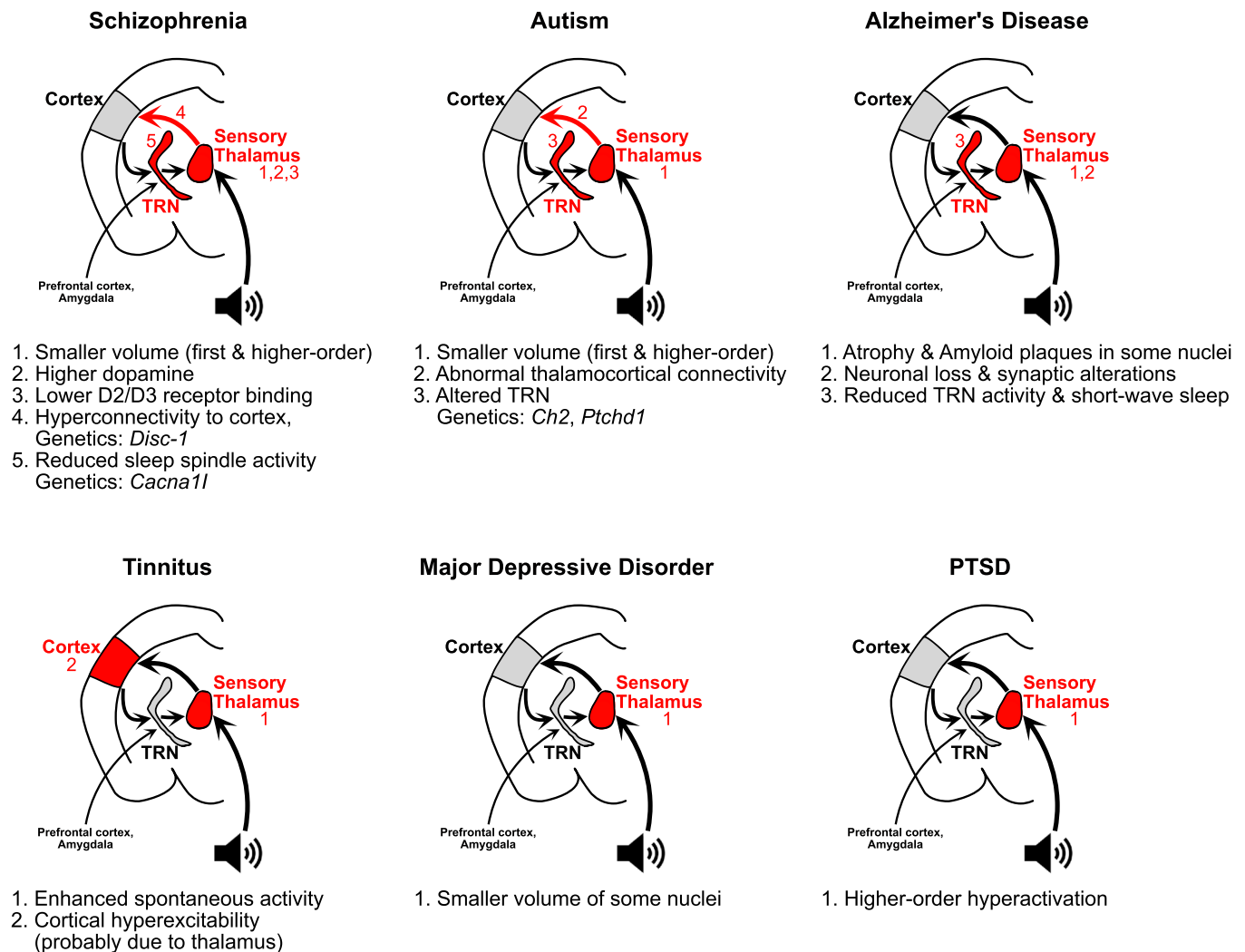


Fig. 3. Summary of identified disease alterations in sensory thalamus. Schizophrenia and autism are linked to genetic mutations that trigger morphological and functional changes in sensory thalamus, TRN and thalamocortical projections. In Alzheimer's disease, amyloid plaques and neuronal loss are found in sensory thalamus, and TRN activity and sleep are also affected. In tinnitus, auditory thalamus and cortex are hyperexcitable. Finally, patients with major depressive disorder and PTSD also show sensory thalamus alterations. The schemes depict the mouse brain anatomy but recapitulate both human and mouse findings of altered regions (red) and unaffected ones (grey).

Dgcr8 was proposed as a model of the 22q11.2 syndrome, and these mice have abnormal numbers of thalamic D2 receptors and synaptic transmission between MGB and cortex (Chun et al., 2014). The latter was reversed by the treatment with antipsychotic drugs and dopamine receptor antagonists (Chun et al., 2014). Later, it was found that *Dgcr8* deficiency triggers a microRNA loss (miR-338-3p), which appears to be the root of the thalamocortical disruption and can be replenished in adult mice to rescue it (Chun et al., 2017). Finally, the genes *Disc-1* and *Cacna1l* are also associated to schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Krol et al., 2018). *Disc-1* is prominently expressed during brain development and may be involved in the establishment of thalamocortical connections (Austin et al., 2004), and *Cacna1l* has allelic variants that alter TRN neuron excitability (Baez-Nieto et al., 2022), which is the main inhibitory controller of sensory thalamus. Furthermore, TRN participates in the generation of sleep spindle activity, which is reduced in schizophrenic patients (Ferrarelli et al., 2007). For these reasons, TRN has been proposed to be involved in schizophrenia pathogenesis (Krol et al., 2018; Ferrarelli and Tononi, 2011; Steullet et al., 2018).

Overall, abnormalities in the structure and function of sensory thalamus may underlie some of the symptoms arising in schizophrenia. Thalamic volume loss, alterations in sensory responsiveness and

impairment of thalamocortical connectivity and transmission appear to be common hallmarks in schizophrenic patients (Jiang et al., 2021). Recent studies suggest that these deficits may arise from genetic deficiencies, which may be compensated exogenously to alleviate some of the symptoms (Chun et al., 2017).

8.2. Autism

Autism spectrum disorder (ASD) is a set of lifelong neurodevelopmental conditions, which manifest during early childhood, and cause impaired social interactions, executive dysfunction (Cook et al., 2013) with repetitive and inflexible patterns of behavior and altered sensory and information processing (Lai et al., 2014; Ayub et al., 2021). Individuals diagnosed with ASD show hypo- and hyperreactivity to sensory stimuli (World Health Organization, 2024; Balasco et al., 2020). One of the suggested causes of this altered sensory perception is that ASD patients have altered thalamocortical connectivity, in sensory but also many other thalamic and cortical regions (Ayub et al., 2021; Woodward et al., 2017; Linke et al., 2023; Karavallil Achuthan et al., 2023). Furthermore, studies in animal models of ASD have reported fewer and smaller neurons in first and higher-order auditory thalamus, with respect to controls (Mansour et al., 2021). Patients with ASD also

exhibit smaller thalamic volume (Tsatsanis et al., 2003; Tamura et al., 2010), and the magnocellular portion of LGN shows reduced activity in adults with autism (Schelinski et al., 2024).

Another thalamic link to ASD is its inhibitory control via TRN. The genes *Chd2* and *Ptch1* are highly expressed in TRN (Krol et al., 2018), and their mutations have been linked to autism (Iossifov et al., 2012; Pinto et al., 2010). In line with this, it has been proposed that decreased thalamic inhibition triggers sensory thalamus to transmit to cortex excessive, unfiltered sensory information that disrupts attention (Baran et al., 2023).

Overall, research suggests that thalamic function is affected in ASD, with part of the symptoms (i.e. altered stimulus sensitivity, abnormal sensory gating) possibly being linked to changes in sensory thalamus nuclei and inhibitory control. However, thalamocortical connectivity in more executive areas is likely key as well and may underlie social and executive functions.

8.3. Alzheimer's disease

Alzheimer's disease (AD) is a form of dementia that generally impacts memory at first and progressively results in loss of most cognitive functions (Knopman et al., 2021). It is associated to encephalic grey matter loss and cell death caused by the accumulation of the so-called amyloid beta plaques, oligomers and neurofibrillary tangles, initially in the temporal lobes, but also affecting thalamus and other structures (Braak and Braak, 1991).

Among thalamic structures, the anterior nuclei are more prominently affected in AD (Biesbroek et al., 2024), but sensory thalamus also shows changes. Beta-amyloid senile plaques and neurofibrillary tangles can be found in auditory thalamus (Sinha et al., 1993). Moreover, VPL, MD and LP thalamic nuclei show atrophy in AD (Forno et al., 2023; van de Mortel et al., 2021). Pulvinar atrophy appears to occur especially in the earlier cognitive decline stage of AD, referred to as mild cognitive impairment (van de Mortel et al., 2021). In addition, neuronal loss and synaptic alterations are found in MGB in AD patients (Baloyannis et al., 2009).

In mouse models of AD, amyloid plaques can be found in amygdala and sensory thalamus, impairing the learning of fear memories (Knafo et al., 2009). This is similar to human AD patients, who have deficits in fear conditioning (Hamann et al., 2002). Because associative learning of sensory stimuli with negative outcomes heavily depends on amygdala and its direct inputs from sensory thalamus (Barsy et al., 2020; Taylor et al., 2021), it is possible that thalamic deficiencies contribute to the sensory, attentional or memory deficits observed in AD patients (van de Mortel et al., 2021).

Moreover, thalamic inhibitory control may also be affected in AD. In mouse models of the disease, TRN activity is reduced (Hazra et al., 2016), and restoring short wave sleep by chemogenetic TRN activation ameliorates amyloid plaque deposition (Jagirdar et al., 2021).

Altogether, sensory thalamus and TRN show alterations during Alzheimer's disease and may contribute to the course and progression of the disease in addition to other structures such as the hippocampus (Braak and Braak, 1991) or anterior thalamic nuclei (Aggleton et al., 2016).

8.4. Other diseases

Auditory thalamus has been linked to tinnitus, the phantom perception of sound in absence of sound stimulation that is linked to hearing loss (Almasabi et al., 2022). In animal models of tinnitus, MGB shows enhanced spontaneous activity with respect to healthy animals (Cook et al., 2021). This could underlie the cortical hyperexcitability observed in tinnitus patients (Leaver et al., 2011).

Furthermore, sensory thalamus may also play a role in mood and mood disorders. In major depressive disorder (MDD), patients have smaller volume of several thalamic regions, including sensory nuclei (Chibaatar et al., 2023). Also, one way to alleviate symptoms is via light

therapy (Tao et al., 2020), which appears to act via direct projections to lateral habenula from visual thalamus (Huang et al., 2019). Moreover, sensory thalamus has been reported to drive a specific population of parvalbumin-expressing cells in the sensory cortex, which plays a role in stress resilience. Enhancing this pathway had antidepressant-like effects in mice (Li et al., 2023).

In post-traumatic stress disorder (PTSD), the higher order somato-sensory POM shows hyperactivation in mouse models. Inhibiting its activity results in a decrease of defensive responses in mice (Xi et al., 2023).

Finally, studies in developmental dyslexia, a learning disorder with impairment in reading and spelling, revealed dysfunctions of LGN (Galaburda and Livingstone, 1993; Müller-Axt et al., 2017) and MGB (Díaz et al., 2012).

9. Concluding remarks

In this review, we aimed to recapitulate the most recent understanding of sensory thalamus with a focus on functions and disease states. While first-order nuclei are more specialized in reliable encoding of sensory stimuli and higher-order thalamus generally contains more processed information, both participate in perception, associative learning, choice and other cognitive functions. Sensory thalamus is plastic and receives top-down as well as inhibitory (mainly from TRN) and neuromodulatory control, with higher-order nuclei being particularly targeted. Moreover, the impairment of sensory thalamus likely underlies some of the symptoms associated with neuropsychiatric disorders such as schizophrenia or autism as well as Alzheimer's disease. Therefore, expanding our understanding of sensory thalamus is key to pinpoint the mechanisms behind highly complex percepts, emotions and memory formation, as well as to identify more specific and effective therapeutic targets for debilitating diseases of mental health and cognitive decline.

Novel, cutting-edge technological advances such as intravital single cell deep brain imaging of sensory thalamus (Taylor et al., 2021; Hasegawa et al., 2024), high-density electrophysiological recordings (Jun et al., 2017), neuromodulator sensors (Zhuo et al., 2024; Dong et al., 2023; Feng et al., 2019; Jing et al., 2020; Deng et al., 2024) and selective neuron manipulation approaches like chemogenetics (Roth, 2016) and optogenetics (Madisen et al., 2012), combined with behavioral testing, will together enable us to advance our understanding of sensory thalamic function, plasticity and neuromodulation in health and disease.

CRedit authorship contribution statement

Ricardo Paricio-Montesinos: Writing – review & editing, Writing – original draft, Resources, Project administration, Funding acquisition, Conceptualization. **Jan Gründemann:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors declare no conflicts of interest in relation to this work.

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Data Availability

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

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