Review

Conserved multisensory integration of social cues in the thalamus

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https://doi.org/10.1016/j.isci.2024.111678

SUMMARY

The recognition of conspecifics, animals of the same species, and keeping track of changes in the social environment is essential to all animals. While molecules, circuits, and brain regions that control social behaviors across species are studied in-depth, the neural mechanisms that enable the recognition of social cues are largely obscure. Recent evidence suggests that social cues across sensory modalities converge in a thalamic area conserved across vertebrates. These thalamic neurons control social behavior both via direct synaptic projections to other brain areas relevant for social behavior and by exerting brain-wide neuropeptidergic modulatory influence. Conspecifics are recognized by auditory, visual, and somatosensory cues, as well as mechanosensory inputs. These inputs are mostly processed in the mammalian colliculi and homologous structures in other vertebrates and are subsequently integrated in the posterior thalamus. Increased neuronal activity in this area promotes pro-social behavior across vertebrates. We propose a framework for social cue recognition by conspecific frequency-tuning in the vertebrate thalamus, discuss the potential roles of these conserved social representations and point to open questions.

INTRODUCTION

Social behaviors are abundant across all sexually reproducing species. Animals have evolved in multiple niche-specific ways to detect conspecifics for the purpose of mating, aggression, or prosocial behavior. The sensory cues that drive social interactions are conveyed via different modalities and carry information about the sender such as their identity, age, sex, or kinship. For instance, vocalization dialects of naked mole rats signal group membership,[1] mother seals can recognize the calls of their pups among thousands,[2] olfactory cues signal the extent of kinship in rats,[3] and some cephalopods use chemotactile cues to distinguish conspecifics.[4] While the study of social cue recognition dates to the very inception of ethology with the discovery of filial imprinting by Konrad Lorenz,[5] the neural underpinnings of how animals detect and integrate social cues are not well described at large for most sensory modalities.

In the few examples to date, neural representations of social sensory cues are found across different stages of the neural processing hierarchy, i.e., distance from the sensory periphery, and degrees of abstraction. For instance, dedicated olfactory networks detect the presence of conspecifics and induce appropriate physiological changes in tetrapods.[6] Sensory neurons in the vomeronasal organ harbor odorant receptors that specifically bind pheromones, thus forming dedicated channels for social olfactory perception.[7] This chemical information is relayed by the accessory olfactory bulb to specific neuronal cell types in the medial amygdala, where discrete conspecific representations emerge. Finally, these representations trigger state-depen-

dent social behaviors through neurons in the ventrolateral part of the ventromedial hypothalamus (VMHvl). Both the medial amygdala and VMHvl are associated nodes of the so-called vertebrate social decision-making network, a group of sex steroid receptor-expressing, interconnected brain regions that are conserved across vertebrates.[8,9]

In contrast to pheromones, the mechanisms used by vertebrate brains to transform other social cues into discrete representations remain largely obscure. As social cues are conveyed across sensory modalities, it is likely that brains integrate multiple sensory modalities in dedicated circuits and even single neurons tuned for social cue recognition. Such cohesive social representations might increase the likelihood of recognizing conspecifics in noisy sensory environments akin to response enhancement through the early multisensory integration of stimulus modalities in cat superior colliculus (SC).[10] Yet, unimodal social cues are often sufficient to trigger specific behavioral adaptations in most cases, as observed for social visual stimuli in stickleback and herring gulls.[11,12] To this date, it remains elusive whether a conserved node for multimodal social representations has evolved in the vertebrate brain. Recent work from both fish and rodents suggests that a *Six3⁻/Gbx2⁺* subregion of the posterior thalamus serves as a multimodal sensory integration hub for social cues and instigates appropriate behavioral responses across vertebrates.

Note to the reader: Rules for proper gene nomenclature are different between the species compared in this work (mainly rodents and fish). To improve readability, we chose to follow mouse conventions – mRNA is written
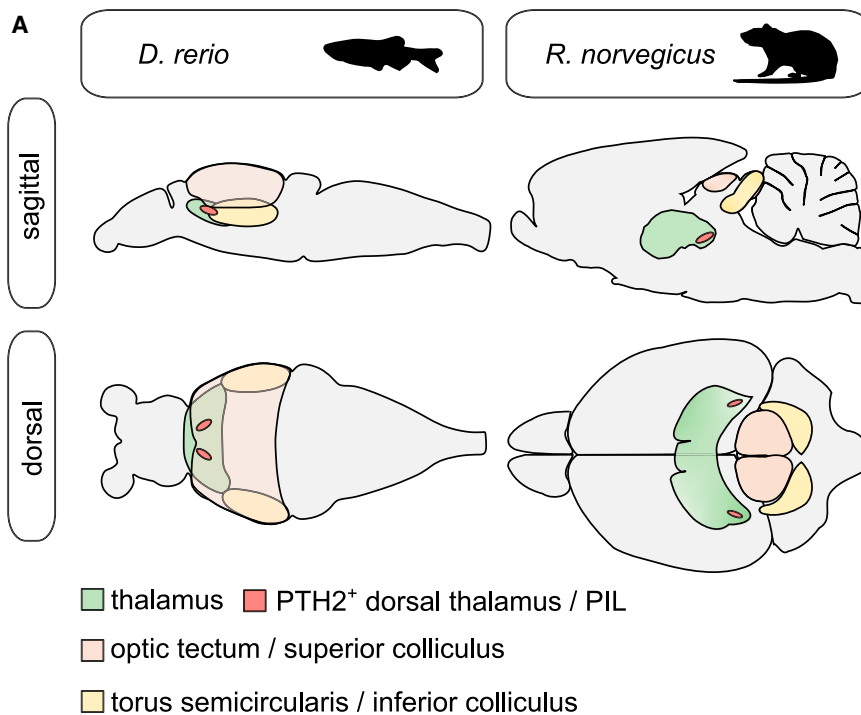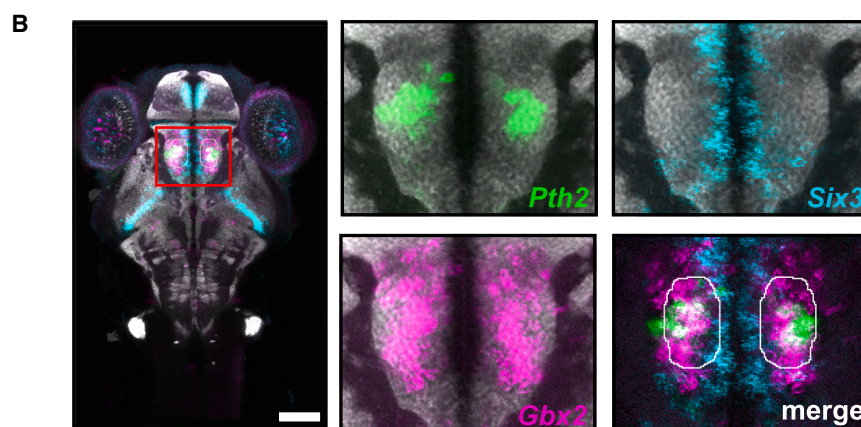
Figure 1. A conserved thalamic area for social cue integration

(A) Both for fish and rodents, relevant brain structures discussed in this work are highlighted. A PTH2-expressing area is found in the lateral thalamus in both animal classes and different sensory cues impinge on this area via the mammalian colliculi or the teleost torus semicircularis and optic tectum.

(B) Genetic markers *Six3* and *Gbx2* for the larval zebrafish thalamus proper support that *Pth2*+ neurons and the bout motion responsive region (white outlines from[20]) are anatomically and molecularly clearly defined (individual slices of HCR datasets obtained from *mapzebrain*[21] superimposed on HuC standard brain). Scale bar indicates 100 μm, a – anterior, p – posterior, l – lateral, m – medial.

with the first letter capitalized and italicized, while protein is capitalized throughout.

Thalamic multimodal sensory integration of social cues across vertebrates

To successfully navigate in groups, animals need to track the presence of conspecifics and use this information to guide behavior. When fish form collectives, visual inputs as well as mechanosensory cues of conspecifics are sufficient to induce shoaling behavior.[13] Both vision and mechanosensation have been demonstrated to be important carriers of social information for teleosts in a wide range of behavioral paradigms.[14–19] Recently, two independent studies discovered that biological motion and mechanosensory cues of conspecifics are detected by partially overlapping populations of neurons in a nucleus of the posterior thalamus proper of developing zebrafish, implicating this area as a hub for integrating social information across sensory modalities to form a representation of the social environment. Furthermore, the results raised the question of whether individual thalamus proper neurons receive input from both modalities, i.e., perform the multisensory integration of conspecific cues (see Figure 1).

Anneser et al. showed that the density of fish in a tank quantitatively, rapidly, and precisely modulates the expression of the neuropeptide parathyroid hormone 2 (*Pth2*) in a bilateral cell cluster in the thalamus proper.[22] The transcriptional regulation of *Pth2* was abolished by the chemical ablation of the lateral line, a sensory organ perceiving water motion or "distant touch"[23,24] and could be triggered by the mechanical induction of water vibration closely mimicking zebrafish tail movement.[22] In the second study, Kappel et al. investigated how the biological motion of conspecifics is perceived and processed in the visual system of the juvenile zebrafish brain.[20] There, they identified distinct brain areas responsive to visual stimuli recapitulating the movement statistics of conspecifics, which are inherently attractive for zebrafish.[16] The area with the highest density of neurons responding to bout-like visual cues was found in the thalamus and laterally overlapped with the *Pth2*+ clusters.[20]

The specificity of *Pth2* expression, which in zebrafish is exclusively found in the bilateral thalamic cluster described above, serves as a molecular marker to identify putative homologous structures in other vertebrates. In rodents, *Pth2*+ cells have been described mainly in two brain areas: the first cluster resides in the medial paralemniscal nucleus at the midbrain-pons junction, the second forms a continuous band of cells in

the subparafascicular thalamus, ranging from the posterior intralaminar complex of the thalamus (PIL) to the periventricular gray of the thalamus (PVG).[25,26] This suggests the mammalian subparafascicular thalamus or at least parts of it is homologous to the socially responsive thalamus domain in teleosts. Based on the detailed description of the available thalamic molecular architecture, expression of the transcription factor *Gbx2* in conjunction with the absence of other key thalamic transcription factors such as *Six3* effectively partition the subparafascicular area from the remaining thalamus in mice.[27] Similarly, both the *Pth2*^{+} area as well as the visually tuned bout-preference neurons are located within a *Six3*^{−}/G*bx2*[+] expression domain in the zebrafish thalamus.[21,28,29] Both in fish and in rodents, the thalamus proper and the PIL, respectively, process inputs from the inferior colliculus or its teleost homologous structure, the torus semicircularis (TS),[30,31] and are populated by *Vglut2*^{+} glutamatergic cells.[20,32] Thus, based both on marker gene expression and hodological, i.e., connectivity data, some parts of the thalamus proper in zebrafish and the subparafascicular area in mammals likely share a common ancestry.

In line with the findings in teleosts described above, several studies showed that PIL neurons in the rodent thalamus are selectively activated in the context of social interactions. In lactating mother rats, *Pth2* levels in the PIL are several-fold increased in comparison to control females and pup-deprived mothers.[33] Furthermore, social interaction between female rats led to an increase of cFOS-immunoreactive cells in the PIL[32] and promoted calcium activity in PIL glutamatergic cells of interacting rats of both sexes.[34] Moreover, direct social interactions between rats led to a >2-fold increase of *Pth2* mRNA in the PIL in comparison to animals reared in social isolation.[35] Increased transcriptional activity in response to sensory cues can be explained by excitation-transcription coupling, which is a prevalent mode of transcriptional regulation for several hundreds of genes.[36–38] In this context, we assume that the neuronal depolarization of thalamic neurons leads to the synthesis of *Pth2* mRNA and can thus be used as a proxy for neuronal activity, which has so far not been mechanistically described for *Pth2* specifically but is common for neuropeptides.[39]

As in zebrafish, social cues evoke activity in the rodent subparafascicular thalamus across sensory modalities. While studies on rodents predominantly implicated touch as the most relevant modality, one group recently demonstrated that the vocalization of pups can trigger responses in oxytocinergic cells of the hypothalamic paraventricular nucleus (PVN) of mice with the PIL contributing 100% of these auditory inputs.[40] Taken together, these recent parallel lines of evidence suggest that multimodal social sensory information converges in a thalamic region in teleosts and mammals partially characterized by expression of *Pth2*, arguing for an evolutionary conserved architecture for social cue processing across vertebrate species.

Mechanisms of social cue recognition

A striking phenomenon of thalamic sensory processing in a social context is that neural activity is narrowly tuned to the temporal frequencies of conspecific cues: Zebrafish neurons selectively respond to mechanosensory and visual stimuli that recapitulate conspecific swim bout frequencies,[20,22] mouse PIL neurons only burst in response to auditory frequencies of pup calls,[40] and túngara frog thalamic neurons fire in response to the frequencies of conspecific vocalizations.[41,42]

In zebrafish, lateral line stimulation through basic water movements in the vicinity of fish was insufficient to trigger *Pth2* transcription.[22] Only after modeling and reproducing the natural tailbeat frequency displayed by age-matched conspecifics with a piezoelectric device *Pth2* levels increased. So far, it is not clear at what level of the sensory processing pathway this kind of specificity emerges. Lateral line signals are propagated to the medial octavolateral nucleus and from there to the lateral part of the teleost TS and the deep layers of the optic tectum.[43] From the midbrain, ascending pathways reach various diencephalic nuclei and some telencephalic areas.[44] Although perception via the lateral line has been implicated in social behavior before, underlying circuit mechanisms that selectively filter social mechanosensory signals have not been described.[17,45,46] It has been shown that social isolation leads to a stronger decrease in *Pth2* levels than the functional impairment of the lateral line alone, however, it is unclear how other modalities influence the transcription of this neuropeptide as no other kind of sensory information on its own leads to a significant increase in transcript levels.[22,47]

Historically, the PIL has been associated with auditory processing. Hodological data indicated that the shell of the inferior colliculus (IC) in rats projects to the PIL.[30,48,49] Recent studies showed that pure tones can at best evoke transient spiking in the rat PIL, while pup calls evoke longer-lasting activity for the entire duration of the playback.[40] Although the rodent PIL also receives input from the auditory cortex, it is more strongly driven by IC projections.[40,50,51] Likewise, animals without neocortex process auditory social information via the IC or its homolog in fish and anurans, the TS: For example, the vocalizing plainfin midshipman *Porichthys notatus* male uses long-duration advertisement calls to attract females. In the ascending auditory pathway of females, increased cFOS staining in response to fish vocalizations (conspecific as well as heterospecific cues versus ambient noise) becomes apparent at the level of the TS, while conspecific calls lead to stronger cFOS signal in the thalamus proper and the anterior hypothalamus.[52,53] In another vocalizing anamniote species, the túngara frog *Physalaemus pustulosus*, electrophysiological recordings in the TS in response to different features of the whine-chuck pattern typical for this species' calls revealed that both spectral components and temporal characteristics of the vocalizations are well represented on a population level. However, the discriminability between actual conspecific calls and noise stimuli derived from these neuronal representations does not explain the far more accurate phonotactic responses of frogs when presented with these kinds of cues, arguing that the auditory information is further processed downstream.[41,42] Indeed, in several frog species (*Rana p. pipiens, Rana catesbeiana,* and *Hyla cinerea*), thalamic neurons extract spectral patterns indicative of conspecific vocalizations by performing an AND-operation, i.e., showing non-linear facilitation in response to the combined presentation of several frequencies that are characteristic of social calls.[54–56] However, it seems likely that the TS still forms the first level of selection

for social cues, given that the presence of interval-counting neurons (ICNs) has been described in several anuran species. These neurons specifically respond after a certain threshold number of social cues have been received with a distinct temporal interval.[57–60]

In line with increased PIL responses to social acoustic frequencies, thalamus proper neurons in juvenile zebrafish fired most strongly to visual stimuli that matched their own motion frequency[20]: Developing zebrafish display burst-and-glide motion that ranges from 0.5 to 3 swim bouts per second. Behavioral experiments revealed that individuals are strongly attracted to virtual black dots that showed apparent motion frequencies of age-matched conspecifics.[16] Neurons in a bilateral cluster of the thalamus proper show the same bout frequency tuning as well as overall speed tuning that matches conspecifics. In contrast to the *Pth2* induction, which increased via mechanosensory stimulation solely via a naturalistic frequency distribution, visual responses in DT are readily triggered by completely regular motion frequencies. Yet, DT neurons respond even stronger to naturalistic motion stimuli replayed from real shoaling episodes. The discrepancies may point to partly differential populations of neurons in DT that respond to one of the two modalities. Anatomically, visually responsive neurons overlap with the $Pth2^+$ domain and are embedded in the $Six3^-/Gbx2^+$ region (Figure 1). EM reconstructions of neurons in this functional domain revealed synaptic input from the OT, superior colliculus homolog, with many OT neurons impinging on a given thalamus neuron. Bout-frequency tuning is prevalent in OT neurons as well, which opens speculation about whether thalamus neurons integrate social motion information over large areas of the visual field to perform more advanced operations such as the spatiotemporal integration of conspecific motion signals by means of AND-operations akin to frog thalamic neurons integrating social call frequencies. This idea is further supported by the high degree of recurrence and feedback in the tectothalamic circuit, with thalamic neurons impinging laterally and back onto OT neurons.[20]

In mammals, anatomical studies have demonstrated the connectivity of IC/SC to PIL and PIL to IC/SC,[49,61] homologous to the bidirectional DT-OT circuit. Yet, there is little insight into how and where the mammalian brain processes visual social cues so far. Studies on face recognition in humans and non-human primates provide the sole examples for the visual processing of social cues in the mammalian brain: the face patch system that consists of six clusters located in the macaque superior temporal sulcus of inferotemporal (IT) cortex contains almost exclusively neurons tuned to the visual display of faces,[62] with human fMRI studies indicating the same function in a homologous area.[63] In parallel, studies in primates and humans imply the SC and the pulvinar of the thalamus for detecting low-spatial-frequency (LSF) features of faces.[64] This potentially subcortical circuit has been suggested to enable the rapid identification of conspecific emotional states to trigger adaptive innate responses on timescales below 100 ms[65,66] (but a recent study instead indicates input from V1[67]). While the anatomical similarity between the primate SC-pulvinar circuit for face detection and zebrafish tectothalamic circuits for social motion detection is intriguing, future studies should determine whether those pathways are truly homologous based on molecular cell types involved and whether the primate PIL plays any role in it. Research on subcortical circuits for visual social cue recognition in rodents might bridge these phylogenetically separated findings in the future.

The perception of somatosensory social cues in the PIL of rodents is supported by both hodological insights and molecular and functional data on mother rats. Ascending somatosensory afferents arrive from the spinal cord (Rexed Laminae IV-VI), the gracile and cuneate nuclei, and the spinal trigeminal nucleus.[32] The suckling of pups led to a markedly increased number of c-FOS positive neurons in the PIL of the mother rat, as did exposure to a familiar female.[32] Another study showed that direct social touch between rats activated PTH2+ projections from the PIL to other brain areas.[35] The study of this sensory modality is particularly challenging as visual, auditory, and olfactory cues are often present in conjunction with direct touch, for example in the case of suckling pups or social grooming. Nevertheless, in the context of this article, it is interesting to note that grooming and suckling are rhythmic activities that occur within narrow frequency bands.

As stated above, selective PIL firing in response to social cues is likely facilitated by frequency tuning to conspecific stimulus features across all modalities. The auditory thalamus, which contains the PIL and parts of the thalamus proper in fish, has been shown to exhibit increased firing rates in response to the presentation of multiple stimulus modalities[68] and anatomical evidence suggests that this area is well suited to integrate different sensory inputs.[69–72] Across mammals, intrathalamic connections involving the thalamic reticular nucleus and other pathways would allow for multisensory integration between distinct thalamic nuclei.[73–76] In contrast, the discussed evidence suggests that the convergence of social sensory modalities might occur directly at the presynapse of PIL neurons. This direct integration could emerge as a simple AND-operator that facilitates spiking when several modalities are jointly detected. This suggests an efficient neural mechanism for social cue recognition: The specific sensory frequency bands in which animals of the same species appear, move, and communicate, are detected by frequency-tuned neurons at the respective sensory peripheries and stacked in the downstream PIL by nonlinear integration, thereby facilitating the emergence of highly specific multimodal representations. While unimodal social cues might be strong enough to elicit neural and behavioral responses, naturalistic multimodal stimuli would drive stronger responses, leading to graded instead of all-or-none behavioral responses. This is in line with several observations indicating that actual conspecifics elicit stronger effects than controlled unimodal social cues.[16,20,22,47,77,78] The multisensory integration of social cues could also occur in downstream brain regions that mediate behavioral states and responses such as the ventromedial hypothalamus. Yet, multisensory representations emerging upstream in PIL might be computationally advantageous when other environmental and interoceptive signals need to be reconciled with the social environment during behavioral decision-making in effector brain regions (see also Section downstream effects and potential circuit functions).
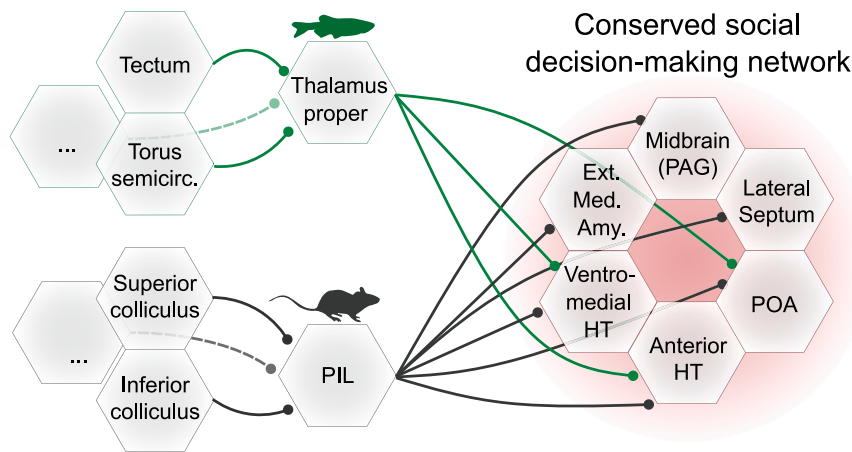
Figure 2. Connections to the social decision-making network
Both in zebrafish and rodents, connections to multiple nodes of the so-called social decision-making network have been demonstrated.[20,26,49] Inputs are incomplete and only show shared demonstrated connections.[20,22,40,49] Abbreviations: Torus semicirc.: Torus semicircularis, PIL: posterior intralaminar complex of the thalamus; PAG: periaqueductal gray; POA – preoptic area; HT: hypothalamus; Ext. Med. Amy. – external medial amygdala.

An open question is whether social experience-dependent *Pth2* expression in the thalamus modulates social cue recognition for any modality. Recent studies have reported different effects of social isolation on affiliative and collective behaviors as well as neuronal tuning to social cues. Kappel et al. showed that bout motion detection in the larval zebrafish is independent of social experience, and thus independent of *Pth2* expression induced by visual display of conspecifics.[20] Likewise, Larsch & Baier demonstrated no effect of social isolation on the behavioral attraction to virtual conspecifics in juvenile (21 dpf) zebrafish.[16] Yet, Tunbak et al. report that social isolation decreases responses to conspecifics in a visual choice assay in juvenile zebrafish.[79] Interestingly, the same behavioral effect can be observed in older juvenile zebrafish (56 dpf) when knocking out *Pth2* entirely.[80] Further, Harpaz et al. find density-dependent effects of the visual social environment on inter-animal distance and turning behavior when testing larval zebrafish in a virtual reality setting.[81] Finally, Zada et al. report decreased group aggregation and alignment as well as diminished preference in the OT for visual shapes that mimic conspecifics following social isolation in developing *Danionella cerebrum*, a species closely related to zebrafish.[82] In summary, there are several lines of evidence that social experience shapes social cue recognition and behavior in teleosts, but it remains to be demonstrated how decreased *Pth2* expression in teleost DT is linked to these effects.

Likewise, several mouse studies have reported that social isolation at juvenile age alters social recognition behavior in adults.[83,84] This effect is at least partly mediated by multiple populations of neurons in the medial prefrontal cortex (mPFC) that project to the paraventricular thalamus (PVT) and nucleus accumbens (NAc), respectively, whose firing is modulated by social experience and whose activation increases the investigation of conspecifics.[85,86] In general, it is well established that oxytocin levels in the brain modulate social investigation.[87] Valtcheva et al. report that virgin female mice show diminished responses of PVN oxytocinergic neurons to pup calls in comparison to experienced dams, with PVT neurons receiving direct input from the PIL.[40] Thus, social experience might modulate social recognition behavior via the PIL and oxytocin release in the rodent PVN. Future studies will determine whether PIL neurons and social experience-dependent *Pth2* expression upstream in the PIL modulate neural activity and behavior downstream in rodents and other mammals (see also Section downstream effects and potential circuit functions).

An entry point to the social decision-making network - Relevant thalamic areas and cell populations

Across vertebrates, several brain areas have been consistently implicated in the regulation of sociality. One of the earliest insights into this came from studies on the regulation of sex-specific reproductive behavior in rodents by Sarah Newman, describing the involvement of six distinct neuroanatomical areas (the lateral septum, midbrain, ventromedial hypothalamus, anterior hypothalamus, medial preoptic area, and the medial amygdala together with the bed nucleus of the stria terminalis) in different combinations in social behavior.[88] Homologous areas have been similarly implicated in, e.g., lizards[89] or fish[90] and appear to be well conserved across vertebrates.[8,91] Although the thalamus is not conceptualized as part of this social behavior network, the subparafascicular area (SPF) that contains PIL in rodents projects to several nodes of this network. Initial work in zebrafish demonstrates similar connectivity in fish thalamus proper.[20] Independent tracer studies in rats show that the amygdaloid complex receives projections from the SPF[30,35,48,92,93] with at least some SPF neurons expressing PTH2.[94] Likewise, projections from the SPF to the lateral septum,[35,94] the preoptic area,[35,40,93,95] the ventromedial hypothalamus,[30,93,96,97] the anterior hypothalamus,[32,35,97,98] and the PAG[35] have been reported, linking this thalamic area to the six initial nodes that Newman proposed (Figure 2).

In contrast to the detailed investigations on mammalian thalamic projections, there is only sparse information on the connectivity of thalamic nuclei in teleosts available. Yet, the datasets at hand suggest that several projections are conserved between teleost thalamus proper and rodent PIL (Figure 2). Connections between the thalamus proper and the preoptic area and rostral hypothalamus have been described in teleosts.[20,21,99] Several authors found a sparse projection to the pallial area which is the putative fish homologue to the mammalian amygdala in goldfish.[100,101] With the availability of dense EM reconstructions of the entire larval zebrafish brain, it is now possible to comprehensively characterize thalamic projection patterns, which will help

to further identify and compare connections between the thalamus and the social behavior network across vertebrates.[102,103]

Downstream effects and potential circuit functions

Although the thalamic cell populations described above have been implicated in the regulation of social behaviors in different contexts, their functional roles have only been characterized in a few cases.[20,22,32,35,80,96] Projections from the PIL to oxytocinergic neurons in the hypothalamic preoptic area have been demonstrated several times, suggesting PIL activity might be linked to oxytocin release in the brain.[32,40,104] Immunostainings revealed that PTH2-expressing terminals closely appose the cell bodies and proximal dendrites of oxytocinergic neurons in the anterior part of the magnocellular paraventricular nucleus.[32] In the same study, correlative light-electron microscopy provided evidence for synaptic connections between these neurons.[32] The optogenetic activation of PIL neurons did not directly induce firing in oxytocinergic neurons but evoked a long-lasting facilitation in evoked spike generation by decreasing the IPSC/EPSC ratio in an NMDAR-dependent manner.[40]

In parallel to synaptic transmission, PIL neurons also release the neuromodulator PTH2. Both glutamatergic and GABAergic neurons in the PVN express the PTH2 receptor (PTHR) and are thus susceptible to modulation by neuropeptidergic activity.[25,35,105] Local infusion of the peptide in the PVN led to an overall increase in pCREB, demonstrating that both synaptic and peptidergic signaling convey information from the subparafascicular thalamus to the hypothalamus.[105] In support of these functional thalamo-hypothalamic connections, PTH2 release from the rodent PIL has been linked to regulating maternal behavior: A functional knock-out of the PTH2 receptor in mother rats leads to impaired growth of the pups. This is best explained by changes in the PVN, resulting in insensitivity to suckling, and thus failure to increase prolactin levels as well as insufficient milk production in the knock-out.[95,106] In line with this argument, mRNA levels of PTH2 were strongly and significantly upregulated in lactating mother rats in the PIL.[33,95] Direct physical touch such as suckling or grooming increased transcription rates of PTH2 and activated PIL neurons based on immediate-early gene expression.[35,95,104]

Furthermore, aspects of social behavior across vertebrates have been demonstrated to depend on information processing in the subparafascicular thalamus, either conveyed directly via synaptic transmission or via peptidergic modulation. The chemogenetic activation of neurons in the PIL stimulates affiliative touch in rats[35] while zebrafish that lack the receptor for PTH2 display decreased social preference and impaired shoaling behavior.[80] Likewise, the chemogenetic ablation of thalamus proper neurons reduces social affiliation in juvenile zebrafish.[20] This behavior has been described to depend on oxytocinergic signaling also in zebrafish, so it is likely that the perception of social cues and the relay via the thalamus proper impinges on oxytocinergic neurons in teleosts as well.[15,79,107,108]

Another behavioral effect influenced by social information processing in the thalamic neuronal populations described above is the regulation of anxiety, stress, and social homeostasis in both fish and rodents. Recent studies increasingly demonstrate adverse health effects of social isolation and suggest social inter-

action as an innate need just such as thirst, hunger, or temperature that is regulated by a homeostatic system.[109] In this framework, the absence of social interaction, i.e., social isolation, triggers behavioral changes to compensate for this lack. Based on Cannon's classic model, homeostatic systems are comprised of a detector to sense changes in a homeostatic quantity, a control center that compares the deviations to an internal "set point," and an effector that produces adaptive physiological and behavioral responses to correct deviations.[110] For such a social homeostatic system, behavioral responses can be grouped into three broad categories based on social isolation studies in rodents[109]: Increased alertness and vigilance, increased motivational state to seek out social connection, and passive coping. Yet, evidence for underlying circuitry that tracks social interaction and triggers physiological changes is scarce. While there is evidence that neural effector systems for these behavioral adaptations overlap with well-described effector networks for other innate needs,[109] how and where a "social detector network" as part of the homeostatic system is implemented in the vertebrate brain is unknown. The discussed *Pth2+* thalamic region in the vertebrate thalamus is well suited to integrate multiple sensory modalities, measure the overall quantity and quality of the social environment, and transmit this information to a respective homeostatic control center. In fact, *Pth2* expression in these neurons quantitatively reflects the social environment in zebrafish. Furthermore, mouse *Pth2*^{+} neurons project to the medial preoptic area, one main presynaptic region of the paraventricular nucleus (PVN).[35] This structure is part of the Hypothalamic-Pituitary-Adrenal (HPA) axis, which is the best-understood effector system for regulating physiological homeostasis through hormonal stress regulation. It is well documented that social environment profoundly modulates the overall HPA response to other acute or chronic stressors, termed social buffering.[111] In larval zebrafish, PIL neurons send neurites into the preoptic area, which contains the PVN homolog (confusingly called the neurosecretory preoptic area (NPO),[112] which might be a direct interface with the first node of this homeostatic effector system. In parallel, the PVN hosts oxytocinergic neurons in both rodents and teleost, which are activated upon social isolation, presumably to increase social affiliative behaviors.[108,113] Here, PIL activity might modulate oxytocin release depending on the social environment, with the first evidence emerging in adult zebrafish studies.[114] Yet, the zebrafish PVN oxytocinergic neurons receive conspecific chemical cues via olfactory bulb and subpallial cholinergic neurons.[108] Here, the general theme that olfactory information, in contrast to e.g., visual or auditory cues, is not routed through the thalamus might apply to social cues as well. Several lines of evidence further suggest that the *Pth2+* thalamus is upstream of a homeostatic effector system that regulates behavioral states: In zebrafish, a premature stop codon in the PTH2 gene changes the response pattern of larval zebrafish to sudden stimuli that normally evoke an escape response. Mutant fish display a generally increased propensity for this so-called startle response, indicating that one role of this peptide is the regulation of appropriate vigilance states.[80,115] In rodents, a knock-out of *Pth2* increases anxiety-like behavior in the elevated plus-maze under stress and prolongs freezing time in a Pavlovian fear conditioning paradigm.[116,117] In agreement with these studies,

intracerebroventricular injection of the PTH2 peptide increased the time rodents spent in the open arms of an elevated plus maze.[118] Taken together, the PIL cluster presents itself as a likely candidate for a social homeostatic control center that integrates conspecific cues and, by using the gene expression of *Pth2* as a set point, modulates homeostatic effector systems and behavioral states and actions downstream.

Conclusions and future directions

In summary, we suggest that parts of the thalamus proper in fish and the PIL in mammals are homologous structures and have a conserved function in the recognition of social cues, ultimately informing other parts of the social decision-making network across the brain and inducing appropriate behavioral changes. While the integrative role of the mammalian PIL has been suggested before,[104,119] we extend this view to include the entire vertebrate lineage and downstream homeostatic functionality. With the idea of nonlinear facilitation mechanisms both within and across frequency-tuned modality-specific neurons in this thalamic area, we propose a computationally easy, experimentally testable, and evolutionarily plausible mechanism of how social representations are sculpted in vertebrate brains.

In zebrafish, transgenic tools are available to target PTH2+ neurons in the thalamus[47] and whole-brain calcium-imaging methods have been developed both for embedded and freely swimming larvae.[120,121] Previous work indicated that social cues of interest to zebrafish can be well controlled and delivered in experimental settings.[16,20,22] It appears to be a straightforward next step to test whether social responses in the thalamus proper are facilitated by the integration of different modalities in individual neurons.

Another interesting question arises by considering how typical movement patterns or vocalizations change over development. While larval zebrafish move in the burst-and-glide pattern discussed above, the frequency of their tail movement and their overall motion change with development. As zebrafish can be kept in isolation from fertilization into adulthood with the sudden presence of conspecifics still inducing increases in *Pth2* transcript levels, there appears to be an innate mechanism to keep this thalamic area tuned to age-matched frequencies that involve no learning from actual conspecifics. To this date, it is unclear what such a mechanism would look like.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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