Commentary

Biological Psychiatry

A Better PIL to Swallow: A Thalamic Node in the Social Brain Network

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Social behavior encompasses a wide range of interactions and behaviors that take place within and between individuals of the same species. Such behaviors have evolved across species to help animals navigate changing social environments, establish hierarchies, find mates, protect offspring, and access resources like food and shelter. Therefore, social interactions are multifaceted and can vary widely, depending on the species, environment, and context (1).

Over the course of a social interaction, individuals need to consistently gather and perceive sensory cues of all modalities pertaining to their partner's identity, sex, reproductive or dominance status, intentions, and emotional state. Accordingly, specialized neural networks in the mammalian brain, sometimes termed the social brain (2), process sensory information received from the environment and use it to regulate an individual's social behavior accordingly. These neural networks developed early along the evolutionary timeline, well before the development of those cortical structures that are responsible for more advanced forms of social communication, such as language. Such neural networks thus comprise mainly limbic structures, bypassing cortical areas (3).

Studies addressing the nature of the social brain have primarily focused on brain areas associated with emotions and hormones, such as the amygdala, septal nuclei, ventral striatum, and hypothalamus (4), with less attention given to the contribution of the thalamus to social behavior regulation. Nevertheless, recent studies have begun to link thalamic areas with various types of social behavior. Specifically, the posterior intralaminar complex of the thalamus (PIL) was recently implicated in social behavior by multiple studies (see below). This brain area is well positioned to convey sensory cues to the social brain, given how it receives inputs from sensory regions such as the inferior and superior colliculus, auditory cortex, and spinal cord, and projects to socially relevant brain regions like the paraventricular nucleus of the hypothalamus, lateral septum, medial preoptic area, and medial amygdala (5). Thus far, the role of the PIL has been largely demonstrated in maternal behaviors, such as pup nursing. Specifically, a subpopulation of PIL glutamatergic neurons expressing parathyroid hormone 2 (PTH2; also termed TIP39) was shown to be activated in response to pup exposure and during suckling. However, PIL involvement in regulating other types of social behavior remains speculative (5).

In the current issue of *Biological Psychiatry*, Leithead *et al.* (6) explored the role of PIL neurons in social interactions with novel conspecifics, focusing on social preference and recognition. They first showed that a large fraction of PIL glutamatergic neurons express the neuronal activity marker c-fos after social interaction. The authors then used fiber photometry to monitor real-time calcium signals in PIL glutamatergic neurons while addressing same- or opposite-sex conspecifics. The recordings showed that PIL neurons in both male and female mice specifically responded to novel conspecifics of both sexes, but not to a novel object, thus indicating response specificity to social stimuli. Finally, Leithead *et al.* examined if and how inhibition of PIL glutamatergic neurons affected sociability using a social preference test, as well as social recognition using a habituation-dishabituation test. In doing so, they revealed that inhibiting neuronal activity of glutamatergic PIL neurons did not affect the tendency of either male or female mice to explore a novel same-sex juvenile more than an object in the social preference test, suggesting that these neurons are not required for sociability. However, in the habituation-dishabituation test, inhibiting PIL glutamatergic neuronal activity blunted the formation of social recognition by female mice over repeated presentations of the stimulus animals. In contrast, such manipulation did not affect male rats, who failed to show habituation upon repeated exposure to the same juvenile animal. The authors thus concluded that although glutamatergic PIL neurons are activated during social investigation bouts, this activity is not essential for the initiation of and engagement in social interaction. Instead, at least in females, such neuronal activity seems to be crucial for memorizing and recognizing previously encountered conspecifics.

The results of the present study lead to two important insights regarding the function of the social brain. First, these findings suggest a crucial role for PIL glutamatergic neurons in social memory. Second, they extend the involvement of the PIL in social interactions beyond the context of parental or sexual behavior. Thus, the PIL seems to function as a node of the social brain network, relaying sensory information obtained during social interactions to other components of the network, which may use these data for recognition of previously encountered individuals.

This study complements two recent studies of PIL function, which together provide a conceptual framework for the role of the PIL in the integration of various social sensory cues, which are subsequently conveyed to the hypothalamus, where they are used for regulating distinct types of social interactions. The first study (7) revealed a subpopulation of PTH2-expressing glutamatergic neurons in the PIL of female rats that innervate GABAergic (gamma-aminobutyric acidergic) neurons in the medial preoptic area. These PIL neurons are activated during social interactions that involve physical touch, with their chemogenetic stimulation enhancing social grooming between

SEE CORRESPONDING ARTICLE ON PAGE 112

https://doi.org/10.1016/j.biopsych.2023.10.020
ISSN: 0006-3223

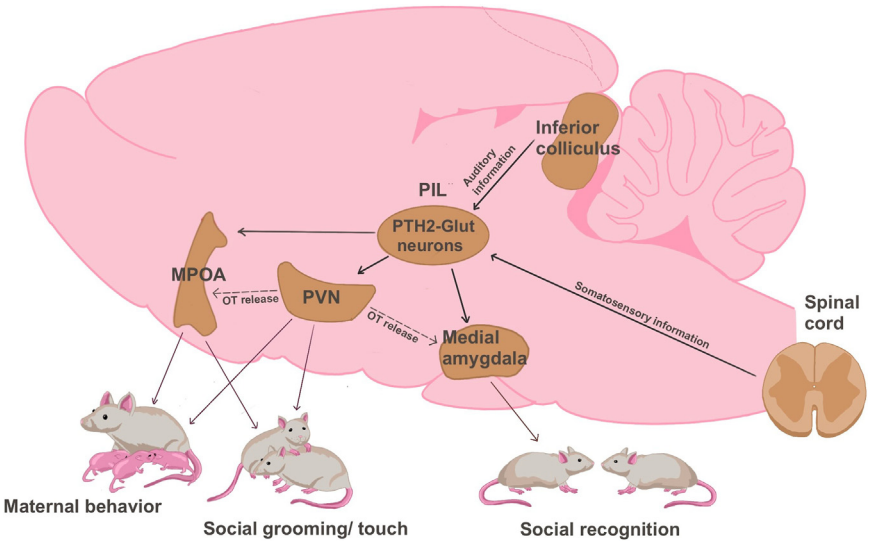

Figure 1. Schematic presentation of the integration of the sensory information by the PIL PTH2-expressing glutamatergic neurons and their projections to distinct subcortical areas, which regulate different aspects of social behavior. MPOA, medial preoptic area; OT, oxytocin; PIL, posterior intralaminar complex of the thalamus; PTH2, parathyroid hormone 2; PVN, paraventricular nucleus of the hypothalamus.

familiar rats in a PTH2-dependent manner. Notably, the PIL receives ascending inputs from neurons found in deep layers of the dorsal horn of the spinal cord (5), which most probably transmit somatosensory information to downstream neurons. The second study (8) revealed a noncanonical auditory pathway from the inferior colliculus and auditory cortex, which induces, via direct activation of PIL glutamatergic neurons, long-lasting excitation in paraventricular nucleus of the hypothalamus oxytocin neurons in response to pup separation calls. This long-lasting excitation, mediated by NMDA receptor–induced disinhibition, is needed for sustained pup retrieval behavior in rat lactating dams. Thus, it seems that PTH2-expressing glutamatergic PIL neurons integrate both somatosensory and auditory inputs to regulate the activity of paraventricular nucleus of the hypothalamus oxytocin neurons and medial preoptic area GABAergic neurons, via both glutamatergic and peptidergic signal transduction pathways. This double regulation of downstream neuronal activity by PIL neurons seems to control various types of social behaviors, such as pup nursing, pup retrieval, and social grooming. While these behaviors are mostly associated with maternal behavior, the current study by Leithead *et al.* (6) expands the PIL role to social recognition, which was previously shown to be dependent on brain oxytocin activity (9) and to require the integration of olfactory, somatosensory, and auditory cues (10). Notably, the aforementioned studies suggest a sexual dimorphism in PIL function—where female-related behaviors such as pup nursing and retrieval, as well as social grooming and social recognition in females, are orchestrated by the PIL, whereas males may rely on other nodes of the social brain. Thus, the PIL would appear to play a general role in integrating somatosensory and auditory (and possibly other) cues for regulating female social interactions via its projections to various nodes of the social brain network, as we suggest in Figure 1.

In summary, the findings of the aforementioned studies clearly show that a complex network of subcortical pathways—especially direct projections from the thalamus to the hypothalamus—mediates multiple aspects of female social behavior, such as mother–infant interactions, social grooming, and touch and social recognition, which are highly conserved among mammals and essential for their survival.

Acknowledgments and Disclosures

SW is supported by Israel Science Foundation and National Natural Science Foundation of China Joint Research Program Grant No. 3459/20, Israel Science Foundation (Grant Nos. 1361/17 and 2220/22), Ministry of Science, Technology and Space of Israel Grant No. 3-12068, Ministry of Health of Israel (Grant No. #3-18380), German Research Foundation (Grant Nos. GR 3619/16-1 and SH 752/2-1), Congressionally Directed Medical Research Program (Grant No. AR210005), and United States-Israel Binational Science Foundation (Grant No. 2019186). MM is supported by German Research Foundation (Grant No. BR 1692/11-1).

The authors report no biomedical financial interests or potential conflicts of interest.

Article Information

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Received Oct 22, 2023; revised and accepted Oct 27, 2023.

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