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Review

Neurobiology of the lateral septum: regulation of social behavior

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Social interactions are essential for mammalian life and are regulated by evolutionary conserved neuronal mechanisms. An individual's internal state, experiences, and the nature of the social stimulus are critical for determining apt responses to social situations. The lateral septum (LS) – a structure of the basal forebrain – integrates abundant cortical and subcortical inputs, and projects to multiple downstream regions to generate appropriate behavioral responses. Although incoming cognitive information is indispensable for contextualizing a social stimulus, neuromodulatory information related to the internal state of the organism significantly influences the behavioral outcome as well. This review article provides an overview of the neuroanatomical properties of the LS, and examines its neurochemical (neuropeptidergic and hormonal) signaling, which provide the neuromodulatory information essential for fine-tuning social behavior across the lifespan.

Highlights

The lateral septum (LS) is neurochemically diverse and ideally positioned to serve as a relay center, which integrates incoming cortical information about the social environment with the internal state and prior social experiences, and then transmits this information to downstream executive regions.

Existing evidence from rodents implicates different neuronal subpopulations expressing receptors for various neuropeptides and hormones within the LS in modulating a variety of social behaviors, including aggression, sexual and parental behavior, as well as general interactions with a conspecific.

This review article suggests that the abovementioned neuromodulatory signals often arising from limbic brain regions communicate the internal state of the organism and influence the integration of cognitive input into neuronal codes in the LS to modulate social behavior under basal and stressful conditions.

The septum – an integrative center for social responses

Successfully coping with social situations is an essential aspect of mammalian life. Cognitive processing of environmental stimuli, which includes social cues, and contextualizing these cues according to prior individual experiences in similar social situations, are vital for generating an appropriate behavioral response (Figure 1, Key figure) [1,2]. Such responses include, but are not limited to, social approach and investigation, aggression, sexual behavior, and maternal care [3–5]. The septum is a subcortical structure of the lower posterior forebrain, located proximally to the brain's midline and is laterally restricted by the lateral ventricles. The septum is ideally positioned to receive incoming cognitive and experience-based information from several cortical areas, including the prefrontal cortex (PFC) and the hippocampus [6]. It integrates this information with inputs from limbic regions such as the basolateral amygdala (BLA), medial amygdala (MeA), ventral tegmental area (VTA), bed nucleus of stria terminalis (BNST), paraventricular nucleus (PVN), and supraoptic nucleus (SON). These inputs report about the subjects' internal state [e.g., social motivation, physiological state, and emotional state (Figure 1)]. The septum, in turn, transmits appropriate signals to downstream hypothalamic and midbrain structures to regulate behavioral outputs (Figure 2A) [7].

The rodent septum was described as a distinct brain region by Meynert in the late 1800s, followed by detailed morphological descriptions of Ramon y Cajal in the early 1900s [8]. Later studies found that it is positioned slightly dorsocaudal to the nucleus accumbens, and rostrodorsal to the hypothalamus and the decussation of the anterior commissure [7]. As a highly heterogeneous structure, the septum is anatomically, neurochemically as well as functionally divided into two main parts: the medial septum (MS) and LS (Box 1). The MS has been extensively studied in the context of the septohippocampal system and is involved in spatial and object recognition, locomotion, and vigilance [9–11]. However, except for a limited body of literature, including a recent study implicating the MS in the regulation of social memory [12], the role of

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Key figure

Integration of internal states and external stimuli by the lateral septum determines the appropriate social response

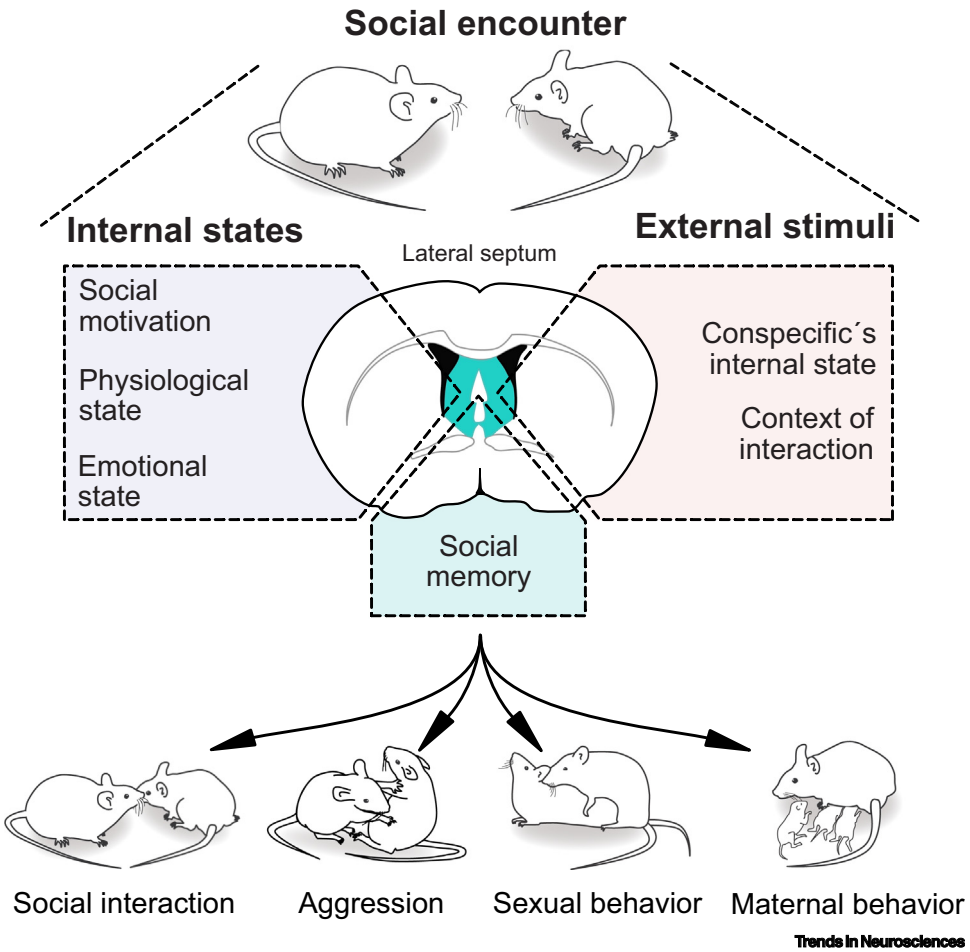


Figure 1. The behavioral response to a social encounter requires the integration of the subject's experiences (social memory) and internal state, for example, social motivation, the physiological (age, sex or reproductive state), and emotional state, with the nature of the external stimuli, such as the conspecific's internal state and the context of interaction. The rodent's lateral septum is essential for this integration process, thus shaping the respective sociobehavioral output, such as social interaction, aggression, sexual behavior, and maternal behavior.

the MS in the larger context of social behavior has been understudied. By contrast, the role of the LS in regulating various aspects of social behavior has been extensively studied in rodents, and also other species such as zebra finches [13], primates [14], and humans (Box 2). These studies suggest that the LS is evolutionarily conserved and might be of fundamental importance in regulating social behaviors with species-specific adaptations [15].

During the past two decades, the application of state-of-the-art techniques, particularly in rodents, has allowed the dissection of the functional neuroanatomy of the LS and its specific role in regulating social and emotional behaviors in detail. In this review, we discuss the role of

Box 1. Anatomy and neurochemistry of the rodent septum

In rodents, the septum is divided into two main parts: the MS and the LS. The MS receives ascending input from the hypothalamus, VTA, substantia nigra, raphe nucleus, locus coeruleus, and hippocampus [99]. Within the MS, glutamatergic, GABAergic, and cholinergic neurons are highly interconnected [100]. One primary circuit, which fine-tunes hippocampal physiology and is indispensable for its behavioral functions, is the septohippocampal pathway. It consists of ascending inputs from the MS and the adjacent diagonal band of Broca, which is functionally related to the MS, via the fimbria/fornix fiber bundle to the hippocampus [101]. Approximately 65% of septohippocampal projections are cholinergic [102]. Septohippocampal projections are crucially involved in aversive associative learning [103] and the formation of spatial memory [104]. Glutamatergic neurons account for approximately 23% of septohippocampal projections [105] and are essential for processing environmental and spatial inputs during initiation of movement episodes, general locomotor states, and running speed [106]. GABAergic neurons form the minority of septohippocampal projections and are implicated in hippocampal neurogenesis [107], operant reward learning [108], and in interaction with the hippocampal cholinergic system, modulation of anxiety-related behavior [109]. Hippocampal GABAergic neurons not only receive GABAergic input from the MS, but also project back to the MS [110], forming a reciprocal long-range circuit, which functionally synchronizes remote areas [111].

Contrary to the MS, the LS is mainly composed of GABAergic neurons, which are reciprocally interconnected with the hypothalamus (see Figure 2A in main text) and periaqueductal gray or form local microcircuits due to the presence of interneurons and extensive collateralization of LS neurons [7]. Moreover, monoaminergic and cholinergic neurons of the amygdala, BNST, medial PFC, locus coeruleus, laterodorsal tegmentum, VTA, nucleus accumbens, and entorhinal cortex project to the LS. Furthermore, the LS receives descending glutamatergic input from the hippocampus via the fimbria/fornix bundle [112]. Importantly, the LS and MS are reciprocally connected to each other [113], forming an intraseptal microcircuit. Thereby, the LS is seen as a crucial region for integrating internal and external stimuli to directly control appropriate behavioral responses to environmental stimuli.

the LS, with particular emphasis on local neuropeptidergic and hormonal signaling in modulating behavioral responses to the social environment throughout the rodent lifespan.

LS-mediated regulation of social behavior across the lifespan

Different stages in the life of a rodent are characterized by specific behaviors, each of which is critical for the animal's health and wellbeing. The LS is essentially involved in fine-tuning many components of these motivated behaviors, including kinship behavior [16], social withdrawal [17], social memory [18], social recognition [19], social fear [20,21], juvenile play-fighting behavior

Box 2. The human septal area

In humans, although the general location of the septal region within the forebrain is comparable with rodents [7], its spatial relationship to the lateral ventricles differs. The human septum consists of two parts: the septum pellucidum, a thin membrane predominantly composed of fiber tracts and glia cells, which separates the lateral ventricles; and the septum verum, which adjoins the ventral boundaries of the lateral ventricles and consists of gray matter and nuclei that are considered part of the limbic system. The septum verum is particularly well developed in higher primates and humans.

In the scientific literature, the human septal region is mentioned infrequently, and is often not classified as a distinct 'social brain' region. Nevertheless, neuroanatomical and functional alterations of the human septal region have been implicated in various social behaviors. In the 1960s, the first human studies revealed the involvement of the septal area in aggression [57] and sexual behavior [114] in men. Functional magnetic resonance imaging performed during online social interaction with a stranger volunteer in a sequential reciprocal trust game, revealed a selective activation of the septal area by unconditional, but not conditional trust, illustrating its involvement in social attachment behavior [115]. Additionally, social learning, which is fundamental to human interactions, is suggested to rest on prediction errors in the septum, which might further project to cortical areas known to represent beliefs about fellow human beings [116].

Autism spectrum disorder (ASD) is associated, in some instances, with neuroanatomical abnormalities of the forebrain and portions of the limbic system, including the septal nuclei [117]. Compared with typically developing individuals, these areas show a reduced neuronal cell size and increased cell packing density, especially within the medial septal nucleus. An age-dependent effect on neuronal size without affecting neuronal quantity has been revealed in the diagonal band of Broca of the septum of individuals with ASD. Specifically, children with ASD showed larger neuronal size, whereas adults with ASD showed smaller neuronal size in these brain regions compared with typically developing individuals. Further studies are needed, however, to more comprehensively examine the potential involvement of the septal region in human sociability, both in ASD and in other conditions associated with altered sociability.

[22], male aggression [23] and female aggression [24], pair-bonding [25], sexual behavior [26], and maternal aggression [27]. The LS contains receptors not only for neuromodulators such as oxytocin (OXT), arginine vasopressin (AVP), dopamine (DA), corticotropin-releasing factor (CRF), and serotonin (5-HT) but also for gonadal hormones, such as estrogen, which are known for their role in the regulation of social behaviors [6]. An examination of the rodent septum along the rostral to caudal axis shows a specific spatial pattern in the expression of neuropeptide receptors. While the MS is overall replete with OXT receptor (OXTR), AVP receptor 1 (V1aR), and CRF receptor 1 (CRFR1), the LS shows a higher degree of spatial specificity for OXTR, V1aR, CRFR1, and CRFR2. The LS also expresses DA receptor D 3 (DRD3) and estrogen receptor 1 (ERα) (Figure 2B). Although these receptors exhibit specific arrangement within the LS, there is a high degree of spatial overlap in their expression (Figure 2B), suggesting the presence of neuronal ensembles expressing a multitude of the abovementioned receptors. This arrangement could account for the seemingly opposing behaviors often affected by the LS. This section summarizes the role of these neuromodulators within the LS in regulating various social behaviors throughout the animal's lifespan.

Early life

Kinship, defined as the tendency to form and maintain close connections with biological relatives, is a typical behavior exhibited by animals during their early life [28]. A recent study investigated the neuronal basis of kinship and provided compelling evidence for an LS-based circuitry involved in regulating kinship behavior in male and female Long-Evans rat pups [16]. Here, aspiration-induced lesions of the LS abolished kinship behavior in rats (aged 2–30 days). A detailed electrophysiological and neuroanatomical analysis showed that kin-responsive cells are positioned in the ventral LS, pointing towards a functional heterogeneity of the septal region. The forementioned study exemplifies the role of the LS in the maintenance of innate social behavior during the crucial phase of infancy. Thus, signaling within the LS seems essential in forming social bonds during early life, and perturbations in this period caused by stressful experiences might have a debilitating effect on adult social behavior. Dopaminergic cells of the VTA code for several key features of social interaction, and a subset of these neurons innervating the rostromedial LS mediate the effects of early-life social deprivation. Daily 3-h separation and isolation of pups from postpartum day 1 to 14 disrupted DRD3-mediated signaling within the LS and consequently impaired adult social interaction in mice [29]. Similarly, daily maternal separation in the first 2 weeks of life resulted in social memory impairments during adulthood in male rats, which coincided with reduced release of the neuropeptide AVP within the LS [30]. In both these cases, restoration of local DA and AVP signaling rescued the observed impairments in social behavior. Early life stress is known to generate cognitive dysfunctions [31], and the abovementioned reversal of impairments caused by severe early-life social isolation strongly suggests the indispensable role of neuromodulation within the LS in processing cognitive information. Social memory deficits elicited by maternal deprivation are present in adult but not juvenile rats [30], suggesting that sexual maturation and the action of gonadal steroids are essential for the observed effects. Thus, the period between early life and adulthood, that is, the juvenile and adolescent phases during which sexual maturation occurs, seems to involve specific adaptations within the LS, which are critical for the socioemotional development of an individual and warrant special attention.

Juvenile and adolescent period

Interactions with conspecifics during the juvenile and adolescent phases are enriching and essential for appropriate socioemotional development in mammals [32]. Play-fighting – the characteristic behavior exhibited by juvenile and adolescent mammals as a precursor to aggressive and sexual behavior in adults – is negatively regulated by the LS, as it is promoted in juvenile rats of both sexes by septal lesions [33]. Although play-fighting is observed in both males and females, the

underlying neuronal mechanisms seem to be different. For instance, the LS of male juvenile rats has higher extracellular glutamate levels than females, and a complete blockade of ionotropic glutamate receptors within the LS impaired social play only in females. The extracellular GABA level within the LS is equal in both sexes and is causally linked to play-fighting, as blockade of GABA-A receptors in the LS decreases social play behavior in both sexes. This study indicates that differential basal excitation levels within the LS may lead to sexually dimorphic regulation of play-fighting behavior [22].

Within the LS, the sister neuropeptides OXT and AVP exert sexually dimorphic effects on juvenile play-fighting behavior [34], often in a context-dependent manner. LS-OXTR agonism reduced home cage play-fighting in female rats, while LS-OXTR antagonism reduced novel cage play-fighting [35]. Sexual dimorphism in LS-AVP signaling is demonstrated by the fact that inhibition of V1aR lowers home cage social play behavior in female rats but enhances home cage social play behavior in males [36]. Seemingly, the concerted actions of the AVP and DA systems within the LS are required to mediate social play behavior in rodents. Both AVP administration into the LS and social play enhance DA release within the LS of female rats, whereas blockade of the LS-DA signaling inhibits social play in both males and females, with the latter requiring a higher dose of the antagonist [37]. This indicates that baseline DA levels are sufficient to maintain social play behavior in males, while AVP-mediated DA release and consequent enhancement of social play behavior is dependent on a sexually dimorphic mechanism in females. Results from these studies suggest that a fine-tuned balance of intrinsic neuromodulatory signaling within the LS is essential in processing of social information during adolescence and it often has context and sex-specific ramifications.

Apart from regulating innate behaviors, such as play-fighting, there is also limited evidence pointing at the LS as mediating the effects of adolescent social stressors on adult social behavior [38]. Exposure to postweaning social isolation or social instability generated dysfunctional social behavior driven by dysregulation in processing rewarding stimuli [39]. For example, social instability during adolescence reduced dendritic spine density and synaptic plasticity within the LS of stressed compared with nonstressed rats, is hypothesized to be elicited by increased glucocorticoid release upon stressor exposure [40]. Despite the aforementioned research, the LS is surprisingly understudied in the context of adult social dysfunctions generated by peripubertal stress procedures.

Summarizing the research on early life, juvenile, and adolescent phases of life, DA, OXT, and AVP signaling within the LS seems crucial for maintaining juvenile and developing adult social behaviors. Moreover, LS neuromodulatory signaling is highly sensitive to the experience of rewarding and stressful stimuli. Hence, perturbations, especially by socially stressful situations, can lead to socio-behavioral dysfunctions, many of which persist until adulthood.

Adulthood

General social interactions (social memory, natural social preference, social fear, social defeat)

The most basic forms of interaction between two conspecifics include social approach and investigation [5]. Cortically driven cognitive processes are vital in regulating these behaviors [41] and neuropeptide signaling within the LS critically modulates the cognitive signals in light of the subject's internal state. Social memory – the ability of an individual to recognize and memorize a conspecific – reflects a combination of processes involved in encoding, storage, and retrieval of social cues [42]. As early as the 1980s, local administration of AVP into the LS of male rats was found to enhance social memory [43], which was in a later publication shown to be mediated by AVP-induced long-term potentiation within the LS [44]. Concordantly, social recognition

impairments in AVP-deficient Brattleboro rats were rescued by AVP infusion into the LS [45], while knockdown of V1aR within the LS resulted in impaired social discrimination abilities of male Wistar rats [46]. Both re-expression of V1aR in the LS of V1aR knockout (KO) mice [47] or pharmacological activation of septal V1aR signaling in adult rats [48] positively affects social recognition. More recently, using an autism mouse model, it was shown that LS-projecting AVP neurons originating in the PVN are essential for social recognition [17]. The abovementioned studies emphasize septal AVP and V1aR signaling as crucial mediators of social recognition and memory.

Considering OXT's abundant expression within the LS of many mammals, including rats and mice [49], it is not surprising that OXT, just like AVP, also plays a significant role in modulating social memory. For instance, social investigation of a novel female positively correlates with OXTR expression within the LS of male prairie voles [50], and a constitutive knockout of OXT impairs social memory in mice [51]. The critical role of OXT signaling within the LS in regulating adult social memory is emphasized by the finding of increased local OXT release during retrieval of social memory. In support of these findings, antagonist-induced blockade of OXTR within the LS of male rats impairs social memory retrieval [18], whereas activation of OXTR-expressing neurons in the LS recovers social memory deficits in an autism mouse model [52]. The hippocampal CA2 is essential for social memory and projects heavily to the LS [53]. Based on these observations, one could posit an interesting scenario wherein neuropeptidergic signaling within the LS involving mainly AVP and OXT might locally interact with CA2-LS inputs to modulate social memory. Intriguingly, the LS OXTR-expressing neurons activated by social stimuli project back to the hippocampal CA1 region [52], suggesting functional feedback regulation. Specifically, we hypothesize that LS OXTR activation potentially modulates the basal activity state of the hippocampus and, consequently, social memory.

Generally, central OXT is crucial for the maintenance of social preference in male rodents [54]. OXT is released within the LS during repeated social investigation in male and female mice, pointing towards a specific role of the local OXT system in social interaction [20,21]. This is supported by the observation that conditional deletion of the OXTR in the LS impaired preference for social novelty in male mice [55]. Disruption of social preference behavior by stressful or traumatic social experiences is processed by the LS, as demonstrated by several studies. For instance, the generation of robust fear and avoidance of conspecifics (i.e., abolished natural social preference) using the social fear conditioning (SFC) paradigm increases the neuronal activity within the LS as measured by cFos levels [20]. Furthermore, LS-OXT infusion reverses social fear and reinstates social preference in both male [21] and female [20] mice, implicating OXTR signaling in the regulation of SFC-induced social fear. During lactation – a physiological state with increased activity of the OXT system – mice exhibit no postconditioning social fear. Both pharmacological blockade of the LS-OXTR neurons and chemogenetic silencing of hypothalamic OXTergic projections to the LS reinstate social fear in lactating mice [20]. In support of an essential role of OXT signaling within the LS in the regulation of behavioral responses to socially stressful experiences, OXTR-positive neurons of the LS mediate the increase in contextual fear following social defeat stress [56]. On the surface, these examples may seem to present opposing effects of OXTR-expressing neurons within the LS: fear reducing for the former versus fear enhancing for the latter. However, a more nuanced look at the results leads us to hypothesize that OXTR-expressing neurons of the LS might modulate the valence of the social stimulus depending on their downstream targets and coexpression of other receptors (Figure 1), which may give rise to different behavioral outputs.

Thus, AVP and OXT signaling within the LS regulates several aspects of general social interactions under basal and stressful conditions. This might occur through the modulation of cortical and

hippocampal inputs the LS. How precisely the LS integrates these different and often opposing signals to affect behavior *via* its downstream targets remains unknown.

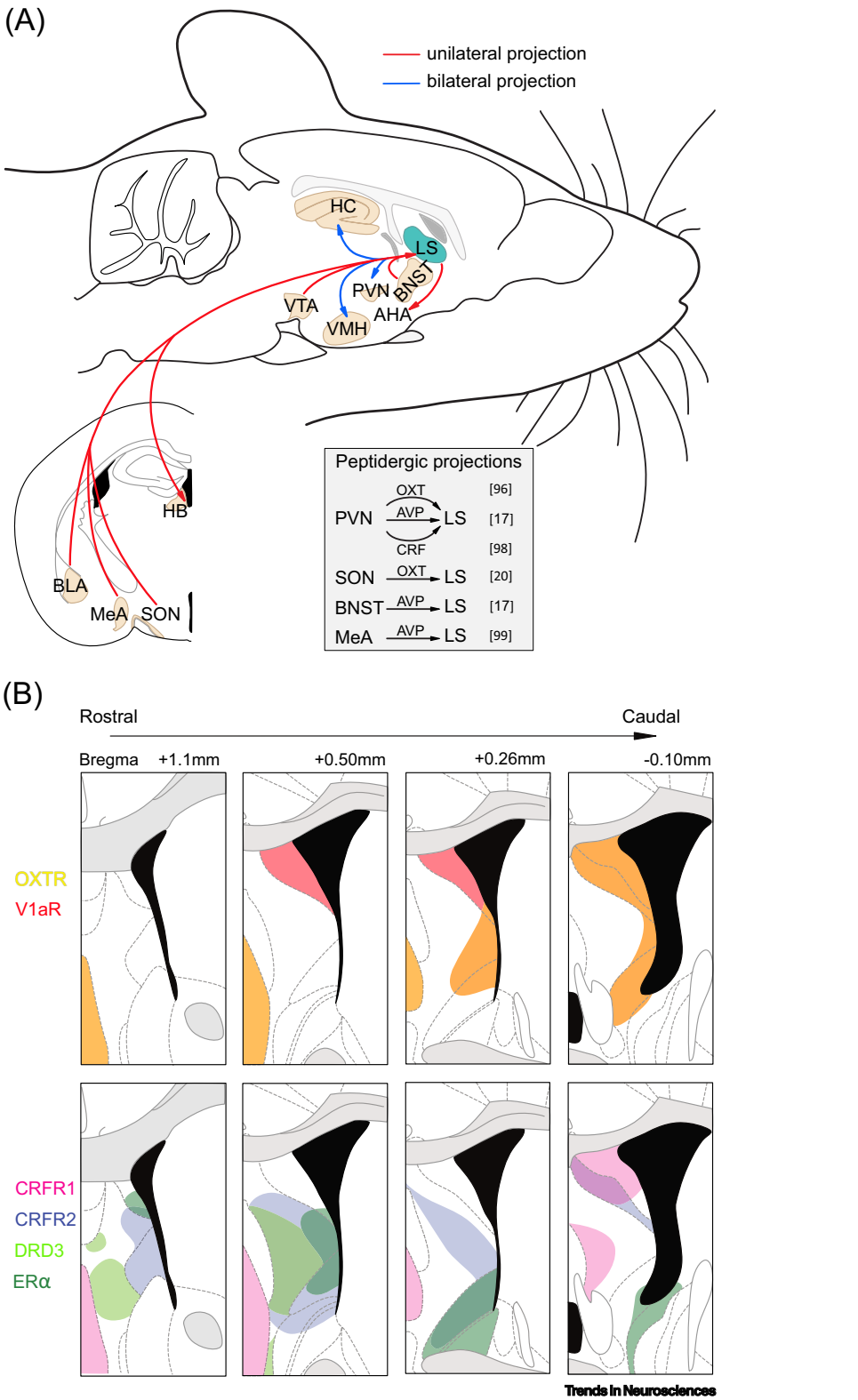
Aggression

Perhaps the most evident example of the crucial role of the LS in regulating stressful social interactions is shown by its ability to modulate aggressive behavior [23,24]. Early studies in patients with septal tumors, who exhibited aggression outbursts and increased irritability ('septal rage'), have implicated the LS in aggression [57]. Rodent studies have supported this observation, as LS lesions in male hamsters and rats exacerbated aggression [58,59]. Further evidence for LS as an inhibitory hub for aggressive behavior comes from studies in which inhibition of the LS using the GABA-A agonist muscimol enhanced aggression in male mice [23] and hamsters [60]. Muscimol-treated hamsters exhibited high levels of aggression independent of social defeat, social hierarchical status, and sex [60]. Recent experiments in male mice shed light on the precise neural circuit behind the suppressive action of the LS on aggression. Specifically, optogenetic stimulation of LS-GABAergic projections [mainly located in the ventral LS (vLS)] to the ventrolateral ventromedial hypothalamus (VMHvl) stopped attacks and reduced aggression in male mice [23].

Although lesion, neuropharmacological, and optogenetic experiments portray a clear picture of the suppressive effect of the LS on aggression, neuronal activity studies using markers such as c-Fos, pERK, and pCREB have provided discordant results. Highly aggressive California mice showed decreased activation of the vLS after aggression [61], whereas testosterone-treated aggressive CD1 mice exhibited an increased number of c-Fos positive cells in the LS [62]. However, contrasting effects are observed in male Wistar rats, which showed both reduced [63] as well as increased [64] neuronal activation in the LS in response to the resident–intruder test. In rat models of abnormal aggression, similar patterns have been found: in rats selectively bred for low anxiety-like behavior (LAB), the display of high and abnormal intermale aggression was associated with decreased number of c-Fos cells in the LS after an aggressive encounter [65]. By contrast, in rats isolated after weaning, high aggression was associated with an increased number of c-Fos cells in the LS after an aggressive encounter [64]. Although these results indicate a profound involvement of the septal region in aggression, the subregions of the LS, that is, the vLS and dorsal (dLS), seem to respond heterogeneously to aggressive interactions, as highly aggressive virgin female Wistar rats show elevated activation of the vLS and reduced activation of the dLS simultaneously [24].

The results described earlier also indicate that the LS presents a topographic representation of aggression: specific subregions might respond differently to sensory inputs and neuromodulatory stimuli regarding the internal state to generate aggressive behavior. In fact, there is evidence for an intricate polysynaptic LS circuit regulating the LS-VMHvl pathway. In male mice, dLS GABAergic neurons, which receive glutamatergic input from hippocampal V1bR-positive neurons, inhibit neurons in the vLS, leading to disinhibition of the VMHvl and, subsequently, to aggression [66]. Conversely, vLS neurons also appear to impinge onto dLS neurons, as activation of OXTR in the vLS increased GABAergic tonic inhibition onto dLS cells [24]. In line with this, tonic pharmacological inhibition, with activation of extra-synaptic δ, but not synaptic $\gamma_{2,}$ GABA-A receptors in the dLS enhances aggression in male hamsters [67].

The main neuromodulatory factors studied in the context of the LS controlling aggressive behavior include sex hormones and the neuropeptides OXT and AVP. Male mice treated with testosterone show increased activation of the LS [62]. Both aggression and neural activity are decreased when animals are treated with the aromatase inhibitor fadrozole, indicating that estrogen within the LS affects intermale aggression. Concordantly, both aggression and the number of Fos-expressing



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cells in the LS positively correlate with the local number of cells expressing ERα, implying that neuroestrogens regulate aggression in male mice via acting on ERα-positive neurons of the LS.

The role of the septal AVP system has been extensively studied in the context of aggression. Reduced LS-V1aR binding has been shown in both dominant and aggressive male mice and highly aggressive virgin female Wistar rats [24]. As for AVP release, highly aggressive male Wistar rats exhibit increased AVP release [68], whereas abnormally aggressive LAB rats show decreased AVP release in the LS [63]. Similarly, mice selectively bred for a short-attack latency show decreased AVP innervation of the LS [69]. Recently, the functional involvement of AVP signaling within distinct LS subregions in female aggression was revealed. Specifically, highly aggressive female rats show reduced V1aR binding within the LS, and fail to show AVP release in the dLS compared with low aggressive females [24]. Additionally, activation of V1aR exclusively in the dLS, but not in the vLS, strongly reduces female aggression in rats, indicating a general inhibitory role of AVP within the dLS in female aggression.

The septal OXT system seems to play a contrasting role to AVP signaling in female aggression regulation [24]: (i) decreased OXTR receptor binding is found in highly aggressive virgin female rats in the vLS; (ii) OXT release within the vLS is more pronounced in aggressive versus non-aggressive females; and (iii) optogenetic stimulation of OXT axons in the vLS increases female aggression. The neuropeptidergic, especially OXTergic and AVPergic, modulation of aggression within the LS is suggested to be mediated by an intrinsic GABAergic circuit within the LS subregions. Specifically, activation of OXTRs in the vLS increases and decreases GABAergic tonic inhibition onto dLS and vLS cells, respectively, whereas, activation of V1aRs via AVP increases tonic inhibition only in the dLS neurons [24,70]. Tonic inhibition of dLS neurons appears to be relevant for aggressive behavior, as activation of extrasynaptic δ, but not synaptic γ2, GABA-A receptors in the dLS is able to enhance aggression in male hamsters [67]. Likewise, blocking GABA-A receptors via bicuculine in the dLS decreases maternal aggression in mice [71]. Thus, one could hypothesize that OXT release and subsequent binding to OXTRs in the vLS increases aggression by enhancing tonic inhibition in V1aR-expressing neurons in the dLS, which is in line with the previously described elevated neuronal activation of the vLS (OXTR-expressing region; Figure 2B) and reduced activation of the dLS (V1aR-expressing region; Figure 2B) of female rats [24]. Here, female aggression seems to be mediated by an intrinsic GABAergic circuit within the septal subregions, suggesting the vLS as a proaggressive versus the dLS as an antiaggressive center.

Although increased OXTR binding has also been reported in the LS of highly aggressive dominant male mice [72], it is currently unknown whether the concerted modulatory action of LS AVP and OXT is similar in the context of male aggression. Further investigations are needed to clarify to what extent gonadal steroids interact with these LS microcircuits. Taken together, distinct dorsal

Figure 2. Connectivity and neurochemistry of the rodent septum relevant for social behavior. (A) The septal area, especially the lateral septum (LS), is connected to various brain regions known to regulate social behavior (see Box 1 in the main text), and receives inputs from some of these regions [17,20,95–98]. Peptidergic projections (see inset for references) regulate the animal's sociobehavioral responses. Bidirectional projections are shown as blue arrows, whereas unidirectional projections are depicted as red arrows. (B) Rostral to caudal topography of socially relevant receptors within the rodent's septum. *In situ* hybridization data were annotated from mouse.brain-map.org and mapped at four septal coronal planes (+1.1, +0.50, +0.26, and -0.10 mm from Bregma). Subregions with overlapping expression of receptors are colored as additive mixture of the respective colors [e.g., orange for expression of oxytocin receptor (OXTR, yellow) and vasopressin receptor 1a (V1aR, red)]. Abbreviations: AHA, anterior hypothalamic area; BLA, basolateral amygdala; BNST, bed nucleus of the stria terminalis; CRFR1, corticotropin-releasing factor receptor 1; CRFR2, corticotropin-releasing factor receptor 2; DRD3, dopamine receptor D3; ERα, estrogen receptor α; HC, hippocampus; LS, lateral septum; MeA, medial amygdala; OXTR, oxytocin receptor; PVN, paraventricular nucleus; SON, supraoptic nucleus; V1aR, vasopressin receptor 1A; VMH, ventromedial hypothalamus; VTA, ventral tegmental area.

versus ventral neuronal populations within the LS engage differently to evoke aggression, highlighting the contrasting roles of vLS and dLS neurons.

Sexual behavior

The chemical neuroanatomy of the LS, with an abundance of receptors for gonadal steroids such as testosterone and estrogen, advocates its potential involvement in reproductive and sexual behavior [73]. Indeed, bilateral electrolytic or chemical lesions of the LS enhanced lordosis behavior in female rats [74]. In males, bilateral lesions of the LS suppress sexual behavior measured by a decrease in the number of mounts and intromissions, and induce heterotypical sexual behavior, such as the lordosis reflex in orchidectomized male rats [26]. This implies a female sexual-behavior-enhancing or male sexual-behavior-suppressing role of the LS. However, a more detailed analysis of signaling pathways within the LS provides a more nuanced picture of its role in regulation of rodent sexual behavior. Lordosis behavior has been inhibited by applying a testosterone derivative into the LS of ovariectomized female rats [75], whereas, similar antiandrogenic treatment within the LS does not alter male sexual behavior [76]. The latter is only inhibited by blockade of both septal β_1 and β_2 adrenoreceptors, indicating the necessity of both forms for male sexual behavior [77]. These data suggest a facilitatory role for the LS in male sexual behavior and an inhibitory influence on female sexual behavior, which is partly mediated by gonadal hormones such as estrogen. Additionally, sexual motivation in male rats is negatively associated with septal ERα and ERβ levels [78]. Although the underlying neurochemical substrates and neuronal networks are not fully understood, the LS seems to significantly contribute to various components of female and male sexual behavior.

Maternal behavior

Many aspects of maternal behavior including maternal care, mother–offspring interactions and offspring protection, ensure the healthy development of the offspring [27]. In preparation for motherhood and to support maternal behaviors during lactation, the brain undergoes plastic morphological and neurochemical changes [79], which also affect neuropeptide signaling within the LS. Both AVP and OXT are released within the LS during birth, but only OXT is locally released during suckling in lactating rats [80]. Underlining the high activity of the brain OXT and AVP systems peripartum, an increased hypothalamic nonapeptide synthesis and elevated OXTR and V1aR expression and binding have been reported in several brain regions [27]. In support, within the mouse dLS, OXTR density positively correlates with the frequency of nursing behavior, whereas V1aR density positively correlates with postpartum licking/grooming of the pups in mouse dams [81]. Similarly, in rats, LS-OXTR levels also correlate with maternal responsiveness and licking/grooming [82]. There is abundant experimental evidence for a functional involvement of OXT and AVP in rodent maternal behavior [27,83], but the specific roles of these signaling pathways within LS are not fully clear. Lesion of the LS in Long-Evans rats results in reduced maternal care behaviors, including nest building and pup retrieval, and are associated with low litter weight [84]. Beyond OXT, other factors, such as prolactin, CRF, and estrogen have been revealed as essential modulators of mammalian maternal behavior [85–87], but their specific involvement within the LS is largely unknown. The relevance of estrogen in this context is supported by the observation of increased activation of ERα-expressing neurons within the LS of rats during maternity [88], but further work is needed to examine the implications of this association.

An important feature of maternal behavior is maternal aggression displayed to protect the offspring [89], and the LS seems to play a vital role in this defensive behavior. Septal lesions in Long-Evans rat dams also disrupt defensive reactions [84], while in mice, GABA-A receptor, CRFR2, and β-adrenergic receptor signaling within the LS mediate maternal aggression and defense [90–92]. Also in mice, agonizing GABA signaling by intraperitoneal chlordiazepoxide

infusion increases maternal aggression [71]. Confirming a specific role of LS-GABA-A receptors in mediating this effect, bicuculline-mediated antagonism within the LS results in inhibition of maternal aggression [90]. Thus, the net increase in LS-GABAergic signaling directly correlates with maternal aggression. Concerning CRF signaling, intracerebroventricular infusion of CRF inhibits maternal aggression and increases c-Fos levels within the LS [93]. Confirming the inhibitory role for LS-CRF signaling on maternal aggression, activating local CRFR1 and CRFR2 by infusion of CRF or the receptor-specific agonists urocortin (UCN) 1 and UCN 3 into the LS significantly inhibits maternal aggression [91]. In summary, the septal region, especially the LS, significantly contributes to various facets of maternal behavior, although the specific involvement of local neuropeptides, GABA, and sex steroids needs to be studied in more detail.

Concluding remarks and future perspectives

The internal state of an individual, including the physiological and emotional state, can profoundly alter behavioral responses to various stimuli. Neurons in the LS are impinged upon by cortical projections carrying information about cognitive processes. Additionally, LS neurons express a wide range of receptors for hormones and neuromodulators, including OXTR, V1aR, DRD3, CRFR1, CRFR2, and ERα, and accordingly can be modulated by subcortical projections releasing their respective neuromodulators. Based on the anatomical, functional, and behavioral data reviewed in earlier sections, we suggest that these subcortical neuromodulatory projections communicate the internal state of the subject in terms of the physiological [20] and emotional state (stress [29], anxiety [94], and fear [20,21,56]), and modulate the cognitive signals regarding social stimuli, which consequently alters the behavioral response. Examples discussed within this review provide compelling evidence for the role of several of these neuropeptides and hormones in the regulation of social behaviors displayed by rodents both under basal conditions and when stressed, at different timepoints throughout the lifespan. How exactly the neuromodulatory signals about the internal state are integrated into the cognitive signals at a circuit and molecular level to fine-tune behavior remains largely unknown. Additionally, a mechanistic understanding of the signaling cascades within the LS and their effects on microcircuit function in the context of social behaviors is only beginning to emerge (see Outstanding questions). Addressing how the septal region, and especially the LS, fits into the puzzle of the social brain, will require an integrative approach and connecting the different lines of current evidence.

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Declaration of interests

The authors declare no competing interests.

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Outstanding questions

Although the LS has been extensively researched in the context of social behavior, the role of the neighboring MS in this context is largely unknown. As the MS expresses neuropeptide receptors relevant for social behavior, it is predisposed to be another region involved in the regulation of sociability. Are there ethologically relevant social behaviors whose regulation the MS is involved in? Moreover, given that the MS and LS are highly interconnected, does the MS contribute to the integration of socially relevant cues within the LS?

The LS receives inputs from multiple cortical regions often presenting competing motivational signals. How does the LS prioritize one over the other, and how does the intraseptal microcircuitry functionally integrate these competing inputs to regulate affective behavior? Do multiple septal circuits, each processing separate inputs, inhibit one another through collateralization of LS neurons?

The CRF system is a major regulator of stress-induced alterations in behavioral responses. However, despite the presence of UCN 3 expressing fibers and heavy expression of its receptor, that is, CRFR2, the LS-CRF system is rarely studied in the context of social behavior. How does the septal CRF system modulate social behavior, especially in the context of stressful situations, such as social fear or social defeat?

Considering the specific patterns of expression of neuropeptide and hormone receptors and the distinct spatial arrangement of inputs into the LS, is there a topographic organization of social behavior in the LS and do the same neuronal ensembles control different types of social behavior?

The human septal area has been understudied in the past decades compared with some of the other brain regions involved in regulating social behavior. How do the functions of the human septal area compare with those of the rodent septum?

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