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Neural mechanisms of social homeostasis

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Abstract

Social connections are vital to survival throughout the animal kingdom and are dynamic across the lifespan. There are debilitating consequences of social isolation and loneliness, and social support is increasingly a primary consideration in healthcare, disease prevention, and recovery. Considering social connection as an "innate need," it is hypothesized that evolutionarily conserved neural systems underlie the maintenance of social connections: alerting the individual to their absence and coordinating effector mechanisms to restore social contact. This is reminiscent of a homeostatic system designed to maintain social connection. Here, we explore the identity of neural systems regulating "social homeostasis." We review findings from rodent studies evaluating the rapid response to social deficit (in the form of acute social isolation) and propose that parallel, overlapping circuits are engaged to adapt to the vulnerabilities of isolation and restore social connection. By considering the neural systems regulating other homeostatic needs, such as energy and fluid balance, we discuss the potential attributes of social homeostatic circuitry. We reason that uncovering the identity of these circuits/mechanisms will facilitate our understanding of how loneliness perpetuates long-term disease states, which we speculate may result from sustained recruitment of social homeostatic circuits.

Graphical abstract:

Here, we explore the identity of neural systems regulating "social homeostasis." We review findings from rodent studies evaluating the rapid response to social deficit (in the form of acute social isolation) and propose that parallel, overlapping circuits are engaged to adapt to the vulnerabilities of isolation and restore social connection. By considering the neural systems regulating other homeostatic needs, such as energy and fluid balance, we discuss the potential attributes of social homeostatic circuitry.

Keywords

social homeostasis; neural circuits; social isolation; loneliness; social rank; motivational state

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Competing interests

The authors declare no competing interests.

Introduction

The 21st century has unleashed a tsunami of opportunities for social engagement and accelerated the flow of social information. Yet as our outlets for social sustenance proliferate, along with the global population[1], there is a paradoxical increase in social isolation within society[2]. The proportion of the population who live alone has risen[3] and an increasing number of people experience loneliness[4,5]. Social isolation presents itself in multiple forms including social rejection, exclusion, ostracism, discrimination, social loss, or neglect—all of which have a significant negative impact on emotional state. Across the animal kingdom, social isolation can threaten survival—individuals lack protection from predators, assistance foraging, support raising offspring, opportunities for social play, and mating prospects. Similarly, in humans, deficits in either objective *quantity* and/or subjective *quality* of social relationships can compromise longevity[6]. Lower social integration (assessed by network size/participation, living arrangements, and frequency of close social contact) is predictive of elevated mortality[6–9], and even just the perception of isolation (colloquially referred to as loneliness) is associated with poor physical and mental health[10,11] and higher mortality rates[6,8,12,13].

However, beyond just constituting an unwelcome emotional side effect of social isolation, loneliness is theorized to represent an "adaptive predisposition" providing the motivational drive to maintain social contact and prevent the aversive consequences of isolation[14,15]. This adaptive response to deviation from an expected quantity/quality of social connections is reminiscent of negative feedback mechanisms triggered by challenges to physiological homeostasis, such as energy balance, thermoregulation, and others.

In our review, we introduce the idea that coordinated adaptations across discrete neural circuits function to maintain "social homeostasis." The term social homeostasis has previously been applied to the maintenance of stable organization within a large group of animals, typically social insects, such as ants, termites, and bees. This "supraorganismal" structure requires tight regulation to maintain stable hierarchical social organization when met with changes in the environment or internal composition[16,17]. Here we propose to extend this concept to the individual level, in order to encourage a mechanistic understanding of how deficiencies in social connection are detected and evaluated, and how effector systems are activated to compensate for perturbations.

Social homeostasis: a widespread phenomenon

Homeostasis classically refers to physiological processes wherein stable states are maintained through compensatory mechanisms[18]. Homeostatic systems are known to exist for a number of physiological needs essential to survival such as thermoregulation, energy balance, and osmoregulation. These rely upon detection of a deviation from a defined homeostatic "set-point," followed by central coordination of a response in a "control center", and the recruitment of "effector systems" that interact with the environment to correct the deviation (Fig. 1). Challenges to physiological homeostasis can also elicit motivated behaviors associated with strong negative "drive" states, such as overheating, thirst, and hunger, designed to appropriately adapt/direct behavior[19–21].

While a change in social connection may not appear to constitute an immediate challenge to internal stability, individuals on the social perimeter are vulnerable and becoming isolated can threaten survival. Even in controlled laboratory environments (where external threats to survival are absent), the presence of social contact is associated with increased lifespan across a range of social species including honeybees, ants, *Drosophila melanogaster*[22,23], mice[24,25], and rats[26–28], as well as in free-ranging groups of macaques[29], and baboons[30]. Therefore, an emerging social neuroscience model posits that evolutionarily conserved neurophysiological mechanisms underlie the adaptive, short-term, self-preservation mode triggered by a lack of social connections/mutual protection[14,31]. This model proposes that loneliness operates as an aversive signal designed to promote adaptation to the vulnerabilities of being alone and motivate reconnection[32]. Thus, the long-term disease states perpetuated by chronic loneliness may result from the continued engagement of neural systems that were intended for short-term preservation.

To begin unravelling how the chronic state of loneliness emerges, it is necessary to first understand the neural mechanisms underlying the response to social deficit. Conceptualizing this as the response of a homeostatic system would apply certain defined principles (Fig. 1). A social homeostatic system would be required to (1) monitor social conditions; (2) detect deviation from a homeostatic "set point" in control centers; and (3) activate effector systems to elicit an appropriate response (e.g., strategies to promote social contact). A deficit in social connections (whether perceived or actual) would be predicted to engage this system. In animals, one way to create a social deficit is to remove social contact entirely. While this only captures the *objective* component of social isolation, it offers controlled conditions for assessing rapid neurophysiological adaptations. Chronic social isolation, particularly in rodents, has been used as a developmental model of early life stress since many of the long-term maladaptive changes resemble features of human neuropsychiatric disease[33]. This rich body of work has been comprehensively reviewed elsewhere for both rodents[33–37] and nonhuman primates[38–40].

Alternatively, here we examine the response to acute social isolation (using under 1 week as an arbitrary operational definition of "acute" for the purpose of the review) in order to identify candidate neural circuits involved in the *rapid* response to social deficit. We focus primarily on experiments in social rodents, including laboratory mice (*Mus musculus*), rats (*Rattus norvegicus*), and prairie voles *(Microtus ochrogaster)*, which are social species, adapted to group living, but with different styles of social behavior. The wild species of mice and rats from which laboratory strains were derived are promiscuous and territorial, but show greater social tolerance in high-density living environments and adopt linear dominance hierarchies that promote group stability[41]. In a laboratory setting, mice and rats prefer social company (even that of other males) over a solitary existence[42,43]. They show conditioned preference for regions previously associated with social contact[44], make nests in close proximity to conspecifics when partially separated[43,45], and will actively work to obtain social contact[46,47]. Alternatively, prairie voles are socially monogamous and form an enduring, selective bond with their partner following mating. They show biparental care towards offspring, tend to live in extended families[48,49], and are well-utilized in the study of social bonding and isolation.

Here, we evaluate social isolation–induced adaptations in these rodents, in light of the phenotype of human loneliness, which may also represent a state of activation of "social homeostatic systems." We have categorized the behavioral and neural adaptations into three broad themes: (1) hypervigilance/arousal; (2) social motivation; and (3) passive coping. We propose that parallel, overlapping circuits mediate the *response* to social deficit (the output of homeostatic "effector" systems) in an effort to heighten attention to environmental stimuli, motivate social reconnection, and limit emotional distress (Fig. 2). While we can only speculate as to the neural identity of the detector, control, and effector systems in a social homeostatic network, we anticipate that a cohesive understanding of the response to social deficit will help unmask candidate neural substrates.

Homeostatic response to social deficit: promoting hypervigilance

An evolutionary perspective on the origins of loneliness proposes that the vulnerabilities of isolation promote hypervigilance to guard against potential threats[50]. Lonely individuals often show high levels of anxiety[51,52], and hypervigilant responses to negative social stimuli, suggestive of heightened recruitment of attentional and self-preservation mechanisms[53]. In rodents, acute isolation can promote behaviors suggestive of enhanced arousal and heightened vigilance. For example, adult rats show an increase in escape-related behaviors over 1–4 days of isolation[54], along with a reduction in exploratory behavior and an increase in self-grooming[55–57]. Targeted manipulations in rodents have unveiled that anxiety-related behaviors arise from activity across distributed, interconnected corticolimbic circuitry, which interpret and evaluate incoming environmental stimuli (reviewed in Ref. 58). One major output system is the hypothalamic–pituitary–adrenocortical (HPA) axis, which regulates arousal, vigilance, and attention, in concert with central arousal circuits including the lateral hypothalamic (LH) orexin/hypocretin system, locus coeruleus (LC) noradrenergic neurons, basal forebrain cholinergic neurons, dorsal raphe nucleus (DRN) serotonergic neurons, and midbrain dopaminergic neurons[59,60]. Several of these neural circuits exhibit rapid adaptations following acute social isolation. Here, we briefly outline the nature of these changes and their potential role in the response of a social homeostatic system.

HPA axis—Glucocorticoid production is initiated by paraventricular hypothalamic nucleus (PVN) secretion of corticotropin-releasing factor (CRF) into the hypophyseal portal system, triggering adrenocorticotropic hormone (ACTH) release by the anterior pituitary that in turn acts on the adrenal cortex to secrete glucocorticoids. The HPA axis is regulated by a negative feedback loop, wherein glucocorticoids bind to receptors in the pituitary and other brain regions including the hippocampus, which subsequently inhibits CRF and ACTH production. While acute activation of the HPA axis can be an adaptive physiological response to salient events, chronic activation of this system, particularly by continued psychosocial stressors, is implicated in the progression of multiple disease states and psychopathologies[61]. Consistent with this, high self-reported loneliness in humans has been associated with elevated daily cortisol output[62–66] and a flattening of diurnal cortisol rhythm[65], suggesting poor regulation of the HPA axis[67].

Heightened HPA axis activity (evidenced by a robust increase in circulating corticosterone and ACTH) is observed after 1–5 days of social isolation in juvenile (3–5 weeks old)[68,69] or

pair-bonded adult[70–72] prairie voles. Peripheral corticosterone levels are also reportedly increased in male mice isolated for 12 h,[73] and both adrenal ACTH and corticosterone are increased in male rats isolated for 24 h in a novel environment[74,75]. This recruitment of the HPA axis during acute periods of isolation may reflect the increased need for vigilance and attention to salient stimuli.

CRF signaling—CRF pathways are a prominent point of convergence for isolation-induced adaptations. Aside from their role in initiating the neuroendocrine response to stress, PVN CRF neurons are pivotal in orchestrating the rapid, complex behavioral adaptations that occur following acute stress (potentially via glutamate coreleasing projections to neighboring hypothalamic regions)[76]. CRF-producing neurons are also widely distributed in extrahypothalamic regions, including the bed nucleus of the stria terminalis (BNST), central amygdala (CeA), nucleus accumbens (NAc), and hippocampus[77–79], which have, likewise, been implicated in the behavioral and physiological responses to stress. Isolation of preadolescent female (but not male) mice for <24 h decreased the excitability of PVN CRF neurons in a glucocorticoid-dependent manner[80]. This finding may reflect glucocorticoid feedback–induced suppression of CRF activity. Consistent with this interpretation, a 24-hour isolation in adult rats decreased CRF mRNA and protein in the PVN[75] and decreased cortical CRF_1 receptor levels[81]. Moreover, these changes in CRF were accompanied by enhanced angiotensin II (ATII) AT_1 receptor expression in the PVN[74]. ATII is a circulating endocrine factor that can trigger CRF production in response to stress[82]. This factor may be necessary for isolation-induced adaptations within the hypothalamic CRF system, as the isolation-induced decrease in CRF mRNA in male rats could be prevented by an AT_1 receptor antagonist[75]. Conversely, a shorter period (1 h) of social isolation in adult male and female prairie voles housed with same-sex siblings, resulted in increased hypothalamic and hippocampal CRF mRNA[83]. This discrepancy may reflect the shorter duration of isolation or the different species under study. However, it highlights the growing need for a thorough understanding of the timeline of adaptations following social isolation.

LC noradrenergic system—The LC is the sole source of noradrenergic innervation to the central nervous system, best known for its role in arousal and vigilance, but more broadly thought to be recruited to combat environmental challenges[84,85]. In adult rats, a 24-hour isolation increased tyrosine hydroxylase (TH; the rate-limiting enzyme in catecholamine synthesis) mRNA in the LC, an effect which could be blocked by an AT_1 receptor antagonist[81]. Thus, the acute response to isolation involves coordination across both peripheral and central neuromodulatory systems.

Homeostatic response to social deficit: engaging social motivational systems

In humans, a deficit in social connections is conceptualized to engage the “social monitoring system”[86] with the purpose of directing attention towards socially relevant information. Accordingly, lonely individuals show enhanced sensitivity to social cues and increased socially affiliative motivation[86–90]. Enhanced social motivation is similarly evident in acutely isolated rodents: when given the opportunity, previously isolated (2–48-hour duration) juvenile and adult rodents spend more time engaged in social behaviors[91–98]. It is suggested that up to 7 days of isolation promotes affiliative social behavior and social

interest in rats[57,92], whereas in adult mice, a significant increase in aggressive behavior was observed after 48 h, but not 24 h of social isolation[99].

For many social species, the inherently rewarding nature of social interactions is a major driving force for social contact. In rodents, one method to evaluate the positive reinforcing properties of social interaction is the social conditioned place preference (social CPP) assay —an adaptation of a test traditionally employed to measure the rewarding properties of drugs of abuse[44]. In this task, animals typically demonstrate preference for a region previously paired with social housing over one paired with isolate housing (~24-hour duration[44]). Notably, therefore, the conditioned approach to a socially conditioned context is a product of both "social reward" and "isolation aversion."[44] Several neuromodulatory systems (including dopamine, oxytocin, and opioid circuits) have been posited to underlie the motivation for social reward. These circuits are also prominent sites of rapid adaptation following social isolation, which we discuss below. Notably, however, it remains to be determined whether the motivational processes of "social reward" and "isolation aversion" are encoded in separable or overlapping neural circuits (see also below).

VTA dopamine system—The midbrain dopamine system has a long-standing role in reward processing[100] and affiliative social behavior[101], and is frequently reported as a site of isolation-induced adaptation. The ventral tegmental area (VTA) dopamine neurons project to multiple regions including the striatum, prefrontal cortex (PFC), and basolateral amygdala (BLA), with the VTA-NAc pathway being particularly well-associated with social reward[102,103]. In juvenile rats, isolation-induced social play was suppressed by D_1- or D_2-receptor blockade in the NAc[104], while in adult rats, 24 h or 4 days of isolation decreased striatal D_2-receptor density[105] and increased mesostriatal TH activity[106], respectively. Isolation-induced changes do not appear to be limited to the mesostriatal pathway, however, as adolescent mice isolated for 1–7 days showed an increase in both striatal and cortical dopamine metabolism[107]. Additionally, in the PFC, decreased $GABA_A$-stimulated chloride influx was evident in a membrane preparation from 24-hour isolated rats[108] along with reduced benzodiazepine binding[81], indicative of reduced cortical $GABA_A$ expression and/or function. Given the functional diversity of dopamine input to striatal subregions[109,110] and dopamine's divergent effects on cortical projector populations[111], further work is necessary to elucidate precisely how these rapid isolation-induced changes to dopamine neurotransmission influence downstream activity.

DRN dopamine system—Another component of the midbrain dopamine system—the DRN dopamine neurons—also exhibits acute isolation-induced adaptations. These dopamine neurons were historically considered a caudal extension of the VTA, but accumulating evidence has revealed distinct downstream projections and functional roles[112–118]. In adult male mice, 24 h social isolation potentiated glutamatergic synapses onto DRN dopamine neurons, and also heightened their activity *in vivo* in response to a novel mouse[118]. Artificially enhancing activity of DRN dopamine neurons with optogenetic stimulation was sufficient to increase social preference. However, in the absence of a social stimulus, mice chose to avoid receiving stimulation of DRN dopamine neurons (demonstrated by real-time and conditioned place avoidance), which suggests the induction of a negative affective

state[118]. DRN dopamine neurons may, therefore, be recruited following acute isolation to elicit “negative drive”-induced social motivation, in a manner distinct from the reward-related social motivation mediated by the VTA-NAc dopaminergic pathway[103]. Consistent with this assertion, optogenetic inhibition of the DRN dopamine population had no effect on sociability in group-housed animals, but it suppressed social preference following 24 h of isolation[118].

The DRN dopamine neurons lie directly upstream of several regions, most notably the BNST and CeA[116,118]. While the explicit role of dopamine in these regions in social behavior remains to be determined, dopamine receptor signaling can modulate synaptic transmission and activity in both the BNST and CeA[115,118–120]. Specifically, in the dorsolateral BNST blunting of long-term potentiation (LTP) is evident just after 24 h of social isolation[121]. Given that dopamine in the BNST can facilitate glutamatergic transmission, via a CRF-dependent process[119], it is tempting to speculate that increased dopamine neurotransmission following acute isolation may occlude LTP.

Interestingly, it was recently revealed that an intermediate duration of isolation in mice (2 weeks) is associated with upregulation of the neuropeptide tachykinin 2 (TAC2; also known as neurokinin B) in several regions including the anterodorsal BNST (adBNST), CeA, and dorsomedial hypothalamus (DMH), with levels gradually increasing from just 30 min post-isolation[122]. Behavioral changes observed following this period of isolation appeared to be mediated by TAC2 upregulation in discrete sites, as chemogenetic silencing of TAC2-expressing neurons in the adBNST, CeA, or DMH selectively prevented persistent freezing, acute freezing, or aggression, respectively[122]. Notably, CRF co-expression was observed in ~50% of TAC2-expressing neurons in the adBNST and CeA[122], which again highlights the involvement of CRF circuits in isolation-induced adaptation. A substantial body of work supports a role for the BNST in mediating sustained responses, and the CeA in mediating rapid responses, to potential/unpredictable threats[123]. This behavioral control is enabled by the far-reaching connections of the BNST and CeA, particularly with hypothalamic and brainstem structures, which underlies their ability to influence autonomic and neuroendocrine functions[124,125]. These regions are therefore well-positioned to drive isolation-induced adaptive responses, under modulatory control from upstream regions, including the DRN dopamine neurons.

This collection of findings compels the hypothesis that dopaminergic signaling may be involved in the initial response to social isolation, but that downstream regions (including the BNST and CeA) might exhibit longer-term remodeling/plasticity following chronic isolation. Indeed, there is considerable evidence to support a similar model for the stages of *drug*-evoked plasticity in the mesocorticolimbic dopamine system. Specifically, a single dose of cocaine is sufficient to potentiate glutamatergic transmission onto VTA dopamine neurons after 24 hours[126]. Synaptic strength returns to baseline levels within a week, however, this VTA plasticity is required for the persistent changes that occur downstream in the NAc following prolonged cocaine exposure[127] (reviewed in Ref. 128). This permissive role of synaptic plasticity in VTA dopamine neurons could similarly be a feature of DRN dopamine neurons in the response to social isolation. Such a feature would predict that acute isolation-induced synaptic changes in DRN dopamine neurons precede, and are necessary for, chronic

isolation-induced adaptations in downstream regions. In this way, the myriad of maladaptive behavioral changes associated with long-term social isolation[37] might result from chronic engagement of neural circuits mediating the acute response to social isolation and persistent remodeling in downstream regions.

Opioid system—The opioid system exerts a broad influence on neural activity through widespread expression of opioid peptides and receptors, most notably within regions connected to positive reinforcement (reviewed in Ref. 129). Opioid signaling plays well-documented roles in regulating pain/analgesia[130], reward processing[129], and social bonding[131], and has also been implicated in isolation-induced social behavior. *In vivo* autoradiography revealed changes to opioid receptor binding, with 7 days of isolation in juvenile rats associated with upregulation of opioid receptor number or affinity in the PFC[57]. Additionally, isolation-induced social play in juvenile rats was attenuated by systemic administration of a μ-opioid (MOR) antagonist[97,132] or a κ-opioid receptor (KOR) agonist[132], but enhanced by administration of a MOR agonist[97]. Furthermore, in the CeA, infusion of an ACTH analog suppressed isolation-enhanced social interest in 7-day isolated rats, but this could be prevented by administration of naltrexone (a MOR and KOR antagonist)[56,133]. Therefore, both opioid and dopamine receptor signaling may be necessary for the heightened sociability evoked by acute isolation.

Hypothalamic oxytocin system—Oxytocin-producing neurons of the PVN, along with the closely related vasopressin (AVP) neurons, are intimately involved in the regulation of social affiliation[134] and have been particularly well-studied in the monogamous prairie vole, as they play a pivotal role in pair bonding[135]. Oxytocin neurons project not only to the posterior pituitary where they release oxytocin into the bloodstream but also to distinct targets within the brain for direct modulation of neuronal activity. One important site for oxytocin action is the NAc, which is a critical hub for the integration of motivationally relevant information and relays information to elicit motor responses[136]. In male prairie voles, 3 days of isolation from a bonded female partner, but not a male sibling, decreased oxytocin mRNA in the PVN and oxytocin receptor binding in the NAc shell[137]. Notably, oxytocin signaling in the NAc is reportedly essential for the expression of social CPP in adult male mice[138]. Specifically, it was elegantly demonstrated that social CPP required activation of oxytocin receptors on presynaptic terminals in the NAc arising from DRN serotonergic neurons—facilitating serotonin release[138]. In addition, social CPP was shown to be dependent on the PVN oxytocin projection to the VTA[139]. Either suppressing activity in the PVN-VTA pathway or VTA dopamine-specific knockout of oxytocin receptors prevented social CPP in male mice[139]. Collectively, these findings illustrate the dynamic balancing of dopamine, oxytocin, and serotonin signaling that is required for the reinforcing properties of social interactions.

Acute isolation has also been demonstrated to disrupt social recognition memory[140]. Rodents possess an innate tendency to investigate novel rather than familiar social stimuli and typically reduce their investigation of a familiar conspecific on repeated exposure[141]. This effect is absent in mice isolated for 24 h or 7 days, who display equivalent investigation of a familiar juvenile compared with the first exposure[142,143]. This lack of social recognition

memory is associated with a suppression of oxytocin-dependent synaptic plasticity in the medial amygdala (MeA) following 7 days of isolation in rats[144]. It has been further revealed that suppression of social recognition memory may result from elevated hippocampal Ras-related C3 botulinum toxin substrate 1 (from the Rho family of small GTPases), which is evident in male mice isolated for 24 h or 7 days[145]. Thus, isolation-induced modifications to oxytocin signaling, in a pathway-specific manner, may contribute to changes in both social motivation and social recognition memory.

Homeostatic response to social deficit: a self-protective coping strategy?

Individuals that self-identify as lonely frequently exhibit features of negative affective state or depression[10,50,146–149]. Furthermore, individuals swayed towards feelings of future loneliness (by receipt of false feedback following a questionnaire) show a reduction in physical pain sensitivity and emotional sensitivity[89]. This suggests the adoption of self-protective strategies to minimize further emotional distress. While we cannot directly measure emotional state in rodents, we can assay motivated behavior as a proxy[58,150]. In rodents, immobility in the forced swim and tail suspension tests is thought to reflect passive coping and/or behavioral despair[151,152] but see Ref. 153. There is a general lack of agreement over whether acute isolation alters immobility in these assays in mice[55,73,154]. However, more consistent results have been obtained in monogamous prairie voles, wherein females or males isolated from their bonded partner (but not from a male sibling) for 3–5 days show an increase in immobility time[70,71,137].

There is also evidence for disruption of reward-related behavior in acutely isolated rodents, specifically in the response to addictive drugs. In rats, a 24-hour social isolation increased preference for ethanol and opioid intake, which was reversed with social housing[155,156]. Reduced pain sensitivity has also been reported, with male mice and juvenile rats exhibiting higher thermal and mechanical pain thresholds following 2–3 days of social isolation[157,158]. The prominent role of dopamine and opioid signaling in mediating the effects of drugs of abuse[159] and analgesia[130,160] makes them strong contenders for underlying these adaptations. In particular, chemogenetic activation of ventrolateral periaqueductal grey (vlPAG)/DRN dopamine neurons can promote antinociception[117], while a lesion of these neurons suppresses both the antinociceptive[161,162] and rewarding[163] properties of exogenous opioids. Furthermore, inhibition of VTA dopamine signaling in mice can induce depression-related behaviors[164], while KOR antagonists are proposed to have antidepressive effects in rodents (see Refs. 165–167). In this way, interactions between the dopamine and opioid systems may underlie isolation-induced changes to reward processing, pain sensitivity, and emotional affect.

In addition to dopaminergic and opioidergic mechanisms, isolation-induced depressive-like behavior may result from changes in the balance of CRF and oxytocin neurotransmission. Specifically, the passive coping behavior observed in pair-bonded prairie voles isolated for 3 days was prevented by NAc shell infusion of a CRF_2 receptor antagonist, or oxytocin, throughout the period of isolation[137]. Microdialysis experiments suggest a mechanism by which this effect is mediated via presynaptic CRF_2 receptor activation on oxytocin terminals in the NAc, which serves to reduce oxytocin release[137]. These findings point towards a

confluence of isolation-induced adaptations in the NAc. The NAc receives strong glutamatergic input from thalamic and cortical regions, enabling it to integrate motivationally relevant information from neuromodulatory nuclei with higher cognitive and sensory input[168]. Thus, this region is aptly poised to adapt goal-directed behavior in response to social deficit.

Proposed attributes of components within a social homeostatic system.

Flexibility—Animals are frequently faced with conflicting signals in the environment, which can elicit competing motivational drives. To ensure survival, animals must appropriately weigh environmental cues and evaluate them in light of current homeostatic need state. Selecting the appropriate behavioral response under these conditions requires dynamic balancing and coordination of neural activity[169]. Thus, a key requirement for a social homeostatic system is its capacity to flexibly adapt to meet other physiological needs. Specifically, a change in environmental conditions and/or need state (e.g., hunger and thirst) may require a shift in the "set point" for social contact in the control center (Figs. 1b and 3). This will be heavily influenced by dynamic factors, such as resource availability, predator threat, mating prospects, and the presence of offspring.

For example, in a state of hypernatremia (elevated plasma sodium, which is associated with the perception of thirst), rats exhibit greater social investigation of a novel intruder[170]. This effect is proposed to have evolved to suppress anxiety in social situations, such as those encountered at a communal source of water, in order to promote social approach and allow drinking behavior[170]. This observation suggests that social motivation can be altered by other physiological needs. Intriguingly, acute hypernatremia in rats is also associated with increased plasma oxytocin, increased c-Fos expression in magnocellular PVN oxytocin neurons, and suppression of ATII production[170]. Given that ATII signaling can drive HPA axis activity, these data suggest that hypernatremia concomitantly suppresses activity within stress-related circuitry, while promoting activity in social reward-related oxytocin pathways, thereby inhibiting stress/anxiety-related behavior and facilitating social interaction. This relationship illustrates overlap and coordination across homeostatic systems and also demonstrates the flexibility of effector systems.

The motivational state of hunger is another essential homeostatic drive which promotes rapid neural adaptations[171,172]. Specifically, the agouti-related protein (AgRP) neurons in the arcuate nucleus of the hypothalamus are essential in the maintenance of energy balance, and their activity rapidly drives feeding behavior in a state of hunger[173]. Interestingly, optically evoked feeding behavior in isolated mice persists, even in the presence of a novel male or female mouse[171]. This finding suggests that AgRP activity in a state of hunger is sufficient to override a competing social motivational drive. Conceptually, it is possible that competing homeostatic drives are integrated into a social homeostatic system at the level of the control center in a "hub-and-spoke" fashion, or they may form an interconnected hierarchical arrangement that converges on effector systems (Fig. 1b). While it is possible that one homeostatic system may be subservient to another, an interconnected network would permit flexible control in a state of motivational need competition, prior to convergence on effector

systems. Precisely how these homeostatic systems interface with one another remains to be elucidated.

Maintaining physiological variables, such as core body temperature and energy levels, within an appropriate dynamic range relies heavily upon a functioning immune system. Inflammation is theorized to be a unifying feature of homeostatic perturbation: providing a protective response to extreme deviations from the homeostatic set point[174,175]. Adverse conditions, including social isolation, can provoke a shift in immune function: enhancing expression of proinflammatory genes and reducing expression of antiviral/antibody-related genes in circulating leukocytes[176]. Social isolation may recruit this response to appropriately prepare an individual for the susceptibilities of being alone, which might include an increased need for a rapid inflammatory response to combat bacterial infections sustained through physical injury, but the reduced need for protection against socially transmitted viral infections[15,176]. This immune response also appears to be recruited in a state of perceived isolation—humans with high self-reported loneliness show enhanced proinflammatory activity but reduced antiviral response[66,177–179]. Immune system changes can also predict subsequent loneliness, suggesting a reciprocal relationship between these two phenomena[64]. Remarkably, classifying rhesus macaques as putatively high in loneliness (by sociability levels and social initiation attempts)[180] revealed leukocyte gene expression changes similar to those observed in lonely human subjects[64]. Mounting evidence for recruitment of inflammatory processes under conditions of actual or perceived social isolation[31] suggests that this state is recognized as a threat to an essential variable. As such, this supports the assertion that social contact may be regulated in a homeostatic manner.

Mixed selectivity—Considering the neural processing of “social homeostatic” information, one possibility is the existence of dedicated neural circuitry. An alternative model would feature overlap between neural systems governing social homeostasis and other highly conserved neural circuitry. This scenario would predict that certain nodes in a social homeostatic network display “mixed selectivity,” similar to neurons underlying other complex cognitive processes[181]. In particular, this is conceivably a feature of “effector” regions in a homeostatic system. The disinhibition of VTA dopamine neurons, for example, has been shown to enhance motivation towards a variety of stimuli ranging from social stimuli to novel objects[182,183]. Furthermore, activation of BLA input to the ventral hippocampus or mPFC not only induces robust anxiety-like behavior in exploratory assays but also suppress social investigation in the resident–intruder assay[184–186]. Perturbations in social behavior are often, but not always, co-expressed with anxiety-related behaviors, and there is significant overlap in underlying neural correlates, which suggests a tight relationship between these two forms of behavioral expression[58,187].

The DRN dopamine system is another prime example of overlapping circuit function. Monitoring fluorescent calcium activity *in vivo* revealed that these neurons are active in response to social stimuli, and this activity is heightened following acute isolation[118]. However, these neurons are also responsive to other salient stimuli, including palatable food and unexpected foot shock, and show greater activity during wakefulness compared with sleep, suggesting an arousal-promoting function[112,115,188]. This diversity of sensitivities is consistent with the notion that neural circuits regulating social homeostasis may promote

attention to a variety of salient stimuli, in an effort to scan the environment for potential threats or opportunities for social engagement. It was also recently reported that optogenetic or chemogenetic inhibition of DRN dopamine neurons during fear conditioning suppressed freezing in response to a footshock-predictive cue, suggesting an additional role in aversive responding[115]. Taken together, these findings illustrate the existence of multiple mechanisms through which DRN dopamine neurons may limit the vulnerabilities of being alone: increasing social motivation, promoting vigilance/arousal, and enhancing responsivity to aversive stimuli.

Considering the potential for mixed selectivity, the recent observation that activation of DRN dopamine neurons not only increases social preference[118] but can promote antinociception[117] could be reconciled in a number of ways. One possibility is that functional heterogeneity exists within this cell population. Another possibility is biological convergence in the representation of *emotional* pain and *nociceptive* pain in DRN dopamine neurons. In accordance with this notion, an emerging hypothesis posits that *social* and *physical* pain are processed by overlapping neural circuitry[189]. This is supported by human imaging studies revealing that social disconnection engages brain regions including the dorsal anterior cingulate cortex and anterior insula cortex[190], which also process the affective component of physical pain[191]. This dual role of DRN dopamine neurons also points towards a potential mechanism through which acute isolation reduces pain perception[157,158]. Opioidergic signaling might contribute to this effect as a MOR agonist has been shown to disinhibit DRN dopamine neurons[117]. It is also interesting to note that inflammatory pain is suppressed by activation of AgRP neurons, suggesting a general reduction of chronic pain perception by strong motivational drive states[192]. Mixed selectivity may, therefore, be a common feature within neural circuits regulating homeostatic needs, and cross-talk between these systems might facilitate the activation or suppression of appropriate “effector” systems (Fig. 1).

Subjective nature of social experience—A third element in conceptualizing a social homeostatic system is the integration of subjective experience. There is mounting support for the notion that subjective or “perceived” isolation (the quality of social relationships) is a stronger predictor of poor health and emotional state in humans than objective isolation (the number/frequency of social contacts)[11,62,146]. Consistent with this, loneliness—independent of social network size—is associated with higher mortality[13,193] increased blood pressure[11,194], higher rate of diabetes, hypertension, arthritis, emphysema[195], and Alzheimer’s disease[196], along with poor health habits stemming from a lack of self-control[197,198]. Thus, in evaluating social needs, a homeostatic system would need to incorporate a *subjective* assessment of social experience, in addition to its overall *objective* nature), which may be heavily influenced by interoceptive signals and internal state (Figs. 1 and 3).

There is an ongoing debate as to whether animals experience emotions in the same way as humans[150,199]. However, it has been reasoned that emotions constitute an internal state, encoded by specific neural circuits, which can give rise to externally observable behaviors[150]. These internal brain states may be subjectively perceived as feelings by the individual[150]. Although the traditional concept of homeostasis refers to a purely automatic

physiological control system, motivational drive states (guided by “homeostatic feelings”) play a significant role in the maintenance of homeostasis[200]. Homeostatic feelings act as “informative regulatory interfaces”—providing means for an animal to sense its physiological state and guaranteeing attention to relevant stimuli[200]. While this process can be adaptive and introduces greater flexibility into homeostatic regulation, it also passes an element of control to the individual, taking homeostatic regulation beyond purely automatic mechanisms[200].

In order to understand the neural mechanisms of social homeostasis, a major hurdle lies in the ability to infer subjective social experience in animals[14]. Although we can never truly know the emotional experience of a rodent, one method of differentiating between individuals is by exploiting the natural variability introduced into groups of animals by social hierarchy. Grouped living can lead to the establishment of social hierarchies in multiple species including fish, birds, rodents, and primates[201–204]. Hierarchies create a scenario in which grouped individuals might have divergent perceptions of their social experience. Social rank can influence access to essential resources including food, territory, and mates[205], and thus a more dominant rank is often a coveted position associated with higher quality of life. Although subordination in animal societies is not always directly related to low social connectedness or unmet social needs, social rank bestows variability in subjective social experience without removing support structure for safety, warmth and other nonsocial benefits of a group.

Strikingly, studies on social hierarchy in mice and rats have revealed underlying neural correlates in the same circuits implicated in the response to social deficit (Fig. 2). These findings include differences between subordinates and dominants in CRF expression in the BNST, CeA, MeA, and mPOA[206], mitochondrial function and dopamine signaling in the NAc[207,208], and glutamatergic synaptic strength in the mPFC[209]. The mPFC, in particular, is frequently implicated in the representation of social rank. Most recently, “winning”-induced plasticity in the tube test was localized to a mediodorsal thalamic (MDT) projection to the dorsomedial PFC (dmPFC), as phasic optogenetic stimulation of the dmPFC, or the MDT–dmPFC projection, immediately induced winning against a previously dominant cagemate[210]. Notably, social rank also predicted the magnitude of behavioral effects elicited upon DRN dopamine manipulations in mice[118]. Optogenetic activation of these neurons promoted social preference and real-time place avoidance, whereas inhibition reduced isolation-induced social preference. However, the behavioral change observed in these assays was greater in dominant animals relative to subordinates[118]. This observation suggests that prior social experience may influence the ability of the DRN dopamine neurons to modulate behavior. Collectively, these findings illustrate that rank-related information may be integrated into multiple neural circuits that respond to social deficit (Fig. 1A). This organization would permit flexible control over homeostatic regulation and adjustment of goal-directed behavior depending on the social opportunities available.

Moving forward, several questions remain in elucidating how social information might be processed through a homeostatic system. For example, is the individual’s “expectation” for social contact encoded upstream in detector regions, or at the level of the control center? And how are different categories of social contact represented? To speculate on this last

point, one possibility is that a social homeostatic system is category blind. Another potential arrangement would involve separate processing streams for the regulation of different social relationships, such as same-sex affiliative, opposite sex, mother–offspring, unfamiliar conspecifics, and others. Indeed, specialized circuits, within discrete hypothalamic nuclei, underlie the expression of parental behavior[211], aggression[212], male intruder-specific behavior[213], opposite sex approach,[214] and mating[212]. If we conceptualize these as discrete "effector systems," then this raises the possibility that decentralized processing of different social "needs" may occur in separable nodes[215]. However, the precise organization of social homeostatic elements remains a topic of conjecture.

Valence of motivational drive—A fourth consideration is the valence of motivational drives that direct social interaction[216]. Motivated behaviors regulating food intake are often distinguished as homeostatic (essential for maintaining energy balance and survival) or hedonic (driven by sensory perception or pleasure in the absence of a need state)[217]. Feeding behavior, therefore, is directed by motivational drives of opposing valence: the negative sensation of hunger and the positive hedonic value of palatable food. In extrapolating to social behavior, equivalent opposing motivational drives may promote social interaction: the aversive state of isolation and the hedonic value of social reward. However, while mechanistic differences exist, the neural systems mediating homeostatic and hedonic *feeding* are proposed to be intertwined, and highly overlapping with reward circuitry[217,218]. Similarly, social reward circuitry is heavily recruited in isolated animals. Engagement of reward circuitry in situations of social deficit may enhance the rewarding value of social contact—potentially similar to how food deprivation enhances the rewarding properties of food[219–222]. In support of this concept, functional magnetic resonance imaging in humans has revealed that more lonely individuals show greater activation of the ventral striatum in response to familiar social cues[223], but contrastingly reduced activation in response to unfamiliar social cues[224]. Similarly, ventral striatal activity is initially high in response to palatable food but diminishes as individuals consume beyond satiety[225].

The coordination of social behavior to meet *homeostatic* needs may, therefore, recruit both positive and negative motivational processes. The DRN dopamine system might be one source of negative motivational drive in response to social deficit[118]. Recruitment of this system aligns with the "drive reduction" hypothesis, in which internal state elicits goal-directed behaviors in order to reduce the intensity of an aversive/negative motivational drive (e.g., hunger and thirst)[226] (Fig.1c). A potentially similar function has been described for arcuate nucleus AgRP neurons and nitric oxide synthase 1 (NOS1) neurons in the subfornical organ (SFO). These neurons show heightened activity during hunger (AgRP) and thirst (NOS1), their activity elicits an aversive state (place avoidance), and they are essential for driving feeding and drinking behaviors, respectively[21,227].

However, the role of valence processing in homeostatic feeding behavior is complex. AgRP neurons are activated in a state of energy deficit[228], and their optical stimulation can voraciously promote food consumption, but also elicits real-time place avoidance (indicative of an aversive state) in the absence of food[173,227,229]. However, AgRP activity is rapidly suppressed on sensory detection of food[227,228,230], which, surprisingly, suggests that ongoing AgRP activity is dispensable for food consumption. This paradox is potentially

reconciled by the observation that brief optical stimulation, as little as 1 min, prior to food availability was sufficient to promote robust, sustained feeding in well-fed mice once food was made available[231]. Furthermore, mice performed operant responses to stimulate AgRP neurons in the presence, but not the absence of food, suggesting that AgRP activity can be positively reinforcing[231]. Therefore, an alternative hypothesis proposes that AgRP activity provides a sustained *positive* valence signal, that potentiates the incentive value of food, and supports transition from foraging to feeding behavior via persistent changes in downstream circuitry[231]. Intriguingly, this is not a feature of SFO NOS1 neurons, as prestimulation was insufficient to drive drinking behavior when water was subsequently made available[231]. Therefore, the relationship between neuronal activity and behavioral regulation may depend on a specific homeostatic need.

While the precise role of DRN dopamine activity in social motivation and valence processing remains to be fully elucidated, drawing insight from other neural circuits that participate in maintaining homeostatic balance provides mechanistic clues into their mode of operation. However, an important consideration for social behavior is that (unlike food detection) initial social contact does not necessarily guarantee a rewarding social experience. Therefore immediate suppression of neural activity on social contact may be inappropriate for DRN dopamine neurons, and activity may persist until a stable relationship has been achieved. Moving forward, it will be important to determine the temporal dynamics of activity within and across neural circuits during the response to social deficit and to understand how valence is represented in these systems.

Outlook

Moving forward, we propose that improving the evaluation of subjective social experience, and standardizing parameters used in studies of social behavior (Table 1), will accelerate the assembly of a cohesive model for social homeostasis. Studies in rodents are continuing to move towards approaches that capture larger, more naturalistic group living[206], and the incorporation of automated tracking is permitting a deeper longitudinal analysis of complex social interaction dynamics[233]. Great promise has arisen from detailed behavioral observations on semifree-ranging groups of nonhuman primates, facilitating classification of social relationship quality in females chacma baboons[30] and putative loneliness in male rhesus macaques[180]. Across the animal kingdom, we may see conservation in neuromodulatory systems for social behavior all the way to invertebrate systems, as recent groundbreaking work in the octopus demonstrates[232].

Current technological approaches in rodents now provide unprecedented temporal and spatial resolution with which to scrutinize neural circuits and have already yielded fascinating results identifying discrete systems mediating specific social behaviors including parental behavior[211], social reward[103,138,139], male intruder-specific behavior[213], opposite-sex approach[214], and social observational learning[234]. The new millennium has brought with it a rapid rise in opportunities for social nourishment together with a growing prevalence of loneliness and social isolation. Given the protective effects of social contact on a vast array of physical and mental health measures, there has never been a more important time to understand the neural mechanisms underlying the need for social connection.

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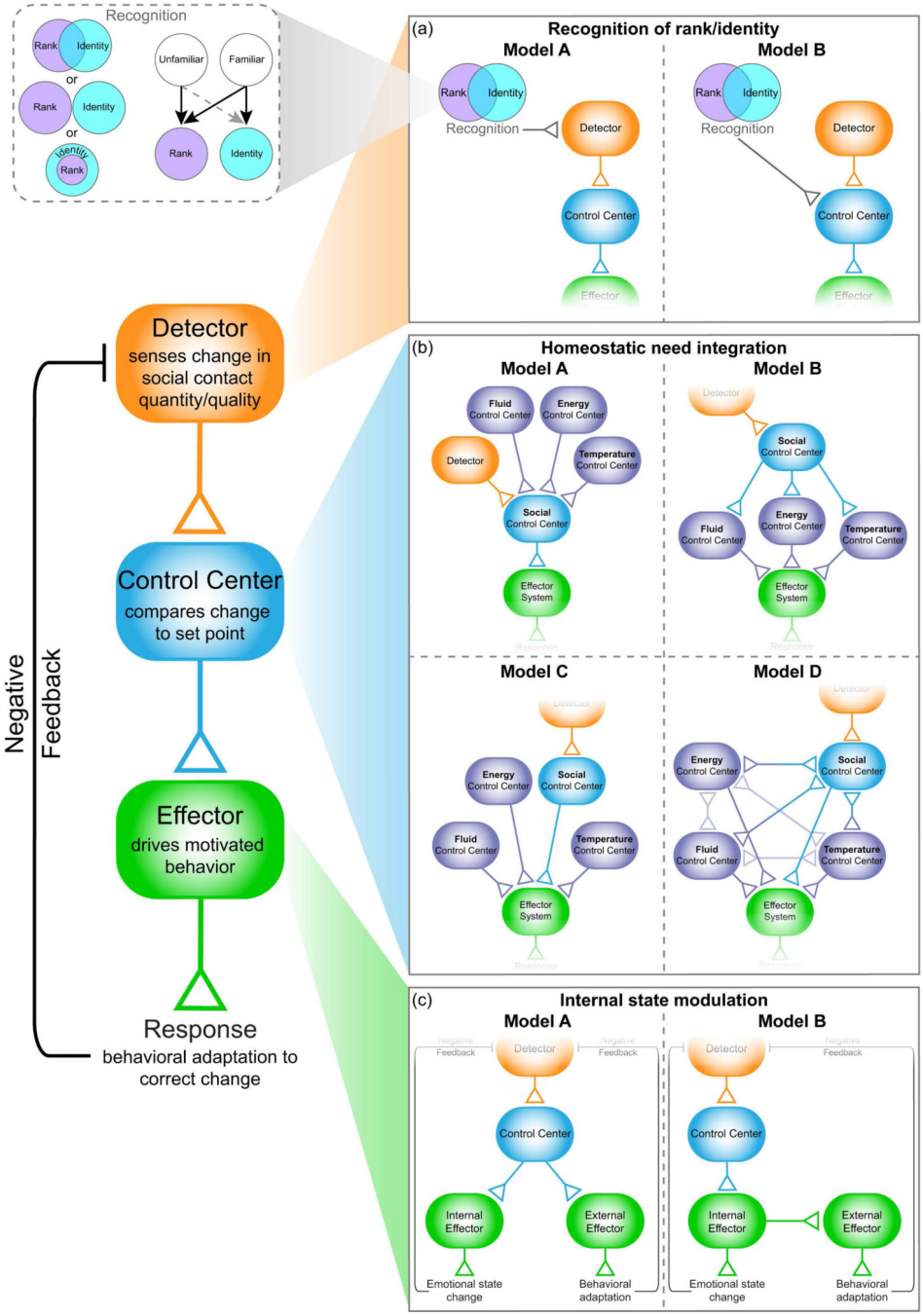

Figure 1.

Proposed model for social homeostasis. Based on Cannon's classic model for homeostatic regulation[18] we propose that a social homeostatic system consists of a *detector* to sense a change in overall quantity/quality of social contact, a *control center* to compare this deviation to the individual's *set-point*, and *effector* systems to correct the change. **(a)** Detection of social signals (both their quantity and quality) would require social recognition. in order to facilitate recall of previous social encounters and determine the expectation for interaction. Information relevant to the *identity* of the social agent (recognizing that

individual as such) as well as estimation of their relative social rank would be required for appropriate evaluation of a deviation. Integration of this information may occur at the level of the detector (*model A*) or the control center (*model B*) stage of processing. Identity and rank information may be represented in an overlapping or nonoverlapping fashion (callout box). For a familiar animal both these variables may be incorporated to set social expectation, but for an unfamiliar animal only rank perception would be available. **(b)** Deviations from the set-point would be evaluated within the control center by comparing the current social input to the homeostatic set-point for quantity and/or quality of social contact. The social control center may integrate information pertinent to other homeostatic needs (e.g., energy balance, fluid balance, and thermoregulation) in a "hub and spoke" fashion (*model A*), or the social control center may be subservient to other homeostatic control systems (*model B*). Alternatively, integration of homeostatic needs may occur in a convergent arrangement onto shared effector systems (*model C*), with interconnections between control centers (*model D*). **(c)** If a deviation from set-point is determined, effector systems may be engaged to correct the change. This process could include activation of "external" effectors to promote behavioral adaptation (e.g., social approach/avoidance) along with "internal" effectors to adjust internal/emotional state (*model A*). Alternatively, engagement of internal effector systems, and a change in emotional state, may itself promote behavioral adaptation (*model B*).

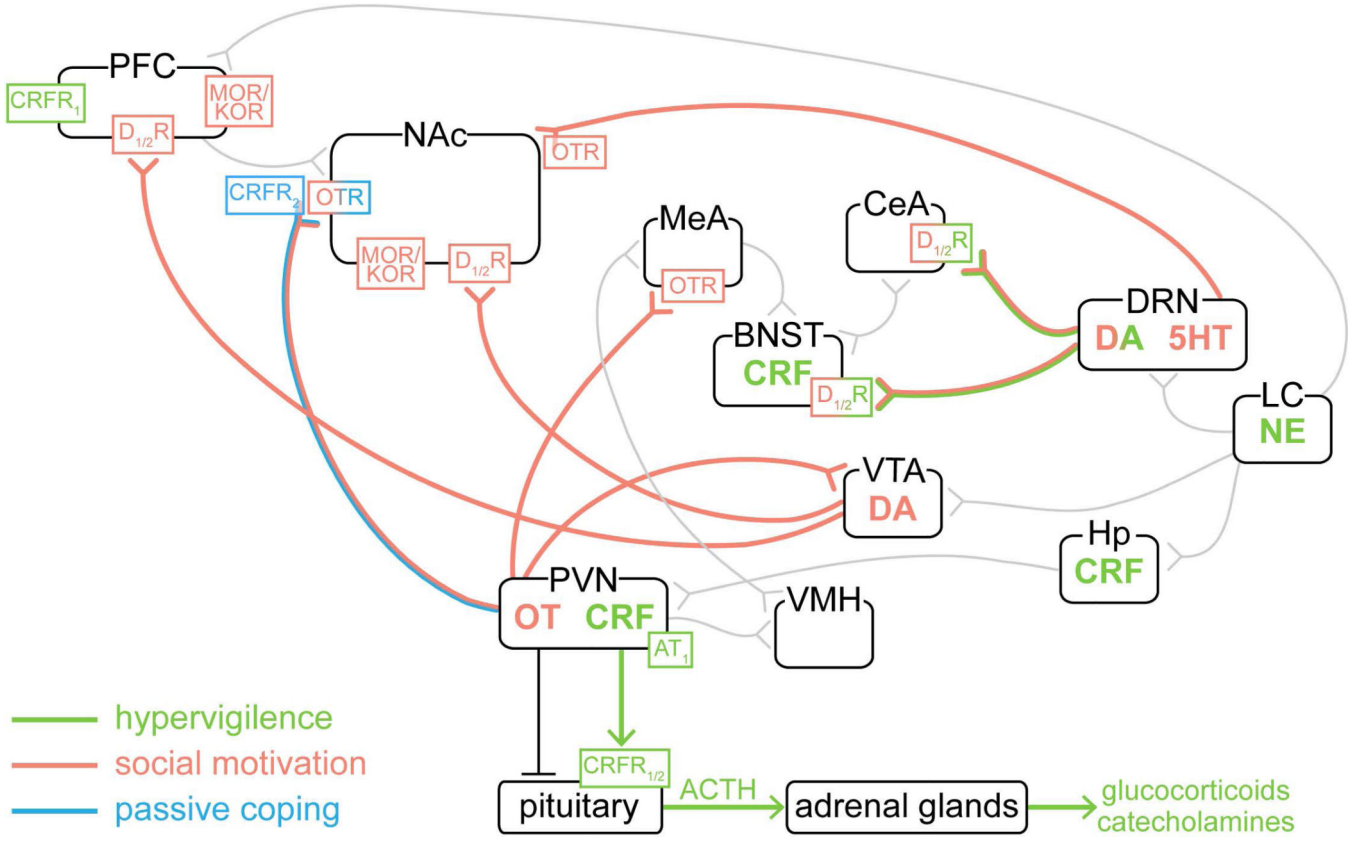

Figure 2.

Neural circuit components implicated in the response to social deficit. Pathways, neuromodulators, neuropeptides, and receptors showing modifications following acute social isolation in rodents. Circuit components are colored based on their involvement in hypervigilance, social motivation, and passive coping. Other prominent projections/connections are shown in grey. Coordinated activity across these parallel, overlapping circuits may function to maintain social homeostasis by heightening attention to environmental stimuli, motivating social reconnection, and limiting emotional distress. 5-HT, 5-hydroxytryptamine (serotonin); ACTH, adrenocorticotropic hormone; AT_1, angiotensin II receptor 1; BNST, bed nucleus of the stria terminalis; CeA, central amygdala; CRF, corticotropin-releasing factor; $CRFR_{1/2}$, corticotropin-releasing factor receptor; DA, dopamine; $D_{1/2}$, dopamine $D_{1/2}$ receptor; DRN, dorsal raphe nucleus; Hp, hippocampus; KOR, κ-opioid receptor; LC, locus coeruleus; MeA, medial amygdala; MOR, μ-opioid receptor; NAc, nucleus accumbens; NE, norepinephrine; OT, oxytocin; PFC, prefrontal cortex; PVN, paraventricular hypothalamic nucleus; VMH, ventromedial hypothalamus; VTA, ventral tegmental area.

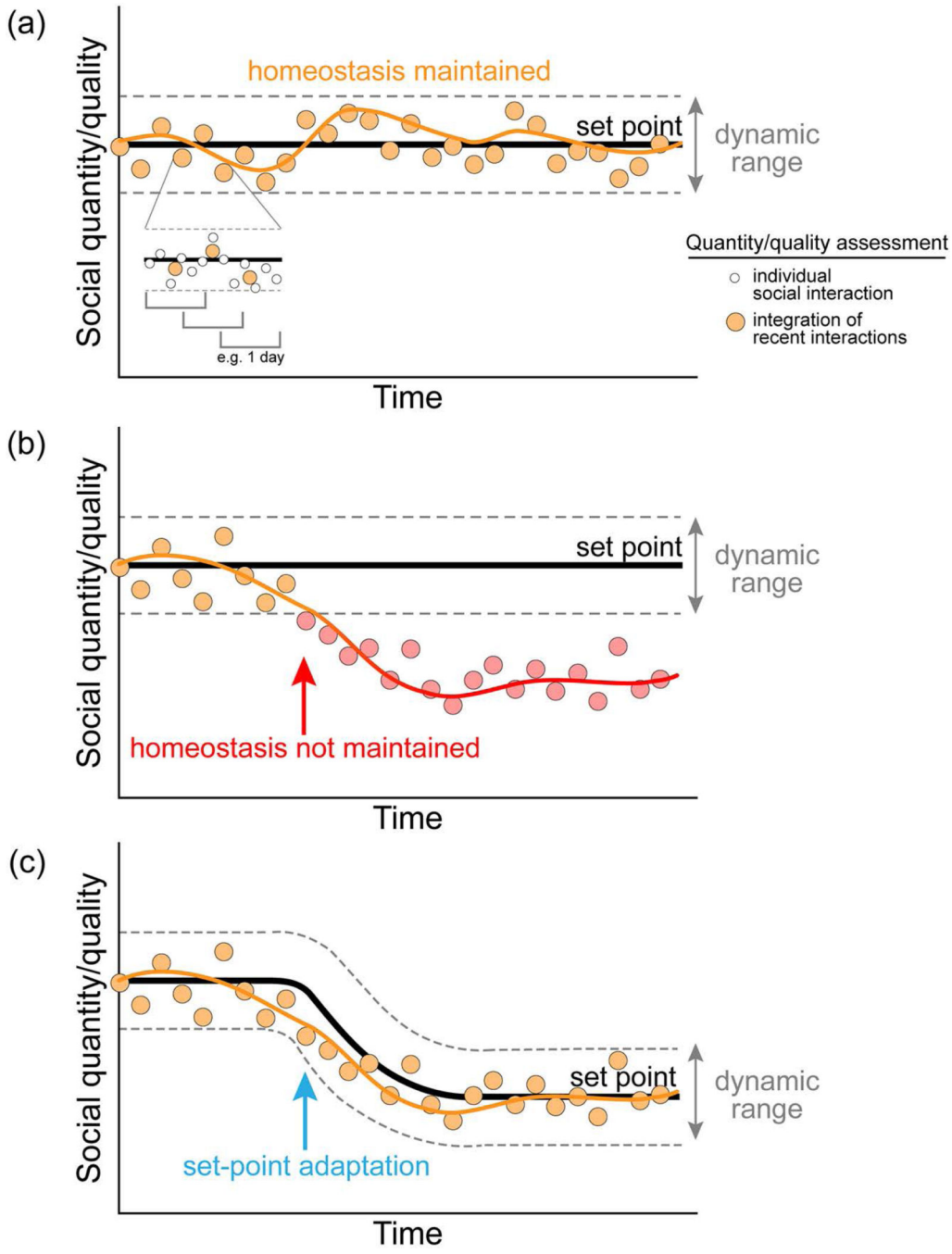

Figure 3.

Long-term integration of social experience within a homeostatic system. **(a)** Under normal conditions, appropriate functioning of a social homeostatic system would maintain social contact quantity/quantity within an acceptable dynamic range. Experienced social interactions may be assimilated and assessed (compared with set-point) in a sliding window fashion across time (e.g., days/months). Social quality and quantity information might be weighted differently depending on the individual (traits) and current environmental conditions. The set-point could be determined by a combination of factors including age,

sex, species-typical behavior, and past history of social encounters. **(b)** Failure of homeostatic system to correct deviations in social contact quantity/quality might result in a chronic deficit. This deficit (whether perceived or actual) may be associated with chronic engagement of homeostatic effector systems, and experienced as a state of loneliness. **(c)** Major life or environmental changes, such as moving away from home, switching jobs, and others, might provoke the need for a shift in set-point. A stable shift in set-point, and acceptance of a new expected quantity/quality for social contact, could represent an adaptive change. This shift may prevent social homeostatic effector systems from being chronically recruited and promote continued balance.

Table 1.

Experimental conditions to report in the methodology of studies on social behavior and/or social isolation to facilitate informative interpretation and reproducibility.

Experimental conditions	
Housing conditions	
Grouped/control animals	**Isolated animals**
Number of cagemates	Prior number of cagemates
Cagemate relationship (siblings/age-matched, etc.)	Cagemate relationship (siblings/age-matched, etc.)
Sexual experience	Sexual experience
	Age at isolation
	Duration of isolation
Extent of experimenter handling	Extent of experimenter handling
Housing type (size, bedding material, etc.)	Housing type (size, bedding material, etc.)
Social rank (if known)	Social rank (if known)
Environmental enrichment	Environmental enrichment
	Proximity of other animals
Normal or reverse light/dark cycle	Normal or reverse light/dark cycle
Measurement of behavioral/neurophysiological parameters	
Time of testing	
Age at testing	
Conditions of behavioral assays	
Stress exposure	
Food/water restriction	
Timeline of conducted experiments	