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The neuroscience of unmet social needs

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ABSTRACT

John Cacioppo has compared loneliness to hunger or thirst in that it signals that one needs to act and repair what is lacking. This paper reviews Cacioppo's and others' contributions to our understanding of neural mechanisms underlying social motivation in humans and in other social species. We focus particularly on the dopaminergic reward system and try to integrate evidence from animal models and human research. In rodents, objective social isolation leads to increased social motivation, mediated by the brains' mesolimbic dopamine system. In humans, social rejection can lead to either increased or decreased social motivation, and is associated with activity in the insular cortex; while chronic loneliness is typically associated with decreased social motivation but has been associated with altered dopaminergic responses in the striatum. This mixed pattern of cross-species similarities and differences may arise from the substantially different methods used to study unmet social needs across species, and suggests the need for more direct and deliberate cross-species comparative research in this critically important domain.

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Social interactions as motivated behavior

Social connections are proposed to be a fundamental basic need of humans (Baumeister & Leary, 1995; Cacioppo, Cacioppo, & Boomsma, 2014; Sheldon & Gunz, 2009). According to this view, social interactions in and of themselves are basic needs of individuals, not just means to fulfill nonsocial needs. Indeed, there is some empirical evidence supporting this hypothesis: Social cues – such as, smiling faces of others or engaging in social interactions, engage the brain reward system similarly to monetary rewards or food rewards in humans (Eskenazi, Rueschemeyer, de Lange, Knoblich, & Sebanz, 2015; Hayden, Parikh, Deaner, & Platt, 2007; Pfeiffer et al., 2014; Rademacher et al., 2010; Spreckelmeyer et al., 2009; Sumiya, Koike, Okazaki, Kitada, & Sadato, 2017) and in non-human social animals (Dölen, Darvishzadeh, Huang, & Malenka, 2013; Gunaydin et al., 2014; Hung et al., 2017; Robinson, Heien, & Wightman, 2002). However, while the empirical research on social reward is quite extensive, investigations on the neural representation of *unmet social needs* are scarcer. Conceptually, a state of need is defined as a condition for which action on the part of the organism is required in order to reach a state of optimal probability of survival (Hull, 1943).

Within the framework of Cacioppo's evolutionary model, feelings of loneliness serve the purpose to signal a deficiency to the organism (i.e., that the current social

bonds are not sufficient to fulfill the need of belonging) and to seek social contact. Thus, in this view loneliness represents a signal that a need is unfulfilled, which produces the drive to seek social contact, just as hunger produces the drive to seek food. This is in contrast to other views on loneliness, which conceptualize it simply as an aversive condition without redeeming features. However, if loneliness indeed represents a drive such as hunger or thirst, it should be represented in the brain in similar ways as other basic drives – the biological implementation of which may be termed “social homeostasis” (Matthews & Tye, 2019).

While the neural circuits underlying hunger and thirst are still growing areas of investigation (Betley, Cao, Ritola, & Sternson, 2013; Livneh et al., 2017; Nieh et al., 2015, 2016; Oka, Ye, & Zuker, 2015; Zimmerman, Leib, & Knight, 2017), even less is known about the neural basis of loneliness. In general, motivation in humans and animals is driven by either the pursuit of rewards, or the avoidance of aversive states (Salamone & Correa, 2012). In the brain, motivation – i.e., the sensation of “wanting” something (Berridge, 2004; Berridge & Robinson, 2003) – has been consistently linked with dopamine (DA) transmission in the so-called “brain reward circuit” (Berridge, 2012; Schott et al., 2008; Wise, 2004). The core brain areas of this reward circuit comprise the dopaminergic midbrain (most midbrain DA neurons residing in

substantia nigra (SN) pars compacta and ventral tegmental area (VTA), but DA neurons are also located in dorsal raphe nuclei and periaqueductal gray (Duzel et al., 2009, 2015) and the striatum (Berridge, 2012; Berridge & Robinson, 2003; Bromberg-Martin, Matsumoto, & Hikosaka, 2010; Kimura, Yamada, & Matsumoto, 2003; Matsumoto & Hikosaka, 2009; Matsumoto & Takada, 2013; Yamada, Matsumoto, & Kimura, 2004). This neural activity in midbrain and striatum has been shown to be associated with the sensation of “wanting” or “craving” in humans (Berridge & Robinson, 2003; Everitt et al., 2008; Kelley & Berridge, 2002) and fMRI studies on addiction and food craving consistently report activation in these regions in response to the target of craving (Malik, McGlone, Bedrossian, & Dagher, 2008; Pursey et al., 2014; Zhang et al., 2016). However, the neural underpinnings of the desire to engage in social interactions (i.e., “social craving”) are far less clear. It is not clear whether social drives and needs are coded in the same neural structures as nonsocial drives and needs, suggesting that they indeed act via similar mechanisms as other fundamental human drives, or whether they rely on separate neural structures (Matthews & Tye, 2019). Previous research studying unmet social needs has focused on the effects of social isolation in animal models and studied neural correlates of loneliness and social exclusion in humans. The following sections summarize the results from these lines of research.

Evidence from animal models of social deprivation

While it is not possible to assess whether or not an animal subjectively feels lonely, animal models using objective isolation (i.e., assigning social animals to isolated living conditions) can give insight into the causal effects of social deprivation on brain and behavior. The evidence from social isolation research in animal models supports two main conclusions: i) social interactions act as primary rewards (Angermeir, 1960; Evans et al., 1994; Hiura, Tan, & Hackenberg, 2018; Martin et al., 2018), meaning that they are inherently pleasurable and motivate behavior in the absence of any other reward and ii) social isolation leads to broad and severe changes in the behavior and brains of animals, even more so if isolation occurs during development (Chen & Baram, 2016; Novick et al., 2018; for reviews). These findings are intriguing and have been used as evidence to support claims that social interactions are basic needs of social animals, including humans, with devastating effects on behavior, brain and health if unmet.

There appears to be a strong correspondence in key elements of social behavior between humans and non-

human social animals. Just as in humans, cooperation and positive social interactions are important for individuals to survive and prosper in many different species (Sussman & Cloninger, 2011). For example, rodents are innately social creatures and fare better in social rather than isolated housing (Van Loo, de Groot, Van Zutphen, & Baumans, 2001; Wills, Wesley, Moore, & Sisemore, 1983). Rats choose to huddle together rather than separate off into isolated individuals or pairs (Wills et al., 1983). Rodents engage in prosocial helping behavior toward cage mates in distress (Bartal, Decety, & Mason, 2011; Bartal, Rodgers, Sarria, Decety, & Mason, 2014; Ben-Ami Bartal & Mason, 2018; Sato, Tan, Tate, & Okada, 2015) which may even reflect empathic motivation (but see Silberberg et al., 2014). Rodents also engage in cooperative behavior (Dolivo, Taborsky, & Herberstein, 2015; Gromov, 2014; Schweinfurth & Taborsky, 2016; Wood, Kim, & Li, 2016). Thus, rodents appear to be a good animal model for studying the effects of social deprivation on brain and behavior. Many studies have investigated the effects of social isolation on the developing brain in rodents, using either pre-weaning isolation (conceptualized as an animal model of early life neglect) or post-weaning isolation (conceptualized as an animal model of adolescent adversity) (Novick et al., 2018). By contrast, here we focus on the effects of social isolation in adult animals that were group reared and thus developed in an adequate social environment, because these effects most likely resemble the effects of loneliness and social exclusion in humans (as opposed to childhood neglect or adolescent adversity). In addition, we focus our review on studies investigating the effects of social isolation on behavioral and neural measures of motivated behavior (as opposed to health-related outcome measures, which are summarized elsewhere (Cacioppo, Capitanio, & Cacioppo, 2014)).

In rodents, even a brief period of isolation increases motivation to seek out and engage with conspecifics (Niesink & Van Ree, 1982; Panksepp & Beatty, 1980) and long-term chronic isolation results in depressive and anxious behaviors (Filipovic, Todorovic, Bernardi, & Gass, 2017) and can also lead to increased aggressiveness in males (Karpova, Mikheev, Marysheva, Bychkov, & Proshin, 2016; Matsumoto, Pinna, Puia, Guidotti, & Costa, 2005; Mumtaz, Khan, Zubair, & Dehpour, 2018; Popova & Petkov, 1990). Animals deprived of social contact will work for contact with conspecifics without any additional rewards and without previous conditioning of the social stimulus (Angermeir, 1960; Evans et al., 1994; Hiura et al., 2018; Martin et al., 2018). For example, in an early experiment isolated rats were trained to press a bar in order to receive partial or full contact with another rat (Angermeir, 1960). The animals' press responses

increased with when the bar delivered more contact. Importantly, the physical contact itself was the reinforcer without any additional reward. Other social species respond in similar ways when deprived of social contact. For example, isolated European starlings will work to see a picture of a conspecific even in the absence of any other reward (Perret et al., 2015).

Social isolation experiments have also been conducted in nonhuman primates, for example in the seminal studies by John Harlow and Steve Suomi (Harlow, Dodsworth, & Harlow, 1965; Harlow & Suomi, 1971). However, these studies focus on the effects of isolation during development, sometimes isolating animals from birth on (with devastating effects on the animal; although see Harlow & Suomi, 1971 for evidence on social recovery following isolation rearing). As in the rodent model, these effects most likely resemble the severe effects of childhood neglect in humans. Studies implementing short-term isolation of adult non-human primates are scarce and the ones that exist focus on isolation-induced cognitive impairment rather than motivated behavior (Washburn & Rumbaugh, 1991).

Naturally occurring social deprivation has also been studied in non-human primates (Brent, Ruiz-Lambides, & Platt, 2017; Capitanio, Cacioppo, & Cole, 2019; Capitanio, Hawley, Cole, & Cacioppo, 2014; Cole et al., 2015). Here, researchers tried to make direct connections between research in human and nonhuman primates. They described a naturally occurring model of loneliness in adult male rhesus monkeys, defined by animals displaying seeking social connections (high frequencies of social initiations) but failing to achieve them (low frequencies of complex interaction; Capitanio et al., 2019, 2014). This research has shown that loneliness in monkeys is associated with up-regulated inflammatory gene expression and down-regulated antiviral response which corresponds to findings in lonely humans (Cole et al., 2015). Individual animals that showed these behavioral markers of loneliness also showed increased social approach, consistent with the observation of increased social preference following isolation in rodents (Capitanio et al., 2014). Because loneliness is operationalized as increased frequency of social initiations (in combination with low frequencies of complex social interactions), the finding that animals which show high frequency of social initiation also show increased social approach behavior in a behavioral testing situation is somewhat circular. However, the authors differentiate between social approach toward safe social targets (juveniles and females) vs risky social targets (adult males) and find that lonely animals are most likely to approach safe targets. This is a very interesting finding, however, it also opens the possibility that there might be an underlying social deficiency in these animals which might better

explain their behavior rather than loneliness (for example social anxiety).

Animal research on social isolation has also given valuable insights on the neural mechanisms underlying social motivation. On a neural level, there is biological evidence that social motivation can be driven by both positive and negative valence, as distinct dopaminergic subsystems drive the aversive motivation to avoid social isolation and the motivation to seek social reward: After 24 hours of acute social isolation, midbrain DA neurons of the dorsal raphe nucleus (DRN) in adult mice are sufficient to drive reengagement in social interaction (Matthews et al., 2016). Optogenetic activation of DRN DA neurons increased sociability and deactivation reduced sociability after isolation, especially in socially dominant mice (Matthews et al., 2016). Importantly, this neural mechanism of “social craving” differs from the neural mechanisms involved in social reward processing. In social reward processing, stimulation of opioid receptors in the nucleus accumbens (NAc) represents the neural substrate of social reward experience (Trezza, Baarendse, & Vanderschuren, 2010; Trezza, Damsteegt, Achterberg, & Vanderschuren, 2011) requiring also coordinated activity of NAc oxytocin and serotonin (Dölen et al., 2013).

In parallel, DA neurons in the VTA seem to play a causal role in social reward: optogenetic activation in these neurons increases social interaction (Gunaydin et al., 2014) and supports positive reinforcement (Tsai et al., 2009; Witten et al., 2011). It is noteworthy that DA neurons in the VTA project most densely to the NAc, whereas DA neurons in the DRN have distinct projections to the extended amygdala, including regions such as the bed nucleus of the stria terminalis (BNST) and central amygdala (CeA) (Matthews et al., 2016; Tye et al., 2011), which are regions commonly linked to anxiety and fear (Davis, 1992; Fadok, Markovic, Tovote, & Lüthi, 2018; Kim et al., 2013; Tye et al., 2011).

Thus, analogous to feeding behavior where distinct neural circuits are underlying the rewarding value of food (Nieh et al., 2015) and the need to obtain food to alleviate the negative state of hunger (Chen, Lin, Kuo, & Knight, 2015; Sternson, Nicholas Betley, & Cao, 2013), social behavior seems to be driven by distinct neural circuits when processing social reward and when driven to alleviate the negative state of social isolation. In sum, animal models provide evidence that social interactions represent a primary reward and basic need of social animals, and that distinct neural mechanisms are implicated in motivation to fulfill an unmet need versus the reward when the need is met.

However, animal research has also shown that social isolation does not only lead to increased social affiliation

motivation but also impacts other motivated behaviors, such as drug and food seeking. For example, social isolation increases voluntary ethanol intake (Hall, 1998; Lallai, Manca, & Dazzi, 2016; Wolffgramm & Heyne, 1991) as well as morphine consumption (Alexander, Coombs, & Hadaway, 1978; Raz & Berger, 2010). Intriguingly, as little as 60-min of daily social-physical interaction with another rat was sufficient to completely abolish the increase in morphine consumption in socially deprived animals (Raz & Berger, 2010). Furthermore, social isolation leads to increased food intake as well as increased visceral adipose tissue mass in mice and rats (Schipper, Harvey, van der Beek, & van Dijk, 2018). Thus, while increasing the drive to socialize with others, social deprivation seems to also increase drives for other rewards such as food and drugs. Conversely, operant access to social interaction was shown to prevent drug self-administration of rats (Venniro et al., 2018).

In line with the behavioral results, studies investigating neural effects of isolation also show broader effects of social isolation on the brains' motivation centres: post-weaning (i.e., "adolescent") social isolation has profound effects on DA systems (Hall, 1998; Novick et al., 2018), ^{for reviews}. The literature on the effects of adult social isolation on DA systems is less extensive, yet, several studies also found that adult social isolation leads to broad effects on DA systems. Isolation leads to increased extracellular concentration of DA in the PFC (Garrido et al., 2013) and enhanced DA synthesis and turnover as revealed by higher dihydroxyphenylacetic acid (DOPAC) levels in the frontal cortex in response to acute stress (Blanc et al., 1980). Isolation also increased general DA synthesis without any additional stressor, as indicated by increased DOPAC and homovanillic acid (HVA) metabolites, but without modification of DA levels (Gambardella, Greco, Sticchi, Bellotti, & Renzo, 1994). In addition, midbrain and striatal tyrosine hydroxylase – the rate-limiting step of the DA synthesis (Daubner, Le, & Wang, 2011) – was found to be elevated in isolated rats (Segal, Knapp, Kuczenski, & Mandell, 1973). Ethanol treatment reduced striatal D2 receptor density of group animals while no alteration of D2 receptor density was observed in isolated animals (Rilke, May, Oehler, & wolffgramm, 1995). However, the effects are not consistent, as other studies also found opposite effects of isolation on DA: social isolation was associated with a blunted DA release in response to chronic alcohol intake compared to group housed mice (Lallai et al., 2016). Broad, but also inconsistent, effects of social isolation on the DA system were also found in other species: Isolation housing of ewes increased overall plasma DA levels (Guesdon et al., 2015). In Zebrafish, acute and chronic isolation was shown to decrease

tonic DA levels (Shams, Chatterjee, & Gerlai, 2015; Shams, Seguin, Facciol, Chatterjee, & Gerlai, 2017).

In sum, these results can be seen as evidence that social isolation has far-reaching effects on behavior and the brain. However, several critical questions remain: First, how should we interpret the findings of isolation-induced increases in food and drug seeking? Are these compensatory behaviors to balance out the lack of social contact? Or are these observed behaviors indicators of more unspecific effects of isolation? And how does that correspond to findings of broad and unspecific isolation-induced changes in DA levels? Importantly, the main underlying challenge that we try to address here is how to connect the results of objective social isolation in animal models to humans' experience when social needs are not met.

Direct measures of neural and behavioral responses in humans can help shed light on this question by identifying potential similarities across species. In humans, research on social deprivation has focused on social rejection and loneliness. The following section summarizes evidence from this literature.

Unmet social needs in humans

One line of research has investigated humans' behavioral and neural responses to social rejection. In healthy human adults, social rejection (i.e., being explicitly and deliberately rejected by one or more interaction partner/s) can cause negative emotions (Eisenberger, Lieberman, & Williams, 2003) and can lead to increased efforts to affiliate with others (Dewall, Maner, & Rouby, 2009; Dewall & Richman, 2011; Maner, DeWall, Baumeister, & Schaller, 2007), but can also lead to withdrawal and antisocial behavior (Dewall & Richman, 2011; Gerber & Wheeler, 2009). The experience of social rejection activates brain areas associated with processing of aversive states like physical pain, such as bilateral anterior insula and anterior cingulate cortex (ACC) (Cacioppo et al., 2013; Eisenberger, 2012; for reviews). Furthermore, a positron emission tomography (PET) study found that social rejection increases opioid release in ventral striatum, amygdala, midline thalamus and periaqueductal grey (PAG) suggesting that endogenous opioids have a role in reducing the experience of social pain (Hsu et al., 2013).

Interestingly, dopamine neurons in the DRN/PAG which were found to drive increased social preference and motivation to seek social contact in rodents (Matthews et al., 2016), were also shown to be associated with physical pain processing (Li et al., 2016). Thus, while social rejection in humans appears to be represented in different brain areas than social isolation in animal

models, both might represent a neural correlate of an aversive emotional state.

However, it might be that social rejection is conceptually not the same state as social isolation. Being deliberately rejected by another person is an aversive act that causes strong aversive emotional responses (Eisenberger, 2012). Isolation, on the other hand, does not include any aversive acts by others, but is characterized by a lack of social interactions. Thus, it is likely that social rejection and social isolation affect social behavior via different mechanisms.

A second line of research – initiated and advanced by John Cacioppo (Cacioppo & Cacioppo, 2018) – has studied the outcomes of perceived loneliness. Feelings of loneliness are conceptualized as serving the purpose to signal a deficiency to the organism and to seek social contact (Cacioppo et al., 2014; Qualter et al., 2015). Yet, the results in humans are not straightforwardly analogous to effects of social isolation in rodents. Unlike isolated rodents, loneliness seems to be associated with *lower* social approach motivation: Loneliness is associated with higher self-centeredness (Cacioppo, Chen, & Cacioppo, 2017), preference for larger interpersonal space (Layden, Cacioppo, & Cacioppo, 2018), increased motivation to avoid bad social outcomes and decreased motivation to approach good social outcomes (Gable, 2006). Lonely individuals pay more attention to negative social stimuli than nonlonely individuals (Cacioppo & Hawkey, 2009; for review). In addition, lonely individuals tend to interpret the behavior of others in a more negative light than nonlonely individuals (Cacioppo & Hawkey, 2005). Furthermore, loneliness was shown to be associated with lower prosocial behavior (Carlson, Charlin, & Miller, 1988; Salovey, Mayer, & Rosenhan, 1991; Williamson & Clark, 1989), although public display of decisions reversed this relationship (Huang, Liu, & Liu, 2016). Indeed, the latest version of John Cacioppo's evolutionary model on loneliness states that the motivation to reengage in social contact can be hampered by various types of fears and cognitive biases that lead to self-centeredness and social avoidance (Cacioppo & Cacioppo, 2018).

There is some evidence linking human loneliness to altered function in dopaminergic reward regions. For example, a seminal paper from John Cacioppo (Cacioppo, Norris, Decety, Monteleone, & Nusbaum, 2009) has shown that lonely individuals show decreased activation of the ventral striatum in response to viewing pleasant social pictures compared to non-lonely individuals. In addition, lonely individuals showed increased visual cortex activation to unpleasant social pictures. This was interpreted as evidence that lonely individuals are less rewarded by social stimuli while paying more

attention to distress of others. However, a recent study failed to replicate these results (D'Agostino, Kattan, & Canli, 2019) in a larger sample. Another study found that lonely people show increased activation in the ventral striatum when viewing pictures of close others compared to non-lonely people (Inagaki et al., 2016).

However, an important caveat of research on loneliness is that it mostly employs a correlational approach: studying individuals who are chronically lonely. Thus, it is unclear whether the identified effects are consequences, causes, or risk factors for loneliness. For example, it might be that people who have lower social approach motivation are more likely to become lonely. Unfortunately, experimental approaches to induced acute isolation are practically non-existent in human participants, making direct comparisons between loneliness research in humans and social isolation research in rodents difficult.

Integration and translation - animal and human research

In summary, the majority of current knowledge on social drives and their neural representation comes from animal models, mostly rodent models. In rodents, social isolation increases social approach motivation mediated by dopaminergic activity, but also increases drug and food seeking behavior and leads to broader changes in the DA system. Evidence from human research on related constructs such as social rejection and chronic loneliness partially aligns with the evidence from animal models: social rejection can lead to increased social approach motivation (but it can also lead to withdrawal and aggression), and chronic loneliness may be associated with increased activity in the dopaminergic reward system in response to viewing pictures of close ones. However, the human results also divert from animal models in important ways. Chronic loneliness is not associated with increased social approach but rather with withdrawal and antisocial behavior. This might correspond to findings of long-term chronic isolation in rodents showing that some animals respond with increased aggressive behavior to this treatment (Karpova et al., 2016; Matsumoto et al., 2005; Mumtaz et al., 2018; Popova & Petkov, 1990). Thus, it might be that chronic and acute isolation have diverging effects on social approach behavior. However, no study so far investigated the effects of acute isolation on social approach behavior in humans and it remains unclear if the discrepancies in human and animal literature are based on differences in the duration of deprivation, the method of inducing the deprivation, or genuine interspecies differences.

The neural correlates of social rejection in humans are typically found in the ACC, but not in midbrain pain or reward related areas. However, the finding that animal social craving is represented in a brain area that has also been associated with pain processing suggests that there might be a convergence of the findings. Yet, it is difficult to directly integrate the evidence from these lines of research. A critical conceptual challenge is that the states studied in humans (i.e., chronic loneliness and rejection) are not the same as the states studied in animals (social isolation). Empirically, it is hard to test whether social isolation is a similar experience for rodents versus humans. In animals, especially in a laboratory environment, much of the sensory input comes from conspecifics. As a result, social isolation in animals is highly confounded with sensory deprivation (Hall, 1998; Krohn, Sørensen, Ottesen, & Hansen, 2006). On the other hand, sensory stimulation and meaningful social interaction can be largely independent in human adults, especially in the modern environment. Thus, being objectively alone does not necessarily induce feelings of loneliness in humans, and being objectively in a crowd does not necessarily induce feeling of connection. Indeed, John Cacioppo has consistently emphasized that while objective social isolation *can* lead to feelings of loneliness, it is the *perceived* isolation rather than objective isolation that is critical to well-being in humans. Even more, research has shown that spending a (limited) time in solitude is in fact something that most humans pursue without being negatively impacted – on the contrary, it seems to be important for one's well-being (Hagemeyer, Neyer, Neberich, & Asendorpf, 2013).

A second challenge for direct translation of rodent research is that the anatomy of the reward circuit is somewhat different across species. While the general mode of action of the reward circuit has been shown to strongly correspond between species (Berridge & Kringelbach, 2008), the dopaminergic midbrain also shows important anatomical differences between primates and rodents (Duzel et al., 2009, 2015). For example, the functional-anatomical parcellation of the dopaminergic complex in rodents does not directly correspond to anatomy and function in primates. Comparisons between species show that it is the dorsal part of the primate substantia nigra (SN) that is most representative of the rat ventral tegmental area (VTA) – the region that has received most of the attention in studies on motivation and reward. Importantly, in humans and non-human primates, ~75% of DA neurons are in the substantia nigra pars compacta (SNc) and only 15% in the VTA (Francois, Yelnik, Tande, Agid, & Hirsch, 1999; Hirsch et al., 1992). Because of these differences, the specific isolation-induced changes in rodent

dopaminergic circuits might not directly map on to mechanisms in the same anatomical regions in humans.

While studies in rodents can give insights into the neural mechanisms of social motivation with relevant implications for the processes in the human brain, there are crucial limitations to the direct translation of findings from rodents to humans. These limitations will affect the development of treatments and drugs for disorders affecting social motivation, such as autism spectrum disorder (ASD) (Chevallier, Kohls, Troiani, Brodtkin, & Schultz, 2012; Kohls, Chevallier, Troiani, & Schultz, 2012), social anxiety disorder (Hofmann, 2007), or depression (Radke, Güths, André, Müller, & de Bruijn, 2014): For example, genetically modified rodent models are frequently used for preclinical drug development to combat the social deficits in ASD (Bales et al., 2014; Chadman, 2011; Foley et al., 2012; Silverman et al., 2015, 2012; Silverman, Tolu, Barkan, & Crawley, 2010) for which social motivation has been postulated to be a core deficit (Chevallier et al., 2012; Kohls et al., 2012). Yet, a prevailing problem in autism research is that while animal models continue to detect potentially promising mechanisms to combat social deficits in ASD, there is a recurrent failure to translate this research to the clinic (Muotri, 2016). This problem, however, is not restricted to ASD research. Similar translational problems have been reported in addiction research: evidence from animal models has had little impact on clinical treatment so far (Heilig, Epstein, Nader, & Shaham, 2016). Even more, this was specifically attributed to the missing consideration of social factors in addiction research (Heilig et al., 2016). Furthermore, a review of highly cited animal research has shown that only about one third of the reported animal preclinical studies were translated at the level of human randomized trials (Hackam & Redelmeier, 2006). Thus, successful bridges between animal and human research could have significant real life benefits.

Future directions

In sum, research on unmet social needs has investigated states of objective social isolation in rodents and rejection and loneliness in humans. Both lines of research suggest that social contact is a primary reward and basic need in social species, that social isolation can have broad nonspecific effects of health and motivated behavior, and that dopaminergic systems are implicated in the motivation to seek social contact following deprivation. However, clear and specific homologies between the neural mechanisms of social motivation across species are lacking.

To address this gap, future research should directly investigate the neural correlates of social motivation following acute short-term isolation of adult primates. One promising approach would be to study social non-human primates like marmosets, an increasingly popular animal model of social cognition. Thus, comparative studies using short-term social isolation in adult nonhuman primates with more complex social organizations might be especially informative. Indeed, John Cacioppo has consistently advocated for more direct and deliberate cross-species comparative research on loneliness (Cacioppo et al., 2015). Another complementary possibility is to study the effects of experimentally induced acute isolation directly in humans, using noninvasive neuroimaging. Hemodynamic responses in midbrain and striatum can be used to make inferences about engagement of the DA system (Duzel et al., 2015; Knutson & Gibbs, 2007). More direct measures of DA transmission in humans are also possible. While research has investigated dopaminergic transmission during processes of reward experience and craving in food and drug motivation using positron emission tomography (PET) (Small, 2001; Volkow et al., 2006), dopaminergic transmission underlying social craving has not been studied so far. Yet, previous research has shown that striatal DA function measured by PET is associated with self-reported trait social attachment (Caravaggio et al., 2017; Farde, Gustavsson, & Jonsson, 1997). Thus, PET might also represent a sensitive measure of state-dependent DA changes underlying social approach motivation. Animal models of social isolation would be powerfully enhanced if a homologous effect of social isolation in the human brain can be identified.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

- Alexander, B. K., Coombs, R. B., & Hadaway, P. F. (1978). The effect of housing and gender on morphine self-administration in rats. *Psychopharmacology*, 58, 175–179.
- Angermeier, W. R. (1960). Some basic aspects of social reinforcement in albino rats. *Journal of Comparative and Physiological Psychology*, 53, 364–367.
- Bales, K. L., Solomon, M., Jacob, S., Crawley, J. N., Silverman, J. L., Larke, R. H., ... Mendoza, S. P. (2014). Long-term exposure to intranasal oxytocin in a mouse autism model. *Translational Psychiatry*, 4, e480.
- Bartal, I. B.-A., Decety, J., & Mason, P. (2011). Empathy and pro-social behavior in rats. *Science*, 334, 1427–1430.
- Bartal, I. B.-A., Rodgers, D. A., Sarria, M. S. B., Decety, J., & Mason, P. (2014). Pro-social behavior in rats is modulated by social experience. *Elife*, 3, e01385.
- Baumeister, R. F., & Leary, M. R. (1995). The need to belong: Desire for interpersonal attachments as a fundamental human motivation. *Psychological Bulletin*, 117, 497–529.
- Ben-Ami Bartal, I., & Mason, P. (2018). Chapter 12: Helping Behavior in Rats. In *Neuronal Correlates of Empathy: From Rodent to Human*, 151–160. San Diego: Academic Press.
- Berridge, K. C. (2004). Motivation concepts in behavioral neuroscience. *Physiology & Behavior*, 81, 179–209.
- Berridge, K. C. (2012). From prediction error to incentive salience: Mesolimbic computation of reward motivation. *European Journal of Neuroscience*, 35, 1124–1143.
- Berridge, K. C., & Kringelbach, M. L. (2008). Affective neuroscience of pleasure: Reward in humans and animals. *Psychopharmacology*, 199, 457–480.
- Berridge, K. C., & Robinson, T. E. (2003). Parsing reward. *Trends in Neurosciences*, 26, 507–513.
- Betley, J. N., Cao, Z. F., Ritola, K. D., & Sternson, S. M. (2013). Parallel, redundant circuit organization for homeostatic control of feeding behavior. *Cell*, 155, 1337–1350.
- Blanc, D., Hervé, G., Simon, D., Lisoprawski, H., Glowinski, A., & Tassin, J. J. & P. (1980). Response to stress of mesocortico-prefrontal DA neurons in rats after long-term isolation. (Vol. 284), 265–267. *Nature*.
- Brent, L. J. N., Ruiz-Lambides, A., & Platt, M. L. (2017). Persistent social isolation reflects identity and social context but not maternal effects or early environment. *Scientific Reports*, 7, 17791.
- Bromberg-Martin, E. S., Matsumoto, M., & Hikosaka, O. (2010). Dopamine in motivational control: Rewarding, aversive, and alerting. *Neuron*, 68, 815–834.
- Cacioppo, J. T., & Cacioppo, S. (2018). Chapter Three - Loneliness in the Modern Age: An Evolutionary Theory of Loneliness (ETL). In *Advances in Experimental Social Psychology*. Vol. 58, 127–197, Academic Press (San Diego).
- Cacioppo, J. T., Cacioppo, S., & Boomsma, D. I. (2014). Evolutionary mechanisms for loneliness. *Cognition and Emotion*, 28, 3–21.
- Cacioppo, J. T., Cacioppo, S., Cole, S. W., Capitanio, J. P., Goossens, L., & Boomsma, D. I. (2015). Loneliness across phylogeny and a call for comparative studies and animal models. *Perspectives on Psychological Science*, 10, 202–212.
- Cacioppo, J. T., Chen, H. Y., & Cacioppo, S. (2017). Reciprocal influences between loneliness and self-centeredness: A cross-lagged panel analysis in a population-based sample of African American, hispanic, and caucasian adults. *Personality and Social Psychology Bulletin*, 43, 1125–1135.
- Cacioppo, J. T., & Hawkley, L. C. (2005). People Thinking About People: The Vicious Cycle of Being a Social Outcast in One's Own Mind. In *The Social Outcast: Ostracism, Social Exclusion, Rejection, and Bullying (Sydney Symposium of Social Psychology)*, 91–108. New York: Psychology Press.
- Cacioppo, J. T., & Hawkley, L. C. (2009). Perceived social isolation and cognition. *Trends in Cognitive Sciences*, 13, 447–454.
- Cacioppo, J. T., Norris, C. J., Decety, J., Monteleone, G., & Nusbaum, H. (2009). In the eye of the beholder: Individual differences in perceived social isolation predict regional brain activation to social stimuli. *Journal of Cognitive Neuroscience*, 21, 83–92.

- Cacioppo, S., Capitanio, J. P., & Cacioppo, J. T. (2014). Toward a neurology of loneliness. *Psychological Bulletin*, *140*, 1464–1504.
- Cacioppo, S., Frum, C., Asp, E., Weiss, R. M., Lewis, J. W., & Cacioppo, J. T. (2013). A quantitative meta-analysis of functional imaging studies of social rejection. *Scientific Reports*, *3*, 2027.
- Capitanio, J. P., Cacioppo, S., & Cole, S. W. (2019). Loneliness in monkeys: Neuroimmune mechanisms. *Current Opinion in Behavioral Sciences*, *28*, 51–57.
- Capitanio, J. P., Hawkey, L. C., Cole, S. W., & Cacioppo, J. T. (2014). A behavioral taxonomy of loneliness in humans and rhesus monkeys (*Macaca mulatta*). *PloS One*, *9*, e110307.
- Caravaggio, F., Chung, J. K., Gerretsen, P., Fervaha, G., Nakajima, S., Plitman, E., ... Graff-Guerrero, A. (2017). Exploring the relationship between social attachment and dopamine D2/3 receptor availability in the brains of healthy humans using [(11)C]-(+)-PHNO. *Social Neuroscience*, *12*, 163–173.
- Carlson, M., Charlin, V., & Miller, N. (1988). Positive mood and helping behavior: A test of six hypotheses. *Journal of Personality and Social Psychology*, *55*, 211–229.
- Chadman, K. K. (2011). Fluoxetine but not risperidone increases sociability in the BTBR mouse model of autism. *Pharmacology Biochemistry and Behavior*, *97*, 586–594.
- Chen, Y., & Baram, T. Z. (2016). Toward understanding how early-life stress reprograms cognitive and emotional brain networks. *Neuropsychopharmacology*, *41*, 197–206.
- Chen, Y., Lin, Y. C., Kuo, T. W., & Knight, Z. A. (2015). Sensory detection of food rapidly modulates arcuate feeding circuits. *Cell*, *160*, 829–841.
- Chevallier, C., Kohls, G., Troiani, V., Brodtkin, E. S., & Schultz, R. T. (2012). The social motivation theory of autism. *Trends in Cognitive Sciences*, *16*, 231–239.
- Cole, S. W., Capitanio, J. P., Chun, K., Arevalo, J. M. G., Ma, J., & Cacioppo, J. T. (2015). Myeloid differentiation architecture of leukocyte transcriptome dynamics in perceived social isolation. *Proceedings of the National Academy of Sciences of the United States of America*, *112*, 15142–15147.
- D'Agostino, A. E., Kattan, D., & Canli, T. (2019). An fMRI study of loneliness in younger and older adults. *Social Neuroscience*, *14*, 136–148.
- Daubner, S. C., Le, T., & Wang, S. (2011). Tyrosine hydroxylase and regulation of dopamine synthesis. *Archives of Biochemistry and Biophysics*, *508*, 1–12.
- Davis, M. (1992). The role of the amygdala in fear and anxiety. *Annual Review of Neuroscience*, *15*, 353–375.
- Dewall, C. N., Maner, J. K., & Rouby, D. A. (2009). Social exclusion and early-stage interpersonal perception: Selective attention to signs of acceptance. *Journal of Personality and Social Psychology*, *96*, 729–741.
- Dewall, C. N., & Richman, S. B. (2011). Social exclusion and the desire to reconnect. *Social and Personality Psychology Compass*, *5*, 919–932.
- Dölen, G., Darvishzadeh, A., Huang, K. W., & Malenka, R. C. (2013). Social reward requires coordinated activity of nucleus accumbens oxytocin and serotonin. *Nature*, *501*, 179.
- Dolivo, V., Taborsky, M., & Herberstein, M. (2015). Cooperation among Norway rats: The importance of visual cues for reciprocal cooperation, and the role of coercion. *Ethology*, *121*, 1071–1080.
- Duzel, E., Bunzeck, N., Guitart-Masip, M., Wittmann, B., Schott, B. H., & Tobler, P. N. (2009). Functional imaging of the human dopaminergic midbrain. *Trends in Neurosciences*, *32*, 321–328.
- Duzel, E., Guitart-Masip, M., Maass, A., Hammerer, D., Betts, M. J., Speck, O., ... Kanowski, M. (2015). Chapter 20 Midbrain fMRI: Applications, Limitations and Challenges. In *MRI: From nuclear spins to brain functions*. New York: Springer.
- Eisenberger, N. I. (2012). The pain of social disconnection: Examining the shared neural underpinnings of physical and social pain. *Nature Reviews Neuroscience*, *13*, 421–434.
- Eisenberger, N. I., Lieberman, M. D., & Williams, K. D. (2003). Does rejection hurt? An fMRI study of social exclusion. *Science*, *302*, 290–292.
- Eskensazi, T., Rueschemeyer, S.-A., de Lange, F. P., Knoblich, G., & Sebanz, N. (2015). Neural correlates of observing joint actions with shared intentions. *Cortex*, *70*, 90–100.
- Evans, M. J., Duvel, A., Funk, M. L., Lehman, B., Sparrow, J., Watson, N. T., & Neuringer, A. (1994). Social reinforcement of operant behavior in rats: A methodological note. *Journal of the Experimental Analysis of Behavior*, *62*, 149–156.
- Everitt, B. J., Belin, D., Economidou, D., Pelloux, Y., Dalley, J. W., & Robbins, T. W. (2008). Review. Neural mechanisms underlying the vulnerability to develop compulsive drug-seeking habits and addiction. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *363*, 3125–3135.
- Fadok, J. P., Markovic, M., Tovote, P., & Lüthi, A. (2018). New perspectives on central amygdala function. *Current Opinion in Neurobiology*, *49*, 141–147.
- Farde, L., Gustavsson, J. P., & Jonsson, E. (1997). D2 dopamine receptors and personality traits. *Nature*, *385*, 590.
- Filipovic, D., Todorovic, N., Bernardi, R. E., & Gass, P. (2017). Oxidative and nitrosative stress pathways in the brain of socially isolated adult male rats demonstrating depressive- and anxiety-like symptoms. *Brain Structure & Function*, *222*, 1–20.
- Foley, A. G., Gannon, S., Rombach-Mullan, N., Prendergast, A., Barry, C., Cassidy, A. W., & Regan, C. M. (2012). Class I histone deacetylase inhibition ameliorates social cognition and cell adhesion molecule plasticity deficits in a rodent model of autism spectrum disorder. *Neuropharmacology*, *63*, 750–760.
- Francois, C., Yelnik, J., Tande, D., Agid, Y., & Hirsch, E. C. (1999). Dopaminergic cell group A8 in the monkey: Anatomical organization and projections to the striatum. *The Journal of Comparative Neurology*, *414*, 334–347.
- Gable, S. L. (2006). Approach and avoidance social motives and goals. *Journal of Personality*, *74*, 175–222.
- Gambardella, P., Greco, A. M., Sticchi, R., Bellotti, R., & Renzo, G. D. (1994). Individual housing modulates daily rhythms of hypothalamic catecholaminergic system and circulating hormones in adult male rats. *Chronobiology International*, *11*, 213–221.
- Garrido, P., De Blas, M., Ronzoni, G., Cordero, I., Anton, M., Gine, E., ... Mora, F. (2013). Differential effects of environmental enrichment and isolation housing on the hormonal and neurochemical responses to stress in the prefrontal cortex of the adult rat: Relationship to working and emotional memories. *Journal of Neural Transmission (Vienna, Austria: 1996)*, *120*, 829–843.
- Gerber, J., & Wheeler, L. (2009). On being rejected: A meta-analysis of experimental research on rejection. *Perspectives on Psychological Science*, *4*, 468–488.
- Gromov, V. S. (2014). Chapter 3 - Complicated Social Structure and the Evolution of Sociality in Rodents: Cooperation as the

- Main Promoting Factor (pp 71–120). In *Social Behavior: Evolutionary Pathways, Environmental Influences and Impairments*, Nova Science Pub Inc; UK ed. edition.
- Guesdon, V., Meurisse, M., Chesneau, D., Picard, S., Levy, F., & Chaillou, E. (2015). Behavioral and endocrine evaluation of the stressfulness of single-pen housing compared to group-housing and social isolation conditions. *Physiology & Behavior*, *147*, 63–70.
- Gunaydin, L. A., Grosenick, L., Finkelstein, J. C., Kauvar, I. V., Fenno, L. E., Adhikari, A., ... Deisseroth, K. (2014). Natural neural projection dynamics underlying social behavior. *Cell*, *157*, 1535–1551.
- Hackam, D. G., & Redelmeier, D. A. (2006). Translation of research evidence from animals to humans. *JAMA*, *296*, 1727–1732.
- Hagemeyer, B., Neyer, F. J., Neberich, W., & Asendorpf, J. B. (2013). The ABC of social desires: Affiliation, being alone, and closeness to partner. *European Journal of Personality*, *27*, 442–457.
- Hall, F. S. (1998). Social deprivation of neonatal, adolescent, and adult rats has distinct neurochemical and behavioral consequences. *Critical Reviews in Neurobiology*, *12*, 129–162.
- Harlow, H. F., Dodsworth, R. O., & Harlow, M. K. (1965). Total social isolation in monkeys. *Proceedings of the National Academy of Sciences*, *54*, 90–97.
- Harlow, H. F., & Suomi, S. J. (1971). Social recovery by isolation-reared monkeys. *Proceedings of the National Academy of Sciences*, *68*, 1534–1538.
- Hayden, B. Y., Parikh, P. C., Deaner, R. O., & Platt, M. L. (2007). Economic principles motivating social attention in humans. *Proceedings of the Royal Society B: Biological Sciences*, *274*, 1751–1756.
- Heilig, M., Epstein, D. H., Nader, M. A., & Shaham, Y. (2016). Time to connect: Bringing social context into addiction neuroscience. *Nature Reviews Neuroscience*, *17*, 592.
- Hirsch, E. C., Mouatt, A., Faucheux, B., Bonnet, A. M., Javoy-Agid, F., Graybiel, A. M., & Agid, Y. (1992). Dopamine, tremor, and Parkinson's disease. *Lancet*, *340*, 125–126.
- Hiura, L. C., Tan, L., & Hackenberg, T. D. (2018). To free, or not to free: Social reinforcement effects in the social release paradigm with rats. *Behavioural Processes*, *152*, 37–46.
- Hofmann, S. G. (2007). Cognitive factors that maintain social anxiety disorder: A comprehensive model and its treatment implications. *Cognitive Behaviour Therapy*, *36*, 193–209.
- Hsu, D. T., Sanford, B. J., Meyers, K. K., Love, T. M., Hazlett, K. E., Wang, H., ... Zubieta, J. K. (2013). Response of the mu-opioid system to social rejection and acceptance. *Molecular Psychiatry*, *18*, 1211–1217.
- Huang, H., Liu, Y., & Liu, X. (2016). Does loneliness necessarily lead to a decrease in prosocial behavior? The roles of gender and situation. *Frontiers in Psychology*, *7*, 1388.
- Hull, C. L. (1943). *Principles of behavior: An introduction to behavior theory*. New York: Appleton-Century.
- Hung, L. W., Neuner, S., Polepalli, J. S., Beier, K. T., Wright, M., Walsh, J. J., ... Malenka, R. C. (2017). Gating of social reward by oxytocin in the ventral tegmental area. *Science*, *357*, 1406–1411.
- Inagaki, T. K., Muscatell, K. A., Moieni, M., Dutcher, J. M., Jevtic, I., Irwin, M. R., & Eisenberger, N. I. (2016). Yearning for connection? Loneliness is associated with increased ventral striatum activity to close others. *Social Cognitive and Affective Neuroscience*, *11*, 1096–1101.
- Karpova, I. V., Mikheev, V. V., Marysheva, V. V., Bychkov, E. R., & Proshin, S. N. (2016). Oxytocin-induced changes in monoamine level in symmetric brain structures of isolated aggressive C57Bl/6 mice. *Bulletin of Experimental Biology and Medicine*, *160*, 605–609.
- Kelley, A. E., & Berridge, K. C. (2002). The neuroscience of natural rewards: Relevance to addictive drugs. *The Journal of Neuroscience*, *22*, 3306–3311.
- Kim, S. Y., Adhikari, A., Lee, S. Y., Marshel, J. H., Kim, C. K., Mallory, C. S., ... Deisseroth, K. (2013). Diverging neural pathways assemble a behavioural state from separable features in anxiety. *Nature*, *496*, 219–223.
- Kimura, M., Yamada, H., & Matsumoto, N. (2003). Tonic active neurons in the striatum encode motivational contexts of action. *Brain and Development*, *25*(Suppl 1), S20–23.
- Knutson, B., & Gibbs, S. E. (2007). Linking nucleus accumbens dopamine and blood oxygenation. *Psychopharmacology*, *191*, 813–822.
- Kohls, G., Chevallier, C., Troiani, V., & Schultz, R. T. (2012). Social 'wanting' dysfunction in autism: Neurobiological underpinnings and treatment implications. *Journal of Neurodevelopmental Disorders*, *4*, 1–20.
- Krohn, T. C., Sørensen, D. B., Ottesen, J. L., & Hansen, A. K. (2006). The effects of individual housing on mice and rats: A review. *Animal Welfare*, *15*, 343–352.
- Lallai, V., Manca, L., & Dazzi, L. (2016). Social isolation blunted the response of mesocortical dopaminergic neurons to chronic ethanol voluntary intake. *Frontiers in Cellular Neuroscience*, *10*, 155.
- Layden, E. A., Cacioppo, J. T., & Cacioppo, S. (2018). Loneliness predicts a preference for larger interpersonal distance within intimate space. *Plos One*, *13*, e0203491.
- Li, C., Sugam, J. A., Lowery-Gionta, E. G., McElligott, Z. A., McCall, N. M., Lopez, A. J., ... Kash, T. L. (2016). Mu opioid modulation of dopamine neurons in the periaqueductal gray/dorsal raphe: A role in regulation of pain. *Neuropsychopharmacology*, *41*, 2122.
- Livneh, Y., Ramesh, R. N., Burgess, C. R., Levandowski, K. M., Madara, J. C., Fenselau, H., ... Andermann, M. L. (2017). Homeostatic circuits selectively gate food cue responses in insular cortex. *Nature*, *546*, 611–616.
- Malik, S., McGlone, F., Bedrossian, D., & Dagher, A. (2008). Ghrelin modulates brain activity in areas that control appetitive behavior. *Cell Metabolism*, *7*, 400–409.
- Maner, J. K., DeWall, C. N., Baumeister, R. F., & Schaller, M. (2007). Does social exclusion motivate interpersonal reconnection? *Journal of Personality and Social Psychology*, *92*, 42–55.
- Martin, C. D., Bool, H. M., George, A. M., Carr, K. A., Epstein, L. H., Hawk, L. W., & Richards, J. B. (2018). Social reinforcement as alternative to sucrose reinforcement is increased by nicotine and methylphenidate in male Fischer-344 rats. *Psychopharmacology*, *235*, 1981–1985.
- Matsumoto, K., Pinna, G., Puia, G., Guidotti, A., & Costa, E. (2005). Social isolation stress-induced aggression in mice: A model to study the pharmacology of neurosteroidogenesis. *Stress*, *8*, 85–93.
- Matsumoto, M., & Hikosaka, O. (2009). Two types of dopamine neuron distinctly convey positive and negative motivational signals. *Nature*, *459*, 837–841.
- Matsumoto, M., & Takada, M. (2013). Distinct representations of cognitive and motivational signals in midbrain dopamine neurons. *Neuron*, *79*, 1011–1024.

- Matthews, G. A., Nieh, E. H., Vander Weele, C. M., Halbert, S. A., Pradhan, R. V., Yosafat, A. S., ... Tye, K. M. (2016). Dorsal raphe dopamine neurons represent the experience of social isolation. *Cell*, *164*, 617–631.
- Matthews, G. A., & Tye, K. M. (2019). Neural mechanisms of social homeostasis. *Annals of the New York Academy of Sciences*.
- Mumtaz, F., Khan, M. I., Zubair, M., & Dehpour, A. R. (2018). Neurobiology and consequences of social isolation stress in animal model-A comprehensive review. *Biomedicine & Pharmacotherapy*, *105*, 1205–1222.
- Muotri, A. R. (2016). The human model: Changing focus on autism research. *Biological Psychiatry*, *79*, 642–649.
- Nieh, E. H., Matthews, G. A., Allsop, S. A., Presbrey, K. N., Leppla, C. A., Wichmann, R., ... Tye, K. M. (2015). Decoding neural circuits that control compulsive sucrose seeking. *Cell*, *160*, 528–541.
- Nieh, E. H., Vander Weele, C. M., Matthews, G. A., Presbrey, K. N., Wichmann, R., Leppla, C. A., ... Tye, K. M. (2016). Inhibitory input from the lateral hypothalamus to the ventral tegmental area disinhibits dopamine neurons and promotes behavioral activation. *Neuron*, *90*, 1286–1298.
- Niesink, R. J. M., & Van Ree, J. M. (1982). Short-term isolation increases social interactions of male rats: A parametric analysis. *Physiology & Behavior*, *29*, 819–825.
- Novick, A. M., Levandowski, M. L., Laumann, L. E., Philip, N. S., Price, L. H., & Tyrka, A. R. (2018). The effects of early life stress on reward processing. *Journal of Psychiatric Research*, *101*, 80–103.
- Oka, Y., Ye, M., & Zuker, C. S. (2015). Thirst driving and suppressing signals encoded by distinct neural populations in the brain. *Nature*, *520*, 349.
- Panksepp, J., & Beatty, W. W. (1980). Social deprivation and play in rats. *Behavioral and Neural Biology*, *30*, 197–206.
- Perret, A., Henry, L., Coulon, M., Caudal, J.-P., Richard, J.-P., Cousillas, H., ... George, I. (2015). Social visual contact, a primary 'drive' for social animals? *Animal Cognition*, *18*, 657–666.
- Pfeiffer, U. J., Schilbach, L., Timmermans, B., Kuzmanovic, B., Georgescu, A. L., Bente, G., & Vogeley, K. (2014). Why we interact: On the functional role of the striatum in the subjective experience of social interaction. *Neuroimage*, *101*, 124–137.
- Popova, J. S., & Petkov, V. V. (1990). Changes in 5-HT₁ receptors in different brain structures of rats with isolation syndrome. *General Pharmacology: The Vascular System*, *21*, 223–225.
- Pursey, K. M., Stanwell, P., Callister, R. J., Brain, K., Collins, C. E., & Burrows, T. L. (2014). Neural responses to visual food cues according to weight status: A systematic review of functional magnetic resonance imaging studies. *Frontiers in Nutrition*, *1*, 7.
- Qualter, P., Vanhalst, J., Harris, R., Van Roekel, E., Lodder, G., Bangee, M., ... Verhagen, M. (2015). Loneliness across the life span. *Perspectives on Psychological Science*, *10*, 250–264.
- Rademacher, L., Krach, S., Kohls, G., Irmak, A., Gründer, G., & Spreckelmeyer, K. N. (2010). Dissociation of neural networks for anticipation and consumption of monetary and social rewards. *Neuroimage*, *49*, 3276–3285.
- Radke, S., Güths, F., André, J. A., Müller, B. W., & de Bruijn, E. R. A. (2014). In action or inaction? Social approach-avoidance tendencies in major depression. *Psychiatry Research*, *219*, 513–517.
- Raz, S., & Berger, B. D. (2010). Social isolation increases morphine intake: Behavioral and psychopharmacological aspects. *Behavioural Pharmacology*, *21*, 39–46.
- Rilke, O., May, T., Oehler, J., & Wolffgramm, J. (1995). Influences of housing conditions and ethanol intake on binding characteristics of D₂, 5-HT_{1A}, and benzodiazepine receptors of rats. *Pharmacology Biochemistry and Behavior*, *52*, 23–28.
- Robinson, D. L., Heien, M. L. A. V., & Wightman, R. M. (2002). Frequency of dopamine concentration transients increases in dorsal and ventral striatum of male rats during introduction of conspecifics. *The Journal of Neuroscience*, *22*, 10477–10486.
- Salamone, J. D., & Correa, M. (2012). The mysterious motivational functions of mesolimbic dopamine. *Neuron*, *76*, 470–485.
- Salovey, P., Mayer, J. D., & Rosenhan, D. L. (1991). Mood and helping: Mood as a motivator of helping and helping as a regulator of mood. *Prosocial Behavior*, *12*, 215–237.
- Sato, N., Tan, L., Tate, K., & Okada, M. (2015). Rats demonstrate helping behavior toward a soaked conspecific. *Animal Cognition*, *18*, 1039–1047.
- Schipper, L., Harvey, L., van der Beek, E. M., & van Dijk, G. (2018). Home alone: A systematic review and meta-analysis on the effects of individual housing on body weight, food intake and visceral fat mass in rodents. *Obesity Reviews*, *19*, 614–637.
- Schott, B. H., Minuzzi, L., Krebs, R. M., Elmenhorst, D., Lang, M., Winz, O. H., ... Bauer, A. (2008). Mesolimbic functional magnetic resonance imaging activations during reward anticipation correlate with reward-related ventral striatal dopamine release. *Journal of Neuroscience*, *28*, 14311–14319.
- Schweinfurth, M. K., & Taborsky, M. (2016). No evidence for audience effects in reciprocal cooperation of Norway rats. *Ethology*, *122*, 513–521.
- Segal, D. S., Knapp, S., Kuczynski, R. T., & Mandell, A. J. (1973). The effects of environmental isolation on behavior and regional rat brain tyrosine hydroxylase and tryptophan hydroxylase activities. *Behavioral Biology*, *8*, 47–53.
- Shams, S., Chatterjee, D., & Gerlai, R. (2015). Chronic social isolation affects thigmotaxis and whole-brain serotonin levels in adult zebrafish. *Behavioural Brain Research*, *292*, 283–287.
- Shams, S., Seguin, D., Faccioli, A., Chatterjee, D., & Gerlai, R. (2017). Effect of social isolation on anxiety-related behaviors, cortisol, and monoamines in adult zebrafish. *Behavioral Neuroscience*, *131*, 492–504.
- Sheldon, K. M., & Gunz, A. (2009). Psychological needs as basic motives, not just experiential requirements. *Journal of Personality*, *77*, 1467–1492.
- Silberberg, A., Allouch, C., Sandfort, S., Kearns, D., Karpel, H., & Slotnick, B. (2014). Desire for social contact, not empathy, may explain "rescue" behavior in rats. *Animal Cognition*, *17*, 609–618.
- Silverman, J. L., Pride, M. C., Hayes, J. E., Puhger, K. R., Butler-Struben, H. M., Baker, S., & Crawley, J. N. (2015). GABA B receptor agonist R-baclofen reverses social deficits and reduces repetitive behavior in two mouse models of autism. *Neuropsychopharmacology*, *40*, 2228–2239.

- Silverman, J. L., Smith, D. G., Rizzo, S. J. S., Karras, M. N., Turner, S. M., Tolu, S. S., ... Crawley, J. N. (2012). Negative allosteric modulation of the mGluR5 receptor reduces repetitive behaviors and rescues social deficits in mouse models of autism. *Science Translational Medicine*, 4, 131-51.
- Silverman, J. L., Tolu, S. S., Barkan, C. L., & Crawley, J. N. (2010). Repetitive self-grooming behavior in the BTBR mouse model of autism is blocked by the mGluR5 antagonist MPEP. *Neuropsychopharmacology*, 35, 976-989.
- Small, D. M. (2001). Changes in brain activity related to eating chocolate: From pleasure to aversion. *Brain*, 124, 1720-1733.
- Spreckelmeyer, K. N., Krach, S., Kohls, G., Rademacher, L., Irmak, A., Konrad, K., ... Grunder, G. (2009). Anticipation of monetary and social reward differently activates mesolimbic brain structures in men and women. *Social Cognitive and Affective Neuroscience*, 4, 158-165.
- Sternson, S. M., Nicholas Betley, J., & Cao, Z. F. (2013). Neural circuits and motivational processes for hunger. *Current Opinion in Neurobiology*, 23, 353-360.
- Sumiya, M., Koike, T., Okazaki, S., Kitada, R., & Sadato, N. (2017). Brain networks of social action-outcome contingency: The role of the ventral striatum in integrating signals from the sensory cortex and medial prefrontal cortex. *Neuroscience Research*, 123, 43-54.
- Sussman, R. W., & Cloninger, C. R. (2011). *Origins of altruism and cooperation*. New York: Springer-Verlag.
- Trezza, V., Baarendse, P. J., & Vanderschuren, L. J. (2010). The pleasures of play: Pharmacological insights into social reward mechanisms. *Trends in Pharmacological Sciences*, 31, 463-469.
- Trezza, V., Damsteegt, R., Achterberg, E. J. M., & Vanderschuren, L. J. M. J. (2011). Nucleus accumbens μ -opioid receptors mediate social reward. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*, 31, 6362-6370.
- Tsai, H.-C., Zhang, F., Adamantidis, A., Stuber, G. D., Bonci, A., de Lecea, L., & Deisseroth, K. (2009). Phasic firing in dopaminergic neurons is sufficient for behavioral conditioning. *Science*, 324, 1080-1084.
- Tye, K. M., Prakash, R., Kim, S.-Y., Fenno, L. E., Grosenick, L., Zarabi, H., ... Deisseroth, K. (2011). Amygdala circuitry mediating reversible and bidirectional control of anxiety. *Nature*, 471, 358-362.
- Van Loo, P. L. P., de Groot, A. C., Van Zutphen, B. F. M., & Baumans, V. (2001). Do male mice prefer or avoid each other's company? Influence of hierarchy, kinship, and familiarity. *Journal of Applied Animal Welfare Science*, 4, 91-103.
- Venniro, M., Zhang, M., Caprioli, D., Hoots, J. K., Golden, S. A., Heins, C., ... Shaham, Y. (2018). Volitional social interaction prevents drug addiction in rat models. *Nature Neuroscience*, 21, 1520-1529.
- Volkow, N. D., Wang, G. J., Telang, F., Fowler, J. S., Logan, J., Childress, A. R., ... Wong, C. (2006). Cocaine cues and dopamine in dorsal striatum: Mechanism of craving in cocaine addiction. *Journal of Neuroscience*, 26, 6583-6588.
- Washburn, D. A., & Rumbaugh, D. M. (1991). Impaired performance from brief social isolation of rhesus monkeys (*Macaca mulatta*): A multiple video-task assessment. *Journal of Comparative Psychology (Washington, D.C.: 1983)*, 105, 145-151.
- Williamson, G. M., & Clark, M. S. (1989). Providing help and desired relationship type as determinants of changes in moods and self-evaluations. *Journal of Personality and Social Psychology*, 56, 722-734.
- Wills, G. D., Wesley, A. L., Moore, F. R., & Sisemore, D. A. (1983). Social interactions among rodent conspecifics: A review of experimental paradigms. *Neuroscience & Biobehavioral Reviews*, 7, 315-323.
- Wise, R. A. (2004). Dopamine, learning and motivation. *Nature Reviews Neuroscience*, 5, 483-494.
- Witten, I. B., Steinberg, E. E., Lee, S. Y., Davidson, T. J., Zalocusky, K. A., Brodsky, M., ... Deisseroth, K. (2011). Recombinase-driver rat lines: Tools, techniques, and optogenetic application to dopamine-mediated reinforcement. *Neuron*, 72, 721-733.
- Wolffgramm, J., & Heyne, A. (1991). Social behavior, dominance, and social deprivation of rats determine drug choice. *Pharmacology Biochemistry and Behavior*, 38, 389-399.
- Wood, R. I., Kim, J. Y., & Li, G. R. (2016). Cooperation in rats playing the iterated Prisoner's Dilemma game. *Animal Behaviour*, 114, 27-35.
- Yamada, H., Matsumoto, N., & Kimura, M. (2004). Tonic active neurons in the primate caudate nucleus and putamen differentially encode instructed motivational outcomes of action. *Journal of Neuroscience*, 24, 3500-3510.
- Zhang, J. T., Yao, Y. W., Potenza, M. N., Xia, C. C., Lan, J., Liu, L., ... Fang, X. Y. (2016). Effects of craving behavioral intervention on neural substrates of cue-induced craving in Internet gaming disorder. *NeuroImage: Clinical*, 12, 591-599.
- Zimmerman, C. A., Leib, D. E., & Knight, Z. A. (2017). Neural circuits underlying thirst and fluid homeostasis. *Nature Reviews Neuroscience*, 18, 459-469.