Current Topics in Behavioral Neurosciences 30

Markus Wöhr
Sören Krach *Editors*

Social Behavior from Rodents to Humans

Neural Foundations and Clinical Implications

Springer

Current Topics in Behavioral Neurosciences

Volume 30

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ISSN 1866-3370 ISSN 1866-3389 (electronic)
Current Topics in Behavioral Neurosciences
ISBN 978-3-319-47427-4 ISBN 978-3-319-47429-8 (eBook)
DOI 10.1007/978-3-319-47429-8

Library of Congress Control Number: 2016952898

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

Sociability is the greatest advantage in the struggle for life
Pyotr Kropotkin, *Mutual Aid: A Factor of Evolution*

"Social Behavior from Rodents to Humans: Neural Foundations and Clinical Implications" provides a broad and accessible overview on the rapidly developing field of social neuroscience. Social neuroscience is an expanding research field devoted to understand how social behavior is implemented by biological factors, and how social experiences in turn impact the brain. A major goal of this volume is to integrate research findings on the neural basis of social behavior across different levels of analysis from rodent studies on molecular neurobiology to behavioral neuroscience to functional neuroimaging data on human social behavior.

Showcasing an array of cutting-edge research programs, leading investigators present new approaches in a field covering a wide range of behaviors, ranging from maternal care, sexual behavior and attachment to social observational learning, social decision making and altruism. In the first two parts, an introduction to the various different kinds of social behaviors in rodents, Part I, and humans, Part II, is provided, with special emphasis being laid onto newly developed paradigms to study communicative functions in rodents, but also proxemics and higher-order social cognition in humans, including second-person neurosciences and hyper-scanning. Importantly, chapters cover a broad range of research based on studies in healthy participants, their application and translation into a clinical context, as well as developmental aspects, as exemplified in Part III, devoted to clinical implications, with a special emphasis on autism spectrum disorder.

Most rodents are social animals, displaying a rich repertoire of social behaviors and living at least substantial parts of their lives in societies in which they use complex ways to communicate with each other, for instance during mating and while forming social bonds. Part I therefore starts off with a comprehensive and insightful overview by Lukas and de Jong (2017) on behavioral methods used to study components of this rich social behavior repertoire in a standardized manner, ranging from affiliative to aggressive encounters: friends or foes? Their overview describes traditional but also novel approaches, such as the recently developed

female intruder test (de Jong et al. 2014). At the neurobiological level, Lukas and de Jong (2017) focus on the neuropeptides oxytocin and vasopressin, key players in regulating social behavior.

Because of the richness of the social behavior repertoire, the ability to recognize and distinguish between individuals—to identify friends and foes, is essential for survival. In the second chapter, Camats et al. (2017) provide an excellent overview on the present knowledge about social memory in rodents, comparing social recognition memory performance across different rodent taxa and behavioral test paradigms. As olfactory signals are of particular relevance for the formation of social recognition memory, they also summarize key components of the brain circuit processing olfactory information linked to social recognition memory. Finally, they give examples of factors that they and their colleagues have identified to interfere with the formation of social recognition memory, such as social isolation, but also elements of the experimental procedures, including anaesthesia or even transportation (Perna et al. 2015). Their careful consideration appears essential to avoid spurious results.

In the third chapter, Kiyokawa (2017) shows that olfactory signals are not only highly relevant for the formation of social recognition memory but also serve important communicative functions. Kiyokawa (2017) describes two types of olfactory communication in rodents. Summarizing own previous findings of an extensive serious of studies (Inagaki et al. 2014), he first describes pheromones, which are released in response to stress and serve as alarm signals to warn conspecifics about danger through activating the fear circuit in the brain. Secondly, he describes appeasing olfactory communication and how this is involved in the fascinating phenomenon of social buffering.

Besides olfactory signals, rodents emit ultrasonic vocalizations. Wöhr et al. (2017) provide an overview on the communicative functions of the two main types of ultrasonic vocalizations emitted by adult rats, 22-kHz calls serving an alarming function and 50-kHz calls serving an affiliative function. They further show that social experiences strongly affect the emission of ultrasonic vocalizations in the sender but also the behavioral responses displayed by the receiver. Behavioral responses elicited in the receiver are typically studied by means of a playback paradigm. Using this approach, they showed that not only juvenile social isolation (Seffer et al. 2015) but also environmental enrichment (Brenes et al. 2015) might have negative effects on ultrasonic communication.

Another approach to study the communicative function of ultrasonic vocalizations is described by Kisko et al. (2017), namely surgical devocalization. In their studies, Kisko et al. (2015; 2017) devocalized rats to test how the lack of ultrasonic vocalizations affects their social play behavior. They found that social play behavior was clearly reduced in pairs of devocalized juvenile rats. Furthermore, in adult rats, devocalization led to a marked increase in aggressive behaviors. Therefore, the two studies highlight the important communicative functions fulfilled by ultrasonic vocalizations and their role in modulating social play and aggression.

In his seminal work, Panksepp helped identify and illuminate the functional neuroanatomies and neurochemistries of seven primary processes, which he named SEEKING/Enthusiasm, RAGE/Anger, FEAR/Anxiety, sexual LUST/Passion,

maternal CARE/Nurturance, separation-distress PANIC/Grief and PLAY/Social Joy. In his chapter, Panksepp (2017) provides a thought-provoking overview on how several of these systems figure heavily in social bonding. Considering depression as an example, he argues that sustained overactivity of the separation-distress PANIC/Grief system, reflecting the "excessive psychological pain of loneliness", can lead to a downward cascade known as psychological despair. Psychological despair, in turn, is characterized by abnormally low activity of the SEEKING/Enthusiasm system, also known as brain reward networks, resulting in amotivational states typical for depression. As 50-kHz calls are believed to reflect activity of the SEEKING/Enthusiasm system in rats ("rat laughter"; Panksepp 2005), Panksepp suggests measuring 50-kHz calls in rat models as a marker to assess treatment efficacy of novel pharmacological compounds for treating depression.

The apparent paradox that altruistic behaviors are expressed by the same individuals that also compete for resources is discussed by Lahvis (2017). He argues that natural selection does not only favor individuals to act in their own interest, implying a "competitive psychology", but also animals displaying helping behavior, presumably at their own expense, suggesting a more "compassionate psychology". He further argues that altruism can only be partially explained by ultimate mechanisms, such as kin selection and reciprocity, and suggests that an additional "stake in others" is necessary for the evolution of altruism: the so called "camaraderie effect". He sees the "camaraderie effect" as a by-product of two highly adaptive psychological experiences, namely social motivation and empathy, which both can be studied in rodents. In fact, there is evidence that rodents do not only derive pleasure from social interactions but also experience empathy (Chen et al. 2009) - the generation of an affective state more appropriate to the situation of another compared to one's own.

In the last chapter of Part I, Hernandez-Lallement et al. (2017) report on a fascinating new behavioral paradigm to assess pro-social decision-making in rats using a social reinforcement framework. In the pro-social choice task, an actor and a partner are trained together in a double T-maze. First, the actor makes a choice and enters one of two different compartments. Then, gets a reward, which is identical irrespective of which compartment it has chosen. However, entering one compartment triggers the delivery of an additional reward for the partner rat, whereas entering the alternative compartment does not yield any additional reward to the partner. By means of this new behavioral paradigm, Hernandez-Lallement et al. (2015) demonstrated that rats prefer mutual rewards, and now discuss factors that could drive social decision making in rodents, with a particular emphasis on inter-individual differences.

"Whether supportive, strategic, combative or romantic, social interactions are at the core of everyday experience" (McCall 2017). It is an essential fact of humankind that we either engage into social interactions or at least constantly simulate and represent ourselves in the context of our surrounding social world. The rise and significance of social media for humans in modern societies is another proof of this principle and a powerful cultural artifact that demonstrates how humans value and nurture the connections between them. Part II is devoted to the question of how the

various facets of sociality and their underlying neural principles, that help us to engage with others, can be understood in the neurosciences of human social interactions. The opening chapter by Keysers and Gazzola (2017) "A Plea for Cross-species Social Neuroscience" thereby bridges Part I with Part II in arguing why it will be essential to integrate animal neuroscience and human neuroscience in order to deepen our understanding of the neural basics of social phenomena. Basing their plea on the spectacular discovery of motor mirror neurons in monkey research more than two decades ago (di Pellegrino et al. 1992), Keysers and Gazzola (2017) provide a convincing argument of how cohesive cross-species neurosciences and models for neural functioning that span over taxonomies of biology could greatly expand our understanding of embodied cognition.

In this line, the following Chapter, "Models, Mechanisms and Moderators Dissociating Empathy and Theory of Mind" by Kanske et al. (2017), tackles the fundamental question of how humans are able to access another person's mind. This a fundamental and necessary capability to socially interact in a meaningful way (Kanske et al. 2015). The authors hereby describe the most influential models for grasping others' perspectives based on two neural routes: an affective route which helps us to directly share others' emotions in an empathic manner and a cognitive route which helps us to represent and reason about others' mental states, called Theory of Mind (ToM). The authors provide a compelling example of how to dissociate these two routes and their underlying neural processes within one paradigm (Kanske et al. 2015) and elaborate how situational and personality factors impact their use and neural functioning during social interaction.

However, what is so appealing for us to engage into social interactions and why do humans and other social beings value and nurture social relations, at first hand? In their Chapter "Reward: From Basic Reinforcers to Anticipation of Social Cues" Rademacher et al. (2017) outline how the human reward system processes all kind of social stimuli that motivate behavior. Importantly, they provide strong empirical arguments showing the rewarding aspects of social connectedness and affiliation do already shape the reward signal in the anticipation of social interaction in structures of the striatum (Rademacher et al. 2010; Spreckelmeyer et al. 2009). The chapter thereby introduces into state-of-the-art neuroimaging paradigms to effectively study the effects that social incentives exert on humans. The authors close the chapter with the role of the neuropeptide oxytocin in mediating the rewarding quality of social interactions by activating dopaminergic reward pathways in response to social cues. This is arguably one of the most famous examples for how human and rodent neuroscience can expand on each other for understanding social cognition.

The question of whether these positive and rewarding aspects of social interaction ultimately lead to human cooperation is asked in the following chapter on "Human Cooperation and Its Underlying Mechanisms" by Strang and Park (2017). While people do share a lot of goods on a voluntary basis even with unrelated others, also defective or egocentric behavior is evident in society. This chapter provides and elaborate overview of current economic games that are useful to examine how cooperative, defective or altruistic behaviors are represented in the human brain. The authors discuss how social punishment in form of deliberate

non-cooperation is applied to maintain social cooperation, and how emotions impact decision making.

Most emotions are triggered by or experienced within social encounters. Our bodies, and hence our brains, are no "completed beings" but always involve the opening towards another person or a group (Deleuze 1993). We feel sad because of a romantic relationship breakdown, we are proud about being honored at school or feel embarrassed because we are ridiculed in front of an audience. Chapter "The Social Neuroscience of Interpersonal Emotions" demonstrates that emotions are interpersonal in nature as we constantly represent ourselves in the context of our surrounding social world. In their review, Müller-Pinzler et al. (2017) describe innovative interpersonal set-ups to evoke authentic emotions in neuroscientific environments. Based on the most recent evidence on guilt, pride, anger, and embarrassment (Müller-Pinzler et al. 2015), they summarize the neural networks that underlie these most prototypical examples of interpersonal emotions. They complete this chapter by explaining the vicarious experience of these interpersonal emotions (Krach et al. 2011) based on the above introduced neural pathways of empathizing and mentalizing (Kanske et al. 2015; Paulus et al. 2014).

Offending social encounters usually trigger anger. In their Chapter "Deconstructing Anger in the Human Brain" Gilam and Hendler (2017) further elaborate the recent experimental advances of bringing realistic social interactions into a neuroimaging environment for studying this so-called basic emotion underlying many interpersonal conflicts. In order to capture the full picture of the human flexibility to control and regulate anger and even adapt anger to socially accepted norms, the authors ultimately stress that spontaneous and dynamic interactive paradigms need to be embedded into neuroscientific research in order to truly understand the interpersonal aspects of emotions.

The underlying neuroendocrine mechanisms of approach and avoidance behavior are targeted in greater detail in Chapter "On the Control of Social Approach–Avoidance Behavior: Neural and Endocrine Mechanisms" by Kaldewaij et al. (2017). While humans possess the capacity to control their behavioral action tendencies, the authors elaborate how evaluations of emotional situations happen in an automatic and implicit way. The chapter reviews current research on the way endogenous hormone levels of testosterone, oxytocin or cortisol modulate approach-avoidance behaviors.

To study social emotions or social phenomena in general, high degrees of experimental control and ecological validity are essential and are therefore addressed in detail in several chapters of the book. The "Science of Proxemics" by McCall, specifically, is a guide to new avenues for the study of social interactions in a multidimensional but highly controlled environment while at the same time one has to account for the "inherently nonlinear" phenomenology of social interactions (McCall 2017). The science of proxemics thereby introduces the principles for studying fundamental aspects of human social behavior in virtual environments. By tracking motion data, location information, and head orientation this innovative paradigm allows to identify characteristic patterns in the way people orient toward or away from each other and engage in mutual, joint or averted gaze (McCall & Singer 2015). The utility and validity of this approach is finally demonstrated by

showing convincing modulations of these markers for social behavior through various experimental manipulations.

Part III is devoted to clinical implications. A particular emphasis is put on the case of autism spectrum disorder, a group of neurodevelopmental disorders characterized by social and communication deficits, paralleled by repetitive and stereotyped patterns of behavior. The first chapter by Schroeder et al. (2017) provides an overview on human core symptoms, candidate genes, and current experimental approaches to study pathomechanisms in rodents. The chapter focuses on genetic rodent models, with an exemplary description of top-ranked models, including Fmr1 mutant mice as a model for fragile X syndrome, the most common known single genetic cause of autism spectrum disorder, but also other models for studying promising candidate genes, such as Neuroligin3 and Neuroligin4 and Shank gene family members, including Shank2 (Schmeisser et al. 2012).

Pietropaolo et al. (2017) take it a step further in the second chapter and critically discuss current strategies for testing promising pharmacological and environmental treatment approaches in rodent models for autism spectrum disorder. In their very insightful discussion, they identify a number of problems inherent to the research field, which delay the study of such treatment approaches. The problems include the presence of a large variety of rodent models, the difficulty in choosing the most appropriate behavioral markers for assessing treatment efficacy, the limited knowledge on the neurobiological bases of autism spectrum disorder and of its etiology, and, finally, the complexity of the disorder itself. As an example of a promising approach, they describe beneficial effects of environmental enrichment on behavioral abnormalities, such as direct reciprocal social interaction deficits, in Fmr1 mutant mice (Oddi et al. 2015)—a model relevant for autism spectrum disorder, yet characterized by lower levels of complexity and clearer etiology.

The third chapter "Neuroimaging-based Phenotyping of the Autism Spectrum" by Bernhardt et al. (2017) questions whether a consistent neuroimaging phenotype would indeed adequately describe the very heterogeneous symptomatology of autism spectrum disorders. The authors review recent advances in our understanding of the structural and functional organization of regional and large-scale brain networks and their disturbances in autism spectrum disorders. A broad spectrum of analyses tools, ranging from diffusion tractography studies to structural neuroimaging covariance and graph-theoretical approaches are introduced and evaluated in their potential to identify biologically and clinically relevant endophenotypes.

The chapters on autism spectrum disorder are closed by a review on "Current Practice and Future Avenues in Autism Therapy" by Poustka and Kamp-Becker (2017). Poustka and Kamp-Becker (2017) provide an overview on established and evidence-based interventions and treatments in autism spectrum disorder. Taken the functional independence and quality of life of persons diagnosed with autism spectrum disorder into consideration, they evaluate the advantages and disadvantages of up-to-date social skill-based or behavior-based interventions, computer-supported trainings, as well as new avenues such as neurofeedback and real-time functional neuroimaging or adjuvant pharmacotherapy including the promising neuropeptide oxytocin.

Baez et al. (2017) introduce a framework for how basically all social cognition depends on contextual factors in their chapter on the "The Social Context Network Model in Psychiatric and Neurological Diseases". The effects of social context thereby rely on the functioning of central hubs in a fronto-temporo-insular brain network, which, if altered, result in impairments to adjust cognition and behavior according to contextual demands. To validate their approach Baez et al. (2017) apply the social context network model to various domains of social cognition and make a compelling case for how it helps to understand the peculiarities in frontotemporal dementia and autism spectrum disorder.

In "Social-Cognitive Deficits in Schizophrenia", Mier and Kirsch (2017) argue why and how the social neurosciences can inform about the emergence of schizophrenia, a severe, highly heritable psychiatric disorder. The authors introduce a neural system-based model of how psycho-social processes such as emotion and intention recognition and executive functioning contribute to the observed hypo- and hyperactivation and aberrant connectivity in schizophrenia.

Finally, future directions are discussed in a translational manner, including the effects of stress. In an elegantly written chapter, Tzanoulinou and Sandi (2017) describe how early life stress programs the social brain. They discuss the physiological and neurobiological consequences of stress during peri-adolescence in the context of rodent paradigms that model human adversity, such as social neglect and isolation, social abuse, and exposure to fearful experiences (Marquez et al. 2013). Furthermore, they discuss peri-adolescent stress as a potent component strongly influencing the social behavior repertoire even of individuals in close contact with stressed individuals and across generations. By revising the existing literature, defining open questions, and debating the adaptive function of observed changes in social behavior such as pathological aggression, they expand the framework in which interactions among peri-adolescent stress, the social brain, and behavior can be better conceptualized.

In closing, we would like to express our profound gratitude to Dr. Bart Ellenbroek, Editor-in-Chief of Current Topics in Behavioral Neuroscience, for allowing us the opportunity to compile this volume entitled "Social Behavior from Rodents to Humans: Neural Foundations and Clinical Implications". Our appreciation is extended to all reviewers for their time, effort and persistence. Finally, we would like to voice a special gratitude to the staff at Springer for their tireless help getting this project off the ground and to completion. In particular, we are indebted to Susanne Dathe and Amudha Vijayarangan for helping us to pursue and secure the appropriate venue for the project.

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Part I
Social Behavior in Rodents

Conspecific Interactions in Adult Laboratory Rodents: Friends or Foes?

Michael Lukas and Trynke R. de Jong

Abstract Interactions between adult conspecifics, including sexual behaviors, affiliation, and aggression are crucial for the well-being, survival, and reproduction of mammals. This holds true for any mammalian species, but certainly for humans: An inability to optimally navigate the social system can have a strong negative impact on physical and mental health. Translational rodent models have been used for decades to unravel the neural pathways and substrates involved in normal and abnormal conspecific interactions. Researchers in the field of translational social neuroscience face a double challenge: Not only do they need to pay considerable attention to the behavioral ecology of their model species or their ancestors, they also have to expect a relatively large variability in behavior and adjust their experimental design accordingly. In this chapter, we will lay out traditional and novel rodent models and paradigms to study sexual, affiliative, and aggressive interactions among adult conspecifics. We will discuss the merits and main findings and briefly consider the most promising novel directions. Finally, we review the modulatory involvement of two major players in mammal social interaction: the central oxytocin and vasopressin system.

Keywords Aggression · Sociality · Sexual behavior · Social preference · Social defeat · Oxytocin · Vasopressin

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Curr Topics Behav Neurosci (2016) 30: 3–24
DOI 10.1007/7854_2015_428
Published Online: 18 May 2016

1 Introduction

Intraspecific social interactions in adults, such as sexual behavior, affiliation, and aggression, are crucial for the fitness of mammals. An individual that adequately decides who to mate with and who to fight against and who to approach and who to avoid strongly increases its chances to survive and reproduce. Conversely, wrong decisions can lead to considerable stress, social isolation, and even death. This holds true for any mammalian species, but certainly for humans (Strang and Park 2017): Our species heavily relies on complex social and sexual ties, negotiation skills, hierarchical structures, shared resources and territories that need to be defended against enemies. An inability to optimally navigate the social system, for example through inborn or developmental behavioral or cognitive impairments, may have a strong negative impact on physical and mental health (Mier and Kirsch 2017; Schroeder et al. 2015; Tzanoulinou and Sandi 2017).

Translational rodent models have been used for decades to unravel the neural pathways and substrates involved in normal and abnormal conspecific interactions. Various paradigms have been consolidated over time to study the neuroscience of social behaviors in rodents in a standardized manner. Traditionally, the emphasis has been placed on basic neuronal networks underlying a specific type of behavior, as well as hormonal or pharmacological manipulations of this behavior. More recently, reciprocal links with other behavioral systems have received increasing attention. Examples of these links are the effects of stress (acute, chronic, or early in life), trait or state anxiety, cognitive skills, and impulse control on positive and negative social interactions, and vice versa the effects of positive and negative social experiences on stress system (re-)activity, mood, and cognition (Tzanoulinou and Sandi 2015). Furthermore, the modeling and treatment of human psychopathologies characterized by social deficits, such as autism spectrum disorders or schizophrenia, using translational laboratory rodents has recently intensified (Pietropaolo et al. 2017; Schroeder et al. 2015).

The field of translational social neuroscience comes with certain challenges. Foremost, neuroscientists will benefit from knowing the behavioral ecology of their model animal or its ancestors far more intimately than is typically necessary for the

study of depression and anxiety or learning and memory. Furthermore, experimental trials in social neuroscience often contain at least two individuals (e.g., mating partners, residents and intruders), each with their own and behavioral state contributing to considerable variability in the results. Avoiding any disturbances or inconsistencies that add to this variability is thus of the utmost importance.

In this chapter, we introduce and discuss both classic and novel rodent models and paradigms to study friendly and unfriendly interactions among adult conspecifics. We focus on inter-species variability in "social lifestyle," and how to relate social behavior in the field to experiments in the laboratory and, ultimately, translate the results to human interactions. Finally, we review the significant modulation of adult interactions by central oxytocin (OXT) and arginine-vasopressin (AVP), as these two neuropeptides are currently under intense investigation as targets to treat human social disorders.

2 Which Rodents Are We Talking About?

The execution of mounts and intromissions during mating, threats and attacks during fighting, or sniffing and adjacent lying during social approach/affiliation is fairly stereotypical across rodent species. On the other hand, the selection of the optimal behavioral response toward another animal (e.g. to approach or avoid, to mate or to fight) is strongly influenced by the "social lifestyle" of a species. While many rodent species have been used in descriptive studies of intraspecific social interactions, only a handful have been used to perform the bulk of translational neurobiological or neuroendocrinological experiments. Since none of these preferred model species display the full array of human sociality, they have been used in laboratories as representatives of separate components of our social life. Thus, pair-bonded and biparental prairie voles (*Microtus ochrogaster*) or California mice (*Peromyscus californicus*) are frequently used to study the neurobiological aspects of the formation and disruption of human family bonds (De Jong et al. 2013; Young et al. 2011), but are less useful to study sexual behavior. The neurobiology of aggression and social defeat is often studied in highly territorial, solitary living Syrian hamsters (*Mesocricetus auratus*, Ferris and Delville 1994) and territorial pair-bonded California mice (Trainor et al. 2011). The naked mole-rat (*Heterocephalus glaber*) is the preferred rodent species to study social organization and dominance hierarchies, based on its unique eusocial lifestyle (Mooney et al. 2015).

However, by far the most popular model species remain the promiscuous, uniparental, group-living, moderately hierarchical rats (*Rattus norvegicus*) and house mice (*Mus musculus*) (Berdoy and Drickamer 2007). Rats and mice can form large coherent social groups and are therefore the preferred species to study sociality, social memory/recognition (Camats Perna and Engelmann 2017), and even play behavior including accompanying ultrasonic vocalizations (Kisko et al. 2017; Wöhr et al. 2017). In addition, they adapt very well to their environment (the basis of their widespread distribution and tendency to live in urban areas (Feng et al. 2014)) and

are thus optimally suited to investigate the effects of epigenetic variability and/or early-life stress on social behavioral profiles (Tzanoulinou and Sandi 2015). Moreover, the well-defined neurobiological pathways underlying stress, anxiety, addiction, and cognition in rats and mice are an excellent basis to investigate the reciprocal connections between these systems and the social behavior network.

Needless to say, the social and sexual behavior typically displayed by a species in the wild may differ profoundly from their behavior in the laboratory. The absence of predatory threats, adverse weather conditions, and food and water shortage combined with controlled housing in small same-sex/same-age groups or in isolation are likely to affect many neurobiological, neuroendocrinological, and behavioral parameters (Calisi and Bentley 2009; Keane et al. 2014). These effects are probably even stronger in animals that are the end product of generations of laboratory breeding, as indicated, for example, by the lower levels of aggression displayed by outbred Wistar rats compared to feral wild-type Groningen rats (Boer et al. 2003). Nevertheless, major hardwired species-specific behavioral strategies such as monogamy versus polygamy or gregarious versus solitary living usually remain intact in a laboratory environment.

3 Friendly Encounters

When two conspecific rodents have a shared goal, and are able to determine that they do so, their interactions will most likely be peaceful. An encounter between two adult conspecifics of opposite sexes will often lead to consensual mating and sometimes even the formation of an affiliate pair-bond, as this is likely to increase the reproductive success of both individuals. In group-living species, adults of the same sex may benefit from collaboration in order to find resources, defend a shared territory, escape predators, and keep warm at night. Displaying affiliative behavior when interacting will facilitate such collaborations. These friendly—sexual and affiliative—interactions among rodents have been studied in detail in various paradigms (see Fig. 1) to understand the equivalent behaviors in humans—especially to find treatments when they are impaired.

3.1 Mating and Pair-Bonding

Place a healthy adult male rodent in a cage with an estrous female conspecific, and the results can be easily predicted: The male will approach the female, sniff her anogenital region to confirm her reproductive state, and become—at some point—sexually aroused. This is defined as the *anticipatory* phase of copulation. The estrous female will respond with proceptive behaviors signaling her willingness to mate, including the stereotypical lordosis posture. This allows the pursuing male to mount her, insert his erect penis (“intromission”), and copulate until sperm is

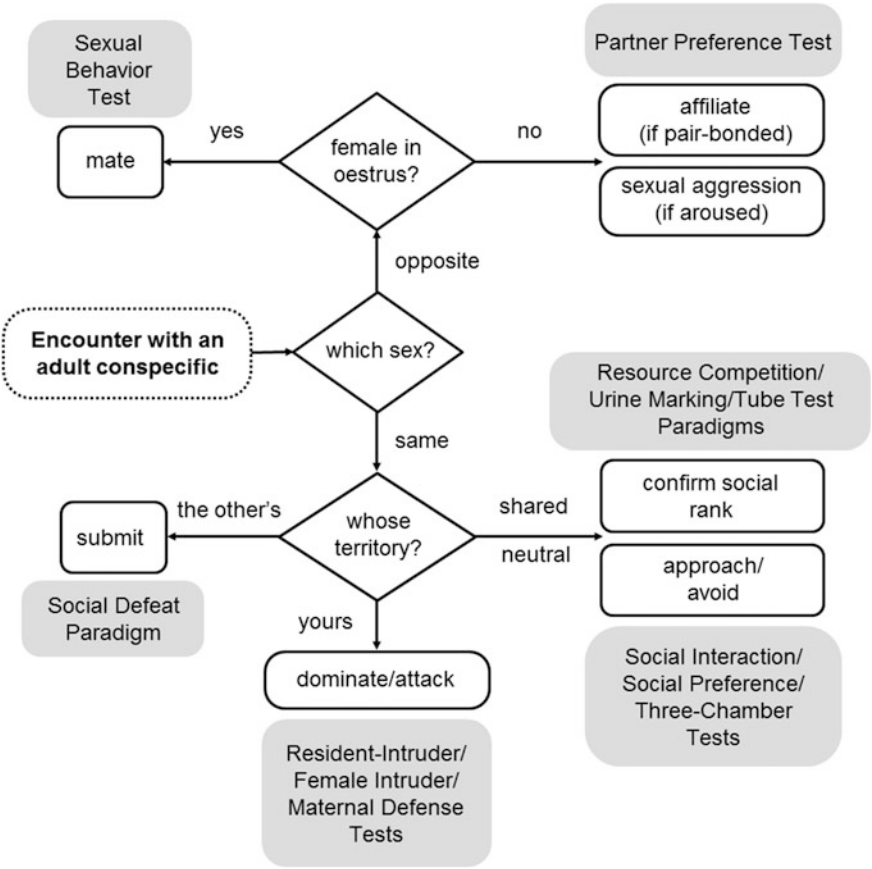

Fig. 1 Flowchart illustrating the various behavioral responses of adult rodents toward conspecifics (*white quadrangles*), and the associated experimental paradigms designed to measure variability in these responses under controlled conditions (*gray quadrangles*)

ejaculated. These behaviors comprise the *consummatory* phase of copulation. Ejaculation is always followed by a post-ejaculatory interval after which copulation is resumed—provided the female is still available.

The neurobiological pathways underlying these sexual behaviors (including the medial preoptic area, posteromedial bed nucleus of the stria terminalis, medial amygdala, and paraventricular and ventromedial hypothalamic nuclei), as well as pharmacological compounds affecting them, have been studied predominantly in rats (Veening and Coolen 2014). Rats normally display a consistent high level of sexual motivation and a rapid transition from the anticipatory to the consummatory phase of mating, typically resulting in 2–3 rounds of copulation in a standard 30-min test, in contrast to the much "slower" house mice. In addition, physical markers of copulatory behavior such as erection, ejaculation, and lordosis are easily

quantified in rats. These features have proven very useful in the search for treatments of physiological sexual disorders in humans such as erectile dysfunction, premature ejaculation, or female arousal disorders (Giuliano et al. 2010).

While the relatively simple central pathways controlling copulatory behavior are by now well understood, the more complex neurobiology of sexual motivation is still under investigation. Even though male and estrous female conspecifics are likely to mate when they meet, they may chose not to. Even promiscuous rats can display preferences for specific individuals, and a minority of rats show very little interest in mating at all: They either avoid or show affiliative behavior toward an opposite-sex stimulus animal (Pfaus et al. 2003). It is of note here that in standard laboratory rat mating tests, the stronger male controls the interaction and leaves little choice for the female to cooperate. Only in special gated or bi-leveled cages can females escape the male and pace the rhythm of the copulation or decide not to mate at all. Unraveling the innate and experiential causes for this variability in motivation is an interesting avenue of investigation to model human sexual motivation.

Aside from the ability and the motivation to mate, there is a third important dimension in male–female conspecific interactions: the development of stable pair-bonds in monogamous species such as prairie voles and California mice (for review see Young et al. 2011). In these species, sexual motivation becomes associated with one particular individual, sometimes after a single mating experience. Pair-bonding is typically tested using a partner preference paradigm, in which a higher time in close proximity to the partner, induced by previous successful mating, versus a novel opposite-sex stranger is the defining parameter. In addition to the profound effects of pair-bond formation on an individual's interactions with its preferred partner, the changes in behavior toward non-preferred individuals are equally dramatic: Sexual interest is inhibited, and in some cases aggression is displayed.

3.2 Sociality

Placing two rodent conspecifics with the same sex together will usually not lead to mating (although exceptions do occur), but the resulting interactions can still be positive and rewarding. In particular, when the animals meet in a neutral territorial context, e.g., in a shared territory like a group cage or in an arena that is novel to both, most rodents will to some extent display affiliate interactions classified in the laboratory as social interaction and/or sociality.

Preference toward a conspecific over a nonsocial stimulus (selective social preference), as opposed to avoidance, is integral to the expression of social interaction, to facilitate the motivation to approach rather than avoid or behave quiescent in varying social contexts. The motivation to initially approach another "neutral" conspecific raised a lot of attention in the last years, as the usage of rodent animal models got more in the focus of research concerning neurodevelopmental disorders

such as schizophrenia or autism spectrum disorders (Pietropaolo et al. 2015; Schroeder et al. 2017; Tzanoulinou and Sandi 2015). Important diagnostic criteria for autism spectrum disorders are deficits in social communication and social interaction across multiple contexts, including deficits in social–emotional reciprocity; deficits in nonverbal communicative behaviors; and deficits in developing, maintaining, and understanding relationships (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition 2013). Therefore, it is not surprising that there are many paradigms to model sociality and social communication available for basic and psychopharmacological animal research.

Preclinical and clinical research indicates that the prosocial neuropeptides OXT and AVP play a major role in promoting sociality (see Sect. 5.2.1 and Lukas and Neumann 2013), so far mainly localized in the lateral septum of male mice (Guzman et al. 2013; Zoicas et al. 2014). As social contact is known to be rewarding under normal circumstances, reduced seeking of social encounters hints toward a disruption of reward-seeking tendencies, if not in general then at least in a social context. Central reward mechanisms classically involve the mesolimbic dopamine pathway (Bromberg-Martin et al. 2010). Indeed, it is suggested that social "wanting" dysfunctions in autism spectrum disorders is caused by a disruption of the dopaminergic–oxytocinergic mesolimbic circuitry including the nucleus accumbens and the ventral tegmental area (Kohls et al. 2012).

As indicated above, the majority of "sociality" research is done in laboratory rats and mice (Lukas and Neumann 2013) as well as California mice (Trainor et al. 2011). Since these species are neither strictly solitary nor overly gregarious, they naturally express a relatively variable spectrum of affiliation and social avoidance dependent on the particular social context. In addition, the general sociality of the animals can be easily deflected to an extreme in case the experimental question demands it. One example would be the induction of strong social avoidance using social defeat (see Sect. 4.2) followed by the assessment of potential prosocial effects of a drug.

Beginning with rodent models of sociality, there are two main groups of test paradigms. The first group measures sociality via exposing a test animal to a freely moving or caged/separated stimulus animal alone. Social interaction with this stimulus animal is then determined in terms of time spent in direct social contact (sniffing), or in general proximity (e.g., adjacent lying or staying in contact zones). The second group of paradigms measures sociality of an experimental animal by comparing its interaction with or proximity to a social stimulus (caged animal) versus a nonsocial stimulus (empty cage). Within this second group, it is possible to differentiate between consecutive and simultaneous presentation of the social and the nonsocial stimulus. For a very detailed and precise methodological description of all the single paradigms available, we kindly refer to the review from Toth and Neumann (2013). It is a matter of discussion, which of the multitude of paradigms is the most suitable to measure sociality. To answer this question, one has to attend to the behavioral, environmental, and developmental context of the animals to be tested. As these tests all depend on a certain behavioral activity (movement/sniffing) of the animal, it is important to adjust the test circumstances. For instance, animals

with a known general lower activity are more likely to show high levels of social interaction when confronted with a social stimulus alone, or a social and a nonsocial stimulus one after the other. An example for this would be the testing of aged rats: Due to their general low locomotor activity, it is possible that during the often standardized limited time the tested animals are not able to efficiently explore several chambers with social and nonsocial stimuli simultaneously. Therefore, interpretations of social versus nonsocial investigation/proximity may be difficult or misleading. In addition, testing highly aggressive animals such as male Syrian hamsters or sexually experienced male or lactating female rats with a freely moving conspecific most certainly results in aggressive interactions (see Sect. 4.1). Thus, using a paradigm with caged or separated stimulus animals would be appropriate here. In particular, challenging are test subjects that have a very high level of innate anxiety, as this may lead to reduced locomotor activity or freezing and consequently low levels of social interaction in an unfamiliar environment. In this case, direct comparisons to a nonsocial stimulus are advised. It is also possible that high trait or state anxiety induces proximity to a social stimulus as this provides relief from stress and anxiety in socially living animals, usually referred to as social buffering (Kikusui et al. 2006), resulting in unexpected high levels of sociality. Here, investigation of social proximity alone without analysis of actual interaction, such as sniffing, can be misleading.

If sociality is analyzed with one of the above-mentioned paradigms, it is possible to differentiate the outcome in roughly three categories: social preference (higher interest in social over nonsocial stimulus), loss of social preference (reduction of social interest to the level of nonsocial stimulus), and social avoidance/fear (less interest/avoidance of social compared to nonsocial stimuli). A differentiation that becomes especially important, if one is interested in changes of sociality following negative, “unfriendly” encounters.

4 Unfriendly Encounters

When two conspecifics have conflicting goals, encounters can become distinctly agonistic, ranging from mutual avoidance to fighting to the death. In territorial species or lactating females, the cost of losing a territory or a litter is so high that virtually all intruders will be attacked, no matter their size or the circumstances. In group-living species, more variability will occur depending on the individual’s social status, social recognition (Camats Perna and Engelmann 2015), social personality, reproductive state, and circumstances in early life (Tzanoulinou and Sandi 2015) as well as recent (social) experiences.

4.1 Social Aggression

Social aggression, as opposed to predatory aggression, is part of the standard behavioral repertoire of rodents in conflict situations. In order to survive and to reproduce, animals need to obtain access to food, water, shelter, and mates, and to raise their offspring. Since crucial resources are often scarce in nature, especially in times of higher population densities or during breeding seasons, fierce competition can occur between two or more conspecifics.

4.1.1 Response to Intrusion

Reactive aggression as a result of one individual threatening to overtake a valuable resource from another is easily induced in the laboratory by first giving experimental animals "ownership" of a territory and a mate (in the resident-intruder test, see Haller 2014) or a litter (in the maternal defense test, see Bosch 2013) and then introducing a smaller/weaker same-sex conspecific intruder. This elicits a fairly stereotypical set of behaviors in the experimental animals, starting with extensive sniffing of the intruder followed by agonistic behaviors that limit the intruder in its movements without causing bodily harm. Examples of these are towering over the intruder, pushing the intruder down to the ground or against a wall, and threatening to attack. The encounter can culminate in one or more attacks, which in rodents typically consist of a rapid clinch fight and biting (Haller 2014). Recent observations have shown that virgin female rats display a similar behavioral repertoire in a resident-intruder setting (de Jong et al. 2014), despite earlier reports of very low levels of aggression among non-lactating females (see for example Blanchard et al. 1988). The moderate levels of pushing, threatening, and attacking female intruders by virgin female residents are not instigated by prolonged cohabitation with a male, but already appear after a short period (48 h) of single housing. Furthermore, this aggressive behavior rapidly increases upon repeated exposure to unknown intruders (once per day for 3–5 consecutive days), especially when the female residents remain isolated in this training period (unpublished observations). This makes the paradigm different from the classic resident-intruder test, in which males are pair-housed with a female for at least a week prior to intrusion and their female mates are only temporarily removed from the cage (i.e., during an intrusion). These findings suggest that in virgin female rats, the defense of resources such as food and water rather than an established territory and/or a mate is sufficient to instigate moderate aggression. The rapid escalation of defensive aggression seen in late pregnancy and early lactation is putatively the result of the profound neuromodulations in the peripartum period (Bosch 2013).

The neural circuitry controlling aggressive behaviors, with an emphasis on attacks, has been studied quite extensively in male rodents (especially rats, mice, Syrian hamsters, and California mice) using the resident-intruder test and includes the hypothalamus and the extended amygdala (Veening et al. 2005). The neural

circuitry controlling aggressive decision making (i.e., when to be aggressive and what level of violence to use) is much less clear. In particular, in the relatively gregarious rat, behavioral responses toward an intruder can range from violent aggression with attacks to mainly non-violent agonistic threats or even tolerance and affiliation, for reasons that are still under investigation. The neuropeptides OXT and AVP play a modulating role here, as discussed in Sect. 5. In addition, there is an increasing interest in the role of cortical pathways exerting behavioral control or the lack thereof (i.e., impulsivity). In particular, the serotonin system is thought to be important for the inhibition of behavioral impulses, such as the aggressive attack of intruders (Takahashi et al. 2011).

The question has arisen whether the defense of resources, which in itself is a healthy and natural behavior among rodents, is an appropriate model for the pathological aggression in humans associated with, for example, intermittent explosive disorder, schizophrenia, borderline personality disorder, antisocial personality disorder, and conduct disorder (Haller 2014; Miczek et al. 2013). One approach to improve the translatability of rodent models is to selectively investigate individuals that display abnormal or extreme behaviors in the resident-intruder test, including (a) attacking without giving the intruder the chance to escape or admit defeat (i.e., very quickly and/or without giving proper warning in the form of threats) and (b) displaying unnecessarily violent attacks (e.g., targeting vulnerable body parts for maximal damage, or attacking anesthetized, already defeated or female intruders) (de Boer et al. 2009; Haller 2014). Although laboratory rats and mice rarely show such extreme/abnormal behaviors spontaneously, some experimental manipulations have been found to induce it. These manipulations include the knockout of genes such as the gene for monoamine oxidase A in mice (Cases et al. 1995), selective breeding examples include short attack latency mice (Natarajan et al. 2009) and low anxiety behavior rats (Beiderbeck et al. 2012), treatment with alcohol (Miczek et al. 2013), depletion or suppression of the central serotonin system (Audero et al. 2013), depletion of corticosterone by adrenalectomy (Haller et al. 2004), or stress during infancy or puberty, such as maternal separation, peripubertal isolation, or peripubertal stress (Sandi and Haller 2015).

A remaining issue is that these animal experiments still rely on reactive aggression in the resident-intruder test, whereas the most violent and treatment-resistant type of human aggression is proactive and calculating, and associated with low levels of empathy ("callous–unemotional traits") (Blair 2010). It is by now well understood that reactive and proactive aggression are two very different behaviors, generally distinguished by increased (reactive aggression) versus decreased (proactive aggression) arousal in response to threatening stimuli, as measured in terms of stress responses and activation of distinct amygdalar and cortical areas. Although animal models are starting to close this translational gap by focusing on individuals that show impaired intruder-induced arousal (Haller 2014), behavioral paradigms that truly model proactive, goal-oriented aggression and/or variability in callous–unemotional traits in rodents are still lacking.

4.1.2 Social Hierarchies

Resident-intruder style paradigms artificially promote aggressive behavior by giving the resident a clear upper hand: The resident has something valuable to defend, the encounter takes place on the resident's territory, and the intruder is unfamiliar and relatively weak. A different picture emerges when group-living rodents, such as laboratory rats, interact with familiar conspecifics with whom they share a territory and its resources (i.e., cage mates in the laboratory). Using violent aggression to continuously defend resources against group mates is no longer feasible and would drain all individuals of much-needed energy.

One solution in this situation is the formation of a stable social hierarchy, in which the more dominant males or females automatically receive first choice of resources (Broom 2002). This solution has evolved in various rodent species, but most strikingly in the naked mole-rats that form large colonies of up to 300 individuals headed by a single dominant and reproductively active female (the queen) and one to three reproductive males. All other males and females are reproductively suppressed and perform subordinate working tasks such as colony maintenance and defense. When the queen is removed, the colony becomes unstable and aggression peaks until a novel queen has established herself and the social order is restored (Mooney et al. 2015).

Rats and mice form social hierarchies as well, but these hierarchies are more fluid and less associated with division of labor and reproduction—at least in laboratory settings (Blanchard et al. 1988; Ziporyn and McClintock 1991). Determining which individuals are (relatively) dominant or subordinate in small groups of rats and mice is therefore more difficult than in naked mole-rats and requires fairly elaborate behavioral paradigms. These include food or water competition paradigms, in which the dominant animal most often obtains the largest amount of a limited resource (Malatynska and Knapp 2005; de Jong et al. 2012); urine marking paradigms, in which small urine marks spread throughout a cage signify dominance whereas large urine pools at the edges signify submissiveness (Desjardins et al. 1973); or "passing behavior" paradigms in which dominant individuals are more likely to take the right of way in cramped burrow systems (Ziporyn and McClintock 1991). Social hierarchies in various rodent species are currently used to measure the behavioral, neurobiological, and physiological correlates of having a dominant or subordinate status. Examples include the multiple markers of chronic stress and depression observed upon subordination in mice and rats (Langgartner et al. 2015; Malatynska and Knapp 2005), the similarities between dominant status and pathological mania (Johnson et al. 2012; Malatynska and Knapp 2005), and the variability in OXT receptor binding dependent on status in naked mole-rats (Mooney et al. 2015).