Title

Bridging the species gap in translational research for neurodevelopmental disorders

Authors

Ryan, AM
Berman, RF
Bauman, MD

Publication Date

2019-11-01

DOI

10.1016/j.nlm.2018.10.006

Peer reviewed

HHS Public Access

Author manuscript

Neurobiol Learn Mem. Author manuscript; available in PMC 2020 November 01.

Published in final edited form as:

Neurobiol Learn Mem. 2019 November ; 165: 106950. doi:10.1016/j.nlm.2018.10.006.

Bridging the species gap in translational research for neurodevelopmental disorders

A.M. Ryan[a,b,c], **R.F. Berman**[a,d], **M.D. Bauman**[a,b,c,*]

[a]The UC Davis MIND Institute, University of California, Davis, United States

[b]Department of Psychiatry and Behavioral Sciences, University of California, Davis, United States

[c]California National Primate Research Center, University of California, Davis, United States

[d]Department of Neurological Surgery, University of California, Davis, United States

Abstract

The prevalence and societal impact of neurodevelopmental disorders (NDDs) continue to increase despite years of research in both patient populations and animal models. There remains an urgent need for translational efforts between clinical and preclinical research to (i) identify and evaluate putative causes of NDD, (ii) determine their underlying neurobiological mechanisms, (iii) develop and test novel therapeutic approaches, and (iv) translate basic research into safe and effective clinical practices. Given the complexity behind potential causes and behaviors affected by NDDs, modeling these uniquely human brain disorders in animals will require that we capitalize on unique advantages of a diverse array of species. While much NDD research has been conducted in more traditional animal models such as the mouse, ultimately, we may benefit from creating animal models with species that have a more sophisticated social behavior repertoire such as the rat (*Rattus norvegicus*) or species that more closely related to humans, such as the rhesus macaque (*Macaca mulatta*). Here, we highlight the rat and rhesus macaque models for their role in previous psychological research discoveries, current efforts to understand the neurobiology of NDDs, and focus on the convergence of behavior outcome measures that parallel features of human NDDs.

Keywords

Animal models; Laboratory rat; Nonhuman primate; Rhesus macaque

1. Introduction

Neurodevelopmental disorders (NDDs) represent a group of childhood conditions that have an onset in the early developmental period, create a delay in achievement of expected milestones, and usually do not have a clear cause or successful treatment. As described in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, "*the disorders typically manifest early in development, often before the child enters grade school, and are characterized by developmental deficits that produce impairments of personal, social,*

*Corresponding author at: The UC Davis MIND Institute, 2805 50th Street, Sacramento, CA 95817, United States. mdbauman@ucdavis.edu (M.D. Bauman).

academic, or occupational functioning. The range of developmental deficits varies from very specific limitations of learning or control of executive functions to global impairments of social skills or intelligence" (DSM-V, 2013). NDDs include a number of intellectual and communication disabilities, autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), specific learning disorders, as well as motor and tic disorders. Moreover, psychiatric disorders such as schizophrenia (SZ), in which symptoms manifest in late adolescence or early adulthood, are increasingly considered to be of neurodevelopmental origins (Catts et al., 2013; Piper et al., 2012; Rapoport, Gied, & Gogtay, 2012). The complexity of NDDs requires coordinated research efforts utilizing both clinical and preclinical approaches in order to identify causes, determine neurobiological mechanisms, and develop novel therapeutic interventions. In this review, we discuss contributions of animal models to our understanding of NDDs, highlighting specific examples from the laboratory rat (*Rattus norvegicus*) and the rhesus macaque (*Macaca mulatta*) to bridge the gap in translational research efforts between animal models and patient populations. Here we will focus on the contributions of these two species to understanding genetic and environmental risk factors, as well as the underlying neural basis of NDDs. The reader is referred to excellent reviews on pharmacotherapeutic interventions for further information on treatment models (Berry-Kravis et al., 2018; Silverman & Crawley, 2014).

While such external factors as the physical or social environment can potentially affect causes and treatments for NDD, ultimately, these disorders arise and are affected by changes in the brain. Studies in humans can explore correlative relationships between the brain and symptoms of NDDs. Yet, in preclinical research, animal models can be used to answer critical questions about how the brain works as a dynamic and complex biological system, from molecular biology through behavior, and what changes may led to the development of NDDs or lead to treatments for NDDs (Abbott, 2016). Animal models can thus be used as experimental systems to explore causative relationships and to directly manipulate variables and test hypotheses about the brain that are difficult or not feasible to be studied in humans (Bauman & Schumann, 2013; Ecker, Spooren, & Murphy, 2012). Furthermore, with animal models, researchers can integrate physiology, behavior, neuroimaging, and postmortem analyses to explore mechanisms of neurodevelopmental disorders in a single subject. Exploratory research in animal models has the potential to play a key role in identifying new therapeutic targets by what has been called "forward translation." Conversely, important feedback from clinical trials can help focus the preclinical search for new therapeutic targets by "reverse translation" ('t Hart, 2015). Yet, the potential for animal models to contribute to either forward or reverse translation relies on the validity of the models for the particular research question under examination and specific experimental design considerations.

The relevance of animal models for human disorders has traditionally been evaluated in three ways: construct validity, face validity, and predictive validity (Willner, 1984). The ideal animal model in this paradigm would demonstrate the same cause (construct validity), analogous behavioral phenotypes (face validity), and the same response to treatments (predictive validity) as the human disease. Research using animal models has generally focused on face validity with respect to modeling the behavioral symptoms of NDDs as presented in traditional DSM criteria. However, the NIH has recently presented a novel framework for psychiatric disorder research called the Research Domain Criteria (RDoC)

initiative that is intended to improve the translational pipeline between preclinical and clinical research. The RDoC provides a more holistic approach to studying psychiatric disorders that integrates biological factors such as genetics and neural circuitry with known behavioral constructs such as fear and anxiety that may be present in multiple disorders and arise through a variety of different mechanisms (Cuthbert & Insel, 2013). Although there is tremendous potential for RDoC to improve translation of basic and clinical neurodevelopmental disorder research (Casey, Oliveri, & Insel, 2014), we are still in the earliest stages of applying RDoC approaches to NDD research efforts (Cosgrove, Kelsoe, & Suppes, 2016; Damiano, Mazefsky, White, & Dichter, 2014).

One of the traditional animal models, the house mouse (*Mus muscuhis*), has been a favored species in biomedical research for years, in part due to their relative low cost and unparalleled genetic manipulations. For NDDs such as ASD and Fragile X that have strong genetic components, research using knockout mouse models have contributed to our understanding of genes that relate to core symptoms of ASD such as *Shank3* and *Fmr1* (Crawley, 2012; Moy & Nadler, 2008). Mice display repetitive behaviors in the lab setting, such as circling, jumping, and backflips, which can be used to explore potential mechanisms for different repetitive behaviors observed in humans with NDDs (Silverman, Yang, Lord, & Crawley, 2010). Other species-typical behaviors can be used in an assay for repetitive behaviors such as self-grooming and excessive digging, which is measured in a marble-burying task (Silverman et al., 2010). Mice are also a social species, so researchers have adapted behaviors from the mouse repertoire for assays that are relevant to symptoms of NDDs such as ASD. These include social approach and preference tests towards either a novel or familiar conspecific in order to explore potential mechanisms for social deficits (Silverman et al., 2010). However, the social behaviors in these tasks primarily consist of proximity and sniffing. Compared to mice, rats exhibit more complex social interactions, including play fighting (Pellis, Pellis, & Dewsbury, 1989), social reward, and empathy (Panksepp & Panksepp, 2013; Panksepp & Watt, 2011; Panksepp, 2007) that enhance their usefulness for studies of NNDs. They also provide an opportunity to explore aspects of social communication through analysis of ultrasonic vocalizations (Seffer, Schwarting, & Wöhr, 2014; Wohr & Schwarting, 2013).

While mice continue to be an important species in NDD research, there are also limitations in relying on a single species. For example, we will miss out on opportunities to exploit the diversity of nervous systems found in different species of animals that may serve to be useful in studying complex human brain disorders (Brenowitz & Zakon, 2015; Yartsev, 2017). A return to studying a once popular animal model, the rat, would offer many of the advantages of mouse models with respect to cost and short gestational period yet rats also have a larger brain body size and expanded repertoire of social and cognitive behaviors (Fig. 1) (Vanderschuren & Trezza, 2014). For an even more sophisticated repertoire of social behavior, nonhuman primates such as the rhesus macaque live in large social groups and communicate with a variety of vocalizations and facial expressions (Fig. 1) (Chang et al., 2013). In this review, we compare and contrast the unique advantages and limitations of rat and nonhuman primate models of NDDs. We will highlight behavioral assays that are commonly used in rats and nonhuman primates to illustrate various approaches that can be used to measure behaviors relevant to NDDs, including: (i) anxiety related behaviors, (ii)

presence of repetitive behaviors and/or restricted interest, (iii) social development and (iv) cognitive development.

2. Rat models

2.1. Features of the species

Rats (*Rattus norvegicus*) were the first mammalian species domesticated in the 1850s for scientific research and now play a central role in research in physiology, pharmacology, neurosciences, genetics and the medical sciences in general. Their origins trace to central Asia and then to Europe in the mid-1500s on ships from Norway, as suggested by their name. Rat distribution is world-wide and they are commonly found in urban areas due to their association with humans (Feng & Himsworth, 2014). They are nocturnal, omnivorous, and breed throughout the year with females having about 6–8 pups per liter with 5–6 g birthweight. With a gestation period of 21–23 days and the capability of producing 6–8 litters per year, they are ideal for intergenerational studies on the heritability of developmental disorders. The young are small and undeveloped taking 14–17 days for eye opening and have been used extensively to study maternal effects on neurodevelopment. Young wean by 3–4 weeks of age, are sexually mature at 3 months, and live 2.5–3.5 years which allows for longitudinal studies across several generations (Calhoun, 1962; Feng & Himsworth, 2014; Perry, 1945).

Rats live in colonies characterized by dominant male and a harem of females that defend their nests and territory. Their social behaviors are rich and complex, including establishment of social hierarchies and robust juvenile play behaviors (Barnett, 1963). Various strains were developed and are still in use, with the most commonly used strains being Sprague-Dawley and Wistar albino rats, and the pigmented Long-Evans hooded rat. Extensive use of rats for toxicological studies began in 1920 with the testing of drugs for lethality and skin and eye irritation, and later to identify potential carcinogenic chemicals (Parasuraman, 2011). Toxicity profiles of standard drugs and for investigational new drugs (IND) began in the 1960s after thousands of babies were born with birth defects caused by thalidomide. Rats as models of disease are also used extensively in drug development and for establishing biomarkers of disease (Denayer, Stöhr, & Van Roy, 2014). Rats are quickly becoming a species of choice for neurodevelopmental studies, including autism, because of their larger body and brain size, richer and more complex social interactions, more human-like physiology, excellent learning, and memory capabilities when compared to mice.

While the advantages of the short gestational period in rats is akin to the more common model organism of the mouse, rats also have larger brains than mice, which is a major benefit for electro-physiological, neurochemical and neuroanatomical studies. In particular, PET and MRI imaging continues to be challenging in the mouse, even when using relatively high field 7 T magnets. In contrast, high resolution *in vivo* PET and MRI imaging has been achieved using a variety of pulse sequences in the rat for many years. Most importantly, rats exhibit a rich behavioral profile that allow more sophisticated studies of learning, memory, executive functions, and complex social interactions. Several investigators have developed protocols in order to study play behavior (Burgdorf, Kroes, Beinfeld, Panksepp, & Moskal, 2010; Ku, Weir, Silverman, Berman, & Bauman, 2016; Panksepp, 1981; Siviy & Panksepp,

1987), bi-directional social communication via ultrasonic vocalizations (USVs) (Berg et al., 2018), and prosocial motivational behaviors that appear to share, at least on the surface, some features of empathy (Ben-Ami Bartal, Decety, & Mason, 2011).

Gene knockouts and targeted mutations in rats have only been possible since 2003 (Zan et al., 2003), although the recent development of CRISPR-Cas9 and zinc-finger nuclease (ZFN) technologies have made the generation of rat models faster. This has resulted in the rapid generation of rat transgenic and knockout models relevant to NDDs, and it is expected that the use of rats will increase dramatically. Some of the currently available mutant knockout rats that are particularly relevant for research on NDDs include: *FMR1* (fragile X mental retardation protein 1), *Nlgn3* (neuroligin 3), *Nrxn1* (neurexin 1), *Pten* (Phosphatase and tensin homolog), *MGluR5* (metabotropic glutamate receptor 5), *MeCP2* (methyl CpG binding protein 2), *MET* (met oncogene), *Cntnap2* (contactin associated protein like 2), *Cacn1c* (voltage dependent L-type calcium channel 1c), *Rbfox1* (RNA binding fox-1 homolog-1), *Gabarb3* (Gaba A receptor β3 subunit), and *Shank3* (SH3 and multiple Ankyrin repeat domains 3). Knock-outs are also available for research on neurodegenerative disease (e.g., Alzheimer's & Parkinson's disease), SZ, pain, and optogenetics. There is also a repository, the Rat Resource and Research Center (http://www.rrrc.us/) that maintains high quality and well-characterized inbred, hybrid, and mutant rats that are important to across the biomedical research community.

2.2. Rat behavioral assays relevant to NDDs

As many NDDs, such as ASD, are behaviorally defined disorders, preclinical models rely on behavioral phenotyping tools to evaluate the distinctive clinical features in a nonhuman species. Much effort has focused on developing behavioral assays relevant to clinical features including (i) anxiety, (ii) repetitive behaviors/restricted interests, (iii) social development and (iv) cognitive development. There are, however, challenges in modeling these complex behavioral manifestations of NDDs in nonhuman species. Here, we focus on specific examples of rat and nonhuman primate behavioral phenotyping approaches that are relevant to human NDDs. For an excellent review on mouse behavioral phenotyping tools, readers are referred to Silverman et al. (2010).

(i) Anxiety—The open-field test is the primary test of anxiety used in rats and mice. It was originally developed by C.S. Hall in 1934 as a test to measure emotionality in rodents (Cosgrove et al., 2016) and is now one of the most widely used measures of emotionality and locomotor behavior in research on NDDs. The open-field consists of a brightly lit square or circular arena enclosed by walls sufficiently high to prevent escape. Animals are typically videotaped for 30–90 min in the field. Infrared beam breaks followed by computerized analysis are used to analyze such measures as total distance moved, movement velocity, time spent in the margins near the walls (i.e., thigmotaxis) versus time in the center, number of center crossings, and number of rearing episodes. Greater time spent in the margins of the field, along with increased defecation and urination (i.e., number of fecal boli deposited) are considered evidence of increased anxiety and fear. Although the open-field has been widely used as a measure of anxiety, it has been conceptually difficult to distinguish between fear and anxiety, with some who consider fear and anxiety to be part of a continuum (Casey et

al., 2014). Additionally, great variability exists in how different laboratories carry out the test (e.g., construction, time in the open-field, illumination), sometimes making it difficult to compare results between laboratories (Damiano et al., 2014).

The other commonly used indices of anxiety are the elevated plus-maze and the closely related elevated zero-maze. The plus-maze consists of 4 arms radiating out from a central platform, two of which have closed walls and two of which are open, whereas the zero-maze is a circular runway with two enclosed and two open quadrants. Both of these tests take advantage of rodents' natural aversion to open, unprotected spaces; therefore, it is interpreted as anxiety when animals spend more time in the closed arms than in the open arms. The elevated plus-maze has been used extensively in psychopharmacological studies, and research on anxiolytics in particular where anxiety-reducing drugs result in animals spending more time in open arms ('t Hart, 2015).

(ii) Repetitive behavior—In rodents, duration of self-grooming bouts can be quantified as an index of repetitive or stereotyped behaviors (Lewis, Tanimura, Lee, & Bodfish, 2007). In addition, quantification of repetitive digging behaviors as seen in the task of burying a marble has been proposed as a measure of anxiety in rodents (Archer, Fredriksson, Lewander, & Soderberg, 1987; Broekkamp, Rijk, Joly-Gelouin, & Lloyd, 1986; Njung'e & Handley, 1991). Marble-burying has been widely used in the field of anxiety research because both antidepressant and anti-anxiety drugs have been shown to reduce marble-burying behavior (Borsini, Podhorna, & Marazziti, 2002). However, other groups use it as a measure of perseverative digging behavior rather than novelty-induced anxiety (Gyertyán, 1995; Thomas et al., 2009). In mice, we know that marble-burying is sensitive to strain, brain lesions, and pharmacological treatment (Deacon, 2006). While the pathophysiology of repetitive restrictive behaviors has been studied extensively in mice, relatively few studies in rats have focused on such behaviors in relation to NDDs (Garner, 2005; Lewis & Kim, 2009). Mouse marble-burying paradigms have been adapted for use in rats (Llaneza & Frye, 2009; Schneider & Popik, 2007), yet, our lab did not observe the characteristic defensive burying response that has been described in the mouse literature (Ku et al., 2016), suggesting that digging and burying behaviors may differ across muroid species (Webster, Williams, Owens, Geiger, & Dewsbury, 1981).

(iii) Social—Deficits in social play are a prominent feature of NDDs, including ASD (Jordan, 2003; Young, Brewer, & Pattison, 2003), that can be measured in preclinical animal models by measuring the frequency and duration of species-typical play behaviors. Indeed, play is a behavior common in many young mammalian species, including human children, juvenile monkeys, and rats (Panksepp, Siviy, & Normansell, 1984; Potegal & Einon, 1989; Trezza, Campolongo, & Vanderschuren, 2011). The rat social repertoire includes a prolonged period of juvenile play that may provide a preclinical model system to explore social impairments in more detail than is possible with other rodent models (Pellis, Burghardt, & Palagi, 2015; Vanderschuren, Niesink, & Van Ree, 1997).

Social interest is commonly assessed in mice with automated behavioral assays, such as the three-chamber social approach, which provides a relatively simple assay as determined by the duration of time the experimental animal spends near another animal that is confined to a

small cage (Yang, Silverman, & Crawley, 2011, chap. 8). Although the three-chambered social approach test is commonly used as a first line screening assay for autism-like phenotypes in mouse models (Kas et al., 2014; Manduca et al., 2014; Niesink & Van Ree, 1989; Siviy, Love, DeCicco, Giordano, & Seifert, 2003), there are perhaps limitations in relying heavily on a social assay that does not allow animals to freely engage in reciprocal social behavior. The measures of sociability generated in the three-chamber assay have been interpreted as an all-or-none result that should be restricted to comparison with a single experimental group, rather than a comparison between groups (Silverman et al., 2010). Although this behavioral task has been useful in mouse models of ASD, it may not be sensitive to more subtle impairments in social behavior that may be detected in rats, nonhuman primates, and other species that engage in reciprocal social behaviors, such as juvenile play (Peters, Pothuizen, & Spruijt, 2015).

Given that rats are generally considered to have a more extensive social repertoire than mice, the rat may provide an opportunity to augment simple automated procedures by creating opportunities to focus on more complex ASD-relevant social interaction assays. There is a rich literature describing numerous approaches for quantifying juvenile rat social interactions (Panksepp, 1981; Peters et al., 2015; Thor & Holloway, 1984). Play fighting is the most common form of play behavior in rats (Pellis & Pellis, 1998; Poole & Fish, 1975) and is initiated when one partner uses their snout to nuzzle the nape of the neck of the other animal and the partner, in turn, defends its nape from such attacks by rotating to its dorsal surface or evading the attacker. As compared to mice, rats exhibit more complex patterns of play fighting characterized by reciprocal bouts of attack, defense and counter attacks (Pellis et al., 1989). Our own work in rat models of NDDs suggests that analysis of complex reciprocal social interactions paired with sophisticated social communication assays, such as ultrasonic vocalization (USV) playbacks, provide an in-depth evaluation of rat social development (Berg et al., 2018; Ku et al., 2016). Future efforts should further capitalize on the complex social behavior of the rat model by in-corporating other aspects of social communication, such as USVs (Seffer et al., 2014; Wohr & Schwarting, 2013) as well as assays of more complex social processing, including social reward and empathy (Ben-Ami Bartal et al., 2011; Panksepp & Panksepp, 2013; Panksepp & Watt, 2011; Panksepp, 2007). It is also important to note that many factors influence rat social behavior, including the choice of strain, length of social isolation preceding the test, familiarity with the testing environment and properties of the testing environment such as cage size, lighting, and bedding (Himmler, Pellis, & Pellis, 2013; Himmler et al., 2014; Niesink & Van Ree, 1983; Spruijt, Peters, de Heer, Pothuizen, & van der Harst, 2014; Vanderschuren, Niesink, Spruijt, & Van Ree, 1995; Varlinskaya, Spear, & Spear, 1999).

(iv) Cognition—The Morris water maze is one of the most widely used behavioral tests of spatial learning and memory (D'Hooge & de Deyn, 2001; Garthe & Kempermann, 2013). It was developed by Richard Morris in the 1980s as a way to study spatial memory in rats (Morris, Garrud, Rawlins, & O'Keefe, 1982). The “maze” typically consists of a 1–2 m diameter pool of water in which the water is made opaque with milk or non-toxic paint and an escape platform is hidden just below the water surface. A video camera positioned above the maze and computerized tracking software are used to record and analyze maze

performance, including latency to find the escape platform, distance swum, and swim speed. Over several days of training, animals are placed in the maze and allowed to swim in order to find the location of the escape platform. This maze learning is typically followed by a probe trial in which the escape platform is removed, and the time spent swimming in the vicinity of the former platform location is used as an index of memory for spatial location. The hippocampus is particularly important for spatial learning, and damage to this structure impairs maze performance (Morris et al., 1982). A virtual water maze has also been developed for human research on spatial memory systems in which participants have to find a hidden goal in a circular arena (Fajnerová et al., 2014).

Other forms of cognitive testing adapted for rats assess what they do when there is a change in information in the environment. Children with ASD engage in highly repetitive, inflexible and perseverative behaviors compared to children with attention deficit disorder (ADHD) or typically developing children (Lewis et al., 2007). Children with ASD also show reduced cognitive flexibility in tests requiring set shifting such as the Wisconsin card sort test, or during reversal learning (Archer et al., 1987; Broekkamp et al., 1986; D'Cruz, Mosconi, Ragozzino, Cook, & Sweeney, 2016). In reversal learning, the reward contingencies in a previously learned discrimination are reversed. Therefore, the subject needs to actively withhold the initially trained response and emit a new response to a previously unrewarded stimulus. This requires cognitive flexibility, sometimes referred to as *cognitive control* or *response inhibition*, among others (Gyertyán, 1995). Reversal learning in rats is frequently tested in a T-shaped maze. Rats are first trained select one of the two arms where a food or water reward is available and the training continues until the percent of correct choices reaches a criterion (e.g., 80% correct). The reward is then shifted to the previously non-rewarded arm of the maze. In this situation, the rat must learn to withhold responding to the first arm and learn to respond to the newly rewarded one. Rats readily learn this type of discrimination and reversing to the new arm usually requires fewer trials than the initial learning for the first arm. Reversal learning has been studied in a variety of behavioral paradigms in rats, monkeys and humans, including the use of more complex mazes, operant tasks and touch screens. The underlying neural systems for reversal learning are thought to involve frontostriatal circuitry, as well as dopamine and serotonin innervation of the frontal cortex (Bissonette & Roesch, 2017; Njung'e & Handley, 1991). Furthermore, deficits in reversal learning have been reported in offspring of pregnant rats exposed to the viral mimic poly IC in the rodent maternal immune activation (MIA) model of ASD (Thomas et al., 2009).

For successful translation of findings from animal models to humans, it is essential that the tasks used in animals resemble as closely as possible those used in humans. To a great extent, computer controlled touchscreen systems satisfy this requirement, and have been used for more than 20 years to assess cognitive functions in a variety of species, including rats, humans, and nonhuman primates (Lynch & Green, 1991; Markham, Butt, & Dougher, 1996; Murray, Gaffan, & Mishkin, 1993). In this method, computer-generated graphic stimuli are presented to a rat on a computer touch screen, and the rat learns to touch the appropriate stimulus by nose poke for a food pellet reward (Bussey et al., 2008). The procedures are typically fully automated, use rewards to motivate learning and performance, and support a variety of learning tests, including visual discrimination and reversal learning,

object-location paired-associates learning, visuomotor conditional learning and visual pattern separation (Horner et al., 2013). The high translational potential of this platform resides in its similarity to human CANTAB (Cambridge Neuropsychological Test Automated Battery) tests, and its ability to assess complex neuropsychological constructs including attention, cognitive flexibility, and complex memory functions. The approach has been used to examine attentional deficits in a Shank 3-deficient rat that models the Phelan-McDermid syndrome (PMS). PMS is a relatively common monogenic and highly penetrant cause of ASD and intellectual disability (ID), and frequently presents with attention deficits. Using a touchscreen, treatment with oxytocin was shown to attenuate deficits in attention and visual recognition memory in these Shank 3-deficient rats (Harony-Nicolas et al., 2017).

2.3. Historical use of rodents in research

It may come as a surprise to most researchers of NDDs that the rat used to be the most commonly used rodent for such studies not so long ago. The history of rats used in research has a long and interesting history extending back more than 150 years, with research beginning as early as the 19th Century when investigators interbred rats to study the inheritance of coat colors. Rats then became the focus of early psychological research on the nature of maze learning and intelligence, beginning with the studies of Willard S. Small at Clark University who is credited as the first to use a maze to study rodent learning (Small, 1901). His maze was based on a diagram of a garden hedge maze with an open space and 6 cul-de-sacs at Hampton Court. By the 1940s, the rat had become so heavily used in research —psychological research in particular—that psychologist Frank Beach delivered a provocative Presidential Address at the 1949 meeting of the American Psychological Association in which he warned his peers of the dangers of relying so heavily on a single species. He relayed the Lewis Carrol poem, “The Hunting of the Snark” as an allegory about meeting a dangerous “Boojum” which causes one to disappear, while meeting a “Snark” was safe. This was used as a warning that the rat had become the “Boojum” and was responsible for the looming demise of comparative psychology and the narrowing of research to rats (Beach, 1950).

Approximately 40 years ago, the animal model of choice began to change as the mouse became the premier mammalian model for genetic research, particularly in the area of NDDs (Kazdoba, Leach, & Crawley, 2014). This is due, in part, to the development in the late 1980s of molecular technology for targeted disruption of mouse embryonic stem cells and germline transmission to offspring, which made it possible to create transgenic and knockout mice (Bevan, 2010; Capecchi, 1989; Koller, Marrack, Kappler, & Smithies, 1990; Zijlstra et al., 1990). The innovations in transgenic mice made it possible to model human disorders directly resulting from identified gene mutations, including Fragile X syndrome, Angelman syndrome and Rett Syndrome. It also made it possible to create mouse models to model gene mutations including single nucleotide polymorphisms (SNPs) and copy number variations (CNVs) gene variants in order to determine their possible association with developmental disorders. The increase in the use of mice created a new concern that the mouse is the new “Boojum.” Macri and Richter in “The Snark was a Boojum – reloaded” documented the fact that more than 60% of animals used for research in 2011 in Europe were mice, and although data on mouse use are not available for the United States, they are

almost certain to be similar (Macri & Richter, 2015). In fact, the call for more diversity in the use of animal models in neuroscience research is being heard in the neuroscience community (Yartsev, 2017). These mouse models have provided important information at almost every level of basic biological and biomedical research, but there remains an open question concerning how far they can take the field of ASD research (Hyman, 2014). This situation now has renewed an interest in expanding the use of rats in research as an additional species in order to replicate and validate what has been found in the mouse.

2.4. Current use of rats in NDD research

The laboratory rat has made important contributions to NDD research though prenatal and postnatal toxicology studies with valproate (Dufour-Rainfray et al., 2010; Raza et al., 2015; Schneider & Przewlocki, 2005), fetal alcohol syndrome (Schneider & Popik, 2007), and studies of pervasive environmental toxins including polychlorinated biphenyls (PCBs) and polybrominated diethyl ethers (PBDEs) (Vanderschuren et al., 1997). Advances in gene editing technology in rats and other mammalian species have resulted in the rapid expansion of rat models to explore genetic factors, either causal or contributing, to NNDs including Fragile X syndrome (Hamilton et al., 2014), Rett syndrome (Thor & Holloway, 1984) and ASD (Berg et al., 2018; Burgdorf, Moskal, Brudzynski, & Panksepp, 2013; Zhang-James et al., 2014). These rat models are rapidly being used to explore and development potential therapeutic interventions for ASD (Galvao et al., 2015; Kirsten, Chaves-Kirsten et al., 2015; Kirsten, Queiroz-Hazarbassanov, Bernardi, & Felicio, 2015). In the following section, we highlight contributions of the rat model to specific examples of environmental and genetic risk factors for NDDs.

2.5. Example of NDD: prenatal maternal immune activation

The Maternal Immune Activation (MIA) model of ASD and SZ is a particularly relevant example of ongoing cross-species research on etiology of NDDs. These studies examine brain development and behavior of offspring exposed in utero to maternal immune system activation. The model is based on evidence that maternal infection is associated with an increased risk for ASD and SZ, and findings of altered cytokine profiles and activation of microglia and astrocytes in postmortem brains in ASD (Patterson, 2012). In addition, several studies have found an association between immune system-related genes and ASD (Onore, Careaga, & Ashwood, 2012) and the presence of elevated antibodies to brain proteins in the sera of some mothers of children with ASD (Edmiston, Ashwood, & Van de Water, 2017; Edmiston, Jones, Vu, Ashwood, & Van de Water, 2018). In the MIA model, the immune system is activated by systemic injection of the double-stranded RNA viral mimic polyinosinic:polycytidylic acid (poly IC). Poly IC interacts with toll-like receptor 3 (TLR3) on macrophages, B-cells and dendritic cells and simulates a viral infection. MIA studies were originally carried out in mice where maternal immune system activation was shown to produce offspring that show some of the core deficits in ASD, including reduced social interactions, stereotyped repetitive behaviors and altered brain development (Hsiao, McBride, Chow, Mazmanian, & Patterson, 2012; Patterson, 2012). In an effort to translate these findings across species, the MIA model has now been extended to rats and nonhuman primates.

Studies in rats, recently reviewed by Careaga, Murai, and Bauman 2017), reported abnormal behaviors in MIA-exposed offspring in a variety of tests, including altered reversal learning (both slowed and enhanced), increased motor stereotypies, and changes in ultrasonic vocalization. The larger brain of the rat has also allowed for longitudinal structural MRI studies, which has shown decreased brain volume in several cortical regions, as well as the hippocampus, amygdala, striatum, nucleus accumbens and increased volumes in the thalamus, ventral mesencephalon and major white-matter tracts (Crum et al., 2017). Studies of ultrasonic vocalization in rat offspring of MIA rats show an increase in aversive 22-kHz ultrasonic vocalizations. This change in affective signaling suggests that MIA may have persisting effects on communication and emotional behavior in exposed rat offspring (Yee, Schwarting, Fuchs, & Wohr, 2012). Recent studies in rats have also found changes in hippocampal neuron excitability in MIA offspring (Patrich, Piontkewitz, Peretz, Weiner, & Attali, 2016). Additionally, late gestation MIA exposure (i.e., gestational day 19) results in impairments in working memory, sensory motor gating deficits, and altered glutamatergic and dopaminergic signaling in the cortex, hippocampus and striatum (Meehan et al., 2017; Rahman et al., 2017). These studies in rats have not only replicated much of what has been reported in the mouse MIA model, but extend the results to changes in the trajectory of brain development and alterations in neurotransmitter signaling pathways, and ultimately to maximized translational comparisons with nonhuman primate MIA models.

2.6. Example of NDD: Fragile X

One of the first neurodevelopmental disorders for which rat knockouts (KOs) were developed was the genetic disorder Fragile X syndrome (FXS). Mouse models for this disorder were developed more than 20 years ago by the Dutch-Belgium Consortium due to the relative ease of modifying the genome in the mouse (“Fmr1 knockout mice: a model to study fragile X mental retardation. The Dutch-Belgian Fragile X Consortium,” 1994). Research with this mouse model has provided important insights into the molecular, cellular, and behavioral pathology of FXS, and while there have been some recent successes (Kazdoba, Leach, Silverman, & Crawley, 2014), the translation of these findings to treatments for FXS has been challenging (Berry-Kravis et al., 2018). As a result, additional mammalian models have been developed for studying such disorders. The first rat KOs relevant to neurodevelopment disorders included FXS and neuroligin 3 (Nlgn3) knockouts. These mutant rats were created in the Sprague-Dawley breed by SAGE laboratories using zinc-finger nuclease (ZFN) technology. The ZNF targeting strategy deleted 122 base pairs (bp) across the junction of intron 7 and exon 8 of the *Fmr1* gene resulting in a loss of FMRP, with 58 bp’s deleted at the junction of exon 5 and intron 5 for the Nlgn3 KO. The first behavioral characterization of these two rat models was carried out by the Paylor laboratory (Hamilton et al., 2014). They examined a number of ASD relevant behaviors in these rats by measuring behavior in the three-chamber social approach task, dyadic social interactions, prepulse inhibition and a “wood block chewing” test of repetitive behavior. The results demonstrated that the *Fmr1* KO and Nlgn3 KO rats showed several neurobehavioral features relevant to ASD, including significantly fewer play events in the social interaction test. Play behavior is a type of social interaction that is clearly relevant to ASD; while rats show robust and complex play behaviors (Ku et al., 2016), those in mice are much more limited and less complex. In addition, *Fmr1* KO’s showed increased perseverative wood-block chewing

behaviors, while Nlgn3 KO's showed less of these repetitive behaviors. However, neither *Fmr1* nor *Nlgn3* KO's showed abnormal social approach behavior, changes in anxiety, learning deficits, acoustic startle differences, or abnormal grooming or rearing, so that the behavioral phenotype of the rat with respect to modeling Fragile X symptoms was relatively modest. However, the ability to assess complex play behaviors in the rat at a level beyond that achieved in the mouse demonstrated the added utility of developing these additional rodent models.

More recent studies have taken advantage of the rat's larger brain and complex cognitive abilities to expand what is known about FXS. For example, the neural mechanisms used to process speech have been studied in rats. Electrophysiological findings indicate that the rat auditory system responds differently to English consonants versus vowel sounds, and their behavioral and neural response thresholds for degraded speech shows parallels with human thresholds (Engineer, Centanni, Im, & Kilgard, 2014). In this study, rats were trained to discriminate specific words from similar non-target words in a food-rewarded lever press operant task. Multiunit local field potentials were then recorded from auditory cortex in anesthetized rats. Researchers found normal discrimination of simple speech sounds in Fragile X KO rats, but reduced firing rates of neurons to speech sounds in the primary auditory cortex. The Fragile X KO rats were generally impaired in temporal and spectral processing of sound, similar to children with FXS who show impaired sensory-motor gating in prepulse inhibition (Frankland et al., 2004). The Fragile X mental retardation protein (Fmrp) is widely expressed in auditory brainstem neurons. In Fragile X KO rats, collections of neurons in the brainstem, such as the superior olivary complex and medial superior olive, showed abnormal morphology and there was also a reduction in molecular markers for GABAergic transmission in the brainstem (Ruby, Falvey, & Kulesza, 2015). These results suggest that the auditory processing deficits in FSX may be due to defective auditory brainstem and cortical networks.

The phenotype of the rat KO model of FXS not only parallels much of the symptomatology of FXS, but closely mirrors what has been reported in the mouse Fragile X knockout. Till et al. (2015) demonstrated that the rat *Fmr1* KO showed an absence of FMRP, as required by the model, as well as enhanced protein synthesis, increased spine density on CA1 pyramidal neurons in the hippocampus, and impaired learning and memory (Till et al., 2015). While mouse models have also reported impaired learning, this study in rats found that cognitive deficits were for hippocampal-dependent, but not hippocampal-independent, episodic memory. Specifically, the memory deficit affected associative binding of context and place, for there were no deficits in spatial reference memory, spatial reversal learning, delayed context, or place learning. The deficit was only evident when rats were required to remember both context and place. These results reveal novel aspects of the effects that *Fmr1* loss has on memory and learning in FXS.

Children with FXS show abnormal attention abilities that have been linked to their inability to modulate brain arousal states (Cornish, Scerif, & Karmiloff-Smith, 2007), and several studies have found attention deficits in *Fmr1* mutant mice (Kramvis, Mansvelder, Loos, & Meredith, 2013). Recent studies in the rat FXS KO model have been able to directly assess change in brain arousal states using combined depth EEG, recordings of multi-unit activity

(MUA) and recordings of singleneuron spike activity (Berzhanskaya et al., 2017). The results demonstrate that FXS KO rats are unable to modulate EEG electrical activity in the visual cortex between movement and quiet wakefulness compared to wild type rats, and appear to remain in the activated electrical state whether in quiet wakefulness or movement-dependent state. Considered together, these findings suggest that disrupted inhibitory connectivity in the visual cortex impairs the ability to modulate exit from an activated state appropriate to current behavioral state; this may contribute to the deficits in attention and sensory processing seen in children with FXS.

3. Nonhuman primate models

3.1. Features of the species

In comparison with research using rodents, nonhuman primate research accounts for a very small percentage of research and procedures in the United States (APHIS, 2016). The vast majority of nonhuman primate research is performed in macaque species (Lankau, Turner, Mullan, & Galland, 2014), so our discussion of nonhuman primates will be centered on the rhesus macaque. It is important to note that there are other nonhuman primate species used in research, including squirrel monkeys (*Saimiri sciureus*) (Lyons, Parker, & Schatzberg, 2010; O'Shea et al., 2018), titi monkeys (*Callicebus cupreus*) (Bales et al., 2017; Mason & Mendoza, 1998) and a growing interest in the common marmoset (*Callithrix jacchus*) as model organisms to study the neurobiology of NDDs. Transgenic common marmosets have been created (Park et al., 2016) and, although less-studied than rhesus macaques, the monogamous social group structure seen in common marmosets (Miller et al., 2016) and titi monkeys (Bales et al., 2017) may make them more favorable models for prosocial human social behavior.

While mouse and rat models will continue to serve as important animal models in preclinical research, there are limitations in relying on these species to study complex and uniquely human brain disorders. Rodents shared their last common ancestor with humans more than 70 million years ago (Gibbs et al., 2004), whereas rhesus macaques diverged from human evolution around 25 million years ago (Kumar & Hedges, 1998), resulting in more similar genetics, neurobiology, and behavior. Because of these similarities, we are able to test hypotheses about NDDs from molecular mechanisms through complex behavior with assays that correspond more closely to behavior or neurobiology observed in humans than is possible in studies using rodent models.

Like humans, rhesus macaques are generally diurnal, omnivorous, and highly social, for they live in complex social groups consisting of multiple males and females. Both species also have long gestations, give birth usually to one offspring at a time, and have an extended period of maternal care (Phillips et al., 2014), although macaques mature approximately four times faster than humans. Macaque social signals reflect that they use vision as their primary sensory modality, which is similar to humans and not similar to rodents that rely on olfaction (Ross, 2000). In order to navigate their social world, macaques must rapidly process social information from a variety of signals such as facial expressions, gestures, and vocalizations (Chang et al., 2013). Infant macaques must then learn these social signals (Weinstein & Capitanio, 2012; Weinstein, Bales, Maninger, Hostetler, & Capitanio, 2014); studying this

social development could contribute to our understanding of development in the context of social deficits observed in NDDs.

There are also aspects of the rhesus macaque brain that more closely mirror aspects of the human brain than is observed in rodent ones. For example, the prefrontal cortex expanded considerably during primate evolution and is considered one of the key regions for regulating social cognition in primates (Amodio & Frith, 2006; Smaers et al., 2011). Researchers question whether rodents have a homologous prefrontal cortex region because there are cytoarchectonic regions identifiable in human and nonhuman primate brains that are not present in rodents (Bicks, Koike, Akbarian, & Morishita, 2015; Geschwind & Rakic, 2013; Preuss, 1995). Secondly, for the amygdala, a brain region implicated in NDDs such as ASD, nuclei distribution is different in the rodent amygdala (Chareyron, Banta Lavenex, Amaral, & Lavenex, 2011) but is nearly identical between human and nonhuman primates (Rutishauser, Mamelak, & Adolphs, 2015; Schumann, Vargas, & Lee, 2016). Finally, there are areas of the brain that are important for advanced social cognition such as Von Economo neurons and the fusiform gyrus that are found in nonhuman primates but are not present or are poorly developed in rodents (Cook, Bird, Catmur, Press, & Heyes, 2014; Weiner & Zilles, 2016).

The increased similarly between nonhuman primates and humans can provide a bridge from rodent models to patient populations. However, the greater physical, psychological, and social needs of nonhuman primates when housed in captivity also elicit greater ethical considerations for their participation in research and increase the cost for their care. Ultimately, the increased cost and ethical factors, along with the longer life history and development, can constrain the use of nonhuman primates in research. While studies using nonhuman primates need to be carefully considered, we provide examples below of ways in which nonhuman primate models provide particular advantages and can be used to improve translation of preclinical research efforts for NDDs.

3.2. Nonhuman primate behavioral assays

(i) Anxiety—In monkeys, the Human Intruder Test (HIT) is a paradigm initially developed by Kalin and Shelton (1989) and is used to elicit a range of responses between monkeys to an unknown human. The HIT was modeled after assessments for human infants such as Ainsworth Strange Situation procedure (Ainsworth & Bell, 1970), in which an infant encounters a stranger in an unfamiliar room. In the HIT, an unfamiliar human approaches a monkey housed by itself in a cage and stands still in front of the cage in two positions: profile, in which the intruder's profile is oriented towards the cage, and stare, in which the intruder is frontally oriented towards the cage and maintains eye contact with the monkey. While these two phases of the test are consistent, there is variation in how the HIT is otherwise conducted. Sometimes the test monkey is removed from its home environment and placed in an unfamiliar room as originally performed by Kalin and Shelton (1989) but not always (Capitanio, 1999; Coleman et al., 2017). Sometimes, additional phases are added, such as a baseline phase with the monkey alone prior to the entrance of the intruder (Coleman et al., 2017; Corcoran et al., 2012; Kalin & Shelton, 1989; Kalin, Larson, Shelton,

& Davidson, 1998) or an additional phase where the intruder has his or her back facing the monkey (Coleman et al., 2017; Hamel et al., 2017; Peterson et al., 2017).

In the presence of the human intruder, the adaptive response that monkeys tend to display is to remain motionless or freeze when the intruder is in the profile phase, possibly to avoid detection, and then display threatening or defensive behavior when the intruder sustains eye contact with the monkey in the stare phase (Kalin & Shelton, 1989, 1998; Peterson et al., 2017). There is variation in the frequency or duration of these responses between monkeys, and repeated testing of monkeys demonstrated that behavioral responses tend to be stable between sessions (Hamel et al., 2017; Kalin & Shelton, 1989, 1998). Furthermore, monkeys that displayed more freezing (Kalin et al., 1998), negative emotional behaviors (Capitanio, Mendoza, & Cole, 2011) and more threatening behaviors (Hamel et al., 2017) had higher plasma (Capitanio et al., 2011; Kalin et al., 1998) and hair (Hamel et al., 2017) cortisol concentrations than monkeys that displayed fewer of these behaviors.

(ii) Repetitive Behaviors—Repetitive behaviors in nonhuman primates present in a similar way as they do in humans. First of all, there is a range in severity for stereotypies performed from mild stereotypies to severe ones in which the animal cannot be interrupted while performing the behavior (Novak, Kelly, Bayne, & Meyer, 2012). Secondly, the immediate trigger for the performance of these behaviors for an individual animal is usually unclear. Finally, once these behaviors are incorporated into the repertoire, they can become intractable with no clear treatments to mitigate their frequency or severity. With respect to studying repetitive behaviors in nonhuman primates, there is no standardized ethogram for the categorization of repetitive behaviors. However, they are generally considered whole body or motor behaviors (pacing, swinging, rocking), or self-directed (hair-pulling, eye-poking), which typically involves the hand or mouth to perform the behavior (Gottlieb, Capitanio, & McCowan, 2013; Lutz, Well, & Novak, 2003). An individual monkey may incorporate multiple forms of repetitive behavior into their repertoire and never perform other forms of repetitive behaviors. As opposed to research with rodents, there is no established behavioral assay like marble-burying to screen for or assess the frequency of repetitive behaviors in nonhuman primates. Researchers instead quantify repetitive behaviors performed either in naturalistic scenarios such as the animal's home cage or during experimental manipulations such as the Human Intruder Test (see above). While restricted interests are associated with repetitive behaviors in the symptomology of ASD (DSM-V), there is currently no assay to specifically screen for or test the degree of restricted interests in nonhuman primates. However, there are tests for cognitive flexibility (see below) which may capture the perseverative aspect of restricted interests in nonhuman primates.

(iii) Social behaviors—Because of their rich social behavior repertoire and similar emphasis on facial expressions in social interactions, nonhuman primate models show promise for contributing to our understanding of the neural mechanisms behind social behavior. Most research on nonhuman primate social behavior is performed through direct observation of monkeys freely interacting in their naturalistic setting such as their home cages (Bauer & Baker, 2016; Bauman, Lavenex, Mason, Capitanio, & Amaral, 2004b; Harlow, Dodsworth, & Harlow, 1965; McCormack, Sanchez, Bardi, & Maestripieri, 2006;

Winslow, Noble, Lyons, Sterk, & Insel, 2003). However, social behavior in these free interactions is sensitive to such factors as rank differences between individuals and history of previous interactions, so these interactions may not be the best way to quantify an animal's sociability especially with respect to understanding potential social deficits. Our research team has developed social battery testing in rhesus macaques that is adapted from rodent models that use social chambers. In our two-chambered social approach task, we can quantify whether the test macaque approaches or spends time with a novel conspecific verses an alternate chamber with no animal present (Bauman et al., 2014; Bauman, Bliss-Moreau, Machado, & Amaral, 2011; Bauman, Lavenex, Mason, Capitanio, & Amaral, 2004a; Bliss-Moreau, Moadab, Bauman, & Amaral, 2013; Machado, Whitaker, Smith, Patterson, & Bauman, 2015). Experimental test batteries for alterations in social behavior in rhesus macaques have also been developed to assess social preference for caretakers versus other familiar humans (Goursand & Bachevalier, 2007; Goursand, Wallen, & Bachevalier, 2014).

In addition to these social behavior measures, there are promising developments in the use of eye-tracking in nonhuman primates to investigate social attention and face processing. Eye-tracking entails using technology to measure eye gaze and what stimuli are the focus of visual attention. In humans, researchers have found characteristic aberrant patterns in people with ASD (Frazier et al., 2017; Papagiannopoulou, Chitty, Hermens, Hickie, & Lagopoulos, 2014) with respect to visual attention for social stimuli. Adaptation of human eye-tracking paradigms for use in nonhuman primates can contribute to our understanding of the neurobiology of social attention and processing. In eyetracking paradigms, macaques can process two-dimensional face stimuli as faces (Sliwa, Duhamel, Pascalis, & Wirth, 2011) and, like humans, focus more on the eye region than other parts of the face (Dahl, Wallraven, Bülthoff, & Logothetis, 2009; Gothard, Erickson, & Amaral, 2004). Eye-tracking studies in rhesus macaque infants can further contribute to our understanding of how this preference develops in primates (Paukner, Bower, Simpson, & Suomi, 2013; Paukner, Simpson, Ferrari, Mrozek, & Suomi, 2014; Simpson, Jakobsen, et al., 2017; Simpson, Miller, Ferrari, Suomi, & Paukner, 2016; Zhang, Noble, Winslow, Pine, & Nelson, 2012). For example, three-week-old macaques already look longer at faces than non-face stimuli (Simpson, Jakobsen, et al., 2017) and look more at normal versus atypical linearly arranged faces (Paukner et al., 2013). One-week-old macaque infants who imitated facial gestures also viewed neutral macaque faces more in an eye-tracking paradigm at 10–28 days old than those who did not imitate, suggesting that there may be differences in social attention biases between monkeys at a young age (Paukner et al., 2014). In this respect, the use of eye-tracking in nonhuman primates as a model for social attention and processing has the potential to contribute to both preventative and therapeutic interventions in patient populations for ASD and potentially other NDDs.

(iv) Cognition—Because nonhuman primates more closely resemble human behavior, development, and rely on vision as the primary sensory modality, there is a strong translational potential for using similar cognitive test batteries in both human and nonhuman primates. Most cognitive assessments in monkeys use methods that can be also used in humans. For example, the Wisconsin General Testing Apparatus (WGTA) (Harlow, 1945) is

a three-dimensional apparatus that remains one of the most widely utilized approaches to test cognitive function and flexibility in monkeys and also has a long history of use to test cognitive functioning in children (Overman, Pierce, Watterson, & Coleman, 2013; Vaughter & Cross, 1965). More recently, the development of computerized touchscreen devices has made it possible to test more complex questions in cognitive assessments. Originally developed for testing patients with neurodegenerative diseases (Sahakian et al., 1988) CANTAB has since been utilized for studies with nonhuman primates (Weed et al., 1999), and more wide-ranging populations of adults (Robbins et al., 1998) and children (Luciana, 2003; Syväoja, Tammelin, Ahonen, Kankaanpää, & Kantomaa, 2014). CANTAB software tests multiple aspects of visual attention, memory, and executive function. As many as 19 tests are currently available (www.cambridgecognition.com).

Another form of testing that has been developed for both human and nonhuman primates is prepotent response inhibition, in which the primate is tasked with inhibiting a dominant motor response during a cognitive task. For the anti-saccade task, a participant typically stares at a screen and then when a stimulus is presented on one side of the screen, is instructed to suppress the tendency to look at the stimulus and instead look or saccade to the opposing side of the screen (Hallett, 1978). In humans and macaques, this task has been determined to be affected by the prefrontal cortex (humans: Fukushima, Fukushima, Miyasaka, & Yamashita, 1994; macaques: Funahashi, Chafee, & Goldman-Rakic, 1993; Hussein, Johnston, Belbeck, Lomber, & Everling, 2014). There is potential for this task to be used in translational animal model studies, for there are differences in performance in the anti-saccade task between people in a control group from those diagnosed with a number of disorders, from SZ, ADHD, and Alzheimer disorders (Everling & Fischer, 1998; Munoz & Everling, 2004).

The most relevant forms of cognitive testing with respect to NDDs are for learning and memory as well as flexibility. In monkeys, visual discrimination entails learning to identify one stimulus as correct and others as incorrect and is a learning paradigm most commonly used as an initial training step before more complex assessments (Buckley & Gaffan, 1998; Friedman & Selemon, 2010; Griffin & Harlow, 1966). For memory, the more complex assessment is commonly a delayed nonmatch to sample (DNMS) task (Golub, Hogrefe, & Germann, 2007; Kelly et al., 2014; Sanchez, Hearn, Do, Rilling, & Herndon, 1998). For this task, the monkey must keep the previous stimulus in its working memory during the delay in order to select the novel stimulus as the correct choice. It is generally assumed that monkeys attend to novel stimuli more than familiar ones, so while delayed match to sample is also a possible test, they will select the new stimulus more quickly.

For flexibility, the most straightforward assessment is a reversal learning task, in which one tests in how many trials it takes for a monkey to switch from selecting a previously rewarded but no longer rewarded stimulus to a newly rewarded stimulus (Mahut & Cordeau, 1963; Makori, Watson, Hogrefe, Lalayeva, & Oneda, 2013; Wright, Vandewater, Parsons, & Taffe, 2013). Using CANTAB, researchers are beginning to use more complicated stimuli to test flexibility in monkeys such as in the intradimensional/extradimensional set-shifting task (ID/ED). In this task, stimuli can be more complicated with multiple dimensions, such as lines superimposed on shapes, and monkeys must learn during intra and extra dimensional shifts

whether the shape (intra) or line (extra) are relevant for reinforcement (Crean, Vandewater, Katner, Huitron-Resendiz, & Taffe, 2011; Golub et al., 2017; Weed et al., 1999).

3.3. Historical use of nonhuman primates in NDD research

In 1916, Robert Yerkes described the untapped potential for studying nonhuman primate physiology and behavior (Yerkes, 1916). In subsequent comparative psychology research in the mid-20th Century, researchers used nonhuman primates to probe questions about environmental effects on development under the nature vs. nurture paradigm. Harry Harlow's work with infant rhesus macaques demonstrated the pervasive effects of the early social environment on emotional development and behavioral outcomes. When separated from their mother shortly after birth, infant macaques displayed profound behavioral deficits when they encountered strange situations or interacted with other monkeys (Harlow et al., 1965). More recent experimental paradigms have advanced this research and demonstrated that less extreme forms of stressful environments, such as separation from the mother but contact with peers, can also adversely affect development, such as through the development of abnormal and self-injurious behaviors (Bauer & Baker, 2016; Bellanca & Crockett, 2002; Champoux, Metz, & Suomi, 1991; Conti et al., 2012; Gottlieb et al., 2013; Lutz et al., 2003; Rommeck, Gottlieb, Strand, & McCowan, 2009; Winslow et al., 2003). Social behavior development was also affected, for when housed together, maternally reared macaques consistently achieved higher social rank than macaques reared without their mothers (Bastian, Sponberg, Suomi, & Higley, 2003; Dettmer et al., 2017), suggesting that macaques raised without a mother may have displayed species-inappropriate levels of affiliative or agonistic behavior.

The studies described above were not specifically designed as models of NDDs, but did provide novel insight into environmental influences on behavioral development. Early attempts to develop nonhuman primate models of NDDs utilized a neural-systems approach to evaluate the role of specific brain structures, such as the amygdala, which had been implicated in ASD pathophysiology (Baron-Cohen et al., 2000; Bauman, 1991). Early studies by Bachevalier described impairments in social development in peer-reared rhesus monkeys that sustained bilateral damage to the amygdala and surrounding cortex early in development (Bachevalier, 1994). However, subsequent studies of rhesus monkeys with more selective amygdala lesions that were raised in an enriched social environment failed to replicate these early social deficits (Bauman et al., 2004a, 2004b; Prather et al., 2001). Although amygdala lesion research has provided valuable insight into the role of the amygdala in socioemotional development (Bliss-Moreau et al., 2013; Bliss-Moreau, Bauman, & Amaral, 2011; Bliss-Moreau, Moadab, Santistevan, & Amaral, 2017; Bliss-Moreau, Toscano, Bauman, Mason, & Amaral, 2010, 2011; Moadab, Bliss-Moreau, & Amaral, 2015; Moadab, Bliss-Moreau, Bauman, & Amaral, 2017; Raper et al., 2013; Raper, Stephens, Sanchez, Bachevalier, & Wallen, 2014), the low construct and face validity of the neonatal amygdala lesion model would argue against this approach as a valid animal model to study NDDs.

3.4. Current use of nonhuman primates in NDD research

Research using nonhuman primate models has contributed to our understanding of NDDs with respect to both etiology and potential treatments. Nonhuman primates can be used both to understand how factors affect a brain more similar to our own, but also, we can conduct more naturalistic studies of social development and further probe how potential gene-by-environment interactions contribute to the development of NDDs. First of all, results of research using nonhuman primates supported human epidemiology studies that there is no association between components in vaccines or the schedule of vaccinations and deficits in neurodevelopment ultimately leading to ASD (Taylor, Swerdfeger, & Eslick, 2014). There were no behavioral differences between male macaques that received either thimerosal-containing vaccines or the 2008 expanded pediatric vaccine schedule and macaques that received no vaccinations (Curtis et al., 2015) and no evidence of neuropathology (Gadad et al., 2015). Secondly, recent advances in genetic modification tools provide opportunities to explore genetic risk factors in species more related to humans than rats and mice (Chen, Niu, & Ji, 2016; Jennings et al., 2016; Qiu & Li, 2017). Transgenic longtailed macaques (*Macaca fascicularis*) that expressed extra copies of *MECP2*, a gene linked to ASD symptoms in humans (Ramocki et al., 2009), displayed aberrant behaviors that may be relevant to ASD (Liu et al., 2016). Although these macaques did not display all of the behavioral phenotypes of MECP-2 duplication symptoms such as seizures, improvements in gene editing technology such as CRISPR demonstrate the potential for transgenic nonhuman primates to bridge the gap between ASD relevant mouse and rat models especially by contributing to current gene-by-environment interaction studies (Kinnally et al., 2010; Kinnally, Lyons, Abel, Mendoza, & Capitanio, 2008).

Research with nonhuman primates has also served to elucidate potential mechanisms behind promising treatments identified in ASD patient populations, including the oxytocin (OT) system (Green & Hollander, 2010; Modi & Young, 2012). Although the data emerging from ASD treatment studies are compelling, many questions remain regarding the therapeutic potential of OT treatment in humans (Bethlehem, van Honk, Auyeung, & Baron-Cohen, 2012; Churchland & Winkielman, 2012; Evans, Dal Monte, Noble, & Averbeck, 2014). Studies using rhesus macaques have demonstrated that inhaled oxytocin penetrates the central nervous system (CNS) (Dal Monte, Noble, Turchi, Cummins, & Averbeck, 2014), enhances social behavior and attention (Chang, Barter, Ebitz, Watson, & Platt, 2012; Dal Monte et al., 2014; Parr, 2014; Parr, Modi, Siebert, & Young, 2013; Putnam, Roman, Zimmerman, & Gothard, 2016; Simpson, Paukner, et al., 2017), and attenuates social vigilance (Chang & Platt, 2013; Ebitz, Watson, & Platt, 2013), though chronic administration of OT may reduce social attention over time in a dose dependent manner (Parr et al., 2016). More research is needed on how intranasal OT can be applied therapeutically to improve social behavior deficits, and nonhuman primate models for complex social behavior can be particularly useful for evaluating intranasal OT as a potential ASD-relevant pharmacological intervention.

Recent progress in identifying potential causes of NDDs has led to increasingly targeted and translational preclinical research efforts, of which nonhuman primate models have served to bridge the gap between rodent models and NDD patient populations (Watson & Platt, 2012).

In the following section, we highlight a series of epidemiologically informed models designed to directly evaluate prenatal immune-based risk factors initially identified through studies in patient populations.

3.5. Example of NDD: maternal-fetal immune risk factors

Recent evidence suggests that the prenatal environment—particularly, maternal fetal immune environment—may be a promising area of neurodevelopmental disorder etiology research (Estes & McAllister, 2016; Fox-Edmiston & Van de Water, 2015; Patterson, 2011). Experiences that alter the maternal-fetal immune environment may disrupt the finely orchestrated events of neural development, thereby increasing the risk of offspring CNS disorders (Estes & McAllister, 2016; Knuesel et al., 2014; Meltzer & Van de Water, 2017). Nonhuman primates may prove particularly relevant to evaluating immune-based prenatal risk factors given the similarities between nonhuman primates and humans in gestational and neurodevelopmental timeline, immune systems, and placental physiology. Below we describe two prenatal immune-based risk factors implicated in ASD: (i) maternal autoantibodies that target fetal brain tissue and (ii) prenatal exposure to immune challenges that activate the maternal immune system.

(i) Maternal autoantibodies associated with ASD - During mid-late gestation, immunoglobulin G (IgG) isotype antibodies from the mother are transported across the placenta in order to equip the immunologically naive fetus with protection (Kuo et al., 2010). However, in addition to immunoprotective antibodies, autoantibodies that react to fetal ‘self’-proteins can also cross the placenta. A subset of mothers who have a child with ASD produce IgG antibodies targeting fetal brain proteins (for reviews, Braunschweig & Van de Water, 2012; Fox-Edmiston & Van de Water, 2015). Specific combinations of these anti-brain antibodies targeting proteins at 37 and 73 kDa have only been found in mothers who have a child with ASD and not in mothers of typically developing children. The recently identified protein targets of these antibodies play critical roles in neural development, supporting the hypothesis that prenatal exposure to anti-brain autoantibodies can disrupt the trajectory of brain development and ultimately lead to one form of ASD (Braunschweig et al., 2013).

As maternal autoantibodies become increasingly implicated in ASD, it has become imperative to utilize animal models to evaluate causative effects between prenatal exposure to anti-brain antibodies and altered neurodevelopment. Rodent model systems have revealed changes in brain and behavioral development following prenatal exposure to ASD-associated antibodies (Camacho et al., 2014; Martinez-Cerdeno et al., 2016). A pilot study of rhesus macaques prenatally exposed to nonspecific ASD-associated maternal antibodies produced offspring that exhibited high levels of motor stereotypies (Martin et al., 2008). A subsequent nonhuman primate model that utilized ASD-specific maternal antibodies found only mothers of human children with ASD yielded offspring with social impairments, including increased protectiveness from their mothers, inappropriate social approach with a novel animal and deficits in reciprocal social interactions with familiar peers (Bauman et al., 2013). Male monkeys exposed to these ASD-specific autoantibodies also demonstrate enlarged brain volumes that parallel features of children exposed to the same maternal

antibodies in utero (Nordahl et al., 2013). Similar to children with ASD, differences in brain volume in male monkeys exposed to ASD-specific autoantibodies are predominantly accounted for by increases in frontal lobe volume. The convergence of findings between the animal models and clinical populations highlights the translational potential of using a cross-species approach that capitalizes on the strengths of both rodent and nonhuman primate model systems.

(ii) Prenatal immune challenge models - Other prenatal challenges, such as maternal infection during pregnancy, have also been associated with an increased risk of neurodevelopmental disorders, including ASD and SZ (Brown & Derkits, 2010; Brown, 2012; Meyer, Feldon, & Dammann, 2011). Clearly not all women exposed to infections during pregnancy go on to have a child with altered neurodevelopment, suggesting that genetic susceptibility, gestational timing, and intensity of the prenatal challenge are critical factors to consider. Animal models are playing a key role in determining the mechanisms by which prenatal infection may alter fetal brain development. Initial nonhuman primate studies by Coe and colleagues evaluated the effects of prenatal exposure to viral or bacterial infections on subsequent brain and behavioral development of the offspring (Short et al., 2010; Willette et al., 2011). Rhesus macaques born to dams exposed to low dose endotoxemia in the third trimester exhibited subtle alterations in behavior and failed to show species-typical attenuation of startle responses on tests of prepulse inhibition (Willette et al., 2011). At 1 year of age, the exposed offspring exhibited a global increase in white matter volume paired with region-specific alterations in gray matter compared to controls. In a similar study, rhesus macaques born to dams infected with influenza in the third trimester did not differ from controls on measures of behavioral development, but did exhibit global reductions of cortical gray matter and reduced white matter in the parietal lobe (Short et al., 2010).

The diversity of infections associated with alterations in neurodevelopment suggests that the maternal immune response may be the critical link between prenatal exposure to infection and subsequent alterations in fetal brain development. The emerging maternal immune activation (MIA) hypothesis has been directly tested in animal models by artificially activating the immune system of pregnant rodents with the viral mimic, poly IC. Rodent pups born to dams treated with poly IC at mid-gestation demonstrate behavioral abnormalities, neuropathology, and altered gene expression relevant to both ASD and SZ (reviewed in: Boksa, 2010; Meyer & Feldon, 2012; Meyer, Feldon, & Fatemi, 2009; Patterson, 2009).

Our laboratory adapted this approach to develop the first MIA nonhuman primate model by using a modified form of poly IC to stimulate the primate maternal immune response. Pregnant rhesus macaques injected with poly IC at the end of either the first or second trimester produced offspring with abnormal motor stereotypies and repetitive behaviors (Bauman et al., 2014). While both first and second trimester MIA offspring produced fewer affiliative vocalizations than controls, only the first trimester MIA offspring showed signs of atypical social interactions with unfamiliar peers. Given that neurodevelopmental disorders, including ASD and SZ, are characterized by changes in social cognition and emotion, as well as altered visual attention devoted to facial expressions, we then initiated a series of

noninvasive eye-tracking studies to provide further insight into the nature of the social impairments observed in the MIA offspring. As juveniles, male rhesus macaques born to first trimester MIA-treated dams differed from controls on several measures of social attention, particularly when viewing macaque faces depicting the “fear grimace” facial expression (Machado et al., 2015). Compared to controls, these MIA offspring had a longer latency before fixating on the eyes, fewer fixations directed at the eyes, and spent less total time fixating on the eyes of the fear grimace faces. The lack of attention to the eye region exhibited by offspring of MIA-treated animals represents a significant departure from social processing in normal macaques and typically developing humans (Leonard, Blumenthal, Gothard, & Hoffman, 2012) and parallels findings of both ASD and SZ clinical populations (King & Lord, 2011). Collectively, the changes in brain, behavior and immune function observed in the nonhuman primate MIA model lends support to the hypothesis that prenatal infection acts as a “neurodevelopmental disease primer” that is possibly relevant to a number of neurodevelopmental disorders (Meyer, 2014), including ASD (Careaga et al., 2017).

4. Conclusion

As our understanding of NDDs improves through studies in patient populations, so does our ability to develop more precise preclinical models to evaluate potential etiologies, identify underlying pathophysiology, and ultimately create novel therapeutic and preventative strategies. Mice have become the favored species for biomedical research in part because of their wider possibilities for genetic manipulations as well as their lower financial and ethical considerations in comparison to other mammalian species. However, the complex nature of NDDs especially with respect to understanding causes and seeking treatments for deficits in prosocial behavior as seen in ASD may make it necessary to assess validity in other species that have a behavioral repertoire that more closely mirrors human behavior. The renewed interest in the laboratory rat as a model system to study complex NDDs provides a powerful translational tool. Although rodent models will continue to be the logical starting point for these preclinical research efforts, we suggest that it may ultimately be necessary to use a species that is more closely related to humans, such as the rhesus macaque. In order to move the assessment of validity in these models forward, we advocate for more coordinated research efforts between laboratories that utilize rat and nonhuman primate models to advance mechanistic understanding and evaluate the efficacy of biological treatments for NDDs.

Acknowledgments

M.D.B and R.F.B. receive support related to this manuscript from the MIND Institute Intellectual and Developmental Disabilities Research Center (U54 HD079125). A.M.R. receives support from the UC Davis Autism Research Training Program (T32MH073124). The authors would like to thank Anurupa Kar, Allison Lau and Lauren Pedersen for assistance with manuscript and figure preparation.

References

Abbott A (2016). US mental-health chief: Psychiatry must get serious about mathematics. Nature News, 539(7627), 18.

Ainsworth MD, & Bell SM (1970). Attachment, exploration, and separation: Illustrated by the behavior of one-year-olds in a strange situation. Child Development, 41(1), 49–67. [PubMed: 5490680]

American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders: DSM-5 (5th ed.). Arlington, Virginia: American Psychiatric Association.

Amodio DM, & Frith CD (2006). Meeting of minds: The medial frontal cortex and social cognition. Nature Reviews Neuroscience, 7(4), 268–277. [PubMed: 16552413]

Animal and Plant Health Inspection Service (APHIS) (2016). Annual Report Animal Usage by Fiscal Year. Riverdale, MD Retrieved from < https://www.aphis.usda.gov/animal_welfare/downloads/reports/Annual-Report-Animal-Usage-by-FY2016.pdf > .

Archer T, Fredriksson A, Lewander T, & Soderberg U (1987). Marble burying and spontaneous motor activity in mice: Interactions over days and the effect of diazepam. Scandinavian Journal of Psychology, 28(3), 242–249. [PubMed: 3441771]

Bachevalier J (1994). Medial temporal lope structures and autism - A review of clinical and experimental findings. Neuropsychologia, 32(6), 627–648. [PubMed: 8084420]

Bales KL, del Razo RA, Conklin QA, Hartman S, Mayer HS, Rogers FD, ... Witczak LR (2017). Focus: Comparative medicine: Titi monkeys as a novel nonhuman primate model for the neurobiology of pair bonding. The Yale Journal of Biology and Medicine, 90(3), 373–387. [PubMed: 28955178]

Barnett SA (1963). The laboratory rat: A study in behavior. Chicago: Aldine Publishing Company.

Baron-Cohen S, Ring HA, Bullmore ET, Wheelwright S, Ashwin C, & Williams SC (2000). The amygdala theory of autism. Neuroscience & Biobehavioral Reviews, 24(3), 355–364. [PubMed: 10781695]

Bastian ML, Sponberg AC, Suomi SJ, & Higley JD (2003). Long-term effects of infant rearing condition on the acquisition of dominance rank in juvenile and adult rhesus macaques (*Macaca mulatta*). Developmental Psychobiology, 42(1), 44–51. [PubMed: 12471635]

Bauer SA, & Baker KC (2016). Persistent effects of peer rearing on abnormal and species-appropriate activities but not social behavior in group-housed rhesus macaques (*Macaca mulatta*). Comparative Medicine, 66(2), 129–136. [PubMed: 27053567]

Bauman ML (1991). Microscopic neuroanatomic abnormalities in autism. Pediatrics, 87(5 Pt 2), 791–796. [PubMed: 2020538]

Bauman MD, Bliss-Moreau E, Machado CJ, & Amaral DG (2011). The neurobiology of primate social behavior In Decety J, & Cacioppo JT (Eds.). Handbook of social neuroscience. New York: Oxford University Press.

Bauman MD, Iosif AM, Ashwood P, Braunschweig D, Lee A, Schumann CM,... Amaral DG (2013). Maternal antibodies from mothers of children with autism alter brain growth and social behavior development in the rhesus monkey. Translational Psychiatry, 3, e278 10.1038/tp.2013.47. [PubMed: 23838889]

Bauman MD, Iosif AM, Smith SE, Bregere C, Amaral DG, & Patterson PH (2014). Activation of the maternal immune system during pregnancy alters behavioral development of rhesus monkey offspring. Biological Psychiatry, 75(4), 332–341. 10.1016/j.biopsych.2013.06.025. [PubMed: 24011823]

Bauman MD, Lavenex P, Mason WA, Capitanio JP, & Amaral DG (2004b). The development of social behavior following neonatal amygdala lesions in rhesus monkeys. Journal of Cognitive Neuroscience, 16(8), 1388–1411. [PubMed: 15509386]

Bauman MD, Lavenex P, Mason WA, Capitanio JP, & Amaral DG (2004a). The development of mother-infant interactions after neonatal amygdala lesions in rhesus monkeys. Journal of Neuroscience, 24(3), 711–721. [PubMed: 14736857]

Bauman MD, & Schumann CM (2013). Is 'bench-to-bedside' realistic for autism? An integrative neuroscience approach. Neuropsychiatry (London), 3(2), 159–168. 10.2217/npy.13.18. [PubMed: 24000295]

Beach FA (1950). The Snark was a Boojum. American Journal of Psychology, 5, 115–124.

Bellanca RU, & Crockett CM (2002). Factors predicting increased incidence of abnormal behavior in male pigtailed macaques. American Journal of Primatology, 58(2), 57–69. [PubMed: 12386914]

Ben-Ami Bartal I, Decety J, & Mason P (2011). Empathy and pro-social behavior in rats. Science, 334(6061), 1427–1430. 10.1126/science.1210789. [PubMed: 22158823]

Berg EL, Copping NA, Rivera JK, Pride MC, Careaga M, Bauman MD, ... Silverman JL (2018). Developmental social communication deficits in the Shank3 rat model of phelan-mcdermid syndrome and autism spectrum disorder. Autism Research. 10.1002/aur.1925.

Berry-Kravis EM, Lindemann L, Jønch AE, Apostol G, Bear MF, Carpenter RL, ... Gasparini F (2018). Drug development for neurodevelopmental disorders: Lessons learned from fragile X syndrome. Nature Reviews Drug Discovery, 17(4), 280. [PubMed: 29217836]

Berzhanskaya J, Phillips MA, Gorin A, Lai C, Shen J, & Colonnese MT (2017). Disrupted cortical state regulation in a rat model of Fragile X syndrome. Cerebral Cortex, 27(2), 1386–1400. 10.1093/cercor/bhv331. [PubMed: 26733529]

Bethlehem RA, van Honk J, Auyeung B, & Baron-Cohen S (2012). Oxytocin, brain physiology, and functional connectivity: A review of intranasal oxytocin fMRI studies. Psychoneuroendocrinology. 10.1016/j.psyneuen.2012.10.011.

Bevan MJ (2010). The earliest knockouts. Journal of Immunology, 184(9), 4585–4586. 10.4049/jimmunol.1090023.

Bicks LK, Koike H, Akbarian S, & Morishita H (2015). Prefrontal cortex and social cognition in mouse and man. Frontiers in Psychology, 6, 1805 10.3389/fpsyg.2015.01805. [PubMed: 26635701]

Bissonette GB, & Roesch MR (2017). Neurophysiology of rule switching in the corticostriatal circuit. Neuroscience, 345, 64–76. 10.1016/j.neuroscience.2016.01.062. [PubMed: 26851774]

Bliss-Moreau E, Bauman MD, & Amaral DG (2011). Neonatal amygdala lesions result in globally blunted affect in adult rhesus macaques. Behavioral Neuroscience, 125(6), 848–858. 10.1037/a0025757. [PubMed: 21988521]

Bliss-Moreau E, Moadab G, Bauman MD, & Amaral DG (2013). The impact of early amygdala damage on juvenile rhesus macaque social behavior. Journal of Cognitive Neuroscience, 25(12), 2124–2140. 10.1162/jocn_a_00483. [PubMed: 24047387]

Bliss-Moreau E, Moadab G, Santistevan A, & Amaral DG (2017). The effects of neonatal amygdala or hippocampus lesions on adult social behavior. Behavioural Brain Research, 322(Pt A), 123–137. 10.1016/j.bbr.2016.11.052. [PubMed: 28017854]

Bliss-Moreau E, Toscano JE, Bauman MD, Mason WA, & Amaral DG (2010). Neonatal amygdala or hippocampus lesions influence responsiveness to objects. Developmental Psychobiology, 52(5), 487–503. 10.1002/dev.20451. [PubMed: 20583145]

Bliss-Moreau E, Toscano JE, Bauman MD, Mason WA, & Amaral DG (2011). Neonatal amygdala lesions alter responsiveness to objects in juvenile macaques. Neuroscience, 178, 123–132. 10.1016/j.neuroscience.2010.12.038. [PubMed: 21215794]

Boksa P (2010). Effects of prenatal infection on brain development and behavior: A review of findings from animal models. Brain, Behavior, and Immunity, 24(6), 881–897.

Borsini F, Podhorna J, & Marazziti D (2002). Do animal models of anxiety predict anxiolytic-like effects of antidepressants? Psychopharmacology (Berlin), 163(2), 121–141. [PubMed: 12202959]

Braunschweig D, Krakowiak P, Duncanson P, Boyce R, Hansen RL, Ashwood P,... Van de Water J (2013). Autism-specific maternal autoantibodies recognize critical proteins in developing brain. Translational Psychiatry, 3, e277 10.1038/tp.2013.50. [PubMed: 23838888]

Braunschweig D, & Van de Water J (2012). Maternal autoantibodies in autism. Archives of Neurology, 69(6), 693–699. [PubMed: 22689191]

Brenowitz EA, & Zakon HH (2015). Emerging from the bottleneck: Benefits of the comparative approach to modern neuroscience. Trends in Neurosciences, 38(5), 273–278. 10.1016/j.tins.2015.02.008. [PubMed: 25800324]

Broekkamp CL, Rijk HW, Joly-Gelouin D, & Lloyd KL (1986). Major tranquillizers can be distinguished from minor tranquillizers on the basis of effects on marble burying and swim-induced grooming in mice. European Journal of Pharmacology, 126(3), 223–229. [PubMed: 2875886]

Brown AS (2012). Epidemiologic studies of exposure to prenatal infection and risk of schizophrenia and autism. Developmental Neurobiology, 72(10), 1272–1276. 10.1002/dneu.22024. [PubMed: 22488761]

Brown AS, & Derkits EJ (2010). Prenatal infection and schizophrenia: A review of epidemiologic and translational studies. American Journal of Psychiatry, 167(3), 261–280. 10.1176/appi.ajp.2009.09030361. [PubMed: 20123911]

Buckley MJ, & Gaffan D (1998). Perirhinal cortex ablation impairs visual object identification. Journal of Neuroscience, 18(6), 2268–2275. [PubMed: 9482811]

Burgdorf J, Kroes RA, Beinfeld MC, Panksepp J, & Moskal JR (2010). Uncovering the molecular basis of positive affect using rough-and-tumble play in rats: A role for insulin-like growth factor I. Neuroscience, 168(3), 769–777. 10.1016/j.neuroscience.2010.03.045. [PubMed: 20350589]

Burgdorf J, Moskal JR, Brudzynski SM, & Panksepp J (2013). Rats selectively bred for low levels of play-induced 50 kHz vocalizations as a model for autism spectrum disorders: A role for NMDA receptors. Behavioural Brain Research, 251, 18–24. 10.1016/j.bbr.2013.04.022. [PubMed: 23623884]

Bussey TJ, Padain TL, Skillings EA, Winters BD, Morton AJ, & Saksida LM (2008). The touchscreen cognitive testing method for rodents: How to get the best out of your rat. Learning and Memory, 15(7), 516–523. 10.1101/lm.987808. [PubMed: 18612068]

Calhoun JB (1962). The ecology and sociology of the Norway rat. Bethesda, Maryland: U.S Department of Health, Education, and Welfare.

Camacho J, Jones K, Miller E, Ariza J, Noctor S, Van de Water J, & Martinez-Cerdeno V (2014). Embryonic intraventricular exposure to autism-specific maternal autoantibodies produces alterations in autistic-like stereotypical behaviors in offspring mice. Behavioural Brain Research, 266, 46–51. 10.1016/j.bbr.2014.02.045. [PubMed: 24613242]

Capecchi MR (1989). Altering the genome by homologous recombination. Science, 244(4910), 1288–1292. [PubMed: 2660260]

Capitanio JP (1999). Personality dimensions in adult male rhesus macaques: Prediction of behaviors across time and situation. American Journal of Primatology, 47(4), 299–320. [PubMed: 10206208]

Capitanio JP, Mendoza SP, & Cole SW (2011). Nervous temperament in infant monkeys is associated with reduced sensitivity of leukocytes to cortisol's influence on trafficking. Brain, Behavior, and Immunity, 25(1), 151–159. 10.1016/j.bbi.2010.09.008.

Careaga M, Murai T, & Bauman MD (2017). Maternal immune activation and autism spectrum disorder: From rodents to nonhuman and human primates. Biological Psychiatry, 81(5), 391–401. 10.1016/j.biopsych.2016.10.020. [PubMed: 28137374]

Casey BJ, Oliveri ME, & Insel T (2014). A neurodevelopmental perspective on the research domain criteria (RDoC) framework. Biological Psychiatry, 76(5), 350–353. 10.1016/j.biopsych.2014.01.006. [PubMed: 25103538]

Catts VS, Fung SJ, Long LE, Joshi D, Vercammen A, Allen KM, ... Weickert CS (2013). Rethinking schizophrenia in the context of normal neurodevelopment. Frontiers in Cellular Neuroscience, 7, 60 10.3389/fncel.2013.00060. [PubMed: 23720610]

Champoux M, Metz B, & Suomi SJ (1991). Behavior of nursery/peer-reared and mother-reared rhesus monkeys from birth through 2 years of age. Primates, 32(4), 509–514.

Chang SW, Barter JW, Ebitz RB, Watson KK, & Platt ML (2012). Inhaled oxytocin amplifies both vicarious reinforcement and self reinforcement in rhesus macaques (*Macaca mulatta*). Proceedings of the National Academy of Sciences of the United States of America, 109(3), 959–964. 10.1073/pnas.1114621109. [PubMed: 22215593]

Chang SW, Brent LJ, Adams GK, Klein JT, Pearson JM, Watson KK, & Platt ML (2013). Neuroethology of primate social behavior. Proceedings of the National Academy of Sciences of the United States of America, 110(Suppl. 2), 10387–10394. 10.1073/pnas.1301213110. [PubMed: 23754410]

Chang SW, & Platt ML (2013). Oxytocin and social cognition in rhesus macaques: Implications for understanding and treating human psychopathology. Brain Research. 10.1016/j.brainres.2013.11.006.

Chareyron LJ, Banta Lavenex P, Amaral DG, & Lavenex P (2011). Stereological analysis of the rat and monkey amygdala. The Journal of Comparative Neurology, 519(16), 3218–3239. 10.1002/cne.22677. [PubMed: 21618234]

Chen Y, Niu Y, & Ji W (2016). Genome editing in nonhuman primates: Approach to generating human disease models. Journal of Internal Medicine, 280(3), 246–251. 10.1111/joim.12469. [PubMed: 27114283]

Churchland PS, & Winkielman P (2012). Modulating Social Behavior with Oxytocin: How does it work? What does it mean? Hormones and Behavior, 61(3), 392–399. 10.1016/j.yhbeh.2011.12.003. [PubMed: 22197271]

Cambridge Cognition, Ltd. (2018). Retrieved from < www.cambridgecognition.com > .

Coleman K, Lutz CK, Worlein JM, Gottlieb DH, Peterson E, Lee GH, … Novak MA (2017). The correlation between alopecia and temperament in rhesus macaques (*Macaca mulatta*) at four primate facilities. American Journal of Primatology, 79(1), 1–10. 10.1002/ajp.22504.

Conti G, Hansman C, Heckman JJ, Novak MFX, Ruggiero A, & Suomi SJ (2012). Primate evidence on the late health effects of early-life adversity. Proceedings of the National Academy of Sciences of the United States of America, 109(23), 8866–8871. 10.1073/pnas.1205340109. [PubMed: 22615410]

Cook R, Bird G, Catmur C, Press C, & Heyes C (2014). Mirror neurons: From origin to function. Behavioral and Brain Sciences, 37(2), 177–192. 10.1017/S0140525X13000903. [PubMed: 24775147]

Corcoran CA, Pierre PJ, Haddad T, Bice C, Suomi SJ, Grant KA, … Bennett AJ (2012). Long-term effects of differential early rearing in rhesus macaques: Behavioral reactivity in adulthood. Developmental Psychobiology, 54(5), 546–555. 10.1002/dev.20613. [PubMed: 22072233]

Cornish K, Scerif G, & Karmiloff-Smith A (2007). Tracing syndrome-specific trajectories of attention across the lifespan. Cortex, 43(6), 672–685. [PubMed: 17710820]

Cosgrove VE, Kelsoe JR, & Suppes T (2016). Toward a valid animal model of bipolar disorder: How the research domain criteria help bridge the clinical-basic science divide. Biological Psychiatry, 79(1), 62–70. 10.1016/j.biopsych.2015.09.002. [PubMed: 26531027]

Crawley JN (2012). Translational animal models of autism and neurodevelopmental disorders. Dialogues in Clinical Neuroscience, 14(3), 293. [PubMed: 23226954]

Crean RD, Vandewater SA, Katner SN, Huitron-Resendiz S, & Taffe MA (2011). Chronic alcohol consumption impairs visuo-spatial associative memory in periadolescent rhesus monkeys. Drug and Alcohol Dependence, 114(1), 31–40. 10.1016/j.drugalcdep.2010.09.002. [PubMed: 20951512]

Crum WR, Sawiak SJ, Chege W, Cooper JD, Williams SCR, & Vernon AC (2017). Evolution of structural abnormalities in the rat brain following in utero exposure to maternal immune activation: A longitudinal in vivo MRI study. Brain, Behavior, and Immunity, 63, 50–59. 10.1016/j.bbi.2016.12.008.

Curtis B, Liberato N, Rulien M, Morrisroe K, Kenney C, Yutuc V, … Hewitson L (2015). Examination of the safety of pediatric vaccine schedules in a non-human primate model: Assessments of neurodevelopment, learning, and social behavior. Environmental Health Perspectives, 123(6), 579–589. 10.1289/ehp.1408257. [PubMed: 25690930]

Cuthbert BN, & Insel TR (2013). Toward the future of psychiatric diagnosis: The seven pillars of RDoC. BMC Medicine, 11, 126 10.1186/1741-7015-11-126. [PubMed: 23672542]

Dahl CD, Wallraven C, Bülthoff HH, & Logothetis NK (2009). Humans and macaques employ similar face-processing strategies. Current Biology, 19(6), 509–513. [PubMed: 19249210]

Dal Monte O, Noble PL, Turchi J, Cummins A, & Averbeck BB (2014). CSF and blood oxytocin concentration changes following intranasal delivery in macaque. PLOS One, 9(8), e103677 10.1371/journal.pone.0103677. [PubMed: 25133536]

Damiano CR, Mazefsky CA, White SW, & Dichter GS (2014). Future directions for research in autism spectrum disorders. Journal of Clinical Child & Adolescent Psychology, 43(5), 828–843. 10.1080/15374416.2014.945214. [PubMed: 25216048]

D'Cruz AM, Mosconi MW, Ragozzino ME, Cook EH, & Sweeney JA (2016). Alterations in the functional neural circuitry supporting flexible choice behavior in autism spectrum disorders. Translational Psychiatry, 6, e2016 10.1038/tp.2016.161.

Deacon RM (2006). Digging and marble burying in mice: Simple methods for in vivo identification of biological impacts. Nature Protocols, 1(1), 122–124. [PubMed: 17406223]

Denayer T, Stöhr T, & Van Roy M (2014). Animal models in translational medicine: Validation and prediction. New Horizons in Translational Medicine, 2(1), 5–11.

Dettmer AM, Wooddell LJ, Rosenberg K, Kaburu SS, Novak MA, Meyer JS, & Suomi SJ (2017). Associations between early life experience, chronic HPA axis activity, and adult social rank in rhesus monkeys. Social Neuroscience, 12(1), 92–101. 10.1080/17470919.2016.1176952. [PubMed: 27063359]

D'Hooge R, & de Deyn PP (2001). Applications of the Morris water maze in the study of learning and memory. Brain Research Reviews, 36(1), 60–90. [PubMed: 11516773]

Dufour-Rainfray D, Vourc'h P, Le Guisquet AM, Garreau L, Ternant D, Bodard S, … Guilloteau D (2010). Behavior and serotonergic disorders in rats exposed prenatally to valproate: A model for autism. Neuroscience Letters, 470(1), 55–59. 10.1016/j.neulet.2009.12.054. [PubMed: 20036713]

Ebitz RB, Watson KK, & Platt ML (2013). Oxytocin blunts social vigilance in the rhesus macaque. Proceedings of the National Academy of Sciences of the United States of America, 110(28), 11630–11635. 10.1073/pnas.1305230110. [PubMed: 23798448]

Ecker C, Spooren W, & Murphy DG (2012). Translational approaches to the biology of Autism: False dawn or a new era? Molecular Psychiatry. 10.1038/mp.2012.102.

Edmiston E, Ashwood P, & Van de Water J (2017). Autoimmunity, autoantibodies, and autism spectrum disorder. Biological Psychiatry, 81(5), 383–390. 10.1016/j.biopsych.2016.08.031. [PubMed: 28340985]

Edmiston E, Jones KL, Vu T, Ashwood P, & Van de Water J (2018). Identification of the antigenic epitopes of maternal autoantibodies in autism spectrum disorders. Brain, Behavior, and Immunity, 69, 399–407. 10.1016/j.bbi.2017.12.014.

Engineer CT, Centanni TM, Im KW, & Kilgard MP (2014). Speech sound discrimination training improves auditory cortex responses in a rat model of autism. Frontiers in Systems Neuroscience, 8, 137 10.3389/fnsys.2014.00137. [PubMed: 25140133]

Estes ML, & McAllister AK (2016). Maternal immune activation: Implications for neuropsychiatric disorders. Science, 353(6301), 772–777. 10.1126/science.aag3194. [PubMed: 27540164]

Evans SL, Dal Monte O, Noble PL, & Averbeck BB (2014). Intranasal oxytocin effects on social cognition: A critique. Brain Research, 1580(69-77), 10.1016/j.brainres.2013.11.008.

Everling S, & Fischer B (1998). The antisaccade: A review of basic research and clinical studies. Neuropsychologia, 36(9), 885–899. [PubMed: 9740362]

Fajnerová I, Rodriguez M, Levčík D, Konrádová L, Mikoláš P, Brom C, … Horáček J (2014). A virtual reality task based on animal research - spatial learning and memory in patients after the first episode of schizophrenia. Frontiers in Behavioral Neuroscience, 8, 157 10.3389/fnbeh.2014.00157. [PubMed: 24904329]

Feng AY, & Himsworth CG (2014). The secret life of the city rat: A review of the ecology of urban Norway and black rats (*Rattus norvegicus* and *Rattus rattus*). Urban Ecosystems, 17(1), 149–162.

Fmr1 knockout mice: a model to study fragile X mental retardation. The Dutch-Belgian Fragile X Consortium. Cell78(1), 23–33. [PubMed: 8033209]

Fox-Edmiston E, & Van de Water J (2015). Maternal anti-fetal brain igg autoantibodies and autism spectrum disorder: Current knowledge and its implications for potential therapeutics. CNS drugs, 29(9), 715–724. [PubMed: 26369920]

Frankland PW, Wang Y, Rosner B, Shimizu T, Balleine BW, Dykens EM, … Silva AJ (2004). Sensorimotor gating abnormalities in young males with fragile X syndrome and Fmr1-knockout mice. Molecular Psychiatry, 9(4), 417–425. 10.1038/sj.mp.4001432. [PubMed: 14981523]

Frazier TW, Strauss M, Klingemier EW, Zetzer EE, Hardan AY, Eng C, & Youngstrom EA (2017). A meta-analysis of gaze differences to social and nonsocial information between individuals with and without autism. Child and Adolescent Psychiatry, 56(7), 546–555. 10.1016/j.jaac.2017.05.005.

Friedman HR, & Selemon LD (2010). Fetal irradiation interferes with adult cognition in the nonhuman primate. Biological Psychiatry, 68(1), 108–111. 10.1016/j.biopsych.2010.02.021. [PubMed: 20399419]

Fukushima J, Fukushima K, Miyasaka K, & Yamashita I (1994). Voluntary control of saccadic eye movement in patients with frontal cortical lesions and parkinsonian patients in comparison with that in schizophrenics. Biological Psychiatry, 36(1), 21–30. [PubMed: 8080899]

Funahashi S, Chafee MV, & Goldman-Rakic PS (1993). Prefrontal neuronal activity in rhesus monkeys performing a delayed anti-saccade task. Nature, 365(6448), 753. [PubMed: 8413653]

Gadad BS, Li W, Yazdani U, Grady S, Johnson T, Hammond J, … German DC (2015). Administration of thimerosal-containing vaccines to infant rhesus macaques does not result in autism-like behavior or neuropathology. Proceedings of the National Academy of Sciences of the United States of America, 112(40), 12498–12503. 10.1073/pnas.1500968112. [PubMed: 26417083]

Galvao MC, Chaves-Kirsten GP, Queiroz-Hazarbassanov N, Carvalho VM, Bernardi MM, & Kirsten TB (2015). Prenatal zinc reduces stress response in adult rat offspring exposed to lipopolysaccharide during gestation. Life Sciences, 120, 54–60. 10.1016/j.lfs.2014.10.019. [PubMed: 25445220]

Garner JP (2005). Stereotypies and other abnormal repetitive behaviors: Potential impact on validity, reliability, and replicability of scientific outcomes. ILAR Journal, 46(2), 106–117. 10.1093/ilar.46.2.106. [PubMed: 15775020]

Garthe A, & Kempermann G (2013). An old test for new neurons: Refining the Morris water maze to study the functional relevance of adult hippocampal neurogenesis. Frontiers in Neuroscience, 7, 63 10.3389/fnins.2013.00063. [PubMed: 23653589]

Geschwind DH, & Rakic P (2013). Cortical evolution: Judge the brain by its cover. Neuron, 80(3), 633–647. 10.1016/j.neuron.2013.10.045. [PubMed: 24183016]

Gibbs RA, Weinstock GM, Metzker ML, Muzny DM, Sodergren EJ, Scherer S, … Collins F (2004). Genome sequence of the Brown Norway rat yields insights into mammalian evolution. Nature, 428(6982), 493–521. 10.1038/nature02426. [PubMed: 15057822]

Golub MS, Hackett EP, Hogrefe CE, Leranth C, Elsworth JD, & Roth RH (2017). Cognitive performance of juvenile monkeys after chronic fluoxetine treatment. Developmental Cognitive Neuroscience, 26, 52–61. 10.1016/j.dcn.2017.04.008. [PubMed: 28521247]

Golub MS, Hogrefe CE, & Germann SL (2007). Iron deprivation during fetal development changes the behavior of juvenile rhesus monkeys. Journal of Nutrition, 137(4), 979–984. [PubMed: 17374664]

Gothard KM, Erickson CA, & Amaral DG (2004). How do rhesus monkeys (*Macaca mulatta*) scan faces in a visual paired comparison task? Animal Cognition, 7(1), 25–36. [PubMed: 14745584]

Gottlieb DH, Capitanio JP, & McCowan B (2013). Risk factors for stereotypic behavior and self-biting in rhesus macaques (*Macaca mulatta*): Animal's history, current environment, and personality. American Journal of Primatology, 75(10), 995–1008. 10.1002/ajp.22161. [PubMed: 23640705]

Goursand AP, & Bachevalier J (2007). Social attachment in juvenile monkeys with neonatal lesion of the hippocampus, amygdala and orbital frontal cortex. Behavioural Brain Research, 176(1), 75–93. 10.1016/j.bbr.2006.09.020. [PubMed: 17084912]

Goursand AP, Wallen K, & Bachevalier J (2014). Mother recognition and preference after neonatal amygdala lesions in rhesus macaques (*Macaca mulatta*) raised in a semi-naturalistic environment. Developmental Psychobiology, 56(8), 1723–1734. 10.1002/dev.21233. [PubMed: 25042548]

Green JJ, & Hollander E (2010). Autism and oxytocin: New developments in translational approaches to therapeutics. Neurotherapeutics, 7(3), 250–257. 10.1016/j.nurt.2010.05.006. [PubMed: 20643377]

Griffin GA, & Harlow HF (1966). Effects of three months of total social deprivation on social adjustment and learning in the rhesus monkey. Child Development, 37(3), 533–547. [PubMed: 4961534]

Gyertyán I (1995). Analysis of the marble burying response: Marbles serve to measure digging rather than evoke burying. Behavioural Pharmacology, 6(1), 24–31. [PubMed: 11224308]

Hallett PE (1978). Primary and secondary saccades to goals defined by instructions. Vision Research, 18(10), 1279–1296. [PubMed: 726270]

Hamel AF, Lutz CK, Coleman K, Worlein JM, Peterson EJ, Rosenberg KL, … Meyer JS (2017). Responses to the Human Intruder Test are related to hair cortisol phenotype and sex in rhesus macaques (*Macaca mulatta*). American Journal of Primatology, 79(1), 1–10. 10.1002/ajp.22526.

Hamilton SM, Green JR, Veeraragavan S, Yuva L, McCoy A, Wu Y, … Paylor R (2014). Fmr1 and Nlgn3 knockout rats: Novel tools for investigating autism spectrum disorders. Behavioral Neuroscience, 128(2), 103–109. 10.1037/a0035988. [PubMed: 24773431]

Harlow HF (1945). Studies in discrimination learning in monkeys: V. Initial performance by experimentally naive monkeys on stimulus-object and pattern discriminations. Journal of General Psychology, 33(1), 3–10. 10.1080/00221309.1945.10544491.

Harlow HF, Dodsworth RO, & Harlow MK (1965). Total social isolation in monkeys. Proceedings of the National Academy of Sciences of the United States of America, 54(1), 90–97. [PubMed: 4955132]

Harony-Nicolas H, Kay M, Hoffman JD, Klein ME, Bozdagi-Gunal O, Riad M, … Castillo PE (2017). Oxytocin improves behavioral and electrophysiological deficits in a novel Shank3-deficient rat. eLife, 6, e18904 10.7554/eLife.18904. [PubMed: 28139198]

Himmler BT, Pellis VC, & Pellis SM (2013). Peering into the dynamics of social interactions: measuring play fighting in rats. Journal of Visualized Experiments, 71(4288), 10.3791/4288.

Himmler SM, Modlinska K, Stryjek R, Himmler BT, Pisula W, & Pellis SM (2014). Domestication and diversification: A comparative analysis of the play fighting of the Brown Norway, Sprague-Dawley, and Wistar laboratory strains of (*Rattus norvegicus*). Journal of Comparative Psychology, 128(3), 318–327. 10.1037/a0036104. [PubMed: 24749500]

Horner AE, Heath CJ, Hvoslef-Eide M, Kent BA, Kim CH, Nilsson SRO, … Bussey TJ (2013). The touchscreen operant platform for testing learning and memory in rats and mice. Nature Protocols, 8, 1961–1984. 10.1038/nprot.2013.122. [PubMed: 24051959]

Hsiao EY, McBride SW, Chow J, Mazmanian SK, & Patterson PH (2012). Modeling an autism risk factor in mice leads to permanent immune dysregulation. Proceedings of the National Academy of Sciences of the United States of America, 109(31), 12776–12781. 10.1073/pnas.1202556109. [PubMed: 22802640]

Hussein S, Johnston K, Belbeck B, Lomber SG, & Everling S (2014). Functional specialization within macaque dorsolateral prefrontal cortex for the maintenance of task rules and cognitive control. Journal of Cognitive Neuroscience, 26(9), 1918–1927. [PubMed: 24666129]

Hyman SE (2014). How far can mice carry autism research? Cell, 158(1), 13–14. 10.1016/j.cell.2014.06.032. [PubMed: 24995974]

Jennings CG, Landman R, Zhou Y, Sharma J, Hyman J, Movshon JA, … Feng G (2016). Opportunities and challenges in modeling human brain disorders in transgenic primates. Nature Neuroscience, 19(9), 1123–1130. 10.1038/nn.4362. [PubMed: 27571191]

Jordan R (2003). Social play and autistic spectrum disorders: A perspective on theory, implications and educational approaches. Autism, 7(4), 347–360. [PubMed: 14678675]

Kalin NH, Larson C, Shelton SE, & Davidson RJ (1998). Asymmetric frontal brain activity, cortisol, and behavior associated with fearful temperament in rhesus monkeys. Behavioral Neuroscience, 112(2), 286–292. [PubMed: 9588478]

Kalin N, & Shelton S (1989). Defensive behaviors in infant rhesus monkeys: Environmental cues and neurochemical regulation. Science, 243, 1718–1721. [PubMed: 2564702]

Kalin NH, & Shelton SE (1998). Ontogeny and stability of separation and threat-induced defensive behaviors in rhesus monkeys during the first year of life. American Journal of Primatology, 44(2), 125–135. [PubMed: 9503124]

Kas MJ, Glennon JC, Buitelaar J, Ey E, Biemans B, Crawley J, … Steckler, T. (2014). Assessing behavioural and cognitive domains of autism spectrum disorders in rodents: Current status and future perspectives. Psychopharmacology (Berlin), 231(6), 1125–1146. 10.1007/s00213-013-3268-5. [PubMed: 24048469]

Kazdoba TM, Leach PT, & Crawley JN (2016). Behavioral phenotypes of genetic mouse models of autism. Genes, Brain and Behavior, 15(1), 7–26. 10.1111/gbb.12256.

Kazdoba TM, Leach PT, Silverman JL, & Crawley JN (2014). Modeling fragile X syndrome in the Fmr1 knockout mouse. Intractable & Rare Diseases Research, 3(4), 118–133. 10.5582/irdr.2014.01024. [PubMed: 25606362]

Kelly B, Maguire-Herring V, Rose CM, Gore HE, Ferrigno S, Novak MA, & Lacreuse A (2014). Short-term testosterone manipulations do not affect cognition or motor function but differentially

modulate emotions in young and older male rhesus monkeys. Hormones and Behavior, 66(5), 731–742. 10.1016/j.yhbeh.2014.08.016. [PubMed: 25308086]

King BH, & Lord C (2011). Is schizophrenia on the autism spectrum? Brain Research, 1380, 34–41. 10.1016/j.brainres.2010.11.031. [PubMed: 21078305]

Kinnally EL, Capitanio JP, Leibel R, Deng L, LeDuc C, Haghighi F, & Mann JJ (2010). Epigenetic regulation of serotonin transporter expression and behavior in infant rhesus macaques. Genes, Brain and Behavior, 9(6), 575–582. 10.1111/j.1601-183X.2010.00588.x.

Kinnally EL, Lyons LA, Abel K, Mendoza S, & Capitanio JP (2008). Effects of early experience and genotype on serotonin transporter regulation in infant rhesus macaques. Genes, Brain and Behavior, 7(4), 481–486. 10.1111/j.1601-183X.2007.00383.x.

Kirsten TB, Chaves-Kirsten GP, Bernardes S, Scavone C, Sarkis JE, Bernardi MM, & Felicio LF (2015). Lipopolysaccharide exposure induces maternal hypozincemia, and prenatal zinc treatment prevents autistic-like behaviors and disturbances in the striatal dopaminergic and mTOR systems of offspring. PLOS One, 10(7), 1–18. 10.1371/journal.pone.0134565.

Kirsten TB, Queiroz-Hazarbassanov N, Bernardi MM, & Felicio LF (2015). Prenatal zinc prevents communication impairments and BDNF disturbance in a rat model of autism induced by prenatal lipopolysaccharide exposure. Life Sciences, 130, 12–17. 10.1016/j.lfs.2015.02.027. [PubMed: 25817235]

Knuesel I, Chicha L, Britschgi M, Schobel SA, Bodmer M, Hellings JA, … Prinssen EP (2014). Maternal immune activation and abnormal brain development across CNS disorders. Nat Rev Neurol, 10(11), 643–660. 10.1038/nrneurol.2014.187. [PubMed: 25311587]

Koller BH, Marrack P, Kappler JW, & Smithies O (1990). Normal development of mice deficient in beta 2M, MHC class I proteins, and CD8+ T cells. Science, 248(4960), 1227–1230. [PubMed: 2112266]

Kramvis I, Mansvelder HD, Loos M, & Meredith R (2013). Hyperactivity, perseveration and increased responding during attentional rule acquisition in the Fragile X mouse model. Frontiers in Behavioral Neuroscience, 7, 1–13. 10.3389/fnbeh.2013.00172. [PubMed: 23423702]

Ku KM, Weir RK, Silverman JL, Berman RF, & Bauman MD (2016). Behavioral phenotyping of juvenile long-evans and sprague-dawley rats: Implications for preclinical models of autism spectrum disorders. PLOS One, 11(6), e0158150 10.1371/journal.pone.0158150. [PubMed: 27351457]

Kumar S, & Hedges SB (1998). A molecular timescale for vertebrate evolution. Nature, 392(6679), 917–920. 10.1038/31927. [PubMed: 9582070]

Kuo TT, Baker K, Yoshida M, Qiao SW, Aveson VG, Lencer WI, & Blumberg RS (2010). Neonatal Fc receptor: From immunity to therapeutics. Journal of Clinical Immunology, 30(6), 777–789. 10.1007/s10875-010-9468-4. [PubMed: 20886282]

Lankau EW, Turner PV, Mullan RJ, & Galland GG (2014). Use of nonhuman primates in research in North America. Journal of the American Association for Laboratory Animal Science, 53(3), 278–282. [PubMed: 24827570]

Leonard TK, Blumenthal G, Gothard KM, & Hoffman KL (2012). How macaques view familiarity and gaze in conspecific faces. Behavioral Neuroscience, 126(6), 781–791. 10.1037/a0030348. [PubMed: 23067381]

Lewis M, & Kim S (2009). The pathophysiology of restricted repetitive behavior. Journal of Neurodevelopmental Disorders, 1, 114–132. 10.1007/s11689-009-9019-6. [PubMed: 21547711]

Lewis MH, Tanimura Y, Lee LW, & Bodfish JW (2007). Animal models of restricted repetitive behavior in autism. Behavioural Brain Research, 176(1), 66–74. [PubMed: 16997392]

Liu Z, Li X, Zhang JT, Cai YJ, Cheng TL, Cheng C, … Qiu Z (2016). Autismlike behaviours and germline transmission in transgenic monkeys overexpressing MeCP2. Nature, 530(7588), 98–102. 10.1038/nature16533. [PubMed: 26808898]

Llaneza DC, & Frye CA (2009). Progestogens and estrogen influence impulsive burying and avoidant freezing behavior of naturally cycling and ovariectomized rats. Pharmacology, Biochemistry and Behavior, 93(3), 337–342.

Luciana M (2003). Practitioner review: Computerized assessment of neuropsychological function in children: Clinical and research applications of the Cambridge Neuropsychological Testing

Automated Battery (CANTAB). Journal of Child Psychology and Psychiatry, 44(5), 649–663. [PubMed: 12831110]

Lutz C, Well A, & Novak M (2003). Stereotypic and self-injurious behavior in rhesus macaques: A survey and retrospective analysis of environment and early experience. American Journal of Primatology, 60(1), 1–15.

Lynch DC, & Green G (1991). Development and crossmodal transfer of contextual control of emergent stimulus relations. Journal of the Experimental Analysis of Behavior, 56(1), 139–154. 10.1901/jeab.1991.56-139. [PubMed: 1940759]

Lyons DM, Parker KJ, & Schatzberg AF (2010). Animal models of early life stress: Implications for understanding resilience. Developmental Psychobiology, 52(7), 616–624. [PubMed: 20957724]

Machado CJ, Whitaker AM, Smith SE, Patterson PH, & Bauman MD (2015). Maternal immune activation in nonhuman primates alters social attention in juvenile offspring. Biological Psychiatry, 77(9), 823–832. 10.1016/j.biopsych.2014.07.035. [PubMed: 25442006]

Macri S, & Richter SH (2015). The Snark was a Boojum - reloaded. Frontiers in Zoology, 12(Suppl. 1), S20 10.1186/1742-9994-12-S1-S20. [PubMed: 26816519]

Mahut H, & Cordeau J (1963). Spatial reversal deficit in monkeys with amygdalo-hippocampal ablations. Experimental Neurology, 7(5), 426–434. 10.1016/0014-4886(63)90023-2.

Makori N, Watson RE, Hogrefe CE, Lalayeva N, & Oneda S (2013). Object discrimination and reversal learning in infant and juvenile nonhuman primates in a nonclinical laboratory. Journal of Medical Primatology, 42(3), 147–157. 10.1111/jmp.12041. [PubMed: 23480632]

Manduca A, Campolongo P, Palmery M, Vanderschuren LJ, Cuomo V, & Trezza V (2014). Social play behavior, ultrasonic vocalizations and their modulation by morphine and amphetamine in Wistar and Sprague-Dawley rats. Psychopharmacology (Berlin), 231(8), 1661–1673. 10.1007/s00213-013-3337-9. [PubMed: 24221828]

Markham MR, Butt AE, & Dougher MJ (1996). A computer touch-screen apparatus for training visual discriminations in rats. Journal of the Experimental Analysis of Behavior, 65(1), 173–182. 10.1901/jeab.1996.65-173. [PubMed: 8583196]

Martin LA, Ashwood P, Braunschweig D, Cabanlit M, Van de Water J, & Amaral DG (2008). Stereotypies and hyperactivity in rhesus monkeys exposed to IgG from mothers of children with autism. Brain, Behavior, and Immunity, 22(6), 806–816. 10.1016/j.bbi.2007.12.007.

Martinez-Cerdeno V, Camacho J, Fox E, Miller E, Ariza J, Kienzle D, … Van de Water J (2016). Prenatal exposure to autism-specific maternal autoantibodies alters proliferation of cortical neural precursor cells, enlarges brain, and increases neuronal size in adult animals. Cerebral Cortex, 26(1), 374–383. 10.1093/cercor/bhu291. [PubMed: 25535268]

Mason WA, & Mendoza SP (1998). Generic aspects of primate attachments: Parents, offspring and mates. Psychoneuroendocrinology, 23(8), 765–778. [PubMed: 9924737]

McCormack K, Sanchez MM, Bardi M, & Maestripieri D (2006). Maternal care patterns and behavioral development of rhesus macaque abused infants in the first 6 months of life. Developmental Psychobiology, 48(7), 537–550. 10.1002/dev.20157. [PubMed: 17016838]

Meehan C, Harms L, Frost JD, Barreto R, Todd J, Schall U, … Hodgson DM (2017). Effects of immune activation during early or late gestation on schizophrenia-related behaviour in adult rat offspring. Brain, Behavior, and Immunity, 63, 8–20. 10.1016/j.bbi.2016.07.144.

Meltzer A, & Van de Water J (2017). The role of the immune system in autism spectrum disorder. Neuropsychopharmacology, 42(1), 284–298. 10.1038/npp.2016.158. [PubMed: 27534269]

Meyer U (2014). Prenatal poly(i:C) exposure and other developmental immune activation models in rodent systems. Biological Psychiatry, 75(4), 307–315. 10.1016/j.biopsych.2013.07.011. [PubMed: 23938317]

Meyer U, & Feldon J (2012). To poly(I:C) or not to poly(I:C): Advancing preclinical schizophrenia research through the use of prenatal immune activation models. Neuropharmacology, 62(3), 1308–1321. 10.1016/j.neuropharm.2011.01.009. [PubMed: 21238465]

Meyer U, Feldon J, & Dammann O (2011). Schizophrenia and autism: Both shared and disorder-specific pathogenesis via perinatal inflammation? Pediatric Research, 69(5 Pt 2), 26R–33R. 10.1203/PDR.0b013e318212c196.

Meyer U, Feldon J, & Fatemi SH (2009). In-vivo rodent models for the experimental investigation of prenatal immune activation effects in neurodevelopmental brain disorders. Neuroscience & Biobehavioral Reviews, 33(7), 1061–1079. 10.1016/j.neubiorev.2009.05.001. [PubMed: 19442688]

Miller CT, Freiwald WA, Leopold DA, Mitchell JF, Silva AC, & Wang X (2016). Marmosets: A neuroscientific model of human social behavior. Neuron, 90(2), 219–233. [PubMed: 27100195]

Moadab G, Bliss-Moreau E, & Amaral DG (2015). Adult social behavior with familiar partners following neonatal amygdala or hippocampus damage. Behavioral Neuroscience, 129(3), 339–350. 10.1037/bne0000062. [PubMed: 26030432]

Moadab G, Bliss-Moreau E, Bauman MD, & Amaral DG (2017). Early amygdala or hippocampus damage influences adolescent female social behavior during group formation. Behavioral Neuroscience, 131(1), 68–82. 10.1037/bne0000181. [PubMed: 28054806]

Modi ME, & Young LJ (2012). The oxytocin system in drug discovery for autism: Animal models and novel therapeutic strategies. Hormones and Behavior, 61(3), 340–350. 10.1016/j.yhbeh.2011.12.010. [PubMed: 22206823]

Morris RG, Garrud P, Rawlins JN, & O'Keefe J (1982). Place navigation impaired in rats with hippocampal lesions. Nature, 297(5868), 681–683. [PubMed: 7088155]

Moy SS, & Nadler JJ (2008). Advances in behavioral genetics: Mouse models of autism. Molecular Psychiatry, 13(1), 4–26. [PubMed: 17848915]

Munoz DP, & Everling S (2004). Look away: The anti-saccade task and the voluntary control of eye movement. Nature Reviews Neuroscience, 5(3), 218. [PubMed: 14976521]

Murray EA, Gaffan D, & Mishkin M (1993). Neural substrates of visual stimulus-stimulus association in rhesus monkeys. Journal of Neuroscience, 13(10), 4549–4561. [PubMed: 8410203]

Niesink RJ, & Van Ree JM (1983). Normalizing effect of an adrenocorticotropic hormone (4–9) analog ORG 2766 on disturbed social behavior in rats. Science, 221(4614), 960–962. [PubMed: 6308767]

Niesink RJ, & Van Ree JM (1989). Involvement of opioid and dopaminergic systems in isolation-induced pinning and social grooming of young rats. Neuropharmacology, 28(4), 411–418. [PubMed: 2546087]

Njung'e K, & Handley SL (1991). Evaluation of marble-burying behavior as a model of anxiety. Pharmacology, Biochemistry and Behavior, 38(1), 63–67.

Nordahl CW, Braunschweig D, Iosif AM, Lee A, Rogers S, Ashwood P, … Van de Water J (2013). Maternal autoantibodies are associated with abnormal brain enlargement in a subgroup of children with autism spectrum disorder. Brain, Behavior, and Immunity, 30, 61–65. 10.1016/j.bbi.2013.01.084.

Novak MA, Kelly BJ, Bayne K, & Meyer JS (2012). Behavioral disorders of nonhuman primates In Abee CR, Mansfield K, Tardif S, & Morris T (Eds.). Nonhuman primates in biomedical research(2nd ed.). New York: Academic Press.

O'Shea DJ, Kalanithi P, Ferenczi EA, Hsueh B, Chandrasekaran C, Goo W, … Yeom KW (2018). Development of an optogenetic toolkit for neural circuit dissection in squirrel monkeys. Scientific Reports, 8, 1–20. 10.1038/s41598-018-24362-7. [PubMed: 29311619]

Onore C, Careaga M, & Ashwood P (2012). The role of immune dysfunction in the pathophysiology of autism. Brain, Behavior, and Immunity, 26(3), 383–392. 10.1016/j.bbi.2011.08.007.

Overman W, Pierce A, Watterson L, & Coleman JK (2013). Use of a non-navigational, non-verbal landmark task in children. International Journal of Behavioral Development, 37(6), 485–497. 10.1177/0165025413493876.

Panksepp J (1981). The ontogeny of play in rats. Developmental Psychobiology, 14(4), 327–332. 10.1002/dev.420140405. [PubMed: 7250521]

Panksepp J (2007). Can play diminish ADHD and facilitate the construction of the social brain? Journal of the Canadian Academy of Child and Adolescent Psychiatry, 16(2), 57–66. [PubMed: 18392153]

Panksepp J, & Panksepp JB (2013). Toward a cross-species understanding of empathy. Trends in Neurosciences, 36(8), 489–496. [PubMed: 23746460]

Panksepp J, Siviy S, & Normansell L (1984). The psychobiology of play: Theoretical and methodological perspectives. Neuroscience & Biobehavioral Reviews, 8(4), 465–492. [PubMed: 6392950]

Panksepp J, & Watt D (2011). Why does depression hurt? Ancestral primary-process separation-distress (panic/grief) and diminished brain reward (seeking) processes in the genesis of depressive affect. Psychiatry, 74(1), 5–13. [PubMed: 21463165]

Papagiannopoulou EA, Chitty KM, Hermens DF, Hickie IB, & Lagopoulos J (2014). A systematic review and meta-analysis of eye-tracking studies in children with autism spectrum disorders. Social Neuroscience, 9(6), 610–632. 10.1080/17470919.2014.934966. [PubMed: 24988218]

Parasuraman S (2011). Toxicological screening. Journal of Pharmacology & Pharmacotherapeutics, 2(2), 74–79. 10.4103/0976-500X.81895. [PubMed: 21772764]

Park JE, Zhang XF, Choi S, Okahara J, Sasaki E, & Silva AC (2016). Generation of transgenic marmosets expressing genetically encoded calcium indicators. Scientific Reports, 6, 1–12. 10.1038/srep34931. [PubMed: 28442746]

Parr LA, Brooks JM, Jonesteller T, Moss S, Jordano JO, & Heitz TR (2016). Effects of chronic oxytocin on attention to dynamic facial expressions in infant macaques. Psychoneuroendocrinology, 74, 149–157. 10.1016/j.psyneuen.2016.08.028. [PubMed: 27621197]

Parr LA, Modi M, Siebert E, & Young LJ (2013). Intranasal oxytocin selectively attenuates rhesus monkeys' attention to negative facial expressions. Psychoneuroendocrinology, 38(9), 1748–1756. 10.1016/j.psyneuen.2013.02.011. [PubMed: 23490074]

Parr LA (2014). Intranasal oxytocin enhances socially-reinforced learning in rhesus monkeys. Frontiers in Behavioral Neuroscience, 8(278), 10.3389/fnbeh.2014.00278.

Patrich E, Piontkewitz Y, Peretz A, Weiner I, & Attali B (2016). Maternal immune activation produces neonatal excitability defects in offspring hippocampal neurons from pregnant rats treated with poly I:C. Scientific Reports, 6, 19106 10.1038/srep19106. [PubMed: 26742695]

Patterson PH (2009). Immune involvement in schizophrenia and autism: Etiology, pathology and animal models. Behavioural Brain Research, 204(2), 313–321. 10.1016/j.bbr.2008.12.016. [PubMed: 19136031]

Patterson PH (2011). Maternal infection and immune involvement in autism. Trends in Molecular Medicine, 17(7), 389–394. 10.1016/j.molmed.2011.03.001. [PubMed: 21482187]

Patterson PH (2012). Maternal infection and autism. Brain, Behavior, and Immunity, 26(3), 393 10.1016/j.bbi.2011.09.008.

Paukner A, Bower S, Simpson EA, & Suomi SJ (2013). Sensitivity to first-order relations of facial elements in infant rhesus macaques. Infant and Child Development, 22(3), 320–330. 10.1002/icd.1793. [PubMed: 23997657]

Paukner A, Simpson EA, Ferrari PF, Mrozek T, & Suomi SJ (2014). Neonatal imitation predicts how infants engage with faces. Developmental Science, 17(6), 833–840. 10.1111/desc.12207. [PubMed: 24995706]

Pellis SM, Burghardt GM, & Palagi E (2015). Modeling play: Distinguishing between origins and current functions. Adaptive Behavior, 23(6), 331–339.

Pellis SM, & Pellis VC (1998). Play fighting of rats in comparative perspective: A schema for neurobehavioral analyses. Neuroscience & Biobehavioral Reviews, 23(1), 87–101. [PubMed: 9861614]

Pellis SM, Pellis VC, & Dewsbury DA (1989). Different levels of complexity in the play-fighting by muroid rodents appear to result from different levels of intensity of attack and defense. Aggressive Behavior, 15(4), 297–310.

Perry JS (1945). The reproduction of the wild brown rat (*Rattus norvegicus Erxleben*) Proceedings of the Zoological Society of London: Vol. 115, (pp. 19–46). Oxford, UK: Blackwell Publishing Ltd No. 1–2.

Peters SM, Pothuizen HH, & Spruijt BM (2015). Ethological concepts enhance the translational value of animal models. European Journal of Pharmacology, 759, 42–50. 10.1016/j.ejphar.2015.03.043. [PubMed: 25823814]

Peterson EJ, Worlein JM, Lee GH, Dettmer AM, Varner EK, & Novak MA (2017). Rhesus macaques (*Macaca mulatta*) with self-injurious behavior show less behavioral anxiety during the human intruder test. American Journal of Primatology, 79(1), 1–8.

Phillips KA, Bales KL, Capitanio JP, Conley A, Czoty PW, t Hart BA, … Voytko ML (2014). Why primate models matter. American Journal of Primatology. 10.1002/ajp.22281.

Piper M, Beneyto M, Burne TH, Eyles DW, Lewis DA, & McGrath JJ (2012). The neurodevelopmental hypothesis of schizophrenia: Convergent clues from epidemiology and neuropathology. The Psychiatric Clinics of North America, 35(3), 571–584. 10.1016/j.psc.2012.06.002. [PubMed: 22929867]

Poole TB, & Fish J (1975). An investigation of playful behaviour in *Rattus norvegicus* and *Mus musculus* (Mammalia). Journal of Zoology, 175(1), 61–71.

Potegal M, & Einon D (1989). Aggressive behaviors in adult rats deprived of playfighting experience as juveniles. Developmental Psychobiology, 22(2), 159–172. [PubMed: 2925003]

Prather MD, Lavenex P, Mauldin-Jourdain ML, Mason WA, Capitanio JP, Mendoza SP, & Amaral DG (2001). Increased social fear and decreased fear of objects in monkeys with neonatal amygdala lesions. Neuroscience, 106(4), 653–658. [PubMed: 11682152]

Preuss T (1995). Do rats have a prefrontal cortex? The Rose-Woolsey-Akert reconsidered. Journal of Cognitive Neuroscience, 7, 1–24. [PubMed: 23961750]

Putnam PT, Roman JM, Zimmerman PE, & Gothard KM (2016). Oxytocin enhances gaze-following responses to videos of natural social behavior in adult male rhesus monkeys. Psychoneuroendocrinology, 72, 47–53. 10.1016/j.psyneuen.2016.05.016. [PubMed: 27343726]

Qiu Z, & Li X (2017). Non-human primate models for brain disorders - towards genetic manipulations via innovative technology. Neuroscience Bulletin. 10.1007/s12264-017-0115-4.

Rahman T, Zavitsanou K, Purves-Tyson T, Harms LR, Meehan C, Schall U, … Weickert CS (2017). Effects of immune activation during early or late gestation on N-methyl-d-aspartate receptor measures in adult rat offspring. Frontiers in Psychiatry, 8, 77 10.3389/fpsyt.2017.00077. [PubMed: 28928676]

Ramocki MB, Peters SU, Tavyev YJ, Zhang F, Carvalho CM, Schaaf CP, … Zoghbi HY (2009). Autism and other neuropsychiatric symptoms are prevalent in individuals with MeCP2 duplication syndrome. Annals of Neurology, 66(6), 771–782. 10.1002/ana.21715. [PubMed: 20035514]

Raper J, Stephens SB, Sanchez M, Bachevalier J, & Wallen K (2014). Neonatal amygdala lesions alter mother-infant interactions in rhesus monkeys living in a species-typical social environment. Developmental Psychobiology, 56(8), 1711–1722. 10.1002/dev.21234. [PubMed: 24986273]

Raper J, Wallen K, Sanchez MM, Stephens SB, Henry A, Villareal T, & Bachevalier J (2013). Sex-dependent role of the amygdala in the development of emotional and neuroendocrine reactivity to threatening stimuli in infant and juvenile rhesus monkeys. Hormones and Behavior, 63(4), 646–658. 10.1016/j.yhbeh.2013.01.010. [PubMed: 23380162]

Rapoport JL, Gied JN, & Gogtay N (2012). Neurodevelopmental model of schizophrenia: Update 2012. Molecular Psychiatry, 17(12), 1228–1238. 10.1038/mp.2012.23. [PubMed: 22488257]

Rat Research & Resource Center. (2010). Retrieved from < http://www.rrrc.us/ > .

Raza S, Himmler BT, Himmler SM, Harker A, Kolb B, Pellis SM, & Gibb R (2015). Effects of prenatal exposure to valproic acid on the development of juvenile-typical social play in rats. Behavioural Pharmacology, 26, 707–719. 10.1097/FBP.0000000000000169. [PubMed: 26230723]

Robbins TW, James M, Owens AM, Sahakian BJ, Lawrence AD, McInnes L, & Rabbitt PM (1998). A study of performance on tests from the CANTAB battery sensitive to frontal lobe dysfunction in a large sample of normal volunteers: Implications for theories of executive functioning and cognitive aging. Cambridge Neuropsychological Test Automated Battery. Journal of the International Neuropsychological Society, 4(5), 474–490. [PubMed: 9745237]

Rommeck I, Gottlieb DH, Strand SC, & McCowan B (2009). The effects of four nursery rearing strategies on infant behavioral development in rhesus macaques (*Macaca mulatta*). Journal of the American Association for Laboratory Animal Science, 48(4), 395–401. [PubMed: 19653949]

Ross CF (2000). Into the light: The origin of anthropoidea. Annual Review of Anthropology, 29, 147–194.

Ruby K, Falvey K, & Kulesza RJ (2015). Abnormal neuronal morphology and neurochemistry in the auditory brainstem of Fmr1 knockout rats. Neuroscience, 303, 285–298. 10.1016/j.neuroscience.2015.06.061. [PubMed: 26166728]

Rutishauser U, Mamelak AN, & Adolphs R (2015). The primate amygdala in social perception - insights from electrophysiological recordings and stimulation. Trends in Neurosciences, 38(5), 295–306. 10.1016/j.tins.2015.03.001. [PubMed: 25847686]

Sahakian BJ, Morris RG, Evenden JL, Heald A, Levy R, Philpot M, & Robbins TW (1988). A comparative study of visuospatial memory and learning in Alzheimer-type dementia and Parkinson's disease. Brain, 111(3), 695–718. [PubMed: 3382917]

Sanchez MM, Hearn EF, Do D, Rilling JK, & Herndon JG (1998). Differential rearing affects corpus callosum size and cognitive function of rhesus monkeys. Brain Research, 812(1–2), 38–49. [PubMed: 9813233]

Schneider T, & Popik P (2007). Attenuation of estrous cycle-dependent marble burying in female rats by acute treatment with progesterone and antidepressants. Psychoneuroendocrinology, 32(6), 651–659. [PubMed: 17561352]

Schneider T, & Przewlocki R (2005). Behavioral alterations in rats prenatally exposed to valproic acid: Animal model of autism. Neuropsychopharmacology, 30(1), 80–89. [PubMed: 15238991]

Schumann CM, Vargas M, & Lee A (2016). Synopsis of primate amygdala neuroanatomy In Amaral DG, & Adolphs R (Eds.). Living without an amygdala. Guilford Press.

Sefffer D, Schwarting RK, & Wöhr M (2014). Pro-social ultrasonic communication in rats: Insights from playback studies. Journal of Neuroscience Methods, 234, 73–81. 10.1016/j.jneumeth.2014.01.023. [PubMed: 24508146]

Short SJ, Lubach GR, Karasin AI, Olsen CW, Styner M, Knickmeyer RC, … Coe CL (2010). Maternal influenza infection during pregnancy impacts postnatal brain development in the rhesus monkey. Biological Psychiatry, 67(10), 965–973. 10.1016/j.biopsych.2009.11.026. [PubMed: 20079486]

Silverman JL, & Crawley JN (2014). The promising trajectory of autism therapeutics discovery. Drug Discovery Today, 19(7), 838–844. [PubMed: 24362109]

Silverman JL, Yang M, Lord C, & Crawley JN (2010). Behavioural phenotyping assays for mouse models of autism. Nature Reviews Neuroscience, 11(7), 490–502. 10.1038/nrn2851. [PubMed: 20559336]

Simpson EA, Jakobsen KV, Damon F, Suomi SJ, Ferrari PF, & Paukner A (2017a). Face detection and the development of own-species bias in infant macaques. Child Development, 88(1), 103–113. 10.1111/cdev.12565. [PubMed: 27223687]

Simpson EA, Miller GM, Ferrari PF, Suomi SJ, & Paukner A (2016). Neonatal imitation and early social experience predict gaze following abilities in infant monkeys. Scientific Reports, 6, 20233 10.1038/srep20233. [PubMed: 26831763]

Simpson EA, Paukner A, Sclafani V, Kaburu SS, Suomi SJ, & Ferrari PF (2017b). Acute oxytocin improves memory and gaze following in male but not female nursery-reared infant macaques. Psychopharmacology (Berlin), 234(3), 497–506. 10.1007/s00213-016-4480-x. [PubMed: 27837331]

Siviy SM, Love NJ, DeCicco BM, Giordano SB, & Seifert TL (2003). The relative playfulness of juvenile Lewis and Fischer-344 rats. Physiology & Behavior, 80(2–3), 385–394. [PubMed: 14637239]

Siviy SM, & Panksepp J (1987). Juvenile play in the rat: Thalamic and brain stem involvement. Physiology & Behavior, 41(2), 103–114. [PubMed: 3685158]

Sliwa J, Duhamel JR, Pascalis O, & Wirth S (2011). Spontaneous voice-face identity matching by rhesus monkeys for familiar conspecifics and humans. Proceedings of the National Academy of Sciences, 1–6 201008169.

Smaers JB, Steele J, Case CR, Cowper A, Amunts K, & Zilles K (2011). Primate prefrontal cortex evolution: Human brains are the extreme of a lateralized ape trend. Brain, Behavior and Evolution, 77(2), 67–78. 10.1159/000323671.

Small WS (1901). Experimental study of the mental processes of the rat. II. American Journal of Psychology, 12(2), 206–239.

Spruijt BM, Peters SM, de Heer RC, Pothuizen HH, & van der Harst JE (2014). Reproducibility and relevance of future behavioral sciences should benefit from a cross fertilization of past recommendations and today's technology: “Back to the future”. Journal of Neuroscience Methods, 234, 2–12. [PubMed: 24632384]

Syväoja HJ, Tammelin TH, Ahonen T, Kankaanpää A, & Kantomaa MT (2014). The associations of objectively measured physical activity and sedentary time with cognitive functions in school-aged children. PLOS One, 9(7), e103559 10.1371/journal.pone.0103559. [PubMed: 25061820]

't Hart BA (2015). Reverse translation of failed treatments can help improving the validity of preclinical animal models. European Journal of Pharmacology, 759, 14–18. 10.1016/j.ejphar.2015.03.030. [PubMed: 25823810]

Taylor LE, Swerdfeger AL, & Eslick GD (2014). Vaccines are not associated with autism: An evidence-based meta-analysis of case-control and cohort studies. Vaccine, 32(29), 3623–3629. 10.1016/j.vaccine.2014.04.085. [PubMed: 24814559]

Thomas A, Burant A, Bui N, Graham D, Yuva-Paylor LA, & Paylor R (2009). Marble burying reflects a repetitive and perseverative behavior more than novelty-induced anxiety. Psychopharmacology (Berlin), 204(2), 361–373. [PubMed: 19189082]

Thor DH, & Holloway JWR (1984). Developmental analyses of social play behavior in juvenile rats. Bulletin of the Psychonomic Society, 22(6), 587–590.

Till SM, Asiminas A, Jackson AD, Katsanevaki D, Barnes SA, Osterweil EK, … Kind PC (2015). Conserved hippocampal cellular pathophysiology but distinct behavioural deficits in a new rat model of FXS. Human Molecular Genetics, 24(21), 5977–5984. 10.1093/hmg/ddv299. [PubMed: 26243794]

Trezza V, Campolongo P, & Vanderschuren LJ (2011). Evaluating the rewarding nature of social interactions in laboratory animals. Developmental Cognitive Neuroscience, 1(4), 444–458. [PubMed: 22436566]

Vanderschuren LJ, Niesink RJ, Spruijt BM, & Van Ree JM (1995). Influence of environmental factors on social play behavior of juvenile rats. Physiology & Behavior, 58(1), 119–123. [PubMed: 7667408]

Vanderschuren LJ, Niesink RJ, & Van Ree JM (1997). The neurobiology of social play behavior in rats. Neuroscience & Biobehavioral Reviews, 21(3), 309–326. [PubMed: 9168267]

Vanderschuren LJ, & Trezza V (2014). What the laboratory rat has taught us about social play behavior: Role in behavioral development and neural mechanisms. Current Topics in Behavioral Neurosciences, 16, 189–212. 10.1007/7854_2013_268. [PubMed: 24338663]

Varlinskaya EI, Spear LP, & Spear NE (1999). Social behavior and social motivation in adolescent rats: Role of housing conditions and partner's activity. Physiology & Behavior, 67(4), 475–482. [PubMed: 10549884]

Vaughter RM, & Cross HA (1965). Discrimination reversal performance in children as a function of prereversal experience and overlearning. Psychonomic Science, 2(1–12), 363–364.

Watson KK, & Platt ML (2012). Of mice and monkeys: Using non-human primate models to bridge mouse- and human-based investigations of autism spectrum disorders. Journal of Neurodevelopmental Disorders, 4(1), 21 10.1186/1866-1955-4-21. [PubMed: 22958282]

Webster DG, Williams MH, Owens RD, Geiger VB, & Dewsbury DA (1981). Digging behavior in 12 taxa of muroid rodents. Animal Learning & Behavior, 9(2), 173–177.

Weed MR, Taffe MA, Polis I, Roberts TW, Koob GF, Bloom FE, & Gold LH (1999). Performance norms for a rhesus monkey neuropsychological testing battery: Acquisition and long-term performance. Cognitive Brain Research, 8(3), 185–201. [PubMed: 10556598]

Weiner KS, & Zilles K (2016). The anatomical and functional specialization of the fusiform gyrus. Neuropsychologia, 83, 48–62. 10.1016/j.neuropsychologia.2015.06.033. [PubMed: 26119921]

Weinstein TA, Bales KL, Maninger N, Hostetler CM, & Capitanio JP (2014). Early involvement in friendships predicts later plasma concentrations of oxytocin and vasopressin in juvenile rhesus macaques (*Macaca mulatta*). Frontiers in Behavioral Neuroscience, 8, 295 10.3389/fnbeh.2014.00295. [PubMed: 25221489]

Weinstein TA, & Capitanio JP (2012). Longitudinal stability of friendships in rhesus monkeys (*Macaca mulatta*): Individual- and relationship-level effects. Journal of Comparative Psychology, 126(1), 97–108. 10.1037/a0025607. [PubMed: 22352887]

Willette AA, Lubach GR, Knickmeyer RC, Short SJ, Styner M, Gilmore JH, & Coe CL (2011). Brain enlargement and increased behavioral and cytokine reactivity in infant monkeys following acute prenatal endotoxemia. Behavioural Brain Research, 219(1), 108–115. 10.1016/j.bbr.2010.12.023. [PubMed: 21192986]

Willner P (1984). The validity of animal models of depression. Psychopharmacology (Berlin), 83(1), 1–16. [PubMed: 6429692]

Winslow JT, Noble PL, Lyons CK, Sterk SM, & Insel TR (2003). Rearing effects on cerebrospinal fluid oxytocin concentration and social buffering in rhesus monkeys. Neuropsychopharmacology, 28(5), 910–918. [PubMed: 12700704]

Wohr M, & Schwarting RK (2013). Affective communication in rodents: Ultrasonic vocalizations as a tool for research on emotion and motivation. Cell and Tissue Research, 354(1), 81–97. 10.1007/s00441-013-1607-9. [PubMed: 23576070]

Wright MJ Jr., Vandewater SA, Parsons LH, & Taffe MA (2013). Δ9tetrahydrocannabinol impairs reversal learning but not extra-dimensional shifts in rhesus macaques. Neuroscience, 235, 51–58. 10.1016/j.neuroscience.2013.01.018. [PubMed: 23333671]

Yang M, Silverman JL, & Crawley JN (2011). Automated three-chambered social approach task for mice. Current Protocols in Neuroscience. 10.1002/0471142301.ns0826s56 Unit 8 26.

Yartsev MM (2017). The emperor's new wardrobe: Rebalancing diversity of animal models in neuroscience research. Science, 358(6362), 466–469. 10.1126/science.aan8865. [PubMed: 29074765]

Yee N, Schwarting RK, Fuchs E, & Wohr M (2012). Increased affective ultrasonic communication during fear learning in adult male rats exposed to maternal immune activation. Journal of Psychiatric Research, 46(9), 1199–1205. 10.1016/j.jpsychires.2012.05.010. [PubMed: 22687817]

Yerkes RM (1916). Provision for the study of monkeys and apes. Science, 43(1103), 231–234. 10.1126/science.43.1103.231. [PubMed: 17834280]

Young RL, Brewer N, & Pattison C (2003). Parental identification of early behavioural abnormalities in children with autistic disorder. Autism, 7(2), 125–143. 10.1177/1362361303007002002. [PubMed: 12846383]

Zan Y, Haag JD, Chen KS, Shepel LA, Wigington D, Wang YR, … Gould MN (2003). Production of knockout rats using ENU mutagenesis and a yeast-based screening assay. Nature Biotechnology, 21(6), 645–651. 10.1038/nbt830.

Zhang B, Noble PL, Winslow JT, Pine DS, & Nelson EE (2012). Amygdala volume predicts patterns of eye fixation in rhesus monkeys. Behavioural Brain Research, 229(2), 433–437. 10.1016/j.bbr.2012.01.009. [PubMed: 22285417]

Zhang-James Y, Yang L, Middleton FA, Yang L, Patak J, & Faraone SV (2014). Autism-related behavioral phenotypes in an inbred rat substrain. Behavioural Brain Research, 269, 103–114. 10.1016/j.bbr.2014.04.035. [PubMed: 24780868]

Zijlstra M, Bix M, Simister NE, Loring JM, Raulet DH, & Jaenisch R (1990). Beta 2-microglobulin deficient mice lack CD4-8+ cytolytic T cells. Nature, 344(6268), 742–746. 10.1038/344742a0. [PubMed: 2139497]

Fig. 1.

Laboratory rats and rhesus monkeys are highly social animals that engage in complex, reciprocal social interactions, including juvenile play.