Published in final edited form as:
Neuropharmacology. 2014 January ; 76(0 0): . doi:10.1016/j.neuropharm.2013.05.047.

Rats are the smart choice: Rationale for a renewed focus on rats in behavioral genetics

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Abstract

Due in part to their rich behavioral repertoire rats have been widely used in behavioral studies of drug abuse-related traits for decades. However, the mouse became the model of choice for researchers exploring the genetic underpinnings of addiction after the first mouse study was published demonstrating the capability of engineering the mouse genome through embryonic stem cell technology. The sequencing of the mouse genome and more recent re-sequencing of numerous inbred mouse strains has further cemented the status of mice as the premier mammalian organism for genetic studies. As a result, many of the behavioral paradigms initially developed and optimized for rats have been adapted to mice. However, numerous complex and interesting drug abuse-related behaviors that can be studied in rats are very difficult or impossible to adapt for use in mice, impeding the genetic dissection of those traits. Now, technological advances have removed many of the historical limitations of genetic studies in rats. For instance, the rat genome has been sequenced and many inbred rat strains are now being re-sequenced and outbred rat stocks are being used to fine-map QTLs. In addition, it is now possible to create “knockout” rats using zinc finger nucleases (ZFN), transcription activator-like effector nucleases (TALENs) and related techniques. Thus, rats can now be used to perform quantitative genetic studies of sophisticated behaviors that have been difficult or impossible to study in mice.

Keywords

QTL; GWAS; rats; behavioral genetics; addiction

1. Introduction

For over a century, the rat has been favored for studying neurobiological processes and for providing neuropsychological models for human behavioral disorders (Jacob 1999; Logan 2005; Weiss and Feldon, 2001); due in part to its complex behavioral repertoire. Accordingly, many of the behavioral assays used to assess phenotypes of interest and validate pharmacological agents were designed and optimized for use in rats. However, the mouse became the model of choice for mammalian geneticists in the 1990s, after the first mouse study was published demonstrating the capability of engineering the mouse genome through embryonic stem (ES) cell technology (Thomas and Capecchi, 1990). This "knockout" technology allowed mice to be produced that lacked a single, specific gene and was a key factor in choosing the mouse to be the next mammal after humans to have its genome sequenced (Waterston, 2002). Thus, the dominance of the mouse as a genetic tool has been long-lasting, despite the abundance of rich behavioral and physiological phenotypes that can be measured in the rat (Jacob 1999). However, the rat genome was released in 2004 (Gibbs et al., 2004), significantly enhancing efforts at comparative genomics and enabling cross-species data integration. A new build of the rat genome incorporating novel sequence data and mapping technologies was released in March 2012 and is currently being annotated (http://www.ncbi.nlm.nih.gov/assembly/382928/). In addition, genetic analyses of experimental rat crosses has allowed for the identification of hundreds of rat quantitative trait loci (QTLs) that were associated with drug-related traits (http://rgd.mcw.edu/rgdweb/search/qtls.html?100). However (as with the QTL studies conducted by mouse geneticists), few genes were identified relative to the number of QTLs. Furthermore, mouse models still possessed a clear advantage for experimental genetics due to the relative ease of obtaining homologous recombination in mouse ES cells, which has allowed the production of 'knock out' and similar genetic models in mice. *Thus, two major obstacles have plagued rat geneticists and discouraged the widespread use of rats as a genetic model organism:* 1) forward genetic approaches in rats such as QTL mapping failed to identify genes due to difficulties in narrowing QTLs intervals, and 2) the rat genome has not allowed itself to be genetically manipulated in the same way as the mouse, hindering reverse genetic approaches. Now, due to technical advances, these two obstacles have been overcome, allowing for both the localization and functional validation of genes underlying complex traits in rats. Rats and mice have advantages for the understanding of human disease above and beyond what is possible when studying humans directly. Rats possess a rich behavioral repertoire compared to mice; furthermore, their large size makes it easy to carry out detailed physiological measurements not feasible in smaller animal models such as mice (Abbott, 2004). Furthermore, almost all human genes known to be associated with disease have orthologues in the rat genome (Gibbs et al., 2004) and most disease genes identified in rats have also been shown to play a role in human diseases (Aitman et al., 2008). Lastly, because rats and mice are experimental model organisms, researchers can perform potentially stressful, invasive, or even terminal procedures not possible in humans, such as measuring gene expression in key brain regions.

In this review, we discuss how the wealth of new genetic technologies, combined with the phenotypic diversity of the rat make them ideally suited for use in genetic studies of complex behavioral traits. We describe in detail three phenotypes that have been difficult to implement in mouse models, but that have been successfully used in rats. While our review focuses on addiction-related phenotypes, many of these same arguments apply to other

complex behavioral and physiological traits. The advantage of using rats as behavioral and neurobiological models is not new. In light of recent technological advances, we argue that complex behavioral tasks that have been difficult or impossible to pursue in mice can now be successfully studied in rats.

2. Genetic Approaches in Rat Models of Substance Abuse Disorders

Genetic techniques used for addiction research in rat models include both “phenotype-to-genotype” and “genotype-to-phenotype” approaches. Phenotype-to-genotype, or forward genetics, begins with the measurement of the trait of interest in order to uncover the underlying genetic architecture in a population. Genotype-to-phenotype, or reverse genetics, is a method to discovering the function of a gene by examining the phenotypic effects that result from a targeted mutation. Both techniques are useful for integrating results from human and rat genetics studies.

2.1. Forward Genetics (QTL mapping)

Forward genetic strategies seek to identify the genes and alleles that give rise to variability in a trait of interest. Thus, forward genetics is an unbiased approach that is useful for hypothesis generation. Traditionally, QTL studies have used F_2 crosses between two inbred strains, recombinant inbred (RI) lines or similar populations. Associations between the genetic markers and phenotypes are analyzed to determine the location of the QTLs. Due to limited recombination, these populations are not well suited to fine-mapping the identified loci, which is a necessary pre-requisite to identifying the underlying causative gene(s). This drawback has challenged mouse and rat geneticists for years. However, human genome-wide association studies (GWAS) have been successful precisely because they take advantage of the large number of accumulated recombinations observed among unrelated human subjects. Recombination degrades the non-random associations between adjacent polymorphisms; these associations between nearby markers are known as linkage disequilibrium (LD). Populations that have been intercrossed for multiple generations accumulate many recombinations, which causes a rapid breakdown of LD between adjacent markers. Thus, only markers that are very close and thus in LD with a functional polymorphism will show a significant association with the trait of interest. Populations with more degraded LD allow for more accurate mapping of QTLs, provided that enough markers are genotyped and can ultimately lead to the identification and validation of the causative polymorphism.

Now, as technologies for genotyping have evolved rapidly over the past decade, it is no longer expensive or difficult to perform GWAS in rats. The same improvements in genotyping technology that have been widely used in human genetics and are beginning to be applied to mouse genetics (Parker and Palmer, 2011) also possess enormous but largely unrealized potential to revolutionize rat genetics. Genome technologies such as high-throughput sequencing, RNASeq, or high-density SNP chips would not be useful for standard F_2 crosses, but are extremely helpful when populations with more degraded LD are used. Rat populations such as heterogeneous stocks and commercially available outbred rats have been used for decades for physiological and behavioral analyses and possess very low levels of LD. Now, these highly recombinant rat populations are increasingly attracting the attention of geneticists and their use promises to streamline what has been a very slow and expensive process: definitive identification of the genes that underlie QTLs.

2.1.1. Heterogeneous stocks (HS)—Heterogeneous stocks are created by interbreeding more than two (often eight) inbred strains followed by many generations of randomized outcrossing (Flint and Eskin 2012; Parker and Palmer, 2011). In mice, the diversity outcross (DO) and the heterogeneous stock (HS) mice have been successfully used for the high-

resolution mapping of multiple complex traits (e.g. Svenson et al., 2012; Valdar et al., 2006). The heterogeneous stock rat (N:NIH-HS) was developed by the National Institutes of Health in 1984 (Hansen and Spuhler 1984) to serve as a source of genetically segregating animals for both experimental and selection studies. Similar to HS and DO mice, the HS rat was originally derived from eight inbred founder strains that are both genetically (Saar et al., 2008) and phenotypically (see Johannesson et al., 2009) distinct: ACI/N, BN/SsN, BUF/N, F344/N, M520/N, MR/N, WKY/N and WN/N. This stock was then outbred for over 50 generations using a rotational outbreeding scheme to minimize the amount of inbreeding, drift, and fixation. The number of generations of outbreeding determines the degree to which LD from the original founder chromosomes is degraded (Mott and Flint, 2002). After 50 generations of outbreeding, the genetic make-up of the resulting progeny represents a random mosaic of the founding animals, with an average distance between recombination events per individual of about one centiMorgan (Mott et al., 2000), enabling the fine-mapping of QTL to only a few Mb (see Solberg Woods et al., 2010a; 2012; Johannesson et al., 2009).

Based on the predisposition of several of the founder strains, and work conducted in the N:NIH-HS rat colony, we expect this resource to be particularly useful for fine-mapping behavioral traits. For example, the MR/N strain exhibits increased emotionality (Overstreet et al., 1992) and the WKY rat has been used as a model of depression (Pare, 1989; Solberg et al., 2004). In addition, the eight inbred founder strains of the N:NIH-HS rats display significant variation in 16 different measures of behavioral and physiological response to ethanol (Spuhler and Deitrich, 1984). As expected, the N:NIH-HS rat colony exhibits significant variation in several behavioral traits including anxiety, fear and depression as well as behavioral and physiological responses to stress (Diaz-Moran et al., 2012; Lopez-Aumatell et al., 2008, 2009) and to ethanol (Spuhler and Deitrich, 1984; Foroud et al., 2000). These studies indicate that the N:NIH-HS rat will be ideal for studying the genetics of many behavioral traits including alcohol- and drug-related traits, anxiety, fear and depression.

The eight founder strains of the N:NIH-HS rat colony have been fully sequenced and this information is now publicly available on the Rat Genome Database (http://rgd.mcw.edu/; Consortium GSaM, submitted). Although genetic mapping in HS will not always lead to gene-level resolution, Keane et al. (2011) have demonstrated that availability of founder sequence, combined with RNA expression levels, can quickly lead to candidate functional variants. To the extent that the polymorphisms in the founder strains are known, haplotype mapping can be performed even at markers that are not directly genotyped (Svenson et al., 2012). The N:NIH-HS is not without limitations: it requires maintaining a large breeding colony and QTL mapping in the N:NIH-HS requires accounting for relatedness (Cheng et al., 2011; Valdar et al., 2009); nevertheless, we expect the HS rat colony to significantly move forward the field of rat behavioral genetics.

2.1.2. Laboratory Outbred Rats—While many laboratory rodents have been deliberately inbred, a number of populations have also been maintained using outbred breeding schemes that maintain large numbers of individuals in each generation and that avoid crosses between closely related individuals. Commercially available outbred mice have been shown to be a powerful way to fine-map QTLs to intervals as small as 100Kb (Aldinger et al., 2009; Yalcin et al., 2004; 2010), and the same may be true in outbred rats. Outbred rats such as the Sprague Dawley exhibit hybrid vigor with long life spans, high disease resistance, early fertility, large and frequent litters, low neonatal mortality, rapid growth, and large size. The primary advantage for using outbred stocks for genetic studies is the ability to achieve mapping resolution at the single gene level due to much greater breakdown of LD (Chia et al., 2005, Flint et al., 2005). This has been demonstrated in QTL

mapping studies utilizing outbred mice (Yalcin et al., 2004, 2010), but remains to be seen in outbred rats. Most outbred rat stocks are derived from small and relatively homogeneous populations, suggesting a low proportion of rare alleles. In fact, many available rat stocks trace their ancestry to a stock that was maintained at the Wistar Institute. Both Sprague-Dawley and Long Evans stocks were similarly derived from a small number of breeders; each of them descendants from a single mating between a Wistar female and males of different origins (Lopez-Aumatell et al., 2008). However, it is possible that many relatively rare variants will exist in these populations as a result of uneven sampling for the foundation population, genetic drift, and new mutations; thus some of the problems familiar to human genetics will also exist when performing GWAS using outbred stocks. It is also important to note that the somewhat limited genetic diversity of outbred colonies means that they (like HS rats) cannot be used to analyze the effects of all variants that potentially exist across *Rattus Norvegicus* (see Yalcin et al., 2010). Because some parts of the genome may possess little functional variation it might be necessary to study multiple populations to capture the full spectrum of genetic variation (see Roberts et al., 2007). Because outbred stocks can be purchased from commercial vendors, they do not require maintenance of an expensive colony. Although commercially available outbred rat stocks have not been utilized for genetic mapping to date, success in mice (Yalcin et al., 2010; Zhang et al., 2012), suggests that this may be a promising avenue for genetic mapping in rat in the future.

2.2. Reverse Genetic Approaches

Although the entire genome sequence of the rat has been available for almost a decade, lack of reverse genetic tools hindered translational comparisons of gene function. Gene targeting is indispensable for reverse genetics and the generation of animal models of disease. The mouse has become the most commonly used animal model system owing to the success of ES cell–based targeting technology (Capecchi, 2005), whereas rats have lacked convenient tools for genome modification. In mice, gene targeting in ES cells is achieved by homologous recombination in ES cells. In species without established germline-competent ES cells, targeted gene modification is not feasible, thus limiting their use as a model system. Therefore, even though the rat has been a preferred model for studying many human diseases; the lack of tools for gene modification has limited its use in genetic studies. Non-homologous approaches that use DNA microinjection into rat embryos have been used for over 20 years, but methods for homologous recombination rat ES cells have proven difficult. Recently, considerable progress has been made with rat ES cell-based gene targeting technology (Buehr et al., 2008; Kawamata and Ochiya, 2010; Li et al., 2008; Tong et al., 2010). For example, Tong et al. (2010) successfully designed a targeting vector to disrupt the tumor suppressor gene p53 in rat ES cells by means of homologous recombination. Furthermore, the p53 gene-targeted mutation in the rat ES cell genome could transmit through the germ line via ES cell rat chimaeras to create p53 gene knockout rats. However, time-consuming backcrossing is often necessary when ES cells are not available from the desired strain (Ledermann, 2000). Now, the application of engineered zinc-finger nucleases (ZFNs) and transcription activator-like effector (TALE) domains for efficient TALE nucleases (TALENs) may overcome the limitations of ES cell technology. ZFNs and TALENs induce double-strand breaks at desired loci that can be repaired by error-prone non-homologous end-joining DNA repair pathway to yield targeted mutations at the break sites (Cui et al., 2011; Geurts et al., 2009; Wood et al., 2011). This approach enables precise genome engineering to generate modifications such as point mutations, accurate insertions and deletions, and conditional knockout and knockin rats. Two significant advantages of this approach are speed (~ 4 months from gene selection to knockout animal) and ability to apply ZFNs/TALENs to any rat strain that is amenable to obtaining embryos for microinjection (Dwinell et al., 2011). Currently, two major projects are underway to systematically knock out a large number of genes in rats: the PhysGen Knockout Program (http://rgd.mcw.edu/

wg/physgenknockouts) and SAGE labs (http://www.sageresearchmodels.com/research-models). The mission of PhysGen Knockout program is to knock out a large number of genes nominated by genome wide association studies, combine these gene knockouts (KO) with hypertensive and normotensive strains, and phenotypically characterize them. SAGE seeks to provide off-the-shelf knockout rats for genes relevant to psychiatric, cardiovascular, immunological, and oncological diseases. An important and powerful attribute of these technologies is the ability to apply them to different strain backgrounds, including inbred and outbred rat strains (A.M.G. unpublished), thus reducing the need for time-consuming backcrosses into a particular model strain to achieve the desired phenotype. As Dwinell et al. (2011) note, the ability to apply ZFN/TALEN technology at a rapid pace across such a wide variety of strains and disease models has not previously been possible, even in mice. Several knockout rat phenotypes have now been published (Chen et al., 2012; Chu et al., 2012; Feng et al., 2012; Gopalakrishnan et al., 2012; Mashimo et al., 2010; Moreno et al., 2011; Rangel-Filho et al., 2013; Zschemisch et al., 2012) utilizing the SS/Jr, SS/JrHsdMcwi, FHH/EurMcwi, and LEW/Ztm, inbred and the Wistar Hannover outbred strains. Furthermore, stimulation of the double-strand breaks can also stimulate homology-dependent repair, allowing for site-specific ‘knock in’ of new sequences into the mouse and rat genomes (Cui et al., 2011; Meyer et al., 2010, 2012) Thus, the establishment of gene targeting technology in rat ES cells and ZFNs/TALENs, in combination with advances in genomics and the existing foundation of physiological and pharmacological data in this species, now provide a powerful new platform to explore the genetic underpinnings of drug-related traits in rats that may have translational relevance to substance abuse disorders in humans.

3. Advantages of using rats in modeling drug abuse related behaviors

Most of the behavioral tests used by behavioral geneticists were originally established in rats and later adapted for mice. Below we discuss three examples of behavioral tests relevant to drug abuse that are of great translational interest and are particularly well-suited to rats, but have been challenging to implement in mice. In large part, we believe this is due to the fact that mice are not simply “smaller rats”, but rather a different species that occupies a slightly different ecological niche, resulting in distinctive social and foraging behaviors, impulsivity and stress-coping strategies (Sousa et al., 2006). Another reason why these particular tasks have been difficult to use in mice may be due to sensory deficits in KO, inbred, and RI mouse lines that muddy the interpretation of performance on tasks that require numerous sessions to acquire (e.g., impulsivity tasks) or tasks that rely on visual or auditory stimuli (e.g., incentive salience) (see Clapcote et al., 2005; Cook et al., 2001 for examples).

3.1. Impulsivity

One focus of drug abuse research has been on the relationship between impulsivity and drug abuse (see de Wit, 2009; Dick et al., 2010 for reviews). Theoretical interpretations (De Wit & Richards, 2004) and empirical studies with humans (Reynolds et al., 2008, Sonuga-Barke, 2002) indicate that there are two unrelated forms of impulsivity; motor or “action” impulsivity and cognitive impulsivity. The dissociation between motor impulsivity (action impulsivity) and cognitive forms of impulse control have led to the development of two different approaches to measuring impulsive behavior in rodents. Impulsive action is measured using a variety of tasks, the common factor being a measure of premature responding. Premature responses are unrewarded responses that occur too soon or prior to the presentation of a “go” stimulus. These premature responses have the effect of delaying the next reward. The task most often used to measure “action” impulsivity is the 5 choice serial reaction time task (5CSRTT; Robbins, 2002), but other tasks in which animals are required to inhibit responding are also used. These include the stop-signal task (Eagle & Robbins, 2003, Feola et al., 2000), choice reaction time tasks designed to measure attention

related processes (Carli et al., 1983, Sabol et al., 2003) and responding on DRL schedules of reinforcement (Lovic et al., 2011a, 2011b).

Cognitive forms of impulsivity are measured using a variety of delay discounting tasks that measure choices between small immediate and large but delayed rewards (Evenden & Ryan, 1996, Mazur, 1988, Richards et al., 1997). These tasks are designed to determine the degree to which a delay causes the value of reinforcers to decrease. Greater discounting of reward value by delay indicates greater impulsivity. These tasks, involving cognitive choice behavior require extensive training. An important feature of these tasks is that the interval between trials is controlled so that choice of the smaller immediate reward always has the worst outcome in terms of overall reward amount.

A wide variety of empirical studies with rats have produced results indicating the importance of the disassociating action and cognitive impulsivity. For example, lesions of the subthalamic nucleus in rats have been found to increase action impulsivity and to decrease cognitive impulsivity (Uslaner & Robinson, 2006). Developmental studies with rats have found that chronic treatment with atomoxetine (Sun et al., 2012) and corticosterone (Torregrossa et al., 2012) during adolescence and social isolation during infancy (Lovic et al., 2011a) have differential effects on action and cognitive impulsivity. A drug abuse related study reported that action impulsivity was associated with nicotine self-administration while cognitive impulsivity was associated with enhanced vulnerability to relapse (Diergaarde et al., 2008). And finally, Lovic et al. (2011b) reported that the incentive salience of reward cues was related to action impulsivity but not cognitive impulsivity.

The following section is not meant to provide an exhaustive review of the current literature on impulsive behavior in rodents; rather we will select a specific impulsivity task in particular to illustrate the utility of using rats instead of mice (see Young et al., 2012 for a review of differences between mouse and rat performance on the 5CSRTT). We (J.B.R.) developed the adjusting amount procedure to measure the subjective value of delayed rewards, i.e. delay discounting (Richards et al., 1997). In the section below we discuss our experience using the delay discounting task with rats and mice in order to highlight the difficulty of training mice on a task that was initially developed for use with rats.

The adjusting amount procedure is simply a psychophysical testing procedure for determining indifference points between small immediate rewards and larger delayed rewards. The adjusting amount procedure that we developed for rats was the product of much trial and error testing. Trial and error testing was used to determine the size of the test chamber, the use of snout poking as the operant response , the precise arrangement of the snout poke holes on the intelligence panel, the duration of the testing and even the amounts of water that were used as reinforcers. The adjusting amount procedure has been successfully used in rats to characterize the effects of deprivation (Richards et al., 1997), reinforcer magnitude (Farrar et al., 2003), opiate agonists and antagonists (Kieres et al., 2004), dopamine agonists and antagonists (Wade et al., 2000), chronic amphetamine (Richards et al., 1999), and lesions of the nucleus accumbens (Acheson et al., 2006) on delay discounting.

We have adapted the adjusting amount procedure to mice in order to take advantage of genetic technology that was available for mice but not for rats (at that time). Although we and others have managed to train mice on the adjusting amount procedure (Mitchell, 2011, Richards et al., 2011, Wilhelm et al., 2007), using the adjusting amount procedure in mice is difficult. It takes significantly longer to train and test the mice than rats and the resulting data are more variable. There are many possible reasons for the difficulty in training mice. There are the obvious physical problems associated with using mice; i.e., the mouse's

smaller size requires a different apparatus and reward amounts. Mice and rats may also have fundamentally different behavioral predispositions. For example, some researchers believe that the odors of animals previously tested in the same test chamber may be more disruptive in mice than in rats. Finally, there are remarkable differences in gross activity levels between mouse strains commonly used as background strains for genetic manipulation (i.e, C57BL/6J, 129SvJ).

It is tempting to consider that the difficulty of training and the poor performance of mice on the delay discounting task is because they are “dumb”. Rather, the poor performance of mice on the adjusting amount procedure may be because the procedure has been “tuned” for use with rats. William Timberlake (Timberlake, 2001, 2002) has pointed out that many of the commonly used behavioral paradigms have been “tuned” for use with a specific species. He refers to this as “niche” related learning. As examples he cites the use of key lights for pigeons and moving levers for rats. In both cases responding can be “auto shaped” by pairing with food using Pavlovian conditioning procedures. According to Timberlake these response manipulandum have been “tuned” in that they have been selected and modified to take advantage of niche related learning mechanisms that are specific to the target species. Timberlake goes on to say that considering niche related learning may “be critical in adapting a battery of rat tests to work with another species, such as mice”. An important implication of Timberlake’s “tuning hypothesis” is that rats may perform poorly relative to mice on tasks that have been “tuned” for mice and vice versa. Timberlake’s message implies that simply shrinking the size of an operant chamber or some other apparatus designed for rats in order to use it with mice may not be a successful strategy because these devices and accompanying procedures were designed for niche related leaning mechanisms that are specific to rats. New developments in ethologically relevant operant task design that are related to naturally occurring mouse foraging behaviors may prove useful in generating viable translational mouse models. In the meantime or as an alternative, studies of delay discounting can be performed using the better established paradigms for rats.

3.2. Self-Administration

Laboratory animal and human models of drug self-administration have been extensively used to measure the rewarding qualities of drugs, predict the abuse liability of novel drugs, and evaluate treatments for abuse and dependence. Self-administration paradigms seek to exploit the reinforcing effects of drugs of abuse to measure motivation for drug reward and reinforcement. The nucleus accumbens, central amygdala, and ventral pallidum are known to play a critical role for the acute reinforcing effects of drugs in rats, mice, and humans (Koob and Volkow, 2010). A typical experiment involves placing rats implanted with intravenous catheters in operant chambers each equipped with two levers; pressing the active lever delivers unit doses of the drug while the inactive lever is without consequence and used as an index of general motor response. A visual cue usually accompanies the delivery of the drug (Corrigall and Coen, 1989). Each session lasts between 1 and 23 hours per day. Prior operant training for food is common (Corrigall and Coen, 1989); but food training or priming drug injections are not always required (Valentine et al., 1997). Some of the most compelling evidence that this procedure can be used to model addiction comes from the finding that compulsive cocaine self-administration persists even in the face of punishment in trained rats (Deroche-Gamonet et al., 2004; Vanderschuren and Everitt, 2004). In addition, many “prolonged access” procedures have revealed that only a subset of rats develop an addiction-like phenotype, and it takes many (50+) days of self-administration to see the phenotype emerge. Therefore, the prolonged access procedures are thought to provide a more realistic model of addiction than short access procedures. Similarly, when nicotine is self-administered by rats, it achieves pharmacokinetic profiles (Matta et al., 2007; Rose et al., 1999) and plasma levels (Shoaib and Stolerman, 1999)

similar to those found in smokers. Although both nicotine and the cue light are weak reinforcers, nicotine synergistically enhances the rewarding properties of the cue light (Palmatier et al., 2006). Therefore rats press more on the active lever that delivers nicotine. Nicotine in the range of 0.015–0.06 mg/kg/infusion consistently results in an inverted U-shaped dose response curves (Chen et al., 2007; Corrigall and Coen, 1989; Donny et al., 1998; O'Dell et al., 2007; Shoaib et al., 1997; Valentine et al., 1997).

Self-administration can model complex aspects of drug taking behavior. For example, most smokers begin during adolescence. Correspondingly, adolescent rats have been found to acquire nicotine self-administration faster than adults (Chen et al., 2007; Levin et al., 2007) (but see Shram et al., 2008). The critical role of social environment in smoking initiation has also been modeled in adolescent rats (Chen et al., 2011), and the effect of genetic factors has been demonstrated using a variety of rat strains (Brower et al., 2002; Chen et al., 2012; Shoaib et al., 1997). When given prolonged access, signs of nicotine withdrawal (O'Dell et al., 2007; Paterson and Markou, 2004) and dependence (O'Dell et al., 2007) can be observed. Operant response for nicotine can be extinguished and nicotine seeking behavior can be reinstated by a nicotine associated cue (Liu et al., 2007; Paterson et al., 2005) or exposure to stress (Buczek et al., 1999). Vareniclin, a smoking cessation drug, has been shown to reduce nicotine self-administration and drug-seeking (Le Foll et al., 2012), providing further validation for the model.

In general, training mice to self-administer intravenous drugs is significantly more challenging for a variety of reasons, including: 1) their much smaller body size makes surgery and equipment setup more difficult, 2) mice are more likely to develop adverse health consequences during long sessions and prolonged access procedures, 3) mice display higher inter- and intra-subject variability, and 4) mice are less adaptable to changes in experimental conditions (e.g. drug doses) (Thomsen and Caine, 2007). Furthermore, compulsive cocaine intake when punished has not been demonstrated in mice. Despite these challenges, self-administration studies in mice have made tremendous contributions to improving our understanding of the roles various nicotinic acetylcholine receptor subunits play in the behavioral effects of nicotine (Tuesta et al., 2011). But it is important to note that these studies either first trained mice with cocaine (Epping-Jordan et al., 1999; Picciotto et al., 1998), failed to control for general motor response from the same animal (Pons et al., 2008), did not control for intravenous saline (Cahir et al., 2011), or required priming injections of nicotine before each session (Metaxas et al., 2010; Orejarena et al., 2012). These compromises were made, at least partially, because of the difficulty in unequivocally demonstrating operant behavior specific for nicotine in C57BL/6J mice. For example, Contet et al. (2010) used a limited access procedure similar to those used in rats and trained C57BL/6J mice to self-administer 0.01 or 0.03mg/kg nicotine. They found that although mice selectively pressed the active lever, there was no dose response in the range of 0–0.06 mg/kg/infusion, while a higher dose suppressed lever response (Contet et al., 2010). Furthermore, the light cue alone maintained lever responses in naive mice similar to those found in nicotine mice. Therefore, the contribution of nicotine in maintaining lever press response cannot be differentiated from those of the cue light in mouse models. More recently, Yan et al. (2012) used nose-poking as the operant behavior and found C57BL/6J mice were able to self-administer intravenous nicotine without prior operant training. Although this replicated some of the findings typical of rats such as extinction of operant behavior and reinstatement of drug seeking by nicotine injection, stress, or the visual cue (Yan et al., 2012); the number of active nose pokes failed to respond to different nicotine doses (0–0.06 mg/kg/infusion). Fowler and Kenny (2011) modified the lever response procedure (e.g. reducing the speed of nicotine infusion, extending the duration of the cue light, conducting the sessions during the light cycle when the animals were less active, and used at least five consecutive days for the dose response test) (Fowler and Kenny, 2011) and

demonstrated that C57BL/6J mice responded more for nicotine than for saline, and observed a classical inverted U-shaped dose response curve. Using this model, it was shown that Chrna5 null mice markedly increased nicotine self-administration (Fowler et al., 2011). However, despite these remarkable advances, there is still a lack of agreement between laboratories regarding the exact test condition under which the reinforcing effect of nicotine can be unequivocally demonstrated in mice. It remains to be seen whether results obtained under any particular set of conditions can be generalized to other situations. Furthermore, with the much faster nicotine metabolism in mice (Matta et al., 2007), it is still unknown if the plasma nicotine levels in self-administering mice are comparable to smokers. Lastly, it will be technically very challenging to test the vulnerability of adolescent mice to intravenous nicotine due to their small body size.

3.3. Incentive Salience

When environmental stimuli (e.g. people, places, paraphernalia, etc.) are repeatedly paired with rewards, including drugs of abuse, such stimuli not only become predictors of impending reward, but they can also acquire incentive motivational properties, or become imbued with “incentive salience” via Pavlovian learning mechanisms (see Berridge, 2001). The motivational properties of drug-associated cues are thought to be important in motivating ongoing drug-taking behavior, and especially in precipitating relapse, despite a desire to remain abstinent (Everitt and Robbins, 2005; Kruzich and Congleton, 2001; Robinson and Berridge, 1993; Stewart et al., 1984; Tomie, 1996). However, recent studies have demonstrated that there is considerable individual variation in the ability of reward-associated cues to control behavior (e.g., Flagel et al., 2009; Meyer et al., 2012; Robinson and Flagel, 2009). When rats are exposed to a classical Pavlovian conditioning situation wherein the brief presentation of an illuminated lever (conditional stimulus, CS) is repeatedly paired with the delivery of a food pellet (unconditional stimulus, US), the CS comes to elicit a conditional response (CR). For some rats, referred to as “sign-trackers”, the CR consists of approach towards and manipulation of the lever-CS. Furthermore, for these individuals the CS itself becomes ‘wanted’ in that they will work for presentation of the CS in the absence of food reward (Flagel et al., 2011a; Robinson and Flagel, 2009). For others, termed “goal-trackers”, the lever-CS serves merely as a predictor of reward and the CR consists of approach towards the location of food delivery, and for these animals the cue is a less effective conditioned reinforcer (Meyer et al., 2012).

Importantly, variation in the propensity to attribute incentive salience to a food cue predicts the extent to which drug cues gain motivational control over behavior. For example, rats that sign-track to a food-associated cue will do the same for a drug-associated cue (Flagel et al., 2010; Yager and Robinson, 2012). In addition, Saunders and Robinson (2010) have demonstrated that a cocaine-associated cue is more effective at maintaining drug-taking behavior and in instigating relapse in sign-trackers relative to goal-trackers. These phenotypes also show profound differences in the dopamine system and in the neural circuitry that is activated in response to a reward cue (Flagel et al., 2010; Flagel et al., 2011a; 2011b; Saunders and Robinson, 2012). Finally, there is evidence that this trait—the propensity to attribute incentive motivational value to reward cues—is heritable (Flagel et al., 2010). As discussed by Flagel et al. (2013) in the current Neuropharmacology issue, rats that are selectively bred on the basis of locomotor response to novelty differ on this trait. Bred high-responder (bHR) rats are sign-trackers and bred low-responder (bLR) rats are goal-trackers, and the overlap between these phenotypes has remained stable over several generations. These findings are especially interesting given that there is no relationship between the tendency to attribute incentive salience to reward cues and locomotor response to a novel environment in outbred rats, suggesting that the two traits may be dissociable.

Nonetheless, the fact that the sign-tracker/goal-tracker trait was co-selected across multiple generations of the bHR/bLR lines is evidence for heritability.

In sum, the propensity to attribute incentive salience to reward cues is a complex psychological trait (Meyer et al., 2012) that appears to be heritable (Flagel et al., 2010) and likely impacted by gene x environment interactions (e.g, Lomanowska et al., 2011). Utilizing a rat model of incentive salience to gain a better understanding of the interplay between genetic, epigenetic, environmental and neurobiological factors that contribute to addiction liability and impulse-control disorders has important implications for the development of novel therapeutic interventions. To date, only one study has been published on Pavlovian conditioned approach and goal tracking performance in mice (Tomie et al., 2012). Unlike findings in rats, there is a positive correlation between sign-tracking and goal-tracking in the mice used in this study. This may be due to species differences surrounding how rats and mice search for and obtain food or it may be due to difficulties in getting mice to engage the levers during behavioral training (similar to Timberlake's arguments about behavioral tuning as discussed in section 3.1). Regardless, it remains unclear as to what psychological process or neural system mediates sign-and goal-tracking behaviors in mice, and even though they show what appears to be related behavior does not allow one to infer they are the same as in rats.

4. Bioinformatics and resources

In addition to developing mapping populations and genetically modified rats, bioinformatics tools must be developed to fully utilize and synthesize strain, genome sequence, gene expression, physiological, and behavioral data. Many powerful mouse resources such as the knockout mouse project (KOMP), the Collaborative Cross, GeneNetwork, and the Allen Brain Atlas have no counterpart in rats. The rat community should carefully examine the experiences of the mouse community as they develop their own catalogs and databases. However, bioinformatics resources are growing in the rat community (see Aitman et al., 2008). For example, the Rat Genome Database (www.rgd.mcw.edu), serves as a repository for genomic, genetic, functional, physiological and disease data for more than 650 inbred rat strains and over 2,275 rat models that have been used to study the genetics of complex diseases (Dwinell et al., 2011; Laulederkind et al., 2012). In addition, it collects homology data between rat, mouse and human to improve translational research. Other resources include the Rat Phenome Project (http://www.anim.med.kyoto-u.ac.jp/nbr/phenome.aspx), which has characterized ˜200 rat strains as models of human diseases and collected strain data for a range of neurobehavioral and anatomical categories; and the Rat Resource and Research Center (http://www.rrrc.us/), which collects, preserves, and supplies inbred, hybrid and mutant rats to researchers offer significant resources to the rat genetics and genomics community. Collectively, these databases allow for more accurate rat models of human diseases by linking genes with physiological and behavioral traits.

5. Conclusions

There is no question that mice have provided a powerful model for associating drug-abuse phenotypes with specific genes and polymorphisms. The use of rat genetic models is now growing due to the availability of genetic technologies, their superiority as a model organism for many behavioral tasks, and the wealth of already existing behavioral and physiological data that has been generated over many decades. Thus, it is no longer necessary to use mice for behavioral experiments that they are ill-suited for solely due to their technical advantages as a genetic organism. The decision to use mice or rats can instead depend upon the behavioral endpoint being studied. As we have discussed in this article, the ability to use rats for genetic studies is particularly important when complex

behavioral traits such as delay discounting, self-administration, or incentive salience are studied because it is not clear that these behaviors can be adequately assessed in mice. The phenotypic advantages long held by rats, in combination with breakthroughs in genotyping technology, improvements in manipulating rat ES cells, and development of bioinformatics resources are leading to the emergence of rats as a powerful translational genetic tool; and may provide the basis for rapid advances in our understanding of the genetic bases of addiction-related behaviors in humans.

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- Rat models have been used for decades to study physiology and behavior.
- Superior genetic techniques (i.e., knockout technology) caused a shift towards mice
- Tools for forward genetics are readily available in rats (HS, commercial outbreds)
- Tools for reverse genetics are now quite good (ZFN, TALENs)
- Rats can now be used for quantitative genetic studies of sophisticated behaviors