

Chapter 2

Animal Models of Behavioral Processes that Underlie the Occurrence of Impulsive Behaviors in Humans

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Abstract In this chapter, we describe a systematic approach for measuring three separate behavioral processes in laboratory animals that may result in failure to inhibit maladaptive behavior: (1) insensitivity to delayed consequences, (2) poor response inhibition, and (3) lapses of attention. We have developed procedures to measure these behavioral processes in both rats and mice. These measures use the same testing apparatus to measure each process in the two species, and these procedures are similar to parallel procedures used to measure these processes in humans. We describe the results from studies that support the validity of these test procedures in two different strains of mice (C57BL/6NTac, and 129/SvEvTac), as consistent differences in behavior indicate that C57 mice are more impulsive than 129s mice. This systematic characterization of differences in impulsivity between C57 and 129s mice illustrates both the wealth of data that can be obtained using these procedures and the potential usefulness of these procedures for characterizing impulsive behavior in rodents and humans.

Introduction

Inhibitory control, broadly defined, refers to factors that regulate the performance of inappropriate or maladaptive behaviors. Failure of inhibitory processes increases the probability of maladaptive “impulsive” behaviors, such as drug abuse. The term “impulsivity” has been used to refer to personality constructs, as well as to specific behavioral measures, both in natural and laboratory settings. Impulsivity has been studied in the context of personality theory (Eysenck 1993; Zuckerman 1994), clinical and behavioral psychology (Ainslie 1975; Milich and Kramer 1984; Rachlin and Green 1972), clinical and biological psychiatry (Linnoila and Virkkunen 1992; McCowen et al. 1993), and behavioral economics (Kirby and Herrnstein 1995).

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Although impulsivity has been extensively studied in various scientific contexts, there is no widely agreed upon operational definition of this concept. As a personality construct, impulsivity has been conceptualized and measured in many different ways (Barratt and Patton 1983; Eysenck 1993; Tellegen 1982; Zuckerman 1994). In laboratory studies, impulsivity has been defined as an inability to wait or to plan, an inability to inhibit behavior resulting in a pattern of socially inappropriate behavior, or as insensitivity to negative or delayed consequences.

The Diagnostic and Statistical Manual of Mental Disorders IV (APA 1994) includes a wide range of impulsive behaviors as key symptoms of many psychiatric disorders. These symptoms include impatience, difficulty waiting or delaying responses, frequently interrupting or intruding on others, Attention Deficit Hyperactivity Disorder (ADHD), failure to plan ahead (Antisocial Personality Disorder), excessive spending, sexual promiscuity, substance abuse, reckless driving and binge eating (Borderline Personality Disorder), and substance abuse, shoplifting, aggressiveness, gambling, fire-setting, and poor anger control (Impulse Control Disorders). Whether these apparently heterogeneous behaviors share some core features and common underlying processes or whether they represent separate deficits is not known. In the following sections, we describe three behavioral processes that give rise to impulsive behaviors, and the procedures designed to measure them in laboratory animals.

As a pattern of observable behavior in the natural setting, impulsivity has been measured using checklists and surveys by parents, teachers, and other observers (e.g., Achenbach and Edelbrock 1979; Kendall and Wilcox 1979). In the laboratory setting, impulsivity has been operationally defined and measured with tasks measuring specific constructs, such as insensitivity to delayed consequences, inability to wait, or inability to withhold a prepotent response. It has been difficult to reconcile these various indices of impulsivity, and it is unlikely that these behaviors reflect a single underlying process (Milich and Kramer 1984). A key challenge to researchers has been identifying and separating the behavioral and neurobiological processes underlying the expressions of impulsive behavior.

Three Models of Impulsive Behavior

Establishing valid animal models of impulsive behavior is problematic. In humans, impulsivity is most often measured using paper and pencil self-report instruments and rating scales based on the observations of parents and teachers. These types of measures cannot be used to measure impulsivity in nonhuman animals. It is not clear what “impulsive” behavior looks like in animals. Instead, animal researchers must develop laboratory tasks that measure behavioral processes thought to underlie failure of inhibitory control in humans. These behavioral tasks can then be used as operational definitions of impulsive behavior in animals. An important advantage of using laboratory-based models of impulsive behavior is that similar tasks can be used across species.

We have identified several behavioral processes that may underlie impulsive behavior and that can be studied in both humans and nonhuman animals in the laboratory. The range of definitions and measures of “impulsivity” makes it difficult to speculate on the nature of the deficit(s) that make some individuals more likely to emit inappropriate or maladaptive behaviors. However, over the past few years, two behavioral processes have been identified that may underlie the occurrence of impulsive behaviors (de Wit and Richards 2004; Castellanos et al. 2006; Sonuga-Barke 2002). These underlying behavioral processes are *delay discounting* and *response inhibition*, separable explanations for the occurrence of impulsive behaviors, such as drug abuse. According to the delay discounting approach, impulsive individuals exhibit stronger preferences for immediate rewards (e.g., taking a drug) over more delayed rewards (e.g., succeeding in work or school), even though the delayed rewards are larger. Similarly, when choosing between an immediate positive outcome (e.g., euphoria from a drug), and the possibility of delayed negative consequences (e.g., job loss, relationship problems), impulsive individuals are relatively less sensitive to the possibility of punishment. According to the response inhibition approach, individuals may fail to inhibit maladaptive behaviors because of a relative inability to suppress prepotent highly reinforcing behaviors, such as drug taking (e.g., during periods of intended abstinence).

Both of these independent operational definitions of impulsivity have face validity and empirical support, but until recently few studies have examined the correlations between the two. Sonuga-Barke (2002) found that although ADHD children in general were impaired on both tasks, the two measures were not correlated. Instead, there appeared to be two subpopulations of ADHD patients, one of whom exhibited sensitivity to delay while the other had poor inhibitory control. Similarly, a recent factor-analytic study of a variety of personality and behavioral measures of impulsivity in normal adults revealed two components, an impulsive disinhibition component which included the response inhibition component (measured using the Stop Task) and impulsive decision-making component which included delay discounting. Performance on the delay discounting and Stop Tasks was clearly uncorrelated (Reynolds et al. 2006a). We conclude that delay discounting and response inhibition are separate behavioral processes each of which may underlie the occurrence of an impulsive behavior, such as drug use.

A third behavioral process, *lapses of attention*, may also underlie impulsive behaviors. Although impulsivity is closely linked to attention, as in the case of children with ADHD, impairments in attention have rarely been studied as determinants of impulsive behavior. From our point of view, it seems likely that impairments of attention may lead to the occurrence of impulsive behaviors, such as persistent drug abuse. For example, relapse is one of the most persistent problems in substance abuse. Although many former drug users are able to abstain from using drugs for limited periods of time, an alarmingly high proportion return to using their drugs, even after extended periods of abstinence. It is likely that abstaining from drug use after heavy habitual use requires an active and sustained attention to maintain response suppression. A single lapse of attention to the goal of abstinence can result in renewed drug consumption. When viewed in this way,

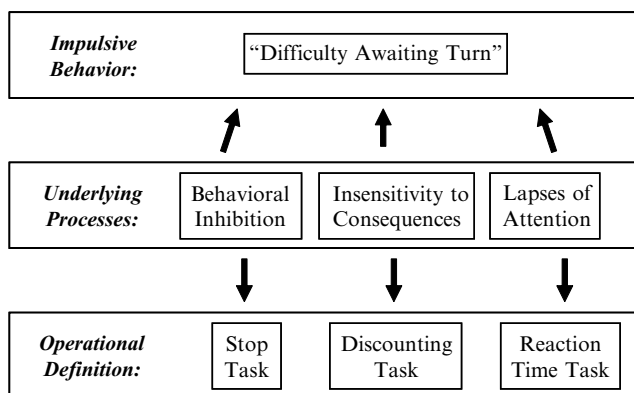


Fig. 2.1 See text for explanation

it seems surprising that the relationship between attention and impulsive behaviors has not been the focus of more research.

Figure 2.1 summarizes our approach to understanding impulsive behavior and measuring impulsivity in humans and rodents. The DSM IV gives “difficulty awaiting turn” as an example of an impulsive behavior that may occur in a child with ADHD. According to our approach, at least three separable underlying behavioral processes could lead to the occurrence of this specific impulsive behavior. As is indicated in Fig. 2.1, the child may fail to wait because it is unable to inhibit the behavior of getting out of line. Alternatively, the child may be insensitive to the delayed consequences (positive or negative of waiting in line). Lastly, the child may fail to wait in line because he is unable to sustain attention to cues, both external and internal, that maintain appropriate waiting behavior. As is indicated in the bottom row of Fig. 2.1, each of these hypothetical behavioral processes can be operationally defined and measured using laboratory-based tasks. We propose that the failure to inhibit maladaptive behavior may, like “Difficulty Awaiting Turn,” result from any of these behavioral processes.

Delay Discounting

Delay discounting refers to a preference for smaller, more immediate rewards over larger, more delayed rewards (Ainslie 1975; Herrnstein 1981; Logue 1988; Rachlin and Green 1972, 1989). This definition of impulsive behavior is based on the observation that organisms “discount” the value of delayed consequences, such that the value of delayed rewards or punishments is inversely related to the delay of their occurrence. According to this model, impulsive individuals discount delayed events more markedly. Consistent with this, discounting is more pronounced in drug users including opioid-dependent individuals (Kirby et al. 1999; Madden et al. 1997), cocaine users (Coffey et al. 2003), alcohol abusers (Vuchinich and Simpson 1998), cigarette smokers (Bickel et al. 1999; Mitchell 1999), and individuals with

unspecified histories of drug dependence (Allen et al. 1998) compared to control samples. The fact that delay discounting tasks have been developed for use with both humans and other animals makes it particularly useful for translational research of this kind.

The effects of delay on reward value have been studied in humans (Green et al. 1994; Rachlin et al. 1991; Richards et al. 1999b), pigeons (Mazur 1987), rats (Bradshaw and Szabadi 1992; Richards et al. 1997), and mice (Mitchell et al. 2006). In all four species, the curves that result from the devaluation of reward value by delay are well described by the hyperbolic function of Mazur (1987):

$$V = bA / (1 + kD),$$

where V is value, A is the amount of the delayed reward, D is the delay to reward and k and b are free parameters. The value of k indicates more rapid devaluation of reinforcer value by delay and greater impulsivity. The value of b indicates a side bias that is independent of delay. The shape of the hyperbolic discount function is illustrated in Fig. 2.2. Fitting discount points to the hyperbolic discount equation to determine the value of k provides a quantitative measure of impulsivity. As is indicated in Fig. 2.2, organisms that discount the value of the delayed reward more steeply are considered to be more impulsive. Larger values of k indicate steeper discount functions, such as the one depicted by the dashed line in Fig. 2.2.

We have developed an adjusting amount (AdjAmt) procedure that allows us to determine how much animals value delayed rewards (Richards et al. 1997). The AdjAmt procedure allows us to determine the value of a large reward at different delays in terms of a smaller immediate reward. As is illustrated in Fig. 2.2, the best fitting hyperbolic discount equation can then be determined for each subject and the value of k used as a quantitative measure of impulsivity.

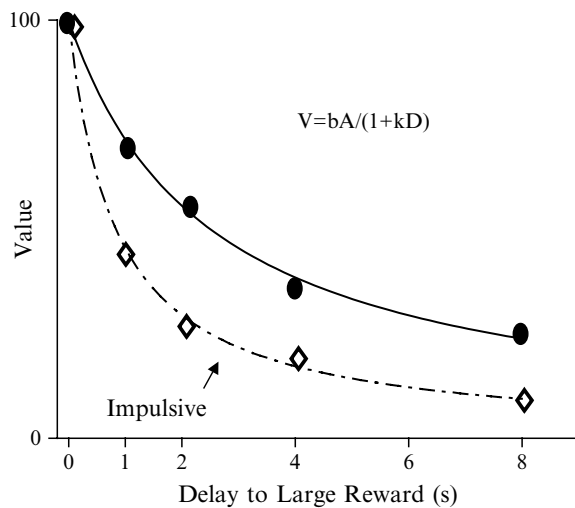


Fig. 2.2 Two hypothetical hyperbolic discount functions showing how the value of a reward decreases with delay. The *dashed line* indicates more rapid (impulsive) discounting of the delayed reward

In rats we have used this procedure 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. 1999a), and lesions of the nucleus accumbens (Acheson et al. 2006) on impulsivity.

Delay Discounting Task

The AdjAmt procedure is outlined in Fig. 2.3 and described by Richards et al. (1997). Test sessions consist of discrete choice trials plus a variable number of forced trials. Each trial is separated by an intertrial interval (ITI). During the ITI, all of the stimuli in the chamber are off (Fig. 2.3, panel 1). Illumination of the light above the center snout poke hole (Fig. 2.3, panel 2) signals the start of each trial. The first response (snout poke) to the center hole after the beginning of a trial results in the offset of the stimulus light above the center hole and the onset of the stimulus lights above the left and right water dispensers (Fig. 2.3, panel 3). Inserting the head into the water dispenser on the left always results in the presentation of the standard alternative, which is the delayed delivery of a fixed amount of water. Inserting the head into the dispenser on the right always yields the adjusting alternative, which is immediate delivery of a variable amount of water (the animals used in this procedure are water restricted).

When the animal chooses the standard alternative, the lights above both the standard and adjusting alternatives are turned off and a tone turned on (Fig. 2.3, panel 4A). This tone remains on throughout the delay period. At the end of the delay period a fixed, large amount of water is delivered and the tone turned off for the remainder of the 30-s trial (Fig. 2.3, panel 4B). Note that when the rat chooses the delayed standard alternative, the ITI duration is adjusted so that it is equal in duration to the ITI following choices of the immediate adjusting alternative. This adjustment of the ITI is important because it ensures that the overall rate of reinforcement is the same for both the delayed and immediate alternative.

When the animal chooses the adjusting alternative, water is delivered immediately and the stimulus lights above the left and right water dispenser apertures turn off for the remainder of the ITI (Fig. 2.1, panel 5). During each session the amount of water available on the adjusting alternative is systematically varied. If the animal chooses the standard alternative, the amount delivered on the adjusting alternative is increased by 10% on the next trial. If the animal chooses the adjusting alternative, the amount delivered on the adjusting alternative is decreased by 10% on the next trial.

Forced trials are used to ensure that the rats are exposed to the consequences of choosing both the delayed fixed large amount of water from the standard alternative and the immediate adjusted small amount of water from the adjusting alternative. Choice of either the standard or the adjusting alternative on two consecutive trials is followed by a forced trial in which only the stimulus light above the required alternative is turned on after the central snout poke response and only responses to the illuminated side are reinforced.

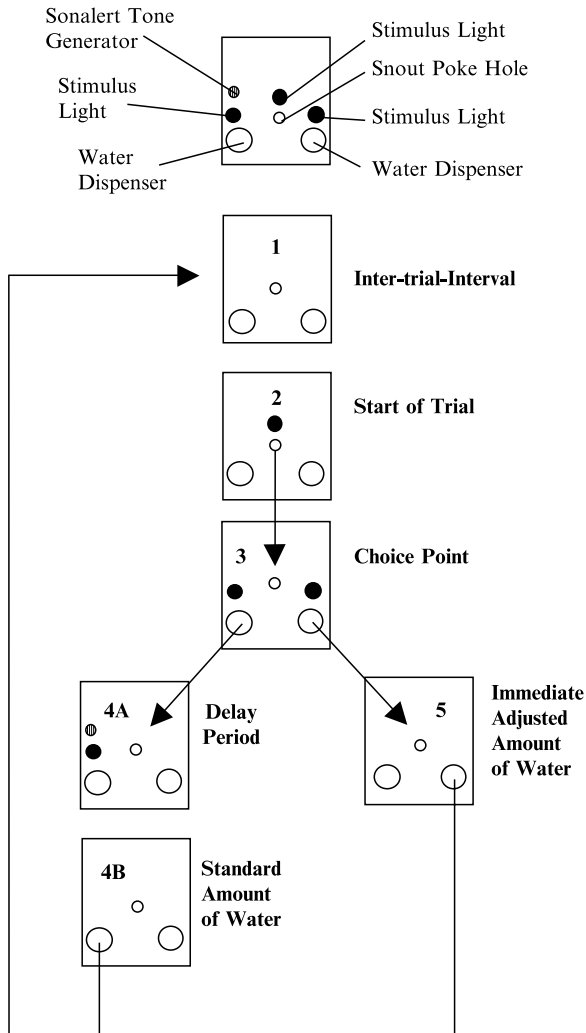


Fig. 2.3 A schematic illustration of the phases of the adjusting-amount procedure. *Panels 1–5* indicate when the various stimuli were turned on during the different phases of the test procedure. A *darkened* stimulus marker shows that the stimulus is on. See text for explanation

The primary dependent measure is the indifference point, which represents the value of the delayed reinforcer. The indifference point is operationalized as the median amount of water available on the adjusting alternative during the last half of the test session. Forced trials are not included in this calculation. Smaller indifference points, indicating greater discounting of the delayed reward, are the primary measure of impulsivity on this task.

The AdjAmt procedure is based on a procedure developed by Mazur (1987) for pigeons which adjusted the delay to the reinforcer. In contrast, the AdjAmt procedure

adjusts the amount or magnitude of the reinforcer. More recently, alternative methods for measuring discounting in rodents have been developed which adjust the delay to reinforcement and use fixed small and large reinforcers (e.g., one food pellet or three food pellets). For example, Evenden and colleagues (Evenden and Ryan 1996) and Robbins, Everitt and colleagues (Cardinal et al. 2004; Winstanley et al. 2006, 2004; Cardinal et al. 2000) utilize a procedure which progressively increases the delay across the session, whereas Carroll and colleagues (Perry and Carroll 2008; Perry et al. 2005, 2008) and Szabadi and colleagues (da Costa Araujo et al. 2009) increase/decrease the delay within the session dependent on the rat's responses. Presumably, all of these procedures provide valid measures of delay discounting.

Delay Discounting in C57 and 129s Mice

We parametrically characterized delay discounting in the two strains of mice (C57BL/6NTac and 129/SvEvTac), on the delay discounting procedure, as these strains have been shown to differ in impulsivity. Each strain was tested using the adjusting amount (AdjAmt) procedure described above, providing discount functions for five delays (0, 1, 2, 4, and 8 s) to reward. These discount functions were fit to the best fitting hyperbolic discount functions for each mouse across the five delays. Fitting the hyperbolic discount function provided a quantitative measure of the rate of discounting to compare across strains of mice. Both strains of mice learned the task and generated characteristic hyperbolic discount functions. We found that C57 mice behave more impulsively on the task than 129s mice. Figure 2.4 shows the rate of discounting for C57 mice was greater than the rate of discounting for 129s mice and that C57 mice had larger k values than 129s mice

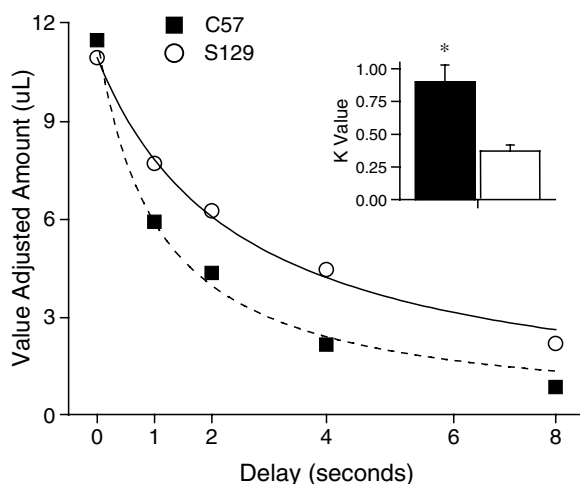


Fig. 2.4 Delay discounting functions for C57 and 129s mice

(indicating greater discounting). The pattern of behavior generated by C57 mice indicates that their behavior is poorly controlled by delayed consequences relative to 129s mice.

Response Inhibition

Impairments in the ability to inhibit the expression of inappropriate behaviors are characteristic of several psychiatric disorders, most notably ADHD. Response inhibition has typically been operationally defined by the Stop Task which measures the ability to stop a motor response after its execution has been initiated (Logan 1994). Stop Task performance is impaired in children with ADHD (Brandeis et al. 1998; Jennings et al. 1992, 1997; Oosterlaan and Sergeant 1996, 1998a, b; Oosterlaan et al. 1998; Quay 1997; Rubia et al. 1998, 1999; Tannock et al. 1989, 1995). The psychomotor stimulant methylphenidate, which is used to treat ADHD, also ameliorates impairments on the Stop Task in ADHD children (Tannock et al. 1989, 1995). Cocaine abusers perform more poorly than control subjects on the Stop Task, suggesting that response inhibition may also play a role in substance abuse (Fillmore and Rush 2002). Thus, the Stop Task may be an important laboratory model for studying basic behavioral and biological processes that mediate impairments in impulse control relating to substance abuse.

We have shown that psychoactive drugs produce similar effects on the Stop Task in rats and in humans. For example, alcohol increased Stop time without affecting Go time in both rats and humans (de Wit et al. 2000; Feola et al. 2000), and amphetamine decreased Stop times in both humans and rats whose initial Stop times were slow. The increase in Stop time after alcohol is consistent with an increase in impulsivity, whereas the decrease in Stop time after amphetamine is consistent with a decrease in impulsivity. These findings lend support to the use of the animal model to study the neurobiological basis of impulsivity.

Stop Task

The Stop Task procedure that we have developed for rodents is modeled after the Stop Task procedure developed for humans by Logan (1994) and colleagues. The diagram in Fig. 2.5 provides a schematic representation of the apparatus and procedure. Each trial begins with the chamber's center light illuminated. The animal is then required to place its snout in the center snout poke hole just below the center light and to hold it there for a varying time period, after which the center light is turned off. Following the offset of the center light (Go signal), the animal is required to remove its snout from the center snout poke hole and move to the right water dispenser for a water reward. The time elapsed from the offset of the center light (Go signal) to the animal breaking the photo beam in the right water dispenser is the Go reaction time (RT) measure. In order to induce the animal to make the

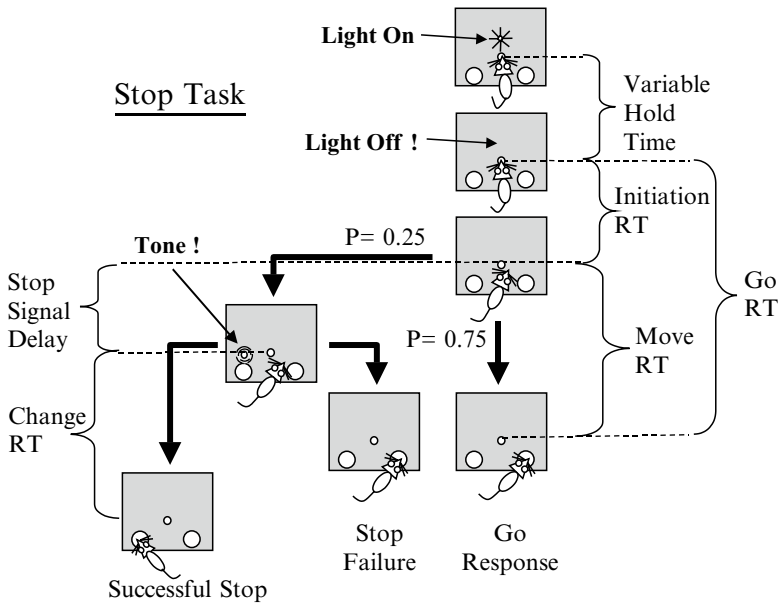


Fig. 2.5 Flow chart of the Stop Task procedure. See text for explanation

Go RT as fast as possible, the amount of water the animal receives for making the Go response depends upon the speed of the animal's Go RT.

On 25% of trials, the Go signal is followed by a tone that serves as a Stop signal. The Stop signal requires the animal to inhibit the Go response to the right water dispenser and emit a head poke response to the left water dispenser in order to get a water reinforcer. If the animal fails to stop the Go response (i.e., an interrupted photo beam in the right water dispenser), it does not receive any water on that trial. If the animal successfully stops the Go response, it receives a water reward when it interrupts the photo beam in the left water dispenser. The amount of water that the animal receives for making the change response to the left water dispenser is equal to the amount of water that it receives for the most recently reinforced Go response. The time elapsed between the presentation of the Stop signal (tone) and the animal breaking the photo beam in the left water dispenser is defined as the change RT measure.

The elapsed time between the Go signal (offset of the center light) and presentation of the Stop signal (tone) is referred to as the stop signal delay. The stop signal delay adjusts in increments of 20 ms depending upon performance on the preceding Stop trial. For example, if the animal successfully stops, the Stop signal delay is increased by 20 ms on the next Stop trial. If the animal fails to stop, the Stop signal delay is decreased by 20 ms on the next Stop trial. Adjusting the Stop signal delay in this fashion allows the animal to be able to successfully stop the Go response approximately 50% of the time.

In addition to the 50% inhibition point, the Stop signal delays at which the animals can inhibit the Go response 25 and 75% of the time are also obtained. These points

are determined by using separate Stop signal delays. The 25% inhibition point is determined by increasing the Stop signal delay after every correct stop and decreasing the Stop signal delay only after three stop failures have occurred. The 75% inhibition point is determined by increasing the Stop signal delay only after three successful stops and decreasing the Stop signal delay after every stop failure. The 25, 50, and 75% Stop signal delays are pseudo randomly presented throughout the test session so that one Stop signal delay of each type is presented every three Stop trials. The Stop signal delay at which the animal fails to stop 50% of the time is used to estimate how long it takes the animal on average to stop or “inhibit” an ongoing response. This estimate is referred to as the Stop RT and is calculated by subtracting the average Stop signal delay from the mean of the Go RT. A similar calculation is used to determine the 25 and 75% Stop RTs. These points in conjunction with the 50% Stop RT are used to construct an inhibition function. Logan (1994) describes a similar procedure for constructing an inhibition function in humans. The slope of the inhibition function may be an important indicator of the behavioral processes that are involved in stopping. The primary measure of impulsivity is the Stop RT. Faster Stop RTs indicate better response inhibition and less impulsiveness.

It is arguable that the Stop Task described above is best described as a change task because the animal is required both to stop the Go response and then perform an alternative response in order to receive reinforcement. Eagle and colleagues (Eagle et al. 2008; Eagle and Baunez 2009) have developed a rodent Stop Task which does not require a specific response to be executed in order to receive reinforcement. In their task, the animal is required to refrain from making any response at all on Stop trials for a specified limited hold period. If the animal does not make a Go response during the limited hold period, it receives reinforcement. We would make two points about this procedure. First, although no specific response is specified, it is likely that the animal is doing something during the limited hold period that precedes reinforcement. The contingency of reinforcement imposed by this procedure can be described as differential reinforcement of other behavior. The point being that it is likely the rat learns to perform an alternative response of some sort during the limited hold period. When viewed this way, this procedure can also be considered a change task. Second, the limited hold period proceeding reinforcement imposes a delay to reward which most likely decreases the potential reinforcing value of Stop trials in comparison to go trials where the reinforcement occurs immediately. This delay to reward may bias inhibition functions obtained using this procedure and may be differentially affected by drugs and brain lesions that are tested using this procedure.

Stop Task Performance in C57 and 129s Mice

Figure 2.6 shows the inhibition functions for C57 and 129s strains of mice. These inhibition functions are constructed from the Stop RTs at which the mice were able

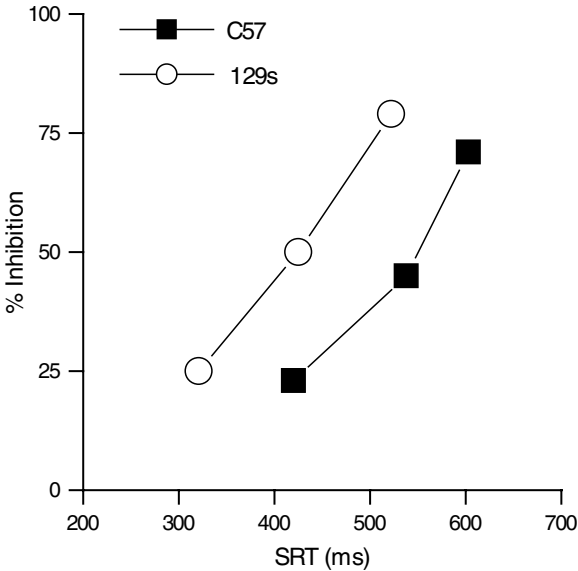


Fig. 2.6 Comparison of Stop Task performance in C57 and 129s mice. *Table* shows various performance measures on Stop Task

| Dependent Measure | Strain | |
|--------------------|----------|-----------|
| | C57 | 129s |
| Go Reaction Time | | |
| Mean | 701 ± 38 | 639 ± 37 |
| Standard Deviation | 355 ± 40 | 226 ± 28* |
| Stop Reaction Time | 536 ± 37 | 418 ± 30* |
| Stop Signal Delay | 165 ± 7 | 221 ± 13* |

Note: Values are in milliseconds. *indicates 129s strain is different from corresponding C57 strain $p < 0.05$

to stop 25, 50, and 75% of the time. Typically, the Stop RT is defined as the time it takes the mouse to stop 50% of the time. Determining the additional 25 and 75% Stop RTs allows a more thorough characterization of the functional relationship between the Stop signal delay and length of time it takes the animal to stop (Stop RT). Figure 2.6 shows that the inhibition function for the C57 strain is shifted to the right compared to the 129s mice, indicating that they have slower Stop RTs. The longer Stop RTs indicate that C57 mice have impaired response inhibition relative to 129s mice. The Go RTs are not significantly different, while the Stop signal delays for C57 mice are significantly shorter which indicates that this effect is not due to differences in the Go RT. From these data, we would conclude C57 mice have impaired response inhibition in comparison to 129s mice.

Lapses of Attention

We propose that impairments of sustained attention may also lead to the occurrence of maladaptive behaviors, such as drug abuse. Simply put, in some instances, failure to inhibit maladaptive behavior may occur because of poor stimulus control. This idea has received little experimental attention. We have developed a novel experimental approach to measuring lapses of attention using RT tasks in both humans and rodents. The main idea of this approach is illustrated in Fig. 2.7. The top row of Fig. 2.7 shows individual RTs, corresponding to the elapsed time to make a response after the onset of an imperative stimulus (i.e., RT). The distribution of these RTs is portrayed in the histograms shown in the lower portion of Fig. 2.7. The distributions on the left and right panels differ only in the presence of four long RTs in the right panel, which we define as lapses of attention. These occasional lapses of attention cause the tail of RT time distribution to have a rightward skew and have a large impact on the mean, but not the mode, of the RT distribution.

Leth-Steensen et al. (2000) describe the positive skew of RT distribution as a behavioral characteristic in ADHD compared to normal children. They show that the slow responses, or lapses, cause the RT distributions of ADHD children to have

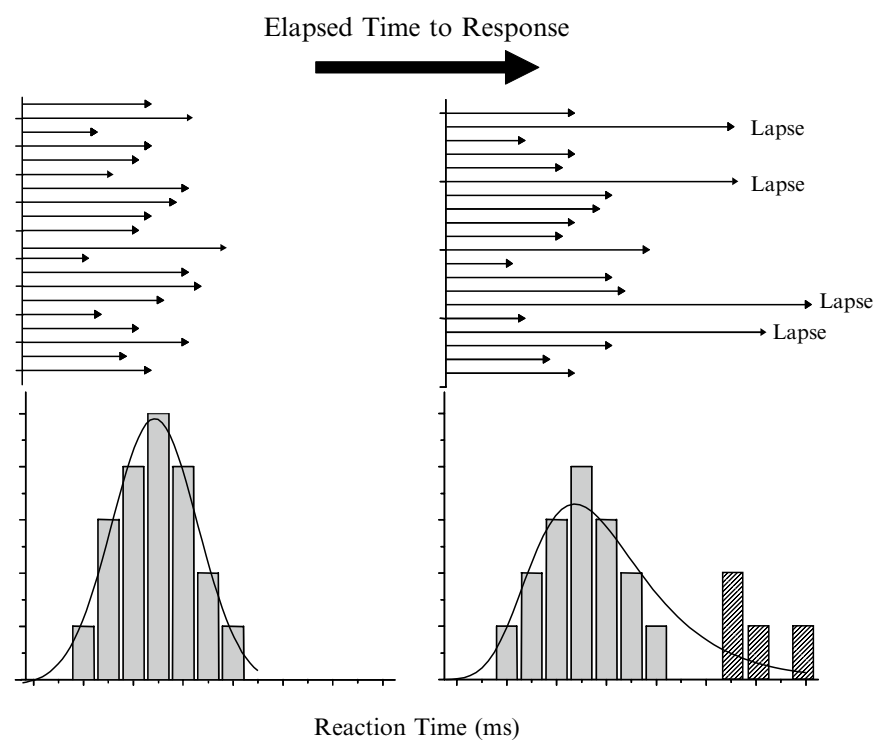


Fig. 2.7 Lapses of attention as indicated by a hypothetical distribution of reaction times

a greater positive skew than the RT distributions of age matched controls, and propose that this skew is an important empirical marker of periodic “lapses of attention” in ADHD children. Importantly, they also suggest that these lapses of attention can be differentiated from the ability to respond quickly. They argue that the peak (modal point) of the distribution of RTs is an indicator of the optimal speed of responding when the subject is attending to the task at the moment that the imperative stimulus is presented. They fitted a complex ex-Gaussian distributional model to the RT distributions, which provides independent measures of the peak and tail of the RT distribution. Although the ex-Gaussian curve-fitting is appropriate, it requires a large number of RTs and sometimes does not provide a good fit to the distribution [13% of the time in Leth-Steensen et al. (2000)]. The ex-Gaussian approach also makes assumptions about the theoretical distributions of RTs that may not be correct.

We have developed a simpler, nonparametric approach for quantitatively characterizing the peak and rightward skew of the distribution of RTs using the mode of the reaction distribution and the average deviation from the mode (DevMod) of the individual RTs. We have found in rats that the psychomotor stimulant methamphetamine decreases lapses of attention and that rats with fetal ethanol exposure have greater lapses of attention (Sabol et al. 2003; Hausknecht et al. 2005). Similarly, this approach has been used to show that both amphetamine and bupropion decrease lapses of attention in healthy young adults (Acheson and de Wit 2008) and that stimulant treatment reduces lapses of attention in children with ADHD (Spencer et al. 2009).

The DevMod approach starts with the observation that unlike the mean, the mode (defined as the most frequent RT) is not affected by a rightward skew of the distribution tail and therefore provides an estimate of response speed from those trials in which the subject was attending when the imperative stimulus was presented. The deviation of the individual RTs from the mode provides a measure of the tail of the distribution. A convenient and useful method for measuring the mean DevMod is to subtract the mode from the mean. If the distribution is skewed to the right, then the DevMod or difference between mean and mode metric is greater than zero. The larger the tail of the RT distribution the greater the positive value of the DevMod. That is:

$$\text{Mean RT} = \text{Mode} + \text{DevMod}.$$

Thus, the mode reflects response speed on the trials in which the subject attends to the stimulus. The difference between the mean and the mode reflects the degree to which the subject has “lapses of attention” (i.e., is not attending to the task). Following this logic, the mode of the RT distribution may be thought to reflect perceptual processing, decision making and motor speed, while the DevMod measure is thought to primarily reflect variability in responding due to momentary changes in attention, such as a lapse of attention.

The use of attention tasks to measure impulsive behavior in animals is not novel. Premature responses that occur during the performance of the five choice serial RT task have been used as indicators of impulsive tendencies (Robbins 2007). Premature responses are responses that occur in the absence of the imperative stimulus. Both

premature responses and lapses (very slow responses) indicate that the animals are not attending to the imperative stimulus. In the case of premature responses the failure of attention is actively expressed, whereas in the case of lapses the failure of attention is passively expressed. Both premature responses and lapses reflect poor stimulus control and both can underlie the occurrence of maladaptive behaviors.

Choice RT Task

A two choice RT procedure is used to measure lapses of sustained attention. This task is implemented using the same apparatus used for the discounting and Stop Tasks described above. The animals are trained to hold their snout in the center snout hole until either the left or right stimulus light is turned on (Fig. 2.8). The amount of time required for the rat to hold its snout in the center snout poke hole before the onset of the imperative stimulus (left or right stimulus lights) is called the hold time. As described below, the hold time is determined individually for each animal. Once the hold time criteria is reached and the imperative stimulus is presented, the animal must put its head into the water dispenser below the imperative stimulus or the trial will terminate (the imperative stimulus turned off) and the trial is counted as an omission. After the presentation of the imperative stimulus, a head entry response into the water dispenser associated with the stimulus light is reinforced if the RT is shorter than a criterion RT. If the animal's RT is longer than the criterion RT, it will not receive a water reward.

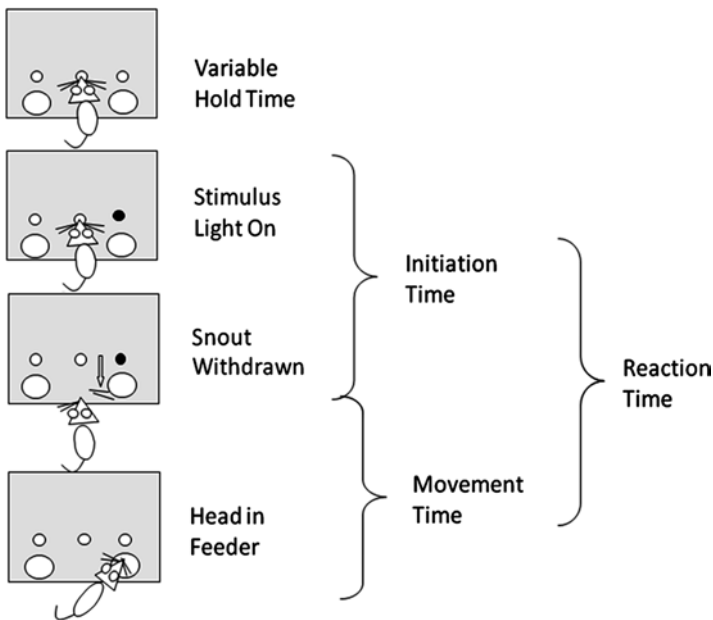


Fig. 2.8 Flow chart for choice reaction time procedure. See text for explanation

The purpose of using a criterion RT is to selectively reinforce fast responses. The criterion RT for reinforcement is adjusted for each individual animal according to the following rules. For every two correct responses that are faster than the criterion time limit, the criterion is reduced. For every incorrect or slow response, the criterion time limit is increased. Adjusting the criterion RT in this manner results in each animal being reinforced on approximately three out of four trials when the correct side is chosen. Because of the adjusting nature of the procedure, the actual rate of reinforcement is the same for fast and slow animals.

As was mentioned above, the onset of the imperative stimulus is contingent upon the animals holding their snouts in the center snout poke hole for a variable hold time period. An average hold time is specified for each individual animal at the start of each test session. The hold time is cumulative. This means that the animal is not required to hold its snout in the hole for the entire hold time in one continuous snout poke. Any pattern of snout poking that equals the criterion hold time is acceptable. For example, if the hold time is 4 s, the animal can meet this requirement by holding its snout in the hole for 2 s on the two different occasions (i.e., two snout pokes of 2 s duration meets the 4 s criterion). The average hold time is adjusted for each test session depending upon performance during the previous test session. If the animal completes more than a specified number of trials during the previous test session, the average hold time is increased. If fewer trials are completed on the previous test session, then the average hold time is decreased.

As is shown in Fig. 2.8, the RTs produced by this testing procedure can be broken down into initiation and move components. However, initiation RT, defined as the latency to remove the snout from the center hole after the onset of the imperative stimulus, is our primary measure because it isolates the part of the RT that is most likely to reflect lapses of attention. Additional dependent measures are (1) premature responses, (2) omissions, (3) average hold time, and (4) mode. (1) Premature responses are defined as the animal pulling its snout out of the center hole before the onset of the stimulus light and inserting its head into one of the two water dispensers. Because individual animals have different hold time requirements, the premature responses for each individual are calculated as: premature responses divided by total time that the animal actually holds its snout in the center hole. This measure takes into account the total time that the animal has the opportunity to make a premature response. (2) Omissions are defined as trials in which 2 s elapses after the presentation of the imperative stimulus without a head entry into either the left or right water dispensers. It is important to note that the DevMod measure includes both omissions and shorter intervals that do not meet the arbitrary criterion for an omission. Another important dependent variable is (3) the average hold time, which reflects the animal's ability to wait for the onset of the imperative stimulus. The direction and degree to which the distribution is skewed is determined by the DevMod measure. This is calculated by subtracting the modal RT from the mean RT. (4) The mode of the distribution is calculated using the Half-Range Mode method (Hedges and Shah 2003). Distributions with large positive skew, indicating the presence of lapses of attention, have correspondingly greater DevMod.

Choice RT Performance in C57 and 129s Mice

We have compared the performance of C57 and 129s strains of mice on the choice RT task. As is depicted in Fig. 2.9, the distributions of initiation RTs are different for the two strains of mice. The 129s strain produced an RT distribution with a clear mode, at about 150 ms, indicating that it took 150 ms to initiate the response to the imperative stimulus. In contrast, the mode for the C57 mice occurs immediately

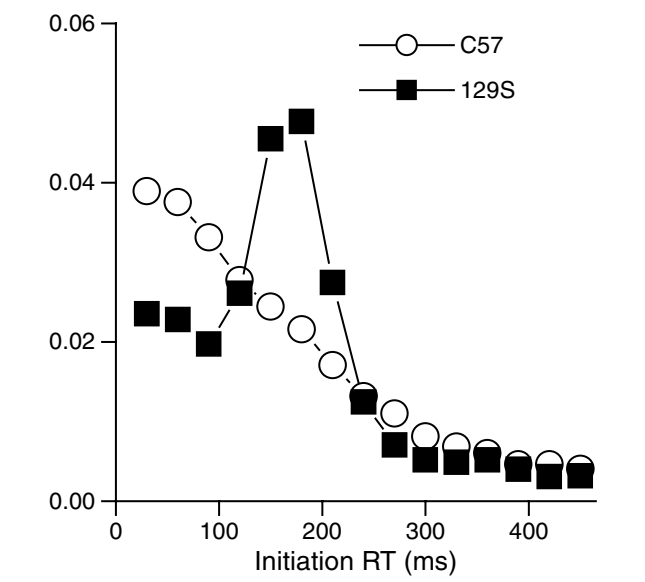


Fig. 2.9 Reaction time distributions for C57 and 129s mice. *Table* indicates various performance measures on choice reaction task

| Dependent Measure | Strain | |
|--------------------------|-------------|--------------|
| | C57 | 129s |
| Initiation Reaction Time | | |
| Mean | 375 ± 28 | 399 ± 51 |
| Standard Deviation | 563 ± 39 | 582 ± 76 |
| Mode | 62 ± 8 | 150 ± 15* |
| | 313 ± 27 | 249 ± 42* |
| | 0.44 ± 0.08 | 0.33 ± 0.11* |
| Percent Correct | 82.8 ± 3.5 | 86.8 ± 5.0 |
| Hold Time (s) | 1.03 ± 0.23 | 3.09 ± 0.66* |
| Omitted Trials | 10.6 ± 1.7 | 9.5 ± 4.3 |

Note: Unless otherwise indicated, values are in milliseconds.
*indicates the difference between the 129s and C57 strains is significant (p <.05)

after the onset of the imperative stimulus. This pattern of results indicates that initiation of the response by C57 mice was not under the control of the imperative stimulus, suggesting that C57 mice were not attending to the imperative stimulus. It is notable that despite the obvious difference in the shapes of the initiation RT distributions, there were no significant differences between the means and standard deviations of the distributions between the two strains. In contrast, there were significant strain differences in both the mode and DevMod measures. This highlights the importance of an analysis that quantitatively characterizes the shape of the distributions. Other measures that produced significant differences between the two groups were the hold time and premature response measures. The C57 mice had significantly shorter hold time durations than the 129s mice and had more premature responses. These results are consistent with the analysis of the RT distributions above indicating that the C57 mice were not attending to the imperative stimulus. Premature responses are widely interpreted as being indicative of impulsive behavior in humans and rodents (Robbins 2007). In the present case at least, it seems likely that the occurrence of these impulsive premature responses in C57 mice is the result of poor stimulus control (or attention to the imperative stimulus). The distribution of RTs for C57 mice indicated that the failure of stimulus control was actively expressed. We argue that both the active and passive expression of inattention may underlie the occurrence of maladaptive behavior. Taken together, these results indicate that C57 mice are more likely to emit impulsive behaviors (such as premature responses) than 129s mice and that this impairment may be due failures of attention.

Limitations and Future Directions

Animal Models of Impulsive Behavior Require Extended Training

A general problem with the animal models described above is that it requires many weeks or even months to train the procedures. It is arguable that extended training of animals on tasks that are designed to measure behavioral processes that underlie impulsivity do not reflect the spontaneity that may be part of the occurrence of impulsive behavior in humans. In reply to this, we would argue that impulsive behavior in humans is usually identified in circumstances in which they have extensive experience and training. However, as it is defined, behaviors that are labeled as impulsive often occur in situations, where past experience and training have exposed the individual to the consequences of their actions. The behavior would not be considered impulsive if the individual is naïve to the possible maladaptive consequences of their behavior. For example, the failure of a child with ADHD to wait in line is only considered to be impulsive when it is known that the child has a history of being trained to wait in line.

However, the requirement of extensive training in animals is a procedural problem. For example, it would be difficult to train rats on the tasks described in this

chapter during the 30-day period of adolescence in rats. This limitation precludes the use of these procedures to measure the behavior of adolescent rats. The requirement of extended training in animals is also an impediment to train the same animal on several different tasks, making it difficult to evaluate the degree to which they measure overlapping or separable processes (Sonuga-Barke 2002). Although it may be possible to train the same rodent on all three tasks, each task has been measured at a different age. In rodents, with their short life span, the difference of 6 months may make a large difference in performance. In contrast, all three tasks can be easily tested in human subjects. In human work, construct validity is enhanced by the consideration of a multimethod, multitrait matrix (Cronback and Meehl 1955) which involves testing same task on multiple tasks. The long duration of training required in animals prevents the development of construct validity using this method. An important direction for future research is to develop animal models that can more rapidly measure behavioral processes that underlie the occurrence of impulsive behavior.

Do the Human and Animal Tasks Measure the Same Behavioral Process?

All three of the animal laboratory models of impulsive behavior considered in this chapter bear remarkable similarity to parallel human paradigms. Indeed, that is one of their strengths. However, there are some important differences, and these should be clearly articulated and considered.

Among the tasks described above, the greatest differences between human and rodent models occur in the measurement of delay discounting. In humans, the delays and consequences are for the most part hypothetical. Human subjects are required to make judgments about imaginary delays and consequences. Furthermore, the hypothetical delays used with humans (days, weeks, months, or years) are much longer than those used in animals studies (usually much less than a minute).

Attempts to develop laboratory tasks for human adults that involve real-time delays and rewards have not been particularly successful (however, see Shiels et al. 2009; Reynolds and Schiffbauer 2004; Reynolds et al. 2006b). One problem with developing real-time tasks in human adults is that they often do not discount when ITIs are used. In animal studies, the rate at which the animal can make choices between immediate and delayed rewards is held constant by imposition of an ITI. This ITI ensures that the delay to the next choice is the same after choosing either the immediate or delayed alternatives. Without the ITI, exclusive choice of the immediate alternative would result in a higher rate of reinforcement. Inter-trial delays are used in animal studies in order to ensure that the task is measuring the animal's sensitivity to delay of reinforcement and not rate of reinforcement. This means that in tasks with it is, such as the AdjAmt procedure described above, the between trial inter-reinforcer interval is the same regardless of choice of the small immediate or large delayed reinforcer during the current trial. The discounting behavior of animals on delay discounting tasks with ITIs

indicates that they are sensitive to the within trial delays to reinforcement and not the inter-trial delays. If the animals somehow understood that choice of either the small immediate or delayed large alternative resulted in equivalent overall delays to reinforcement they would probably have exclusive choice of the larger reinforcer. In an important study, Lane and colleagues (Lane et al. 2003) reported that many human adults did not discount and demonstrated exclusive choice of the delayed large reinforcer in a laboratory task when an ITI was imposed. In laboratory tasks with real delays and rewards, it is necessary to use short delays in order to have test sessions of reasonable duration. It may be that under these circumstances humans are sensitive to the overall rate of reinforcement and not the within trial delays imposed by the task.

It is not clear if the difference in discounting between humans and animals performing real-time laboratory tasks represents a qualitative or quantitative difference in discounting between humans and animals. One possible explanation is that humans integrate decisions about reinforcement across a larger time window making them less sensitive to within trial delays and more sensitive to the overall between trial rates of reinforcement. On the other hand, both the real-time animal and hypothetical human tasks have empirical similarities in that they both produce hyperbolic-like discount functions. Furthermore, as we reviewed in the introduction, there are now many studies indicating that impulsive populations of humans, such as drug abusers discount hypothetical delayed rewards more steeply. Understanding the differences and similarities of delay discounting in human and animal subjects is an important area for future research.

In contrast to the delay discounting task, the measures of response inhibition (Stop Task) and lapses of attention (choice RT task) used in humans and animals are relatively similar. Although both the stop and choice RT tasks are often used without explicit reinforcers in humans, there are many examples of these two tasks being used with explicit reinforcers (Leth-Steensen et al. 2000; Kuntsi et al. 2009; Oosterlaan and Sergeant 1998a; Stevens et al. 2002). The use of reinforcers in animals (and humans) increases the internal validity of these two tasks. Failures of inhibition lead to the absence of reinforcement on the Stop Task and lapses of attention lead to slow RTs that are not reinforced on the choice RT procedure. In comparison to delay discounting, there are fewer studies that indicate a relationship between response inhibition and lapses of attention and the occurrence of impulsive behaviors. This is particularly true of lapses of attention which have only recently been considered as a possible cause of impulsive behavior. An important direction for future research is to determine the predictive validity of animal models that measure behavioral processes that underlie the occurrence of impulsive behavior.

Is Drug Self-Administration in Animals Impulsive?

Another problem for establishing the validity of animal models of impulsive behavior is that behaviors that are routinely considered to be impulsive in humans

may not be impulsive in laboratory animals. For example, in this chapter, we have on several occasions referred to drug abuse as an impulsive behavior. In humans, taking drugs despite knowledge of, or experience with, the negative consequences associated with abusing drugs is often considered to be impulsive. Indeed, human addicts often persist in abusing drugs even after they experience the negative consequences associated with drug abuse. These negative consequences have not been well modeled in animal self administration studies. That is, there are positive consequences to self-administer the drug, but no explicit negative consequences to self-administration in animals. Thus, there is no reason to predict that more impulsive animals should have a greater propensity to self-administer drugs because there are no explicit negative consequences associated with drug consumption. If there are implicit negative consequences of drug consumption in laboratory animals, it is unclear what these consequences are (i.e., the subjects are housed, fed, and watered independently of how much drug they consume) or, if the animals are capable of associating these negative consequences with drug consumption. Furthermore, whereas drug abuse is by definition maladaptive in human drug users, it is not at all clear that self administration of drugs by laboratory animals is maladaptive. Researchers have long argued that when drugs of abuse are viewed as reinforcers they act in the same way as natural reinforcers, such as food and water. It is not surprising then, that laboratory rats respond to produce IV injections of drugs of abuse – why should not they? In contrast, there are many explicit negative consequences for drug consumption in human drug users, such as legal, financial, and social/family costs. Although it is possible to construct animal models of self administration that include explicit negative consequences (Deroche-Gamonet et al. 2004; Economidou et al. 2009; Pelloux et al. 2007), commonly used laboratory models of drug consumption do not incorporate explicit negative consequences, and therefore it is questionable if drug consumption in these models would relate to impulsive tendencies. Future research examining the relationship between animal models of impulsivity and drug self-administration models in which drug consumption has negative consequences are needed.

Comparison of C57 and 129s Mouse Strains on Three Laboratory Models of Impulsive Behavior

The C57 mice were found to be more impulsive than 129s mice on all three tasks. In comparison to the 129s mice, the C57 mice discounted delayed rewards more, had slower stop RTs, and exhibited impairments in sustained attention. These results indicate that all three tasks can be used together to test the genetic basis of impulsive behavior in mice. The strength of the three behavioral tasks we used to characterize impulsive behavior in C57 and 129s mice is that they have a strong conceptual basis, and a methodology that can be applied to humans, rats, and mice. The results of this study support the use of these procedures to identify heritable processes in mice that may contribute to impulsive behavior in humans.

Other studies have also reported pronounced behavioral differences in these two strains of mice that are relevant to impulsivity. Specifically, C57 mice consume more alcohol (Crabbe et al. 1999), are more sensitive to the rewarding effects of both cocaine (Kuzmin and Johnson 2000; Miner 1997) and sucrose solutions (Bachmanov et al. 1996a, b) than the 129 strain. Compared to 129s mice, C57 mice are more active in the open field, more responsive to the motor activating effects of cocaine (Crabbe et al. 1999; Kuzmin and Johnson 2000; Schlussman et al. 1998), demonstrate larger startle responses to tactile and acoustic stimulation and demonstrate less prepulse inhibition (Crawley et al. 1997). These behavioral patterns indicate that C57 mice are more active and reactive to environmental stimuli compared to 129s mice. A final line of evidence suggesting a consistent pattern of differences between the two strains comes from a study by Logue et al. (1998). These authors tested inbred mouse strains on a response inhibition procedure in which the mice were required to withhold a nose poke response for 1–8 s until an auditory stimulus was presented. The 129s mice were better able to inhibit their responses compared to C57 mice. The higher alcohol consumption, greater responsiveness to hedonic stimuli, higher activity levels, and diminished ability to learn to suppress nose poking in C57 mice are consistent with our results indicating that C57 mice are more impulsive than 129s mice. These studies demonstrate that it is possible to use laboratory models of impulsive behavior to measure impulsive tendencies in mice. In future research, the use of these tasks in mice will allow us to address this important issue by testing genetically modified mice in order to identify neurobiological and genetic factors that contribute to impulsive behavior. For example, important new information may be gained by testing mice in which the neurobiological substrates that mediate the effects of stimulant drugs have been altered.

Implications for Drug Abuse Prevention

The factors that influence drug use in humans can be divided into two broad categories of reward-related and impulsivity-related factors (de Wit and Richards 2004). The majority of drug abuse research using human and animal models has focused on reward-related factors, while impulsivity-related factors have received less experimental attention. Research on reward-related factors focuses on understanding the reinforcing or hedonic qualities of drugs of abuse. Because the goal of research on reward-related factors is to study the reinforcing aspects of drug consumption in isolation, factors that may decrease drug consumption are minimized in these animal models. Research on reward-related factors suggests that decreasing the reinforcing and/or hedonic qualities of drugs of abuse and associated stimuli may be an effective prevention strategy. In contrast, the animal models discussed in this chapter focus on impulsivity-related factors that normally inhibit or limit the use of drugs. These factors may allow drug users to resist the reinforcing effects of abused drugs. This research asks questions about why human and nonhuman animals may choose to consume drugs despite negative consequences that make

drug consumption maladaptive. This approach suggests that increasing the influence of unwanted negative consequences over drug taking behavior may be an effective prevention strategy.

In this chapter, three behavioral processes were identified: delay discounting, response inhibition and attention. These processes may mediate the ability of the unwanted negative consequences to decrease drug taking behaviors. This suggests that behavioral treatments that target these behavioral processes (particularly during development) may be effective for decreasing drug abuse. Furthermore, behavioral interventions and pharmacotherapies that target these behavioral processes may be effective strategies for decreasing relapse to drug abuse. Recent studies provide some support for the use of stimulants, such as methylphenidate and amphetamine as a pharmacotherapy for cocaine abuse in adults with and without ADHD (Mooney et al. 2009; Levin et al. 2007; Konstenius et al. 2009; Castells et al. 2007). The effectiveness of these stimulant drugs, in treating relapse to drug abuse is generally attributed to partial agonist effects at the dopamine receptor that compete with the effects of drugs of abuse. However, it is also possible that the positive effects of these drugs are due to impulsivity-related factors. Laboratory studies have shown that treatment with methylphenidate and other stimulants decreases lapses of attention (Spencer et al. 2009; Leth-Steensen et al. 2000) and increases response inhibition (Tannock et al. 1995) in individuals with ADHD, suggesting that treatment with methylphenidate and other stimulants may decrease drug abuse by decreasing behavioral tendencies that cause drug abusers to ignore the negative consequences of their actions.

Consideration of the impulsivity-related factors described in this chapter indicates that behavioral interventions designed to improve sustained attention, ability to inhibit prepotent responses, and the delay of gratification would be effective in decreasing the occurrence of impulsive behaviors, such as drug abuse. In their review of impulsivity as a construct, Milich and Kramer (1984) concluded that while there is general agreement that impulsivity is of great importance in childhood behavioral problems, it is difficult to come to a general agreement about what the term impulsivity meant. With this in mind, an important contribution of this chapter for drug abuse prevention may be the identification of behavioral tasks that operationally define some of the processes that may lead to the occurrence of maladaptive behaviors, such as drug abuse. This suggests that performance on laboratory tasks designed to measure sustained attention, response inhibition, and delay discounting may provide a measure of the effectiveness of early childhood interventions that promote the development of behavioral regulation capacity (Chap. 1, this book).

Conclusion and Summary

A basic tenet of our approach to understanding and developing human and nonhuman animal models of impulsivity is that there is no single underlying behavioral process that is common to the general expression of behaviors that are labeled as

impulsive. Instead, we propose that impulsivity can be best defined at the behavioral level as a failure to inhibit the occurrence of behaviors that are maladaptive. According to this approach, maladaptive impulsive behaviors may occur because of a number of different underlying behavioral processes. In this chapter, we have identified three possibilities, delay discounting, response inhibition, and lapses of attention. It seems likely that there are other underlying behavioral processes that may also lead to the occurrence of impulsive behavior. The idea that different behavioral processes may contribute to impulsive tendencies is not new. For example, Barratt's Impulsiveness Scale, version 11 (Patton et al. 1995) has nine subscales (i.e., attention, motor impulsiveness, nonplanning impulsiveness, etc.), which are designed to measure different psychological process that contribute to impulsivity. If this kind of multiple process approach provides the best characterization of impulsive behavior, then it seems likely that no single behavioral task can adequately measure impulsive tendencies in human and nonhuman animals. In the comparison between C57 and 129s mice described above, it turned out that the C57 mice were more impulsive on all three behavioral tasks. However, it is certainly possible that comparisons of other strains of mice may reveal differences on only one or two of the behavioral tasks or that only a subset of processes has predictive validity in a particular situation. Preclinical research using animal laboratory models (and human laboratory models), of impulsive behavior needs to take into account that different behavioral processes may underlie the occurrence of impulsive behaviors.

In conclusion, the underlying causes of impulsive tendencies in humans remain poorly understood. The present multiprocess model, with parallel procedures across species, is one approach for improving our understanding of impulsive behavior. Although further development and refinement are clearly needed, this model offers a truly translational approach to studying one of the thorniest but widely cited constructs in the drug abuse literature. If these procedures can be used to identify genetic and environmental factors that contribute to impulsive behavior, then we will be in a better position to prevent or manage these difficult behavioral tendencies.

Acknowledgments The research described in this chapter and preparation of the manuscript was supported in part by grants R01DA010588 and R21DA014183, Jerry Richards PI and by R01MH069434, Larry Hawk PI. This work could not have been accomplished without the help of a number of coworkers, including Ashley Acheson, Andy Farrar, Artur Kieres, and Kathy Hausknecht. We thank Becky Ashare for her comments on the manuscript.

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Bardo, M.T.; Fishbein, D.H.; Milich, R. (Eds.)

2011, XIV, 335 p., Hardcover

ISBN: 978-1-4419-1267-1