How do genotype, stimulus conditions, and acute dopaminergic administration interact to influence the temporal allocation of credit?

By

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Abstract

The importance of delay discounting to many socially important behavioral problems has led to investigations of the genetic, biochemical, and environmental mechanisms responsible for variations in the form of the discount function, but the extant experimental research in these areas has yielded disparate results. The present study examined potential Gene X Drug X Environment interactions in delay discounting by examining d-amphetamine’s effects on delay discounting in two mouse strains using a novel procedure. BALB/c and C57BL/6 mice responded on a six-component concurrent-chained schedule in which the order of terminal-link delays preceding a larger-reinforcer was randomized across components. Across conditions, components were presented as mixed or multiple schedules and effects of a dose-range of d-amphetamine were determined. Dose-effects on generalized matching sensitivity to reinforcer magnitude and delay were characterized by multi-model inference. For BALB/cs, there were no effects of schedule on model parameters under control conditions, however, d-amphetamine dose-dependently decreased delay sensitivity and this effect was greater under the mixed schedule. For C57BL/6s, control estimates of sensitivity to reinforcement were higher under the multiple schedule and d-amphetamine dose-dependently decreased sensitivity to reinforcement under the multiple and increased sensitivity to reinforcement under the mixed schedule. These results suggest a genotype X environment interaction describing d-amphetamine’s effects on delay discounting. Differences in the baseline form of the discount function were generated by a genotype X signaling condition interaction and the effects of d-amphetamine were baseline-dependent.
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Chapter 1: Introduction

In human and non-human animals, behavior such as publishing manuscripts or lever-pressing may be strengthened by consequent phylogenetically or ontogenetically important events, such as reinforcers (e.g., publishing a paper or a milk delivery). This statement is embodied in Thorndike’s Law of Effect and developed further by B. F. Skinner using more sophisticated experimental techniques free from constrains of puzzle-boxes and mazes. But Thorndike’s Law of Effect must come with a caveat: As time passes since its emission, the ability for a class of behavior to be strengthened decreases. The empirical curve capturing this relation is commonly called the delay of reinforcement gradient (Killeen, 2011; Lattal, 2010). At any moment in time there may be several potential gradients representing different classes of behavior competing for the influential effects of several qualitatively or quantitatively different reinforcers. It is via delay of reinforcement gradients that subsequent reinforcers operate. But what are these gradients (cf. Killeen, 2011)? What form(s) do they take (Johansen et al., 2009; Killeen, 2001)? How can we as scientists develop a formal model that can describe such an intervening variable (Killeen, 1994)? What can these gradients tell us about psychiatric disorders or behavioral anomalies (Savgolden et al., 2005; Dombrovski et al., 2011)? Because of the ubiquity of these gradients and the motivation to answer the above questions, a great deal of attention has been devoted to their study by basic and translational researchers (e.g., Madden & Bickel, 2010; Sonuga-Barke, Bitsakou, & Thompson, 2010; Sonuga-Barke, 2011; Winstanley 2006). This line of research is now termed temporal or delay discounting. Discount rate, or the decline in preference for a reward as a function of the increase in delay to its receipt, is often used as an index of impulsivity (Ainslie, 1975; Evenden, 1999; Rachlin, 1974). Impulsivity has been invoked as an underlying component of a number of psychiatric disorders such as attention-deficit hyperactivity disorder (ADHD), mania, substance abuse, pathological gambling, and other personality disorders (DSM IV; Winstanley, Eagle, & Robbins, 2006). In the context of delay discounting, impulsivity is precisely defined as a pattern of choosing smaller, more immediate rewards at the expense of a larger, but more delayed rewards.

Laboratory preparations used to assess impulsivity in nonhumans have been adapted from concurrent-chained schedules of reinforcement (Autor, 1969; Davison & McCarthy, 1988; Herrnstein, 1964). These schedules of reinforcement comprise a chain containing two distinct links, an initial or “choice” link and a terminal or “outcome” link. In a delay discounting procedure the terminal-links differ in relative reinforcer magnitude and delay. A number of quantitative frameworks assume that relative responding in the initial links reflects preference for the terminal-link stimulus of greater conditional reinforcing value or efficacy (Baum, 1974b; Baum & Rachlin, 1969; Davison & McCarthy, 1988; Grace, 1994; Mazur, 1987; Killeen, 2011).

Monoamine neurotransmitters, specifically serotonin (5-HT) and dopamine (DA), have been heavily
implicated in the neurobiology of impulsivity (see Winstanley, 2010 for a recent review). The effects of psychomotor stimulants, such as d-amphetamine, on delay discounting are of clinical relevance to the treatment of disorders such as ADHD (Killeen, 2013, Killeen et al., 2013; Winstanley et al., 2006; Sonuga-Barke et al. 2011). The existing preclinical literature pertaining to acute psychomotor stimulant effects on delay discounting, however, has shown that the discounting rate of individual subjects can be increased (e.g., Cardinal et al., 2000; Pitts & Febbo, 2004; Sagvolden et al., 1992) or decreased (Evenden & Ryan, 1996; Winstanley et al., 2003) following acute administration. One of the compelling hypotheses for these inconsistencies is the dependence of amphetamine’s effects on the stimulus conditions present at moment of choice and the correlations between terminal-link stimulus, presented after the choice has been made and during the delay to a larger-magnitude reward.

The stimulus conditions during the choice phase in the initial-links can be investigated by arranging stimuli that are uniquely correlated with the forthcoming delay differentials in the terminal-links (Kragelöh & Davison, 2003 with concurrent schedules), an arrangement called a multiple schedule. In contrast, under a mixed schedule identical stimuli are presented during the choice phase regardless of the upcoming delay differential. The mixed schedule is the more common approach in the animal literature, while the multiple schedule is more common in the human literature, if only because a human participant is shown a card or a computer with the specific pair of delays written on it.

Another technique, known as marking, presents a discrete stimulus immediately after the initial-link choice occurs (see Johansen et al., 2009 Rachlin, 1976; Williams, 1994, 1999). A related technique may be applied to the terminal-links, in which the prevailing delays may be correlated with particular stimuli that “bridge” the temporal gap between choice and reinforcer delivery (i.e., bridging; see Johansen et al., 2009; Rachlin, 1972; Williams, 1994, 1999). A mixed schedule presents identical bridging stimuli for all terminal-link delays, while the multiple schedule presents unique bridging stimuli for each of the terminal-link delays arranged in the procedure. So, in summary, the stimulus conditions that are pertinent to temporal discounting are 1) the mixed/multiple schedules, which designate the stimulus condition during the choice phase (initial link; see Figure 4), 2) marking stimuli, a brief stimulus following choice (see Figure 5, and 3) bridging stimuli, which span the delay between the execution of the choice and the delivery of the consequence (see Figure 6).

In our laboratory, we have adapted a 6 component, concurrent-chained schedule of reinforcement to measure delay discounting by inbred mouse strains. This procedure randomizes the delay to reward in the terminal-links, drawing from recent literature on rapid within and across-session acquisition procedures (e.g., Davison & Baum, 2000; Grace, Bragason, & McLean, 2003). Using a mixed, concurrent-chained schedule, with bridging stimuli prevailing during the terminal-links, we found that BALB/c mice displayed higher estimates of sensitivity to reinforcer magnitude
(i.e., additional reinforcers are more valuable), as indicated by the height of the curves drawn through the open and closed circles in Fig. 1. The BALB/c mice also discounted at higher rates compared to the C57Bl/6 mice, as indicated by the steepness of the curves drawn through the open and closed circles in Fig. 1. With BALB/c mice, we have assessed the effects of acute \textit{d}-amphetamine administration under mixed and multiple concurrent-chained schedules, with both schedules arranging either identical or delay-specific, bridging stimuli during the terminal-links. Using linear mixed effects modeling based on the generalized matching law (GML), we showed that mixed conditions fostered a bias for the larger, delayed reinforcer and thus an upward shift in the discount function relative to multiple conditions. The multiple condition, however, resulted in shallower discount functions, consistent with the delay-specific stimuli resulting in enhanced discriminative control over the response producing the delayed reward. This model also showed that \textit{d}-amphetamine increased estimates of sensitivity to reinforcer magnitude under both schedules, but amphetamine’s effects were attenuated when a multiple schedule was introduced (Fig. 2). The attenuation of amphetamine’s effects by the multiple schedule is consistent with the idea that the presence of an exteroceptive stimulus can enhance discriminative control over responding and thereby diminish the impact of a disruptor such as a drug or a toxic substance. (e.g., Laties & Weiss, 1966; Miller, Saunders, & Bourland, 1980; Zeeb, Floresco, & Winstanley, 2010; Wood).

In studies of delay discounting, the effects of dopaminergic drugs are altered by the presence of conditional stimuli during both choice and outcome links. A study in our laboratory showed that \textit{d}-amphetamine’s effects depend upon how well dimensions of reinforcement (magnitude and delay) delivered in the terminal-links is correlated with prevailing bridging stimuli. Furthermore, we have demonstrated basal differences in impulsivity between BALB/c and C57Bl/6 mice: the C57Bl/6 displays flatter delay gradients than the BALB/c. These basal strain differences in impulsivity provide another baseline from which to characterize the effects of dopaminergic drugs. This proposal seeks to extend previous studies by comparing the effects of \textit{d}-amphetamine under initial link mixed and multiple, concurrent-chained schedules with an inbred mouse strain that we have shown to be relatively “self-controlled” as compared to a strain to be relatively “impulsive.”

Below I first review the evolution of quantitative assessments of choice in stable environments. Following this review, an introduction to the quantification of choice in dynamic environments, or choice in transition, will be provided. An emphasis in each of these reviews will be on the role of stimuli arranged during choice and delays to reinforcement on the speed of acquisition and the final form of the discount function. At the end of the introduction, I provide a review of how insights from these bodies of literature have been used to understand drug effects on delay discounting. The present review will focus heavily on quantitative and theoretical models used to assess choice and
their extensions to delay discounting. Formal representations such as these are central to science: They help us define, represent, explain, predict, and control the enduring phenomena under study (Killeen, 2013).

The Quantitative Assessment of Choice

Herrnstein (1961, 1964, & 1970) pioneered the empirical study of choice for two sources of reinforcement through the theoretical framework of the matching law and the quantitative law of effect. These early papers revolutionized the conceptualization and study of free-operant choice through quantitative measures. The critical theme Herrnstein presented is a simple but profound idea: All behavior is choice (1970). The core principle of this early instantiation is that preference for a particular alternative, always defined in terms of relative behavior or time allocation, is proportional to the relative reinforcement (i.e., rate, immediacy, magnitude, probability, etc.) available for that alternative in relation to all other existing alternatives (extraneous reinforcement).

Concurrent Schedules of Reinforcement

In his original investigation of choice, Herrnstein (1961) established key-pecking under two independent, concurrent variable-interval schedules ranging from 90 to 180 s for the “rich” key and 90 s to extinction for the “lean” key. The overall rate of reinforcement was held constant for the duration of the experiment at 90 s on average. When a changeover delay of 1.5 s was imposed to control for rapid rates of switching or alternating patterns of responding, the proportion of pecks made to one of the keys equaled the proportion of reinforcers obtained while responding on that key. This relationship is known as strict, or proportional, matching because the relative rate of responding on an alternative exactly matched the relative rate of reinforcement derived from that alternative.

After Herrnstein’s original experiments on choice and relative rate of reinforcement, Catania (1963) extended research on matching to incorporate other reinforcement dimensions. Specifically, he kept the relative rate of reinforcement constant between two independently scheduled VI 120 VI 120 s schedules, but manipulated relative reinforcer magnitude by varying the duration of grain hopper presentations from 3 to 6 s. Although reinforcer magnitude had previously shown to have no effect on response rate in single schedule preparations, relative responding matched the relative reinforcer magnitude ratio between the two operand.

Chung and Herrnstein (1967) conducted a quantitative assessment of the effects of relative reinforcer delay on relative responding. In this study, pigeons’ key-pecking was reinforced under a concurrent-chained schedule in which the initial-links were two independently-scheduled VI 60-s and the terminal-links were fixed-time (FT) schedules. The terminal-link for one key was always FT 8 s while the terminal-link for the other key varied from FT 1 s to FT 30 s across different conditions. Chung and Herrnstein found that relative responding in the initial links matched relative terminal-link delay or its reciprocal, immediacy. That is, the relationship between relative initial-link responding and
terminal-link delays was negative and approximately linear. Thus, three dimensions of reinforcement, relative rate, magnitude, and delay, could now be brought under the theoretical framework of the matching law and, decades later, this formed a theoretical base for the experimental analysis of delay discounting. It also forms the procedural basis for the proposed study.

**Concurrent-chained Schedules of Reinforcement**

Concurrent-chained schedules of reinforcement, originally introduced by Autor (1960, 1969) and extended by Herrnstein (1964) and Chung and Herrnstein (1967), have been used extensively in a number of different fields to study choice for more than five decades. These schedules were originally employed to determine whether the matching law could describe the allocation of behavior for delayed unconditional reinforcement maintained or signaled by conditional reinforcing stimuli. Under the concurrent-chained schedule, an organism chooses between two separate schedules of reinforcement, rather than between two reinforcers as under a simple concurrent schedule. Thus, it is a combination of the concurrent schedule, in which two or more schedules operate simultaneously, and the chain schedule in which two or more schedules operate in succession. The first schedule, or the *initial link*, is a concurrent schedule. After response requirements on one of the two initial-links have been completed, one of two mutually exclusive second schedules, or *terminal-links*, is made available, and the other alternative is removed. Upon completing the terminal-link schedule requirements, reinforcement is delivered and the initial-links are then reinstated, usually after an intertrial interval (ITI). A typical concurrent-chains arrangement is diagrammed in Figure 3.

Responding under concurrent VI or FR schedules in the initial links may be reinforced by access to one of two mutually exclusive terminal-link schedules (e.g., FI, FT, VI, VT, etc.), and these terminate in reinforcement delivery. Relative responding in the initial-links is a measure of preference for the terminal-link schedules or a measure of the conditional reinforcing value of, or control by, the stimuli correlated with the terminal-link schedules.

In Autor’s original experiments, pigeons responded on independently scheduled VI 60s initial links that operated concurrently on two-separate keys, forming a *conc* VI 60s VI 60s schedule for access to the terminal links. Completing the schedule requirements for entry into one of the terminal-links paused the schedule operating on the other initial link key, darkened that key, and responses to it had no programmed consequences. The terminal-links were pairs of VI, VR, or differential reinforcement of alternative behavior (DRA) schedules in which one key schedule was fixed and the schedule for the other key varied across conditions. By measuring relative responding in the initial links, Autor found that relative responding in the initial-links approximately matched the relative rates of reinforcement in the terminal-links. Similarly, Herrnstein (1964b) applied the mathematical principles from his original experiments to study the conditional reinforcing value of terminal-link stimuli. Using a concurrent-chained
schedule with independently scheduled Conc VI VI 60 s initial links, which were correlated with either VR VR, or VR VI terminal links, Herrnstein also showed that relative responding on the two initial-link keys approximated relative rates of unconditional reinforcement provided in the terminal-links.

**Generalized Matching and Concatenated Matching**

The generality of Autor and Herrnstein’s original findings that the relative allocation of behavior to an alternative was proportional to the rate of reinforcement for that alternative was soon challenged. Deviations from strict matching occurred frequently in concurrent schedules, and these resulted in the formulation of the generalized matching law by Baum (1974b). This equation, which resembles Steven’s (1957) power-law formulation for psychophysical judgments, introduced a bias term that accounted for a constant preference for one alternative over another due to reasons other than reinforcement contingencies (i.e., lever force requirements, handedness) and an exponent representing sensitivity to reinforcement. This sensitivity exponent indicated the degree to which preference was more or less extreme than the programmed contingencies (i.e., over and undermatching, respectively): This relation, a power function, is frequently expressed in logarithmic terms yielding the linear equation:

\[
\log \left( \frac{B_L}{B_R} \right) = a \log \left( \frac{R_L}{R_R} \right) + \log(b)
\]  

(1)

In Equation 1, \( R_i \) is the relative dimension of reinforcement manipulated, \( b \) or bias is the constant preference favoring the left or right alternative respectively, and \( a \) represents response-allocation sensitivity to dimensions \( R_i \). The generalized matching law can be further generalized to concatenate multiple dimensions of reinforcement simultaneously under study. Baum and Rachlin (1969) proposed that response allocation in concurrent schedules matched the “value” of the alternative schedules and a multiplicative relation between different independent variables determined that value. That is, different reinforcement dimensions such as rate, magnitude, immediacy, and probability could be combined to produce the intervening variable reinforcement value. Conceptualized in this manner, a more general form of the generalized matching law in logarithmic terms becomes

\[
\log \left( \frac{B_L}{B_R} \right) = \sum_{t=1}^{n} a_t \log \left( \frac{X_{tL}}{X_{tR}} \right) + \log(b) = \frac{V_L}{V_R}
\]

(2)

Equation 2 states that the matching law represents scaling of the relative value correlated with each alternative, which is determined by an additive (in log terms) concatenation of reinforcer ratios (Killeen, 1972). Although deviations from the linear assumption of the GML frequently occur in concurrent chains, some of the more empirically developed models of concurrent-chains choice can all be traced to the generalized matching law (Grace, 1994; Mazur, 1987, 2001, Squires & Fantino, 1971).
Rapid Acquisition of Choice in Variable Environments

The focus of much research on choice in the experimental analysis of behavior has been on steady state operant behavior. With extraordinary gains in steady state choice research propelled by the matching relation, research began to emphasize behavioral dynamics (Marr, 1992). Whereas steady state refers to the asymptotic level of behavior following some manipulation, behavior in transition is the way in which response allocation adjusts from one steady state to another. There have been a number of approaches to examine behavior in transition or behavioral dynamics in concurrent schedules of reinforcement (e.g., Palya, 1992). For example, some research has examined preference in free-operant and discrete trials, concurrent ratio and interval schedules as a function of unpredictable step changes in ratios of different dimensions of reinforcement (Bailey & Mazur, 1990; Mazur, 1992; Mazur & Ratti, 1991). Another approach, which models behavior in transition to changing reinforcer rate ratios within a single session, has been taken previously in our laboratory (Banna & Newland, 2009; Newland et al., 1994; Newland et al., 2004). Each of these approaches has shown that choice can adjust rapidly, within a few reinforcers, to within-session step changes in reinforcer rate ratios.

Other approaches have used random across-session variations in reinforcer rate ratios in concurrent schedules, and reinforcer delay ratios in concurrent chained schedules, to generate “behavioral transfer functions” (Grace Bragason & McLean, 2003; Hunter & Davison, 1985). These studies have varied reinforcer rate or delay ratios across sessions according to a pseudorandom binary sequence (PRBS). For example, on day one the reinforcer delay ratio might be 10: 5, on the second day 5:10, on the third day 10:20, etc. The PRBS provides a way to assess the acquisition of choice to changes in reinforcement ratios that are unpredictable. In order to quantitatively assess the effects of previous and current sessions contingencies on current choice, each of these studies have analyzed data in terms of multiple regression analyses based on an extension of the GML (i.e., Eq. 2):

\[
\log \left( \frac{\beta_{\text{OLL}}}{\beta_{\text{OSR}}} \right) = a_{0R} \log \left( \frac{R_{0L}}{R_{0R}} \right) + a_{1R} \log \left( \frac{R_{1L}}{R_{1R}} \right) + a_{2R} \log \left( \frac{R_{2L}}{R_{2R}} \right) + \ldots + a_{iR} \log \left( \frac{R_{iL}}{R_{iR}} \right)
\]

(3)

In equation three, the log response ratio in session \( i \) is determined additively by a series of terms representing the reinforcer ratios in the current and previous sessions. The session numbers are indicated by the subscripts (i.e., 0 for the current session, 1 for the immediately preceding session, and so forth) and each session has a correlated reinforcement sensitivity parameter \( (a_{IR}) \). Equation 3 provides a way to demonstrate how reinforcer ratios influence response allocation for the current and previous sessions and can also be modified to include previous trials or blocks of trials (i.e., any sort of lag). This type of analysis, coupled with the PRBS procedure, provides the opportunity to model choice in as a function of frequent and unpredictable changes in reinforcer dimensions. Furthermore, the PRBS
procedure can be used as a tool to determine the time frame over which local reinforcement history controls responding and the conditions that affect this time frame (i.e., stimulus control). Overall, these findings and procedural amendments replicated those found with simple concurrent and concurrent-chained schedules and showed that subjects’ initial-link response allocation adjusted rapidly to randomized, across-sessions changes in reinforcer and terminal-link delay ratios.

In addition to randomized-across session changes in reinforcement contingencies, researchers have used procedures that involve frequent and unpredictable changes in reinforcer dimensions within single experimental sessions to examine choice in transition. Employing a procedure initially proposed by Belke and Heyman (1994), Davison, Baum and colleagues (e.g., 2000, 2002, 2003) have conducted several parametric assessments of choice in concurrent schedules when reinforcement contingencies changed in a randomized manner throughout a session. The basic procedure involved a seven-component, mixed-concurrent schedule of reinforcement in which reinforcement rate ratios of 27:1, 9:1, 3:1, 1:1, 3:1, 9:1, and 27:1 were presented in a randomized manner within each session. In the initial study, several variations the basic above procedure were investigated, including overall rate of reinforcement (i.e., 2.22 vs. 6 reinforcers min\(^{-1}\)) and the number of reinforcers per component (ranging from 4 to 12), although they reported that none of these manipulations affected the basic findings.

Davison and Baum analyzed the data by calculating log response ratios as a function of successive reinforcers delivered within each component of a session. Of interest was how response ratios changed on a reinforcer-by-reinforcer basis to the richer alternative arranged in a particular component. In cases where the ratio was more disparate (i.e., 3:1 vs. 27:1), response ratios also became more disparate. The upshot is that sensitivity to the current reinforcer rate ratio in effect increased from around 0 at the beginning of a component to approximately 0.5 as a function of reinforcers delivered in a component. This asymptotic level of sensitivity is comparable to those reviewed in the above steady state procedures.

Although, preference in the current component changed rapidly as a function of reinforcers delivered, lag sensitivity analyses (e.g., Eq. 4) showed that preference at the beginning of a component was also controlled by the previous component’s reinforcer ratio. Hysteresis diminished rapidly after successive reinforcer deliveries in the current component, consistent with the rapid adjustment of choice to the current component contingencies. The findings from these and subsequent studies (e.g., Davison & Baum, 2002, 2003, 2005, 2006, 2008) lend credence to the notion that preference in concurrent and concurrent-chained schedules develops rapidly when reinforcer ratios changed frequently and unpredictably within each experimental session.

**Stimulus Control in the Analysis of Choice**
Research on choice in concurrent and concurrent-chained schedules has been primarily focused on manipulations of the response-reinforcer contingency. Ferster and Skinner (1957) and Findley (1958), however, defined concurrent behavior in such a way as to highlight the fact that under concurrent schedules each operant is part of a three-term contingency involving discriminative stimuli. Catania (1966) and Rilling (1977) continued to promote the idea that discriminative stimuli are important in determining preference in choice situations and argued that concurrent schedules may be simply described as discriminative training procedures. Indeed, in Baum’s formulation of the generalized matching law (1974), he suggested that sensitivity to reinforcement is influenced by discriminative stimuli correlated with each alternative (Baum, 1979). Research concerned with discriminative control over concurrent performance originally emerged from Davison and colleagues (e.g., Boldero, Davison, & McCarthy, 1985; Davison & Jenkins, 1985; Davison & Tustin, 1978; McCarthy & Davison, 1979, 1980, 1981, 1982, 1984) and Nevin and colleagues (Nevin, 1969; Nevin, Jenkins, Whittaker, & Yarensky, 1982; Nevin, 1981a, 1981b) integrating research and theory from signal-detection.

Part of this line of research, pioneered by Bourland and Miller (1978), was concerned with the role of discriminative stimuli in determining the allocation of behavior using Findley (1958) changeover-key concurrent-schedules. Bourland and Miller (1981) and Miller, Saunders, and Bourland (1980) showed that changes in sensitivity to reinforcement as a function of changes in reinforcement schedules were accounted for by the discriminability between stimuli correlated with particular reinforcer rates. Specifically, Miller and colleagues, using a Findley (1958) procedure, programmed independent VI schedules with different reinforcement-rate ratios in the presence of similar vs. different vs. identical line orientations presented on the response key (Bourland & Miller, 1981; Miller et al., 1980). Results showed that when the stimuli correlated with each component were identical, lower values of sensitivity to reinforcement were found when compared to the different conditions. These results confirmed the speculation by Baum (1979) that the discriminability between stimuli correlated with different reinforcement rates is a large determinant of preference and thus sensitivity to reinforcement.

Few studies have investigated the role of stimulus control on choice in transition using global measures of preference. Using a three-key procedure, Hanna, Blackman, and Todorov (1992) exposed pigeons to 20 different ratio combinations of 5 different overall reinforcement rates. These concurrent schedule combinations were presented as either mixed or multiple schedules. In the mixed concurrent schedule, the same stimulus conditions prevailed for each of the 20 different reinforcer rate ratio combinations used in the study. In the multiple schedule, distinctive discriminative stimuli (i.e., key color) were correlated with each of the 20 reinforcement rate ratio combinations. The results showed that the enhanced discriminative control provided by the multiple schedule stimuli increased the speed
with which preference stabilized and this was accompanied by an increase in the speed with which sensitivity to reinforcement reached asymptote, relative to the mixed conditions.

Krägeloh and Davison (2003) extended this line of research using the multi-component concurrent schedule procedure developed by Belke and Heyman (1994) and extended by Davison and Baum (2000). Specifically, they arranged a seven-component concurrent schedule in which the reinforcement rate ratios changed unpredictably after 10 reinforcers were delivered in each component. Across conditions, components were either presented as a multiple schedule (i.e., different red—yellow key flash frequency for each reinforcer ratio) or a mixed schedule (i.e., same red—yellow key flash frequency across all ratios). Like Hanna et al. (1992), the results showed that sensitivity to reinforcement under the multiple schedule increased from around 0.40 before the first reinforcer was even delivered in a component to around 0.80 at the end of the component. In contrast, sensitivity to reinforcement under the mixed schedule increased from zero to around 0.40. Lag sensitivity analyses (a version of Eq. 3) showed that hysteresis diminished at a much faster rate in the multiple schedule conditions. The authors concluded that the distinctive stimuli correlated with each reinforcer ratio resulted in greater discriminability between reinforcement ratios and promoted enhanced discriminative control over choice at each reinforcer ratio. These results suggest that multiple schedules facilitate acquisition of preference in concurrent schedules and that stimulus control is more closely aligned with long-term, molar reinforcement effects.

The Effects of Drugs on Choice in Transition

More recent studies have used randomized reinforcer delay or rate presentation-procedures, involving within or between session changes in the reinforcement ratios (Davison & Baum, 2006; Grace et al., 2003), to assess the effects of acute drug administration (e.g., Rodewald et al., 2010; TA et al; Maguire et al; 2009). In these studies, the frequent within- or across-session changes in relative reinforcement value are unsignaled (e.g., mixed concurrent or concurrent chained). For example, Rodewald et al. (2010) and Maguire et al. (2009), used the multi-component concurrent schedules procedure (e.g., Davison & Baum, 2000) and Ta et al., (2008) used a rapid acquisition concurrent-chains procedure (Grace et al., 2003) to assess sensitivity to within- or between-session changes in reinforcer rate, delay, and magnitude ratios, respectively. All of these studies used the GML to estimate sensitivity to the reinforcer ratio following d-amphetamine administration. Each of these studies reported that amphetamine decreased sensitivity to the respective dimensions of reinforcement in a dose-dependent fashion. Importantly, and consistent with previous studies, lag-sensitivity analyses showed that preference was most strongly controlled by the current reinforcement differential, with little effect from previous sessions or components. On the basis of these findings, Pitts and colleagues argued that sensitivity to reinforcement might provide a locus from which to identify
potential behavioral mechanisms of \( d \)-amphetamine’s action.

**Delay Discounting and Impulsivity**

Much of the original research on steady-state choice and contemporary research on behavior in transition has been concerned with across- or within-session manipulations of a single dimension of reinforcement. A number of studies have analyzed steady-state preference as a function of changes in multiple dimensions of reinforcement (Baum & Rachlin, 1969). Research pioneered by Rachlin and Green (1972) concerning choice between smaller magnitude, immediate reinforcers and larger magnitude and more delayed reinforcers is of particular importance. This line of research, now commonly referred to as delay or temporal discounting, is currently one of the most heavily studied areas in psychology and neuroscience (see Madden & Johnson, 2010 for a review). Delay discounting is considered to be a ubiquitous feature of intertemporal choice that describes the systematic reduction in preference for an alternative as the delay to its receipt increases. If preference for a larger, delayed reinforcer (LLR) relative to a smaller, sooner reinforcer (SSR) declines steeply as the delay to its receipt increases, then this pattern of behavior is labeled impulsive (Ainslie, 1975; Rachlin & Green, 1972; Rachlin, 1974). On the other hand, self-control is demonstrated if preference for LLR declines at a relatively slower rate as a function of delay.

Any non-human laboratory procedure involving choice between delayed reinforcement is necessarily a concurrent-chained schedule of reinforcement. Thus, all delay-discounting procedures are variants of concurrent-chained schedules of reinforcement. Conceptualized this way, the terminal-links in a discounting procedure differ in relative magnitude and delay. Choice in the initial links, often measured as the logarithm of the ratio of responses produced by each initial link schedule, is assumed to reflect preference for the terminal-link stimulus of greater “value” (Baum & Rachlin, 1969; Grace & Mclean, 2006). Terminal-link value has been successfully modeled using the concatenated generalized matching law (GML; Baum & Rachlin, 1969; Davison, 1983; Killeen, 1972; Rachlin, 1971). The GML predicts that choice is determined independently by each reinforcer dimension obtained in the terminal links. A version of the GML suitable for the typical delay discounting preparation (e.g., Grace, 1999) may be written

\[
\log \left( \frac{B_{LLR}}{B_{SSR}} \right) = s_1 \log \left( \frac{D_{LLR}}{D_{SSR}} \right) + s_2 \log \left( \frac{M_{LLR}}{M_{SSR}} \right) + \log(b)
\]

(4)

where \( B_i, D_i, \) and \( M_i \) are response rate, reinforcer delay, and reinforcer magnitude, respectively. Sensitivity to reinforcement \( s_i \) captures the extent of changes in preference with changes in the relative value of each dimension for an individual subject, while \( b \) captures constant preference independent of the reinforcement ratios. Eq. 4 predicts that the form of the discounting function is determined by an additive effect of each reinforcement dimension and the sensitivity of an individual subject to each of these dimensions. As applied to delay discounting procedures, greater
values of delay sensitivity $s_1$ indicate steeper discounting. Magnitude sensitivity $s_2$ changes the y-intercept and the height of the discount function. The GML and its daughters have been shown to describe discount functions accurately across a variety of procedures and, importantly, to predict reversals of preference in individual subjects (e.g., Ainslie & Herrnstein, 1981; Grace et al., 2012; Logue et al., 1984, Grace, 1999; Pitts & Febbo, 2004).

**Behavioral Mechanisms of Drug Action in Delay Discounting**

Behavioral pharmacologists have applied the formal quantitative frameworks such as the matching law (Herrnstein, 1970) to the behavioral effects of drugs with the goal of revealing behavioral mechanisms of drug action (e.g., Dallery & Soto, 2004; Heyman, 1983; 1992; Heyman & Monaghan, 1990; Logue et al., 1992; Pitts & Febbo, 2004, Pitts, 2014). A behavioral mechanism of drug action has been defined as an explanation of a drug’s effect on behavior in terms of the general sets of environmental events maintaining that response class prior to drug administration (Thompson, 1984; Sidman, 1959). For example, Pitts & Febbo (2004) analyzed discount functions generated by pigeons using the GML in an attempt to isolate the behavioral mechanisms of methamphetamine’s effects on discounting. They found that methamphetamine dose-dependently decreased impulsivity by decreasing GML estimates of sensitivity to reinforcer delay ($s_1$ in Eq. 1). On the basis of this finding, Pitts and Febbo argued that the GML might provide a framework from which to identify potential behavioral mechanisms of drug action on delay discounting.

The behavioral manifestations of impulsivity are closely aligned with the regulation of reinforcement and inhibitory processes by monoaminergic neurotransmission. For example, acute $d$-amphetamine and methylphenidate usually decrease discounting rate in human and non-human animals (Killeen et al., 2013). The pharmacological mechanism of action for these psychomotor stimulants is the enhancement of dopaminergic activity, indirectly, by inhibiting reuptake into the presynaptic neuron and promoting the release or synthesis of dopamine in the presynaptic neuron (in addition to noradrenergic and serotonergic systems, but with less potency). The use of selective dopaminergic agonists can help characterize specific neurochemical mechanisms of behavior, but the results have been somewhat ambiguous. For example, D1 receptors may play a primary role in discounting rate, as shown when D1 antagonists, but not D2 antagonists increase discount rate. On the other hand, decreases in discount rate following $d$-amphetamine administration depends on activation of D2 receptors, as demonstrated when $d$-amphetamine induces decreased impulsivity after pretreatment with D1, but not D2 antagonists (Van Galeen et al., 2006).

**Stimulus Control and Delay Discounting**

The manipulation of stimulus conditions prevailing during the initial and terminal-links are relatively understudied variables in the delay-discounting literature. When they have been investigated, the locus of interest has
been largely in the terminal-links. Within-session discounting procedures have arranged conditions in which no stimulus is presented to designate terminal-link entry (concurrent-tandem schedules) or a stimulus is presented to signal the transition from the initial to the terminal link (concurrent-chained schedules; Cardinal et al., 2000). Under either of these arrangements, however, the different delays to the larger reward arranged across components were not differentially correlated with particular stimuli (i.e., mixed-chained or -tandem schedules; Evenden & Ryan, 1996 procedure). Mixed-chained schedules usually foster higher preference for the delayed alternative under control conditions relative to mixed-tandem schedules. The latter result is usually interpreted in one of two ways, neither mutually exclusive. First, is in terms of the conditional reinforcing property of the chain’s terminal-link stimuli, which are correlated with the larger-magnitude alternative. The second emphasizes the discriminative function of the chain stimuli. By demarcating the chain’s components, temporal (i.e., discriminative) control over responding in the terminal-links is enhanced (Miller & Bourland, 1981). The argument that there is enhanced control over the transition from the initial to the terminal links and enhanced would predict greater sensitivity of choice in the initial-links to the reinforcer dimensions in the terminal links. 

\[\text{d-Amphetamine\ has\ been\ shown\ to\ increase,}\\]
\[\text{decrease,}\\]
\[\text{or\ result\ in\ no}\]
\[\text{change\ in\ impulsive\ choice\ depending\ on\ these\ arrangements.}\]
\[\text{d-Amphetamine\ increases\ preference\ for\ the\ delayed}\]
\[\text{alternative,}\\]
\[\text{relative\ to\ control\ conditions,}\\]
\[\text{under\ mixed-chained\ schedules.\ This\ effect\ is\ nonexistent\ or\ opposite\ with}\]
\[\text{mixed-tandem\ schedules\ (Cardinal\ et\ al.,\ 2000;}\\]
\[\text{Evenden\ &\ Ryan,\ 1996)\ The\ results\ are\ consistent\ with\ theories}\]
\[\text{that\ d-amphetamine\ enhances\ the\ effects\ of\ conditional\ reinforcers\ correlated\ with\ the\ greater\ magnitude\ alternative\ or\ exerts}\]
\[\text{its\ greatest\ effects\ when\ the\ transitions\ from\ initial\ to\ terminal-links\ are\ made\ more\ discriminable\ (i.e.,\ chained-schedules).}\]

An important stimulus condition that has been less well characterized in the discounting literature is a multiple-chained schedule (Slezak & Anderson, 2009). Multiple chained-schedules may be arranged in either the initial or terminal-links. When arranged in the initial links, unique stimuli are correlated with the delay ratio that will appear in the terminal-links for the current component. These uniquely correlated stimuli usually extend throughout the delays to reinforcement in the terminal-links. When arranged solely in the terminal-links, each delay to the LLR is correlated with unique stimuli that are presented only after entering the terminal-link and remain present until reinforcement is delivered (i.e., bridging). In our laboratory, we have examined the performance of BALB/c mice in 6-component, mixed and multiple, bridging concurrent-chained schedules; in the latter, unique stimuli appeared during the terminal links. The mixed condition fostered higher preference for the LLR alternative at shorter delays relative to the multiple-chained condition and discount rate tended to be lower under the multiple schedule.
We found differences in discounting between the two conditions after acute administration of \(d\)-amphetamine. Figure 2 shows preference for the LLR under both conditions plotted for each dose of \(d\)-amphetamine: \(d\)-Amphetamine increased choice for the LLR across nearly all delays, but this effect was dampened under the multiple schedule, especially at the dose of 1.0 mg kg \(^{-1}\). This finding suggests that discriminative control by the multiple schedule stimuli over responding in the terminal-links attenuated the drug’s effect. This is reminiscent of classic studies by Laties, Weiss, and colleagues with clocked fixed-interval schedules and fixed consecutive number schedules, mentioned earlier, in which a discriminative stimulus attenuated \(d\)-amphetamine’s behavioral effects, but it may not be the identical phenomenon. In the Laties and Weiss procedures, a unique stimulus was presented prior to the response whereas in the bridging procedure, the unique stimulus is presented \emph{after} the choice response has occurred, but before/during terminal-link responding. Providing a unique stimulus during terminal-link responding may provide greater temporal control over responding in the terminal-links and thus greater resistance to effects of \(d\)-amphetamine. It seems that \(d\)-amphetamine’s effects on impulsivity depend on terminal-link context and the initial to terminal-link transition.

A multiple schedule arranged in the initial-links has not been conducted in the context of a multi-component delay discounting procedure. By arranging a multiple schedule in the initial links, the speed at which choice adjusts to changes in reinforcer delays across components should increase. Additionally, the asymptotic levels of delay sensitivity and, thus discount rate should also be elevated (increased impulsivity) relative to a mixed-arrangement. Evidence for these hypotheses come from studies employing mixed and multiple, multi-component concurrent schedules in which the reinforcer rate ratios changed unpredictably across components of a session (see above Krageloh & Davison, 2003).

It is the main objective of this proposal to compare the acquisition and form of the discount function by two inbred mouse strains in initial link, mixed and multiple schedule arrangements. Additionally, the effects of acute dopaminergic drug administration have been least well characterized under these types of schedule arrangements. A hypothesis is that stimulant administration will increase discount rate under this arrangement relative to a bridging arrangement in the terminal-links. By highlighting the upcoming delays to larger and smaller reinforcers arranged in the terminal-links, stimulants may enhance discrimination or conditional discriminations of delay ratios and shift preference to smaller, sooner rewards at relatively shorter delays. Lastly, we have not characterized the effects of stimulants on the form of discount functions generated by C57Bl/6 mice. In other studies, we have shown that \(d\)-amphetamine increases estimates of sensitivity to reinforcer rate ratios in concurrent schedules to a greater extent for
the C57Bl/6 mice relative to the Balb/c mice. A hypothesis, then, is that the effects of stimulants on discount functions generated by C57Bl/6 mice may be exaggerated or in opposing directions relative to the Balb/c mice.

**An eligibility model of delay discounting**

Although the GML has proven to be a powerful tool for describing the acquisition and asymptotic levels of choice in delay discounting procedures, it is an atheoretical account that lacks a mechanistic explanation of the phenomena; it has even be said to be a useful tautology (Killeen, 1972; Rachlin, 1971). The absence of efficient behavioral causes (Aristotle, 384 to 322 B. C.) for discounting a reinforcer by delay extends to the daughter models based on the GML (e.g., Grace, 1994, Fantino, 1971; Mazur, 1987). In order to gain a more complete account of how and why discounting occurs and how reinforcer magnitude influences discounting, an alternative model providing a deeper theoretical basis will be considered.

Among others, Killeen (1981, 1994, 2005, 2011) views conditioning as an assignment-of-credit problem: When behavior encounters stimuli and reinforcers in an ongoing stream, the question of origin or their causes immediately arises. If some epoch in an organism’s behavioral stream is decomposed, there are \( r \) potential responses (causes) that could have led to a reinforcer; \( r \) being a measure of the richness of the context. The number of \( r \) potential causes grows to \( r^n \) as additional epochs are added to the stream, where \( n \) is the number of epochs. A combination of any of these \( r \) causes occurring \( n \) instances ago, coupled with those in the most recent instant, may be assigned credit for producing a reinforcing event. It is this causal chain that will be selected (strengthened) by a reinforcer. If each of these decomposed epochs lasts \( \delta \) seconds, then \( n \) is equal to the delay \( (d) \) between a behavioral event and consumption of a reinforcer divided by the length of a decomposed epoch, \( n = d/\delta \). Consequently, the candidate paths grow as \( r^{d/\delta} \).

Viewed in the continuous limit, the time constant of the gradients for these potential causes, \( \tau \), as delays lengthen becomes \( e^{-d/\tau} \). The time constant is equal to the inverse of the continuous version of the richness of the context, \( \tau = 1/r \). In this view, accurate allocation of credit for the reinforcer decreases exponentially and that the rate depends on the complexity of the environment. This framework suggests that gradients become flatter in barren environments with relatively few distractors, alternative sources of reinforcement, or potential causes interposed during the delay between a response and reinforcer (and vice versa). Delay of reinforcement gradients are a central manifestation of the effects of the passage of time in human and non-human animal behavior. These equations and assumptions, however, assume credit is being allocated under the most basic and ideal conditions. For the present proposal, however, delay gradients
have been shown to reflect a gene X environment interaction: they depend upon the genetic background and the salience of the prevailing reinforcing stimuli, which can be altered by marking and bridging signals correlated with their presence. Allowing for such biases, the model will more accurately reflect credit allocation under different contexts and for different strains of mice (see Eq. A1, 1 for development).

Delay of reinforcement gradients may be grounded in the exponential increase in candidate paths between a potential cause and a reinforcing event (Killeen, 2013). They may be viewed as a universal process of stimulus generalization (Shepard, 1987a, 1987b) – “the ubiquitous exponential decay between psychological distance and generalization…– a robust result of minimal inferences an organism must make when confronted with two stimuli and forced to judge whether they go together” (Killeen, 1992). That is, the associability between a response and a reinforcing event declines exponentially with time’s passage (Eq. A1, 1). There are several lines of theoretical and empirical work that support this notion (Killeen, 2001a, 2001b, 2005; Johansen et al., 2009), including the neurobiology of reinforcement learning (Niv et al., 2002; Singh & Sutton, 1996; Sutton & Barto, 1990). Here, the purported mechanism of delay discounting is that irrelevant stimuli correlated with reinforcers and nontarget responses competing with relevant, reinforcer-correlated stimuli and target responses. In this view, longer delays are not said to be responsible for discounting or to shift preference because the “value” of a reward decreases. In this view, time cannot be a cause for such declines, only a vehicle for such causes (Killeen, Fetterman, & Bizo, 1997). Interposing delays between choice and outcome allows a greater opportunity for other candidate paths to be assigned credit and thereby interfere with the ability of the reinforcer to selectively increase the probability of the target response(s).

These ideas and models developed in the appendix suggest that marking or bridging stimuli might influence delay discounting by facilitating the appropriate assignment of credit. This is in stark contrast to the GML and similar models positing hyperbolic-like discounting (Mazur, 1987) because they do not address the effects of such stimuli or contextual manipulations (nor are any general mechanisms provided, but that is a story for another day). The strength of such stimuli as conditional reinforcers can be modeled by a decomposition of the conditioning process into brief acts of discriminative and conditional reinforcing control by arranged CSs according to their temporal proximities to reinforcement (see Eq. A1, 2). Marking and bridging CSs may have differential effects on the form of the discount function. For example, marking should result in enhanced discrimination of the target response thereby simplifying the assignment of credit problem, but should do so in a delay-independent manner. This would result in a proportional upward shift in the discount function, represented by parameter $c$ in Eqs. A1. 1-4. Bridging on the other hand, should
result in enhanced discrimination selectively at longer delays, because these discriminations are inherently more difficult, and have little or no effect at shorter delays. This would manifest as the slope of the discount function becoming less steep (λ & τ in Eqs. A1-A4), as the target response(s) would have a greater probability of being reinforced than if the bridge was not available. The following analogy may help: if there is a gap between two mountains that is only one foot apart, a bridge is unnecessary, as we can readily make such a jump, but if the gap is 100 feet, jumping is no longer an option, we must either utilize a bridge or forever stay on one mountain. Of course, different individuals will be able to make a farther jump than others.

According to the GML and related research (Kragelöh & Davison, 2003) arranging a multiple schedule in the initial-links, should enhance stimulus control by the delay-ratios in each component, relative to a mixed schedule. This would manifest as faster acquisition of control by the delay-ratio and greater preference for the shorter delay in effect (in the present proposal, greater choice for the LLR). This results in greater impulsivity and thus steeper discount functions. This may seem contradictory, but the component-specific stimuli signal the delay ratio more saliently than they do the difference in reinforcer magnitude between the terminal-links. Thus control should be greater by the immediacy of reinforcement yielding steeper discount functions.

The alternative interpretation provided by the eligibility model also predict steeper discounting in the multiple schedule arrange in the terminal-links relative to the mixed, but arrives at this conclusion for different reasons. Stimulus control by the shorter-delay is indeed enhanced, but the additional “distraction” provided by the multiple schedule stimuli before and after choice will increase as the delay to reinforcement increases. This means that at the longer delays the stimuli and the responses they engender will capture most of the effects of the reinforcer. As Williams (1991, 1994) has shown, presenting stimuli before reward delivery results in “blocking” of the effects of the reinforcer on the choice response. At the shorter delays, however, this distraction is lessened and may even enhance discrimination similar to marking (Williams, 1994). The result should be a function that has a higher y-intercept and a steeper slope, relative to the mixed schedule. As the eligibility model predicts, interposing stimuli and responses between choice and the reinforcer delivery will result in greater difficulty allocating credit: A steeper discounting function and a relatively more impulsive organism relative to a mixed schedule, which presents rather inconspicuous stimuli that are identical across delays and thus will be less likely to intervene and occasion responses that are “off-task” to the originating choice response.

The shape of the primary reinforcement delay gradient given by Eq. A1, 1 cannot be retroactively affected by differential reinforcer magnitudes. Reinforcer magnitude is proposed to act differentially on the tails of the secondary reinforcement gradients given by Eq. A1, 2. Paradoxically, larger reinforcers are more effective as delays lengthen
because disruptive effects of reinforcer delivery itself are minimized (Bizo, Kettle, & Killeen, 2001; Grace, 1994; Killeen & Smith, 1984). Evidence for this paradox is also provided by the ubiquitous preference reversal, in which subjects prefer a larger reward to a smaller when both are delayed, but as the delay to the smaller becomes imminent, subjects reverse their preference. In order to modify the above assumptions for self-control paradigms, as in the present proposal, the strength of CSs signaling different delays and reinforcer magnitudes is accomplished by adding the valence parameter, $v$, a constant representing the incentive value or marginal discount rate of the larger relative to the smaller reinforcer (Eq. A1, 4).

This theory and the equations in Appendix 1 can be modified further to be more parsimonious, mechanistic, and empirically validated by assuming a constant rate of transitioning between different classes of target and nontarget responses throughout the interreinforcer intervals that compete for credit allocation (See Eq. A1, 4). This assumption is part of a unified model of choice (see Killeen & Fantino, 1990) with one of the leading theories of interval timing: Killeen and Fetterman’s Behavioral Theory of Timing (1988). In studies of interval timing, animals often emit a sequence of nontarget responses (i.e., adjunctives; Killen & Pellón 2013) before engaging in the target response (usually lever-pressing on a FI schedule). In this view, different classes of adjunctive behavior come to serve as discriminative stimuli that mediate the timing of an interval, while also simultaneously competing with target responses for credit allocation. For example, during a FI 10 s the organism may first disengage from consummatory responses (head-entries), followed by a period of general activity (moving about the chamber), then move towards to operandum of interest and finally, engaging in the target response. Because each of the stages of adjunctive behavior are in proximity to reinforcement, they are all captured by the effects to the reinforcer, but to differing extents. Those classes that are reinforced at earlier parts of the interval come to serve a discriminative function for later classes of behavior, such as making a “correct” lever press at the appropriate time (Killeen & Pellón, 2013).

The behavioral theory of timing posits that transitions between classes of behavior are caused by an internal (presumably neurobiological) pacemaker that emits pulses at a constant rate according to a Poisson process. After a probabilistic number of pulses are registered, they serve to move the organism from one class of behavior to another, until emission of the target response(s) or terminal response(s). According to the theory, however, the rate of the pacemaker varies proportionally with the reinforcement density in the procedural context. The higher the rate of reinforcement, the faster an organism cycles through classes of behavior. Effectively, this produces a greater number
of adjunctive states, intervening target and nontarget responses, and a shortening of temporal estimates relative to a context with a lower rate of reinforcement.

Applying this logic to studies of delay discounting, increasing the number of nontarget responses that intervene between choice and reinforcer delivery increases the probability that a nontarget response class will be assigned credit for a reinforcing event. Thus an “impulsive” organism with higher rates transitioning among different response classes does not actually “discount” the delayed reward more quickly, but rather sequences through an elevated number of response classes that may be reinforced (i.e., “assigned credit”). This elevation in overall response rate (target and non-target) increases the number of potential causes for the reinforcer. Although there is a constant rate with which behavioral events occur during a particular interreinforcement interval, resulting in an exponential decline in preference, decreases in reinforcement rate at longer delays decreases the likelihood with which different adjunctive responses intervene. The result is a function that is steep at shorter delays and that flattens at longer delays, consistent with the frequently used hyperbolic model of delay discounting (Mazur, 1987; See Eq. A4 for development).

The advantage of using the above approach is that it provides a mechanistic account of how and why discounting occurs and offers parameters that are theoretically consistent with other paradigms and thus more easily interpreted. If we modify Eq. A1, 4 to accommodate changes in discount rate as a function of overall reinforcement density (τ) and allow the reinforcing effectiveness parameter (v) to represent the ratio of amount values (α) arranged in the terminal links we find:

\[
\frac{R_{LLR}}{R_{Total}} = \left[ \frac{M_x}{M_1} \frac{e^{-\frac{d_x}{\tau'}} + \tau' \left(1 - e^{-\frac{d_x}{\tau'}}\right)/d_x}{e^{-\frac{d_1}{\tau'}} + \tau' \left(1 - e^{-\frac{d_1}{\tau'}}\right)/d_1} \right]^{-1}
\]

Eq. 5, henceforth called the eligibility model, provides a model for self-control experiments that allows for the separation of the effects of relative incentive reinforcer value (α; marginal discount rate), the proportional rate with which target and nontarget responses occur during an IRI (λ; and the time constant of response traces at each delay (τ’)), and biases that may arise from genetic, sensory, motivational, or contextual changes that are unique to individual subjects of strain of mouse (c). The model contains those three free parameters, and from those we can calculate the frequency with which competing responses intervene for credit allocation at each delay (λ’) and the time constant of response traces at each delay (τ’), allowing for more detailed analyses of the data. The model is not \textit{ad hoc}, as are most
models of delay discounting. This model predicts radical changes in preference dependent on the presence and modality of initial and terminal link stimuli that mark or bridge responses occurring before or during the delay to the reinforcer, as described above (see Killeen, 2011; Appendix Eq. A1 - A4). It is consistent with the important roles of conditional stimuli in preference for delayed outcomes, builds on previous theories of concurrent chains choice and interval timing (Killeen, 1985b; Killeen & Fetterman, 1988; Fantino & Killeen, 1990), and is the basis of the coupling coefficient in the most comprehensive treatment of schedule-controlled operant behavior: Mathematical Principles of Reinforcement (Killeen, 1994; Killeen & Sitomer, 2003).
References


Figures

Figure 1.

Mixed Schedule

<table>
<thead>
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<th>Delay to LLR (s)</th>
<th>Preference for LLR</th>
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</thead>
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<tr>
<td>1.25</td>
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<tr>
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<td>0.25</td>
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<tr>
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<td>0.50</td>
</tr>
<tr>
<td>70.79</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Balb/c (1st) Predicted
C57Bl/6 (1st) Predicted

\[ \alpha = 0.01, \lambda = 0.56 \]

\[ \alpha = 0.77, \lambda = 1.43 \]
Figure 2.
Figure 3.
Figure 4.

Time into Trial (s)

Stimuli Present (identical)

Mixed

Stimuli Present (Component specific)

Multiple
Figure 5.

Marking (identical brief stimulus)
- Mixed

Marking (Delay-specific, brief stimuli)
- Multiple

Time into Trial (s)
Figure 6.

Stimuli Present (identical)

Mixed

Stimuli Present (Delay-specific)

Multiple

Time into Trial (s)
Figure 7.
Figure captions

**Figure 1.** Preliminary data for the present experiment showing preference for 4 reinforcer presentations over 1 reinforcer presentation as a function of the delay to its receipt (1.25 to 70.79 s) for Balb/c (open circles) and C57Bl/6 mice (closed circles) responding under the mixed schedule version of the procedure. The solid and dashed lines drawn through the open and closed circles, respectively, were derived from the eligibility model (Eq. 5). Mean parameter estimates from Eq. 5 are shown in the legend. These estimates show that the incentive value of the reinforcer is higher for the Balb/c’s and that the rate at which adjunctive responses intervene during delays is smaller for the C57Bl/6’s. Error bars represent +/- 1 SEM.

**Figure 2.** Data from a previous study showing Balb/c log response ratios (LLR/SSR) as a function of the log delay ratios (LLR/SSR) at each dose of d-amphetamine (mg kg⁻¹) for mixed and multiple-bridging arrangements, respectively. The straight lines drawn through each set of data points were derived from a linear-mixed effects model based on the GML (Eq. 4). This model showed that mixed conditions fostered a bias for the LLR relative to the multiple condition as evidenced by the upward shift in the function and multiple schedules showed shallower discount functions. Additionally, d-amphetamine dose-dependently increased sensitivity to reinforcement magnitude under both conditions, represented by an increase in the y-intercept and upward shift in the function across doses. Error bars represent +/- 1 SEM.

**Figure 3.** A typical concurrent-chained schedule of reinforcement. Concurrent responding in the choice phase (initial links) produces access to one of the mutually exclusive terminal links according to some schedule (FR 1). Upon entry to the terminal-links a stimulus change may occur and fulfillments of the response requirements in the terminal links (e.g., FI 30 s) produce access to the reinforcer of a particular magnitude (4 reinforcers). After reinforcer delivery the initial links are reinstated and the cycle begins again.

**Figure 4.** A diagram of mixed and multiple, concurrent-chained schedules arranged in the initial-links. The diagram shows that when the choice phase begins for a short delay, stimuli are presented that prevail to the delivery of the reward. For the long delay, the identical stimuli are presented, but for a longer period of time. For the multiple schedule, different stimuli are presented during the choice phase that extend to the delivery of the reinforcer for the short and long delays, respectively.

**Figure 5.** A diagram of mixed and multiple concurrent-chained schedules arranging marking stimuli to occur simultaneously with a response. The Mixed schedule diagram shows that when the choice phase begins no stimuli are presented, but upon the response that results in entry into the terminal-link of a shorter delay, a brief stimulus is presented. For the longer delay, the exact same stimulus is presented upon the response that enters the terminal-link. For the multiple schedule, a different brief stimulus is presented when the response that results in entry to the terminal-link occurs for the short and long delays, respectively.

**Figure 6.** A diagram of mixed and multiple concurrent-chained schedules arranging bridging stimuli to occur after entering the terminal-links that prevails until reward delivery. The Mixed schedule diagram shows that when the choice phase begins no stimuli are presented, but upon entry into the terminal-link of a shorter delay, stimuli are presented for the remainder of that delay. For the longer delay, the exact same stimulus is presented when entering the terminal-link, but it remains presented for a longer period of time. For the multiple schedule, different stimuli are presented when entering terminal-links of a shorter and longer delay that prevail until reward delivery.

**Figure 7.** Sensitivity to the current and previous delay as a function of 4 blocks of 4 initial-terminal-link cycles for mixed and multiple-bridging conditions, respectively. These data were taken from each block of 4 choices at each delay and averaged over the last 5 consecutive sessions before drug administration. The speed with which preference adjusted to the current delay across blocks of a component did not differ between the two schedule arrangements. The bottom panel shows the log response ratios (LLR/SSR) for mixed and multiple-bridging conditions as a function of the log delay ratio (LLR/SSR) taken from the final block of 4 choices and averaged over the last five sessions, as sensitivity was shown to be asymptotic. The bias fostered by the mixed condition can be seen as the upward shift in the discount function at the shortest delays relative to the multiple schedule arrangement. Error bars represent +/- 1 SEM.
Appendix A

Mathematical development of the Eligibility Model (Killeen & Fantino, 1990; Killeen, 2011)

Eq. A1: Credit allocation for primary reinforcement

If we assume that there are \( r \) potential causes for a reinforcer in the last instant and an additional \( r \) events occurring in the prior, penultimate instant, then the combination of any one of the prior events with those in the ultimate instant could have been the causal chain leading to the reinforcer (i.e., \( r^2; r^3 \) for the penultimate instant to \( r^n \)). Because each instant is assumed to last \( \delta \) s, then \( n = d/\delta \) and the candidate path grows as \( r^{d/\delta} \). Translating this equation into the continuous limit yields \( e^{d/\tau} \), whereas in the text, \( \tau \) is the time constant of the traces and \( \tau = 1/r \). It follows that any one path of causes is eligible for \( 1/e^{d/\tau} \) of the credit for reinforcement under the most ideal conditions. As mentioned in the text, contextual manipulations will be differentially experienced for individual mice within a strain and across strains. Allowing for such biases with the parameter \( c \), the causal impact of primary reinforcing events decreases with prior time (time preceding the reinforcer) according to:

\[
ce^{-d/\tau}, \quad t > 0
\]  

This equation is a point estimate of the proportion of credit allocated to a response occurring \( d \) seconds before a reinforcing event, where \( c \) represents biases induced by context or genetics, \( d \) represents the delay between a response and a reinforcer, and \( \tau \) represents the time constant of causal traces or the inverse of the richness of the context. More simply, this equation represents how credit is allocated for a primary reinforcer occurring sometime after several classes of responses occur.

Eq. A2: Credit allocation for secondary reinforcement

In order to address situations in which there are reward correlated stimuli prevailing during choice, immediately after choice, or during the delay to reinforcement, we must alter Eq. A1 to include such effects. In the case of bridging, a response causes the onset of a stimulus and after a delay, \( d \) a reinforcer. If we assume that each of the temporal regularities of the stimulus is eligible for credit according to Eq. A1 and that each element of the stimulus generalizes with the next, then temporal eligibility adds linearly. This yields an integral that assumes temporal elements of the stimulus make linearly independent contributions to the total association or amount of credit allocated. According to this hypothesis, any one element of the stimulus is indiscriminable from the next, allowing us to compute an average
associability for a particular element (e.g., the element just after the response in the case of marking, or the entire delay in the case of bridging). It follows that any one element has an average associability given by:

\[
\frac{\int_0^d ce^{-t/\tau} dt}{\int_0^d dt} = \frac{c\tau(1 - e^{-d/\tau})}{d} \tag{2}
\]

Whereas in Eq. A1, \( c \) represents bias, \( \tau \) represents the time constant of the casual traces, but now for primary and secondary reinforcement, and \( d \) represents the delay to reinforcement. The bias parameter in Eq. A2 now explicitly includes the effects of conditional stimuli and may prove important in delineating the effects of different stimulus conditions (i.e., marking and bridging). In theory, marking should increase the value of \( c \), while bridging should increase the value of \( \tau \). These assumptions await adequate experimentation.

**Eq. A3: Credit allocation in self-control situations**

In order to apply Eq. A2 to the present self-control study, it requires a scale that maps reinforcer magnitude into the effectiveness of presenting additional reinforcers greater than one. The simplest of these is a power function, which will be used as the basic assumption for this proposal. The power function assumption is identical to that used in the GML. It follows that the associative strength of a response in the presence of a CS immediately followed by a stimulus change and CSs that may bridge the temporal gap, \( d \), to a reinforcing event of physical magnitude \( a \), is equal to the product of the impact of the reinforcing event, \( a^a \), on the sum of the unconditional (Eq. A1) and conditional effects (Eq. A2) of prevailing reinforcing events. Assuming that the relative salience of stimulus elements and responses are assumed to be comparable for unconditional and conditional reinforcing events produces a bias \( c \), and:

\[
a^a c \left[ e^{-d/\tau} + \frac{\tau(1 - e^{-d/\tau})}{d} \right] \tag{3}
\]

**Eq. A4: Constant probability of credit competition**

If we assume there is a constant and proportional probability of transitioning from one class of behavior to another during an interreinforcer interval, \( \lambda \), then the proportional probability of remaining in a class of behavior is equal \( 1/\lambda = \tau \). Where \( \lambda \) describes the average richness of the context in terms of rate of different classes of behavior occurring. The richer the context, the higher \( \lambda \) becomes, and the greater overall probability that intervening events will compete with target responses for credit allocation. If we then assume that the richness of a particular context, or the constant probability of responding occurring, is proportional to the rate of reinforcement, and thus the probability of
transitioning from one class of behavior to another is proportional to the rate of reinforcement, as described by BeT (Killeen & Fetterman, 1988), then $\lambda'$ represents this probability at a given rate of reinforcement. Then, $1/\lambda' = \tau'$ is equal to the dwell time in a particular class of behavior at a given rate of reinforcement. This is equal to the time constant describing credit allocation, because increases in the number of classes of behavior an animal cycles through, given an increase in reinforcement rate, makes the allocation of credit more difficult. Under these assumptions, the equation representing $\tau'$ is the constant of proportionality, $\lambda$ divided by the average time spent responding in the initial-link (IL) plus the average time spent in the terminal-links $(TL_1 + TL_2)$ for each delay ratio (i.e., the IRI), yielding

$$\tau' = \frac{\lambda}{(IL + (TL_1 + TL_2)/2)}^{-1} \quad (4)$$

Where $\tau'$ at a given delay gives the average dwell time in a class of behavior and $\lambda$ gives the proportional probability of transitioning from one class of behavior to another during a given IRI. For the present study, estimating $\lambda$ will yield 6 values of $\tau'$ and 6 values of $\lambda'$ that describe changes in credit allocation as a function of the delay of reinforcement.
Appendix B

Calculating AICc and utilizing the model comparison approach (Sanabria & Killeen, 2009)

Parameters from the GML and the EM will be estimated for each rat by either minimizing the sum of squared deviations between prediction derived from either Eq. 3 or Eq. 5 using solver in Microsoft Excel or by maximizing the log likelihood function using LME versions of the above two equations in Systat 13. Model fitting assessed which parameters from each of these equations were required to vary across strain or dose of drug to describe changes in individual performance. Models that allow all possible combinations of invariant parameter values, where none, each of the parameters alone, and all other possible combinations were permitted to vary freely across strain and doses within each mouse. The criterion for model selection will be determined using the corrected Akaike Information Criterion (AICc) (Burnham & Anderson, 2002). AICc covaries positively with residual sums of squares and number of free parameters, therefore a lower AICc (i.e., less positive or more negative value) indicates a better account of the data given the degrees of freedom in the model. AICc = 2k + n ln(RSS/n) + [2(k+1)/(n-k-1)], where k is the number of free parameters in the model, n is the total number of observations, and RSS is the residual sum of squares over all animals.
Chapter 2: Experiment 1

Abstract

The importance of delay discounting to many socially important behavior problems has stimulated investigations of biological and environmental mechanisms responsible for variations in the form of the discount function. The extant experimental research, however, has yielded disparate results, raising important questions regarding Gene X Environment interactions. The present study determined the influence of stimuli that uniquely signal delays to reinforcement on delay discounting in two inbred mouse strains using a rapid-acquisition procedure. BALB/c and C57BL/6 mice responded under a six-component, concurrent-chained schedule in which the terminal-link delays preceding the larger-reinforcer were presented in a randomized-order across components of a session. Across conditions, components were presented as mixed or multiple schedules. A generalized matching-based model was used to incorporate the impact of current and previous component reinforcer-ratios on current component response allocation. Reinforcer magnitude and delay sensitivity were higher for BALB/c mice, but within-component preference reached final levels faster for C57Bl/6 mice. For BALB/c mice, the acquisition of preference across blocks of a component was faster under the multiple than the mixed schedule, but final levels of sensitivity to reinforcement were unaffected by schedule. The speed of acquisition of preference was not different across schedules for C57Bl/6 mice, but sensitivity to reinforcement was higher across each block under the multiple than the mixed schedule. Overall, differences in the acquisition and final form of the discount function were determined by a Gene X Environment interaction, and the presence of delay-specific stimuli attenuated genotype-dependent differences in magnitude and delay sensitivity.

Keywords: Delay discounting, Random delay presentation, signaled delays, Generalized matching law, Mouse strains, Rapid acquisition.
In the context of delay discounting, “impulsivity” is defined as a preference for smaller, more immediate reinforcers at the expense of a larger, but delayed reinforcers (Ainslie, 1974; Madden & Bickel, 2010; Rachlin & Green, 1972). Steep discounting of delayed reinforcers has been invoked as an underlying process common to a number of human psychiatric maladies, including attention-deficit hyperactivity disorder (ADHD), mania, substance abuse, pathological gambling, poor health behavior, overeating, and other personality disorders (DSM V; Bickel et al., 2012; Sonuga-Barke, Wiersema, van der Mere, & Roeyers, 2010; Winstanley, Eagle, & Robbins, 2006). Elevated discount rates are a reliable predictor of individuals meeting diagnostic criteria for these disorders (Mackillop et al., 2011). An important goal of future discounting research, therefore, is to isolate the biological and environmental variables that contribute to differences in discount rate among vulnerable clinical populations and in preclinical models of neuropsychiatric disorders (Nestler & Hyman, 2010).

One avenue for localizing such differences has been to describe the relation between delay discounting and the genetic and biochemical substrates upon which environment-behavior relations operate (e.g., Huskinson et al., 2012; Stein et al., 2012). Several studies have shown that delay discounting of a particular commodity, within an individual or a particular clinical population, is temporally stable, may extend across other commodities or contexts, and is, to some extent, heritable (e.g., Friedel, DeHart, Madden, & Odum, 2014; Kirby, 2009; see Odum, 2011a). In a review of the behavioral genetics of delay discounting, Mackillop (2013) presented evidence that genetic variation related to monoamine neurotransmission is significantly correlated with variation in discount rate (see also Bickel et al., 2012; Winstanley, 2010). As noted elsewhere (de Wit & Mitchell, 2010; Mitchell, 2011) however, there is a paucity of concordant results regarding genetic and biochemical markers of impulsivity and these inconsistencies suggest a role for contextual or environmental influences in determining the form of the discount function (e.g., Berry et al., 2014; Bickel, Landes, Hill, & Baxter, 2011; Dixon, Jacobs, & Sanders, 2006; Odum & Baumann, 2010; Stein et al., 2013).

In laboratory investigations of delay discounting, changes in preference under invariably ascending or descending within-session delay progressions are often interpreted as changes in the rate of discounting (e.g., Cardinal et al., 2000; Evenden & Ryan, 1996). Changes in response allocation under these procedures could also reflect the influence of other mechanisms, such as changes in sensitivity to reinforcer magnitude (e.g., Pitts & Febbo, 2004). Response allocation may also be affected by the presence or absence of stimuli that signal delays to reinforcement and thus serve a discriminative or conditional reinforcing function (Mazur, 1997; Williams & Dunn, 1991). Importantly, when the order of delays systematically increases or decreases within a session, delays in previous trial blocks can enhance or attenuate preference by exerting control over choice at delays in subsequent trial blocks (i.e., carry-over effects; Pitts & McKinney, 2005; Christensen & Grace, 2009).
The first goal of the present study was to determine within-session discount functions using a randomized delay-presentation procedure adapted from rapid-acquisition methods used to study choice dynamics (Davison & Baum, 2000, Aparicio, 2007, 2008; Aparicio & Baum, 2006, 2009). Such a procedure would retain the utility of the within-session procedure for assessing the effects of genetic, pharmacological, and environmental interventions on delay discounting (see de Wit & Mitchell, 2010; Winstanley, 2010 for reviews), while potentially mitigating systematic carryover effects on preference. A recent study by Tanno, Maguire, Henson, and France (2014) with rats showed that preference for larger, delayed reinforcers was higher when delays were presented in a descending compared to an ascending-delay progression, confirming that the order of delay-progression produced systematically different influences over preference (see also Maguire, Henson, & France, 2014). As an additional methodological refinement, the present study employed dependent schedules during the choice phase (initial links) to facilitate within-session acquisition and control equal exposure to each terminal-link alternative (Beebe & White, 2013). This method of controlling terminal-link entry rate is seldom used to examine delay discounting (e.g., Evenden & Ryan, 1996; but see Grace, Sargisson, & White, 2012), but the majority of studies employing rapid-acquisition procedures to investigate choice have used dependent schedule arrangements (e.g., Davison & Baum, 2000; Grace et al., 2003). The controlled terminal-link entry rate provided by dependent scheduling is preferable to independent scheduling, because the latter allows the relative frequency of exposure to each terminal-link alternative to be governed by preference, confounding programmed and obtained relative reinforcer magnitude and delay-ratios (Beeby & White, 2013).

The second goal of the present study was to determine the effects of component stimuli that uniquely signal relative terminal-link delays to reinforcement in each component (i.e., multiple, concurrent-chained schedule). Previous research concerning the effects of signaling conditions on delay discounting has only addressed the effects of signaling (identically or uniquely) the start of a terminal-link delay interval, by marking or bridging the response-reinforcer delay, on asymptotic preference. These studies showed similar levels of delay discounting under signaled (identical and unique) and unsignaled delays to reinforcement (Cardinal et al., 2000; Slezak & Anderson, 2009) but have also arranged strictly increasing or decreasing delays to reinforcement. With extended exposure to systematically and invariably changing reinforcer delays, stimulus control by other, possibly more salient environmental stimuli (e.g., lever position, passage of time, order of delay) will develop and could attenuate or prevent control by the signaling arrangements (Kragelöh & Davison, 2003). That is, stimuli that are redundant with delay-progression are unlikely to acquire differential discriminative control relative to conditions in which no such stimuli are present if delay-progression is the more salient controlling variable. In contrast, several studies have demonstrated that multiple, concurrent schedules, as compared with mixed, concurrent schedules, result in faster acquisition and higher asymptotic
levels of preference, following unpredictable within- or between-session changes in relative reinforcer-ratios (e.g., Cerutti, & Catania, 1986; Hanna, Blackman, & Tordorv, 1992; Kragelöh & Davison, 2003; White & Pipe, 1987; Williams & Fantino, 1978;). Therefore, under the rapid-acquisition procedure used in the present study, we predicted that differentially signaling components would increase the speed of acquisition of preference within a component and asymptotic sensitivity to reinforcer ratios across components relative to nondifferentially signaled components (i.e., mixed schedule).

The third goal of this study was to examine the role of genetic variables in determining the form of the discount function under each terminal-link stimulus condition. A common method for studying the relations between genetic variables and delay discounting has been to compare two or more inbred rodent strains responding under choice procedures. For example, several studies conducted in rats have reported that the Lewis strain displays higher discount rates compared to the Fischer 344 strain (Anderson & Diller, 2010; Anderson & Woolverton, 2005; Garcia-lecumberri et al., 2010; Huskinson, Krebs, & Anderson, 2012) and, in mice, the BALB/c strain displays an elevated discount rate compared to C57Bl/6 mice (Helms, Reeves, & Mitchell, 2006; Otobe & Makino, 2004). It is becoming increasingly clear, however, that the effect of genotype on measures aimed at characterizing complex processes, such as delay discounting, may sometimes result from differential sensitivity to contextual variables manipulated across studies (e.g., Hutsell & Newland, 2013). For example, differences between Lewis and Fischer 344 rats in delay discounting can be augmented or attenuated depending on the procedural arrangement (Stein et al., 2012; Wilhelm & Mitchell, 2009). Therefore, we asked whether delay discounting under a rapid-acquisition procedure would be sensitive to differences between these two strains and whether the stimulus arrangements would affect the extent of these differences. These two strains were selected because they show marked neurochemical and behavioral differences, including serotonergic and dopaminergic functioning (Yochum et al., 2010) and indices of motoric capacity and mnemonic functioning (Hutsell & Newland, 2013).

Method

Subjects. Eight experimentally naïve BALB/c and seven C57BL/6 mice obtained at approximately 5 - 7 weeks of age from Harlan Laboratories were housed in pairs (4 total per cage) in translucent, plastic OptiMICE® cages (Animal Care Systems Inc.) attached to an OptiMICE® HVAC quality air controller. The OptiMICE® system was located in an AAALAC-accredited facility and the vivarium was temperature-controlled (minimum 21° C) under a light-dark cycle (lights on 0630 - 1630). Mice were weighed daily and caloric intake was restricted to maintain all mice at a target weight of 24g by feeding a measured quantity of standard laboratory chow following each experimental
session (~ 2 – 2.5 g). Mice had free access to water while in their home cages. Experimental sessions were conducted daily, between 1200 and 1400 hours.

**Apparatus.** Experimental sessions were conducted in 11 operant conditioning chambers modified to accommodate mice (12.0" L x 9.5" W x 11.5" H). The chambers, manufactured by Med Associates Inc. (St. Albans, VT, Model ENV-007), were enclosed in sound-attenuating cabinets. The rear wall in each chamber was equipped with two Sonalert® tone generators located at the top of the chamber equidistant (L and R) from a centrally located houselight. The front walls of each chamber were equipped with two retractable response levers (ENV-312-2R). Above each lever, a LED could be illuminated and depressions to each lever exceeding a force of approximately 0.05 N were counted as effective responses. A liquid dipper system (ENV-302W-SX) located equidistant from the two response levers was used to deliver sweetened condensed milk. Liquid reinforcer presentations consisted of 0.1 cc of a 3:1 solution of water: milk. In an adjacent room, a Windows® PC with Med Associates® IV programming and interface system controlled experimental events and collected data with a temporal resolution of 0.1 s.

**General Procedure.** Upon completion of autoshaping for the left and right levers using a procedure previously described (see Paletz et al., 2004), subjects transitioned to initial training for the delay discounting procedure. Animals were exposed to a 6-component concurrent-chained schedule of reinforcement with 12 initial-terminal link cycles per component. Each cycle began by simultaneously inserting the left and right levers into the chamber and LEDs located above each lever were illuminated. The initial-link schedule for each of the 6 components was a dependent fixed ratio (FR) 1 schedule (Stubbs & Pliskoff, 1969) with no changeover delay. To ensure equal experience with each alternative, the dependent schedule was arranged such that of every 4 cycles, 2 entries were arranged into each of the mutually exclusive terminal-links. Thus, at the beginning of a cycle, an alternative (left or right) was pseudo-randomly selected with a probability of 0.5 as the alternative that produced terminal-link entry. No more than three consecutive entries to the same terminal link were possible. A single response on the lever that had been selected for terminal-link entry resulted in access to its correlated terminal link. Presses on the other alternative were recorded but these responses produced no programmed consequences. Thus, the mouse was forced to experience a particular terminal-link alternative pseudorandomly selected during that cycle. The opposing lever retracted once a terminal link was entered. The lever correlated with the terminal-link entered remained extended, but responses had no programmed consequences, and the LED above the lever changed from solid to a blinking rate of 0.5 s on, 0.5 s off until reinforcer delivery. Each of the terminal-links consisted of a fixed-time (FT) schedule of X s, and after timing out, resulted in either one or four presentations of sweetened condensed milk (described below). Following reinforcer presentations, there was a 3-s blackout and then the initial-links were reinstated. After 12 initial-terminal link cycles in a component,
there was a 10-s blackout, followed by the next component. A session ended after each of the six components was completed (i.e., 72 completed initial-terminal-link cycles) or 75 min.

Preliminary Training: Isodelay Phase. During initial training, the terminal-link correlated with the smaller reinforcer always consisted of a fixed-time (FT) 1.25 s schedule across components, which after timing out, resulted in one presentation of sweetened condensed milk for 1.2 s. During preliminary training, the “larger” terminal-link also consisted of a FT 1.25 s schedule across components but after timing out, resulted in four presentations of sweetened condensed milk for 1.2 s, separated by 0.5 s each (e.g., Davison & Baum, 2003). Determination of which levers were correlated with the delivery of the smaller and larger reinforcer first was counterbalanced across-subjects and within-strain. This phase was used to examine the impact of relative reinforcer magnitude on response allocation when relative reinforcer delays were equated. Each subject completed preliminary training with each lever (i.e., left & right) being correlated with the larger-reinforcer in order to assess sensitivity to reinforcer magnitude and bias for individual subjects of each strain. Stability of choice was determined by analyzing log (Base 10) response ratios (larger/smaller) across cycles of a session, binned into blocks of 4 cycles. After at least five sessions were completed, choice was deemed stable if the slope of the regression line fitted to response ratios as a function of the last 10 blocks was less than 0.05 and confirmed by visual analysis. After stabilization of choice, the above process was repeated by reversing which of the levers (i.e., left or right) was the richer alternative. In order to obtain estimates of sensitivity to reinforcer magnitude and bias for each subject, these averaged log response ratios were regressed against the log of the reinforcer magnitude ratios (i.e., log(4/1) = 0.60; log(1/4) = -0.60). The resulting slope and y-intercept of the regression line produced estimates of sensitivity to reinforcer magnitude and bias for each subject of a strain, respectively.

Delay Discounting. Following isodelay assessments of sensitivity to reinforcer magnitude, subjects were exposed to a delay discounting procedure that was identical to the training procedure with the exception that six geometrically spaced delays were interposed during the terminal-links correlated with the larger-reinforcer across components of a session. The geometrically spaced delays (0.35 log units) to the larger reinforcer were 1.25, 2.81, 6.31, 14.12, 31.62, and 70.79 s. The reinforcer magnitude ratio was always 4:1. At the beginning of each 12-cycle component, one of the six delays was randomly selected, without replacement, to serve as the terminal-link delay producing the larger-reinforcer during that component. The initial-links remained a dependent, concurrent FR 1, FR 1 schedule without a changeover delay: During each component, six entries resulted in access to the smaller-sooner terminal-link and six entries into the larger-later terminal-link (no more than three entries in a row to a given terminal link). This ensured equal exposure to each alternative and controlled the overall delay to reinforcement in each component. The terminal-link delay to the smaller, sooner reinforcer (SSR) was always a FT 1.25 s across
components, while the terminal-link delay to the larger, later reinforcer (LLR) was an FT $X$-s, where $X$ equals the delay randomly selected for that component. Upon terminal-link entry, the lever correlated with the delay in effect remained extended until reinforcer delivery, and responses on it were recorded but had no programmed consequences, while the opposing lever retracted. Each component ended following 12-chained schedule completions (cycles) per component. Following reinforcer delivery there was a blackout of 3-s and following completion of each component a blackout of 10-s. A session ended after each of the six delays was sampled once (72 initial – terminal link cycles) or 75 min.

**Mixed and Multiple Schedules.** Every subject experienced the procedure when components were presented as mixed (i.e., nondifferentially signaled) and, separately, as multiple (i.e., differentially signaled) schedules. The order of exposure was counterbalanced such that each subject of a strain experienced mixed and multiple schedules according to an ABA design. The mixed schedule consisted of presenting identical stimulus conditions during all initial-terminal link cycles for each component. Specifically, when a terminal-link was entered, regardless of the delay and magnitude of its correlated reinforcer, the LED light above the lever that was selected changed from solid to blinking at rate of 0.5 s on, 0.5 s off until reinforcer delivery, while the opposing lever retracted.

Under the multiple schedule, each component (i.e., each delay-ratio) was correlated with a distinct auditory stimulus. These component-correlated stimuli commenced during the initiation of the initial-links (i.e., choice phase) and remained present throughout the terminal-link (outcome phase). The component-correlated stimuli terminated only during reinforcer presentations and blackouts, and were reinstated upon the initiation of a new cycle or component. The multiple schedule stimuli were pulsating combinations of low and high tones cycling on/off at different rates that were uniquely correlated with a particular component (see Table 1) as in, for example, Kragelöh & Davison (2003).

All other procedural aspects were identical between mixed and multiple schedules. Subjects responded under each schedule for 50 sessions and data from sessions 45-50 of each condition were selected for subsequent analysis.

**Results**

The results of the present study will be presented according to the order in which the different phases of the experiment were conducted. First, we present the baseline assessments of sensitivity to reinforcer magnitude during an isodelay phase in which terminal-link delays were equated across all components of a session. Next, the acquisition of response allocation under the delay discounting procedure will be presented under each schedule of reinforcement (i.e., condition) according to the ABA design. Finally, individual subject and mean indices of acquisition and final levels of preference from the last presentation of each mixed and multiple schedules are shown. Omitting the first condition (i.e., “A” phase of the “ABA” design) was done to eliminate the possibility of any effects of initial acclimation to the procedure present in the first condition. Although no effects of initial acclimation were apparent, we did not include
data from this phase, but only analyzed data from the last presentation of each condition. Because the order in which conditions were presented had no effect on the acquisition and extent of response allocation for mice of either strain, response ratios were averaged across subjects of a strain under the final presentation of each mixed and multiple schedules, respectively.

When describing interactions among two or more independent variables, full statistics (F and p values) for the highest-order interaction are listed. All statements describing differences in dependent variables for lower-order interactions and main effects between strain and across conditions of the experiment are supported by a p value that is less than 0.01, as determined by statistical analyses using t-tests or mixed analyses of variance (ANOVA) with schedule or block as repeated measures, but full statistics are not listed to improve clarity and readability.

**Isodelay Magnitude Sensitivity.** In the first analysis, initial-link response ratios were calculated across blocks of IL-TL cycles when the terminal-link reinforcer-magnitude ratio was constant (i.e., 4:1) and the terminal-link delay ratios were equated and constant across all components (i.e., FT 1.25 s). This analysis was performed for individual subjects when each lever was correlated with the larger reinforcer. For all subjects, stable choice (across levers) occurred within 6-10 sessions (432-720 IL-TL cycles). Figure 1 shows estimates of magnitude sensitivity for each individual subject of a strain. Overall, mean sensitivity to magnitude for the BALB/c mice (mean = 0.75, n = 8) was greater compared to the C57Bl/6 mice (mean = 0.47, n = 7), a group difference that was reflected in individual subject estimates (t(13) = 6.56, p < 0.001). Mean estimates of bias were not different from zero for BALB/c (mean = -0.012; range = -0.047 – 0.053, t (7) = 0.59, p =0.57) or C57Bl/6 mice (mean = 0.018, range = -0.04 – 0.038, t (6) = 0.45, p = 0.67), indicating no lever-bias for mice of either strain.

**Across-Component Response Allocation.** In the second analysis, we investigated how initial-link response allocation changed as a function of the changing ratio of arranged terminal-link value in each component, where value reflects an additive combination of reinforcer magnitude and delay ratios (Baum & Rachlin, 1969; Grace, 1994). That is,

\[
\frac{V_{\text{LLR}}}{V_{\text{SSR}}} = \log \left( \frac{M_{\text{LLR}}}{M_{\text{SSR}}} \right) - \log \left( \frac{D_{\text{LLR}}}{D_{\text{SSR}}} \right)
\]

(1)

where V represents terminal-link value, M is arranged terminal-link reinforcer magnitude (constant 4:1 ratio), D is arranged terminal-link reinforcement delay in a component, each subscripted for both response alternative, where LLR and SSR represent the terminal-links correlated with large and smaller reinforcers, respectively.

Individual subjects’ initial-link response ratios (LLR/SSR) were calculated as a function of blocks of IL-TL cycles (i.e., successive reinforcers) within each component (i.e. delay-ratio) from sessions 45-50 of each condition. Here, a block was defined as 4 IL-TL cycles of a component, yielding three blocks per component. Similar to previous
studies utilizing rapid-acquisition procedures (e.g., Davison & Baum, 2000; Grace et al., 2003; Schofield & Davison, 1997), log initial-link response ratios (LLR/SSR) were taken from the final block of four IL-TL cycles (i.e., block three) in each component from sessions 45-50 of each condition.

Figure 2 shows block three log initial-link response ratios (symbols) and arranged reinforcer value-ratios (solid lines; Eq. 1) in each component from the final 5 sessions of each condition for representative subjects of each strain. Inspection of Figure 2 for the BALB/c mice (open symbols) reveals that response allocation readily tracked changes in arranged terminal-link value. Neither the schedule in effect nor the order of schedule presentation, however, influenced the extent of response allocation across components. In contrast, for the C57Bl/6 mice (filled symbols), response allocation under the mixed schedule (squares) was relatively insensitive to the changes in arranged relative reinforcer-value across components. The insensitivity of response allocation is indicated by the narrow range (i.e., contraction) of response ratios across components under the mixed schedule. Under the multiple schedule (triangles), however, response allocation was under a greater degree of control by the unpredictably changing reinforcer value-ratios arranged across components. The increased sensitivity is apparent in the wide swings (i.e., expansion) in response-ratios across components under the multiple schedule.

Within-Component Acquisition. The subsequent analyses characterized responses with respect to their occurrence in blocks of responses and reinforcers (i.e., within-component). Figure 3 shows mean log initial-link response ratios as a function of successive reinforcer presentations (i.e., IL-TL cycles) in each component (i.e., delay-ratio) for both strains under mixed and multiple schedules. The data were taken from the final five sessions of each condition and response ratios were calculated as a function of blocks of reinforcer presentations in each component. The first data point in each component shows response ratios before the first reinforcer delivery in a component (reinforcer 0), and then preference after four, eight, and twelve reinforcers, corresponding to the end of blocks one, two, and three respectively. For the BALB/c mice, choice before the first reinforcer delivery in a component did not show indifference but instead a slight bias toward the larger reinforcer. The mean log response ratio (across all components) emitted before any reinforcers were obtained was 0.10 under the mixed and 0.13 under the multiple, indicating that initial component choice under both schedules was influenced to a greater extent by the positive sessional reinforcer magnitude ratio (log mean sessional reinforcer magnitude ratio = 0.60 & delay-ratio = -0.87).

Under the mixed schedule, response ratios before the first reinforcer were not differentiated by the value-ratio in that component; that is, they nearly fell on top of each other. In contrast, initial-component response ratios under the multiple schedule began closer to the arranged component reinforcer value ratio. When components were nondifferentially signaled, the separation in response ratios towards the component reinforcer value ratio developed in
a positively accelerating manner after an increasing number of component reinforcers were delivered. The greatest change in response ratios occurred during the final four cycles of a component (i.e., reinforcers 8 -12), during which response ratios approached the arranged component reinforcer value ratio. Under the multiple schedule, log response ratios began at a value closer to the programmed ratios, changed by smaller amounts as the number of component reinforcer deliveries increased (e.g., Kragelöh & Davison, 2003), but reached the final component levels faster than the mixed schedule. Final levels of response allocation in each component, however, were approximately the same under each schedule.

For the C57Bl/6 mice, the mean log response ratio (across components) before any reinforcers were obtained was -0.25 under the mixed and -0.07 under the multiple schedule. In contrast with the BALB/c mice, the C57Bl/6 mice displayed a bias in favor of the smaller terminal-link. The negative value for preference suggests that initial component choice under both schedules was influenced to a greater extent by a combination of the sessional reinforcer magnitude and delay ratios (i.e. the sessional reinforcer value ratio; Eq. 1). Under the mixed schedule, the mean response ratio (-0.25) before any reinforcers were delivered was nearly identical to the sessional mean reinforcer value ratio (log mean sessional reinforcer value-ratio = -0.27), indicating that initial component preference was primarily under the control of the sessional reinforcer value ratio (cf. Landon & Davison, 2001; Landon, Elliffe, & Davison, 2002). Initial component response ratios under the multiple schedule, however, began closer to their respective component reinforcer-value ratio, that is, there was greater differentiation in response-ratios (see also Kragelöh & Davison, 2003). When components were nondifferentially signaled, the majority of separation in response ratios towards the component reinforcer value ratio developed after just the first four reinforcers in a component. After block 1, response ratios changed only slightly, quickly reaching their final within-component levels that were far short of the arranged component reinforcer value ratio. Under the multiple schedule, initial component response ratios were more differentiated, but they changed at approximately the same rate as under the mixed schedule as more component reinforcers were obtained. Preference, however, began and ended closer to the current component reinforcer value ratio, implying elevated control by the component relative reinforcer value ratio across all blocks (e.g., Kragelöh & Davison, 2003).

Previous studies in which the presentation of relative reinforcer-ratios was randomized across components of a session (i.e., Davison & Baum, 2000; Grace et al., 2003; Schofield & Davison, 1997) have quantified the extent to which preference in a component is determined by the current reinforcer-ratio and by the reinforcer-ratio in the previous component. These analyses have been based on a generalized matching model (GML; Baum, 1974; Davison & McCarthy, 1988) in which performance across blocks of reinforcer presentations in a component is regressed
against the current and previous components’ reinforcer ratios (e.g., Davison & Baum, 2000; Schofield & Davison, 1997). We employed an extension of the model provided by Davison and Baum (2000) assuming a constant, additive effect of reinforcer magnitude and the effects of current and previous components’ log reinforcer delay ratios as a function of blocks of 4 IL-TL cycles (i.e., 3 blocks per component). The equation used for this analysis was

$$\log \left( \frac{B_{LLR}}{B_{SSR}} \right) = \frac{1}{s_m} \log \left( \frac{M_{LLR}}{M_{SSR}} \right) - \frac{1}{s_p} \log \left( \frac{D_{LLR}}{D_{SSR}} \right) - \frac{1}{s_c} \log \left( \frac{D_{LLR}}{D_{SSR}} \right)$$

(2)

where $B$ is initial-link response rate, $M$ is arranged terminal-link reinforcer magnitude (constant 4:1 difference), $D$ is arranged terminal-link reinforcement delay, each subscripted for both response alternative (LLR and SSR) and previous and current component ($p$ and $c$), while $i$ is the block of four IL-TL cycles, where $i = 0$ before the first reinforcer, to $i = 1$ after four cycles and $i = 3$ after 12 cycles. The parameter $s_m$ is the y-intercept of the function and represents sensitivity to reinforcer magnitude across all blocks of the current component. The slope parameters $s_p$ and $s_c$ represent sensitivity to the previous ($p$) and current ($c$) component reinforcer-delay ratios in block $i$ of the current component. The parameter $s_c$ is identical to the delay sensitivity parameter used in traditional GML analyses (e.g., Davison, 1987; Grace, 1994, 1999) and represents the discount rate. Equation 2 was fitted to log initial-link response ratios at each block within a component from sessions 45-50 of the final presentation of the mixed and multiple schedule. This equation required that seven parameters be estimated for each subject under each schedule arrangement: A delay-sensitivity parameter for the immediately preceding ($s_p$) and current ($s_c$) component delay ratios for each of the three blocks of the current component and a single magnitude sensitivity parameter ($s_m$) that remained constant across all blocks and components. The magnitude sensitivity parameter was fixed across components within each schedule presentation because the relative reinforcer magnitude-ratio remained unchanged across components of a session. Sensitivity parameters were estimated for individual mice by the method of least squares using Solver in Microsoft Excel®.

Figure 4 shows individual and mean sensitivity to reinforcer magnitude estimates for BALB/c (open symbols) and C57Bl/6 mice (filled symbols), under mixed (squares) and multiple (triangles) schedules, obtained from fits of Equation 2. A two-way ANOVA revealed a strain X schedule interaction ($F(2, 26) = 21.232, p < 0.001$). Mean magnitude sensitivity was higher for the BALB/c mice than the C57Bl/6 mice across each phase of the experiment (Tukey’s multiple comparison, $p’s < 0.001$). For the BALB/c mice, magnitude sensitivity was relatively high and undifferentiated across phases of the experiment (isodelay mean $s_m = 0.75$; mixed = 0.77; mult = 0.79; all $p’s > 0.57$). For the C57Bl/6 mice, magnitude sensitivity was higher under the isodelay assessment and multiple schedule than the mixed schedule (mean isodelay $s_m = 0.47$; mult = 0.51; mix = 0.21; both $p’s < 0.001$), but multiple schedule magnitude
sensitivity was not different from estimates obtained under the isodelay assessment ($p = 0.35$). Note that magnitude sensitivity was much higher for mouse C93 under the multiple schedule compared to all other mice. Excluding mouse C93’s data from the analysis, however, did not alter the statistical conclusions.

The inclusion of (unequal) terminal-link delays to reinforcement altered magnitude sensitivity selectively for the C57Bl/6 mice compared to magnitude sensitivity under the isodelay (equal terminal-link delay) condition, but only when components were nondifferentially signaled. Spearman $\rho$ correlation coefficients between isodelay magnitude sensitivity (Fig. 1) and magnitude sensitivity after the introduction of delays (Fig. 4) were examined to assess the extent to which individual subjects’ magnitude sensitivity was affected by the introduction of delays to the larger reinforcer and how stimulus arrangement influenced this effect. For the BALB/c mice, Spearman $\rho$ correlations were high and positive under both schedules (mixed $\rho = 0.84$, multiple $\rho = 0.82$, both $p’s < 0.01$). These high correlations coupled with the nearly identical isodelay and mixed and multiple magnitude sensitivities (Figs. 1 & 4) indicate that the introduction of delays, under either schedule, did not affect magnitude sensitivity for individual mice across phases of the experiment. For the C57Bl/6 mice, however, the Spearman $\rho$ correlations between isodelay and post-delay magnitude sensitivity depended upon the schedule in effect. Under the multiple schedule, the Spearman correlation was $\rho = 1.00$ ($p < 0.01$). The Spearman correlation was $\rho = 0.14$ and indistinguishable from zero ($p = 0.72$) under the mixed schedule, indicating that levels of isodelay magnitude sensitivity were unrelated to levels of magnitude sensitivity under only the mixed schedule.

Figure 5 shows mean sensitivity to the current ($s_{ci}$) and previous ($s_{pi}$) components’ reinforcer delay-ratios as a function of block ($i$) for both strains, under each schedule, obtained from fits of Equation 2. There were Strain X Block X Schedule interactions describing effects on current and previous component delay sensitivity (Both $F’s (2, 26) > 15$, $p’s < 0.001$). For both strains regardless of schedule, sensitivity to the current delay increased and sensitivity to the previous delay decreased across blocks of a component. Sensitivity to the current delay was higher for the BALB/c mice compared to the C57Bl/6 mice at the final two blocks (both $p’s < 0.001$), but sensitivity was not different at block 1 ($p = 0.57$). The C57Bl/6 mice, however, reached final levels of current delay sensitivity (i.e., Block 3) faster than the BALB/c mice, overall. That is, response allocation changed to a lesser degree across blocks for the C57Bl/6 than the BALB/c mice (see Fig. 3).

For the BALB/c mice, within-component acquisition was faster under the multiple than the mixed schedule, in agreement with figure 3. That is, sensitivity to the current component’s delay (top, solid lines) was higher and sensitivity to the previous component’s delay (bottom, dashed lines) was lower under the multiple than the mixed schedule in blocks 1 and 2 (all $p’s < 0.001$). Final levels of current and previous delay sensitivity (Block 3), however,
were not different across schedule (mean mixed $s_{c3} = 0.73$; multiple = 0.75; both $p$’s $> 0.67$). For the C57Bl/6 mice, the speed with which sensitivity to the current delay increased and sensitivity to the previous delay decreased to final levels did not differ between the two schedules (see Fig. 3). Sensitivity to the current delay, however, was higher under the multiple compared to the mixed schedule across all three blocks (All $p$’s $< 0.001$). Indeed, maximum sensitivity to the current delay (Block 3) was higher under the multiple schedule than the mixed (mean multiple $s_{c3} = 0.53$; mixed = 0.31), while estimates of sensitivity to the previous delay were not different across schedule arrangement at any block (all $p$’s $> 0.62$). In general, Equation 2 provided a good description of the data, on average accounting for 88% of the variance (All %VAC $> 80$%) in the log response ratios across subjects, strains, and conditions.

To summarize results shown in the previous analyses, figure 6 shows mean and representative subjects’ discount functions for each strain responding under mixed and multiple schedules. The obtained data (symbols) were taken from block three of each component and averaged across the last five sessions of the final presentation of mixed and multiple schedules, respectively. In order to demonstrate the competence of extending the GML lag analysis to characterize final levels of response allocation to changing reinforcer value-ratios across components, we also assessed the model’s fit to the discount functions obtained only from block three of each of the final schedule presentations. The model’s predictions for block 3 response ratios at each component for mice of each strain, responding under each schedule, were achieved in the same manner as the obtained data. The fits of the GML lag model to response ratios from final block of each component, incorporating carryover from the previous components’ reinforcer delay ratios ($s_{p3}$), were excellent, in accord with previous studies using similar analyses (Davison & McCarthy, 1989; Davison & Baum, 2000). Table 2 gives the parameters $s_m$ (i.e., magnitude sensitivity) and $s_D$ (i.e., $s_{c3}$ in Eq. 2; delay sensitivity) of the GML lag model and goodness of fit indices for BALB/c and C57Bl/6 mice responding under mixed and multiple schedules, respectively.

For the BALB/c mice, discount functions were nearly identical under mixed and multiple schedules. The predictions shown in Figure 5 demonstrate that for the BALB/c mice, sensitivity to reinforcer magnitude and delay was relatively high and unaffected by schedule, as indicated by the nearly identical y-intercepts and slopes of the functions, at levels higher than the C57Bl/6 mice (Table 2; Figure 4 & 5, Block 3). For the C57Bl/6 mice, the y-intercepts of the discount function were much higher under the multiple than the mixed schedule. Additionally, the slopes of the functions differed under each schedule; preference for the larger reinforcer decreased at a higher rate as a function of changes in the relative reinforcer delay ratios under the multiple compared to the mixed schedule. The predictions shown in figure 5 confirm that sensitivity to reinforcer magnitude and delay was higher under the multiple than the
mixed schedule for the C57Bl/6 mice (Table 2, bottom). For both strains, the mean discount functions (inset panels) under each schedule reflect those of individual subjects (surrounding panels).

Finally, to determine the degree to which levels of sensitivity to reinforcer magnitude and delay were related to one another, Spearman ρ correlation coefficients were generated between individual subjects’ estimates of sensitivity to reinforcer magnitude and delay obtained under each schedule (listed in Table 2). For the BALB/c mice, the Spearman ρ correlation between sensitivity to reinforcer magnitude and delay across schedule were low, positive (ρ = 0.106, p = 0.69), suggesting that the two GML parameters were orthogonal for this strain (e.g., Grace, 1995, 1999). For the C57Bl/6 mice, however, the Spearman ρ correlation between magnitude and delay sensitivity were high, positive (ρ = 0.88, p < 0.001), indicating that when sensitivity to reinforcer magnitude increased for an individual subject, sensitivity to reinforcer delay also increased (or visa versa).

Discussion

The goals of the present work were to (1) explore the speed and extent of changes in delay discounting when terminal-link reinforcer-value ratios changed frequently and randomly across components of a session, (2) compare the effects of differentially and nondifferentially signaled components on the acquisition of choice and the final form of the discount function, (3) examine how genetic variables influenced the effects of different stimulus arrangements on choice. These aims were accomplished by comparing response allocation in two inbred mouse strains under mixed and multiple schedule arrangements of a novel delay discounting procedure. The procedure used in the present study allowed for the detection of differences in delay discounting between BALB/c and C57Bl/6 mice, extending previous research on delay discounting among inbred strains of rodents (Helms et al., 2006; Huskinson, Krebs, & Anderson, 2012; Pinkston & Lamb, 2011; Stein et al., 2012; see Mitchell, 2011 for a review). Additionally, the present study showed, within-subjects, that the acquisition and final form of the discount function, and thus the extent of these strain differences, depended upon whether components were presented as mixed or multiple schedules. In an attempt to identify possible behavioral mechanisms (cf. Pitts, 2014) by which strain- and schedule-effects emerged across phases of the experiment, we used a GML-based analysis that incorporated the effects of relative reinforcer magnitude and current and previous terminal-link delay-ratios.

Methodological Considerations. A number of studies have used multiple regression analyses based on the GML to demonstrate that preference in concurrent-chained schedules readily adapts to unpredictable changes in relative reinforcer delay (e.g., Grace et al., 2003; Ta et al., 2008). The use of a GML-based analysis in the current study confirmed that response allocation for each strain was increasingly sensitive to the delay currently in effect across blocks, while sensitivity to the previous delay diminished across those blocks (Davison & Baum, 2007; Grace et
al., 2003; Grace & McLean, 2006; Ta et al., 2008). This finding is important because numerous investigations of delay discounting have used within-session procedures based on Evenden and Ryan (1996) and the effects of previous-component delays on current component preference are not examined. When the progression of delays systematically increases or decreases within-session, there is a possibility of increased control by the order of previous delays to reinforcement over current choice (i.e., carry-over or hysteresis) relative to procedures that randomize the within-session progression of delays. Moreover, the direction of carry-over likely depends on the specific delay-progression (Christensen & Grace, 2009). Tanno et al. (2014) demonstrated that preference for a larger reinforcer was lower when delays were increased compared to when delays were decreased systematically and invariably within-session, confirming differential control over choice at the current delay by the order in which previously experienced delays were presented.

Research examining the effects of stimulus conditions on delay discounting under steady-state procedures, in which delays systematically and invariably increase or decrease within- and across-sessions, have found similar levels of preference under signaled (identically and uniquely) and unsignaled delays to reinforcement (e.g., Cardinal et al., 2000; Slezak & Anderson, 2009). This may be because signaled and unsignaled delays to reinforcement are unlikely to exert differential effects if stimulus control by the order of delay presentation is the stronger controlling variable (Maguire et al., 2014; Tanno et al., 2014), and under ascending or descending delay progressions, any stimulus conditions arranged are redundant with delay-order. That is, control over response allocation by the sequence of delays or some correlate (e.g., session time) could compete with control by other conditional stimuli (e.g., Pearce & Hall, 1978). When the delays to reinforcement change unpredictably within- and across-sessions, however, there can be no stimulus control by the overall order of delay-progression, allowing signaled relative reinforcer delays to exert stronger discriminative control over choice.

The present study also differed from previous delay discounting studies by instituting dependently scheduled initial-links (Beeby & White, 2013; Grace et al., 2012; Stubbs & Pliskoff, 1969). The dependent schedule controlled equal access to each terminal-link alternative, ensuring that programmed and obtained relative reinforcement dimensions were not confounded with preference. Response allocation in the initial-links was therefore influenced by relative delays and magnitudes of reinforcement, but not the frequency with which each terminal-link was encountered (Eqs. 1 & 2; see Grace et al., 2012), as it is in conventional delay discounting procedures (e.g., Evenden & Ryan, 1996; Mazur, 1987). Additionally, the forced terminal-link entry provided by the dependent schedule accomplishes the same goal as forced-choice trials in traditional procedures, without additional amendments, and thereby helps to eliminate bias in choice resulting from interspersing forced-choice and free-choice trials during components (see Cardinal et al.,
2004 for a similar discussion). Lastly, the presence of multiple responses on the preferred alternative (when it is not scheduled for delivery) seen with dependent scheduling results in a greater dynamic range over which preference can vary and produces more graded functions at the individual subject level relative to independent scheduling, which often results in near exclusive choice for the more highly valued alternative (i.e., step-functions).

*Delay Discounting.* Both within-component acquisition and final-component preference differed between strains. The speed at which preference adjusted to the current-component reinforcer value-ratio was generally slower for the BALB/c than C57Bl/6 mice, but this was due partly because response allocation changed to a greater extent within a component for the BALB/c than C57Bl/6 mice.

The consistently higher y-intercepts (magnitude sensitivity) and steeper slopes (delay sensitivity) of the discount function for the BALB/c compared to the C57Bl/6 mice across phases of the experiment are generally consistent with previous studies using other delay discounting procedures (Otobe & Mankino, 2004). The results of the current study, combined with previous work, suggest persistent differences between these strains in both sensitivity to reinforcer amount and delay (i.e., discount rate). Interestingly, the steeper discount rates for the BALB/c than the C57Bl/6 mice are also consistent with persistent differences between these strains in the coupling of reinforcers to target responses under fixed-ratio schedules of reinforcement (Hutsell & Newland, 2013). Using mathematical principles of reinforcement (MPR, Killeen, 1994), Hutsell and Newland (2013) showed that the rate parameter λ was higher for BALB/c than C57Bl/6 mice, indicating that the influence of a reinforcer dissipates quickly, so it is coupled with fewer prior responses. Therefore, according to MPR, the delay of reinforcement gradient for BALB/c is steeper than that of C57Bl/6 mice (e.g., Killeen, 1994, 2012). The present study adds further support for this conclusion, and suggests that delay sensitivity (i.e., discount rate) and λ in MPR likely index similar behavioral mechanisms (cf. Killeen, 2012).

The impact of differentially signaled components on response allocation in the present study are largely in agreement with the rapid-acquisition literature (e.g., Kragelöh & Davison, 2003), but is unique to the delay discounting literature. Early in a component, response allocation for both strains was under a greater degree of control by the current component reinforcer value-ratio and to a lesser degree of control by the previous component reinforcer value-ratio when responding under the multiple compared to the mixed schedule. For the BALB/c mice, differentially signaling components affected only initial levels of response allocation and the speed at which sensitivity to the current and previous delays reached final levels, but the final form of the discount function (i.e., magnitude and delay sensitivity) was approximately identical under each schedule. For the C57Bl/6 mice, differentially signaling components altered initial and final levels of response allocation by increasing sensitivity to reinforcer magnitude and
delay across all blocks of a component and final discount functions under the multiple showed higher y-intercepts and steeper slopes relative to the mixed schedule. The extent of strain differences in delay discounting, then, were augmented under when components were nondifferentially signaled and attenuated when components were differentially signaled, primarily due to increases in magnitude and delay sensitivity for the C57BL/6 mice under the multiple schedule.

**Magnitude and Delay Sensitivity: C57Bl/6 Mice.** Under the isodelay assessments of preference, there was no response bias for either strain, but sensitivity to reinforcer magnitude was lower for the C57Bl/6 than the BALB/c mice. That is, control over response allocation by relative reinforcer magnitude was diminished under isodelay assessments of preference for the C57Bl/6 relative to the BALB/c mice. Interestingly, sensitivity to reinforcer magnitude changed across phases of the experiment for the C57Bl/6 mice selectively. For this strain, magnitude sensitivity under the mixed schedule (0.21) was lower than under the isodelay conditions (0.46) and the multiple schedule (0.51).

Individual subject magnitude sensitivity under the mixed schedule was not correlated with magnitude sensitivity under isodelay conditions ($\rho = 0.14$), but magnitude sensitivity was highly correlated between isodelay and multiple schedule conditions ($\rho = 1.00$). These correlations, coupled with fluctuations in magnitude sensitivity, suggest that control by relative reinforcer magnitude over choice decreased when reinforcer-delay ratios were nondifferentially signaled. When components were differentially signaled, however, control over preference by relative reinforcer magnitude was preserved at levels seen under isodelay conditions for individual subjects. Similar to previous reports (Davison & Baum, 2003; Green & Snyderman, 1980; Orduna, Valencia-Torres, Cruz, & Bouzas, 2013), these results may suggest an interaction between reinforcer magnitude and current and previous-component delay ratios for the C57Bl/6 mice, but this interaction was modulated by the stimulus condition in effect.

For the C57Bl/6 mice, fluctuations in magnitude sensitivity induced by the schedule in effect were accompanied by nearly identical changes in current delay sensitivity ($\rho = 0.88$). The changes in delay sensitivity are readily explained by a stimulus control hypothesis. Reinforcer-delay ratios changed unpredictably across components of a session so when components were differentially signaled, initial and final component response allocation was under a greater degree of control by the current reinforcer delay-ratio than when components were nondifferentially signaled (cf., Kragelöh & Davison, 2003). That is, under the multiple schedule, sensitivity to the current reinforcer delay was higher, and thus the rate of discounting was elevated, than under the mixed schedule.

In contrast to the changing delay ratios, the reinforcer-magnitude ratio was constant across all components and conditions, so no ambiguity existed as to which alternative provided the larger reinforcer. Why, then, should
magnitude sensitivity for the C57Bl/6 mice be lower under the mixed than the multiple schedule? If reinforcer magnitude and delay ratios combined in a multiplicative manner to influence choice under the mixed schedule, then magnitude sensitivity could be altered in a similar manner as delay sensitivity. The present study arranged unequal reinforcer magnitude and delay ratios across alternatives and the mean sessional log reinforcer value-ratio favored the smaller-sooner terminal-link (log sessional mean reinforcer value-ratio = -0.27; Eq. 1). The diminished control by the current component reinforcer value ratio under the mixed schedule caused response ratios to lie very close to the sessional reinforcer value ratio before any reinforcers were delivered in a component. Also, under the mixed schedule, preference throughout a component was under a greater relative degree of control by the sessional mean log reinforcer value-ratio (i.e., previous component delay) than by current component reinforcer value-ratio causing response ratios across components to be more constricted. In contrast, under the multiple schedule, initial component response ratios were more dilated, falling farther from the sessional mean and their average was closer to indifference, indicating a greater degree of control by the current component reinforcer value ratio. Additionally, preference throughout a component came under a greater degree of control by the current component reinforcer value ratio as more reinforcers were delivered in a component. The end result was that magnitude and delay sensitivity were higher overall under the multiple than the mixed schedule for the C57Bl/6 mice, with persistent differences observed in the final form of the discount function.

Reinforcer magnitude and current delay sensitivity were generally 0.20 to 0.30 higher throughout each block of a component when components were differentially than when nondifferentially signaled (e.g., Kragelöh & Davison, 2003). These results illustrate that differentially signaling components enhanced discriminative control over choice by the current component’s reinforcer value ratio at a more global level (all blocks). It is unclear, however, whether differentially signaling components per se resulted in higher sensitivity to reinforcement or whether this arose from control over response allocation by the current component reinforcer-value ratio beginning in components at higher levels.

**BALB/c Mice.** For the BALB/c mice, magnitude sensitivity was nearly identical across all phases of the experiment, that is, it was independent of both relative reinforcer delay and schedule arrangement. The high correlations between individual subject magnitude sensitivity across phases of the experiment confirm that individual subject magnitude sensitivity was relatively unaffected by procedural arrangement. Sensitivity to reinforcer magnitude and delay were very high and nearly identical under each schedule, and were higher than the C57Bl/6 mice, overall. The correlation between individual subject reinforcer magnitude and delay sensitivity across schedule was not different from zero (ρ = 0.11), indicating that relative reinforcer magnitude and delay were independently controlling choice.
In contrast to the C57Bl/6 mice, for the BALB/c mice regardless of schedule, response ratios before any reinforcers were delivered in a component were greater than zero, indicting a small initial-bias in favor of the terminal-link alternative correlated with the larger reinforcer. This bias suggests greater control over initial preference by the sessional reinforcer magnitude distribution and a lesser degree of influence by sessional reinforcer delay ratios compared to the C57Bl/6 mice. Because initial component delay sensitivity was similar between BALB/c and C57Bl/6 mice under mixed and multiple schedules, respectively (Fig. 5), the higher magnitude sensitivity for the BALB/c mice seems to be the primary reason that initial component response allocation was biased in opposing directions for each strain.

For the BALB/c mice, differentially signaling components affected only the initial levels of sensitivity to the current and previous delays and the speed with which sensitivity to the current and previous delay approached final levels within a component. That is, the multiple schedule increased discriminative control by the current component’s delay-ratio and decreased the impact of the previous component’s reinforcer-delay ratio during the first 8 reinforcer deliveries in a component. In contrast to Kragelöh & Davison (2003), using pigeons, and the C57Bl/6 mice (here), there was no difference in final levels of sensitivity to the current and previous delay-ratios between mixed and multiple schedules. The lack of difference in final levels of sensitivity across signaling arrangement verifies that much of the change in response allocation under the mixed schedule occurred during the final four reinforcer deliveries in a component. The differences in the speed of acquisition, but not the extent of final performance may suggest that separate processes govern different aspects of response allocation for this strain.

Summarily. The present study extended recent research on the acquisition of choice to frequent and unpredictable within- and across-session changes in relative reinforcement dimensions (Davis & Baum, 2000; Grace et al., 2003; Rodewald et al., 2010; Ta et al., 2008). The current study blended methods from these lines of research to obtain discount functions within a single session and assess the impact of reinforcer magnitude and current and previous delays to reinforcement on preference. To our knowledge, this is the first study to examine choice under a rapid-acquisition procedure using mice as subjects, extending previous work with pigeons (e.g., Davison & Baum, 2000) and rats (e.g., Aparicio, 2007, 2008). The procedure adopted here controlled exposure to each alternative (i.e., terminal-link entry) through dependent scheduling. Randomizing the presentation of delays across components of a session may have helped to mitigate systematic carry-over (i.e., order) effects seen in traditional (e.g., ascending) delay discounting procedures. Further, the randomized presentation of delays may be better suited to assessing the effects of discriminative stimuli on delay discounting, as control by such stimuli over choice under strictly ascending or descending procedures is likely overshadowed by the order of delay presentation.
The present study also extended previous work on rodent strain differences in delay discounting and revealed consistent differences in both the acquisition and final form of the discount function (i.e., magnitude and delay sensitivity) between BALB/c and C57Bl/6 mice. The extent of these strain differences, and the form of the discount function for an individual subject, however, was modulated by the stimulus conditions under which choice was assessed. This gene X environment interaction suggests that the observed strain differences in delay discounting emerged partly from genotype-dependent sensitivity to the maintaining stimulus conditions. Such interactions are important in understanding the degree to which biological variables contribute to steep delay discounting (Mackillop, 2013) and how the environment may enhance or attenuate the influence of these variables (Bickel et al., 2011; Odum & Baumann, 2010; Odum, 2011a; Sonuga-Barke et al., 2010; Stein et al., 2012). Future research may profitably investigate the extent to which the environment modifies the role of genes and neurochemistry in order to describe variables that contribute to differences in discount rate among vulnerable populations.

Author Note
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References


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Tables

Table 1. Delay to larger, later reinforcers and duration of auditory stimuli used in the multiple schedule.

<table>
<thead>
<tr>
<th>TL Delay to LLR (s) vs. 1.25 s SSR</th>
<th>Low/High Tone Durations (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.25</td>
<td>0.15/1.19 s</td>
</tr>
<tr>
<td>2.81</td>
<td>0.74/0.6 s</td>
</tr>
<tr>
<td>6.30</td>
<td>0.92/0.42 s</td>
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<td>14.12</td>
<td>1.04/0.3 s</td>
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<tr>
<td>31.62</td>
<td>1.13/0.21 s</td>
</tr>
<tr>
<td>70.79</td>
<td>1.19/0.15 s</td>
</tr>
</tbody>
</table>

1Duration of pulsating low/high tones (in s) arranged for each of the 6 components (reinforcer delay-ratios) under the multiple schedule version of the procedure. No unique auditory stimuli were presented during the mixed schedule.
Table 2. Parameter estimates from fits of the GML based lag-model to the data shown in Figure 6.

**BALB/c mice**

<table>
<thead>
<tr>
<th>Subject</th>
<th>$s_M$ (Mix)</th>
<th>$s_M$ (Mult)</th>
<th>$s_d$ (Mix)</th>
<th>$s_d$ (Mult)</th>
<th>$R^2$ (Mix)</th>
<th>$R^2$ (Mult)</th>
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</thead>
<tbody>
<tr>
<td>B1</td>
<td>0.78</td>
<td>0.73</td>
<td>0.69</td>
<td>0.79</td>
<td>0.90</td>
<td>0.95</td>
</tr>
<tr>
<td>B2</td>
<td>0.88</td>
<td>0.98</td>
<td>0.72</td>
<td>0.74</td>
<td>0.92</td>
<td>0.83</td>
</tr>
<tr>
<td>B3</td>
<td>0.85</td>
<td>0.91</td>
<td>0.75</td>
<td>0.83</td>
<td>0.84</td>
<td>0.81</td>
</tr>
<tr>
<td>B4</td>
<td>0.76</td>
<td>0.73</td>
<td>0.76</td>
<td>0.68</td>
<td>0.82</td>
<td>0.91</td>
</tr>
<tr>
<td>B5</td>
<td>0.66</td>
<td>0.74</td>
<td>0.89</td>
<td>0.94</td>
<td>0.95</td>
<td>0.89</td>
</tr>
<tr>
<td>B6</td>
<td>0.80</td>
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<td>0.82</td>
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**C57Bl/6 mice**

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<th>Subject</th>
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<th>$s_M$ (Mult)</th>
<th>$s_d$ (Mix)</th>
<th>$s_d$ (Mult)</th>
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\(^1\)Estimates of sensitivity to reinforcer magnitude, sensitivity to reinforcer delay, and percent variance accounted for are shown for each individual subject responding under mixed and multiple schedules, respectively. Estimates of each parameter and percent variance accounted under each schedule are shown for BALB/c mice (top) and C57Bl/6 (bottom). See text for further explanation.
Figure 1.

Sensitivity to Reinforcer Magnitude ($s_M$)

BALB/c  C57Bl/6
Figure 2.
Figure 3.
Figure 4.

Sensitivity to Reinforcer Magnitude ($s_M$)

BALB/c

C57Bl/6

Sensitivity to Reinforcer Magnitude ($s_M$)

0.00

0.25

0.50

0.75

1.00

MIX

MULT

MIX

MULT
Figure 5.

**BALB/c**

**C57BL/6**

BLOCK of 4 CYCLES

Sensitivity to Current or Previous Delay

Mixed
Multiple

0.00 0.25 0.50 0.75 1.00

1 2 3

Mixed
Multiple

1 2 3
Figure 6.

Balb/c

MEANS

LOG10 DELAY RATIO (LLR/SSR)

LOG10 RESPONSE RATIO (LLR/SSR)

C57Bl/6

MEANS

LOG10 DELAY RATIO (LLR/SSR)

LOG10 RESPONSE RATIO (LLR/SSR)
Figure Captions

Figure 1. Mean (gray lines) and individual subjects’ (circles) sensitivity to reinforcer magnitude under isodelay assessments. Open circles denote individual BALB/c and filled circles C57Bl/6 mice.

Figure 2. Response allocation (symbols), expressed as log response ratios (LLR/SSR), and the log reinforcer value-ratio (grey lines) as a function of component number. Each component used a different delay ratio and delays were presented randomly across components. Data are shown from the final five consecutive sessions of each schedule presentation according to an ABA design. The figure shows data from representative BALB/c (open symbols) and C57Bl/6 mice (filled symbols) mice responding under mixed (squares) and multiple (triangles) schedules.

Figure 3. Mean log response ratios as a function of successive reinforcer presentations in a component. Mean log response ratios are shown for each component (i.e., delay-ratio) before the first reinforcer delivery and following 4, 8, and 12 reinforcer deliveries in each component. The top graphs show response allocation for the BALB/c mice under mixed (left) and multiple (right) schedules, while the bottom graphs show performance for the C57Bl/6 mice.

Figure 4. Mean (grey lines) and individual subjects’ (symbols) estimates of sensitivity to reinforcer magnitude (sm) obtained from fits of Eq. 1. Estimates are shown for BALB/c (open symbols, left) and C57Bl/6 mice (filled symbols, right) responding under mixed (squares) and multiple (triangles) schedules.

Figure 5. Mean estimates of sensitivity to the current ($S_{ci}$) and previous component ($S_{pi}$) reinforcer delay ratio as a function of three blocks of 4 cycles within a component obtained from fits of Eq. 1. Mean estimates are shown for BALB/c (open symbols) and C57Bl/6 mice (filled symbols) responding under mixed (squares) and multiple (triangles) schedules.

Figure 6. Obtained (symbols) or GML predicted (lines) log response ratios (LLR/SSR) a function of arranged component log delays ratios (LLR/SSR). Obtained response ratios were taken from the final block of a component and averaged across the last five consecutive sessions of the final presentation of mixed and multiple schedules. Obtained and predicted response ratios are shown for BALB/c (open symbols, top) and C57Bl/6 (filled symbols, bottom) mice responding under mixed (squares, solid lines) and multiple (triangles, dashed lines) schedules. Figures for each strain show individual subject (surrounding panels) or mean (inset panel) obtained and predicted log response ratios obtained under mixed and multiple schedules, respectively.
Chapter 3: Experiment 2

Abstract

Rationale Amphetamine has been reported to increase and decrease preference for larger-delayed reinforcers depending on genetic background, delay-progression, and signaling conditions.

Objective The present study examined whether both patterns of d-amphetamine’s effects could be reproduced by investigating delay discounting in two mouse strains responding under different signaling arrangements of a novel procedure.

Methods BALB/c and C57BL/6 mice responded under a six-component, concurrent-chained schedule in which the order of delays preceding the larger-reinforcer was randomized within-session. Across conditions, components were presented as mixed or multiples schedules. Each subject experienced both schedule arrangements and administration of d-amphetamine occurred under each. Dose- and schedule-effects on generalized matching sensitivity to reinforcer magnitude and delay were determined by multi-model inference.

Results For BALB/cs, d-Amphetamine decreased sensitivity to delay, but more so under the mixed schedule. For the C57Bl/6s, baseline estimates of reinforcer magnitude and delay sensitivity were higher under the multiple schedule, but lower overall compared to the BALB/cs. d-Amphetamine decreased reinforcer magnitude and delay sensitivity under the multiple schedule, while the opposite pattern occurred under the mixed.

Conclusions These results suggest a genotype X environment interaction describing d-amphetamine’s effects on delay discounting. Across-strains and within-subjects, d-amphetamine decreased discount rate when baseline levels were high and increased it when baseline levels were low. For the C57Bl/6s, there was a co-dependency between changes in reinforcer magnitude and delay sensitivity. Thus, differences in the baseline form of the discount function were generated by a genotype X signaling condition interaction and d-amphetamine affected delay discounting in a baseline-dependent manner.
The decaying influence of a reinforcer over behavior as a function of the temporal distance to its presentation, the “discount rate,” (Killeen, 2009, 2011) is often used as an index of impulsivity (Madden & Johnson, 2010; Rachlin & Green, 1972). Excessive discounting of delayed reinforcers has been invoked as an underlying process common to a number of human psychiatric maladies (e.g., Bickel et al., 2012) and importantly, elevated discount rates are a reliable predictor of individuals meeting diagnostic criteria for these disorders (Mackillop et al., 2011). An important goal of future discounting research, therefore, is to characterize the variables that contribute to differences in discount rate among vulnerable clinical populations and in preclinical models of psychiatric disorders.

One avenue for localizing the mechanisms that contribute to differences in the form of the discount function is to describe the relation between delay discounting and the genetic and biochemical substrates upon which environment-behavior relations operate. For example, several studies comparing the behavior of inbred rodent strains that differ along specific neurochemical (e.g., monoaminergic neurotransmission) or behavioral dimensions have reported that the Lewis strain of rat displays higher discount rates compared to the Fischer 344 strain (e.g., Anderson & Diller, 2010) and that the BALB/c mouse discounts at an elevated rate compared to C57Bl/6 strain (e.g., Otobe & Makino, 2004). It is becoming increasingly clear, however, that the effect of strain or of pharmacological interventions on measures aimed at characterizing complex functions of the nervous system may sometimes result from differential sensitivity to contextual variables manipulated across studies. Under progressively increasing fixed-ratio schedules, differences in response rate functions depend not only on genotype but also the kind of reinforcer used (Hutsell and Newland, 2013). Differences in delay discounting between Lewis and Fischer 344 rats can be augmented or attenuated depending on the procedural arrangement (Stein et al., 2012) and the effects of d-amphetamine on delay discounting seem to depend on strain (Huskinson, et al., 2012). Moreover, the existing preclinical literature pertaining to psychomotor stimulant effects on delay discounting has shown that the discount rate of individual subjects can be increased (e.g., Cardinal et al., 2000) or decreased (Evenden & Ryan, 1996) following acute administration of d-amphetamine, depending on a variety of environmental or procedural parameters.

Evenden and Ryan (1996) introduced one of the most commonly used procedures to assess the impact of genetic, pharmacological, and environmental variables on delay discounting. This procedure most often involves within-session increases in the delay to the larger-magnitude reinforcer across successive blocks of trials. Using this procedure, a discount function can be obtained within a single experimental session, an obvious advantage when assessing the impact of neurochemical or pharmacological variables (de Wit & Mitchell, 2010; Winstanley, 2010).
In studies of strain and drug effects on delay discounting, changes in preference under ascending- or descending-delay procedures are often interpreted as changes in the rate of discounting, and thus reflective of ‘impulsivity.’ Changes in delay discounting under such procedures could, however, reflect the influence of other mechanisms, including changes in sensitivity to reinforcer magnitude (Pitts & Febbo, 2004) or the presence of conditional stimuli. Importantly, when the order of delays systematically increases or decreases within a session, delays in previous trial blocks can enhance or attenuate preference by exerting control over choice at delays in subsequent trial blocks (i.e., carry-over effects; Pitts & McKinney, 2005; Christensen & Grace, 2009).

The first goal of the present study was to determine the effects of \( d \)-amphetamine on within-session discount functions using a novel procedure that randomizes the order of delay-presentation across components of a session (e.g., Davison & Baum, 2000; Grace, Bragason, & McLean, 2003). Tanno et al. (2014) and Maguire et al. (2014) demonstrated that preference for larger, delayed reinforcers increased or remained unchanged following \( d \)-amphetamine administration under an ascending delay-progression, while it decreased dose-dependently under a descending-progression, illustrating that \( d \)-amphetamine’s effects were dependent upon the degree to which the order of previously experienced delays influenced preference (see also Slezak & Anderson, 2009). Pope et al. (submitted) recently showed that choice under a delay discounting procedure that randomizes the delays to the larger-reinforcer adjusts rapidly to unpredictable and frequent within-session changes in relative reinforcer delays. This procedure retains the power and functionality of the within-session procedure for assessing drug effects on delay discounting, while also minimizing the degree and direction of systematic carry-over effects on preference and potential interactions with drug administration.

\( d \)-Amphetamine has been reported to increase and decrease preference for delayed reinforcers when delays to the larger-reinforcer are unsignaled (Cardinal et al., 2000; Evenden & Ryan, 1996), identically signaled for all delays (Cardinal et al., 2000; Slezak & Anderson, 2009), or uniquely signaled for each delay (Slezak & Anderson, 2009). Perhaps one reason for the disparate findings is that these studies have also arranged strictly increasing or decreasing delays to reinforcement. With extended exposure to systematically and invariably changing delays to reinforcement, stimulus control by other environmental stimuli (e.g., passage of time, order of delay) will develop and compete with stimulus control by the arranged conditions (Kragelöh & Davison, 2003), possibly preventing the development of differential drug effects. In addition to signaling conditions, the effects of \( d \)-amphetamine on delay discounting depend on genetic background, and the order of delay-progression, suggesting that it is necessary to examine these variables together in a single study. Here, we extend previous work by examining the effects of \( d \)-amphetamine on delay
discounting by BALB/c and C57Bl/6 mice under conditions in which components were differentially (i.e., multiple schedule) and nondifferentially signaled (i.e., mixed schedule). Under the same procedure, Pope et al. (submitted) demonstrated that overall, BALB/c mice generated discount functions with higher y-intercepts and steeper slopes relative to C57Bl/6 mice. They also showed that discount functions for BALB/c mice were unaffected by signaling condition, while discount functions for C57Bl/6 mice displayed higher y-intercepts and steeper slopes under the multiple compared to the mixed schedule. Previous studies have shown that d-amphetamine increases choice for larger, delayed reinforcers when baseline discount functions are relatively steep and decreases preference for larger, delayed reinforcers when baseline discount functions are relatively shallow (e.g., Huskinson, Krebs, & Anderson, 2012; Maguire et al., 2014; Tanno et al., 2014). Therefore, we predicted that preference for larger, delayed reinforcers would increase when choice was under a greater degree of baseline control by relative reinforcer-dimensions and decrease when choice was under a lesser degree of control by relative reinforcer-dimensions.

Behavioral pharmacologists often apply formal quantitative frameworks, such as the matching law (Herrnstein, 1970) and mathematical principles of reinforcement (Killeen, 1994), to the behavioral effects of drugs with the goal of revealing behavioral mechanisms of drug action (e.g., Killeen & Bradshaw, 2013; Pitts & Febbo, 2004; Pitts, 2014). In studies of delay discounting, two dimensions of reinforcement, relative reinforcer magnitude and delay, control the degree of response allocation while genetic background, signaling conditions, and/or drug administration can interact to alter the influence each of these dimensions has over choice (i.e., Gene X Drug X Environment interactions). As such, the final goal of the study was to determine signaling- (i.e., schedule) and dose-effects on generalized matching law (GML; Baum, 1974b, Grace, 1999) sensitivity to reinforcer magnitude and delay through multi-model inference (e.g., Sanabria & Killeen, 2009; Burnham & Anderson, 2002).

Method

Subjects. Eight BALB/c and seven C57BL/6 mice used in our previous study (Pope et al., submitted) were housed in pairs in translucent, plastic OptiMICE® cages containing rodent bedding attached to an OptiMICE® HVAC quality air controller (Animal Care Systems Inc.). The vivarium was temperature-controlled (minimum 21° C) under a light-dark cycle (lights on 0630 - 1630); experimental sessions were conducted daily during the light period between 1200 and 1400 h. Caloric intake was restricted to maintain all mice at a target weight of 24g by feeding a measured quantity of standard laboratory chow immediately following each experimental session (~ 2 g). Mice had free access to water when in their home cages.
**Apparatus.** Experimental sessions were conducted in 11 operant conditioning chambers modified to accommodate mice (12.0" L x 9.5" W x 11.5" H). The chambers, manufactured by Med Associates Inc. (St. Albans, VT, Model ENV-007), were enclosed in sound-attenuating cabinets. The rear wall in each chamber was equipped with two Sonalert® tone generators located at the top of the chamber equidistant from a centrally located houselight. The front walls of each chamber were equipped with two retractable response levers (ENV-312-2R). Above each lever, a LED light could be illuminated and responses to each lever exceeding approximately 0.05 N were counted as effective responses. A liquid dipper system (ENV-302W-SX) located equidistant from the two response levers was used to deliver sweetened condensed milk. Liquid reinforcement consisted of 0.1 cc presentations of a 3:1 solution of water:milk. In an adjacent room, a Windows® computer with Med Associates® IV programming and interface system controlled experimental events and collected data with a temporal resolution of 0.1 s.

**General Procedure.** The procedure was identical to that used in Pope et al. (submitted). Mice were exposed to a 6 component, concurrent-chained schedule of reinforcement with 12 initial—terminal link cycles per component. The delay to the larger-delayed reinforcer was randomly selected without replacement at the beginning of each component. These delays, which were fixed time (FT) schedules of X s, served as the terminal-link for the larger reinforcer. The terminal-link delays to the larger reinforcer were geometrically spaced: 1.25, 2.81, 6.31, 14.12, 31.62, and 70.79-s. The terminal-link delay to the smaller reinforcer was fixed at FT 1.25-s across all components. The reinforcer magnitude ratio was always 4:1. The determination of which levers were correlated with the smaller and larger reinforcer were counterbalanced across mice.

Each session began with the random selection of one of the six terminal-link delays to the larger reinforcer for the first component. The left and right levers were inserted into the chamber as the LEDs located above each lever was illuminated. The initial-link (or choice-phase) schedule for each of the 6 components was a dependent fixed ratio (FR) 1 schedule (Stubbs & Pliskoff, 1969) without a changeover delay; at the beginning of a cycle an alternative (left or right) was pseudo-randomly selected with a probability of 0.5 as the alternative that produced terminal-link entry. Therefore, an equal number (six) of entries into each terminal-link was guaranteed during each component of the procedure. This controlled terminal-link-entry procedure ensured equal experience with each alternative and controlled the overall delay to reinforcement within a component. A single initial-link response on the lever selected for terminal-link entry at the beginning of a cycle resulted in access to its correlated terminal link. Presses on the other alternative, the one not selected for terminal-link entry on that cycle, were recorded and used in forming measures of preference but they produced no programmed consequences. Once a terminal link was entered, the opposing lever retracted, but
the lever correlated with the terminal-link entered remained extended and the light above the lever changed from solid to its designated blinking rate of 0.5 s on, 0.5 s off for the duration of that particular delay. If the terminal-link correlated with the smaller reinforcer was entered, a FT 1.25 s schedule commenced; after timing out it resulted in one presentation of sweetened condensed milk for 1.2 s. If the terminal-link correlated with the large reinforcer was entered, a FT $X$ s (where $X =$ the delay selected for the current component) commenced. After the FT $X$ s timed out, there were four presentations of sweetened condensed milk for 1.2 s, separated by 0.5 s each. Following reinforcer presentations there was 3-s blackout followed by the initial links being reinstated. After 12 initial – terminal link cycles in a component, there was a 10-s blackout, followed by the random selection (without replacement) of the next delay. Sessions ended after each of the six components was completed (i.e., 72 completed initial-terminal-link cycles) or 75 min.

Mixed and Multiple Schedules. Every subject experienced the procedure when components were presented as mixed (nondifferentially signaled) and multiple (differentially signaled) schedules. The order of exposure was counterbalanced such that each subject of a strain experienced mixed and multiple schedules. Under the mixed schedule, identical stimulus conditions occurred during all initial-terminal link cycles for each component. Specifically, when a terminal-link was entered, regardless of the delay and magnitude of its correlated reinforcer, the LED light above the lever that was selected changed from solid to its designated blinking rate of 0.5s on, 0.5 s off until reinforcer delivery, while the opposing lever retracted.

When subjects respond under the multiple schedule, each component (i.e., delay-ratio) was correlated with a distinct auditory stimulus. These component-correlated stimuli were presented non-contingently during the beginning of the initial-links (choice phase) and remained present throughout the designated terminal-link delays during a cycle (outcome phase). The component-correlated stimuli terminated only during reinforcer presentations and blackouts, and were reinstated upon the initiation of a new cycle or component. The multiple schedule stimuli were pulsating combinations of low and high tones cycling on/off at different rates that were perfectly correlated with a particular component (see Table 1). All other procedural aspects were identical between mixed and multiple schedules. Subjects responded under each schedule for 50 sessions, after which drug administration began and then the schedules were switched.

Drug Administration. Drug administration began when initial-link preference during the last block of 4 IL-TL cycles of a component showed no systematic trend over the final 5 consecutive sessions. All animals received $i.p.$ injections of $d$-amphetamine sulfate (Sigma-Aldrich, St. Louis, MO, USA), dissolved in a 0.9% saline solution at a
volume of 1.0 ml kg\(^{-1}\) of body weight. The doses investigated were 0.1, 0.17, 0.30, 1.0, and 1.7 mg kg\(^{-1}\) \(d\)-amphetamine, calculated as the salt. All doses of \(d\)-amphetamine and saline vehicle were administered \(i.p.\) 5 min prior to each experimental session in a room adjacent to the room where experimental sessions were conducted. Drugs were administered on Tuesdays and Fridays, saline vehicle on Thursdays, while Mondays, Wednesdays, Saturdays, and Sundays served as noninjected control sessions.

**Data Analysis.** The primary measure of preference was the number of initial-link responses on the LLR lever relative to the responses on the SSR lever during the last block of four trials. Preference was expressed as a log ratio of initial-link to terminal-link responses (log\(_{10}\) [LLR/SSR], and it was examined as a function of the log ratio of reinforcer delays (log\(_{10}\) [LLR/SSR]) arranged across components. Response ratios from the final block (i.e., block 3) of each component were used for analysis because the impact of the previous delay was negligible by that point (Pope et al., under review). Our previous study showed that the order of schedule exposure did not affect preference for mice of either strain (Pope et al., submitted), therefore data collected for individual mice of each strain were collapsed under mixed and multiple schedules, respectively.

**Model Comparison.**

The Model. When GML assumptions are applied to delay discounting data collected under concurrent-chained schedules of reinforcement, relative response ratios (i.e., a measure of preference) are predicted as a function of the relative reinforcer magnitude and delay ratios to be (Grace, 1999):

\[
\log \left( \frac{B_{LLR}}{B_{SSR}} \right) = s_m \log \left( \frac{M_{LLR}}{M_{SSR}} \right) - s_d \log \left( \frac{D_{LLR}}{D_{SSR}} \right)
\]

where \(B_i\), \(D_i\), and \(M_i\) are relative response rate, reinforcer delay, and reinforcer magnitude, arranged across components of a session and subscripted by each response alternative (LLR & SSR). The parameter \(s_m\) represents sensitivity to reinforcer magnitude and affects the y-intercept of the function, while the parameter \(s_d\) represents sensitivity to reinforcer delay and affects the slope of the function (i.e., discount rate). Note that since the magnitude ratio the same, 4:1, for all conditions, so the first term is the Y intercept. Eq. 1 predicts that the form of the discounting function for an individual subject is determined by multiplicative effect of sensitivity to reinforcer magnitude and delay, a relation that becomes additive in log space.

**Implementation.** First, log initial-link response ratios (LLR/SSR) taken from the final block of each component (delay) were averaged over the final 5 consecutive control sessions under each schedule (Pope et al., submitted). To fit the model to the data, we estimated parameters from the GML for each subject by minimizing the sum of squared
deviations between predictions derived from Equation 1 and observed response ratios, using Solver in Microsoft Excel. Model fitting first assessed which parameters \((s_M, s_D)\) are required to vary across the schedule of reinforcement to describe changes in individual performance for mice of each strain. Model comparison was carried out independently for each strain because our previous study demonstrated that strain differences in magnitude and delay sensitivity during baseline were modulated by signaling conditions (Pope et al., submitted). We compared models that allowed all combinations of invariant parameters where the same values of \(s_M\) and \(s_D\) serve for data collected under both schedules (i.e., one estimate of each parameter per subject), only \(s_M\), only \(s_D\), and both \(s_M\) and \(s_D\) are permitted to vary freely across schedule for each mouse of a strain. The best model to describe individual performance for mice of each strain under control conditions was used as the base model from which to assess \(d\)-amphetamine’s effects. Following drug administration, individual subjects’ log initial-link response ratios obtained from the final block of each component (i.e., delay) were taken at each dose under mixed and multiple schedules, respectively. Model-fitting was then used to assess which parameters \((s_M, s_D)\) are required to vary across dose and schedule to describe changes in individual performance for mice of each strain. We compared models that allowed all possible combinations of invariant parameter values, where none, only \(s_M\), only \(s_D\), and both \(s_M\) and \(s_D\) were permitted to vary freely across dose. Additionally, all of these possible parameter combinations were allowed to vary identically or differentially across mixed and multiple schedules, to determine the best model to describe individual performance for mice of each strain following \(d\)-amphetamine under each schedule (see Sanabria & Killeen, 2009).

**Criterion for Model Selection.** Residual sums of squares does not take into account the number of free parameters used in a model, and thus the model with the greatest number of free parameters will always provide the lowest RSS. Therefore, we use a transform of the residual sums of squares that takes model parsimony into account. The Akaike Information Criterion (AIC) (Burnham & Anderson, 2002) corrects the residual sum of squares for the model for the number of free parameters in the model to provide an unbiased estimate of the information-theoretic distance between model and data. Here, the criterion for model selection was determined using the corrected Akaike Information Criterion (AICc) (Burnham & Anderson, 2002), which penalizes small sample sizes

\[
AIC_c = 2k + n \ln \left( \frac{RSS}{n} \right) + \frac{2k(k + 1)}{(n - k - 1)}
\]

where RSS is the residual sum of squares over all mice of a strain, \(k\) is the number of free parameters in the model, and \(n\) is the total number of observations (data points) for a strain. AICc covaries positively with residual sum of squares
(RSS) and number of free parameters, therefore a lower AICc (i.e., less positive or a more negative value) indicates a better account of the data given the degrees of freedom in the model.

We compared all possible combinations of different models for each strain under analysis, characterized by Equation 1. In order to determine how likely a model is the best model, given the data, relative to all other models tested, relative AICc scores must be computed. Relative AICc scores are calculated by first identifying which model achieves the lowest AICc (i.e., the best model). The comparison between models is made by subtracting all models’ AICc values from the best model’s AICc. This gives the best model a relative AICc of 0 and all other models a positive value, indicating how many more units likely the best model was compared with other models. Thus the smaller the relative AICc the better the adjusted fit to the data, with the best model having a value of 0. A relative AICc of 4 means that the data are $e^4$ – approximately 50 times – more probable under the best model compared to the other model tested, after taking into account the difference in number of free parameters (Killeen, Sanabria, and Doglov, 2009). In order to normalize relative AICc, Akaike weights were determined for each model. Akaike weights were used in model averaging and evaluate the likelihood that a model was the best model, given the data, relative to all models tested. To calculate Akaike weights, we first calculated the relative likelihood of a model, which is $e^{-0.5 \times \text{Relative AICc for that model}}$. The Akaike weight for a model is just the relative likelihood of the model, as calculated above, divided by the sum of these values across all models. Therefore an Akaike weight of ~1.0 indicates a ~100% likelihood a model was the best model tested, given the data. Akaike weights greater than 0.50 (very conservative) is our criterion for claiming strong support for one model over another.

**Results**

*Control/Vehicle Discount Functions.* Figure 1 shows mean log initial-link response ratios as a function of log terminal-link delay ratios for each strain responding under mixed and multiple schedules during non-injected control conditions and following vehicle administration. Mean log response ratios were a decreasing linear function of log delay ratios, as expected, but the height and steepness of the function depended on the strain and stimulus arrangement. Discount functions for the BALB/c mice displayed higher y-intercepts and steeper slopes than the C57Bl/6 mice, independent of schedule, while discount functions for the C57Bl/6 mice had higher y-intercepts and steeper slopes under the multiple relative to the mixed schedule. The mean deviation between log initial-link response ratios during control conditions and in vehicle-only conditions was 0.07, suggesting that the injection of vehicle had a negligible effect on preference. Because data collected following vehicle administration did not differ from non-injected control
for mice of either strain, the best model under non-injected control conditions served for data collected following vehicle administration (described next).

*Model Comparison: BALB/c.* When the model comparison approach was applied to control data (Pope et al., submitted), AICc indicates that the best model for the BALB/c mice (Table 2, top) is to use a single estimated value of reinforcer magnitude and delay sensitivity for individual subject data collected under each schedule (i.e., there is no effect of schedule; $s_M\text{ Constant, } s_D\text{ Constant}$). Specially, the model that best traded off RSS and free parameters, according to AICc, is the model that uses a single estimate of each parameter to serve across mixed and multiple schedules for an individual subject ($\text{AICc } = -457.3$, Akaike weight = 0.96). This is confirmed in Fig. 1 (Top panels); the discount functions under the mixed and multiple schedules for the BALB/c mice very nearly superpose, indicating no effect of schedule on either parameter.

Drugs can affect any one of the parameters provided by the GML, alone or in combination, and may affect them differentially under each schedule arrangement. For the BALB/c mice, the best model (lowest AICc, highest Akaike weight; Table 1 bottom) following d-amphetamine administration allowed only changes in $s_d$ as a function of d-amphetamine dose, and this change was allowed to vary independently for each schedule within an individual subject ($s_M\text{ Constant, } s_D\text{ Both}$; RSS = 4.49; AICc = -2562.3; Akaike weight ~1.0). All other models allowing different combinations of parameters to be held constant or vary across schedule and dose provided higher AICc and lower Akaike weights. Hence, the model that best traded off RSS and free parameters for the BALB/c mice, according to AICc and Akaike Weights, was the model that allowed dose-related changes in delay sensitivity, and to differing extents across schedule, while holding sensitivity to reinforcer magnitude constant at control values across dose and schedule.

*Model Comparison: C57Bl/6 Mice:* For the C57Bl/6 mice in contrast, the best model for control data (Pope et al., submitted) required a separate estimate of sensitivity to reinforcer magnitude and delay ($s_d$ and $s_m$) under each schedule to describe performance of an individual subject (Table 3 top, $s_M\text{ Vary, } s_D\text{ Vary}$). All other models tested provided poorer fits, as indexed by RSS (All RSS > 0.21). Additionally, AICc indicated that allowing both parameters to vary freely as a function schedule significantly improved fits relative to all other models tested, which estimated fewer parameters (AICc = -413.1; Akaike weight ~1.0). According to this model, sensitivity to reinforcer magnitude and delay were higher under the multiple relative to the mixed schedule. This can be seen in Fig. 1 (bottom panel); the multiple schedule produced a mean discount function with a higher y-intercept and steeper slope than the mixed schedule.
Following *d*-amphetamine administration, the best-fitting model for the C57Bl/6 mice (Table 3, bottom), according to AICc, allowed both \(s_m\) and \(s_d\) to vary freely from control values as a function of dose and differentially across the two schedule arrangements to describe performance of an individual subject (\(s_m\) *Both*, \(s_d\) *Both*; RSS = 1.74; AICc = -2408.1; Akaike weight ~1.0). All other models tested provided poorer fits, as indexed by RSS and AICc indicates that allowing both parameters to vary freely as a function of dose and differentially across schedule significantly improved fits relative to all other models tested, which estimated fewer parameters.

*Model Comparison: Summary.* Figure 2 (left column) shows log initial-link response ratios (LLR/SSR) as a function of log reinforcer delay-ratios (LLR/SSR) for the BALB/c mice following each dose of *d*-amphetamine and the predictions from the best-fitting GML model (Table 2). Graph A shows obtained and predicted discount functions for each dose of *d*-amphetamine for BALB/c mice under the mixed schedule, while graph B shows performance under the multiple schedule. Note that the y-intercepts of the functions do not significantly change as a function of dose and are not different across schedule (i.e., no change in sensitivity to reinforcer magnitude), in accordance with the best-fitting model. The steepness of the functions’ slope, however, become shallower with increasing doses of *d*-amphetamine and become shallower at lower doses under the mixed schedule (A) relative to the multiple (B) (i.e., delay sensitivity) for BALB/c mice.

The right column of figure 2 shows these discount functions and predictions from the best-fitting GML model for the C57Bl/6 mice (Table 3). *d*-Amphetamine dose-dependently increased the y-intercepts of the discount functions under the mixed (C) and decreased y-intercepts under the multiple schedule (D) (i.e., magnitude sensitivity), while the function became steeper under the mixed and shallower under the multiple. (i.e., delay sensitivity).

To better illustrate dose-effect relationships under each schedule as a function of reinforcer delay, figure 3 shows log initial-link response-ratios for BALB/c mice as a function of dose for representative terminal-link delays to the larger reinforcer. In accordance with the best-fitting model, response allocation at the 1.25s delay (i.e., reflecting \(s_M\) in Eq. 1; Graph A) shows negligible changes as a function of dose under both schedules. Again in accordance with the model-comparison approach, *d*-amphetamine dose-dependently increased preference for the larger reinforcer as delay lengthened, and this increase occurred under both schedules. That is, as the dose of *d*-amphetamine increased, preference for the larger reinforcer also increased, and this occurred to a greater extent as delays lengthened, indicating that the rate of delay discounting decreased. In addition, the increase in choice for the larger reinforcer at the two longest delays (Graphs C & D) is greater and occurs at lower doses under the mixed schedule (squares) than the multiple (triangles) schedule, indicating that the rate of discounting decreased to a greater extent under the mixed.
Figure 4 shows the same graphs for the C57Bl/6 mice. In accordance with the best-fitting model, response allocation at the 1.25s delay (Graph A) shifted towards the larger reinforcer in a dose-dependent manner dose under the mixed (squares), while shifting towards the smaller reinforcer under the multiple schedule (triangles). A reverse pattern occurred at the longer delays (Graphs B-D). Preference shifted in a delay- and dose-dependent manner towards the smaller reinforcer under the mixed schedule, while shifting towards the larger reinforcer under the multiple. That is, as the dose of \(d\)-amphetamine increased, preference for the larger reinforcer decreased under the mixed schedule and did so to greater extents as delays lengthened. In contrast, under the multiple schedule, as the dose of \(d\)-amphetamine increased, preference for the larger reinforcer also increased, and did so to greater extents as delays lengthen. In summary, the y-intercepts of the discount function (i.e., magnitude sensitivity) and the rate of discounting increased under the mixed, while decreasing under the multiple, in dose-dependent fashions.

To provide an overall summary, figure 5 shows mean dose-effect functions for each of the parameters provided by the best-fitting GML model for the BALB/c mice (Graphs A & B) and C57Bl/6 mice (Graphs C & D). For the BALB/c mice, magnitude sensitivity \((s_m)\) was unaffected by dose or schedule (Panel A) but delay sensitivity \((s_d)\) dose-dependently decreased under each schedule, and at a greater rate under the mixed schedule. For the C57Bl/6 mice, magnitude and delay sensitivity decreased under the multiple schedule and increased under the mixed schedule in dose-related fashions.

Overall, the GML model comparison approach provided a parsimonious account of the mechanisms by which \(d\)-amphetamine affected preference for mice of each strain under different stimulus conditions. Additionally, the best-fitting models provided excellent descriptions of the data for each strain. For the BALB/c mice under control conditions, the best fitting model, on average, accounted for 91\% of the data under control conditions and an average of 75\% of the data across dose. For the C57Bl/6 mice under control conditions, the best-fitting model account for an average of 90\% of the data under control conditions and an average of 77\% of the data across dose.

**Discussion**

The importance of delay discounting to many socially important behavioral problems has led to investigations of the genetic, biochemical, and environmental mechanisms responsible for variations in the form of the discount function (e.g., Bickel et al., 2013; Mackillop, 2013). The experimental research in these areas, however, has yielded disparate results, raising important and difficult questions about Gene X Drug X Environment interactions in delay discounting. Differences in delay discounting among inbred rodent strains, which often differ along specific neurochemical dimensions, can be augmented or attenuated depending on the procedure under which preference is
assessed (e.g., Stein et al., 2012). \(d\)-Amphetamine has been shown to increase (Cardinal et al., 2000; Pitts & McKinney, 2005; Slezak & Anderson, 2011; Slezak et al., 2013; van Gaalen et al., 2006; Winstanley et al., 2003, 2005) and decrease (Cardinal et al., 2000; Evenden & Ryan, 1996; Slezak & Anderson, 2009) preference for larger, delayed reinforcers depending upon the strain of mouse in question (Huskinson et al., 2012), the presence or absence of signaling delays to reinforcement (Cardinal et al., 2000; Slezak & Anderson, 2009), and the progression in which delays to the larger reinforcer are presented (Maguire et al., 2014; Tanno et al., 2014). The present study was designed to investigate potential interactions by comparing the effects of \(d\)-amphetamine delay discounting by two inbred mouse strains under different signaling arrangements using a procedure that randomized the terminal-link delays to the larger reinforcer across components of a session.

For mice of both strains, preference adjusted rapidly to changing reinforcer delay-ratios as they changed frequently and randomly across components of a session. In our previous study (Pope et al., submitted, Fig 4), a GML-based lag analysis confirmed that, overall, response allocation for each subject was increasingly sensitive to the delay currently in effect during a particular component, while sensitivity to the previous delay diminished towards zero after only twelve trials. Similar rapid adjustments in choice has also been reported with simple choice, i.e., when reinforcer ratios, but not reinforcer delays, change rapidly and randomly (Davison & Baum, 2007; Grace et al., 2003; Grace & McLean, 2006; Ta et al., 2008). These findings are important first because it shows that such a concurrent-chains procedure the effects of genetic background, signaling conditions, and drug administration on delay discounting without additional complications or training time (see also Beeby & White, 2013; Grace, Sargisson & White, Pitts & Febbo, 2004; Pope et al., submitted). Second, the randomized presentation of terminal-link delays to reinforcement minimizes the degree and direction of hysteresis present in strictly alternating sequences of within-session delay progressions (Maguire et al., 2014; Tanno et al., 2014). Randomizing presentations of delays within and across-sessions may be especially warranted when examining drug effects, as drugs may exert different effects depending on the degree and direction of control over choice by the order of previously experienced delays (i.e., carry-over; Tanno et al., 2014; Maguire et al., 2014). Finally, randomization of terminal-link delays within and across sessions may be better suited for examining the role of stimulus conditions in modulating the effects of amphetamine on delay discounting (Pope et al, submitted). Determining the influence of stimulus conditions on the effects of amphetamine under steady-state procedures, in which delays systematically and invariably increase or decrease within and across-sessions, may be difficult if stimulus control by the order of delay presentation is the stronger controlling variable (Krageloh & Davison, 2003; Maguire et al., 2014; Tanno et al., 2014; e.g., Cardinal et al., 2000; Slezak & Anderson,
When the delays to reinforcement change frequently and randomly within- and across-sessions there can be no stimulus control by the order of delay-progression. As demonstrated in the current study, eliminating control by the order of delay progression may allow stronger or weaker levels of stimulus control to develop, depending on the arranged conditions, which may in turn permit the emergence or detection of differential effects of \( d \)-amphetamine.

A major obstacle in interpreting the effects of genetic, pharmacological, and environmental interventions on delay discounting lies in separating the influence of relative reinforcer magnitude and delay. The use of mathematical models in an attempt to characterize these interacting influences has proven fruitful in studying the effects of neurobiological interventions on delay discounting (Valencia-Torres et al., 2012; Ho et al., 1999; Pitts & Febbo, 2004; Pitts, 2014). The quantitative framework provided by the GML allows for a precise approach to analyzing \( d \)-amphetamine’s mechanisms of action in terms of an interaction between strain and reinforcement schedule. Previous studies have reported that BALB/c mice discount at a higher rate compared to C57Bl/6 mice (e.g., Otobe & Mankin, 2004). Studies using other species have shown that \( d \)-amphetamine alters preference through changes in sensitivity to reinforcer delay (e.g., Ta et al., 2008), magnitude (e.g., Maguire et al., 2008) or a combination of these (e.g., Pitts & Febbo, 2004). Changes in these mechanisms could, in turn, depend on an interaction between strain and the signaling conditions under which choice was assessed (Pope et al., submitted). The model comparison approach provided an opportunity to consider individual subject differences across these variables in terms of the goodness-of-fit and number of free parameters (see also Sanabria & Killeen, 2009).

Similar to Huskinson et al. (2012), the model-comparison approach revealed that the effects of \( d \)-amphetamine on the form of the discount function depended upon mouse strain. Further, the behavioral mechanisms through which amphetamine exerted its effects on delay discounting differed between the two strains: for the BALB/c mice, sensitivity to reinforcer delay was solely affected following \( d \)-amphetamine, while both sensitivity to reinforcer magnitude and delay were affected for the C57Bl/6 mice (Fig 5 & 7). Most important, however, the present study was able to reproduce, within- and across-strain, increases (Cardinal et al., 2000; Pitts & McKinney, 2005; Huskinson et al., 2012; Slezak & Anderson, 2009; Tanno et al., 2014) and decreases (Evenden & Ryan, 1996; Maguire et al., 2014; Slezak & Anderson, 2009; Tanno et al., 2014) in preference for larger-delayed reinforcers all within a single study and thereby it was possible to identify the conditions under which these swings in preference occur. These increases and decreases in preference were dependent on an interaction with genotype and the degree of stimulus control exerted by the conditions under which choice was assessed.
Under \(d\)-amphetamine, the rate of discounting decreased, within-subjects, for BALB/c mice both when components were differentially and nondifferentially signaled, and this occurred in the absence of any significant changes in magnitude sensitivity (Fig. 7; e.g., Cardinal et al., 2000; Tanno et al., 2014). Although the effects of amphetamine on the form of the discount function were qualitatively similar under differentially and nondifferentially signaled components, there were notable quantitative differences (c.f., Slezak & Anderson, 2009). Preference for larger, delayed reinforcers increased at a greater rate as a function of \(d\)-amphetamine dose under the mixed compared to the multiple schedule. In contrast, amphetamine decreased the rate of discounting for the C57Bl/6 mice when components were differentially signaled, but also decreased sensitivity to reinforcer magnitude, that is choice for the larger-reinforcer at the shortest delays (i.e., \(y\)-intercept; Fig 3, 6, & 7) (e.g., Maguire et al., 2014; Slezak & Anderson, 2009; Tanno et al., 2014). When components were nondifferentially signaled, however, \(d\)-amphetamine had the opposite effects on sensitivity to reinforcer magnitude and delay for the C57Bl/6 mice (Fig. 3, 4, & 7). The rate of discounting increased, and thus preference for larger, delayed reinforcer decreased, but choice for the larger-reinforcer at the shortest delays increased (e.g., Cardinal et al., 2000; Van Galeen et al., 2006).

An alternative way of viewing these effects is by noting that the effects of amphetamine depended upon the baseline levels of control by relative reinforcer magnitude and delay. Such a baseline-dependent effect is, similar to Huskinson et al.’s (2012), who compared the effects of amphetamine on delay discounting in Lewis and Fischer 344 rats, and Maguire et al. (2014) and Tanno et al., (2014), who analyzed \(d\)-amphetamine’s effects under different delay-progressions. In the present study baseline differences in delay discounting represented a within-subject, genotype X signaling condition interaction. For the BALB/c mice, baseline sensitivity to reinforcer magnitude and delay was high under both schedules, while for the C57Bl/6 mice, the enhanced stimulus control over preference provided by differentially signaling components increased sensitivity to reinforcer magnitude and delay compared to when components were nondifferentially signaled. Under baseline conditions in which sensitivity to reinforcer magnitude and/or delay, or control over initial-link choice by relative-terminal-link reinforcer dimensions, was relatively high (i.e., BALB/c mice both schedules; C57Bl/6 mice multiple schedule) amphetamine decreased sensitivity to reinforcer delay (BALB/c mice both schedules), or both sensitivity to reinforcer magnitude and delay (C57Bl/6 mice, multiple schedule). When baseline sensitivity to reinforcer magnitude and/or delay were relatively low (C57Bl/6 mice, mixed schedule), amphetamine increased both sensitivity to reinforcer magnitude and delay. Interestingly, these results are somewhat similar to results reported by Maguire et al. (2014) and Tanno et al. (2014) examining the effects of \(d\)-amphetamine under ascending and descending delay-progressions (see also Huskinson et al., 2012). In those studies, as
in the current study, when baseline preference for larger, delayed reinforcers was relatively low (i.e., ascending-progression), amphetamine increased choice for larger, delayed reinforcers, and when baseline preference for larger delayed reinforcer was relatively high (descending-progression), amphetamine decreased preference for larger, delayed reinforcers. The similarities between these studies with the current study may suggest that amphetamine’s effects do not depend upon the order of delays per se, as the current study used a randomized-delay progression, but depends upon the degree of baseline control by the current vs. previous component reinforcer delays, which can be altered by delay-order, the schedule of reinforcement, and a subject’s genetic background.

For the BALB/c mice, the high delay sensitivity decreased following d-amphetamine administration, but control by relative reinforcer magnitude was not significantly altered under either schedule. Thus, the observation that these two reinforcement dimensions independently control choice (see Pope et al., submitted) was also seen in d-amphetamine’s effects. The greater decrease in delay sensitivity observed when components were nondifferentially signaled is reminiscent of research on the effects of drugs on behavior under differing degrees of baseline discriminative control (e.g., Laties & Weiss, 1966, 1972); the delay-specific stimuli shifted d-amphetamine’s dose-effect curve to the right by a factor of approximately 2 at the longer delays. Interestingly, in our previous study (Pope et al., submitted), the multiple schedule increased initial levels of sensitivity to delay and the speed at which it reached final levels across blocks of a component relative to the mixed schedule (Kragelöö & Davison, 2003). That is, when components were differentially signaled, initial component choice was under a greater degree of discriminative control by the (otherwise unpredictably) changing reinforcement delays. Thus, the delay-specific stimulus increased initial levels delay sensitivity, accelerated the acquisition of preference, and attenuated the effect of d-amphetamine as compared with the mixed schedule in which no stimuli other than experience with early trials in a block predicted the reinforcer delays in the current component.

Quite a different pattern appeared in the C57Bl/6 mice: both sensitivity to reinforcer magnitude and delay were affected following d-amphetamine administration and their correlation depended on the signaling condition under which choice was assessed. When d-amphetamine increased sensitivity to one dimension of reinforcement (e.g., magnitude) under the mixed schedule, sensitivity to the other dimension of reinforcement also increased and this occurred when baseline levels of each were relatively low. The inverse pattern occurred when sensitivity to reinforcement was relatively high during baseline conditions, that is, under the multiple schedule. Pitts and Febbo (2004), Maguire et al., (2014), and Tanno et al. (2014) all found similar correlated changes in y-intercepts and slopes of the discount function following stimulant administration, but under different procedural arrangements. The co-
dependency observed for the C57Bl/6 mice suggests that \textit{d}-amphetamine’s effects on preference were determined by an interaction between relative reinforcer magnitude and delay that was modulated by the degree of stimulus control provided by the schedule of reinforcement (for a discussion, see Pope et al., submitted).

\textit{Conclusions}. Since it was not necessary to incorporate a separate term for individual mice, it can be concluded that the effects appeared similarly across all mice in the same strain. This point to the power of using an inbred strain, in which all mice are near homozygotes—genetic determinants were highly homogeneous. It would be interesting to attempt the same model-fitting approach in an outbred strain to determine if separate terms are required for individuals.

The results of the current study offer evidence that a procedure which randomizes delay-presentation across components of a session, is a powerful technique for assessing the effects of genetic, pharmacological, and environmental interventions on delay discounting. The elimination of systematic carry-over effects (i.e., delay-order effects) is important in resolving discrepancies across studies of delay discounting. As an indication of the utility of this technique, we were able to produce the two contrasting effects of \textit{d}-amphetamine on the form of the discount function in a single experiment. In doing so systematically it was possible to conclude that these two patterns are orderly, reproducible, and dependent upon the genetic background and stimulus support for behavior. For C57Bl/6 mice, \textit{d}-amphetamine increased both the low baseline preference for a larger reinforcer when delays were equated (i.e., magnitude sensitivity) and the low baseline discount rate (frequently taken as a marker of impulsivity) when components were nondifferentially signaled. \textit{d}-Amphetamine had the opposite effect when components were differentially signaled, that is, when baseline levels of sensitivity to reinforcer magnitude and delay were higher. In contrast, response allocation by the BALB/c mice, which was highly sensitive to both relative reinforcer magnitude and delay during baseline, showed a \textit{d}-amphetamine-induced decrease in sensitivity to relative reinforcer delay only, (i.e., amphetamine decreased impulsivity), blunting of this decrease by the presence of exteroceptive stimuli correlated with reinforcement, and no impact on magnitude sensitivity. The results of the present study extend recent work on genetic and environmental influences in determining the effects of \textit{d}-amphetamine on delay discounting and support a baseline-dependent effect of \textit{d}-amphetamine that depends upon and Gene X Environment interaction.

\textbf{Acknowledgement}

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References


Table 1.

GML Model Comparison BALB/c: Control

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GML Model Comparison BALB/c: $d$-Amphetamine

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1 The results of the GML model comparison for the BALB/c mice under control conditions (top table) and following $d$-amphetamine administration (bottom table). The first column in the top table specifies which of the GML parameters was allowed to vary across schedule to describe baseline performance of an individual subject. The first column in the bottom table specific which of the GML parameters was allowed to vary across schedule and dose to describe performance of an individual subject following drug administration. For both tables, RSS is the residual sum of squares over all mice, $k$ is the number of free parameters in the model. As each model was fitted to data from each individual mouse, a set of free parameters was estimated for each mouse under control conditions and following drug administration. Thus, for the BALB/c mice under control conditions, $k = 8$ mice X (2 GML parameters + schedule-sensitive GML parameters) + 1 variance parameter and n is the total number of observations= 8 rats X 2 schedules of reinforcement X 6 reinforcer delays = 96. Following $d$-amphetamine administration, $k = 8$ mice X (2 GML parameters + dose-sensitive GML parameters X 6 doses) + 1 variance parameter and n is the total number of observations= 8 rats X 2 schedules of reinforcement X 6 reinforcer delays X 6 doses = 576. The final column in both tables shows Akaike weights. Data for the model with the lowest AICc and highest Akaike weight are underlined for control conditions and follow $d$-amphetamine administration. The row labeled None in the bottom table gives statistics when all parameters were fixed over $d$-amphetamine at the values determined by the best model under control conditions. See text for further explanation.
Table 2.

GML Model Comparison C57Bl/6: Control

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GML Model Comparison C57Bl/6: $d$-Amphetamine

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The results of the GML model comparison for the C57Bl/6 mice under control (top table) and following $d$-amphetamine administration (bottom table). All information provided in the table is identical to Table 2 for the BALB/c mice, the only difference is that there were only 7 C57Bl/6 mice, not 8, making the total number of observations under control conditions n = 84, and following $d$-amphetamine n = 504.
Figure 1.

BALB/C

C57BL/6
Figure 2.

A

D-Amphetamine (B MIXED)

- Log\textsubscript{10} Response Ratio (LLR/SSR)
- Log\textsubscript{10} Delay Ratio (LLR/SSR)
- Control (0 mg kg\textsuperscript{-1} AMPH)
- 0.1 mg kg\textsuperscript{-1} AMPH
- 0.17 mg kg\textsuperscript{-1} AMPH
- 0.3 mg kg\textsuperscript{-1} AMPH
- 1.0 mg kg\textsuperscript{-1} AMPH
- 1.7 mg kg\textsuperscript{-1} AMPH

B

D-Amphetamine (B MULT)

- Log\textsubscript{10} Response Ratio (LLR/SSR)
- Log\textsubscript{10} Delay Ratio (LLR/SSR)
- Control (0 mg kg\textsuperscript{-1} AMPH)
- 0.1 mg kg\textsuperscript{-1} AMPH
- 0.17 mg kg\textsuperscript{-1} AMPH
- 0.3 mg kg\textsuperscript{-1} AMPH
- 1.0 mg kg\textsuperscript{-1} AMPH
- 1.7 mg kg\textsuperscript{-1} AMPH

C

D-Amphetamine (C MIXED)

- Log\textsubscript{10} Response Ratio (LLR/SSR)
- Log\textsubscript{10} Delay Ratio (LLR/SSR)
- Control (0 mg kg\textsuperscript{-1} AMPH)
- 0.1 mg kg\textsuperscript{-1} AMPH
- 0.17 mg kg\textsuperscript{-1} AMPH
- 0.3 mg kg\textsuperscript{-1} AMPH
- 1.0 mg kg\textsuperscript{-1} AMPH
- 1.7 mg kg\textsuperscript{-1} AMPH

D

D-Amphetamine (C MULT)

- Log\textsubscript{10} Response Ratio (LLR/SSR)
- Log\textsubscript{10} Delay Ratio (LLR/SSR)
- Control (0 mg kg\textsuperscript{-1} AMPH)
- 0.1 mg kg\textsuperscript{-1} AMPH
- 0.17 mg kg\textsuperscript{-1} AMPH
- 0.3 mg kg\textsuperscript{-1} AMPH
- 1.0 mg kg\textsuperscript{-1} AMPH
- 1.7 mg kg\textsuperscript{-1} AMPH
Figure 3.

A. 1.25-s Delay

B. 6.3-s Delay

C. 31.62-s Delay

D. 70.79-s Delay

Log₁₀ Response Ratio (LLR/SSR) vs. d-amphetamine dose (mg kg⁻¹ i.p.)

Legend:
- MIXED
- MULT

Y-axis: Log₁₀ Response Ratio (LLR/SSR)
X-axis: d-amphetamine dose (mg kg⁻¹ i.p.)
Figure 4.
Figure 5.
**Figure Captions**

**Figure 1.** Mean log response ratios as a function of log delay-ratios for BALB/c mice (top) and C57Bl/6 mice (bottom) responding under mixed and multiple schedules. For the both strains, the square symbols represent mean response ratios averaged over the final consecutive control sessions when mice responded under the mixed schedule, while the triangle symbols represent mean response ratios averaged over the final 5 consecutive control sessions when mice responded under the multiple schedule. The solid line represents mean response ratios taken from three sessions of vehicle administration when mice responded under the mixed schedule, while the dashed line represents mean response ratios averaged over three sessions of vehicle administration. When error bars are present, they represent +/- 1 SEM.

**Figure 2.** Mean obtained (symbols) and predicted (lines) log response ratios as a function of log delay ratios for each dose of D-amphetamine administered. The panels show obtained and predicted response ratios following each dose of amphetamine for BALB/c (Panels A & B) and C57Bl/6 (Panels C & D) mice responding under mixed and multiple schedules. The predicted response ratios (lines) were derived from the best-fitting models for BALB/c (Table 2) and C57Bl/6 mice (Table 3), respectively. Error bars represent +/- 1 SEM. See text for further explanation.

**Figure 3.** Mean log response ratios as a function of D-amphetamine dose for representative delays to the larger reinforcer for BALB/c mice responding under mixed (squares) and multiple (diamonds) schedules. Panel A shows log response ratios as a function of D-amphetamine dose at the 1.25 s delay, Panel B at the 6.3 s delays, Panel C at the 31.62 s delay, and Panel D at the 70.79 s delay, under mixed and multiple schedules, respectively. Error bars represent +/- 1 SEM. See text for further explanation.

**Figure 4.** Mean log response ratios as a function of D-amphetamine dose for representative delays to the larger reinforcer for C57Bl/6 mice responding under mixed (squares) and multiple (diamonds) schedules. Panel A shows log response ratios as a function of D-amphetamine dose at the 1.25 s delay, Panel B at the 6.3 s delays, Panel C at the 31.62 s delay, and Panel D at the 70.79 s delay, under mixed and multiple schedules, respectively. Error bars represent +/- 1 SEM. See text for further explanation.

**Figure 5.** Mean parameter estimates from the best-fitting GML models for BALB/c (Panels A & B) and C57Bl/6 (Panels C & D) mice responding under mixed (squares) and multiple (diamonds) schedules. Panels A & C show means sensitivity to reinforcer magnitude for BALB/c (Panel A) and C57Bl6/ (Panel C) under mixed and multiple schedules. Panels B and D show mean sensitivity to reinforcer delay for BALB/c (Panel B) and C57Bl6/ mice (Panel D) under mixed and multiple schedules. Error bars represent +/- 1 SEM. See text for further explanation.