Choice in C57BL/6n Mice: Behavioral and Pharmacological Mechanisms of Concurrent Schedule Performance

by

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Abstract

Evidence from clinical and laboratory studies converge on the same neurochemical and neuroanatomical substrates underlying choice behavior. The findings suggest that behavioral adjustments in choice procedures are the product of specific neurochemical pathways, and DA, NE, and 5-HT neurotransmitter systems in the frontal cortex might be especially important (Robbins & Roberts, 2007). However, the findings are either mixed (e.g., dopaminergic agonist and RL) or poorly explored in mice (e.g., noradrenergic agonist and RL). To examine the impact of three monoamine transporter blockers, the behavior of mice was established under concurrent schedules of reinforcement. Characteristic features of concurrent responding were seen, including equal allocation of responding when the probability of reinforcement for one alternative was 0.5 and preference (i.e., bias) for the richer alternative when the reinforcer probabilities were unequal. Undermatching was seen, a finding typically observed with concurrent schedules and the changeover rate was highest when the two alternatives produced the same reinforcement probabilities. To examine rate-dependent effects, mice producing high- and low response rates were examined separately. For the high rate group, one of the doses tested for both *d*-amphetamine and atomoxetine increased total responses in the equal reinforcement probability condition. Escitalopram increased response rates in the equal reinforcement condition but not the number of reinforcers or response-reinforcer ratio. In the unequal reinforcement ratio condition none of the doses tested produced a significant increase in responding or reinforcement or change the proportion of responses made on the rich.

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5-HT	serotonin
ADHD	attention deficit hyperactivity disorder
ASS	attentional set shifting
ATOM	atomoxetine
BMT	behavioral momentum theory
CUS	chronic unpredictable stress
DA	dopamine
DEC	dose effect curve
DESIP	desipramine
EDS	extradimensional shift
IDS	intradimensional shift
MeHg	methylmercury
NE	norepinephrine
OFC	orbitofrontal cortex
PFC	prefrontal cortex
RL	reversal learning
S+	reinforcement stimulus function
S-	non-reinforcement stimulus function
SNRI	selective noradrenergic reuptake inhibitor

SSRI selective serotonin reuptake inhibitor

Chapter I Behavioral Flexibility in C57BL/6n Mice: Behavioral and Pharmacological Mechanisms of Choice Behavior

Experimental Models of Choice

Reversal Learning. A model of choice that has received much attention in experimental models of drug and toxicant behavioral effects is reversal learning (RL) (Izquierdo, Brigman, Radke, Rudebeck, & Holmes, 2016). In the typical RL procedure as used in neuropsychiatric assessment, participants may be presented with two stimuli, one of which is arbitrarily designated as correct. A consequence such as the word "Correct" may follow selection of the arbitrarily designated target stimulus. After differential responding is established, the stimulus functions are reversed: participants must select the stimulus that previously was incorrect (i.e., previous non-target stimulus) and must avoid the stimulus that was correct previously (Cools, Clark, Owen, & Robbins, 2002). In RL, successful performance requires sensitivity to the original reinforcement contingency and then responding must change when the stimulus functions are reversed. Eventually, behavior is reallocated to the previously incorrect alternative in accordance with the shift in contingencies. In essence, successful RL requires both extinction of the previously reinforced response and acquisition of the newly reinforced (Robbins & Roberts, 2007). Reversal learning is related to another class of experimental procedures that require "attentional set shifting" (Chudasama & Robbins, 2006; Clark, Cools, & Robbins, 2004). Attentional set shifting (ASS) occurs when reinforcement is first correlated with a particular stimulus dimension (e.g., color) and then becomes correlated with a previously irrelevant dimension (e.g., shape). This is also called an extradimensional shift (EDS). A shift from the correct stimulus to a different stimulus on the same stimulus dimension (e.g., red to green) is considered an intra-dimensional shift (IDS). The shift in stimulus function for one stimulus, say

red light, from non-reinforcement (S-) to reinforcement (S+) paired with an opposite shift in stimulus function for a second stimulus (i.e., from S+ to S -), say green light, is considered a discrimination reversal. Further, and importantly, in reversal learning when the response-reinforcement contingencies are switched (i.e., green to red) it is classified as an IDS.

The reversal learning task used in human psychiatric assessment is similar to versions used in nonhuman primate studies. Other, more simplified (i.e., using only discrimination reversals, IDS, EDS, or a combination) non-human analogues of this task have been developed to assess reversal learning in other laboratory models (for a review see Izquierdo & Jentsch, 2012). Generally, the sensory modality and topography of the response used in reversal learning are tailored to the species being studied. For example, visual discriminations among multi-colored response keys may be used with pigeons (Laude, Stagner, Rayburn-Reeves, & Zentall, 2014; Ploog & Williams, 2013). With rodents, spatial or visual discriminations (Paletz, Day, Craig-Schmidt, & Newland, 2007; Reed, Paletz, & Newland, 2006) or olfactory discriminations with olfactory cups (Birrell & Brown, 2000; Mihalick, Langlois, Krienke, & Dube, 2000) are often used. Visuo-spatial discriminations among physical objects or computerized touchscreens are often used in human and primate research (Dias, Robbins, & Roberts, 1996b; Rolls, Critchley, Mason, & Wakeman, 1996). However, the aforementioned sensory modalities and response operanda are not mutually exclusive to the species listed as they can be used in different combinations across species.

When identifying the appropriate methods to address a specific research question several considerations must be made. For example, if a researcher were interested in identifying the maximum number of discriminations possible they might cater the sensory modality being used to the species being studied. Galizio and colleagues have developed an olfactory span task with

which they can train rats to perform up to 80 novel olfactory discriminations within a single 6 hour experimental session (April, Bruce, & Galizio, 2013). Although this method is well suited for such purposes it might not be the ideal method for, say, the assessment of acute administration of pharmacological compounds with the consideration of drug half-life and the development of full dose-response profiles. Using a procedure in which subjects were required to learn a discrimination that remained consistent across performance days as well as perform repeated discriminations on acquisition days, Galizio and colleagues were able to study reversal learning and performance of olfactory discriminations during acute drug administration sessions (Galizio, Miller, Ferguson, McKinney, & Pitts, 2006). In this approach, sessions consist of up to 24 trials in which two scented cups are presented to the subject and responses made to either the correct (S+) or incorrect (S-) cup are video recorded. New cups are presented at the onset of each trial requiring a pre-session preparation of up to 48 scented cups for each subject being tested. In order to generate a chlordiazepoxide dose effect curve (DEC), Galizio and colleagues ran 19 to 65 pre-drug training sessions per subject along with 10 weeks of daily sessions in order to complete 4 administrations of 4 chlordiazepoxide doses and saline. This totaled 23 weeks or over 5 months of running 4 subjects per day M-F (i.e., approximately 6 hours per day). Both the procedure and time course of the discrimination and repeated reversal procedure used by Galizio and colleagues are similar to olfactory discrimination procedures used by other research groups (see, Bissonette et al., 2008; Colacicco, Welzl, Lipp, & Würbel, 2002; Garner, Thogerson, Würbel, Murray, & Mench, 2006; Mihalick et al., 2000).

Although successful in generating DEC for reversal learning, the aforementioned methods are both time and labor intensive. On the other hand, if one were to use automated procedures (e.g., MedPC programming and equipment) capable of running and recording visual

and auditory discrimination procedures for up to 16 subjects simultaneously it would eliminate extraneous pre-session preparation time and post-hoc review and coding of experimental events. This would eliminate approximately 5 hours per day. Further, the use of automated response recording equipment that records responses with the opening (or closing) of electronic switches can greatly reduce the chance of experimenter subjectivity when running and coding experimental events as well as reducing variability in the implementation of experimental conditions (i.e., time of day, session duration, etc.)

Concurrent Schedules. Choice can be studied in experimental settings by arranging separate reinforcement schedules between two response alternatives. This type of experimental procedure is known as a concurrent schedule (Ferster & Skinner, 1957). A variety of reinforcement schedules can be used in concurrent schedules arrangements. In concurrent ratio schedules, reinforcement is delivered according to the number of responses emitted. Once the specified ratio requirement has been met for either response alternative, reinforcement is delivered. Each schedule type can be programmed according to a fixed or variable value. Variable schedules arrange reinforcement according to a list of multiple values which all average to a central value. For example, a variable-ratio (VR) 10 schedule consists of a list of ratio values which averages 10 (i.e., on average the schedule arranges reinforcement every 10 responses). If the concurrent schedules are programmed dependently, then a probability gate determines which of the two reinforcement schedules will be programmed at the start of the experiment and following each reinforcement delivery. Once the programmed reinforcement schedule is completed, and a reinforcer is delivered, the probability gate then sets up the next reinforcer on the left or right according to the schedule of reinforcement associated with either side. For example, if the first schedule is programmed to, say, the left response alternative, the

reinforcement schedule associated with the right response alternative will not be active until the probability gate assigns a reinforcement cycle to the right side. This allows the proportion of reinforcers programmed on the two response operanda to be fixed while promoting response allocation, and thus exposure, to both reinforcement schedules by punishing exclusive responding. In concurrent schedule arrangements, the shift from the correct response device to a different response device on the same stimulus dimension (e.g., right to left) can be viewed as an intra-dimensional shift (IDS). The shift in stimulus function for one stimulus, say left nosepoke light, from non-reinforcement (S-) to reinforcement (S+) paired with an opposite shift in stimulus function for a second stimulus, say right nosepoke light (i.e., from S+ to S -), can be viewed as a discrimination reversal. In concurrent schedule arrangements, a changeover (CO) response away from the previous S+, now S-, to the new S+, previously S-, indicates sensitivity to changes in the environment and appropriate adaptation of response strategies, that is, behavioral flexibility (Lapiz, Bondi, & Morilak, 2007).

The Role of Monoamines in Choice

Dopamine and Choice

***Dopamine function*.** The orbitofrontal cortex (OFC) is a region richly innervated by dopaminergic projections to and from the nucleus accumbens (NA) (Volkow & Fowler, 2000). The OFC has been suggested to play a role in RL (Dias et al., 1996a; Dias, Robbins, & Roberts, 1997). Thus, one might predict that dopamine (DA) plays a significant role in RL. However, mixed findings have been reported for the role of DA in RL.

Pharmacological studies: dopaminergic agonist and antagonist. Robbins & Roberts (2007) have reported a dissociation between pre-frontal DA and RL. The dissociation between pre-frontal DA functioning and RL has been supported by lesion and acute drug studies with

humans and marmosets (Roberts et al., 1994; Rogers et al., 1999). For example, oxidopamine lesions to the orbital, dorsolateral and medial (Roberts et al., 1994) DA system in marmosets selectively improved EDS while showing no effect on visual or serial discrimination reversals. Also, Rogers et al. (1999) found that modulation of DA with systemic methylphenidate, a DA reuptake inhibitor, had little impact on RL in humans. On the other hand, several lines of research have reported that systemic DA modulation does influence RL performance in humans, vervet monkeys, rats, and mice. For example, human RL deficits have been reported following administration of D_2 receptor agonist (Cools et al., 2009). Also, following repeated cocaine treatment, which modulates DA levels throughout the central nervous system, RL deficits have been reported in vervet monkeys (Jentsch, Olausson, De La Garza II, & Taylor, 2002). Errors in RL were associated with a single acute dose of cocaine as well as with a history of chronic, repeated high-dose exposure (Jentsch et al., 2002), in the absence of differences in the original discrimination. Acute administrations of the D_2/D_3 receptor antagonist raclopride but not the D_1/D_5 receptor antagonist SCH 23390 also impaired RL in vervet monkeys (Lee, Groman, London, & Jentsch, 2007). In mice, reversal learning deficits have been reported following administration of D_2 antagonist (De Steno & Schmauss, 2009) and D_1 agonist (Izquierdo et al., 2006). In rats, oxidopamine lesions to the nucleus accumbens produced RL deficits (Taghzouti, Louilot, Herman, Le Moal, & Simon, 1985). Finally, rats gestationally exposed to MeHg show both RL deficits (Paletz et al., 2007; Reed et al., 2006) and hypersensitivity to acute doses of cocaine (Reed & Newland, 2009) and *d*-amphetamine (Rasmussen & Newland, 2001).

Pharmacological mechanisms: reinforcer efficacy. Much research has been conducted to investigate the behavioral role of DA in operant behavior. Some studies suggest that DA plays a role in signaling the value/efficacy of a reinforcer (Roesch, Calu, & Schoenbaum, 2007;

Schultz, 2007; Takahashi, Roesch, Stalnaker, & Schoenbaum, 2007). Roesch et al., (2007) measured the firing of dopaminergic neurons in the ventral tegmental area with differently valued rewards. The level of DA firing immediately preceding and following reinforcer delivery was positively correlated with the magnitude and immediacy of the reinforcer, respectively. In contrast, DA activity in the ventral striatum was associated with presentation of conditioned reinforcers (i.e., stimuli paired with reinforcement delivery). Moreover, dopaminergic activity in the ventral tegmental area is higher when reinforcer delivery follows the presentation of a discriminative stimulus associated with extinction and dopamine levels are lower when the presentation of a discriminative stimulus associated with reinforcement is instead followed by extinction, also called prediction errors (Roesch et al., 2007). These studies have provided evidence for 3 distinct DA pathways involved in learning. Dopamine activity in the ventral tegmental area is associated with reward value and prediction-error (Roesch et al., 2007), DA activity in the dorsolateral striatum is involved with discrimination (Takahashi et al., 2007), and DA activity in the ventral striatum has been associated with conditioned reinforcement (Schultz, 1998, 2002, 2007). If reward value, prediction-error, conditioned reinforcement, and discrimination are all contingent on DA activity, then increasing DA tone might enhance reinforcer efficacy thereby facilitating performance in a behavioral task emphasizing behavioral adjustment to shifts in response-reinforcement and response-extinction contingencies.

Dopamine and reversal learning: implications for current experiment. While studies using systemic DA modulation often report changes in RL performance, the nature of the change in performance associated with agonist and antagonists appear mixed in many species. That is, in some instances systemic administration of DA agonists (Cools et al., 2009; Izquierdo et al., 2006; Jentsch et al., 2002) or antagonists (Lee et al., 2007; Taghzouti et al., 1985) impair RL

performance, while in limited instances systemic DA modulation has no effect on RL (Roberts et al., 1994; Rogers, Blackshaw, et al., 1999). These seemingly disparate findings might be reconciled by considering the role of striatal DA in reversal learning. The only study that reported DAergic manipulation limited to PFC areas (i.e., orbital, dorsolateral and medial) resulted in no change in RL performance (Roberts et al., 1994). Moreover, the striatum is involved with associative learning (Takahashi et al., 2007), and DA activity in the ventral striatum has been associated reinforced behavior (Robbins, Cador, Taylor, & Everitt, 1989: (Schultz, 1998, 2002, 2007).

Systemic administration of DA agonists might increase dopamine release following reinforcer delivery. Greater DA release might in turn enhance the strengthening effect of reinforcer delivery on reinforced behavior thereby increasing task engagement, relative to non-drug (control) performance. A dose-dependent increase in task engagement would be reflected by an increase in the total number of responses made during a concurrent-schedule session.

The strengthening effect of dopamine release following reinforcement delivery can be extended to the development of choice in concurrent schedule procedures arranging unequal reinforcement rates. Takahashi et al, (2007) found that DA activity in the dorsolateral striatum was associated with the development of discriminative responding in which greater DA activity occurs following responses paired with reinforcer delivery but not to responses paired with extinction. In concurrent schedule procedures the proportion of responses that are made to each response device provide a metric of choice.

Norepinephrine and Choice

***Norepinephrine function*.** The noradrenergic system is thought to mediate several behaviors including attention, behavioral activation, and alertness (Lapiz et al., 2007). The effect

of noradrenergic manipulation on concurrent VR performance in mice has not been explored but in other species, the effects of noradrenergic manipulation have been tested using a wide range of procedures.

Pharmacological studies: noradrenergic agonist and antagonist. Both acute and chronic administration of desipramine (DESIP), a selective norepinephrine (NE) reuptake inhibitor (SNRI), improved reversal learning performance in a serial reversal learning task with rats (Seu & Jentsch, 2009). Administration of atomoxetine (ATOM), an SNRI, improved reversal performance without influencing discrimination performance in a 4-position discrimination task in rats (Emanuele Seu, Lang, Rivera, & Jentsch, 2009). Guanfacine, a selective alpha-2A adrenergic agonist, improved reversal learning in a visual object discrimination procedure in aged rhesus monkeys (Steere & Arnsten, 1997). In a similar line of research, chronic SNRI treatment has been found to alleviate laboratory analogues of attention deficit hyperactivity disorder (ADHD) symptoms such as inattention and impulsivity (Seu & Jentsche, 2009; Robinson et al., 2008). For example, ATOM has been found to reduce motor impulsivity and inattention in a stop signal reaction time task and 5-choice serial reaction time task without influencing perseveration (Robinson et al., 2008). The effects of SNRIs have also been assessed in ASS in which response allocation among concurrently available response alternatives must shift following IDS. Administration of atipamezole, an alpha2adrenergic autoreceptor antagonist, (Lapiz & Morilak, 2006), ATOM (Cain, Wasserman, Waterhouse, & McGaughy, 2011) and DESIP, (Lapiz et al., 2007), improved ASS performance in rats. Further, treatment with DESIP has been found to reverse chronic unpredictable stress (CUS)- induced set-shifting deficits (Bondi, Jett, & Morilak, 2010). Thus, noradrenergic agonists have been found to improve RL

and ASS performance in rodents. Moreover, NA agonists have been found to reduce motor impulsivity and inattention (Robinson et al., 2008; Seu & Jentsch, 2009).

Pharmacological mechanisms: motor impulsivity. Again, ATOM has been found to reduce inattention and motor impulsivity in a stop signal reaction time task and 5-choice serial reaction time task, respectively (Robinson et al., 2008). Moreover, coeruleo-cortical NE projections to forebrain sites including the neocortical mantle and hippocampus have been implicated in ASS (Bondi et al., 2010; Lapiz et al., 2007). Thus, noradrenergic function seems to mediate motor impulsivity and attention. Further, C57BL/6n mice exhibit increased locomotor activity in open field tests (Crawley et al., 1997), high levels of novelty induced locomotion (Puglisi-Allegra & Cabib, 1997), and a drug-self administration profile similar to drug addicts (i.e., a high-impulsivity population),

Previous experiments in our laboratory have indicated that C57BL/6n mice consistently omit trials in RL procedures (see figure 1) suggesting that non-compatible behaviors (e.g., locomotor activity, grooming) are competing with task engagement. I hypothesize that noradrenergic dysfunction mediated the omission rates, via motor impulsivity, in RL performance. Therefore, in a concurrent schedule procedure, acute administration of atomoxetine could increase attention and task engagement. Such an effect would be evident in a dose-dependent increase in responding.

Serotonin and Choice

Serotonin function. Serotonin functioning has been associated with reinforced behavior. For example, lesions to the dorsal and median raphe nuclei, two ascending serotonergic pathways, have been found to alter sensitivity of response allocation and choice to variations in

reinforcement delay (Mobini et al., 2002). Moreover, the effect of serotonergic manipulation on RL has been explored in many species using a wide range of procedures.

Pharmacological studies: serotonergic agonist and antagonist. Depletion of serotonin in the OFC (Clarke, Walker, Dalley, Robbins, & Roberts, 2007) and prefrontal cortex (PFC) (Clarke et al., 2004, 2005) of marmosets has been associated with increased perseveration and overall RL impairment. Further, 5, 7-dihydroxytryptamine depletion of 5HT in the OFC in marmosets has also been associated with an increased number of pre-potent responses in a response inhibition task (Man, Dalley, & Roberts, 2010). Administration of fluoxetine, a selective serotonin reuptake inhibitor (SSRI), in C57BL/6n mice resulted in fewer perseverative errors and trials to reach 50% of reversal criterion during reversal learning performance (Brigman et al., 2010). In rats, administration of escitalopram, an SSRI, facilitated reversal learning (Brown, Amodeo, Sweeney, & Ragozzino, 2012). In humans, Citalopram, an SSRI, decreased the latency to extinction of responding on a stimulus associated with loss (Chamberlain et al., 2006). Thus, low serotonin has been associated with increased perseveration in RL whereas serotonergic agonists consistently decrease perseveration in RL.

Pharmacological mechanisms: resistance to extinction. One mechanism that might drive preservative responding in RL could be poor sensitivity to extinction. As previously mentioned, depletion of serotonin in the OFC (Clarke et al., 2007) and PFC (Clarke et al., 2004, 2005) of marmosets has been associated with increased perseveration. On the other hand, SSRI administration has been found to decrease perseveration in RL with mice (Brigman et al., 2010), facilitate reversal learning in rats (Brown, Amodeo, Sweeney, & Ragozzino, 2012), and decrease the latency to extinction of responding to a stimulus associated with loss (Chamberlain et al., 2006). Thus, several lines of research have provided evidence that perseveration is closely tied to

serotonin levels and that, relative to baseline levels, depletion or enhancement of serotonin signaling corresponds to high or low levels of perseveration, respectively.

5-HT and Perseveration: Implications for the Current Experiment

If perseveration can be understood as poor sensitivity to extinction, then the proportion of behavior dedicated to the side more frequently associated with extinction, relative to the response alternative more frequently associated with reinforcement, would provide a metric of this potential mechanism in concurrent schedule performance. On the other hand, in concurrent schedule arrangements that program equal reinforcement rates, the potential influence of sensitivity to extinction is shared equally between the response alternatives. As such, resistance to extinction provides a poor mechanistic account of perseveration under such conditions.

An alternative measure of perseveration would be the total number of visits made to the response alternative more frequently associated with extinction. If a concurrent schedule were to program reinforcement to one response alternative according to, say, a 0.5 probability, then a CO would be expected following close to every reinforcer delivery, since a large proportion of responses made to an alternative immediately following reinforcement are paired with extinction. Conversely, the same would apply following reinforcement on the other response alternative, a combination that would likely promote frequent changeovers and equivalent responding. On the other hand, a concurrent schedule programming reinforcement to, say, the left response device with a greater than 0.5 probability would pair fewer left responses with extinction thereby making a CO to the right alternative less likely. Likewise, the opposite would occur following reinforcement delivery on the right side making CO response to the left side more likely following reinforcement. Over the course of the session, this might promote a response pattern

with fewer CO responses since fewer reinforcers are delivered to the side for which CO responses are more likely.

Neural Correlates

Monoamines appear important to RL, IDS, EDS, and ASS performance. The importance only makes sense in light of the influence that monoamine levels have on the functioning of the cortical and striatal regions upon which they are found. Several lines of research have sought to understand the functional connectivity among these areas and the extent to which disruption or other alterations to these areas influence RL, IDS, EDS, and ASS.

Dias et al., (Dias, Robbins, & Roberts, 1996b) examined performance of marmosets on reversal and EDS using an animal analog of the Wisconsin Card Sorting Task following cortical lesions. Lesions to the PFC impaired EDS as well as reversals while sparing IDS. Other studies by the same research group have dissociated EDS and reversal deficit within functionally separate areas of the PFC. That is, lesions to the OFC have been associated with selective deficits in reversal learning while lesions to the lateral PFC have been associated with selective deficits in EDS (Dias et al., 1996a; Dias, Robbins, & Roberts, 1997). Further, single unit recordings in the macaque PFC have demonstrated a reversal in neuronal firing from a previously rewarded stimulus to a newly rewarded stimulus (Rolls, Critchley, Mason, & Wakeman, 1996; Thorpe, Rolls, & Maddison, 1983). Single unit recording studies have also identified neuronal responses in the ventral striatum that reflect OFC neuronal output suggesting functional connectivity (Rolls, Thorpe, & Maddison, 1983).

Individual differences in dopamine levels have been associated with RL deficits. According to Lauglin and colleagues, D_2 receptor levels in mice are correlated with reversal learning competency but not acquisition of the original discrimination (Laughlin, Grant,

Williams, & Jentsch, 2011). Similarly, in vervet monkeys, D_2-like receptor availability is positively correlated with RL performance (Groman et al., 2011). Moreover, RL performance is impaired in dopamine D_2 receptor knockout mice (De Steno & Schmauss, 2009; Kruzich & Grandy, 2004; Kruzich, Mitchell, Younkin, & Grandy, 2006) and in humans with DRD2 alleles associated with low receptor expression (Jocham et al., 2009).

Several investigators have studied performance in humans using functional magnetic resonance imaging scanners to determine the extent to which different patterns of neuronal activity are associated with stimulus-response reversals and attentional set shifting (Nagahama et al., 2001). Following reversals, incorrect response activity has been associated with increased activity in the ventrolateral PFC, ventral striatum, medial PFC, right parietal cortex (Cools et al., 2002) as well as the postero-ventral PFC (Nagahama et al., 2001). During the set shifting, neural activity has been associated with the antero-dorsal and postero-ventral PFC (Nagahama et al., 2001).

The aforementioned results implicate the OFC, ventral striatum, and MPFC in RL in both humans and nonhumans. In line with these findings, the OFC and MPFC are structurally similar across humans, primates, and rodents and share similar connections within basal ganglia-thalamocortical circuits in each species (Brown & Bowman, 2002). On the other hand, set shifting has been associated with the lateral PFC in marmosets and the antero-dorsal and postero-ventral PFC in humans. Nonetheless, the role of cortico-striatal networks has been supported by the presence of RL deficits that are associated with damage to these areas.

Deficits in Choice and Decision Making

Human Clinical Disorders. Deficits in RL have been associated with neurological disorders including fronto-temporal dementia (Rahman, Sahakian, Hodges, Rogers, & Robbins,

1999), unipolar depression (Fossati, Amar, Raoux, Ergis, & Allilaire, 1999), ADHD (Itami & Uno, 2002)), neurodegenerative disorders (Parkinson's disease (Cools, Barker, Sahakian, & Robbins, 2001), schizophrenia (Pantelis et al., 1999)), lesions to the prefrontal cortex (Pantelis et al., 1999; Rolls, Hornak, Wade, & McGrath, 1994), drug-addiction (Goldstein & Volkow, 2002; Volkow & Fowler, 2000; Volkow, Fowler, & Wang, 2003),and exposure to environmental contaminants (Paletz, Craig-Schmidt, & Newland, 2006; Reed et al., 2006). According to Rahman and colleagues (1999), patients with frontal variant fronto-temporal dementia exhibit deficits in the reversal stage of visual discrimination learning task. Orbitofrontal dysfunction is suggested to occur in the early stages of frontal variant fronto-temporal dementia (Rahman et al., 1999). Impairments in set shifting, behavioral flexibility, and perseveration have been reported in humans diagnosed with unipolar depression (Fossati et al., 1999) and ADHD (Itami & Uno, 2002). Depression is associated with disruption of monoamine levels including dopamine, norepinephrine, and serotonin in the anterior cingulate cortex and dorsolateral PFC (Rogers et al., 2004). ADHD is characterized by diminished brain volume in the OFC (Schneider, Retz, Coogan, Thome, & Rösler, 2006)

ADHD has a slightly different profile. Coghill and colleagues (2013) reported that individuals with ADHD show deficits in delay aversion, inhibition, and response variability whereas Sjowall and colleagues (2013) found that individuals with ADHD exhibited impairment in inhibition, shifting, and reaction time variability (Coghill, & Matthews, 2013; Sjöwall, Roth, Lindqvist, & Thorell, 2013). Poor response inhibition in individuals with ADHD has been linked to hypoactivity in the frontal cortex (Morein-Zamir et al., 2014). Specifically, response inhibition deficits have been linked to hypoactivity of the right inferior frontal cortex. Thus, several lines of

evidence suggest that ADHD populations show deficits in response inhibition and set shifting, a deficit that might be mediated by frontal-cortex dysfunction.

Dopamine tone may play a role in perseveration on discrimination reversals in Parkinson's patients. Cools and colleagues examined patients with Parkinson's disease, some of whom were treated with indirect or direct dopamine agonists. Patients on drug therapy had a high rate of errors on the reversal procedure compared with controls and Parkinson's patients off medication, even though all groups were similar on acquiring the original discrimination (Cools et al., 2001). Further, L-Dopa treatment elevates DA levels throughout the central nervous system replacing DA in depleted areas (e.g., fronto-dorsal striatal circuits) while possibly leading to excessively high levels in relatively unaffected areas (e.g., fronto-ventral striatal circuits) (Swainson et al., 2000). ASS deficits have also been reported in subjects with schizophrenia (Pantelis et al., 1999) and frontal lobe damage (Pantelis et al., 1999; Rolls et al., 1994). Pantelis et al. (1999) compared ASS performance among individuals with schizophrenia, frontal lobe lesions, and matched controls. The individuals with schizophrenia and frontal lobe lesions showed impairment on extra-dimensional shifting. Compared to the other two groups, individuals with schizophrenia showed impairment in intra-dimensional shifting making more errors and requiring a greater number of trials to perform the shift. Using a similar task to the one reported by Rahman et al., (1999), Rolls et al., (1994) found that individuals with ventral PFC damage produced more errors, relative to controls, in the reversal and extinction conditions. The errors were typically in the form of responses to the previously correct alternative (Rolls et al., 1994). Imaging studies with drug-addicted individuals (Goldstein et al., 2002; Volkow et al., 2000; 2003), have suggested that drug use is associated with striato-cortical circuit damage.

Laboratory Models. Several lines of research with non-human animals have supported the role of monoamines in RL and ASS performance. Following chronic unpredictable stress, a common risk factor for depression in humans, ASS deficits developed in rats. In male juvenile vervet monkeys, low baseline levels of 5HT (and DA) have been associated with poor reversal performance (Groman et al., 2013). Further, of monkeys with low putamen DA, those with high 5HT levels in the OFC showed fewer sessions to criterion in RL performance (Groman et al., 2013). Exposure to environmental toxicants such as methylmercury (MeHg) have been found to increase perseveration in a discrimination reversal procedures (Paletz et al., 2007; Reed et al., 2006). Rats exposed during gestation to MeHg showed more perseverative responding on a reversal procedure on the first reversal but not on the original discrimination (Reed et al., 2006), and, using other procedures, MeHg exposure delayed choice in transition by increasing perseverative responding (Newland, Yezhou, Lögdberg, & Berlin, 1994) and increased sensitivity to acute doses of *d*-amphetamine (Rasmussen & Newland, 2001) or cocaine (Reed & Newland, 2009). In squirrel monkeys, gestational MeHg exposure resulted in concentration of mercury throughout the cortex especially in pyramidal cells of the occipital lobe (Warfvinge, Hua, & Logdberg, 1994). In humans, gestational MeHg exposure is associated with damage to all areas of the cortex (Harada, 1995). Finally, prefrontal depletion of serotonin has been found to disrupt ASS (Clarke et al., 2005, 2004). These studies, along with the aforementioned lesion studies in animals, implicate an important role of neural pathways between the frontal cortex and striatum in reversal learning and ASS tasks (Boulougouris, Dalley, & Robbins, 2007; Chudasama et al., 2003; Dias et al., 1996). Taken together, these studies suggest that monoamine levels may play a role in reversal teaching (Robbins, 2005), perhaps acting through the OFC (Dalley et al, 2004).

Integrating human and non-human deficits in choice behavior. Evidence from many different methods (i.e., clinical and laboratory) suggest the presence of common mechanisms underlying deficits in choice behavior (Cardinal, Pennicott, Lakmali, Robbins, & Everitt, 2001; Chudasama et al., 2003; Rogers, Baunez, Everitt, & Robbins, 2001). The behavioral deficits corresponding to the aforementioned models of choice can be understood in light of several behavioral mechanisms.

Behavioral Mechanisms

Many studies with human subjects have found that lesions to, or deficits in, the OFC disrupt RL performance. Damage to these cortical areas and the resulting cognitive deficits have also been successfully replicated in animals adding face validity to animal models. However successful these techniques may be, they fail to offer explanations of the behavioral mechanisms responsible for said deficits. Although these techniques do not directly address the question of behavioral mechanisms, they do offer several possibilities.

Reinforcer efficacy. Gestational MeHg exposure not only increases perseverative responding, it has also been found to increase responding at higher ratios in progressive ratio schedules (see Paletz et al., 2006, Reed et al., 2006). Further, DA depletion has been found to decrease break-point in progressive ratio schedules (Cetin, Freudenberg, Füchtemeier, & Koch, 2004), DA agonist, which are often abused, maintain very high break-points when self-administered, and the break-point reflects their abuse potential (French, Lopez, Peper, Kamenka, & Roberts, 1995; Griffiths, Findley, Brady, Dolan-Gutcher, & Robinson, 1975; Woolverton, 1995), and DAergic lesions in the OFC have been found to decrease sensitivity to reinforcement delay in a delay-discounting procedure (Kheramin et al., 2004). These findings suggest that gestational MeHg exposure, DA depletion, and DA agonist might alter “incentive value”

(Sagvolden, Johansen, Aase, & Russell, et al., 2005; Mobini, 2000) or reinforcer efficacy (Richardson & Roberts, 1996; Stafford, LeSage, & Glowa, 1998) by altering the immediate impact of a single reinforcer delivery. Thus, the aforementioned studies suggest that fronto-striatal circuits along with the corresponding DA system provide the neural signature of acquired incentive value of a stimulus (Clarke et al., 2005; Flagel et al., 2011; Hwang, Kunkler, Tarricone, Hingtgen, & Nurnberger Jr, 1999). One question that arises from these findings is whether these circuits or neurotransmitter systems can be used to improve performance in operant tasks.

Motor impulsivity. A deficit commonly found in RL procedures are errors of omission. Previous experiments in our laboratory have indicated that C57BL/6n mice consistently omit trials in RL procedures (see figure 1). Errors of omission, or failure to complete a trial within the limited hold, during an experimental session suggest that incompatible behavior (e.g., locomotor activity, grooming) are competing with task engagement. Evidence that supports this possibility can be found in the behavioral profile of C57BL/6n mice. It has been reported that C57BL/6n exhibit high levels of locomotor activity in open field tests (Crawley et al., 1997) and novelty induced locomotion (Puglisi-Allegra & Cabib, 1997). C57BL/6n mice are also likely to self-administer cocaine and alcohol (Helms, Reeves, & Mitchell, 2006). Thus, the C57 strain exhibits several characteristics common to persons diagnosed with ADHD. The aforementioned behavioral profile for C57BL/6n mice might mediate high omission rates in the RL procedure.

Behavioral momentum. Behavioral momentum theory (BMT) is a theoretical framework that has been developed to account for the persistence of operant behavior (Nevin, 1974; Nevin, Tota, Torquato, & Shull, 1990). BMT suggests that response-reinforcer relations govern response rate in a manner consistent with Herrnstein's matching law (Herrnstein, 1970). In essence, Herrnstein's matching law asserts that the relative rate of responding among multiple

sources of reinforcement is proportionate to the relative rate of reinforcement received from each alternative (for review see Davison & McCarthy, 1988). Further, stimulus-reinforcer relations govern the persistence of behavior following a disruption in the stimulus-reinforcer contingency. In BMT, the persistence of behavior following a disruption is referred to as resistance to change. Moreover, resistance to change is considered a measure of response strength. The use of resistance to change as a measure of response strength has an advantage in that it can successfully account for variations in response rate without referring to a change in response strength (Nevin et al., 1990; Nevin, 1974). Thus, according to BMT, perseveration might reflect greater response strength associated with the previous response-reinforcer relation and poor response strength associated with the new response-reinforcer relation. Further, this measure of response strength can be obtained without being confounded by variables that influence response rate but not strength. Thus, it is reasonable to conclude that BMT's concept of resistance to change might account for post-reversal commissions in RL performance.

Current Experiment

Synthesis of aforementioned pharmacological mechanisms. Evidence from clinical and laboratory studies converge on the same neurochemical and neuroanatomical substrates underlying this executive function (Cardinal, Pennicott, Lakmali, Robbins, & Everitt, 2001; Chudasama et al., 2003; Rogers, Baunez, Everitt, & Robbins, 2001). The findings suggest that the behavioral deficits in choice procedures are the product of irregularities in specific neurochemical pathways, and DA, NE, and 5-HT neurotransmitter systems in the frontal cortex might be especially important (Robbins & Roberts, 2007). However, the findings are either mixed (e.g., dopaminergic agonist and RL) or poorly explored in mice (e.g., noradrenergic agonist and RL).

It has been suggested that the behavioral effect of a drug depends jointly on the dose of the drug as well as the programmed contingencies maintaining its behavior (Sidman, 1956). Likewise, the behavioral effect of a given dose depends on the pattern of behavior maintained by the programmed contingencies under non-drug conditions (Kelleher & Morse, 1968). Dews (1955) provided one of, if not the, first reports of the role of schedule-maintained response rates in determining the behavioral effects of drugs. In his study, he reported that the behavioral effects of pentobarbital depended jointly on the dose of the drug and response allocation maintained by the programmed contingencies under non-drug conditions. Dews found that the baseline pattern of responding under different schedules of reinforcement influenced both the magnitude and direction of the drug effect, providing early evidence for what would later be called 'rate-dependent' drug effects (Sanger & Blackman, 1976).

Comparing the behavioral effects of a drug between different schedules of reinforcement can prove difficult if the two schedules maintain different stimulus conditions, reinforcement rates, etc.. Thus, an alternative approach to study behavioral effects of drugs is to program a constant schedule of reinforcement, identify and group subjects according to different non-drug response patterns (e.g., high response rate and low response rate subjects), and finally to make between group comparisons of drug effects (Heffner, Drawbaugh, & Zigmond, 1974; Ray & Bivens, 1966; Will & Checchinato, 1973). One drawback associated with separating subjects between, or among, response rate groups is that doing so reduces the power of all corresponding dependent measures.

Integration of the role of monoamines in behavioral flexibility, and predictions for the current experiment.

Dopaminergic agonists. In an attempt to gather supporting evidence for the distinction between the reinforcer-efficacy effects of stimulants and the motor inhibition effect of SNRIs, comparisons were made between stimulants and SNRIs with C57BL/6n mice. Although stimulants have been reported to decrease motor inhibition and increase locomotor activity (Fletcher, Grottick, Higgins, 2002) dopamine has been associated with reinforcer efficacy (Roesch, 2007) which might improve task engagement. Thus, administration of a dopaminergic agonist was hypothesized to increase reinforcer efficacy and potentially increase response rates.

Serotonergic agonists. Previous studies in our laboratory have indicated that C57BL/6n exhibit high commission errors (especially in the first reversal) in RL performance (see figure 1). The aforementioned correspondence between serotonin levels and perseveration in reversal learning suggests that serotonergic manipulation might likewise limit the persistence of behavior on response alternatives when the response-contingent reinforcer is programmed on the opposing operanda.

Noradrenergic agonists. As stated above, previous experiments in our laboratory have indicated that C57BL/6n mice consistently omit trials in RL procedures (see figure 1) suggesting that non-compatible behaviors are competing with task engagement. Thus, the administration of SNRIs with this strain in this particular task might attenuate the prevalence of non-compatible behaviors and in effect increase task engagement. Moreover, the effects of SNRIs on concurrent-variable ratio performance have not been well explored with mice.

Synthesis of experimental rationale. Although progress has been made, specific behavioral mechanisms of serotonergic, noradrenergic, and dopaminergic drug classes have not been well identified or thoroughly compared to other drug classes.

The goals of this experiment are three-fold. To design an experimental measure of choice behavior amenable to acute-administration of pharmacological compounds, to develop a behavioral/pharmacological intervention to ameliorate behavioral deficits associated with a particular mouse strain, and to compare the function of 3 monoamines within a single experimental preparation. Therefore, I propose to investigate the behavioral effects of acute pharmacological administration of three drug classes (SNRI, SSRI, and DA agonist) using a novel approach to reversal learning that is amenable to rapid assessment of dose-response relationships. Thus, the experiment is designed to identify the functional, behavioral, and pharmacological mechanisms, which maintain behavioral deficits in a specific strain of mice (i.e., C57BL/6n).

Figures

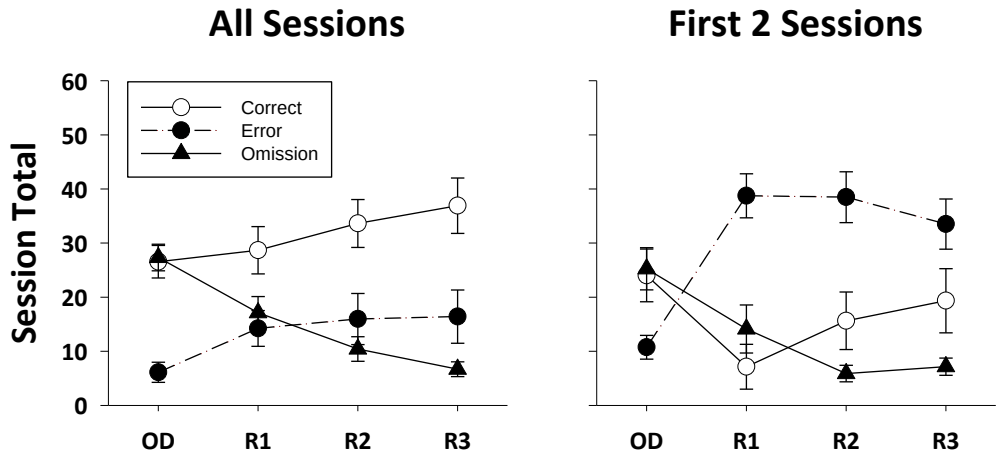

Figure 1: Average number of correct responses (open circle), errors of commission (filled circle), and errors of omission (filled triangle) are plotted as a function of OD and reversal separately for all sessions (left) and the first 2 sessions of OD and each reversal (right). Error bars indicate standard error of the mean.

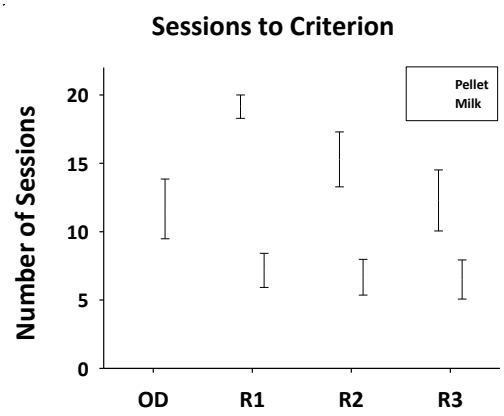

Figure 2: Subjects who did not meet the criterion of 3 consecutive sessions with 85% accuracy were given forced reversals. 90% of C57BL/6n required forced reversals in OD and R1 with pellet reinforcement. Error bars indicate standard error of the mean.

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Chapter II Investigation of Choice in C57BL/6n Mice:

The Role of Monoamines in Concurrent Schedule Performance

Abstract

To examine the impact of three monoamine transporter blockers, the behavior of mice was established under concurrent schedules of reinforcement. Characteristic features of concurrent responding were seen, including equal allocation of responding when the probability of reinforcement for one alternative was 0.5 and preference for the richer alternative when the reinforcer probabilities were unequal. Undermatching was seen, a finding typically observed with concurrent schedules and the changeover rate was highest when the two alternatives produced the same reinforcement probabilities. To examine rate-dependent effects, mice producing high- and low response rates were examined separately. For the high rate group, one of the doses tested for both *d*-amphetamine and atomoxetine increased total responses in the equal reinforcement probability condition. For both drugs, the increase in response rate was accompanied by a significant increase in reinforcement rate; however, the relative distribution of responding to the left and right nosepoke was. Escitalopram increased response rates but not the number of reinforcers or response-reinforcer ratio. In the unequal reinforcement ratio condition none of the doses tested produced a significant increase in responding or reinforcement. Further, the proportion of responses made on the rich nosepoke did not change significantly with any of the drugs tested. Thus, the consistent level of bias failed to suggest the presence of an interaction between the effects of bias and dose or the effects of bias and baseline response rate.

Introduction

Concurrent schedule procedures are widely used to assess choice behavior (Herrnstein & Loveland, 1975; MacDonall, 1988, 1998; Mazur & Fantino, 2014). The general finding from concurrent schedule arrangements is that the allocation of behavior approximates, or matches, the allocation of reinforcement obtained from the corresponding response alternatives (Herrnstein, 1961). Thus, concurrent schedules have been used successfully to identify potential behavioral mechanisms of choice. The prefrontal cortex is thought to play a critical role in this form of learning (Clark et al., 2004), however, the specific neural mechanisms responsible for concurrent schedule performance have received relatively less attention.

The major monoamines including dopamine (DA) (Clark et al., 2004; George, Jenkins, & Killcross, 2011; Rogers, Everitt, et al., 1999), serotonin (5-HT) (Clark et al., 2004; Clarke et al., 2005, 2004, 2007; Roberts et al., 1994), and norepinephrine (NE) (Arnsten & Dudley, 2005; Bondi et al., 2010; Koda et al., 2010; Lapiz & Morilak, 2006) are present in the PFC. These monoamines play different roles in behavior (den Ouden et al., 2013). Systemic DA modulation influences reversal learning performance in humans (Cools et al., 2009), vervet monkeys (Jentsch et al., 2002), rats (Taghzouti et al., 1985), and mice (De Steno & Schmauss, 2009; Izquierdo et al., 2006). The noradrenergic system is thought to mediate attention and behavioral activation (Lapiz et al., 2007). 5-HT in the orbitofrontal cortex (Clarke et al., 2007) and other PFC areas (Clarke et al., 2004, 2005, Man, Dalley, & Roberts, 2010) of marmosets has been associated with perseveration in spatial discrimination reversal (SDR) procedures and inhibition of pre-potent responding in response-inhibition tasks.

Reversal learning procedures are widely used to assess behavioral flexibility (Izquierdo, Brigman, Radke, Rudebeck, & Holmes, 2016). One variant of the reversal learning paradigm,

spatial discrimination reversal (SDR), arranges multiple reinforcement schedules between, or among, spatially separated response operanda (see, Brown, Amodeo, Sweeney, & Ragozzino, 2012; Elias, Dupree, & Eleftheriou, 1973; Reed, Paletz, & Newland, 2006). In SDR procedures, a response on one of two response alternatives is reinforced. Once stable responding consistently occurs on that alternative, responding on the second alternative is reinforced and the first alternative is placed on extinction. Consequently, following the reversal, successful performance requires both extinction of the previously reinforced response and acquisition of the newly reinforced response (Robbins & Roberts, 2007). Arranging reinforcement contingent on a single response, as in the SDR, limits the extent to which slight variations in response rate, and other behavioral patterns indicative of attention, can be identified. Rather than arranging reinforcement contingencies across trials requiring the target response(s) to occur within a discrete time frame, or delay, (i.e., discrete trials procedure) reinforcement schedules can be programmed intermittently according to schedules of reinforcement using free-operant procedures.

Concurrent schedules are one way of studying choice between, or among, intermittent reinforcement schedules. Concurrent schedules typically generate higher response rates, relative to discrete trial procedures. By arranging intermittent reinforcement schedules between spatially separated response operanda, the frequency with which subjects switch between the alternatives, or changeover rate, provides a measure of preference. Previous research has reported that sensitivity to reinforcement, and to slight differences in reinforcement rate, is enhanced in concurrent schedule arrangements (Davison & McCarthy, 1987; Mazur & Fantino, 2014) maintaining behavior on each alternative ensures that performance is not attributed to simple motor disinhibition (Hornack et al. 2004 in Ersche 2008).

Evidence from clinical and laboratory studies converge on the same neurochemical and neuroanatomical substrates underlying choice behavior (Cardinal, Pennicott, Lakmali, Robbins, & Everitt, 2001; Chudasama et al., 2003; Rogers, Baunez, Everitt, & Robbins, 2001). The findings suggest that behavioral changes in choice procedures are the product of irregularities in specific neurochemical pathways, and DA, NE, and 5-HT neurotransmitter systems in the frontal cortex might be especially important (Robbins & Roberts, 2007).

Depletion of serotonin in the OFC (Clarke et al., 2007) and prefrontal cortex (PFC) (Clarke et al., 2004, 2005) of marmosets has been associated with increased perseveration and overall RL impairment. In humans, Citalopram, an SSRI, decreased the latency to extinction of responding on a stimulus associated with loss (Chamberlain et al., 2006). In rats, administration of escitalopram, the S enantiomer of citalopram, facilitated reversal learning (Brown, Amodeo, Sweeney, & Ragozzino, 2012).

Stimulants that promote dopamine have been reported to decrease motor inhibition and increase locomotor activity (Fletcher, Grottick, Higgins, 2002), a combination that might decrease task engagement. However, other studies suggest that DA plays a role in signaling the value/efficacy of a reinforcer (Roesch et al., 2007; Schultz, 2007; Takahashi et al., 2007), a combination that might increase task engagement.

Noradrenergic function has also been suggested to play a role in mediating attention and motor impulsivity. Atomoxetine, a selective norepinephrine reuptake inhibitor (SNRI) has been found to reduce motor impulsivity and inattention in a stop signal reaction time task and 5-choice serial reaction time task without influencing perseveration (Robinson et al., 2008).

The high response rates, sensitivity to reinforcement, as well as the use of CO as a measure of preference make concurrent schedule arrangements an ideal model of operant choice. A

variant of concurrent schedules, concurrent variable ratio (VR) was used in this experiment. Concurrent VR schedules have been said to generate high response rates and reinforcement sensitivity (Herrnstein & Loveland, 1975; MacDonall, 1998, 1999).

The goals of this experiment are three-fold: to design an experimental measure of choice behavior amenable to acute-administration of drugs, to determine whether various monoamine agonists influence the prevalence of behavioral changes associated with a particular mouse strain, and to compare the function of 3 monoamines within a single experimental preparation. Thus, the experiment is designed to identify the functional, behavioral, and pharmacological mechanisms which maintain behavioral deficits in mice.

Methods

Subjects A total of 22 male C57Bl/6Hsd mice were maintained at 24g body weight with post-session feeding of Purina rat chow. Mice were obtained at 6-8 weeks of age and initial training commenced once target weight was reached, about 46-60 days of age. All mice were pair housed with free access to water in a temperature- and humidity-controlled AAALAC-accredited colony room with a 12 hr. light/dark cycle (lights on at 8 am).

Design. A mixed-factorial design with drug group and baseline response rate (high or low) as between-subject variables and dose as within-subject variable making a 3 (*d*-amphetamine (amphetamine), atomoxetine, escitalopram) x 2 (high or low baseline response rate) x 7 (baseline, control, vehicle, and at least 4 doses) design separately for the reinforcement ratio condition (equal reinforcement ratio, unequal reinforcement ratio). An extra subject was delivered giving one drug group an *n* of 8.

The conditions (i.e., equal and unequal reinforcement ratio) remained constant until a minimum of 4 dose determinations were completed. The order of dosing was planned to occur in

ascending order (i.e., dose one to dose four) such that the lowest dose (dose one), tested on day one would be followed by the next highest dose (dose two) later that evening. Following the two-day washout period the second administration day would start with the dose two and end with the next highest dose (dose three), and so on until the third drug administration day. The dosing regimen would occur once for the equal reinforcement ratio condition and repeat for the unequal reinforcement ratio condition.

As is the case with new procedures and experimental variability the range of doses was adjusted during the experiment based on post-session data analysis performed prior to the subsequent dose administration(s) and the order of doses (dose size) did not always conform to the prescribed ascending sequence but, consistent with the initial plan, 4-5 doses were tested for each drug group and ratio condition. Moreover, based on data analysis conducted during the preliminary training it was found that baseline response rates grouped into two clusters. Approximately half of the subjects (n = 9) maintained an average response rate that was close to half the average response rate of the remaining subjects (n = 13). The post-hoc statistical analysis therefore included a baseline-response rate factor in order to determine whether acute-drug effects were dependent on baseline response rates.

Apparatus. Experimental sessions were conducted in 12 identical Med Associates operant conditioning chambers (ENV-007) converted for use with mice. The rear wall in each chamber was equipped with a LED-backlit nosepoke (ENV-310W-X) in the center and two sonalerts at the top located equidistant (L and R) from the centrally located houselight (28V 100ma). The front wall of each chamber contained two led-backlit nosepokes (ENV-312-2R) on the left and right and a reinforcer delivery system in between the two nosepokes in the center of

the wall. The reinforcer delivery system was a 20 mg pellet dispenser (ENV-203M) and trough type pellet receptacle (ENV-200R7M). Pellet dispensers contained 20 mg sucrose pellets.

All Experimental events were controlled and recorded by MED-PC IV software (Med Associates, Georgia, Vermont) for PC on a Windows OS. The computer, power supply and interface cabinet were located in an adjacent room.

Training.

Autoshaping. An autoshaping procedure was used to establish nosepoking maintained by the delivery of 20 mg sucrose pellets (Reed et al., 2006). Responding was first established on the left nosepoke, followed by the right nosepoke. During the first component of autoshaping, sessions began with the illumination of the left nosepoke. While illuminated, responses to the left nosepoke resulted in the delivery of a single reinforcer and the simultaneous onset of a 3 sec tone. The left nosepoke remained active for 30", at which time a 300" timeout began. The two components continued to alternate in this manner until subjects completed 10 nosepokes within a single 30" component or until three hours elapsed, whichever occurred first. Once this criterion was met, a free-operant component began in which the target nosepoke was continuously active and subjects were free to respond. The free-operant phase lasted until subjects completed 40 nosepokes or three hours passed, whichever occurred first. Once reached, all subsequent autoshaping sessions started in the free-operant component. After meeting the free-operant response criterion for the left nosepoke, autoshaping occurred for the right nosepoke, starting in the free-operant component. The average number of sessions required to complete the response requirement of 40 consecutive responses within a single session were consistent for the first nosepoke (m = 3.1, SE = 0.4) and second nosepoke (m = 3.0, SE = 0.3).

Concurrent schedule training. Following autoshaping, concurrent VR training began. The sequence of concurrent-schedule arrangements (detailed in Table 1) nearly doubled response rates from the first phase (m = 156.32, std. error = 26.93) to the fourth, and final, phase (m = 299.77, std. error = 83.64) (refer to Table 3 for all dependent measures). For a detailed description, refer to the appendix. For the first, second, and third training phases, two separate VR schedules were introduced. The two VR schedules were programmed independently, meaning that responding to one schedule had no effect on the second schedule, and vice versa. The ratios were gradually increased from VR3 (1^{st} phase) to VR6 (2^{nd} phase) before reaching the final VR 10 (3^{rd} phase). During the third phase, the independent VR 10 VR 10 remained in operation until response allocation to the left and right VR10 was roughly equivalent. Next, VR10 reinforcement was programmed dependently (4^{th} phase), meaning that subjects had to meet the response requirement on the assigned nosepoke without switching to the other nosepoke before the next reinforcer could be arranged. Reinforcers were assigned to the left nosepoke with a 0.94, 0.50, or 0.06 probability, depending on condition. This produces a nominal 16to1, 1to1, or 1to16 left:right reinforcer ratio. The actual ratio value on a trial was selected sequentially, without replacement, from a 200 value array (m = 10.225, SD = 2.043, min = 7, max = 13). The starting value in the 200-value array from which ratios were drawn was modified prior to each session, and all preceding ratio values were appended to the end of the list. In each reinforcement ratio condition, the NP assignment was selected sequentially, without replacement, from a 380-value list of 0s and 1s in which the frequency of left NP assignment (i.e., 0s) was varied depending on the condition such that for every 17 reinforcers approximately 16, 8, or 1 would be delivered to the left in the 16to1, 1to1, and 1to16 reinforcement ratio conditions, respectively. As stated earlier, reinforcement was arranged on the left nosepoke with either a 0.94, 0.50, or 0.06

probability. The order was randomized such that each condition occurred every 2 to 3 sessions. The 0.50 probability condition continued until 45% to 55% of responses occurred on the left. The unequal reinforcement ratio conditions continued until subjects reliably made greater than 66% of responses on the 'rich' alternative. Both performance criterion had to be met on 4 out of 5 consecutive sessions.

***Equal reinforcement ratio condition*.** One-hour sessions began with the illumination of the two-backlit nosepokes located in the front of the chamber to the left and right of the pellet receptacle. A variable ratio (VR) 10 schedule was assigned to either the left or the right nosepoke. The ratio values were selected sequentially, without replacement, from a 200 value array (m = 10.225, SD = 2.043, min = 7, max = 13). In the equal reinforcement ratio condition, the VR schedule was programmed on the left nosepoke with a 0.5 probability. Once assigned, the VR remained in place until the response requirement was met, or the session ended, whichever occurred first. A changeover from one nosepoke to the other reset the response count on the previously visited nosepoke, regardless of the location of the active VR schedule. Completion of the response ratio lead to the onset of a 4.5 kHz tone, illumination of the houselight, and delivery of a 20 mg sucrose pellet. The tone and houselight were turned off 0.5 sec after the start of the reinforcement cycle at which point the subsequent VR schedule was set up. Responses made to the left or right nosepoke during the 0.5 sec reinforcement cycle were recorded but did not contribute to the subsequent ratio requirement.

Drugs. Subjects were divided randomly into amphetamine (n = 7), atomoxetine (n = 7), or escitalopram (n = 8) drug groups. In order to statistically control for the potential role of baseline response rate and balance this potential source of within-group error variance individual subject baseline response rates were also counterbalanced within drug groups according to the

overall baseline response rate (low rate n = 3, high rate n = 4, for amphetamine, low rate n = 3, high rate n = 4, for atomoxetine, and low rate = 3, high rate = 5, for escitalopram). Drugs were dissolved in saline (0.9% NaCl) and administered intraperitoneally in a 2.5-ml/kg volume 20 minutes prior to experimental sessions for atomoxetine and escitalopram, and 15 minutes prior to experimental sessions for amphetamine. Saline and drug administration sessions began following the appearance of stable responding on both equal and unequal reinforcer ratio sessions. Following each session, the pooled-group average response ratio was determined (i.e., obtained response ratio were summed across individual subjects and divided by the number of subjects). If five consecutive sessions occurred for which the pooled-group average response ratio did not exceed 1.25 standard deviations (relative to the mean of pooled-group averages across the five-session block), then performance was considered stable. This criterion was met for all 3 reinforcement ratio conditions. Acute doses of saline, escitalopram (0.1, 0.224, 1.2, 4, 8, & 16 mg/kg), Amphetamine (0.01, 0.03, 0.224, 0.3, 0.4, & 0.4 mg/kg), and atomoxetine (0.01, 0.03, 0.224, 0.3, 0.4, & 0.56 mg/kg) were tested. Drug dosing was planned in an ascending order although some doses were repeated if the first administration was associated with atypical performance, relative to the corresponding drug group. Drug administration days included a single dose in the morning session (7 am and 8 am) and a second, higher, dose during the evening session (5pm and 6pm) for each squad. For each drug, at least one dose was given during a morning session and later replicated during an evening session in which a different dose was administered during the morning session. The dose-related performance in morning and evening sessions was compared to confirm that dose-effects were not dependent on the time-of-day. Each drug administration day was followed by a 2-day washout period. Drug-injection days

were followed, and preceded, by vehicle injection days in which vehicle injections occurred during either the morning or evening session.

Unequal reinforcement ratio phase. After acute drug administrations were completed for the equal-reinforcement ratio condition, the reinforcement ratio contingencies were modified, and the dose-effect relations were re-assessed. A variable ratio (VR) 10 schedule was assigned to either the left or the right nosepoke according to an eight-to-one ratio. In other words, the VR schedule was consistently assigned to one nosepoke with approximately a .89 probability. The side, left or right, associated with the .89 probability (i.e., the rich side) remained consistent within subjects for the duration of the experimental phase. Within each drug group, the side associated with the rich reinforcement schedule was counterbalanced. With the exception of the modification to the reinforcement ratio, all experimental conditions were identical to the previous, equal reinforcement, phase of the experiment.

Statistical analysis

Data collection. Responses made while a VR schedule was in effect were classified according to the spatial location, left or right, as well as the location of the immediately-preceding response. A response, left or right, that was immediately preceded by a response on the same side was classified as visit responses on the respective nosepoke. On the other hand, a response that was immediately preceded by a response on the opposite side was classified as a changeover response. Each session, the total number of visit and changeover responses made to the left and right nosepoke were recorded separately for each subject. In addition, responses to left and right nosepokes were combined to identify the overall number of visit and changeover responses made by each subject over the course of each session. Raw data were maintained using R©3.2.2 and Microsoft® Excel® 2013.

Data analysis. Prior to statistical analysis, individual subject averages were determined separately for pre-drug baseline, control (non-injection days once drug administration began), vehicle, and repeated dose-determinations (if applicable). Subsequently, individual subject data were combined to create drug-group averages. Drug-group averages were determined separately for the equal reinforcement ratio and unequal reinforcement ratio conditions. After testing for violations of sphericity, two-way RM ANOVAs were performed for dependent measures with dose and rate-group as fixed effects and subject as a random effect. More specifically, the levels of dose included pre-drug baseline, control, vehicle, and each dose tested. The pre-drug baseline was included in addition to non-injection sessions during the acute-dosing phase in order to confirm that performance for control sessions during the acute-dosing phase were not significantly different than performance during pre-drug baseline. First-order simple effects and main effects with dose were followed by tests of simple main effects and Holm-Sidak pairwise comparisons as appropriate. All follow-up pairwise comparisons for each dose were made relative to control sessions (i.e., non-injection sessions occurring during the acute-dosing phase). If covariance was heterogeneous, a RM ANOVA on ranks was performed. All statistical analyses were performed with SigmaPlot 12.5©.

Results

Equal Reinforcement Ratio Phase

Amphetamine

Total nosepokes completed. The two-way repeated measures analysis of variance (RM ANOVA) yielded a significant interaction between dose and rate-group, F (7, 35) = 2.60, p = 0.028, indicating that the effect of different doses depended on rate-group level (see Figure 1 top panel). For high-rate subjects, follow up comparisons between acute drug administration and

control sessions indicated that a significant increase in responding occurred with 0.03 mg/kg (m = 618 NP/session), $t = 4.53$, $p < 0.001$, and 0.056 mg/kg (m = 537 NP/session), $t = 2.84$, $p = 0.44$, relative to control (m = 401.3 NP/session). On the other hand, for the low-rate subjects the only significant change was a decrease in responding with 0.4mg/kg (m = 40 NP/session), t = 2.92, $p = 0.042$, relative to control (m = 201.13 NP/session). Moreover, the main effect of rate-group was also significant, F (1, 35) 17.236, $p = 0.009$. Follow up comparisons of rate groups revealed significant differences for control, vehicle, and all doses, all $p < 0.05$.

Total reinforcers earned. The two-way RM ANOVA yielded a significant interaction between dose and rate-group, F (7, 35) = 2.856, $p = 0.018$, indicating that the effect of different doses depended on rate-group level (see Figure 1). For high-rate subjects, follow-up comparisons between acute drug administration and control sessions indicated that, relative to control (m = 26.9 S_R/session), significantly more reinforcers were earned with 0.03 mg/kg (m = 42.75 S_R/session), $t = 5.586$, $p < 0.001$, and significantly fewer reinforcers were earned with 0.4 mg/kg (m = 18 S_R/session), $t = 3.137$, $p = 0.02$. F or the low-rate subjects the only significant change was a decrease in reinforcers earned with 0.4mg/kg (m = 1.33 S_R/session), t = 3.744, $p = 0.005$, relative to control (m = 13.6 S_R/session). Moreover, the main effect of rate-group was also significant, F (1, 35) 21.007, $p = 0.006$. Follow up, multiple comparisons of rate groups revealed significant differences for control, vehicle, and all doses, all $p < 0.05$.

Total changeover responses. A significant main effect was obtained for dose, F (7, 35) 5.511, $p = 0.001$, and rate-group, F (1, 35) 29.441, $p = 0.003$, driven by a decrease in the number of change over responses with 0.4 mg/kg (m = 22.14 CO/session), t = 2.944, $p = 0.039$, relative to control (m = 27.00 CO/session) (see Figure 1, left panels, and Table 1). The main effect of rate-group was produced by the higher number of change-over responses for the high-rate

subjects (m = 51.11 CO/session) relative to low-rate subjects (m =14.41 CO/session), t = 5.426, $p = 0.003$.

Proportion of nosepokes on right side. Neither the main effects nor the interaction of rate-group and dose were significant (F (1, 35) 0.468, $p = 0.524$, for rate-group, F (7, 35) 1.314, $p = 0.273$, for dose, and F (7, 35) 0.486, $p = 0.838$, for the interaction). The average response proportion for control (m = 0.46 right NP/NP total) indicated a slight left-side bias, however, the lack of a significant change suggests that response allocation remained consistent throughout the equal reinforcement ratio condition.

Response:reinforcer ratio. Neither the main effects nor the interaction of rate-group and dose were significant (F (1, 35) 1.683, $p = 0.251$, for rate-group, F (7, 35) 0.374, $p = 0.912$, for dose, and F (7, 35) 0.651, $p = 0.711$, for the interaction). The average number of responses per reinforcer for non-injected control conditions (m = 14.72 NP total: S_R total) indicates that subjects consistently made a greater number of responses than the minimum requirement programmed by the variable ratio contingency, however, the lack of a significant change suggested that response allocation remained consistent throughout the equal reinforcement ratio condition.

Atomoxetine

Total nosepokes completed. The two-way RM ANOVA yielded a significant interaction between dose and rate-group, $F (7, 35) = 3.773$, $p = 0.004$, indicating that the effect of different doses depended on baseline response rate. For the high-rate group, follow-up comparisons between acute drug administration and control sessions indicated that a significant increase in responding occurred with 0.224 mg/kg (m = 539.25 NP/session), $t = 2.791$, $p = 0.05$, and a significant decrease with 4.0 mg/kg (m = 208.75 NP/session), $t = 2.864$, $p = 0.048$, relative to

control (m = 376.14 NP/session). On the other hand, for the low-rate subjects there were no significant changes in responding relative to control (m = 226.95). The main effect of rate-group was also significant, F (1, 35) 13.031, $p = 0.015$. With the exception of 4.0 mg/kg (t = .314, $p = 0.758$) follow-up comparisons of rate groups revealed significant differences for control, vehicle, and all doses, all $p < 0.05$.

Total reinforcers earned. The two-way RM ANOVA for total reinforcers mirrored the effects for total responses in that a significant interaction between dose and rate-group, $F (7, 35) = 4.664$, $p < 0.001$, indicating that the effect of different doses depended on baseline response rate. For high-rate subjects, follow up comparisons between acute drug administration and control sessions indicated that a significant increase in reinforcer rate occurred with 0.224 mg/kg (m = 33.25), $t = 3.458$, $p = 0.01$, and a significant decrease with 4.0 mg/kg (m = 13.25 S_R/session), $t = 3.136$, $p = 0.021$, relative to control (m = 22.76 S_R/session). On the other hand, for the low-rate subjects there were no significant changes in responding relative to control (m = 13.35) where the largest change was a decrease in reinforcers earned with 0.03 mg/kg (m = 6.00 S_R/session). The main effect of rate-group was also significant, F (1, 35) 7.776, $p = 0.039$. With the exception of 4.0 mg/kg (t = .347, $p = 0.736$), follow-up comparisons of rate groups revealed significant differences for all doses, all $p < 0.05$. The difference between rate-group was most pronounced for 0.03 mg/kg which produced a slight increase in reinforcement for the high-rate group (m = 23.50 S_R/session) and a decrease for the low-rate group (again, m = 6.00 S_R/session).

Total changeover responses. Similar to total responses and reinforcers earned, a significant interaction was found between dose and rate-group, $F (7, 35) = 4.71$, $p < 0.001$, indicating that the effect of different doses depended on rate-group level. For high-rate subjects, follow up comparisons between acute drug administration and control sessions indicated that a

significant increase in responding occurred with 0.224 mg/kg (m = 36.5 CO/session), t = 2.819, p = 0.046, and a significant decrease with 4.0 mg/kg (m = 14.5 CO/session), t = 3.217, p = 0.019, relative to control (m = 26.23 CO/session). On the other hand, for the low-rate subjects there were no significant changes in responding relative to control (m = 20.88 CO/session). The main effect of rate-group was not significant (F (1, 35) 4.701, p = 0.082.

Proportion of nosepokes on right side. Neither the main effects nor the interaction of rate-group and dose were significant (F (1, 35) 0.645, p = 0.458, for rate-group, F (7, 35) 0.421, p = 0.882, for dose, and F (7, 35) 0.648, p = 0.713, for the interaction). The average response proportion for control (m = 0.43 right NP/NP total) indicated a slight left-side bias, however, the lack of a significant change suggests that response allocation remained consistent throughout the equal reinforcement ratio condition. Although the difference was not significant, the high-rate group (m = 0.46 right NP/NP total) was closer to equal responding than the low-rate group (m = 0.38 right NP/NP total) for control sessions.

Response reinforcement ratio. Neither the main effects nor the interaction of rate-group and dose were significant (F (1, 35) 3.125, p = 0.137, for rate-group, F (7, 35) 2.184, p = 0.060, for dose, and F (7, 35) 1.891, p = 0.101, for the interaction). Thus, atomoxetine did not produce a significant change in the number of response made per each reinforcer relative to control (m = 16.91 NP total: S_R total).

Escitalopram

Total nosepokes completed. A significant main effect was found for dose, F (6, 36) 2.89, p = 0.021, produced by a significant increase in responding with 1.2 mg/kg (m = 362.44 NP/session), t = 2.94, p = 0.033, and 8.0 mg/kg (m = 351.8 NP/session), t = 2.79, p = 0.041, relative to control (m = 251.08 NP/session).

Total reinforcers earned. The main effects and interaction of dose and rate-group were not significant relative to control (m = 16.66 S_R/session) (F (1, 36) 1.03, p = 0.349, for rate-group, F (6, 36) 1.58, p = 0.181, for dose, and, F (6, 36) 0.99, p = 0.477, for rate-group x dose interaction).

Total change over responses completed. Escitalopram did not produce a significant change in the number of change-over responses relative to control (m = 21.75 CO/session) (F (1, 36) 0.942, p = 0.369, for rate group, F (6, 36) 1.418, p = 0.235, for dose, and, F (6, 36) 1.33, p = 0.271, for rate-group x dose interaction).

Proportion of responses on right side. The main effects and interaction of dose and rate-group were not significant relative to control (m = 0.47 right NP/NP total) (F (1, 36) 0.67, p = 0.443, for rate-group, F (6, 36) 1.159, p = 0.355, for dose, and, F (6, 36) 0.68, p = 0.667, for the interaction). Thus, a slight left side bias remained consistent throughout the equal reinforcement ratio condition.

Response reinforcement ratio. The interaction between rate-group and dose was not significant (F (6, 36) 0.474, p = 0.823). Likewise, the main effect of rate-group was not significant (F (1, 36) 0.317, p = 0.594) while the main effect of dose approached significance (F (6, 36) 2.195, p = 0.066). Thus, escitalopram did not produce a significant change in the number of response made per each reinforcer relative to control (m = 14.94 NP total: S_R total).

Unequal reinforcement ratio phase

Amphetamine

Total nosepokes completed. The two-way repeated measures analysis of variance (RM ANOVA) yielded a significant main effect of dose, F (6, 30) 6.327, $p < 0.001$, and rate-group, F (1, 30) 18.49, p = 0.008. Follow-up comparisons between acute drug administration and control

sessions indicated that a significant decrease in responding occurred with 0.4 mg/kg (m = 107.43 NP/session) $t = 4.078$, $p = 0.002$, relative to control (m = 322.00 NP/session). Follow-up comparisons of rate groups confirmed a significant differences between the high-rate group (m = 389.40 NP/session) and low-rate group (m = 133.06 NP/session), t = 4.30, $p = 0.008$.

Total reinforcers earned. The two-way RM ANOVA yielded a significant main effect of dose, F (6, 30) = 7.267, $p < 0.0\ 01$, and rate-group, F (1, 30) = 35.281, $p = 0.002$. Follow up comparisons between acute drug administration and control sessions indicated that significantly fewer reinforcers were earned with 0.40 mg/kg (m = 6.71 S_R/session), $t = 4.532$, $p < 0.001$, relative to control (m = 21.52 S_R/session). Follow-up comparisons of rate groups confirmed that the high-rate group (m = 25.20 S_R/session) earned significantly more reinforcers than the low-rate group (m = 8.47 S_R/session), t = 5.940, $p = 0.002$.

Total changeover responses. A significant main effect was obtained for dose, F (6, 30) 3.519, $p = 0.009$, driven by a decrease in the number of changeover responses with 0.4 mg/kg (m = 14.00 CO/session), t = 19.21, $p = 0.040$, relative to control (m = 33.81 CO/session). A main effect was also found for rate-group, F (1, 30) 8.031, $p = 0.037$, resulting from the higher number of change over responses for the high-rate subjects (m = 41.23 CO/session) relative to low-rate subjects (m =13.71 CO/session), t = 5.426, $p = 0.003$. The interaction between rate-group and dose was not significant (F (6, 30) 0.574, $p = 0.748$).

Proportion of nosepokes on rich alternative. Neither the main effects nor the interaction of rate-group and dose were significant (F (1, 30) 0.169, $p = 0.698$, for rate-group, F (6, 30) 1.520, $p = 0.206$, for dose, and F (6, 30) 0.762, $p = 0.762$, for the interaction). The average response proportion for control (m = 0.69) indicated a bias for the rich alternative and the lack of a significant change suggests that response allocation remained consistent throughout the

unequal reinforcement ratio condition. Although the main effect of rate-group was not significant the proportion of rich responses for the high-rate group (m = 0.71) was higher than that of the low-rate subjects (m = .66) for control.

Response reinforcer ratio. A significant interaction was found for rate-group and dose, F (6, 35) 2.829, $p = 0.026$. Follow up pairwise comparisons of rate-group at each dose confirmed a significant difference between the low rate subjects (m = 16.70 NP total: S_R total) and high-rate subjects (m = 7.89 NP/S_R) with 0.4mg/kg, t = 3.136, $p = 0.004$. Main effects of rate-group and dose were not significant (F (1, 35) 1.683, $p = 0.251$, for rate-group, F (7, 35) 0.374, $p = 0.912$, for dose). The average number of responses per reinforcer for control (m = 16.49 NP total: S_R total) indicates that subjects tended to make a greater number of responses than the minimum requirement programmed by the variable ratio contingency, however, the lack of a significant change suggested that response allocation remained consistent throughout the equal reinforcement ratio condition.

Atomoxetine

Total nosepokes completed. With atomoxetine, there was a significant main effect of dose, F (7, 35) 3.18, $p = 0.01$, produced by a significant decrease in responding with 4.0 mg/kg (m = 118.14 NP/session), t = 3.316, $p = 0.015$, relative to control (m = 292.48 NP/session). The largest increase in responding found for 0.01 mg/kg (m = 320.86 NP/session) was not significant (t = 0.443, $p = 0.885$). Neither the main effect of rate-group nor the interaction of rate-group x dose were significant (F (1, 35) 1.33, $p = 0.301$, for rate-group, F (7, 35) 1.728, $p = 0.134$, for the interaction).

Total reinforcers earned. There was a main effect of dose, F (7, 35) 2.685, $p = 0.025$. The largest mean difference was associated with the decrease in reinforcers earned during the 4.0

mg/kg session (m = 9.57 S_R/session), however, the pairwise comparison with control (m = 18.33 S_R/session) was not significant (t = 2.41, p = 0.140).

Total changeover responses. A main effect of dose was found, F (7, 35) 2.78, p = 0.021. The main effect was produced by the significant decrease in CO responses at 4.0 mg/kg (m = 6.86 CO/session), t = 3.047, p = 0.03, relative to control (m = 17.10 CO/session).

Proportion of nosepokes on right side. Neither the main effects nor the interaction of rate-group and dose were significant (F (1, 35) 3.721, p = 0.112, for rate-group, F (7, 35) 0.721, p = 0.655, for dose, and F (7, 35) 0.556, p = 0.786, for the interaction). The average response proportion for control (m = 0.70) indicated a slight right-side bias, however, the lack of a significant change suggests that response allocation remained consistent throughout the equal reinforcement ratio condition.

Response reinforcer ratio. A main effect of dose was found, F (7, 35) 2.474, p = 0.036. The main effect of dose was produced by a significant decrease in the response reinforcer ratio at 4.0 mg/kg (m = 8.41), t = 3.505, p = 0.009, relative to control (m = 17.94). A main effect of rate-group was found, F (1, 35) 15.372, p = 0.011. The main effect of rate-group was produced by a significantly higher response: reinforcer ratio for the low-rate group (m = 17.43), t = 3.921, p = 0.011, relative to the high-rate group (m = 12.95). The interaction of rate-group and dose was not significant (F (7, 35) 0.780, p = 0.608, for the interaction). The average number of responses per reinforcer for control (m = 17.69) indicates that subjects made a greater number of responses than the minimum requirement programmed by the variable ratio contingency, however, the lack of a significant change suggested that response allocation remained consistent throughout the equal reinforcement ratio condition.

Escitalopram

Total nosepokes completed. Neither the main effects nor the interaction of rate-group and dose were significant (F (1, 36) 1.155, $p = 0.324$, for rate-group, F (6, 36) 1.417, $p = 0.235$, for dose, and F (6, 36) 0.470, $p = 0.826$, for the interaction) (see Figure 6).

Total reinforcers earned. The interaction between rate-group and dose was not significant (F (6, 36) 0.463, $p = 0.831$). Likewise, the main effect of rate-group was not significant (F (1, 36) 1.958, $p = 0.211$) while the main effect of dose approached significance (F (6, 36) 2.256, $p = 0.060$).

Total change over responses completed. The main effect of dose was significant (F (6, 36) 2.654, $p = 0.031$). Although the follow-up comparisons were not significant the decrease in changeover responses for 16.0 mg/kg (m = 10.88 CO/session) approached significance (t = 2.766, $p = 0.052$) relative to control (m = 25.00 CO/session. Further, the interaction between rate-group and dose was not significant (F (6, 36) 0.720, $p = 0.636$). Likewise, the main effect of rate-group was not significant (F (1, 36) 0.461, $p = 0.523$)

Proportion of responses on rich side. The main effect of dose approached significance (F (6, 36) 2.331, $p = 0.053$). Although the follow-up comparisons for each dose were not significant the largest increase in the proportion of responses on the rich alternative occurred with 16.0 mg/kg (m = 0.74) relative to control (m = 0.66). Further, the interaction between rate-group and dose was not significant (F (6, 36) 01.221, $p = 0.318$). Likewise, the main effect of rate-group was not significant (F (1, 36) 0.0116, $p = 0.918$).

Response reinforcer ratio. Neither the main effects nor the interaction of rate-group and dose were significant (F (1, 36) 0.129, $p = 0.732$, for rate-group, F (6, 36) 2.252, $p = 0.060$, for dose, F (6, 36) 0.343, $p = 0.909$, for the interaction)). Thus, escitalopram did not produce a

significant change in the number of response made per each reinforcer relative to control (m = 15.44 NP total: S_R total).

Discussion

One key goal of this study was to examine a technique that had the potential to investigate acute drug effects on matching and, perhaps, on response perseveration in a single session. To do this, a novel technique was developed. The technique was modeled using procedural characteristics from commonly used behavioral tasks in extant experimental literature. The procedural characteristics included variable ratio schedules – due to their ubiquitous success in maintaining high response rates – to arrange reinforcement between spatially-separated response devices according to both equally-, and unequally-programmed reinforcement ratios. Within individual sessions, reinforcement was programmed according to dependently arranged concurrent schedules. Variable-ratio schedules were dependently arranged – to avoid the development of exclusive preference – according to equivalent response requirements in order to maintain constant response reinforcement ratios while maintaining equal, or unequal, reinforcement rates between the concurrently available response devices. The goals were to establish responding, maintain high response rates, and to model preference between concurrently-available response devices. To test the model, drugs were selected from three representative classes.

A second goal of the study was to examine the impact of three monoamine- (two catecholamines and one indolamine) transporter blockers on concurrent schedule performance. While there were some consistent drug effects, discussed below, the sensitivity of the preparation proved to be inadequate to the task.

Rate Dependent Effects

Although they are classified under different drug classes, amphetamine, a psychomotor stimulant, and atomoxetine, a selective norepinephrine reuptake inhibitor (SNRI), are both catecholamine agonists and while amphetamine alone blocks the dopamine transporter (DAT), and atomoxetine alone blocks norepinephrine transporter (NET) both DAT and NET transport dopamine as well as norepinephrine (Glaser & Gerhardt, 2012). While this leads one to conclude that both drugs have identical effects on monoamine levels, NET is only prominent in the frontal cortex, whereas DAT is also prominently found in the nucleus accumbens and striatum (Gamo, Wang, & Arnsten, 2010). Moreover, both drugs and are used to treat common symptoms of Attention Deficit Hyperactive Disorder (ADHD). Amphetamine, a psychomotor stimulant, is the active ingredient in Adderall© and Vyvance© while atomoxetine, a non-stimulant, is the active ingredient in Strattera©. For amphetamine and atomoxetine, at least one dose led to a significant increase in response rate for the high-rate subjects (only) without a change in reinforcement rate, CO responding, or the response-reinforcement ratio. Therefore, the significant effect could be characterized as a non-selective increase in response output that, due to the dependently programmed VR schedules, increased the total number of reinforcers earned. In other words, the relative distribution of responding to the left and right nosepoke was unchanged during acute drug administration sessions but the overall rate increase yielded an increase in reinforcers.

It appears that the dose-dependent increase in response rate was driven entirely by the high rate group, a finding that is contrary to commonly reported rate-dependent effects of stimulants (Branch, 1984) but consistent with, at least one, human study (Rapport, DuPaul, & Smith, 1985), rate-increasing effects of motivational variables (Shull et al., 2001) and the role of dopamine in signaling reward value (Schultz, 2007). The seemingly motoric effect of amphetamine is supported by the role of dopaminergic projections from the nucleus accumbens to

the basal ganglia and the resulting activation of the motor loop (Alexander, DeLong, & Strick, 1986). On the other hand, the motoric effect might reflect enhanced stimulus control maintained by reinforcement delivery and the associated conditioned stimuli.

NE is implicated in attentional mechanisms underlying operant behavior (Bondi et al., 2010; Lapiz et al., 2007; Robinson et al., 2008), therefore, a systemic increase in NE signaling might have contributed to increased response rates, regardless of whether it was produced by atomoxetine or amphetamine. Alternatively, the increase in response rate might indicate that other behaviors not maintained by the arranged reinforcement contingencies were differentially punished as a consequence of increased attention to conditioned stimuli associated with responding or the programmed reinforcement cycle. This possibility is supported by studies which have reported attenuation of motor-impulsivity in response-inhibition tasks such as 5-choice serial reaction time tasks (5-CSRTT) and stop signal reaction time tasks (SSRTT) with atomoxetine (an SNRI) (Robinson et al., 2008). It can be inferred that a dose-related increase in response rate increased the proportion of time devoted to nosepoking which inversely decreased the proportion of time spent doing something else (e.g., grooming, exploring the chamber). Therefore, the increase in response rate, regardless of whether it was produced by atomoxetine or amphetamine be characterized as increasing a construct of "task-engagement" along with minimal influence on response allocation. It is worth pointing out that the current discussion of attentional processes and preceding discussion of motor-specific effects are highly speculative based on the limit with which said behavioral and pharmacological mechanisms can be separated with the current dependent measures.

In contrast to the consistent drug effects found with the catecholamine agonist, ecitalopram, the indolamine agonist, increased response rates but not the number of reinforcers

and, therefore, did not result in an overall pattern of responding that aligned the obtained response pattern more closely with the programmed response-reinforcer ratio. Overall, escitalopram had the least of an effect on performance. On one hand, the primary goal of studying escitalopram was to examine potential selective effects on response perseveration. However, when equal reinforcement rates are programmed, the potential influence of sensitivity to extinction is equally shared between the response alternatives. As such, resistance to extinction provides a poor mechanistic account of perseveration under said conditions. On the other hand, since the influence of perseveration is equivalent in each condition, this is an ideal preparation to isolate, and provide a metric of, response bias in order to refute (or affirm) any selective drug effect on response bias. Overall, the proportion of responses made on the right nosepoke did not change with any of the drugs tested. Also, the rate increases occurred on both nosepokes and on the number of changeovers. Thus, any response bias that may have been present remained consistent as indicated by the lack of significant interacts among bias, dose, and baseline response rate.

Concurrent VR10: Unequal-Reinforcer Ratio

In the unequal reinforcement ratio condition *amphetamine* and atomoxetine had relatively little influence on performance, with the exception of the decrease in response rate found at the highest dose tested. Compared to the equal reinforcement rate condition, no dose was found to increase reinforcement rate, response output, or changeover responses. With amphetamine, the response-reinforcement ratio did drop significantly for the low-rate subjects, but not for the high-rate subjects, at the highest dose tested. With atomoxetine, there were no baseline response rate dependent effects. In accord with the equal reinforcement ratio condition, the doses that produced a significant change in response rate, albeit a decrease, did not influencing the proportion of responses made to the rich alternative.

Behavioral Momentum

According to BMT, stimulus reinforcer relations govern the persistence of behavior, or resistance to change. In contrast, BMT posits that response rate is governed by response-reinforcer relations in a manner which, when applied to concurrently available sources of reinforcement, is consistent with Herrnstein's matching law. Therefore, according to BMT, the reduction in response rate found for the highest doses tested in the current experiment can be attributed to disruption to response-reinforcer relations. However, response allocation, which remained consistent even at the highest doses tested, is also thought to be governed by response-reinforcer relations in a manner consistent with the matching law. This discrepancy is partially reconciled when resistance to change is considered. In both the equal and unequal reinforcement rate conditions, spatial location (i.e., left or right) is the only stimulus dimension distinguishing the concurrent schedules of reinforcement. Therefore, spatial location (a stimulus-reinforcer association) must be imbedded within the development and maintenance of preference. If acute drug administration did not influence stimulus-reinforcer relationships to the same extent as response-reinforcer relations then response allocation (governed by stimulus-reinforcer associations) might remain stable in the face of a loss in response rate.

By comparing the disruptive effect of the same dose on response rates in both equal and unequal reinforcement ratio conditions differences in response strength maintained by either schedule can be estimated. The highest doses of atomoxetine and amphetamine were more disruptive to response rates (i.e., produced a greater reduction) in the unequal reinforcement ratio, relative to the equal reinforcement-ratio condition. For escitalopram, the opposite occurred and the highest dose was more disruptive in the equal reinforcement ratio condition relative to the same dose in the unequal reinforcement condition, albeit the difference between conditions

was 3-fold less than the difference in response loss with the catecholamine agonists. Thus, the equal reinforcement ratio condition maintained greater overall response strength relative to the unequal reinforcement ratio condition following disruption to catecholamine signaling. On the other hand, the unequal reinforcement ratio condition maintained greater overall response strength relative to the equal reinforcement ratio condition when the behavioral disruptor involved disruption to serotonin signaling.

Measures of Perseveration.

In the current experiment, it was predicted that escitalopram, by increasing 5-HT signaling, might decrease response perseveration. As previously mentioned, depletion of serotonin in the OFC (Clarke, Walker, Dalley, Robbins, & Roberts, 2007) and PFC (Clarke et al., 2004, 2005) of marmosets has been associated with increased perseveration. On the other hand, SSRI administration has been found to decrease perseveration in RL with mice (Brigman et al., 2010), facilitate reversal learning in rats (Brown, Amodeo, Sweeney, & Ragozzino, 2012), and decrease the latency to extinction of responding to a stimulus associated with loss (Chamberlain et al., 2006).

Response Ratio. If perseveration can be understood as poor sensitivity to extinction, then the response ratio (left divided by right), or, stated differently, proportion of behavior dedicated to the side more frequently associated with extinction, relative to the response alternative more frequently associated with reinforcement, would provide a metric of this potential mechanism in concurrent schedule performance. In other words, if the proportion of responses favored the lean alternative, it would indicate that the subject was perseverating on the lean alternative following reinforcement.

CO responses. Given that the contingencies assigned approximately eight reinforcers to the rich alternative for every reinforcer assigned to the lean, if the total number of CO responses declined without a concomitant decrease in reinforcement rate, then it would seem to indicate that subjects experienced fewer non-reinforced visits; since a CO can only indicate a transition in responding from the rich alternative to the lean alternative, and vice versa. Accordingly, the highest dose of escitalopram, unlike amphetamine and atomoxetine, did produce a significant decrease in CO responding without influencing the number of reinforcers earned. Therefore, when the total number of CO responses is considered along with the total number of reinforcers the aforementioned behavioral effect represents a decrease in perseveration. However, the total number of CO responses fails to indicate what goes on during said visits, which is accounted for by the overall proportion of responses made to either alternative. As stated earlier, if response allocation changed in favor the rich alternative, then it would indicate a decrease in perseveration on the side most frequently associated with extinction. Thus, although the proportion of responses made to the rich alternative did not differ, the decrease in CO responses indicates that subjects made a greater number of responses on the side more frequently associated with extinction thereby exhibiting – the opposite of what was anticipated – a drug induced increase in perseveration.

Response-reinforceer ratio. The obtained response-reinforcement ratio on the left and right nosepokes was predicted to be the strongest measure of perseveration. However, the dependent measure yielded not-one significant main effect of dose or rate-group for either ratio condition.

Conclusions for measures of perseveration. Thus, according to three aforementioned measures, as well as the lack of change in undermatching, this experimental preparation was

unable to detect any change in response perseveration. This does not rule out the potential significance of perseveration, rather, it suggests the current methods are not well suited to characterize the role of monoamines in perseverative responding.

Procedural Considerations

Several aspects of the experimental procedure warrant further consideration. Namely, the inherent difficulty in identifying specific motoric, attentional, and perseverative effects.

As previously mentioned, several characteristics of the experimental arrangement made it difficult to distinguish between motoric and attentional mechanisms. For one, the absence of a clear metric of attention can be attributed in part to the use of a free-operant procedure. On one hand, the use of a free operant procedure appeared successful in maintaining high response rates which likely increased sensitivity to individual differences in baseline response rates, thereby making it possible to identify baseline-response rate, dependent effect while also raising the question of potential motor-specific drug effects. On the other hand, the absence of discrete trial components such as limited holds, or the extension of a timeout component following trial initiation responses occurring prior to the onset of the stimulus conditions signaling the end of the fixed timeout duration, made it difficult to isolate drug effects that might have selectively influenced attention.

Further, future investigation might benefit from the use of a task better suited to characterize the role of monoamine function in perseveration. The dependently programmed reinforcement ratio schedules prescribe an 8:1 pattern of ten-response visits in order to maximize, or rather optimize response allocation towards, response-contingent delivery of reinforcers. Likewise, perseveration on the rich alternative would be evident by failure to transition to the lean alternative following a succession of reinforcers earned on the rich

alternative. Over the course of the entire session, this response pattern for all responses made would result in a response-reinforcement ratio that would exceed the programmed 10:1 response: reinforcer ratio. In other words, each reinforcer that is delivered must be preceded by an average of 10 responses. The ratio of all responses made to an alternative and the total number of reinforcers earned on that alternative would include responses prior to reinforcer delivery (constrained to equal 10) as well as responses made following the arrangement of the schedule on the opposing response alternative, the latter of which would be reflect response perseveration. However, this measure of perseveration (i.e., total number of responses – total number of reinforcers x 10) is inflated by the total number of responses that might occur during un-reinforced visits. If one were to partial out non-reinforced visit responses, then you would be left with the number of perseverative responses. However, to do so would be at the cost of removing a defining characteristic of variable ratio performance and likely erode the validity of the conclusion. Thus, to treat non-reinforced visits as irrelevant in search of a measure of perseveration would require eliminating, or simply ignoring, a substantial portion of overall performance; that is, the robust response rates which are a defining characteristic of performance with intermittent-reinforcement schedules. One feature of the current methods that likely contributed to this difficulty is the fact that a changeover from one nosepoke to the other reset the response count on the previously visited nosepoke. The intention was to prevent the delivery of a reinforcer following the first visit response, an arrangement which is known to reinforce frequent alternation between response alternatives. In concurrent variable-interval schedules, this goal is typically accomplished with the use of a CO delay. Moreover, during preliminary training a CO delay was included in the procedure along with non-resetting ratio counters. However, the CO delay was later removed with the concomitant removal of non-resetting ratio counters in an

attempt to bolster response rates and, after response rates increased, the adjustments were maintained. None the less, and in hindsight, it would be interesting to assess performance with either, or both, of the aforementioned procedural characteristics in place.

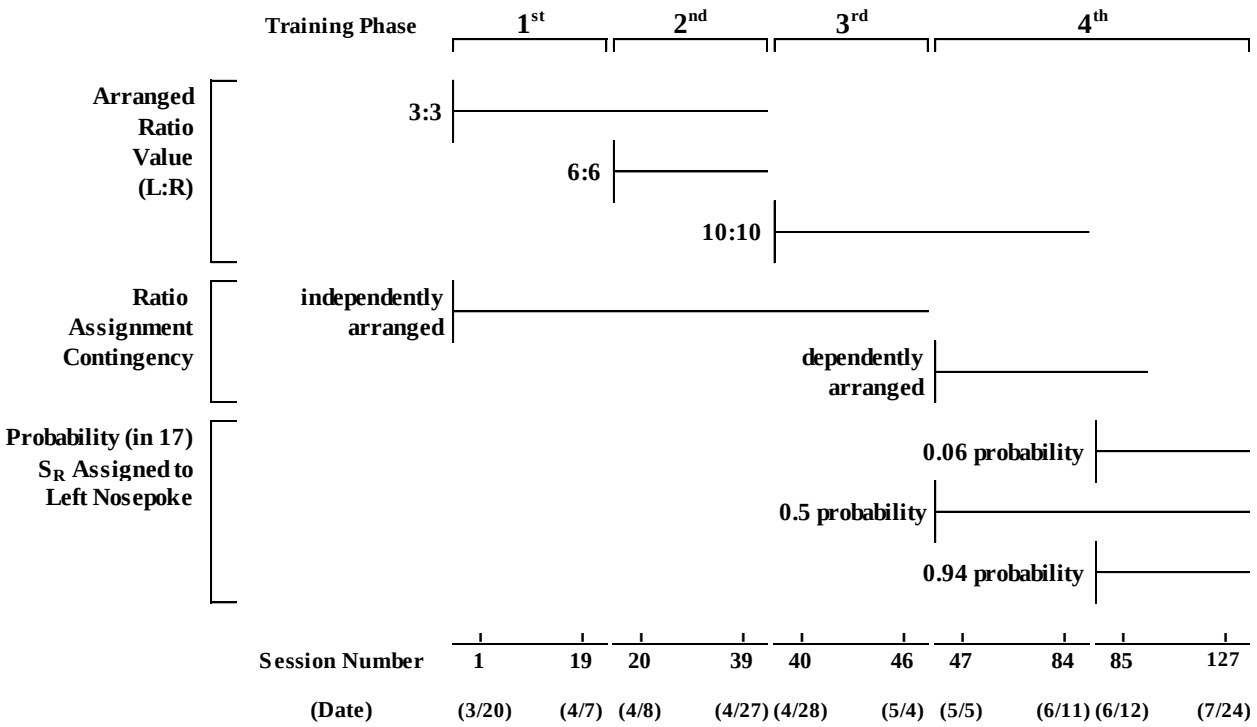
Other Limitations

Another potential limitation of this study is the limit to which it can be nested within the current literature. At the time of this publication, extensive literature searches failed to identify a single behavioral pharmacology study implementing concurrent VR schedules. There are ample investigations utilizing concurrent schedules of reinforcement in a variety of combinations (e.g., concurrent VI VR, concurrent VI VI) but the characteristics of interval-schedule performance does not clearly translate to the current ratio-schedule performance. Likewise, the current ratio-schedule performance does not generalize directly to interval-schedule experiments. While this indicates that the aforementioned results provide a novel contribution to the literature and thus stand alone, it is also the case that the current methodology suffers from want of direct comparison with other investigations. Systematic replication is paramount in maintaining the confirmatory and self-correcting nature of scientific investigation. Thus, while direct comparison would be difficult, the extant literature was just not well-suited to studying acute drug effects.

Other limitations worth mentioning, or re-iterating, include the loss of power associated with splitting drug groups by baseline-response rate during post-hoc analysis. This limitation could surely be remedied through future replication or serve as an important consideration to take into account in future experimental designs. Also, it would have been useful to perform a greater number of replications for the doses tested as well as to test a greater number of intermediate doses in several of the dose-effect curves (e.g., escitalopram). It was also unfortunate that the order of reinforcement ratio conditions was not counterbalanced nor was the

initial nosepoke side during autoshaping and future investigations might benefit from taking both into consideration.

Tables



Phase	1	2	3	4
Conc VR10 VR10	3	8	22	22
Conc VR6 VR6	14	14		
Conc VR3 VR3	5			

Ratio Condition Associated with Highest Response Rate

Table 1: (Left) Timeline of the concurrent schedule conditions prior to final concurrent VR10:10 schedule. The upper x-axis signifies the start and end date for each condition, the lower x-axis specifies the session number corresponding to each date. The lower x-axis signifies the Each row represents a different aspect of the arranged contingencies; VR response requirements (top row), the ratio assignment contingencies (middle row), and probability of reinforcer being assignment to the left NP (bottom row). The order in which the 0.05 and 0.95 probabilities occurred was counterbalanced across subjects. (Right) This table indicates the condition, and *n*, in which subjects achieved the maximum response rate across each of the 4 preliminary-training phases.

Equal Reinforcement Ratio

		NP Total			S_R Total			CO Total			Prop. of NP on Right			NP:S_R Ratio		
	dose	**High**	**Low**	**ALL**	**High**	**Low**	**ALL**	**High**	**Low**	**ALL**	**High**	**Low**	**ALL**	**High**	**Low**	**ALL**
Amphetamine	Control	401.30	201.13	315.51	26.90	13.60	21.20	46.20	18.80	34.46	0.48	0.44	0.46	14.82	14.59	14.72
	Vehicle	354.33	132.00	259.04	24.58	7.67	17.33	38.41	12.00	27.09	0.50	0.45	0.48	16.44	16.11	16.30
	0.030	618.00	163.33	423.14	42.75	12.00	29.57	67.50	15.67	45.29	0.49	0.45	0.47	14.42	13.24	13.92
	0.056	537.00	180.00	384.00	34.00	11.67	24.43	59.50	18.00	41.71	0.53	0.48	0.51	15.64	16.29	15.92
	0.100	443.50	186.33	333.29	30.75	11.33	22.43	56.75	19.00	40.57	0.50	0.50	0.50	14.54	16.65	15.44
	0.224	448.00	155.83	322.79	29.25	9.50	20.79	53.88	13.17	36.43	0.53	0.47	0.51	15.55	15.63	15.58
	0.400	312.50	40.00	195.71	18.00	1.33	10.86	37.50	1.67	22.14	0.41	0.28	0.35	13.38	23.78	17.84
	Total	***389.40***	***133.06***	***279.54***	***29.65***	***9.91***	***21.19***	***51.11***	***14.41***	***35.38***	***0.48***	***0.45***	***0.47***	***14.96***	***16.96***	***15.82***
Atomoxetine	Control	376.14	226.95	312.20	22.76	13.35	18.73	26.23	20.88	23.94	0.46	0.38	0.43	16.74	17.14	16.91
	Vehicle	312.81	152.16	243.96	18.02	8.40	13.90	20.58	11.68	16.77	0.46	0.48	0.47	18.16	18.32	18.23
	0.030	396.25	107.67	272.57	23.50	6.00	16.00	29.00	9.00	20.43	0.47	0.40	0.44	16.90	17.11	16.99
	0.100	468.75	207.33	356.71	27.50	12.33	21.00	32.75	19.33	27.00	0.53	0.41	0.48	16.98	17.19	17.07
	0.224	539.25	110.67	355.57	33.25	8.33	22.57	36.50	9.33	24.86	0.66	0.39	0.54	16.71	8.40	13.15
	1.200	502.00	203.00	373.86	28.25	12.17	21.36	29.63	13.83	22.86	0.46	0.35	0.41	17.95	10.75	14.86
	4.000	208.75	182.00	197.29	13.25	11.33	12.43	14.50	13.67	14.14	0.49	0.51	0.50	16.64	15.70	16.24
	Total	***399.73***	***177.53***	***304.50***	***23.52***	***10.72***	***18.03***	***26.82***	***14.49***	***21.53***	***0.50***	***0.42***	***0.47***	***17.35***	***15.19***	***16.42***
Escitalopram	Control	258.70	238.38	251.08	17.28	15.63	16.66	22.29	20.85	21.75	0.50	0.42	0.47	15.19	14.54	14.94
	Vehicle	261.17	232.97	250.59	16.12	12.44	14.74	21.60	15.72	19.40	0.47	0.39	0.44	16.42	17.59	16.86
	0.224	306.60	263.67	290.50	19.80	14.00	17.63	24.40	21.67	23.38	0.64	0.47	0.58	15.63	18.69	16.78
	1.200	377.60	337.17	362.44	20.10	17.67	19.19	24.20	18.50	22.06	0.53	0.48	0.51	19.52	19.57	19.54
	4.000	242.20	324.67	273.13	16.20	19.00	17.25	16.80	20.67	18.25	0.41	0.48	0.43	16.05	17.29	16.51
	8.000	385.60	318.00	360.25	23.20	17.67	21.13	31.00	19.67	26.75	0.45	0.42	0.44	17.08	18.06	17.45
	Total	***309.24***	***225.75***	***277.93***	***19.18***	***19.18***	***19.18***	***23.94***	***19.61***	***22.32***	***0.50***	***0.44***	***0.48***	***16.68***	***17.44***	***16.96***

Table 2: Obtained averages for each dependent measure according to dose, rate-group, and drug in the equal reinforcement rate condition.

Unequal Reinforcement Ratio

		NP Total			S_R Total			CO Total			Prop. of NP on Rich Side			NP:S_R Ratio		
	dose	**High**	**Low**	**ALL**	**High**	**Low**	**ALL**	**High**	**Low**	**ALL**	**High**	**Low**	**ALL**	**High**	**Low**	**ALL**
Amphetamine	Control	432.00	175.33	322.00	30.00	10.22	21.52	46.67	16.67	33.81	0.71	0.66	0.69	14.30	17.29	15.58
	Vehicle	496.69	138.25	343.07	32.88	9.00	22.64	48.94	14.83	34.32	0.70	0.65	0.68	14.81	15.44	15.08
	0.010	543.25	154.33	376.57	35.25	11.33	25.00	50.50	16.33	35.86	0.71	0.66	0.69	15.40	14.65	15.08
	0.030	312.50	123.67	231.57	20.13	8.33	15.07	28.63	14.00	22.36	0.69	0.73	0.71	15.09	12.39	13.93
	0.100	318.00	106.67	227.43	21.00	6.33	14.71	37.88	9.33	25.64	0.58	0.62	0.59	13.21	16.73	14.72
	0.400	173.75	19.00	107.43	10.50	1.67	6.71	23.25	1.67	14.00	0.71	0.51	0.62	16.70	7.89	12.92
	Total	***389.40***	***133.06***	***279.54***	***25.20***	***8.47***	***18.03***	***41.23***	***13.71***	***29.44***	***0.67***	***0.63***	***0.65***	***15.20***	***14.55***	***14.92***
Atomoxetine	Control	313.58	264.33	292.48	23.08	12.00	18.33	18.92	14.67	17.10	0.74	0.64	0.70	15.55	20.55	17.69
	Vehicle	347.94	161.42	268.00	25.38	10.75	19.11	16.56	11.08	14.21	0.78	0.65	0.72	13.77	14.01	13.87
	0.010	368.00	258.00	320.86	30.50	14.67	23.71	15.25	17.33	16.14	0.84	0.66	0.76	12.47	18.09	14.88
	0.030	345.75	163.50	267.64	23.50	9.83	17.64	18.00	11.17	15.07	0.76	0.61	0.70	14.30	17.24	15.56
	0.100	307.75	118.67	226.71	21.00	7.67	15.29	17.50	5.00	12.14	0.76	0.71	0.74	14.10	19.74	16.52
	0.224	129.50	239.00	176.43	9.25	14.33	11.43	7.25	18.00	11.86	0.82	0.59	0.72	11.01	18.87	14.38
	4.000	173.75	44.00	118.14	14.25	3.33	9.57	9.50	3.33	6.86	0.89	0.57	0.75	9.35	7.47	8.54
	Total	***295.32***	***184.18***	***247.69***	***21.31***	***10.41***	***16.64***	***15.70***	***12.17***	***14.19***	***0.79***	***0.61***	***0.71***	***13.18***	***17.09***	***14.86***
Escitalopram	Control	341.67	205.22	290.50	21.93	12.67	18.46	30.33	16.11	25.00	0.64	0.69	0.66	15.41	15.49	15.44
	Vehicle	272.05	246.17	262.34	17.25	14.33	16.16	25.45	21.67	24.03	0.61	0.66	0.63	13.79	16.41	14.77
	0.100	370.80	266.33	331.63	24.60	16.00	21.38	32.80	20.33	28.13	0.65	0.69	0.66	14.82	15.70	15.15
	0.224	260.60	157.83	222.06	16.30	10.17	14.00	19.50	14.00	17.44	0.71	0.69	0.71	15.78	15.32	15.61
	8.000	367.20	263.33	328.25	22.90	16.33	20.44	22.60	20.33	21.75	0.66	0.66	0.66	16.64	15.84	16.34
	16.000	250.40	200.33	231.63	15.60	11.67	14.13	10.80	11.00	10.88	0.81	0.62	0.74	16.96	18.69	17.60
	Total	***309.24***	***225.75***	***277.93***	***19.18***	***13.31***	***16.98***	***24.05***	***18.03***	***21.79***	***0.66***	***0.65***	***0.65***	***16.13***	***16.75***	***16.36***

Table 3: Obtained averages for each dependent measure according to dose, rate-group, and drug in the unequal reinforcement rate condition.

Figures

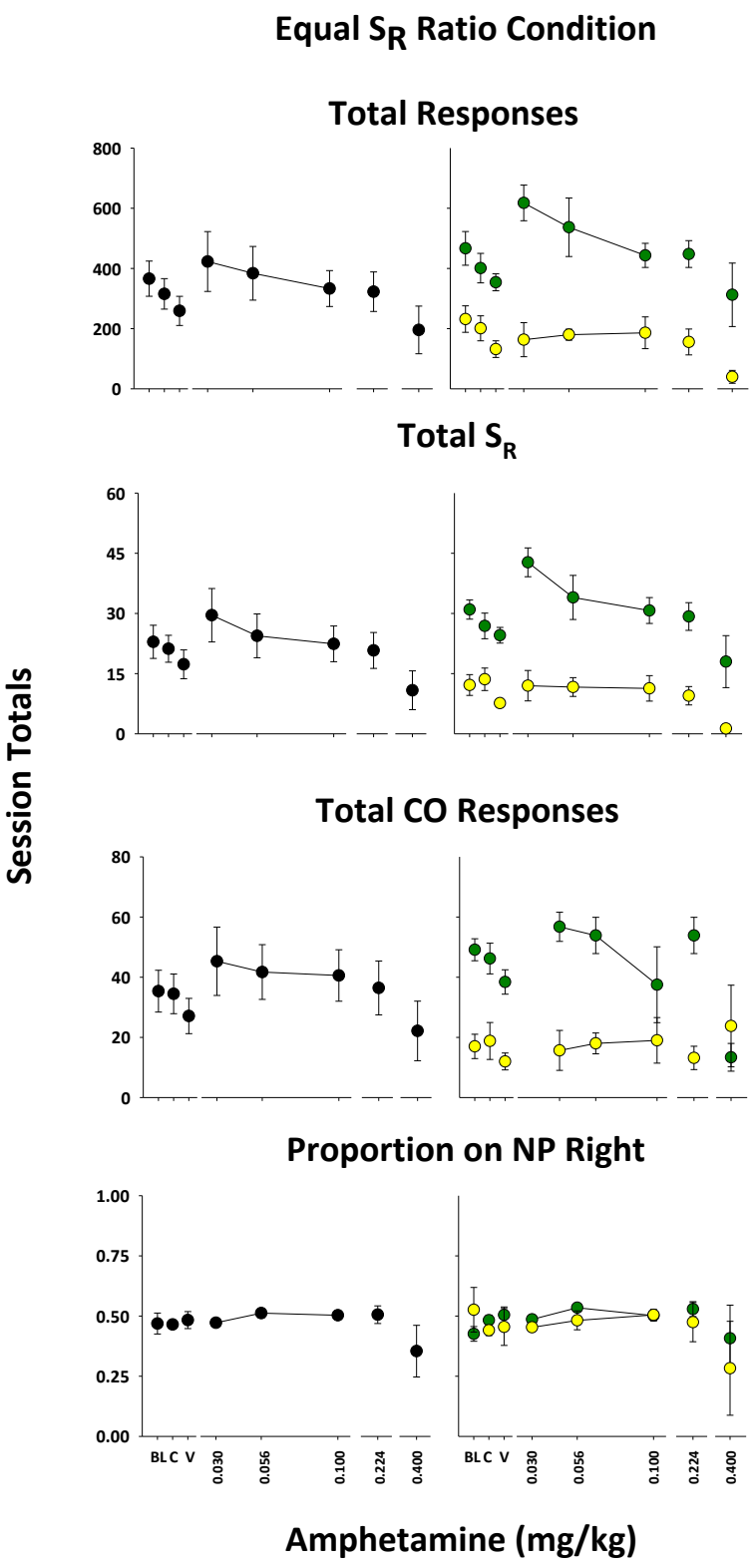
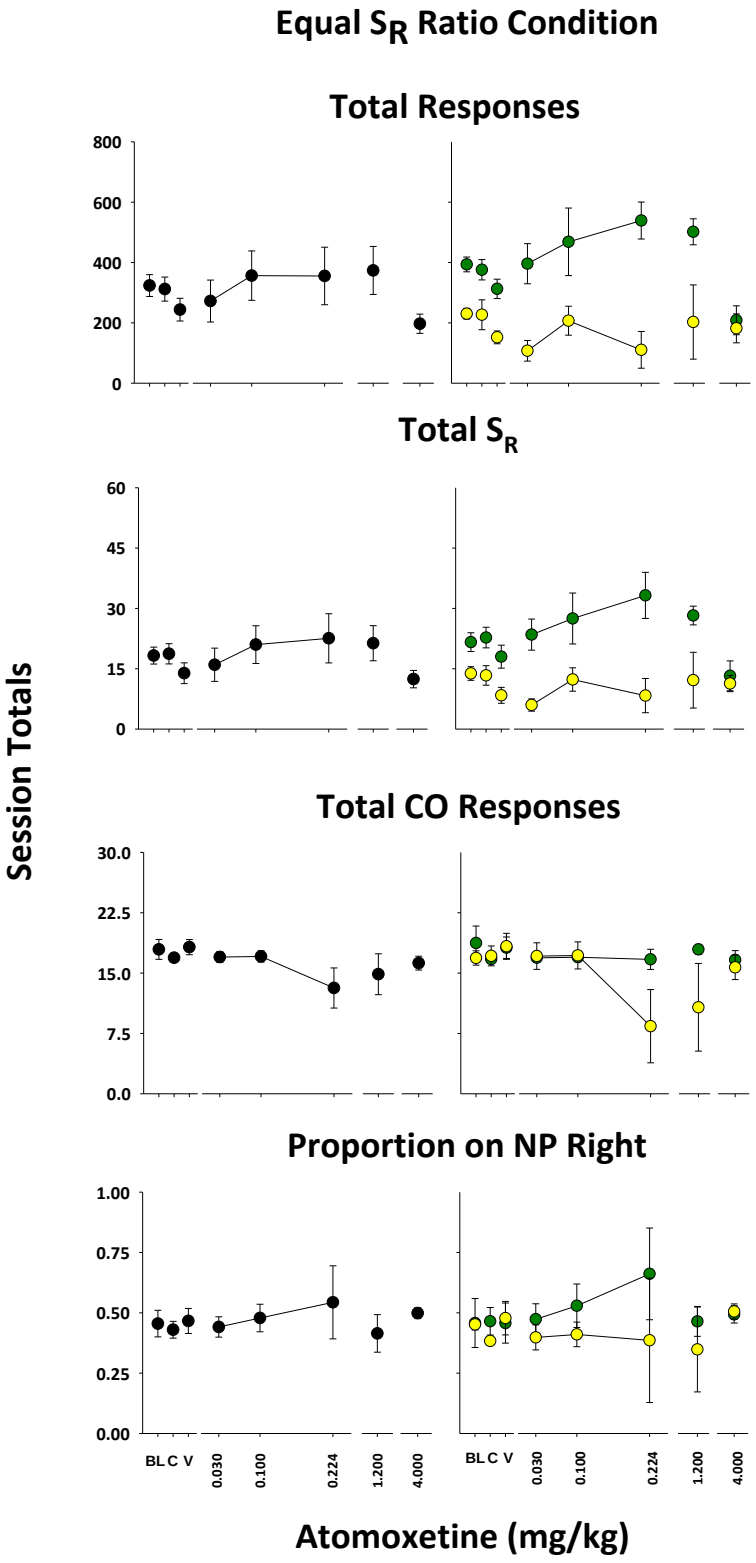

Equal S_R Ratio Condition
Total Responses
800
600
400
200
0
Total S_R
60
45
30
15
0
Session Totals
Total CO Responses
80
60
40
20
0
Proportion on NP Right
1.00
0.75
0.50
0.25
0.00
BL C V
0.030
0.056
0.100
0.224
0.400
BL C V
0.030
0.056
0.100
0.224
0.400
Amphetamine (mg/kg)

Figure 1: Session averages obtained during the equal reinforcement ratio condition for the amphetamine subjects. The dependent measures are the total responses made (top row), total reinforcers earned (upper middle row), total changeover responses made (lower middle row) and proportion of responses made on the right alternative (bottom row) plotted as a function of dose for all subjects (left column) or separately for rate groups (right column). Error bars represent standard error of the mean. Note that pre-drug baseline is included separately along with control (non-injection sessions during the acute-drug phase) and vehicle-injection sessions.


Equal S_R Ratio Condition
Total Responses
800
600
400
200
0
Total S_R
60
45
30
15
0
Session Totals
Total CO Responses
30.0
22.5
15.0
7.5
0.0
Proportion on NP Right
1.00
0.75
0.50
0.25
0.00
BL C V
0.030
0.100
0.224
1.200
4.000
Atomoxetine (mg/kg)

\

Figure 2: Session averages obtained during the equal reinforcement ratio condition for the atomoxetine subjects. The dependent measures are the total responses made (top row), total reinforcers earned (upper middle row), total changeover responses made (lower middle row) and proportion of responses made on the right alternative (bottom row) plotted as a function of dose for all subjects (left column) or separately for rate groups (right column). Error bars represent standard error of the mean. Note that pre-drug baseline is included separately along with control (non-injection sessions during the acute-drug phase) and vehicle-injection sessions.

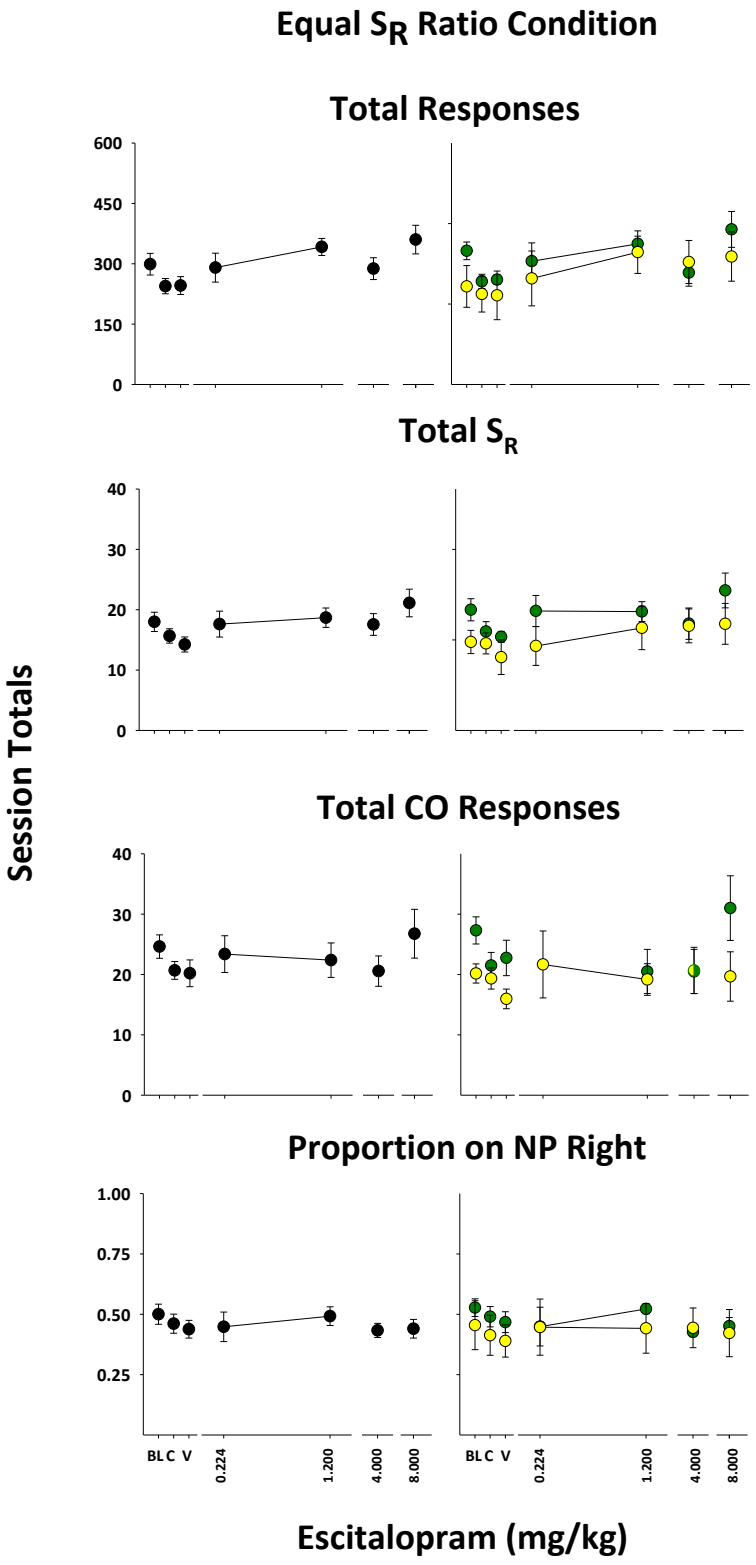

Equal S_R Ratio Condition
Total Responses
600
450
300
150
0
Total S_R
40
30
20
10
0
Total CO Responses
40
30
20
10
0
Proportion on NP Right
1.00
0.75
0.50
0.25
BL C V
0.224
1.200
4.000
8.000
BL C V
0.224
1.200
4.000
8.000
Session Totals
Escitalopram (mg/kg)

Figure 3: Session averages obtained during the equal reinforcement ratio condition for the escitalopram subjects. The dependent measures are the total responses made (top row), total reinforcers earned (upper middle row), total changeover responses made (lower middle row) and proportion of responses made on the right alternative (bottom row) plotted as a function of dose for all subjects (left column) or separately for rate groups (right column). Error bars represent standard error of the mean. Note that pre-drug baseline is included separately along with control (non-injection sessions during the acute-drug phase) and vehicle-injection sessions.

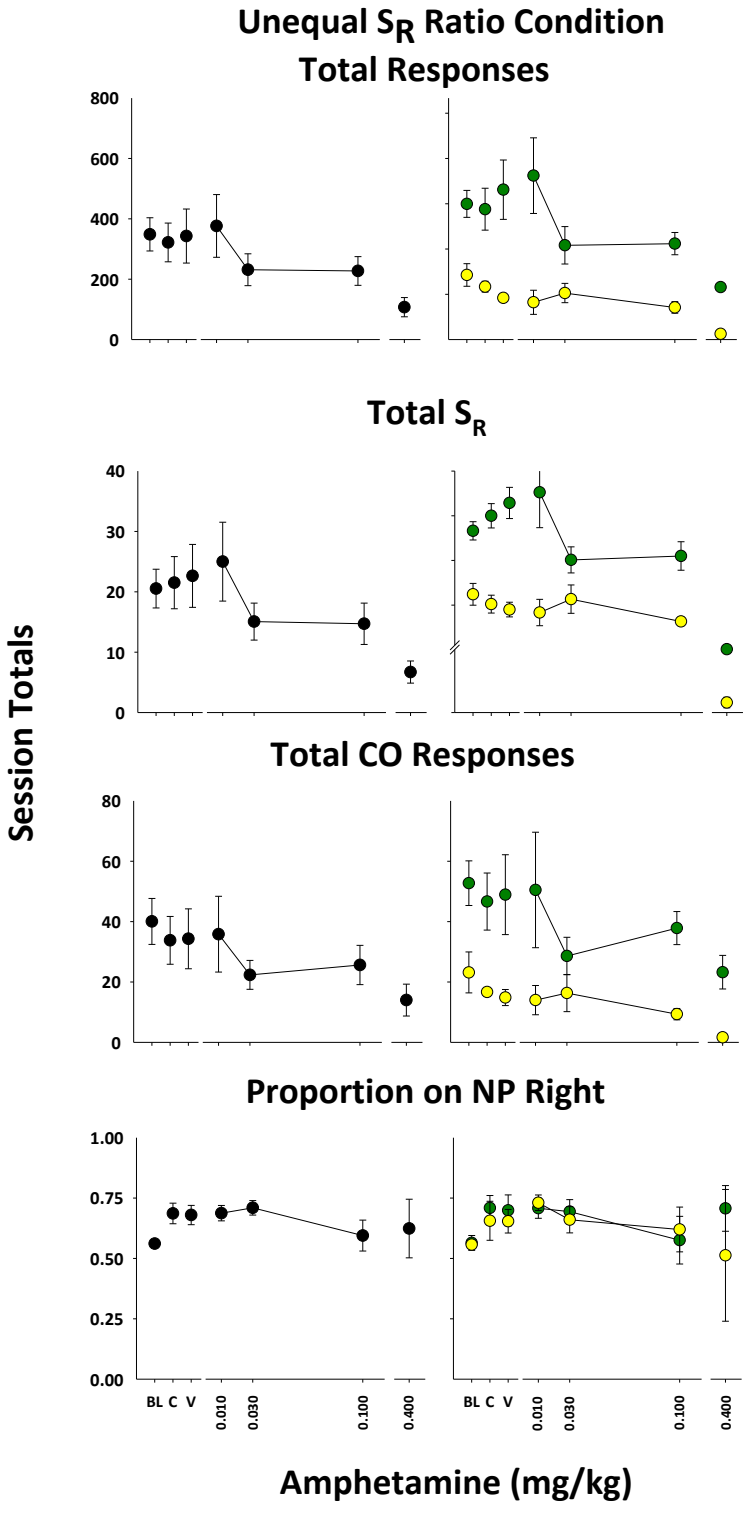

Unequal S_R Ratio Condition
Total Responses
800
600
400
200
0
Total S_R
40
30
20
10
0
Total CO Responses
80
60
40
20
0
Proportion on NP Right
1.00
0.75
0.50
0.25
0.00
BL C V
0.010
0.030
0.100
0.400
Session Totals
Amphetamine (mg/kg)

Figure 4: Session averages obtained during the unequal reinforcement ratio condition for the *d*-amphetamine subjects. The dependent measures are the total responses made (top row), total reinforcers earned (upper middle row), total changeover responses made (lower middle row) and proportion of responses made on the rich alternative (bottom row) plotted as a function of dose for all subjects (left column) or separately for rate groups (right column). Error bars represent standard error of the mean. Note that pre-drug baseline is included separately along with control (non-injection sessions during the acute-drug phase) and vehicle-injection sessions.

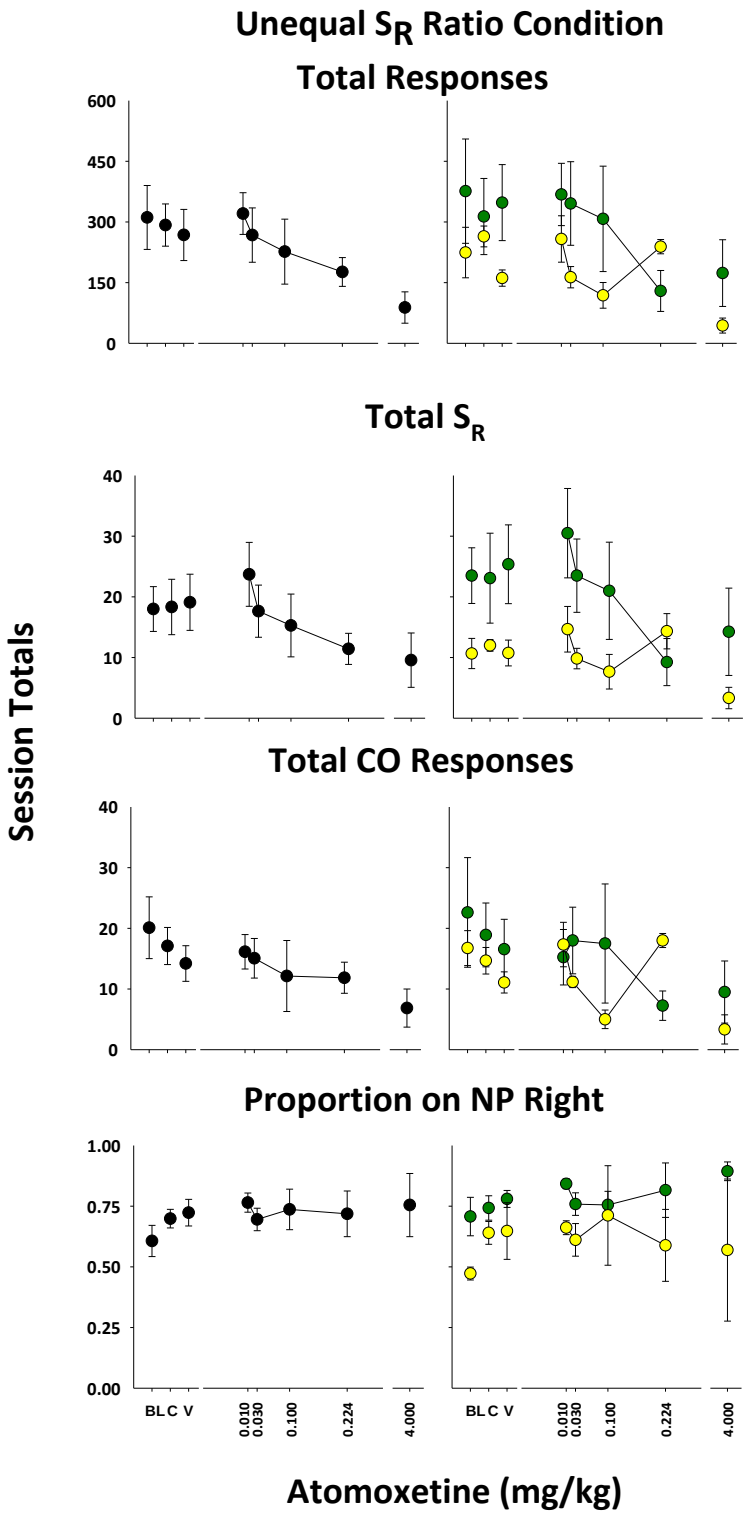

Unequal S_R Ratio Condition
Total Responses
600
450
300
150
0
Total S_R
40
30
20
10
0
Session Totals
Total CO Responses
40
30
20
10
0
Proportion on NP Right
1.00
0.75
0.50
0.25
0.00
BLC V
0.010
0.030
0.100
0.224
4.000
BLC V
0.010
0.030
0.100
0.224
4.000
Atomoxetine (mg/kg)

Figure 5: Session averages obtained during the unequal reinforcement ratio condition for the atomoxetine subjects. The dependent measures are the total responses made (top row), total reinforcers earned (upper middle row), total changeover responses made (lower middle row) and proportion of responses made on the rich alternative (bottom row) plotted as a function of dose for all subjects (left column) or separately for rate groups (right column). Error bars represent standard error of the mean. Note that pre-drug baseline is included separately along with control (non-injection sessions during the acute-drug phase) and vehicle-injection sessions.

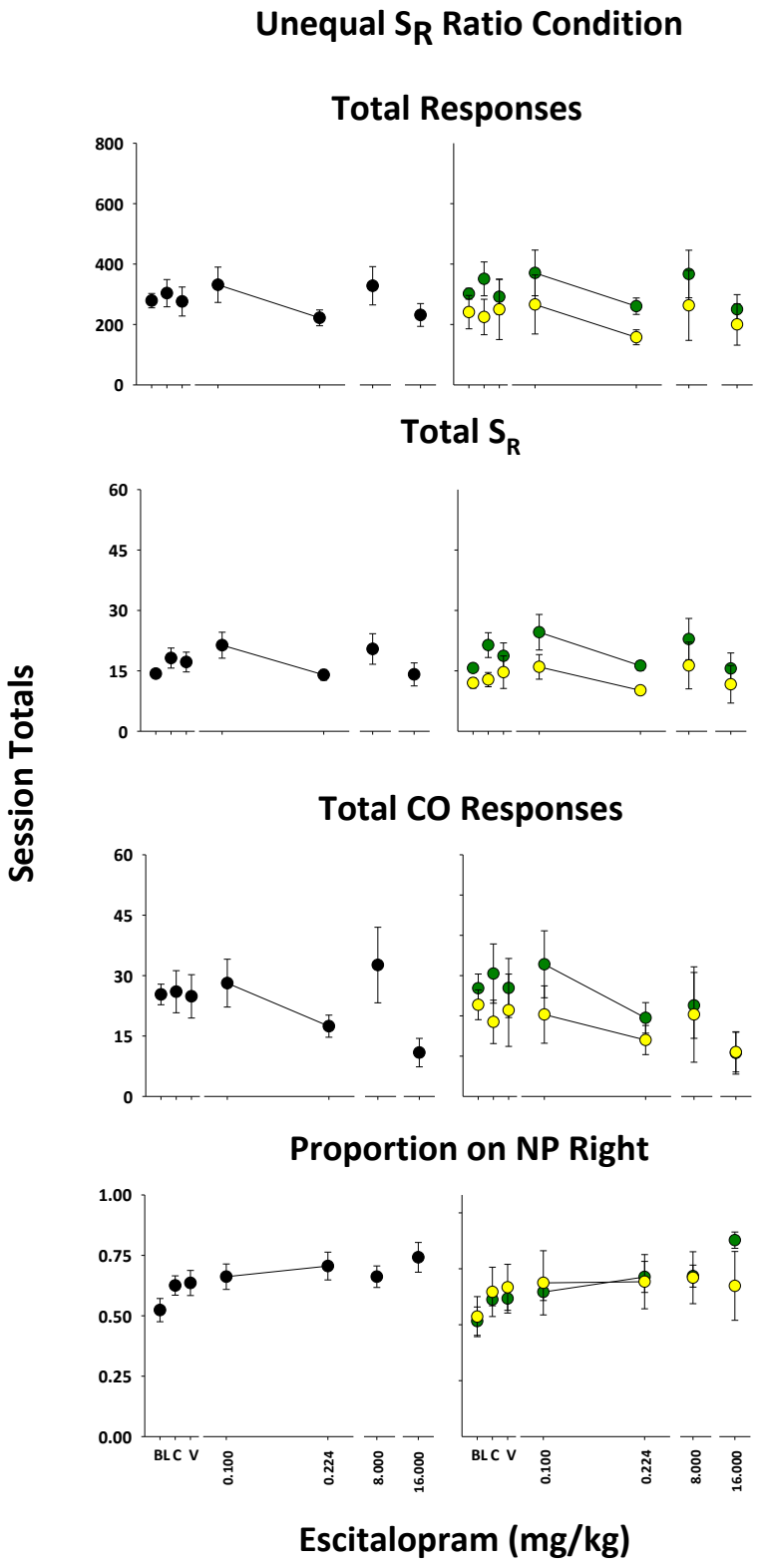

Unequal S_R Ratio Condition
Total Responses
800
600
400
200
0
Total S_R
60
45
30
15
0
Session Totals
Total CO Responses
60
45
30
15
0
Proportion on NP Right
1.00
0.75
0.50
0.25
0.00
BL C V
0.100
0.224
8.000
16.000
BL C V
0.100
0.224
8.000
16.000
Escitalopram (mg/kg)

Figure 6: Session averages obtained during the unequal reinforcement ratio condition for the escitalopram subjects. The dependent measures are the total responses made (top row), total reinforcers earned (upper middle row), total changeover responses made (lower middle row) and proportion of responses made on the rich alternative (bottom row) plotted as a function of dose for all subjects (left column) or separately for rate groups (right column). Error bars represent standard error of the mean. Note that pre-drug baseline is included separately along with control (non-injection sessions during the acute-drug phase) and vehicle-injection sessions.

References

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Appendix

Concurrent Variable Ratio Schedule Training.

Independently Arranged Concurrent VR Schedules.

In order to establish behavioral baseline performance under the control of the final concurrent variable ratio (VR) schedule conditions, subject first progressed through a series of training phases (4 in total). Following autoshaping on the left then right nosepoke, characterized as continuous reinforcement (i.e., fixed ratio (FR) 1, subjects completed 3 phases of concurrent VR schedules. The concurrent VR values were gradually increased across each phase in order to avoiding ratio strain while bringing response rates to the final level desired for acute drug administration. Independently arranged concurrent VR schedules arranged reinforcement between the left and right nosepoke in a 1:1 ratio, respectively, and progressed as follows: concurrent VR3:3 in phase 1, concurrent VR 6:6 in phase 2, and concurrent VR 10:10 in phase 3.

Sixty-minute sessions began with the illumination of the two backlit nosepokes left and right of the pellet receptacle. Completion of the programmed response ratio lead to delivery of a 20mg sucrose pellet followed by a 2s inter reinforcement interval in which responding on the continuously illuminated nosepokes was recorded but did not count toward the response ratio. In the third training phase, observation of subjects during experimental sessions revealed that subjects periodically approximated nosepoke responses without breaking the photobeam and registering a response so a brief tone was added to nosepokes in order to make completed responses more salient. Sessions were run with 11 operant chambers in two 11-subject squads. Experimental sessions were conducted daily, starting at 5 pm and spaced 70-minutes apart.

Dependently Arranged Concurrent VR VR Schedules.

In the 4th phase of training the independently programmed concurrent VR10:10 schedule was switched to a dependently arranged concurrent VR10:10. The dependently arranged VR10:10 procedure was chosen as the equal reinforcement rate condition for subsequent acute drug administration sessions. Following 14 days of dependently arranged VR10:10 (i.e., equal reinforcement rate) sessions, exposure to unequal reinforcement rate sessions began. During the unequal reinforcement rate conditions, sessions began with a VR10:10 and transitioned to either a VR16:1 or 1:16 20 minutes into the experimental session. Occasionally, exclusive responding developed on the rich alternative during experimental sessions; indicating bias. When this happened, the reinforcement ratio in the subsequent session returned to a 1to1 arrangement in order to re-establish responding on the lean alternative. Unbiased responding was typically re-established following one equal-reinforcement rate session.

After 82 days of conducting one session per day, two-session days began in which subjects were run once starting at 7 am (morning session) and a second time starting at 5pm (evening session). This condition was continued from session 104 to 127 in Table 1.

Performance Tracking

Data collection. Dependent measures for concurrent schedule performance included total nosepokes made to the left or right, overall response ratios, and the number of change-over responses from one side to the other. Whole-session data for individual subject were analyzed separately for equal and unequal reinforcement ratio sessions. Individual subject data was aggregated across sessions to determine stability.

Results

Autoshaping

(see chapter 2 for detailed methods). Log-rank survival analysis of time spent in autoshaping for the initial side (Figure 1) did not reveal any group differences (see Table 1). The average number of sessions required to complete the response requirement of 40 consecutive responses within a single session were consistent for the first nosepoke (m = 3.1, SE = 0.4) and second nosepoke (m = 3.0, SE = 0.3). Although the maximum number of sessions required for subjects to meet the criterion totaled six for some subjects, the subjects required fewer sessions to complete the response requirement on the second alternative.

Concurrent Schedule Iterations

Concurrent VRs: Equal-Reinforcer Ratios. The sequence of concurrent-schedule arrangements (detailed in Table 1) nearly doubled response rates from phase 1 (m = 156.32, std. error = 26.93) to phase 4 (m = 299.77, std. error = 83.64) (refer to Table 3 for all dependent measures). Overall, the increase in response output was also associated with a gradual shift in response allocation. The obtained response ratios for the session in which the maximum response rate was achieved showed an overall trend from the initial left side bias (m = 2.52, max = 13.93, std. error = 0.81) to a closer approximation of equal responding (m = 1.46, max = 3.47, std. error = 0.76), a primary goal of arranging equivalent reinforcement ratios.

The relationship between response ratios and response totals for each session during the fourth phase of preliminary training is summarized in Figure 1. As indicated by the distribution of response ratios (i.e., y-axis of Figure 1), the scatterplot distribution primarily fell within the range of 1.0 and 2.5.

Concurrent VR10: Unequal-Reinforcer Ratio. Next, the single dependently arranged ratio value was assigned to either the left or right (henceforth the lean alternative) nosepoke once for every 16 reinforcers set up on the opposing (henceforth the rich alternative) nosepoke. As a

result, the VR10 was assigned to the lean alternative with, on average, a 0.05 probability. The initial position (left or right) of the lean nosepoke was counterbalanced across subjects. Subsequently, the reinforcement-ratio in effect each day was randomized so that each condition was repeated every two to three sessions.

The amount of time allocated to each response alternative, or stated differently the visit duration, was also dependent on the reinforcement ratio in effect (see Figure 2). During the first 20 minutes of transition session and for the entirety of non-transition (equal reinforcement ratio) sessions visit duration to the left and right nosepoke were roughly equivalent. In figure 2, equal visit durations would produce a straight line with a slope of 1.0. On the other hand, during the last 40 minutes (unequal reinforcement ratio component) the visit duration favored the rich nosepoke. In figure 2, this appears as an increase in the slope for the 16:1 sessions, or a decrease in the slope for the 1:16 condition.

When plotted in descending order, it is clear that the response ratios obtained in equal and unequal-reinforcement rate fall into two distinct distributions. The two response-ratio (i.e., rich responses/lean responses) distributions from the unequal reinforcement ratio sessions show a large degree of overlap. Whereas, the distribution of response ratios (i.e., left responses/right responses) from equal reinforcement ratio sessions do not overlap with either of the unequal reinforcement ratio distributions

In phase four, the randomized order of 1to16, 1to1, and 16to1 reinforcement ratio conditions continued for 20 sessions until the proportion of responding was consistently higher on the rich alternative (see Figure 4). Further, the frequency of change-over responses obtained during the first 5 sessions of each reinforcement-ratio condition (see figure 5, upper row) showed an overall decreasing trend that was roughly equivalent across conditions (see dashed line

indicator of 5-session mean in upper left panel of figure 5). During the last 5 sessions of phase 4 the mean change-over rate for the unequal reinforcement-ratio condition, although slight, was consistently lower than the equal reinforcement-ratio condition. Suggesting that subjects spent less time (see figure 2) and made fewer visits to the lean side during unequal reinforcement-ratio sessions.

General Conclusions

The final concurrent ratio schedule maintained relatively equal response ratios in the equal reinforcement rate condition. Further, the obtained reinforcement rate on the lean alternative, determined by the delay between response-contingent delivery of a reinforcer and its assignment to the lean side, was substantially lower than the corresponding reinforcement rate on the rich side. In fact, preference was so extreme, and changeover responses declined so much, that some subjects would fail to advance past the initial reinforcers 'set up' on the lean side due either to a failure to initiate a visit (change over) on the lean side, or failure to complete the response requirement prior to returning to the rich side. It was thus concluded that the reinforcement rate on the rich alternative was in such contrast to that of the lean alternative that contingencies maintained exclusive preference on the rich alternative limiting the total number of reinforcers obtained during the session to approximately 16, depending on the initial VR value assigned to that side.

The transition from independently arranged variable ratio schedules to non-independent (dependent) variable ratio schedules warrants further consideration. Previous research has suggested that response-contingent initiation of VI timers following a changeover increase the frequency and length of response bouts (Silberberg & Schrot, 1974). The combination of dependently arranged, response-contingent reinforcers along with the variable ratio requirement

might have served to increase the discriminability of response-bout initiation and the resulting response-contingent reinforcer delivery. This idea is supported by the improvement in performance, specifically increased CO responses and increased reinforcement rates found in the fourth phase of training.

In conclusion, the final equal and unequal reinforcement ratio conditions were successful in establishing robust response rates. Further, the pattern of time allocation and response allocation differed between the left and right nosepoke during the unequal reinforcement ratio sessions and remained more consistent during the equal-reinforcement ratio sessions.

Tables

DV - Phase	Size	Misssing	Mean	Std Dev	Std Err	C.I.	Range	Max	Min	Median	25%	75%	Sum	Sum of Squares
NPT - 1	22.00	0.00	156.32	126.30	26.93	56.00	415.00	435.00	20.00	106.00	61.75	235.50	3439.00	872585.00
NPT - 2	22.00	0.00	159.27	86.52	18.45	38.36	277.00	313.00	36.00	145.00	85.25	242.00	3504.00	715300.00
NPT - 3	22.00	0.00	186.05	70.95	15.13	31.46	340.00	397.00	57.00	195.50	138.00	230.50	4093.00	867189.00
NPT - 4	22.00	0.00	299.77	188.64	40.22	83.64	598.00	688.00	90.00	261.50	128.75	442.25	6595.00	2724273.00
L-to-R Ratio - 1	22.00	3.00	2.52	3.53	0.81	1.70	13.90	13.93	0.03	0.82	0.38	3.60	47.97	345.45
Ratio - 2	22.00	1.00	2.35	3.85	0.84	1.75	16.96	17.00	0.04	0.49	0.24	3.84	49.38	411.77
Ratio - 3	22.00	1.00	1.67	1.71	0.37	0.78	6.95	7.10	0.16	0.96	0.54	2.15	35.10	117.15
Ratio - 4	22.00	0.00	1.46	0.76	0.16	0.34	3.19	3.47	0.28	1.29	1.00	1.94	32.21	59.24
NP_L - 1	22.00	0.00	80.86	83.73	17.85	37.13	309.00	309.00	0.00	39.50	15.75	121.25	1779.00	291087.00
NP_L - 2	22.00	0.00	77.96	73.99	15.77	32.80	235.00	242.00	7.00	49.00	15.75	135.25	1715.00	248647.00
NP_L - 3	22.00	0.00	106.41	76.38	16.29	33.87	335.00	348.00	13.00	90.00	52.00	143.25	2341.00	371627.00
NP_L - 4	22.00	0.00	158.05	101.95	21.74	45.20	425.00	471.00	46.00	139.50	79.25	202.00	3477.00	767771.00
SR_L - 1	22.00	0.00	16.59	14.99	3.20	6.64	53.00	53.00	0.00	9.00	5.50	30.25	365.00	10771.00
SR_L - 2	22.00	0.00	11.77	8.32	1.77	3.69	33.00	34.00	1.00	9.00	5.75	18.50	259.00	4503.00
SR_L - 3	22.00	0.00	12.59	6.70	1.43	2.97	27.00	30.00	3.00	13.00	7.00	16.25	277.00	4431.00
SR_L - 4	22.00	0.00	14.41	7.06	1.51	3.13	23.00	28.00	5.00	13.50	7.50	20.25	317.00	5615.00
NP_R - 1	22.00	0.00	75.46	98.09	20.91	43.49	415.00	416.00	1.00	32.00	18.75	93.75	1660.00	327300.00
NP_R - 2	22.00	0.00	81.32	71.19	15.18	31.57	265.00	265.00	0.00	63.50	35.00	90.25	1789.00	251919.00
NP_R - 3	22.00	0.00	79.64	45.32	9.66	20.09	199.00	199.00	0.00	78.00	47.75	109.25	1752.00	182656.00
NP_R - 4	22.00	0.00	141.73	119.92	25.57	53.17	501.00	529.00	28.00	113.00	43.75	182.50	3118.00	743910.00
SR_R - 1	22.00	0.00	15.05	15.61	3.33	6.92	68.00	69.00	1.00	10.00	5.75	19.00	331.00	10099.00
SR_R - 2	22.00	0.00	12.96	9.40	2.01	4.17	45.00	45.00	0.00	12.50	6.75	15.75	285.00	5549.00
SR_R - 3	22.00	0.00	9.73	5.64	1.20	2.50	21.00	22.00	1.00	9.00	6.00	13.00	214.00	2750.00
SR_R - 4	22.00	0.00	11.82	7.26	1.55	3.22	25.00	27.00	2.00	11.50	4.75	16.50	260.00	4180.00
CO - 1	22.00	0.00	22.09	14.90	3.18	6.61	65.00	72.00	7.00	16.50	12.25	28.00	486.00	15400.00
CO - 2	22.00	0.00	16.64	8.69	1.85	3.85	34.00	36.00	2.00	15.00	9.00	24.25	366.00	7674.00
CO - 3	22.00	0.00	19.23	10.59	2.26	4.70	40.00	44.00	4.00	16.00	12.00	25.75	423.00	10489.00
CO - 4	22.00	0.00	42.14	24.53	5.23	10.88	80.00	89.00	9.00	36.00	21.50	68.50	927.00	51695.00

Table 1: Measures of central tendency for 1to1 performance across the 4 phases of preliminary training for total responses (NPT, first set of 4 rows), response ratio (LtoR, second set of 4 rows), responses per side (NP_L, third set of 4 rows, NP_R, fifth set of 4 rows), reinforcers earned per side (SR_L, fourth set of 4 rows, SR_R, sixth set of 4 rows), change over responses (CO, seventh set of 4 rows). Session characterized by atypical response patterns (e.g., exclusive responding to one side) were censored from the analyses and noted in the 'Missing' column.

Figures

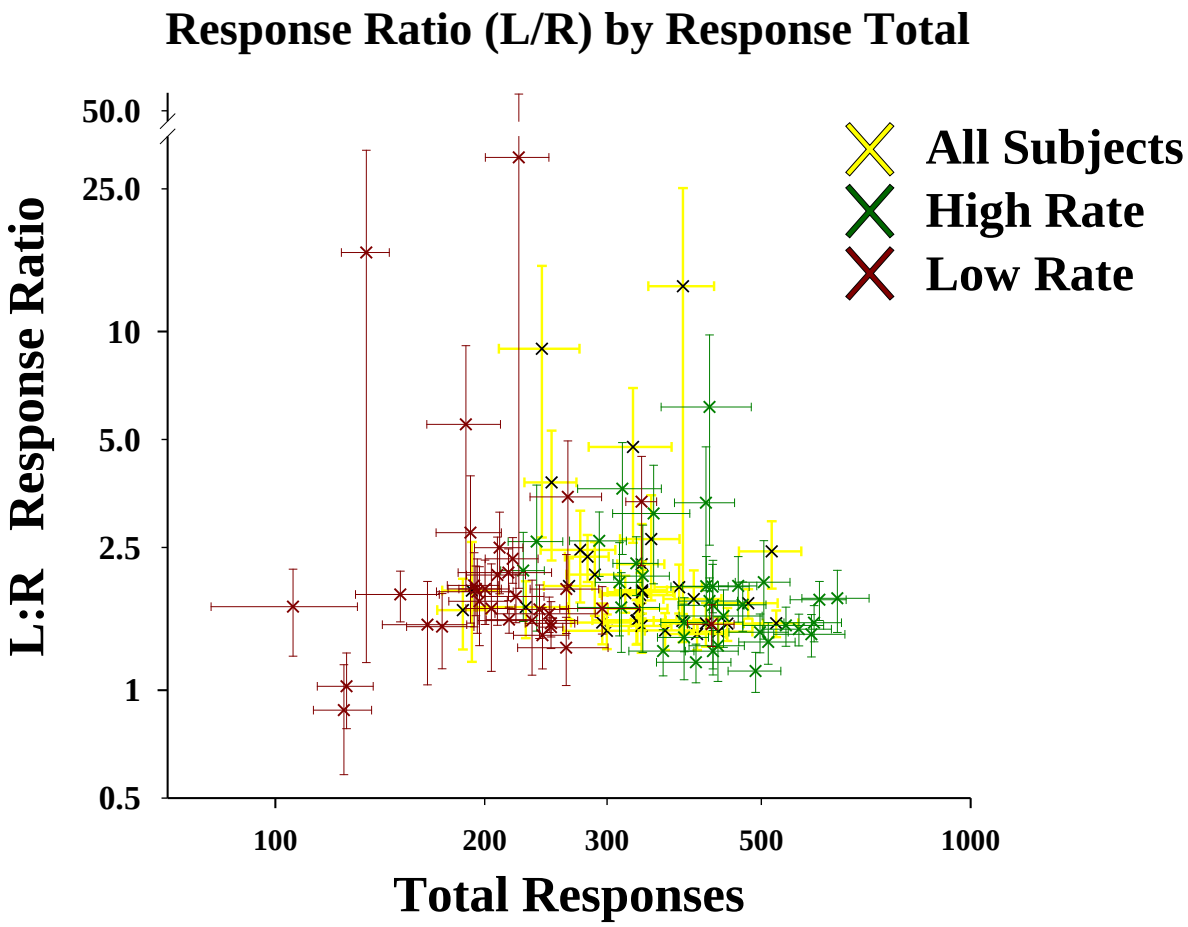

Figure 1: For each session, average obtained response ratios ($\log_{10}$) are plotted as a function of average responses made per session for low-rate subjects (dark yellow), high-rate subjects (green), and group average. Note that the y-axis is log transformed. Vertical and horizontal error bars are standard error of the mean.

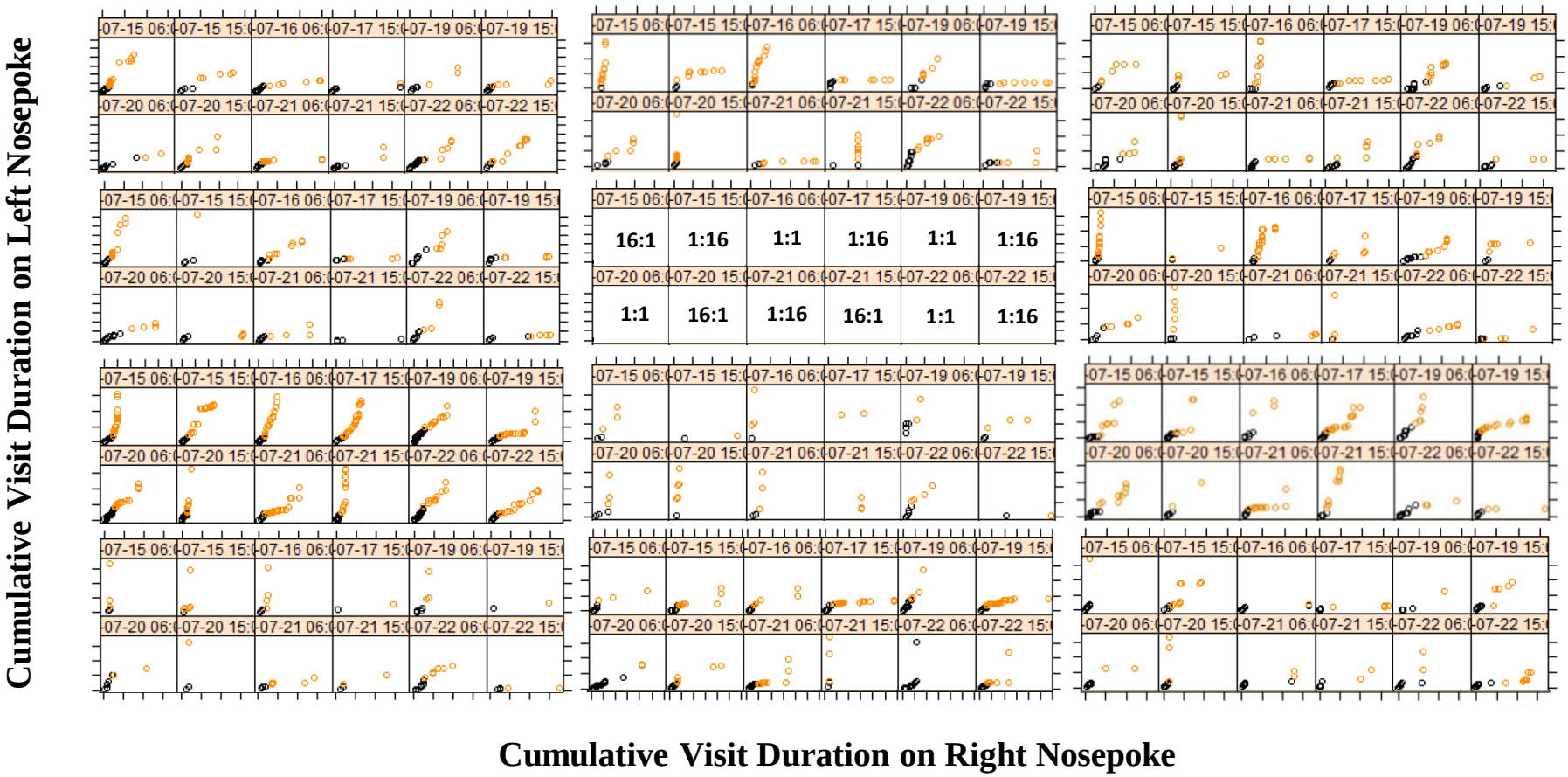

Figure 2: The time point of each changeover response is plotted as a function of the cumulative visit duration on the left and right nosepoke for 16:1, 1:1, and 1:16 reinforcement ratio sessions. Black data points correspond to changeover responses made during the first 20 minutes of the sessions and orange data points correspond to changeover responses made during the last 40 minutes of the session. Half of the subject are included in the figure. The subjects included in the figure are all subjects for which the rich reinforcement rate was first assigned to the left side (i.e., 16:1 was the first unequal reinforcement ratio condition). The sequence of unequal reinforcement ratios were reversed for the other subjects (not shown).

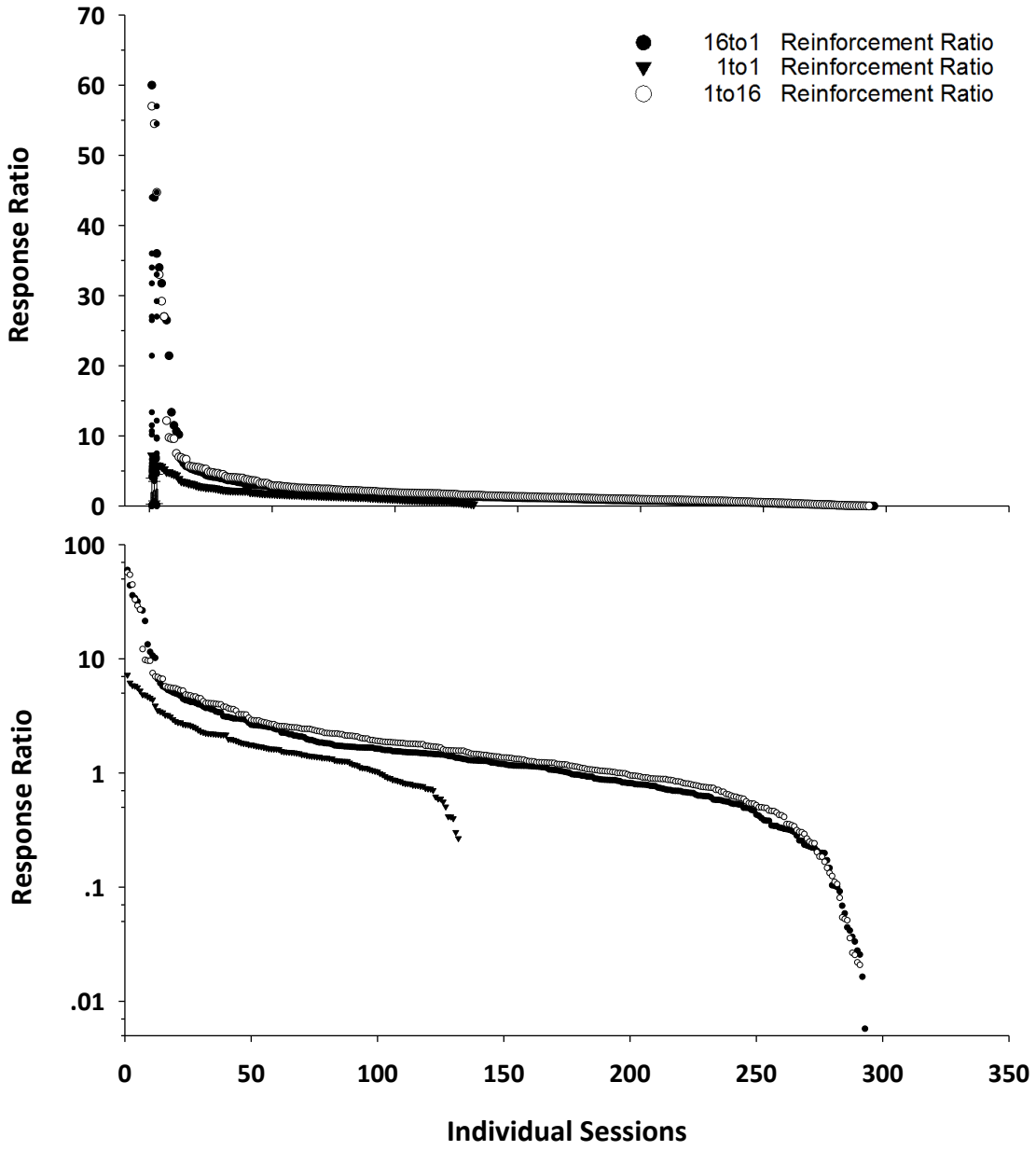

Figure 3: Obtained response ratios are plotted in descending order separately for all 16to1 (0.95 probability), 1to1 (0.5 probability), and 1to16 (0.95 probability) sessions. Note that the response ratio for 16to1 and 1to1 represents the fraction of left responses over right responses. However, the response ratio for 1to16 represents the fraction of right responses over left responses. For the upper graph, response ratios were obtained by dividing obtained responses on the rich (or left) alternative by the obtained response total on the lean (or right) alternative for all unequal (or equal) reinforcement ratio sessions. The lower graph is identical, with the exception that the y-axis is log transformed.

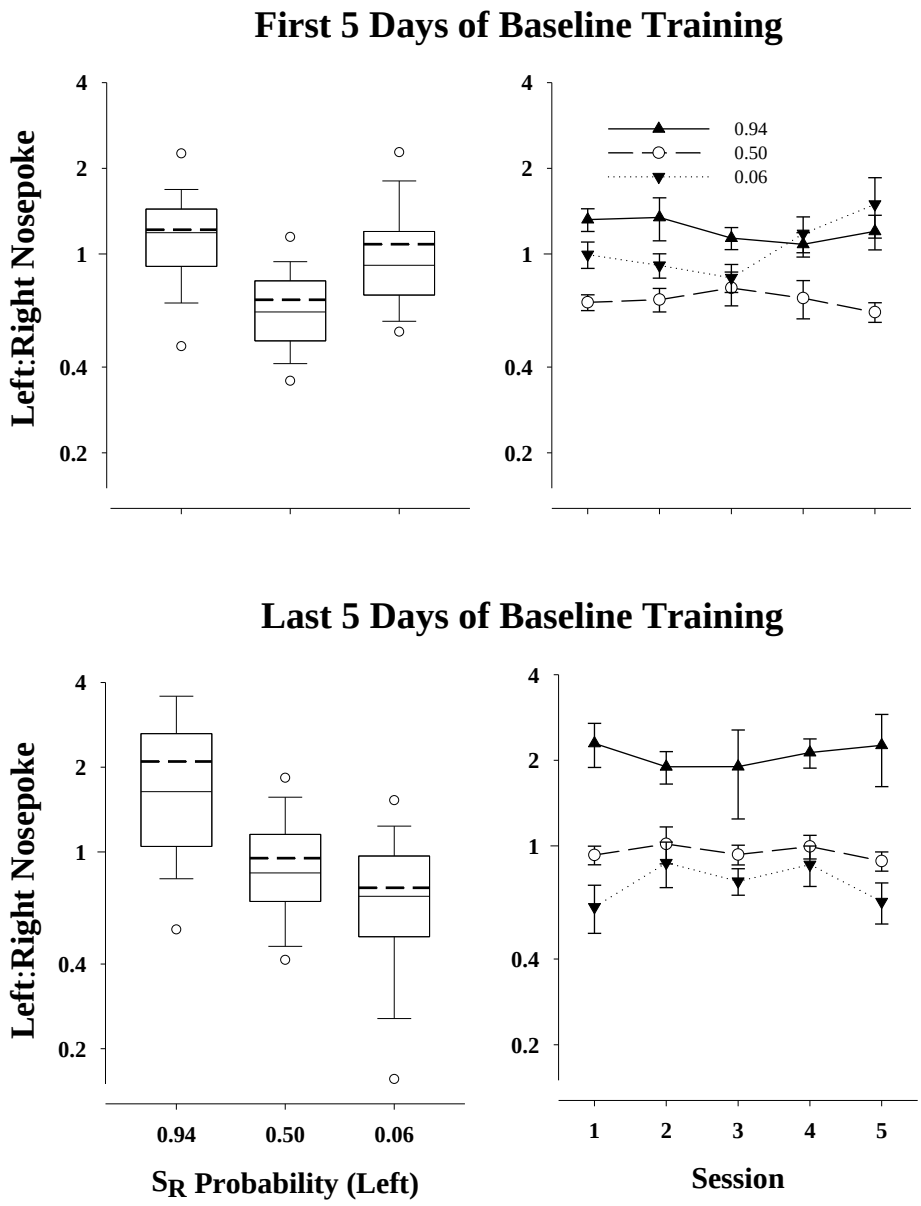

Figure 4: Obtained response ratios (left NP / right NP) are presented for the first 5 baseline sessions (top row) and last 5 baseline training sessions (bottom row) as a function of nominal reinforcer probability. The left column of graphs include the mean (dashed line, grand mean for the corresponding 5 session block), and the solid, horizontal lines within the boxplot represent 25th percentile (bottom), median (middle), and 75th percentile (top). The whiskers indicate the 10th and 90th percentile the open symbols indicate the 5th and 95th percentiles for each condition, while the right column of graphs present group mean performance per session across the corresponding 5-session block. Error bars represent standard error of the group mean.

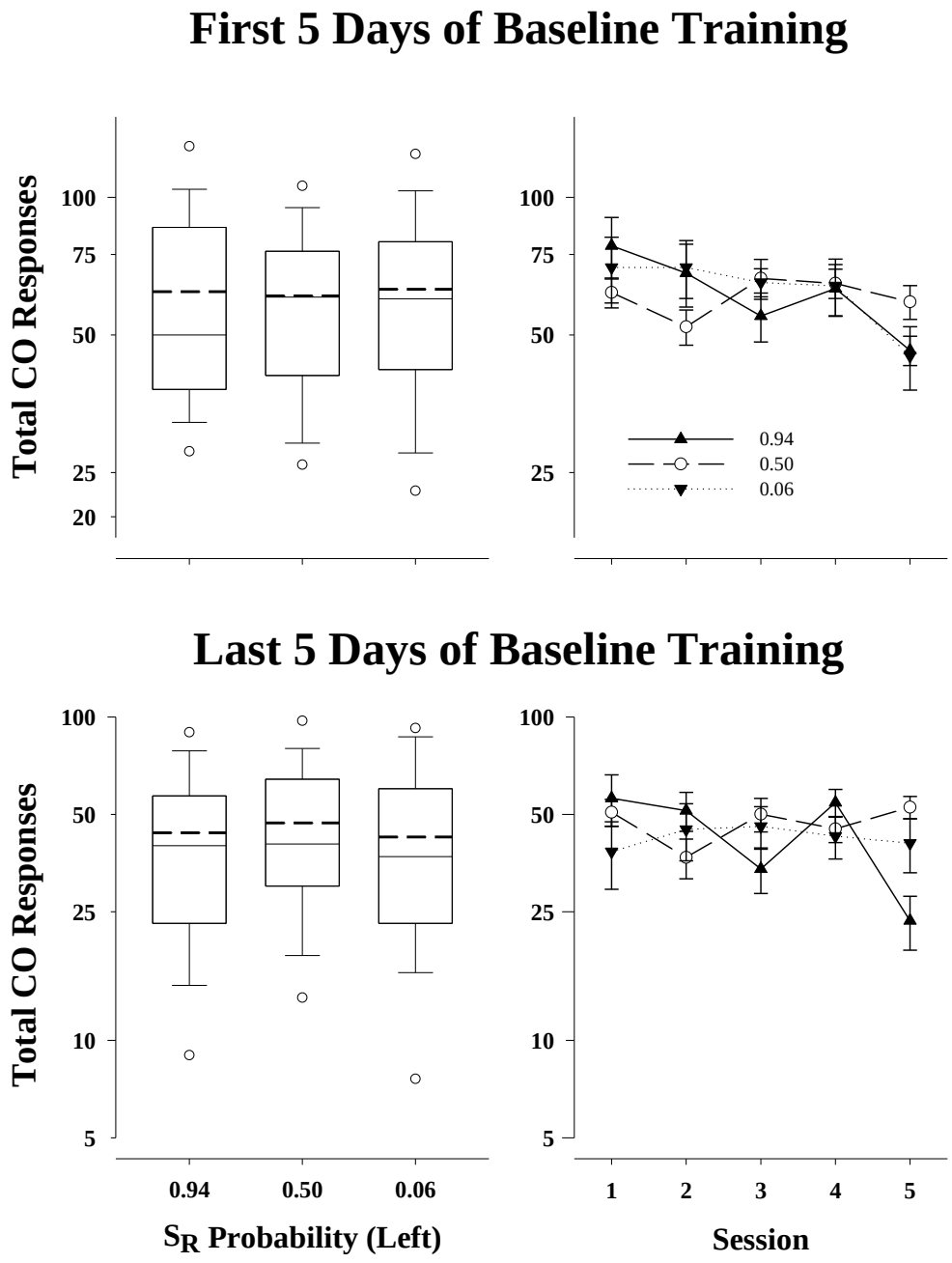

Figure 5: Total change over responses are presented for the first 5 baseline sessions (top row) and last 5 baseline training sessions (bottom row). The left column of graphs include the mean (dashed line, grand mean for the corresponding 5 session block), and the solid, horizontal lines within the boxplot represent 25th percentile (bottom), median (middle), and 75th percentile (top). The whiskers indicate the 10th and 90th percentile the open symbols indicate the 5th and 95th percentiles for each condition, while the right column of graphs present group mean performance per session across the corresponding 5-session block. Error bars represent standard error of the group mean.