DIVERSE DISRUPTORS OF TIMING: PHARMACOLOGICAL AND NON-PHARMACOLOGICAL AGENTS PRODUCE SIMILAR DISRUPTIONS OF TEMPORAL DISCRIMINATION

By

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DIVERSE DISRUPTORS OF TIMING: PHARMACOLOGICAL AND NON-PHARMACOLOGICAL AGENTS PRODUCE SIMILAR DISRUPTIONS OF TEMPORAL DISCRIMINATION

By

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Animals are sensitive to the passage of time in the seconds to minutes range, which is known as interval timing. The controlling mechanisms for this adaptive behavior have attempted to be elucidated by many techniques, including the systematic disruption of timing with the use of diverse agents. Methodological inconsistencies within the timing literature have led to discrepancies that require clarification before further theoretical work should be done. The current studies aimed to answer two main questions in order to better understand discrepancies in the timing literature: 1) What is the impact of a temporal discrimination procedural variation on the disruptive effects of agents and 2) What is the impact of the type of disruptor being used?

In Experiment 1 *d*-amphetamine, nicotine, and haloperidol were used to disrupt temporal discrimination. Experiment 2 used non-pharmacological disruptors to influence the subject's motivation to respond (e.g., food given prior to the experimental session and no longer reinforcing previously reinforced responses). In both experiments the procedure used to assess temporal discrimination required pigeons to classify stimulus duration intervals as short or long. In one variation of the procedure, response alternatives were defined by the location of response keys, while key color defined response alternatives in the second variation.

Experiment 1 found a dose-dependent decrease in the accuracy of classifying temporal intervals and a flattening of the psychophysical curve for all drug types. Experiment 2 also showed this effect due to non-pharmacological disruptors. Experiments 1 and 2 showed similar disruptions of temporal discrimination, regardless of procedural variation or disruptor type. Differences were found in baseline performance between procedural groups, which suggests that these procedures are not functionally identical and could lead to differential results under certain conditions. These experiments increase our understanding of temporal discrimination and can be used with the eventual goal of a common conceptualization of timing supported by the literature. These results hold implications for the discrepancies present in the timing literature and the search for controlling neural and behavioral mechanisms responsible for timing. A complete understanding of temporal behavior could eventually contribute to related fields of inquiry, such as impulsivity and decision-making.

CHAPTER 1
GENERAL INTRODUCTION

Timing

An animal's ability to discriminate one point in time from another is surely adaptive for a number of reasons. For example, it has been found that successful foraging in naturalistic situations (e.g., Bateson, 2003) and laboratory analogues (Brunner *et al*., 1992) relies on accurate temporal discrimination for a variety of species, and this relationship has been experimentally manipulated and confirmed with hummingbirds using replenishing patches (Crystal, 2006; Henderson, *et al*., 2006). Timing also exists on multiple scales, which can be useful for certain activities. There is timing at the millisecond level, interval timing for minutes to seconds, and circadian timing. Interval timing has been shown to play a role in such behavior as optimal foraging (Bateson, 2003), while millisecond timing is useful for other abilities, such as motor control (Edwards *et al*., 2002), and speech generation (Schirmer, 2004). Circadian timing proves to be different from millisecond and interval timing, not just in scale, but also in terms of the neurological mechanisms responsible for this ability. Circadian timing, along with many other timed biochemical processes, has been shown to be controlled by endogenous biochemical oscillators within the area of the suprachiasmatic nuclei (Aschoff, 1984; Czeisler *et al*., 1999), whereas at least some aspects of interval timing have been suggested to rely on neurophysiological oscillations (Keil *et al*., 2001; Matell *et al*., 2003; Berke, 2005; Buhusi and Meck, 2005; Chiba *et al*., 2008). The following experiments will focus on temporal discrimination in the seconds range, which is considered to be interval timing.

While interval timing has been studied in non-human animals and related to behavior in the wild, such as foraging and decision making, connections have also been made between timing and behavioral processes in humans. Impulsive behavior, in which an individual chooses

an immediate option regardless of long-term consequences, provides one example of a behavioral process in which the perception of time must surely play a role. It has been shown that impulsiveness and risk-taking behavior of habitual drug abusers is higher than that of non-drug users (Madden, *et al*., 1997; Kirby, *et al*.,1999; Coffey, *et al*., 2003). In the case of these individuals, distorted perceptions of time may be caused by disruptions to interval timing mechanisms facilitating their tendency to make risky decisions. A more complete understanding of the disruption of temporal discrimination is necessary before any information can be established concerning how timing factors into risky decision-making and the modification of that behavior.

The behavior in question is the ability to perceive and respond to the passage of time, which is a difficult area of inquiry. It is behavior that is sensitive to temporal regularities or events that occurred in the past. Temporal regularities exist in nature, and so developing a system to assess time seems likely. External events become associated with temporal regularities and can serve as time markers, thus creating a dynamic system between external stimuli and neurophysiological processes that then lead to behavioral output. In temporal processing experiments, there is typically some external stimulus to be timed that indicates a temporal interval which is then received neurologically. The external stimulus is received by a number of sensory systems and the activity that occurs on the neurological level during the interval is studied to determine how the neural code is used for accurate timing. Time has often been referred to as not the stimulus itself, but rather a dimension of the stimulus. However, using neurophysiological techniques have allowed for study of the external stimuli presentation and the neural representation and activity that occurs during this presentation. While B.F. Skinner never explicitly studied timing behavior, he was interested in the temporal control of behavior exerted

by interval schedules, and noted in *The Behavior of Organisms* that "Time has not the proper dimensions of a stimulus" (p. 269). Church (2002) has described time as a stimulus attribute that is presented as some perceivable event by the animal; with time as the only dimension that is being modified. The above examples of a temporal stimulus focus on the external properties, but not on how the stimulus is represented neurologically. There is the external stimulus (light, sound, etc) that is presented during experiments. Then, there is the neurological activity during that presentation. This neural representation of the stimulus has been shown, and should be included in a conceptualization of the stimulus. Lejeune *et al*. (2006) also commented on the status of the stimulus during the behavior of timing, stating that if time is similar to stimulus dimension, such as color, then some sort of receptor system must be available. The receptor systems for time are being studied and neural action during temporal intervals has been demonstrated, indicating that there is a receptor system that encodes external temporal information and allows for accurate timing. In this case, time is thought of as internally represented, and the explanation must then be physiological in terms of the neural activity produced by external markers of time. Therefore, the external stimulus in the current set of experiments was the onset of the houselight to indicate temporal responses are to be made. That stimulus is received by the visual system and neural activity is produced and the stimulus is represented neurologically. Even though there was no capability of neurophysiological measurements, the use of pharmacological agents allows for the isolate of particular neurotransmitter systems and brains areas responsible for accurate timing.

Timing behavior is truly ubiquitous and bringing this behavioral class into the laboratory will help researchers to isolate mechanisms that aid in accurate timing. A number of techniques have been used to assess the mechanisms responsible for accurate temporal

processing. These can include disruptions of normal timing by specific pharmacological agents with known neurological effects, the use of individuals exhibiting disorders that lead to neurological deficits or excesses, experimentally induced or pre-existing lesions, as well as genetic knock-out animals. Additionally, normal timing without disruptors may be studied for commonalities across species and neural mechanisms can be assessed with neuroimaging techniques (Ivry and Spencer, 2004); although with generally less spatial and temporal resolution than with more invasive neural recording and pharmacological techniques.

The current set of experiments will use pharmacological and non-pharmacological disruptors of temporal discrimination to determine the form of disruption produced by these agents. The studies will focus on methodological variations in the literature to determine their role, if any in divergent data present in the timing literature. These studies will add to other reports that support particular conceptualizations of timing, with the eventual goal of contributing to a complete understanding of timing behavior.

Studying Timing in the Laboratory

In the laboratory, a number of species, such as pigeons, rats, goldfish, and turtles have been shown to time short intervals, in the seconds to minutes range, accurately and with limited training (Skinner, 1938; Sidman, 1955; Stubbs, 1968; Church and Deluty, 1977; Lejuene and Wearden, 1991; Talton *et al*., 1999). Not surprisingly, timing is also evident in humans (see Allan, 1998). Adults and children over the age of six have shown similar timing abilities in terms of temporal accuracy and judging correctly how much time has passed (Wilkening *et al*., 1987). Strategies for keeping time that are used by humans include activities such as counting out an interval or watching a clock. All other animals and pre-verbal children are capable of timing without those same strategies, and presumably have some other strategies for accurate timing. Even though these time-keeping tactics exist, it has been shown that both humans and

animals show accurate timing even when non-temporal tasks are concurrently presented along with a timing task for the purpose of preventing counting and distraction (Hicks *et al*., 1976; Block and Zakay, 1997; Lejeune *et al*., 1999; Sutton and Roberts, 2002).

There are a number of procedures in which timing behavior can be assessed in the laboratory for both humans and non-human animals. Many studies obtain an animal's baseline measure of temporal discrimination, and then introduce disruptors into these situations in order to guide our understanding of the variables controlling this behavior. Procedures that assess timing behavior can be free-operant, in which training includes reinforcement being given after a fixed period of time. The subject can respond at any point, and at any rate, during the interval. The rate of responding is measured and accurate timing is shown when response rate maximizes close to the time that food would normally be delivered. This is called the peak procedure, and has been used frequently in the timing literature (Catania, 1970; Maricq *et al*., 1981; Meck, 1996; Kraemer *et al*., 1997; Saulsgiver *et al*., 2006). This procedure is classified as an immediate timing task because responding is taking place in the presence of the temporal interval to be timed. This type of timing task is distinguished from retrospective timing tasks, in which decisions about the elapsed time occur after the animal has been exposed to the duration to be timed (Killeen and Fetterman, 1988).

Retrospective timing tasks are often discrete trial procedures, in which animals classify intervals as being short or long based on the previous sample presented. This type of procedure is called the symbolic Matching to Sample of Durations procedure or the temporal bisection procedure (MTSD, Stubbs, 1968; Church and Deluty, 1977). This consists of the presentation of stimuli (houselight or tone) of varying durations followed by two choice alternatives. The subject is trained to classify these durations as *shor*t and *long* by responding on different

response alternatives. Training involves presenting two anchor durations (i.e. 2 vs 8-s) and providing reinforcement when choices are to the short response alternative following a 2-s duration, and when choices are to the long response alternative following the 8-s duration. This training strengthens accurate short and long responses to these two durations. When the discrimination has been learned and temporal accuracy is high, intermediate durations are included, which fall in-between the anchor durations. Classifications of *short* or *long* for all anchor and intermediate durations contribute to a psychophysical curve for time.

Following the presentation of the interval to be timed, response alternatives are immediately available. The nature of these alternatives can be different though. These may be response levers or keys in different locations of the chamber (i.e. left key/lever and the right key/lever). This response variation is typically used for rats (e.g., Church and Deluty, 1977). The procedural variation is spatial in nature and will be referred to as the Location procedure. The other variation of this procedure involves response keys that are illuminated with different colors with location randomized, providing a non-spatial version of the task (i.e. red key and green key). This variation is commonly used for pigeons (e.g., Stubbs, 1968), and will be called the Color procedure. The proportion of responses to the alternative reinforced after long-duration stimuli is then plotted as a function of stimulus duration. This function is typically sigmoid (e.g., Stubbs, 1968; Church and Deluty, 1977; Blough, 1996), and similar to the psychophysical functions obtained for other stimulus dimensions. The psychophysical curve for time obtained using the MTSD procedure provides information about how each individual animal classifies short and long intervals with adequate training and no disruptors present. Each individual animal is therefore free to vary in its classification of intervals as short or long. Performance on this procedure serves as a baseline for temporal discrimination. Disruptors of

timing can then be administered and more information is provided concerning how accurate timing occurs based on the way in which timing is disturbed.

The psychophysical curve that is obtained from the MTSD procedure has a number of different properties that may change based on the introduction of disruptors and other agents. It is important for an analysis to quantify the changes that occur in many aspects of the curve in order to reveal the full spectrum of disruptive effects on timing. Previous studies within the timing literature have only assessed changes in the mid-point and the slope of the curve using a 2-parameter logistic equation to fit the data (Maricq, *et al*., 1981; Maricq and Church, 1983; Meck, 1983, 1986, 1996). However there are other dimensions of the curve that have proven important and have been ignored by that analysis. A hypothetical sigmoid psychophysical curve is shown in Figure 1-1. This is an example of a curve that could be generated for a subject in the current MTSD protocol described above. It also shows how a psychophysical curve would be analyzed with four free parameters based on Blough (1996). The four parameters that are fit to these data include Range, which allows for a measure of stimulus control and accuracy in classifying the shortest and longest durations. Standard deviation (Sd) indicates the slope of the curve, with lower numbers indicating a steeper slope, and higher numbers indicating a shallower slope. Minimum (Min) indicates the elevation of the curve at the lower asymptote. Mean is a measure of the point of subjective equality of the curve (PSE), which indicates the duration at which indifference towards short and long classification occurs. This method allows for more aspects of the curve to be quantified rather than just slope and PSE. Previous research in the timing literature analyzed effects in terms of changes in PSE, however, when other changes in the curve occurred, researchers failed to report these results as there was no quantifiable measure

of other changes. The parameters suggested by Blough (1996) and McClure *et al*. (2005) have proved to be useful in quantifying non-PSE changes in psychophysical curves.

Disruptors of Timing

Pharmacological Disruptors

Attempts to understand the behavioral and neurological mechanisms underlying timing have used a number of techniques, one of which is the administration of pharmacological agents to the animal. Non-human animal studies using rats as the experimental subject and pharmacological manipulation with dopaminergic drugs showed that by using temporal bisection procedures, such as the duration discrimination described above, accurate temporal behavior was disrupted in the form of left and right-ward lateral shifts in the psychophysical curve, which is quantified by a change in derived PSE (Maricq *et al*., 1981; Maricq and Church, 1983; Meck, 1983, 1986, 1996; Chiang, *et al*., 2000, Exp. 1; Cevik, 2003, Exp. 2; Cheng *et al*., 2006). Some of these same reports, as well as others, not only isolated dopamine activity but narrowed this activity to the basal ganglia using pharmacological manipulations with non-humans (Meck, 1983, 1996; Gibbon *et al*., 1997; Drew *et al*., 2003; Mattel *et al*, 2006). Dopamine has been suggested to play an integral role in the immediate increase or decrease in the speed of a clock mechanism that influences temporal judgments based on increased or decreased dopamine levels, whereas acetylcholine manipulations are implicated in the gradual influence of long-term memory storage for the comparison of previous durations to current durations (Buhusi and Meck, 1996; Maricq *et al*., 1981; Meck, 1983, 1986, 1996; Cheng *et al*., 2006; Meck *et al*., 2008).

D-amphetamine and haloperidol have been used extensively in the literature to disrupt temporal discrimination based on their effects on the dopaminergic system and its implication in accurate temporal processing (Maricq *et al*., 1981; Maricq and Chruch, 1983; Meck, 1983, 1986, 1996; Gibbon *et al*., 1997; Drew *et al*., 2003; Buhusi and Meck, 2005; Cheng *et al*., 2006; Mattel

et al, 2006; Meck *et al*., 2008). These drugs are also used based on their social significance. Amphetamine is a commonly used drug of abuse, due to its D_2 agonist properties, similar to most other drugs abuse. Haloperidol is used as an antipsychotic mediation. Amphetamines are psychomotor stimulants that have been shown to increase dopaminergic activity in mesolimbic brain areas, specifically in the nucleus accumbens (Zetterström *et al*., 1983; Carboni *et al*., 1989; Kankaanpaa *et al*., 1998; Rang *et al*., 2003). Haloperidol is a typical antipsychotic drug that is a specific dopamine D_2 receptor blocker. Its effects, which are common to all antipsychotics, are to decrease dopamine activity in the midbrain, specifically in the substantia nigra and ventral tegmentum (White and Wang, 1983; Hand *et al*, 1987; O'Donnell and Grace, 1996; Rang *et al,* 2003). When administered, it will block effects of amphetamine-induced behavior, but it will also have sedating effects on behavior in isolation (Rang *et al*., 2003).

Nicotine has provided an interesting drug to study disruption of temporal discrimination due to its effects on both dopaminergic and cholinergic systems. Nicotine is a stimulant that acts on nicotinic acetylcholine receptors, while also affecting dopamine levels indirectly and showing improvement on cognitive processes (Levin, 1993; Rang *et al*., 2003; Levin *et al*., 2006). Temporal discrimination experiments using nicotine have also shown a disruption of temporal discrimination in the form of a left-ward shift of the curve on the MTSD procedure (Bizot, 1997), and a left-ward shift of the maximal rate of responding on the peak procedure (Hinton and Meck, 1996). This has been interpreted as a temporal effect due to the dopaminergic action of nicotine. Another interesting effect of nicotine on behavior is an improvement in attention and memory in operant tasks due to its neurological actions (Stolerman, 2000; Stolerman *et al*., 2000; Bizarro and Stolerman, 2003; Bizarro *et al*., 2004). The use of nicotine in the current study had

the potential to show increased temporal accuracy, as attention and memory are vital components of temporal processing.

The lateral shifts of the curve due to dopaminergic agents are interpreted as the shortening or lengthening of time due to dopamine's effects on an internal clock mechanism, while acetylcholine influences memory. A shift of the curve to the left, and a decrease in PSE values (using the MTSD procedure), indicates that shorter durations are being responded as if they were longer, and is therefore considered an *overestimation* of time. However, if the curve shifts to the right, this means that longer durations are responded to as if they are shorter, which is an *underestimation* of time (Maricq, *et al*., 1981; Maricq and Church, 1983; Meck, 1983, 1986, 1996).

Changes in PSE can occur in isolation, but it is possible that decreases in accuracy of classifying short and long intervals could also accompany these lateral shifts. If researchers are mainly interested in the lateral position of the psychophysical curve, they may be inclined to ignore the decrease in accuracy, even though this could indicate more complexity in the disruption of temporal behavior. The decrease in accuracy for classifying short and long intervals leads to another finding that is increasingly common in the temporal discrimination literature when disruptors are presented. This result is the form of a flattening of the psychophysical curve, rather than any left-right shifts. This flattening is quantified by the parameter Range discussed above. This parameter provides a measure of the difference between the lower and upper asymptotes of the curve. There are a number of studies that have failed to observe lateral shifts in the psychophysical function and change in PSE due to administration of dopaminergic drugs and rather find a flattening of the curve, decrease in accuracy, and reduction in slope (Stubbs and Thomas, 1974; Rapp and Robbins, 1976; Stanford and Santi, 1998; Chiang

et al. 2000, Exp. 2; Santi, *et al*., 2001; Odum, *et al*., 2002; Cevik, 2003, Exp. 1; McClure, *et al*., 2005; Ward and Odum, 2005; Harper *et al*., 2006; Odum and Ward, 2007; Sanchez-Castillo, *et al*., 2007). This decrease in accuracy has also been found after the administration of nicotine (Popke *et al*., 2000; Ward *et al*., 2009).

The two major changes in psychophysical curves due to the presentation of dopaminergic and cholinergic pharmacological disruptors are either a flattening of the psychophysical curve and decrease in Range, or a lateral shift of the psychophysical curve and change in PSE. These two distinct results provide a major discrepancy in the timing literature that has theoretical implications, and must be clarified before further theorizing can be done. One aim of the current set of experiments is to clarify the conditions under which this discrepancy in results occurs.

Non-Pharmacological Disruptors

Another major class of disruptors used in experiments assessing temporal discrimination are non-pharmacological disruptors. Non-pharmacological disruptors can themselves be split into two classes. First are those that modify the intensity of the stimulus to be timed, such as the brightness of the stimuli. Some studies using this type of disruptor with rats and pigeons have observed that increases in stimulus intensity led to more stimuli being responded to as "long", and decreases in brightness led to more responses to "short" response alternative (Wilkie, 1987; Kraemer, *et al*., 1995; Kraemer, *et al*., 1997). This result has also been found in human psychophysical experiments (Goldstone *et al*., 1978; Brigner, 1986). These changes due to increased stimulus intensity were shown in the form of left-ward shifts of the psychophysical curve for time, and decreases in PSE, indicating more responses to the long choice alternative due to more intense stimuli. This result is not consistent though. Another study, using increased stimulus intensity as the disruptor with pigeons and a slightly different methodology from the studies cited above, found a flattening of the psychophysical curve, but only when the most

intense stimulus was presented initially followed by less intense stimuli (McClure *et al*., In review (c)). Increased stimulus intensity leads to both of the characteristic changes in the psychophysical curve that are found with pharmacological disruptors.

The second type of non-pharmacological disruptor are those in which the motivation of the animal is altered by free-food administration during the session, extinction of previously reinforced trials, or pre-feed before experimental testing. Studies that have used those types of disruptors have shown that changing reinforcement quantity and efficacy led to a flattening of the psychophysical function for time, which can be understood in terms of a decrease in accuracy of responding for temporal intervals and a decrease in slope of the psychophysical curve (Bizo and White, 1994; Killeen, *et al*., 1999; Ward and Odum, 2006, 2007). It has also been shown that food prior to the experimental session and extinction can lead to changes in PSE for some arrangements (McClure *et al*., In Press). The discrepancy within the literature between either a decrease in the accuracy of temporal judgments or a lateral shift of the psychophysical curve that was discussed for pharmacological agents also appears to be relevant when non-pharmacological disruptors are being used. These differences may emerge from the use of different types of non-pharmacological agents, however, methodological consistency is lacking across these studies and we cannot presently conclude that type of disruptor is the sole cause of differential disruption of temporal behavior.

Studies using non-pharmacological agents as disruptors of temporal behavior may use methodologies that are closely comparable to those used in experiments with pharmacological agents. Pharmacological agents are typically presented in varying doses separated by baseline sessions with no injections to minimize the possibility of tolerance developing to the drugs' effects. Chronic dosing of one drug dose can also be given to maximize the possibility of

tolerance and to enable the study of the behavioral effects of drugs during acute and chronic regimens (Dallery and Locey, 2005; Hoffman, *et al*., 1996; Marusich and Branch, 2008; Ward *et al*, 2006). The current experiments present non-pharmacological agents in both acute and chronic regimens, and are closely related to pharmacological presentations. The non-pharmacological disruptors used in the current experiment are those that affect the motivation of the animal to respond, such as food given prior to the experimental session in varying doses as well as acute and chronic regimens. Extinction was also used a disruptor, in which correct responses that were reinforced throughout the course of training were no longer reinforced. This occurred in acute and chronic regimens, again to allow for methodologies that more closely mimic drug administration and also to determine behavioral effects after short and longer periods of exposure to the disruptor.

Neurological Disorders

Neurological disorders provide researchers with a population of individuals that have specific neural distinctions from that of controls. Assessing temporal abilities of these individuals compared to controls has provided information useful to elucidate neurological mechanisms responsible for accurate timing. Neurological disorders can be thought of as another type of disruptor of timing that can studied in human populations or in non-human models using neurophysiological techniques. Studies assessing interval timing using temporal production tasks have shown impairments in timing for individuals with neurological disorders in which dopamine levels are influenced like Parkinson's disease (Malapani *et al*., 1998a; Malapani *et al*, 2002; Praamstra and Pope, 2007; Jones *et al*., 2008) and schizophrenia (Tracy *et al.,* 1998; Volz *et al*., 2001). These studies revealed impairments in the form of underestimation of intervals or increased variance in responses compared to controls.

Neuroimaging techniques have shown activation of the basal ganglia during temporal processing using temporal production and discrimination tasks (Lewis and Miall, 2003a,b; Nenadic *et al*., 2003), though it has been suggested that the basal ganglia is unlikely to be the only relevant substrate in accurate timing (Buhusi and Meck, 2005). Injury or disorders that affect other parts of the brain and do not disrupt interval timing allow for better isolation of relevant areas. For example, cerebellar injury may not lead to inaccurate timing compared to controls, suggesting this region is not an essential area for interval timing, though it could be important for timing on smaller scales (Malapani *et al*, 1998b).

The data discussed above show how a variety of disruptions can influence timing and also how normal timing can be studied with the use of neuroimaging techniques and electrophysiological recordings. The literature on temporal processing is vast, and while some suggest mechanisms based on the data, there are still a number of methodological inconsistencies within the literature and divergent data that must be rectified. One discrepancy discussed above involves the divergent effects of dopaminergic drugs on temporal judgments in the form of either decreases in accuracy or overestimation or underestimation of temporal intervals. Discrepancies within the literature persist and the current experiments attempt to clarify these discrepancies for those using duration discrimination tasks and provide evidence for methodological standards to be used in assessing temporal processing.

Discrepancies in Timing Literature

The literature using pharmacological and non-pharmacological agents to disrupt temporal discrimination reveals a large discrepancy. Some reports show lateral shifts of the curve to the left or right due to the presentation of pharmacological agents (Maricq, *et al*., 1981; Maricq and Church, 1983; Meck, 1983, 1986; Bizot, 1997; Chiang, *et al*., 2000, Exp. 1; Cevik, 2003, Exp. 2; Cheng *et al*., 2006), also with non-pharmacological agents, such as stimulus intensity (Wilkie,

1987; Kraemer, *et al*., 1995; Kraemer, *et al*., 1997), as well as food prior to the session and extinction of previously reinforced responses (McClure *et al*., In Press). However, other studies report a flattening, or loss of accuracy, of the psychophysical curve due to the presentation of pharmacological disruptors (e.g., Stubbs and Thomas, 1974; Rapp and Robbins, 1976; Stanford and Santi, 1998; Chiang *et al*. 2000, Exp. 2; Santi, *et al*., 2001; Odum, *et al*., 2002; Cevik, 2003, Exp. 1; McClure, *et al*., 2005; Ward and Odum, 2005; Harper, *et al*., 2006; Odum and Ward, 2007; Sanchez-Castillo, *et al*., 2007; Ward *et al*., 2009; McClure *et al*., In Review (a, b)). Similar flattenings of the curve have also been reported for non-pharmacological disruptors such as pre-feed, extinction, and stimulus intensity (Wilkie *et al*., 1988; Morgan *et al*., 1993; Bizo and White, 1994; Killeen *et al*., 1999; Ward and Odum, 2006, 2007; McClure *et al*., In Review (c)). It is clear that this discrepancy is not consistent across type of disruptor used. The reasons for this discrepancy remain unknown, and one potential cause for these divergent data is examined in the current studies.

Procedural Variations

One factor that may be contributing to the discrepant results found in different studies using pharmacological and non-pharmacological disruptors of MTSD responding is the use of Location (i.e. left or right keys) or Color (i.e. red or green) choice alternative procedures. The response alternatives are either spatial or non-spatial, which could prove to be an important distinction.

This procedural variation has been largely overlooked in the literature as an important methodological variation, and was developed initially based the use of either rats or pigeons as experimental subjects. The trend in the literature since the development of these procedures has been to use the non-spatial, Color version of the task with pigeon subjects and to the use the spatial, or Location version of the task with rats. There is a confounding of species in much of

the literature making it impossible to determine whether species or procedural differences are responsible for the different results found. It has been shown that when the Color procedural variation is used with pigeons (for both pharmacological and non-pharmacological disruptors) the majority of studies show a loss of accuracy and flattening in the psychophysical curve (Stubbs and Thomas, 1974; Morgan *et al*., 1993; Bizo and White, 1994; Killeen *et al*., 1999; Odum, *et al*., 2002; McClure, *et al*., 2005; Ward and Odum, 2005, 2006, 2007; Odum and Ward, 2007; Ward *et al*., 2009; McClure *et al*., In Review (a,b,c)), whereas studies using rats have commonly employed the Location procedural variation and found lateral shifts in the psychophysical curve (Maricq, *et al*., 1981; Maricq and Church, 1983; Meck, 1983, 1986, 1996; Bizot, 1997; Kraemer, *et al*., 1995; Chiang, *et al*., 2000, Exp. 1; Cevik, 2003, Exp. 2; Cheng *et al*., 2006).

There are exceptions to this species trend. Some studies have found flattening of the psychophysical curve due to pharmacological and non-pharmacological disruptors when the Location variation is used with rats (e.g. Rapp and Robbins, 1976; Wilkie *et al*., 1988; Kraemer *et al*., 1995; Stanford and Santi, 1998; Chiang *et al*., 2000, Exp 2; Santi, *et al*., 2001; Cevik, 2003, Exp 1; Harper *et al*., 2006; Sanchez-Castillo, *et al*., 2007). It appears that when using the Location version of the task with rats, either lateral shifts or a flattening of the curve can result.

Some studies have used the Location procedure with pigeons, and have found a flattening of the psychophysical curve due to disruptor presentation (Odum and Ward, 2007; McClure *et al*. In Review (a)). However, other studies have shown examples of lateral shifts in pigeons, without any decrements in accuracy, using the Location procedure for individual subjects and group averages (McClure *et al*., In Press; McClure *et al*. In Review (b)).

Both spatial and non-spatial versions of the MTSD task have been used with pigeons, and more recently the non-spatial procedure has gained popularity when rats are the experimental subjects. The Color procedure was difficult to use with rats based on their poor color vision, however, non-spatial variations now include stationary vs. moving levers serving as non-spatial cues (Meck *et al*., 1985; Santi *et al*., 1995a, b; Santi *et al*., 1997; Santi and Van Rooyen, 2007; Van Rooyen *et al*., 2008). When drugs have been used to disrupt temporal discrimination using the non-spatial variation with rats, a decrease in accuracy for classifying temporal intervals was found (Santi *et al*., 1995b).

The aforementioned studies make a case that the species used in the experiment is not important, but rather the procedure is the relevant variable. Both flattenings of the curve or lateral shifts can occur in both pigeons and rats, but only when the Location variant is used. There is reason to believe that the Location variant must be used to obtain lateral shifts. There are only two examples in which lateral shifts of the curve were reported for pigeons using the Color (non-spatial) procedure (Wilkie, 1987; Kraemer *et al*., 1997). These studies conclude that lateral shifts occurred due to stimulus intensity; however, both studies also show some decrements in accuracy of the classification of temporal intervals.

These procedural variations seem to be quite important, not just for pharmacological disruptors, but could also play a large role in discrepant findings when non-pharmacological disruptors are used as well. These procedural variations will be explored in the current set of experiments with the use of pharmacological and non-pharmacological agents as a possible reason for discrepancies in the literature and to determine the precise conditions under which certain results appear.

Other Potential Causes

The procedural variations used to assess temporal discrimination (Location and Color) represent one aspect of methodology that could be responsible for discrepant results in the literature. Other reasons for this discrepancy have been suggested as well. Some attention has been given to the length of time required for training and how that can lead to differential disruption to pharmacological agents. Cheng *et al*. (2007) suggested that longer training times led to increased chances of a flattening of the curve, as opposed to lateral shifts that came with shorter training times. Studies vary in the amount of time given to animals to train on the MTSD procedures. Training may be as short as 10-15 sessions until testing with disruptors begins. Other studies take as long as 100 sessions of training until stability is judged. Cheng's exploration of training times does not take into the different criteria used across laboratories to judge stability for subjects. Some laboratories are surely conservative in their stability estimates and look at individual subjects and sessions, while other laboratories judge stability based on group averages over many sessions. Stability criteria and time needed to reach stability are only occasionally noted in published reports, making it difficult to compare across the literature. The hypothesis concerning training times is an intriguing idea, and should certainly be looked more carefully in the literature.

Another potential reason for discrepant findings was suggested by Cevik (2003). This experiment administered methamphetamine at different intervals prior to experimentation. Rats that received drug within 20 minutes of the start of the experimental session were more likely to show the flattening of the psychophysical curve, as opposed to the animals that were injected with drug up to 100 minutes prior to the start of session, which showed left-ward shifts of the psychophysical curve. This study reveals how a methodological inconsistency, which is time from injection to start of the experimental session, could reveal differences in disruption of

temporal behavior. The exploration of differential rates of metabolism for different pharmacological agents, as well as instances of acute tolerance should be examined to determine the nature of these delay differences. These results, while compelling, have failed to be replicated in other related timing experiments in which a free-operant peak procedure was used (Saulsgiver *et al*., In Review). These other potential causes for discrepancies in the literature are relevant and are in need of further investigation, however, at this point, procedural variations provide a methodological variation with the most promise for clarification of discrepant results.

Theories of Timing

Scalar Expentency Theory (SET)

Various theories of timing exist to account for accurate temporal abilities and how disruptors lead to deviations from normal timing. All theories are supported by a number of empirical reports. The most well known model of timing is Gibbon's (1977) Scalar Expectancy Theory (SET). This information-processing model of timing focuses on an internal structure known as the pacemaker, which emits pulses during a given period of time. An accumulator then collects these pulses until the end of a certain interval of time, at which point the value of the accumulator is stored from working memory into reference memory (long-term memory). The accumulator is then able to begin collecting pulses for a given amount of time again. In a timing procedure that measures the perception of time or time production, the stored value of the accumulator is compared to the current value in the accumulator during the timed interval. When the difference falls below a variable threshold, responding begins to occur. The rate of the pacemaker remains approximately fixed, except during drug presentation or other manipulations.

Gibbon's (1977) SET explains timing behavior as a function of a clock-counter framework. Pharmacological agents have been postulated to affect neurological systems that influence different aspects of the pacemaker, accumulator, and memory (Meck, 1996; Buhusi

and Meck, 2005). Meck (1983, 1986, 1996) has extended SET to account for the disruptions of timing caused by pharmacological agents and has implicated dopamine as a neurotransmitter of paramount importance in accurate timing. A number of studies have interpreted left-ward shifts in the psychophysical curve as an *overestimation* of time due to the increased rate of the pacemaker. In those cases, the pacemaker is emitting more pulses than before, which leads to intervals of the same duration being responded to as if they were longer. Dopamine agonists and antagonists would increase and decrease the speed of the pacemaker, respectively, leading to an *overestimation* of time due to the administration of a dopamine agonist and an *underestimation* of time due to a dopamine antagonist (Maricq, *et al*., 1981; Maricq and Church, 1983; Meck, 1983, 1986; Chiang, *et al*., 2000, Exp. 1; Cevik, 2003, Exp. 2). Nicotine and increased stimulus intensity have lead to left-ward shifts in the psychophysical curve which is interpreted as changes in pacemaker rate as well (Wilkie, 1987; Bizot, 1997). Right-ward shifts of the curve due to decreased stimulus intensity have been thought of as a loss of attention to the stimulus due to a less salient stimuli, which Kraemer *et al*. (1995) and Kraemer *et al*. (1997) theorized delayed the collection of pulses by the underlying pacemaker, leading to an *underestimation* of time for less salient stimuli (Kraemer *et al*., 1995; Kraemer *et al*., 1997).

SET's extensions to pharmacological disruptors was based on reports that show changes in PSE and lateral shifts of the curve, which are then interpreted as increases and decreases in clock speed. Many recent reports are unable to replicate lateral shifts of the psychophysical curve using duration discrimination experiments and dopaminergic agonists, which may question the theory, not the data that led to the theory. Consistency in the literature seems necessary prior to the acceptance or rejection of theories based upon these data.

Cortico-Striatal Osciallatory Networks

A number of reports have shown the neural activity that occurs with timing behavior in humans and non-human animals, thus linking the behavior with the neural coding that occurs simultaneously. Many studies that use neurophysiological techniques have suggested *where* the mechanisms of timing occur in the brain; however, the next important question in determining the neurological mechanisms of timing is *how* these areas and systems contribute to specific actions that lead to accurate timing. A theory such as SET that relies on a pacemaker-accumulator framework has been refined and current work in the field interprets timing as a slightly different neural process. These studies reveal neurophysiological components involved in accurate timing, while the interpretation from these studies attempts to explain how these components work. A number of reports point to the role of striatal neurons for accurate interval timing due to their involvement in oscillatory networks (Keil *et al*., 2001; Berke, 2005; Buhusi and Meck, 2005), as well as, the importance of striatal spiny neurons which have been shown to receive dopaminergic information and are responsible for the coding of durations (Matell *et al*., 2003; Chiba *et al*., 2008). Other data in which agents have been used to target long-term memory storage also point to the importance of memory for an interval if the animal is to make a comparison between previously experienced temporal intervals and current intervals (Buhusi and Meck, 2005; Meck *et al*., 2008). Some data support the notion that accurate temporal processing comes about due to oscillatory firings within the striatum in concert with detecting acetylcholine-induced cortical oscillations (Buhusi and Meck, 2005; Meck *et al*., 2008).

After appropriate training with temporal intervals, it has been suggested that oscillations across cortical populations implicated in long-term memory for a given temporal interval synchronize which is detected by, and seen in, the firing of spiny neurons while both clock and memory match (Meck *et al*., 2008). These data provide one potential explanation of what is

happening on the neurological level during the presentation of a temporal interval, as well as, how clock and memory components combine for accurate temporal processing. A timing circuit that relies on cortical oscillations is also consistent with the literature in humans that shows the need for an intact basal ganglia for accurate interval timing (Bares *et al*., 2003; Nagai *et al*., 2004). EEG measures using contingent negative variation (CNV) in humans with neurological disorders also provide evidence consistent with an electrophysiological oscillator system in the cortico-striatal system (Reuter *et al*., 2006; de Tommaso *et al*., 2007; Praamstra and Pope, 2007).

Behavioral Theory of Timing (BeT)

Other theories of timing have attempted to account for this behavior by appealing to different timing mechanisms and relying more heavily on behavior, y*et al*so including a physiological component. The Behavioral Theory of Timing (BeT) allows for a physiological counter, but rate of reinforcement plays a large role in control of the counter and control of behavior (Killeen and Fetterman, 1988). This theory of timing states that signals of reinforcement and also cues that are associated with reinforcement produce mediating behavior that are useful in timing an interval. Chains of behavior may develop, such that behavior that occurs closer to reinforcement is strengthened and comes under the control of the passage of time. In temporal discrimination procedures, the varying time intervals that are presented and are classified as short or long can be associated with mediating behavior that occurred during training. Therefore, a long or short classification by the subject is made due to the behavior the subject engaged in at the point of interruption by the choice alternatives. The mediating behavior is pushed forward by the rate of an internal pacemaker that is influenced by rate of reinforcement. Rate of reinforcement in a given context would affect the *arousal* of the animal, which is a theoretical concept in BeT. This *arousal* leads to the pacemaker speeding up (shorter interpulse time) or slowing down (longer interpulse time). The rate of the pacemaker then

influences the mediating behavior engaged in and temporal judgments of the animal. Much of the physiological data in support of BeT consist of evidence based on counters driven by Poisson processes (Killeen, 2002).

The main parameters of BET are *n*, which is the number of hypothetical behavioral states within an interval to be timed, and tau (τ), which is the average interpulse time. The counter within BeT, which emits the pulses associated with a given interval of time, is said to vary with the rate of reinforcement in the experimental conditions. A very rich or very lean rate of reinforcement will lead to changes in the temporal judgments of an animal due to the effects of BeT's theoretical states of *arousal*, leading to changes in pacemaker rate. Manipulations, such as an increase in the rate of reinforcement, can cause increased *arousal* in the animal, which leads to an increase in the speed of the pacemaker, and a faster progression through behavioral states.

Experiments which have tested BeT have conducted timing assessments using non-pharmacological disruptors that affect the motivation of the animal to respond. Giving an animal food prior to session, as well as free food during the session and extinction of previously reinforced responses are all examples of disruptors that are used when testing the predictions of BeT. BeT predicts that an increase in rate of reinforcement in the form of free food during the experimental session or food given prior to the session should increase *arousal* of the animal, which would correspond to a decrease interpulse time (tau). Alternatively, extinction of previously reinforced responses leads to a decrease in *arousal* and increase in tau. Studies using these types of disruptors have shown support for predicted changes in tau (Morgan, *et al*.,1993; Bizo and White, 1994; Killeen, *et al*., 1999; Plowright *et al*., 2000; Ward and Odum, 2006, 2007).

BeT provides an alternative theory of timing that may be able to account for a decrease in the accuracy of classifying intervals due to non-pharmacological agents, though lacks the same neurophysiological underpinnings that are present in SET and models based on oscillatory networks. Since both non-pharmacological and pharmacological agents will be used in the current set of experiments, our results have the potential of supporting BeT's parameters, as well as being extended to novel pharmacological disruption.

Timing as Stimulus Control

All theories and models of timing have their own shortcomings, which inspires new conceptualizations of the timing process. SET has been extended to account for pharmacological disruptions of timing, yet the pacemaker-accumulator model of timing is not as well-accepted as in the past. For both SET the oscillatory network model an increasing number of empirical reports are providing data that are incompatible with predictions made by these models. At the current time, no adequate explanations have been offered within the SET framework as to why the lateral position of the curve would be unaffected by drug administration while accuracy of temporal classification is the main disruptive effect of drug. BeT fails to make predictions about how drugs would affect the theoretical concept of *arousal* of the animal and how this would affect the counter.

A number of pharmacological disruptors have led to a flattening of the psychophysical curve, indicating a loss of accuracy to classify short and long durations correctly, with the most severe disruption occurring at the extreme durations. This result has been interpreted as a loss of stimulus control, such that the preceding duration is no longer controlling the behavior of classifying the duration, rather than a specific effect on timing (Stubbs and Thomas, 1974; Rapp and Robbins, 1976; Stanford and Santi, 1998; Santi *et al*., 2001; Odum, 2002; Odum, *et al*., 2002; McClure, *et al*., 2005; Ward and Odum, 2005, 2006, 2007; Saulsgiver *et al*., 2006; Odum

and Ward, 2007; Ward *et al*., 2009; McClure *et al*., (In Review, (a, b, c)). In these studies, timing is conceptualized as more of a particular type of stimulus control that can be disrupted by a multitude of agents that have the same effects on behavior regardless of pharmacological action or type of disruptor. The disruptor used could influence a number of aspects of the experimental environment and other behavior, such as attention to the stimulus, motoric activity, or disruption of choice responding. Viewing timing behavior as a type of stimulus control allows for another way to view this behavior and study this ability.

Millisecond Timing

While the temporal scale focused on above was that of interval timing (second to minutes), another scale of temporal processing has been isolated, and is known as millisecond timing. The distinction has been made between interval timing and millisecond timing not only due to the scale but also due to the potential neurophysiological mechanisms involved in both. A brief review of the work conducted with millisecond timing is included, as it provides information on the similarities and differences in mechanisms responsible for this ability compared to interval timing. Most of this research has been conducted using neurophysiological techniques and suggests mechanisms responsible for behavior on this timing scale.

Various reports suggest distinct neurological mechanisms for millisecond timing, while others provide support for common mechanisms of millisecond and interval timing. The cerebellar cortex has been shown to be related to the timing of a conditioned response in a classical conditioning study (Kotani *et al*, 2003; Perrett *et al*., 1993). There is also evidence that the cerebellum is essential for accurate millisecond timing, while not playing a role in accurate interval timing (Koekkoek *et al*., 2003). A demonstration of this nature may provide evidence that different neural structures and systems are responsible for timing on these different scales.

Neuroimaging studies with humans have found that when asked to discriminate periods of time within the millisecond range, increased activation was found in the right pre-frontal cortex, supplementary motor area (SMA) and left cerebellum (Lewis and Miall, 2003a) while another report showed activation of the putamen during millisecond duration discriminations (Fernandez *et al*., 2003). Bueti *et al*. (2008) implicated the basal ganglia and cerebellum during both perceptual and free operant production timing tasks suggesting both a common mechanism for these behavioral tests and common substrates for millisecond and interval timing. Short and long duration discrimination, still within the millisecond range, showed that the presupplementary motor area (preSMA), anterior cingulated, prefrontal and paretal cortices, and the basal ganglia were involved during both of these duration discriminations (Pouthas *et al*., 2005). These studies providing support for the substrates responsible for millisecond timing offer a wealth of information on the location of timing mechanisms, but not a clear picture of how these mechanisms work.

Studies that have suggested how timing mechanisms work typically draw connections between interval and millisecond timing. The basal ganglia are not only important for interval timing but has also been shown to play a role in millisecond timing (Jahanshahi *et al*., 2006; Jones *et al*., 2008). There is other evidence that the dorsal striatum may serve a central role in both millisecond and interval timing, while other substrates are associated with each scale of temporal sensitivity (Matell *et al*., 2003; Matell and Meck, 2004; Chiba *et al*., 2008). And yet other studies suggest that cortical oscillators are responsible for millisecond and interval timing, thus providing another hypothesized common mechanism and explanation for timing on both scales (Buhusi and Meck, 2005; Meck *et al*., 2008). Lewis and Miall (2003) suggested that timing within the millisecond range is "automatic" and controlled by a certain set of neural

mechanisms, while interval timing is "cognitively controlled" and due to cortical oscillatory synchronization within a cortico-striatal network that allows for accurate temporal processing and long term memory storage of experienced durations (Buhusi and Meck, 2005; Meck *et al*., 2008). The work focusing on millisecond timing is advancing the knowledge of mechanisms of temporal processing; however, in the current set of experiments, the focus will remain on interval timing.

Present Experiments

Despite many empirical reports in interval timing, the field still has a number of questions to be answered due to large methodological discrepancies in the literature and disagreement concerning the best conceptualization of timing and its mechanisms. The current set of experiments aim to answer vital questions about interval timing in order to clarify these controversies and better equip the field to tackle applications like impulsivity. By clarifying methodological discrepancies, we may provide clarification and consensus within the literature, as well as recommendations for appropriate methodology. This is all done with the eventual goal of understanding the mechanisms responsible for interval timing that will allow for contributions to be made to the understanding of related behavioral processes.

Two experiments using an MTSD procedure to assess temporal judgments were conducted with both procedural variations (Color and Location). Temporal behavior was disrupted with an array of pharmacological and non-pharmacological agents. In Experiment 1 the disruptive effects of *d*-amphetamine, nicotine, and haloperidol on temporal discrimination were assessed using an acute dosing procedure in which the initial effects of drug were analyzed. Both Color and Location variations of the MTSD procedure were used with pigeons to determine the influence of these two procedures on the resulting data. Experiment 2 tested the disruptive effects of non-pharmacological agents on temporal discrimination, also using both Color and

Location procedural variations. These disruptors included food given prior to session in varying amounts in an acute regimen, acute and chronic extinction of previously reinforced responses, increased density of reinforcement, and free food given at all times.

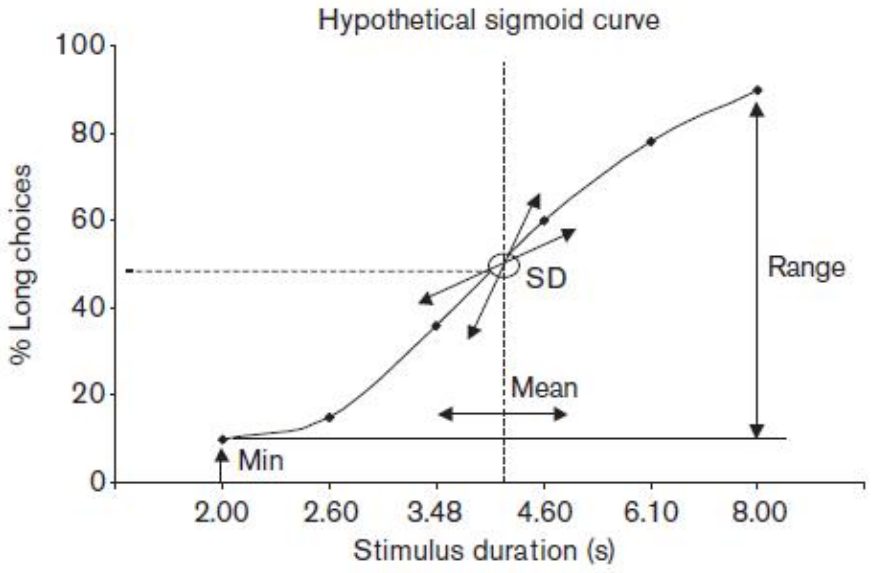

Figure 1-1. Hypothetical sigmoid curve showing four free parameters fit to the curve. Percent of choices to the long alternative is shown as a function of stimulus duration. Range is the difference between the upper and lower asymptotes of the curve. Standard deviation (Sd) is a measure of the slope of the curve. Minimum (Min) is how elevated the lowest point of the sigmoid curve is from the x-axis. Finally, the mean is the measure of the mid-point of the curve in which 50% of responses are to the short alternative and 50% of the responses are to the long alternative. Mean is also referred to the as the point of subjective equality (PSE). [From McClure *et al*., 2005, Behavioural Pharmacology; Copyright Permission].

CHAPTER 2
EXPERIMENT 1

Introduction

Experiment 1 was designed to assess the effects of various pharmacological agents on temporal discrimination. The agents used in the current experiment were *d*-amphetamine, nicotine, and haloperidol, all of which have different neurological effects. Only the initial effects of these drugs on timing were assessed. Each subject in Experiment 1 received all drugs in different orders to provide for a within-subject comparison of drug effects. Two procedural groups were used (Color and Location) to determine their role, if any, in discrepant results in the literature. Differences in procedures may also lead to implications regarding the ease with which studies are compared given the procedure that was employed.

Method

Subjects

Twelve White Carneau pigeons (*Columba livia*), with previous behavioral testing history served as subjects. All birds had some drug history either with *d*-amphetamine or cocaine, but at the time of the current experiment, they had not experienced any drug in at least three months. The birds were individually housed in a humidity and temperature controlled colony room with a 16:8 hour light-dark cycle. Water and grit were continually available in the home cages. Post-session feedings were given when necessary to maintain body weights at 83% of free-feeding levels.

Apparatus

Twelve standard operant test chambers (Med Associates Inc., St. Albans, VT, USA, Model ENV-007) served in this experiment. The chambers had internal dimensions of 30.5 x 24.1 x 29.2 cm. The doors and opposite side panels consisted of clear polycarbonate. The

intelligence panels and back walls were constructed from aluminum. The intelligence panel contained three 2.5-cm diameter circular response keys (Model ENV-123AM) that could be transilluminated with red, green and white light. The three keys were 6.5 cm from the top of the chamber. Each side key was located 2.25 cm from the side walls and the center response key was 6 cm from each side key. The force required to depress a response key was between 0.12 and 0.15 N. Grain could be accessed from a hopper (Model ENV-205M) through a 5.5 by 6.5 cm rectangular opening that was positioned 13 cm below the center response key and 8.5 cm from both sides of the chamber. A light in the hopper activated whenever grain was available, while all other lights in the chamber were extinguished. On the opposite aluminum wall a 28V houselight (Model ENV-215M) was placed 1 cm from the top of the chamber and 11.5 cm from the sides. The equipment was contained in a sound-attenuating chamber (Model ENV-018M) and controlled with Med-PC IV software.

Procedure

Behavioral training

No key peck training was required and temporal discrimination training began immediately. Subjects were randomly distributed into a Color and Location groups. Sessions started with a 5-minute blackout for both procedural groups. Each trial began with white illumination of the center key; a single response to this key initiated the trial. This initiating response terminated the center-key illumination and was followed immediately by houselight illumination for one of the two training durations: either 2 or 8-s. The training durations were chosen randomly, with the limitation that a duration could not appear more than twice in succession, and were presented an equal number of times for each session. Directly following the termination of the houselight illumination, two side response keys were illuminated simultaneously. For the Color group, one alternative was red, the other green. Location of the

colors was randomized with the constraint that no color could appear on the same side more than twice in succession. The location of the reinforced response choice was also randomized across sides, with the constraint that the location could not be the same for more than two trials. A single peck on the *short* key was reinforced with 2-s access to grain following a 2-s duration stimulus; a response on the *long* key was reinforced in the same way after an 8-s stimulus duration. The short key for three out of six subjects was red, while green served as the short for the other three subjects. For the Location group, both choice alternatives were illuminated red. For three subjects in the Location group, the left key was the *short* key, and so a response on the left key after a 2-s duration was followed by 2-s access to grain. A response on the right key after an 8-s duration was reinforced. Short and long keys were counterbalanced for the other three subjects in the Location group. Reinforcement was followed by an average 10-s intertrial interval (ITI), with a range of 1 to 20 s. Incorrect responses led directly to the ITI. Sessions consisted of 96 trials or 50 minutes, whichever came first.

Intermediate duration trials

Once a subject's accuracy in discriminating the training durations was over 80% for five consecutive sessions, intermediate stimulus durations were introduced along with the training stimuli. The values of the intermediate duration stimuli were selected to create four equal logarithmic steps between 2 and 8 s (2.6 s, 3.48 s, 4.6 s, and 6.1 s). Sessions consisted of 96 trials or 80 minutes, whichever came first. Training durations (2 and 8-s) were presented for 48 of the 96 trials, and the four intermediate durations were presented 12 times each. Durations could not appear more than twice in succession in each block of 24 trials. For both procedural groups, correct responses to training durations were reinforced at all times and responses to intermediate durations were never reinforced.

Drug administration

When each bird's psychophysical function and all derived parameters (Range, Standard Deviation, Minimum, and PSE: See below) for the last 10 days of baseline were deemed stable by visual inspection, the acute dosing regimen began. Three different drugs were given to each of the subjects in this experiment in a counterbalanced order. The drugs and doses used were *d*-amphetamine (vehicle, 0.3, 1.0, 1.7, 2.25 and 3.0 mg/kg), nicotine (vehicle, 0.03, 0.1, 0.3, 1.0, and 1.7 mg/kg), and haloperidol (vehicle, 0.01, 0.03, 0.1, 0.3, 0.5, 0.7). *D*-amphetamine was mixed in 0.9% saline solution (approximately 1 ml/kg body weight), while nicotine was mixed with Potassium Phosphate, and haloperidol was mixed in a 0.03% solution of acetic acid and distilled water.

Doses of drug were given twice a week, with each dose being separated by two to three control experimental sessions with no injections. Drug administration involved two to three cycles of all drug doses so that any systematic changes in effect across successive administrations would be evident. All doses of drug, along with vehicle, yielded a dose-response curve (DRC). After all doses for one particular drug had been administered two to three times, comprising one DRC determination, the next drug administration began after 30 experimental sessions with no drug or vehicle injections. All injections were given intramuscularly in the breast muscle. All drugs were administered 5 minutes prior to the animal entering the experimental chamber. Upon entering the experimental chamber, during *d*-amphetamine and nicotine dosing, subjects received a 5-min blackout prior to testing. During haloperidol administration, subjects experienced a 15-min blackout in the experiment chamber prior to the start of the session. Each of twelve subjects experienced all three drugs, therefore making 36 DRC determinations. For 18 of these 36 determinations, injections occurred in a descending (*d*-

amphetamine) or ascending (nicotine and haloperidol) order. The other 18 of 36 determinations were given in random order.

Data Analysis

The data analyzed came from each presentation of each drug dose and vehicle administrations. For each session the proportion of responses to the long response alternative was plotted as a function of the duration of the stimulus on that trial. The resultant psychophysical curves were analyzed by fitting a cumulative Gaussian function with four free parameters, following Blough (1996). The equation fit was the integral of:

$$f(t) = a + \frac{b}{\sqrt{2\pi\sigma}} e^{-\left(\frac{(t-\mu)^2}{2\sigma^2}\right)} \quad (2\text{-}1)$$

where *f(t)* is the proportion of long responses at a given duration *t* of a stimulus, *a* is the minimum of the function (Min), *b* the Range, which is the difference between the point at the upper asymptote of the curve compared to the point at the lower asymptote of the curve, μ the mean (Point of Subjective Equality, PSE), and σ the standard deviation (Sd). All curve fitting was performed using Microsoft Excel® (see McClure *et al*., 2005). An alpha level of .05 was adopted for all statistical analyses.

Results

Psychophysical Curves

Psychophysical curves comparing vehicle with each subject's highest doses are shown for *d*-amphetamine in Figure 2-1. Visual inspection of the psychophysical curves for the Location group at the high dose of *d*-amphetamine showed a flattening of the curve and decrease in accuracy of classifying the training durations for four out of six subjects. The other two subjects showed both a left-ward shift of the curve from vehicle (Subject 648), while the other shows a slight right-ward shift due to *d*-amphetamine (Subject 622). For the Color group, the

high dose of *d*-amphetamine led to a flattening of the curve for all six subjects, also with differing severity. Even in the presence of what appeared to be a shift of the curve laterally for both groups, there was still some decrease of accuracy at one or both extreme durations (Subjects 811, 673, and 4423). The general trend for the high dose of *d*-amphetamine was the same for both the Location and Color group. There was a flattening of the curve, and occasionally shifts of the curve were seen without decrements in accuracy, but only in the Location group.

Curves comparing vehicle with each subject's highest doses are shown for nicotine in Figure 2-2. For the Location group, psychophysical curves were flattened due to nicotine in four out of six subjects. Subjects 648 and 622 both showed left-ward shifts in the curve due to nicotine. For the Color group, all six subjects showed a flattening of the psychophysical curve and while some lateral shifts could be interpreted, they did not occur without decrements in accuracy. Just as with the high dose of *d*-amphetamine, the overall pattern was a decrease in accuracy for classifying intervals. Anytime an exclusive lateral shift did occur without any disruption of accuracy at extreme durations, it occurred in the Location group.

Each subject's highest dose of haloperidol as compared to vehicle is shown in Figure 2-3. During the administration of the highest dose of haloperidol, five out of six subjects in the Location group showed a flattening of the curve, while Subject 673 showed a shift of the curve to the right. For the Color group, five out of six subjects showed a flattening of the curve, while Subject 657 seemed unaffected by the high dose of haloperidol. The trend for all drugs used in this experiment was the same. High doses of *d*-amphetamine, nicotine, and haloperidol led to decreases in accuracy at extreme durations and a flattening of the psychophysical curve. Lateral shifts, when they did occur, only occurred in the Location group.

Averaged psychophysical curves across all subjects for vehicle and the highest dose of drug experienced by all subjects in the Location and Color groups are shown in Figure 2-4. Since subjects had differing high doses, the highest doses experienced by all subjects in both groups are presented in Figure 2-4. The flattening of the psychophysical curve that was seen for the majority of subjects in Figures 2-1, 2-2, and 2-3 is also evident in group averages. The flattening appeared to be more pronounced in the Color group as compared to the Location group, though it was still present for both groups. The averaged curves for the Location group during haloperidol administration revealed a slight right-ward shift of the curve, but this shift is accompanied by a decrease in accuracy at the 8-sec duration. Figures 2-1 through 2-4 showed very little difference across the high doses of *d*-amphetamine, nicotine, and haloperidol across procedural groups. The main difference that did exist between procedural groups is that when a lateral shift of the curve did occur, it only occurred in the Location group.

Derived Parameters

Range. Four parameters were derived from Equation 2-1; Range, Standard Deviation (Sd), Minimum (Min), and the Point of Subjective Equality (PSE). Range values are shown for individual subjects for all *d*-amphetamine, nicotine, and haloperidol doses in Figure 2-5. Range values during vehicle are between .80 and 1.0, indicating high accuracy for classifying 2 and 8-sec durations. As Range values decreased, this indicated that accuracy was decreasing at one or both of the extreme durations. For *d*-amphetamine, higher doses of drug led to decreases in Range for five out six subjects in the Location group, and all six subjects in the Color group. Nicotine administration at higher doses led to decreases in Range for five out of six subjects in the Location group, and for all subjects in the Color group. Haloperidol administration led to decreases in Range for five out of six subjects in both Color and Location groups. The decreases in Range varied in degree based on subject and on dose of drug. The Range values shown in

Figure 2-5 serve to quantify the decreases in accuracy and flattening of the curve that is visible in Figures 2-1, 2-2, and 2-3. All three drugs administered in this experiment led to a decrease in Range in both procedural groups, with very little difference seen between groups and across drug types.

Averaged Range values for all subjects and all three drugs for the Location and Color groups are shown in Figure 2-6. The dose-dependent decreasing trend for individual subjects was also seen in the group averages. Range was found to decrease dose-dependently for all drugs. During nicotine and haloperidol administration, very little difference is seen between Color and Location procedural groups. Anytime differences did occur, they were slight and in the form of lower Range values for the Color group. The Color group had lower Range values compared to the Location group for all doses of *d*-amphetamine administration, with the largest difference occurring at the 3.0 mg/kg dose of *d*-amphetamine.

Each derived parameter was analyzed statistically in two ways. First, a mixed-model ANOVA was run for only the drug doses that all subjects experienced. Some subjects did not experience the lowest dose or in some cases the highest dose, and so the first method of analysis included all subjects. The within-subjects factors for this first method of analysis were Drug (*d*-amphetamine, nicotine, and haloperidol) and Dose (AMP [Vehicle, 1.7, 2.25, and 3.0 mg/kg], NIC [Vehicle, 0.1, 0.3, 1.0 mg/kg], HAL [Vehicle, 0.1, 0.3, 0.5 mg/kg]). The between-subjects factor was Group (Color and Location). The second method of analysis included four doses per drug with the highest dose included. Subjects that did not experience the highest doses were excluded from this analysis. The second method of analysis included eight of the 12 subjects. All factors were the same, except for Dose (AMP [Vehicle, 1.0, 1.7, 2.25, and 3.0 mg/kg], NIC [Vehicle, 0.1, 0.3, 1.0, and 1.7 mg/kg], HAL [Vehicle, 0.1, 0.3, 0.5, and 0.7 mg/kg]). F values

and effect sizes for significant main effects and interactions from these ANOVAs are shown in Table 2-1.

Both methods of analysis found a significant main effect of Dose for Range. This confirms the result shown in Figures 2-1 through 2-5, which was a decrease in Range values at higher doses compared to vehicle and lower doses. The second analysis also showed a Drug by Dose interaction. The largest difference in Range values was between the high dose of haloperidol for all subjects (0.74), and the highest doses of *d*-amphetamine (0.65) and nicotine (0.63). Haloperidol led to less disruption by the high dose than the high dose for *d*-amphetamine and nicotine. All other main effects and interactions for Range were not found to be significant (largest $F = 4.7$).

To determine which Dose was different from the others, post-hoc Scheffe's tests were run comparing Range values for vehicle to all other doses of drug. Results showed that during *d*-amphetamine administration, vehicle was different from the 2.25 mg/kg dose ($t(30) = 6.1$, $p < .05$), as well as from the 3.0 mg/kg dose ($t(30) = 9.4$, $p < .05$). For nicotine, vehicle was different from the 0.3 mg/kg dose ($t(30) = 4.3$, $p < .05$), the 1.0 mg/kg dose ($t(30) = 6.0$, $p < .05$), and the 1.7 mg/kg dose ($t(30) = 7.9$, $p < .05$). For haloperidol, vehicle was different from the 0.3 mg/kg dose ($t(30) = 5.1$, $p < .05$), the 0.5 mg/kg dose ($t(30) = 7.2$, $p < .05$), and the 0.7 mg/kg dose ($t(30) = 7.6$, $p < .05$).

Sd. Sd values represent the slope of the psychophysical curve and are shown for both Location and Color groups for individual subjects for all three drug types in Figure 2-7. Inspection of individual Sd values revealed very little change for many subjects and doses. Increases in Sd, which indicate a more shallow slope of the psychophysical curve, appeared when higher doses of drug were administered, while the largest increases in Sd occurred mostly

for the Color group. Subjects in the Location group showed very little change in Sd across drugs and doses.

Averaged Sd values are shown for both Location and Color groups for all three drug in Figure 2-8. Very little change was found in Sd values due to drug administration, with the highest increase in Sd occurring at higher doses of haloperidol administration. Group averages revealed differences in Sd values during vehicle administration between procedural groups. These differences remain throughout drug administration. Smaller Sd values for the Location group indicates a steeper slope as compared to the Color group.

The statistical analyses described above were employed for Sd values. Both methods of analysis showed a significant main effect of Group. Average Sd group values across all doses and all drugs were 0.10 for the Location group, and 0.17 for the Color group. For vehicle alone, the Location group Sd average was 0.08, while the average Sd value for the Color group was 0.15. These differences in slope between procedural groups can also be seen in Figures 2-1 through 2-3. No other main effects or interactions were found to be significant (largest $F = 2.8$).

Min. Min values for both procedural groups and all drugs are shown in Figure 2-9. Min values indicate the decrement in accuracy at the 2-sec duration. Individual Min values can be seen in the psychophysical curves shown in Figures 2-1, 2-2, and 2-3. Min values did not increase substantially for any subjects during nicotine and haloperidol administration, with the exception of Subject 642 during nicotine administration. During *d*-amphetamine administration, Min values did increase for two out of six subjects in the Location group, and three out of six subjects for the Color group.

Averaged Min values for both procedural groups and all drugs are shown in Figure 2-10. The averaged values showed that increases in Min values occurred mostly during *d*-amphetamine

administration, and only at higher doses. Increases in Min occurred for more subjects during *d*-amphetamine administration compared to nicotine and haloperidol administration. Averaged values for nicotine show an increase in Min for the Color group, however, this is due to the large increases in Min values for Subject 642.

Both methods of statistical analysis revealed a significant main effect of Dose, while only the first method of analysis revealed a significant main effect of Drug. The main effect of Dose can be seen in the higher doses of drug, and is most evident at the higher doses of *d*-amphetamine administration. The post-hoc Scheffe's test revealed significant differences between vehicle and 2.25 mg/kg of *d*-amphetamine ($t(30) = -5.7$, $p < .05$), as well as vehicle and the 3.0 mg/kg dose of *d*-amphetamine ($t(30) = -5.7$, $p < .05$). No differences between doses were found for nicotine or haloperidol (largest $t = -3.1$). Since the first analysis revealed a main effect of drug, Min values across all doses for each drug were compared. No significant differences were found between drugs, however, the largest difference was between *d*-amphetamine Min values were those of haloperidol ($t(30) = 2.7$).

PSE. PSE values for both procedural groups and all drugs are shown in Figure 2-11. Increases in PSE values indicate a shift in the psychophysical curve to the right, while decreases indicate a shift in the curve to the left. Inspection of individual subjects showed a great deal of variability across subjects. Both low and high doses are shown are shown to have an effect on PSE, sometimes within the same subject, making a general trend difficult to identify.

Averaged PSE values for both procedural groups and all drugs are shown in Figure 2-12. Averaged values show very little in PSE values at any dose of drug. During haloperidol administration, increased PSE values are seen at higher drug doses for the Color group, while decreases in PSE are seen for the Location group. Vehicle PSE values are different during *d*-

amphetamine and nicotine administration, with closer values being seen during haloperidol administration.

The first statistical method that was used did not find any significant main effects or interactions (largest F = 2.7). The second method of analysis, however, revealed a significant main effect of Group. Average PSE values across all doses for the Color group was 4.2-s, while the average PSE value for the Location group was 5.2-s. No other main effects or interactions were significant in the second analysis (largest F = 0.9).

Discussion

The initial effects of *d*-amphetamine, nicotine, and haloperidol were shown to be similar across Color and Location procedural groups. Administration of all three drugs decreased Range values in a dose-dependent manner, with higher doses of drug producing larger decrements in temporal accuracy. Min values increased, but this increase mostly occurred when *d*-amphetamine was administered. This result presents the only major difference between all drugs. It appeared that *d*-amphetamine led to decrements in accuracy in which the proportion of choosing long following a 2-s duration increased along with decreases in the proportion of choosing long following an 8-s duration. For nicotine and haloperidol, flattening of the curves and decreases in Range still occurred, however, this was due to disruption of accuracy at long intervals. Again, this difference in Min values presents the only major difference found between these drugs that have different neurological actions. The effect size was determined for all significant results, and the effect size of Drug on Min had a very was very small compared to other effects that were found to be significant. Those with the highest effect size were Dose for Range and Group for Sd. These provide the most robust effects, and differences across drugs were not among the most powerful differences.

Previous studies comparing Color and Location procedural variations have confirmed the results presented here. Two prior studies have assessed the effects of acute *d*-amphetamine administration on Color and Location procedural variations, showing no difference in drug effects based on procedure (Odum and Ward, 2007; McClure *et al*., In Review(a)). These two procedural variations have never been compared with nicotine and haloperidol being used as disruptors. There is reason to believe that differences between procedures arise when other drug regimens are given, such as chronic drug dosing (McClure *et al*., In Review(b)), or when other types of disruptors are used, such as stimulus intensity (McClure *et al*., *In Review* (c)). The conditions under which procedural variations are irrelevant are just as useful to the literature as the conditions in which they are relevant.

Color and Location procedural groups were compared to determine if these pharmacological agents would have different effects based on procedure. The results confirmed that initial effects of the drugs are similar across procedural groups. Some differences between procedural groups did exist however. Sd values were found to be different between Color and Location groups. The Location group had lower Sd values, indicating a higher level of discriminability of temporal intervals. Visually, the slope of the psychophysical curve was steeper for Location subjects as compared to Color subjects. This difference may indicate differing levels of stimulus control for one procedure over another, making one procedural group more likely to be disrupted by drug. Though differential disruption was not the case in the current experiment, any differences in performance between procedural groups, even prior to drug administration, could be problematic when comparisons across studies and procedures are readily made within the literature. This difference between procedures and performance on the variations of the MTSD procedure, even without the presence of drug, has been noted in various

reports in the form of time to reach stability. It has been shown that the spatial procedural variation can be learned more quickly than the non-spatial variation (Chatlosh and Wasserman, 1987; Odum and Ward, 2007). It has also been suggested that the spatial variation is less complicated due to location cues that may aid in accurate temporal judgments (Fetterman *et al*., 1998; Harper and Bizo, 2000). Differences in these procedures could manifest in differential drug effects or different propensities to develop tolerance, which could influence the comparisons made between studies in the timing literature using these procedural variations.

The current study showed similarities in disruption based on different pharmacological agents regardless of procedural variation. *D*-amphetamine, nicotine, and haloperidol have distinct neurological effects, yet they are behaviorally similar when used as disruptors of temporal accuracy. Showing similar disruption of temporal judgments by pharmacologically distinct substances reveals generality concerning the effects of drugs on timing behavior. The generality of disruptors on temporal discrimination can be further extended if disruptive agents are used that are not pharmacological in nature. Experiment 2 will explore non-pharmacological agents, given in acute and chronic presentation regimens, and their disruptive potential for temporal discrimination using the Color and Location variations of the MTSD procedure.

Table 2-1. F values followed by effect sizes in parentheses for significant main effects and interactions for both methods of statistical analysis for Experiment 1.

Parameter	Drug (d.f. = 2, 20)	Dose (d.f = 3, 30 and 4, 24)	Drug by Dose (df. = 8, 48)	Group (d.f. = 1, 10 and 1, 6)
Range		63.5 (0.86)** 43.5(0.88)**	2.4 (0.28)*	
Sd				227.8 (0.96)** 310.9 (0.98)**
Min	4.6 (0.32)*	15.8 (0.61)** 4.2 (0.41)*		
PSE				6.2 (0.51)*

* $p < .05$
** $p < .01$

Note: Table 2-1. F values of mixed model ANOVAs with repeated measures for all drug conditions for parameters Range, Sd, Min, and PSE. Two statistical analyses were performed, one with four subjects excluded, the other with high and low doses excluded. If significant was found in both methods of analysis, both F values and effect sizes are included. Degrees of freedom (df.) are shown in parentheses next to the main effect or interaction. Only df. values are shown for the analysis in which significance was found. F values are shown followed by Partial Eta squared values indicating the effect size. Only statistically significant effects are shown.

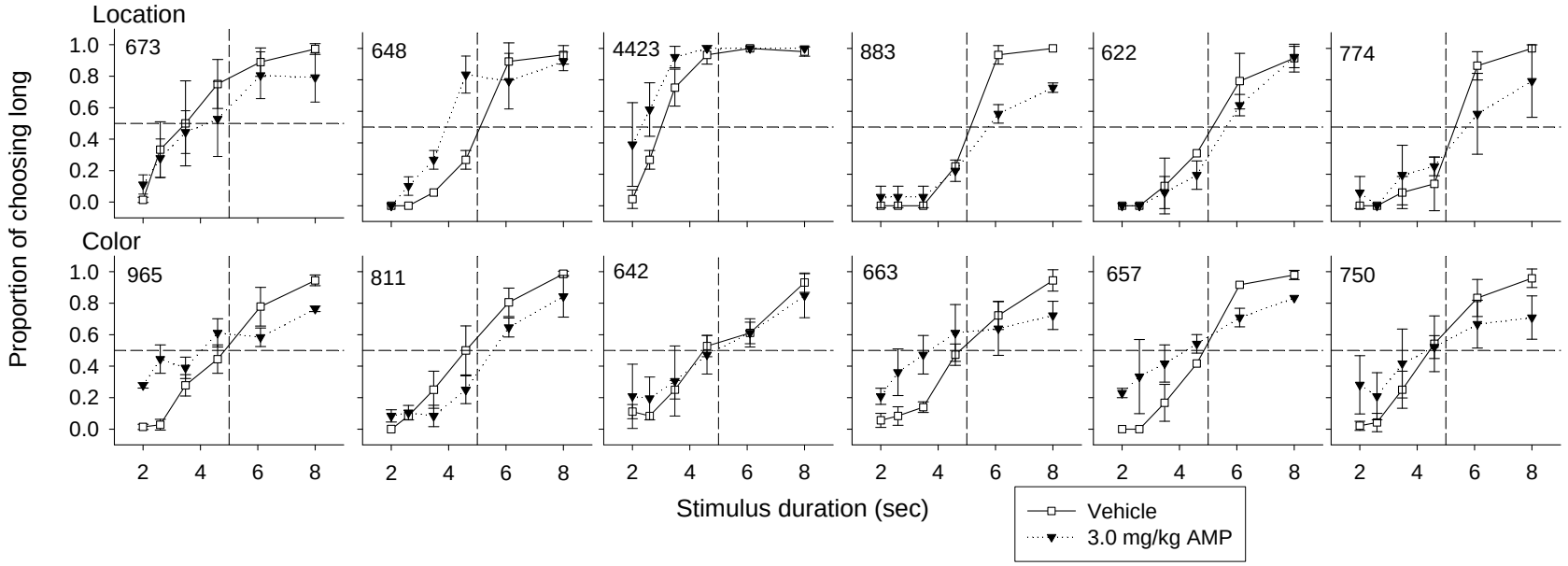

Figure 2-1. Psychophysical curves for the highest dose of *d*-amphetamine compared to vehicle given during Experiment 1. The proportion of choosing the long alternative is shown as a function of stimulus duration. Open squares represent administration of vehicle for an average of two to three administrations; closed triangles represent the averaged psychophysical curve at the 3.0 mg/kg of *d*-amphetamine. Error bars represent standard error of mean. Since drug doses were counterbalanced, subjects are presented in the order in which they received this particular drug type.

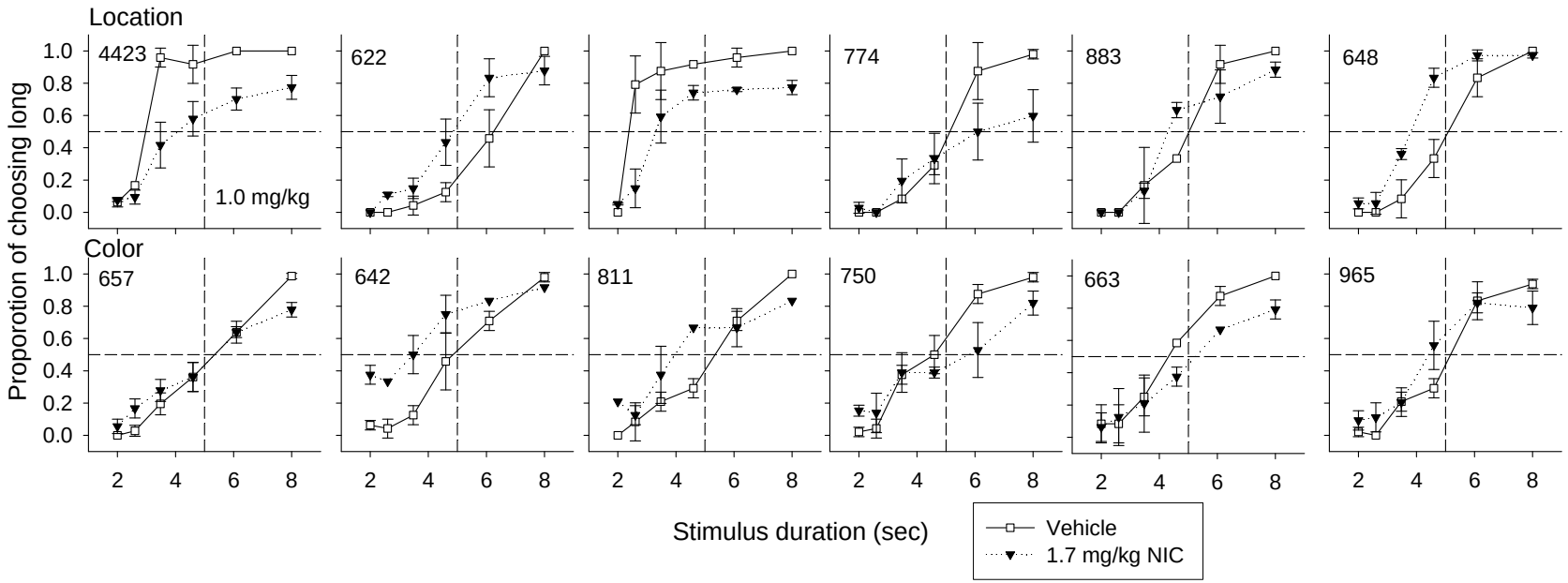

Figure 2-2. Psychophysical curves for the highest dose of nicotine given during Experiment 1. The proportion of choosing the long alternative is shown as a function of stimulus duration. Open squares represent administration of vehicle for an average of two to three administrations; closed triangles represent the averaged psychophysical curve at the 1.7 mg/kg of nicotine for all subjects, except Subject 4423 which had a high dose of 1.0 mg/kg nicotine. All other details are similar to Figure 2-1.

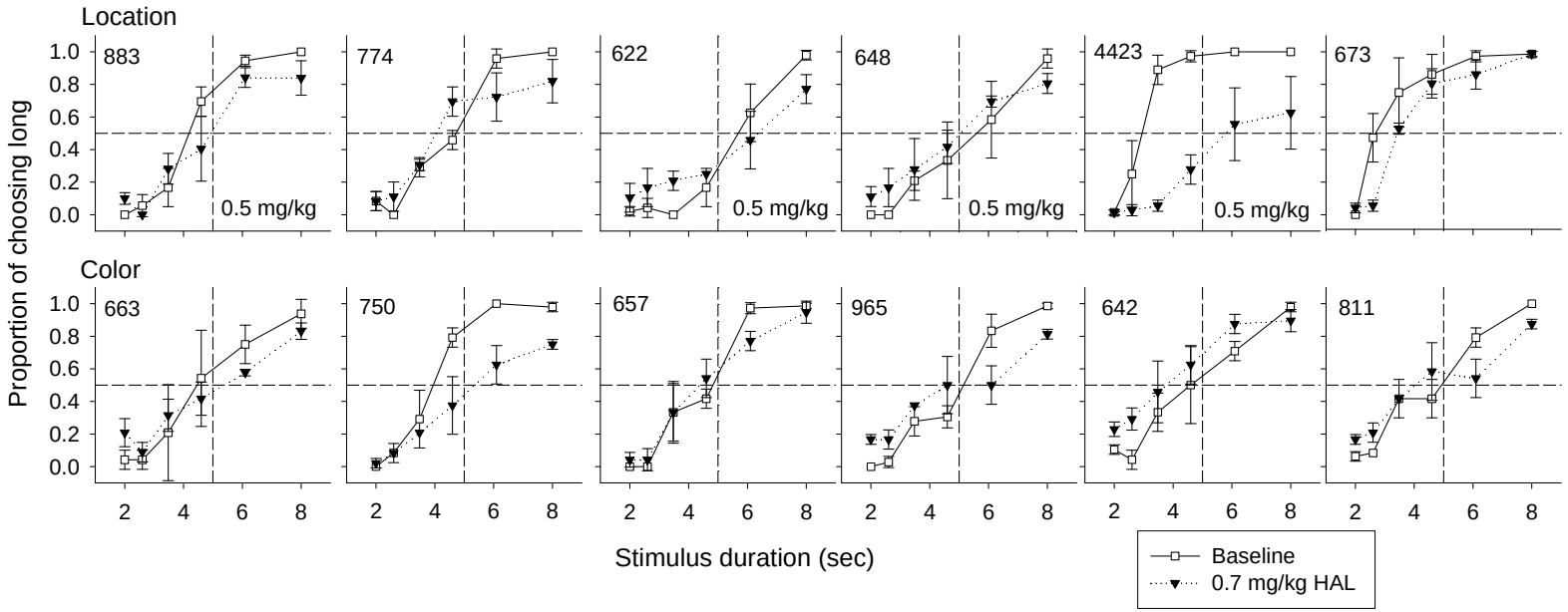

Figure 2-3. Psychophysical curves for the highest dose of haloperidol given during Experiment 1. The high dose was 0.7 mg/kg of haloperidol, except for Subjects 883, 622, 648 and 4423 in which 0.5 mg/kg was the high dose of haloperidol. All other details are similar to Figure 2-1.

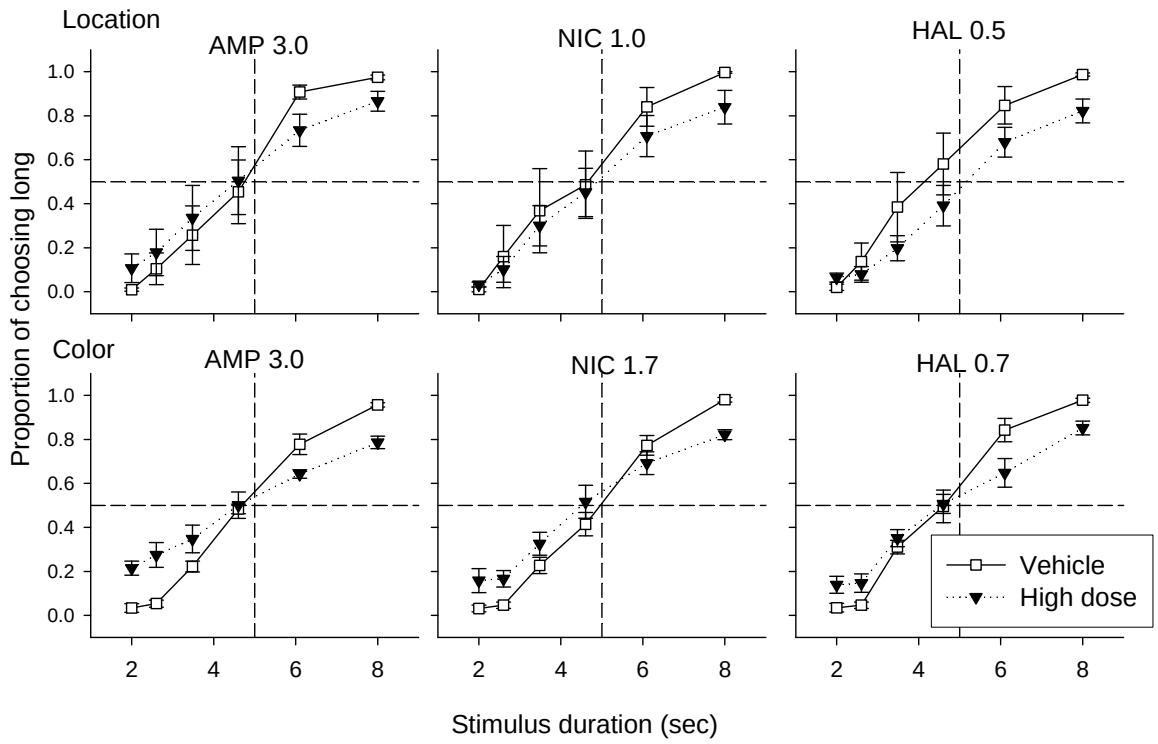

Figure 2-4. Averaged psychophysical curves between groups for the highest dose of drug given to all subjects with that procedural group. The dose of drug and drug type is shown above each panel. All other details are similar to that of Figure 2-1.

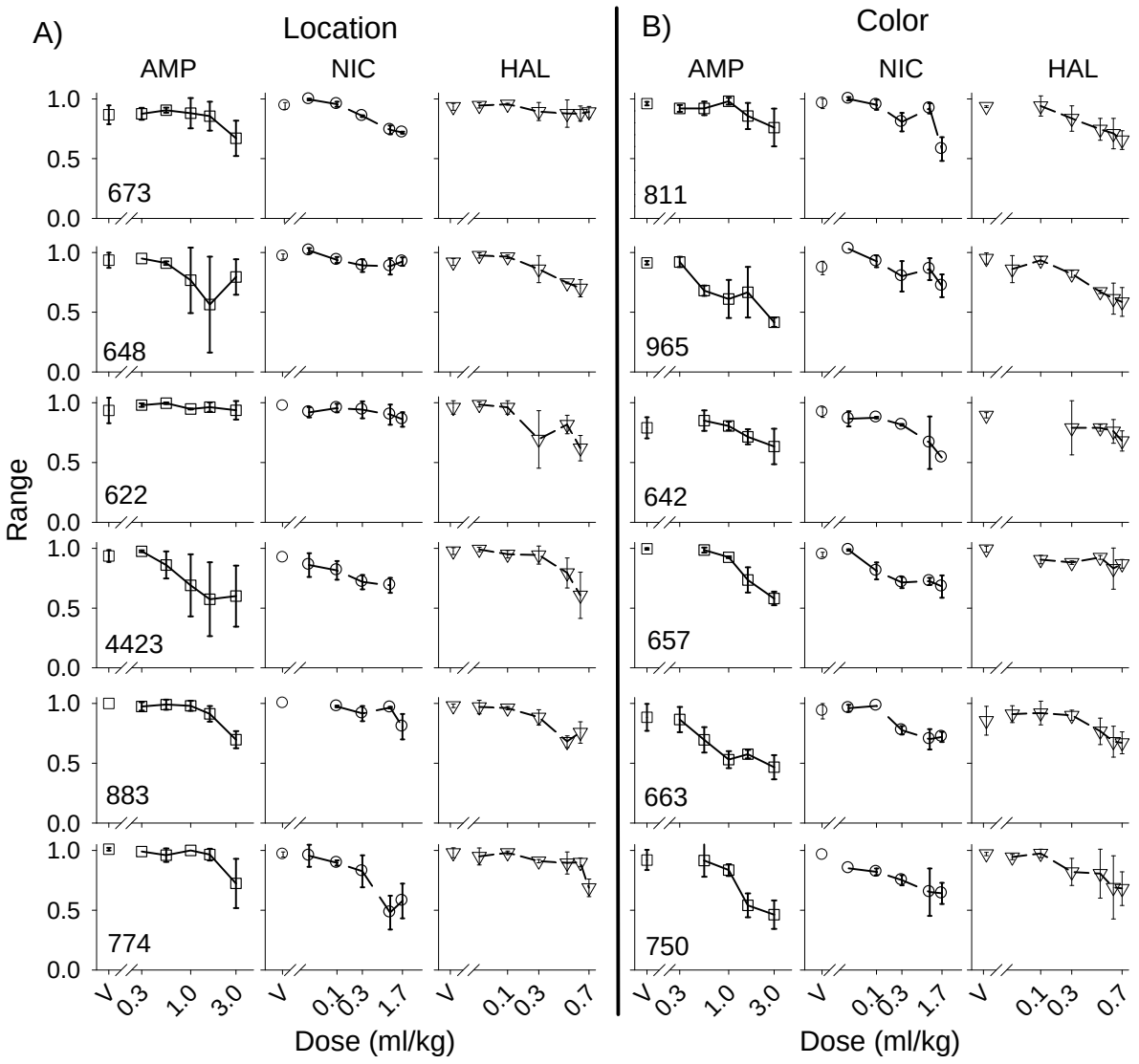

Figure 2-5. Range values for all drug types and all drug doses. A) Location group subjects. B) Color group subjects. The type of drug is noted above each row of panels. Each data point is the average of two or three administrations of that dose. Error bars represent standard error of the mean. Missing data point indicates that the subject did not experience that dose, or responding was completely suppressed.

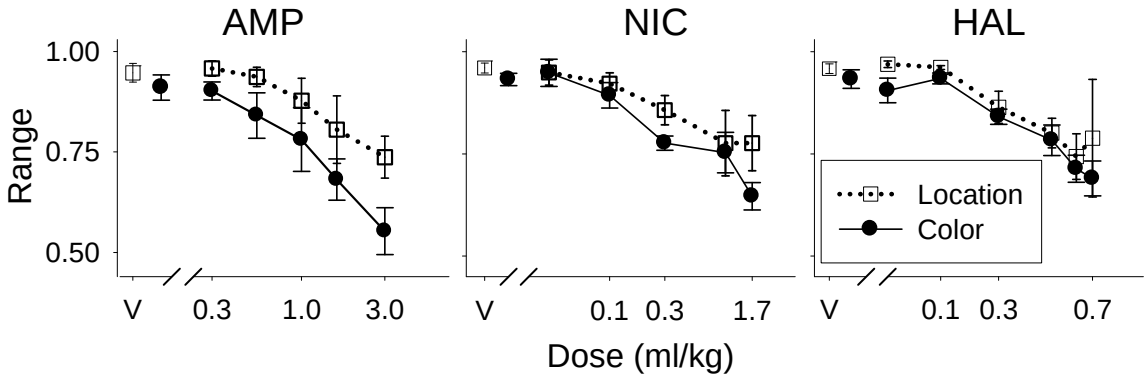

Figure 2-6. Averaged Range values for all drug types, all drug doses, across subjects within a procedural group. Location group Range values are represented with open squares, while Color group Range values are represented with closed circles. The type of drug is noted above each panel. Error bars represent standard error of the mean. Note the difference in scale for Figure 2-6 compared to Figure 2-5.

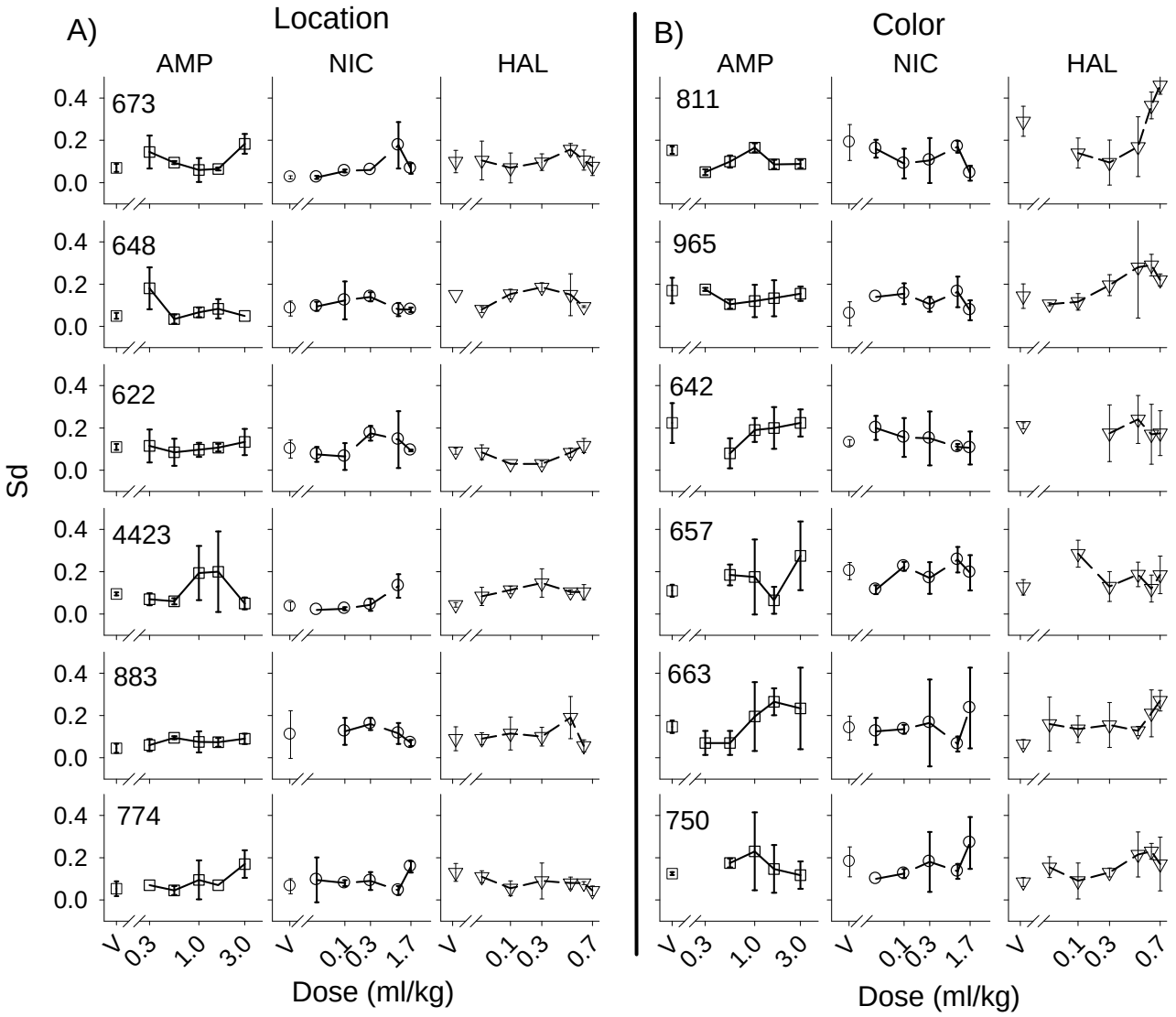

Figure 2-7. Sd values for all drug types and all drug doses. A) Location subjects. B) Color subjects. All details are similar to the Figure 2-5.

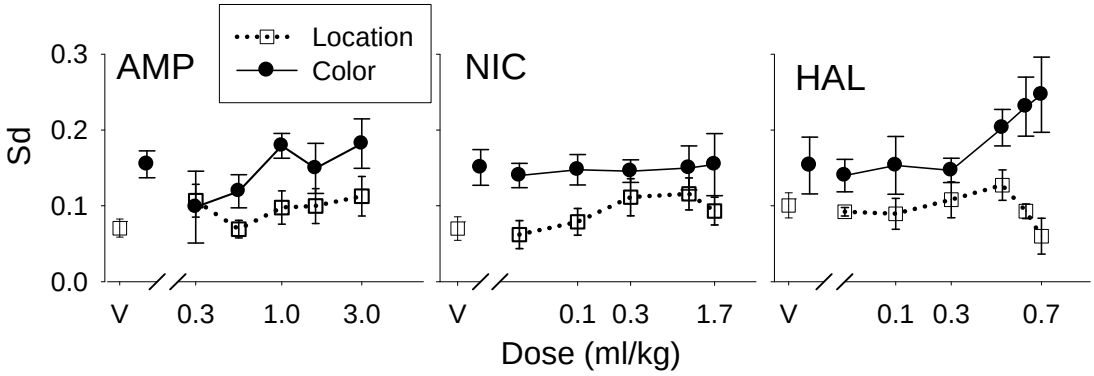

Figure 2-8. Averaged Sd values for all drug types, all drug doses, across subjects within a procedural group. All other details are similar to Figure 2-6.

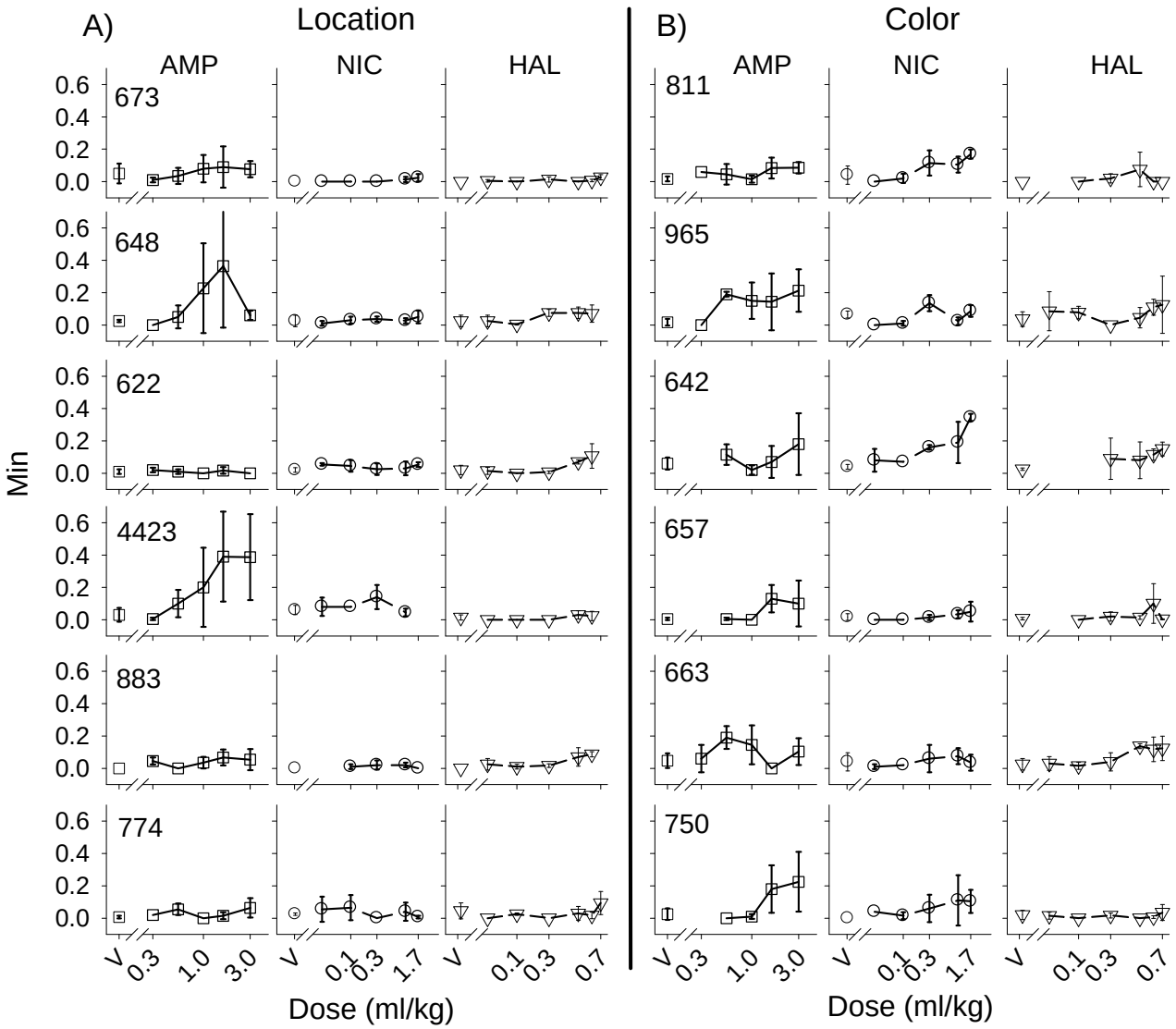

Figure 2-9. Min values for all drug types and all drug doses. A) Location subjects. B) Color subjects. All details are similar to the Figure 2-5.

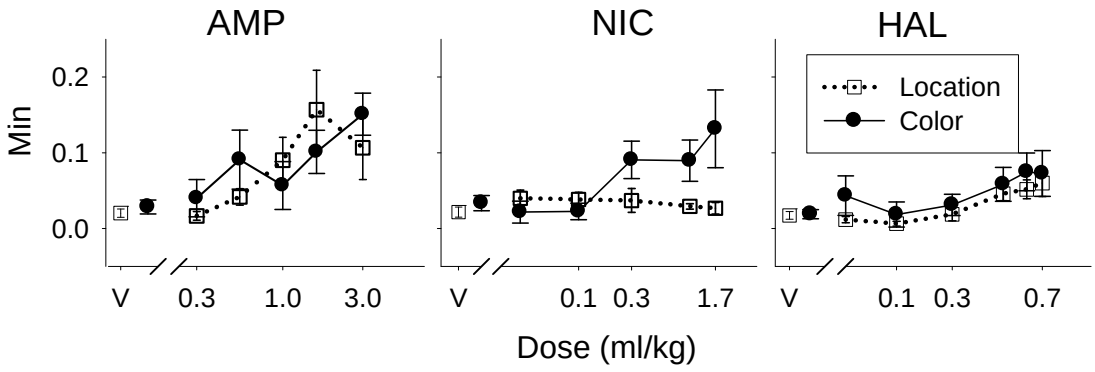

Figure 2-10. Averaged Min values for all drug types, all drug doses, across subjects within a procedural group. All other details are similar to Figure 2-6.

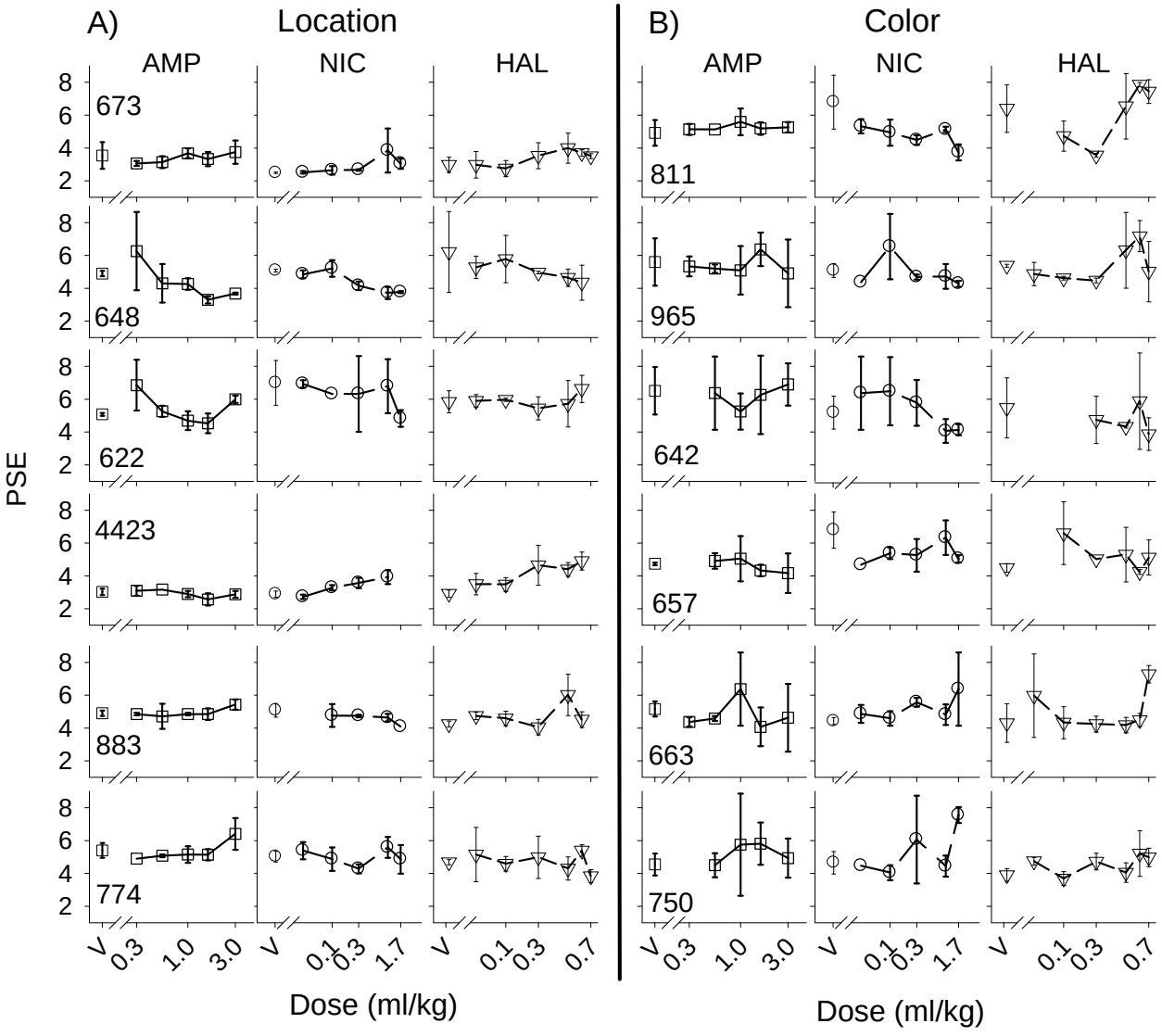

Figure 2-11. PSE values for all drug types and all drug doses. A) Location subjects. B) Color subjects. All details are similar to the Figure 2-5.

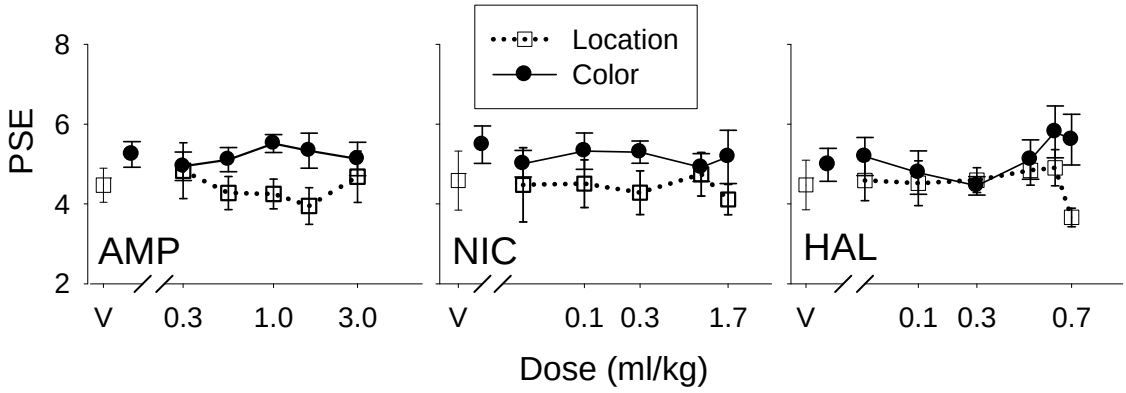

Figure 2-12. Averaged PSE values for all drug types, all drug doses, across subjects within a procedural group. All other details are similar to Figure 2-6.

CHAPTER 3
EXPERIMENT 2

Introduction

The use of non-pharmacological agents in the disruption of temporal behavior provides useful information concerning the conditions under which disruption occurs. The use of pharmacological and non-pharmacological agents may lead to results indicating differences in disruption based on the type of disruptor, or it could result in a similar disruption of temporal behavior. There is the potential for a general class of disruptors, of varying type, that lead to similar disruptions of temporal accuracy. Experiment 2 assessed the effects of non-pharmacological disruptors on temporal discrimination when they were presented in acute and chronic regimens. The disruptors that were used focused on manipulating the motivation of the animal to respond. This included providing varying levels of food to the animal prior to the session, giving free food during the session that is not contingent on correct responses, and finally, discontinuing reinforcement for correct responses. Both Color and Location procedural variations were used in Experiment 2 to determine if the type of disruptor mattered in producing differential effects based on procedure. Experiment 2 not only assessed the procedural variation of Color and Location, but also included a third group for comparison. This third group experienced the Color procedural variation at the time of testing; however, they had had prior experience with the Location version as well. Based on this history with the Location variation, comparisons were made to determine if history played a role in the differential disruption of behavior due to non-pharmacological agents.

Method

Subjects/Apparatus

Experiment 2 consisted of two phases. In Phases 1 and 2, six White Carneau pigeons (*Columba livia*), with previous behavioral testing history, and experience with disruptors served as subjects. The disruptors previously presented to these subjects included exposure to doses of *d*-amphetamine, as well as exposure to increased stimulus intensity during sessions. At the time of the current experiment, at least three months had passed since any subject experienced a disruptor of temporal discrimination. These subjects also had experience with the Location version of the MTSD task, but were being tested on the Color MTSD variation. This group was called Color (Location history: LH). These subjects were used in Phase 1 of Experiment 2, and then immediately began exposure to Phase 2 conditions. During Phase 2, all twelve subjects from Experiment 1 were used, as well as the six subjects from Phase 1. The birds were individually housed in a humidity and temperature controlled colony room with a 16:8 hour light-dark cycle. Water and grit were continually available in the home cages. Post-session feedings were given when necessary to maintain body weights at 83% of free-feeding levels. The apparatus was the same as in Experiment 1.

Procedure

Phase 1

Subjects used during this phase all experienced the Color procedure; however, they all had previous history with the Location procedure. The non-pharmacological disruptors used in Phase 1 were administered in an acute fashion, such that two intervening baseline sessions separated exposure to disruptors. Every third day a different disruptor was presented. Disruptors were presented for an entire daily session. This design was comparable to the methodology used

for acute drug administration in Experiment 1. The non-pharmacological disruptors were inter-block interval food (IBI Food) and Acute Extinction.

The Color procedure that was described and used for the Color group subjects in Experiment 1 was also used in Phase 1. Training procedures, as well as the introduction of intermediate durations were the same. The only difference was that in Experiment 1, a new trial began after the inter-trial interval (ITI) for each trial, which ranged from 1-20 s, whereas in Phase 1 of the current experiment, additional delays irrespective of the ITI were included after a certain number of trials had passed. Each session was separated into four blocks of 24 trials each (96 total trials/session). After each block of 24 trials, a 60-s inter-block interval (IBI) occurred in which all lights in the chamber were extinguished. This occurred during baseline and disruptor sessions. During most sessions, no events occurred during the IBI, however, during the IBI Food disruptor sessions, the hopper was presented on a variable time (VT) 5-s schedule during the 60-s IBI after each block of 24 trials and the subject had access to grain which was not contingent on any responding. The VT 5-s schedule led to approximately 64 2-s access hopper presentations for the entire session. During Acute Extinction (EXT), subjects no longer received reinforcement for any response during the session. Each disruptor was presented for a total of three total sessions, all separated by two baseline sessions. The presentation of disruptors was counterbalanced so that each subject received a different disruptor first. All control (baseline) and disruptor sessions lasted for 96 trials or 80 minutes, whichever came first. For data to be included in analyses, subjects had to complete 48 of 96 trials for that particular session.

Phase 2

Subjects from Experiment 1 remained in the same procedural group (Color and Location) as they had been assigned to in Experiment 1, and all details of the procedure remained the same. Subjects from Phase 1 were also used in Phase 2 of the current experiment. The three procedural

groups in Phase 2 were Location, Color, and Color (LH). The procedure for Color (LH) subjects from Phase 1 of current experiment remained the same, with the only difference being that sessions no longer included a 60-s IBI.

When temporal discrimination was deemed stable via visual inspection of psychophysical curves and derived parameters (Range, Sd, Min, and PSE), the disruptors were presented. The disruptors consisted of Acute Pre-Feed (PF), Chronic Extinction (EXT), and Chronic Free Feed (FF). The Pre-feed (PF) disruptor consisted of giving varying amounts of grain to the subject 20-30 minutes prior to the start of their experimental session. Pre-Feed was given in differing amounts so that behavior could be assessed when the subjects were at different levels of their free feeding weight. Subjects were normally maintained at 83% of their free-feeding weight, and so all baseline (control) sessions correspond to a free-feeding weight of approximately 83%. The four categories in the PF condition differing percentages of subject's free feeding weight, which were 85-89.5%, 90-94.5%, 95-99.5%, and 100-105%. Food was given in an acute fashion, so each pre-feed session was separated by two to five baseline sessions. This acute regimen was only used for PF. Each weight category was assessed at least twice, when responding occurred. The second disruptor was Chronic Extinction (EXT). During this condition, subjects no longer received reinforcement for correct responses that were reinforced during baseline sessions. This disruptor was given in a chronic regimen, which means that EXT sessions were presented for consecutive days until subjects no longer responded during session. During chronic presentations, no control sessions separated disruptor presentations, as was the case in an acute regimen. The EXT condition lasted for 10-13 consecutive sessions. The final disruptor was Chronic Free-feed (FF) in which birds were given free access to food for 10-15 consecutive days.

For all disruptor types and presentations, subjects had to complete 48 of 96 trials for data to be included in the analysis.

Data Analysis

The data analyzed came from each disruptor session, along with the preceding control day for acute disruptors and the last three to five baseline sessions before chronic disruptors were presented. For each session the proportion of responses to the long response alternative was plotted as a function of the duration of the stimulus on that trial. All other details of the data analysis are identical to the methods described in Experiment 1.

Results

Phase 1

The psychophysical curves for all subjects showing IBI Food and EXT disruptors during Phase 1 are shown in Figure 3-1. Changes in the psychophysical curves due to presentation of these disruptors were minimal, if they occurred at all. Accuracy for classifying temporal intervals did not appear to decrease for any subject. If any changes did occur, they were in the form of a lateral shift to the left or right. IBI Food led to a slight right-ward shift in the psychophysical curve for Subject 65, while EXT led to a right-ward shift of the curve for Subjects 945 and 283. Subject 934 showed a left-ward shift of the curve during IBI Food and EXT presentations. Direction of shifts in the curve was not consistent across subjects.

The four parameters derived from Equation 2-1 (Range, PSE, Min, and SD) are shown in Figure 3-2 for both IBI Food and EXT. The changes in lateral positioning of the psychophysical curve visible in Figure 3-1 are quantified by the parameter PSE and are visible in Figure 3-2. The largest changes in any parameters included increases in Sd and PSE values for Subject 945 during EXT, and a decrease in Sd for Subject 65 during IBI Food. Otherwise, no large effects were seen based on the presentation of IBI Food and EXT.

ANOVAs with repeated measures were carried out on all four derived parameters separately. The within subjects factors were Condition (Control, IBI Food, EXT) and Session (3 sessions/condition). Statistical analyses did not reveal any significant main effects or interactions for any parameter (largest $F = 3.4$).

Phase 2

Psychophysical curves

Psychophysical curves for each subject during the highest level of Pre-feed experienced are shown in Figure 3-3. The highest free-feeding weight at which birds continued to respond is shown compared to baseline. The two patterns of disruption seen were in the form of a flattening of the psychophysical curve, during which a lateral shift may or may not have accompanied this effect, and the other was a lateral shift of the curve without any loss in accuracy. For the Location group, three out of six subjects showed a loss of accuracy at an extreme duration, while two other subjects show a left-ward shift in the curve, and the last subject showed no disruption to pre-feed. The Color group had four of six subjects with a loss of accuracy, one showed a right-ward shift of the curve, and one showed no disruption due to pre-feed. The Color (LH) showed three of six subjects with a flattening of the curve in varying degrees, one showing a right-ward shift and two with no disruption. Based on Figure 3-3, it appeared that some disruption did occur for all three procedural groups, and the degree or type of disruption was not different based on group.

Averaged psychophysical curves across all chronic sessions of EXT for each subject are shown in Figure 3-4. Averaged values for the Location group showed a decrease in accuracy at extreme durations for five out of six subjects, and no change for the sixth subject. The Color group however, showed a decrease in accuracy for only one subject, while two out of six showed slight right-ward shifts and two showed no disruption. The Color (LH) group showed loss of

accuracy for four out of six birds, while the other two showed right-ward shifts in varying degrees.

Chronic Free-feed (FF) psychophysical curves averaged across all sessions for each subject are shown in Figure 3-5. During the FF condition, two of six subjects in the Color (LH) group did not respond, so no panels are shown for those subjects (957 and 945). One subject (774) did not respond during chronic FF from the Location group and no panel for that subject either. Averaged values for the Location group showed a decrease in accuracy for one out of five subjects that completed this condition, while one subject showed a left-ward shift in the curve, one showed a right-ward shift in the curve, and the two remaining subjects showed no change in the curve due to FF. The Color group showed a decrease in accuracy for three subjects, one subject showed a slight right-ward shift and two showed no disruption. The Color (LH) group showed loss of accuracy for two of out four subjects that completed the condition, and two with very little change. Overall, the patterns of disruption appeared to be variable across subjects with no consistency of disruption across procedural groups.

Averaged psychophysical curves across all subjects and all disruptor presentations are shown in Figure 3-6. The changes are in the form of a flattening of the psychophysical curve, which is most severe for the Color (LH) group during PF, as well as FF, while the Location group shows the most severe disruption due to EXT presentations. Many subjects showed disruption after a few days of chronic exposure to EXT and FF, which can be seen in individual sessions figures below.

Derived parameters

Range. Four parameters were derived from Equation 2-1, and included Range, Sd, Min, and PSE. Range values for all subjects across individual sessions for all three disruptor conditions (PF, EXT, and FF) are shown in Figure 3-7. The Range parameter quantifies the

flattening of the psychophysical curve and decrease in accuracy at extreme values, with lower Range values indicating a flattening of the curve. During the PF condition, Range appeared to have decreased for four of six Location group subjects, four out of six Color group subjects, and all three Color (LH) group subjects. Larger decreases occurred as the level of PF given increased. During the EXT condition, all subjects showed a decrease in Range at some point. For Subjects 883 and 283, decreases in Range were small, if they occurred at all, before responding was completely suppressed. Decreases in Range typically occurred by the third to fourth consecutive day of EXT. Subject 642, which was in the Color group, required more sessions for temporal behavior to be disrupted in the form of decreased Range. Very little difference was seen between procedural groups in terms of disruption to EXT sessions. During the Chronic FF condition, three of five subjects in the Location group that completed this condition showed very little disruption in Range (Subjects 673, 648, and 622), and continued to respond for 15 consecutive sessions. Subject 4423 showed a decrease in Range during all FF sessions, yet continued to respond. Subject 883 showed no disruption, but only completed the response requirement for one session. All birds in the Color group responded for at least two FF sessions. All subjects, with the exception of 657, showed a decrease in Range at some point during the FF condition. Only four of six subjects in the Color (LH) group responded during the FF condition. All subjects in this group showed decreased Range values due to FF at some point.

If we look not only at Range values, but also continuation of responding through consecutive days of FF, it appeared that the Color (LH) group showed the most disruption, followed by the Color, in which three of six subjects responded for 15 sessions, with only one showing little effect of FF on temporal behavior. The Location group showed four of six

subjects responding for all 15 sessions, with only one out of four showing decreased Range values.

Each derived parameter was analyzed using statistical analyses similar to those described in Experiment 1, with some notable differences. Each non-pharmacological disruptor condition was run in a separate analysis due to the intermittent nature of the PF condition, and the consecutive presentations of the EXT and FF conditions. Also, certain subjects failed to complete all conditions, and so multiple analyses were conducted to compare sub-sets of the subjects. For the PF condition, a mixed-model ANOVA was run with Condition being the within-subject factor (Control, 85-89%, 90-94%, 95-99%, and 100-105%), and Group (Location, Color, and Color [LH]) as the between-subjects factor. These factors were used to analyze the data by excluding some subjects and some PF conditions in two different analyses. First, only subjects that experienced all PF conditions (Control, 85-89%, 90-94%, 95-99%, and 100-105%) were run, which totaled 11 out of 18 subjects (Analysis 1). Second, all 18 subjects were included in the analysis with only the conditions they all completed (Control, 90-94%) (Analysis 2). When significant main effects or interactions were found in both forms of analysis, the smallest F value was reported in the tables. Significant main effects, interactions, and effect sizes are shown for PF in Table 3-1.

For Range, both analyses confirmed a main effect of Condition during PF. Range decreased during PF conditions for all Groups. To determine which Condition of PF was different from Control, post-hoc Scheffe's tests were run comparing Range values for control to each PF level. Results showed that the Range values were different from Control at the 95-99% condition, as well as the 100-105% condition. It was shown that as amount of pre-feed increased, Range values decreased.

For the EXT condition, all subjects experienced a different number of days in which the response requirement was satisfied. Sessions of EXT ranged from 2-13 consecutive sessions across all subjects. For the statistical analysis of all parameters for this condition, EXT days were separated into the first half of EXT sessions and averaged together, and the second half of sessions, which were averaged together and compared. All subjects experienced at least two days of EXT, making it possible to have two blocks of sessions. Separating blocks of sessions allowed for closer inspection of changes in parameters throughout EXT sessions. The within-subject factor was Condition (Control, First ½ sessions block, Second ½ sessions block), with Group (Location, Color, and Color [LH]) as the between-subjects factor. F values and effect sizes can be found for the EXT condition in Table 3-2. For Range, a significant main effect of Condition was found. Scheffe's test revealed that during EXT sessions, both the first and second blocks of EXT were significantly different from Control Range values. A significant Condition by Group interaction was also found. While the first and second blocks of EXT sessions are different from Control, as shown by the significant main effect of Condition, the Location group shows a larger decrease in Range values across Conditions than the Color or Color (LH) groups, thus explaining the Condition by Group interaction.

For the FF condition, the statistical analysis was conducted in much the same way as for the EXT condition, however, three out of 18 subjects did not respond during any FF sessions, and so the remaining 15 subjects were used in this analysis. Out of those 15 subjects, two subjects satisfied the response requirement for only one FF sessions, therefore, blocks of sessions could not be used. All FF sessions were averaged together and compared to Control data. Those values can be found in Table 3-3. A main effect of Condition was found for Range during the FF condition indicating that Range values during FF were lower than Control values. A significant

main effect of Group was also found. On average during Control and FF, the Color (LH) group had the lowest average Range value (0.76); followed by the Color group (0.85), and finally the Location group had the highest Range value (0.92).

Sd. Sd values, derived from Equation 2-1, are shown in Figure 3-8. Small Sd values indicate a steep slope of the psychophysical curve, and larger Sd values correspond to a more shallow slope of the curve. Sd values, and slope, were relatively unchanged during the PF condition, except for decreases in Sd shown for the Color (LH) group. During EXT and FF conditions, there was variability across subjects in terms of increases and decreases in Sd values. The general trend was for Sd values to increase throughout presentations of EXT and FF, but decreases were seen as well, and typically when baseline Sd values were high to begin with. Changes in Sd values occurred consistently with the disruption of Range shown in Figure 3-7.

Statistical analyses run for the Range parameter above were also run for all other parameters. During the PF condition, a significant main effect of Group was found. This result was found for both types of statistical analysis. The average Sd values for each Group were 0.08 for the Location group, 0.13 for the Color group, and 0.17 for the Color (LH) group. This result also had a large effect size, which can be seen in Table 3-1. A significant Condition by Group interaction was also found for Sd, but only in the first analysis run. This effect can be seen for the Color (LH) group at the higher PF conditions, in which Sd values decrease. Only two out of six subjects experienced the 100-105% PF condition, in which the decrease in Sd values was shown. The effect size for this interaction is only 0.34.

During both the EXT and FF conditions, significant main effects of Group, but not Condition were found. While increases in Sd occurred during certain days of EXT and FF presentation, average values were not different from Control values. The average Sd value for

the Color (LH) group was 0.18 during EXT, and was higher than both the Location and Color groups, which had Sd values of 0.12 and 0.13, respectively. During the FF condition, Color (LH) Sd values were 0.16 compared to the Color group Sd value of 0.15. Both those groups were different from the Sd values in the Location group (0.10).

Min. Min values are shown in Figure 3-9. These values indicate the position of the lower asymptote of the psychophysical curve. When PF was given, Min values increased for five total subjects across all three groups. Increases in Min were not specific to one group, but occurred equally across groups, with the largest increase in Min occurring for Subject 934 in Color (LH) group. This led to the largest average Min value, along with the largest measure of variance. During the EXT condition, increases in Min occurred at some point for 13 out of 18 subjects, again not specific to Group, which can also be seen in the averaged Min values. During the FF condition, nine out of 15 subjects showed increases in Min at some point during the FF presentations. The largest increases in Min values during FF were found for the Color (LH) group.

Statistical analyses, conducted as described above for Range and Sd, showed a significant main effect of Condition during PF, EXT, and FF for Min. For PF, Scheffe's test revealed no significant differences between Control and any PF conditions, although the largest difference was between Control and the 100-105% PF condition ($t = 2.6$). During EXT, Scheffe's test revealed that Min values during the second block of EXT sessions were different from Control values. During FF, a main effect of Condition indicates that Control values were different from those during FF sessions. As is seen in Figures 3-11 and 3-12, no differences were shown across procedural groups.

PSE. PSE values for PF, EXT, and FF conditions are shown in Figure 3-10. Increases in PSE values represent a right-ward shift of the psychophysical curves. Consistent changes in PSE values are difficult to see in any of the three conditions. Most subjects showed both increases and decreases in PSE values throughout the course of disruptor presentations. Changes in PSE values typically seemed to accompany decreases in Range values rather than occurring in isolation.

Statistical analyses of PSE values revealed a main effect of Condition during the PF and EXT conditions, with no significant main effects or interaction found during the FF condition. Condition was only found to be a significant main effect during the second form of analysis for PF, in which Control was compared to the 90-94% PF condition for all subjects. PSE Control values during PF were 4.7-s, which was different from the PSE value during the 90-94% PF condition of 5.3-s, indicating a right-ward shift of the curve during pre-feed. During EXT sessions, PSE values were different from Control during the second block of EXT sessions. The averaged PSE value during Control was 4.7-s, compared to the PSE value during the second block of EXT sessions, which was 5.5-s, again indicating a right-ward shift of the curve due to the chronic presentation of EXT sessions. Effect sizes for these main effects of Conditions were low, which confirms the visual interpretation of high variability across subjects in both Figures 3-13 and 3-14.

Discussion

Phase 1 of the current study showed that IBI Food and the acute presentation of EXT sessions did not lead to any disruption of the psychophysical curves or any derived parameter. Though small changes did occur during disruptor presentation, these were not different from baseline and were not consistent across subjects. Based on the lack of any effect due to these

acute disruptors, Phase 2 utilized disruptors of a chronic nature that were more likely to produce disruptions of temporal behavior.

Phase 2 of the current study revealed disruption of temporal behavior in the form of a flattening of the psychophysical curve due to non-pharmacological disruptors that influence the motivation to respond by manipulating establishing operations in the PF and FF conditions, and removal of reinforcing contingencies for correct responses during EXT. Results showed that the psychophysical curve flattened during all disruptor conditions; PF, EXT, and FF. During PF, Range decreased dependently as the amount of pre-feed given was increased. All disruptors led to increases in the Min value, meaning that during disruptor presentations, subjects were responding to 2-s intervals with a higher proportion of choosing long for those intervals. Decreases in choosing the long alternative following an 8-s duration also occurred during all disruptor presentations. Psychophysical curves were also found to shift in lateral position toward the right during PF and EXT conditions. This shift, however, was always accompanied by a decrease in Range values and flattening of the curve.

Three procedural groups were compared in Phase 2, which were Location, Color, and Color (LH). During all three disruptor presentations, average Sd values between groups were different. Sd values for the Color (LH) group were always higher than Location and Color groups. During EXT, Color and Location Sd values were similar, and were lower than Color (LH) values. However, during FF, Color and Color (LH) values were similar, but were higher than Location values. Just as in Experiment 1, Location subjects had lower Sd values than Color subjects, indicating higher discriminability of temporal intervals. Another example of differences between groups was found in Range values during the FF condition. Range values for Color and Color (LH) subjects were lower than for Location subjects during FF, indicating

lower levels of stimulus control by temporal intervals between groups. Though differences in disruption were not found across groups in either Experiment 1 or 2, there could be conditions under which differences in baseline performance on these procedures could impact to obtained results.

Varying amounts of PF were given in an acute regimen, which closely mimics the drug presentation given in Experiment 1. It was shown during this condition that as amount of food given prior to the session increased, Range decreased. The higher values of pre-feed were large enough to produce a disruption of temporal behavior. For EXT and FF conditions, presentation of these disruptors was given across consecutive sessions. Acute sessions of EXT were shown in Phase 1 of the current experiment not to cause any disruption of temporal behavior. However, the chronic presentation of EXT led to decreases in accuracy. Analyses of the first and second halves of EXT sessions showed that more disruption was found during the second half of EXT sessions for Range and Min. Multiple sessions were required to produce disruption of temporal behavior, though responding still persisted. For the FF condition, when subjects were given free access to food at all times, 15 of 18 subjects still continued to respond. Disruption did occur during FF, but often disruption was not seen until two to three sessions into the FF condition.

Disruptors in Phase 1 failed to have a disruptive effect on temporal behavior, but disruptors presented in acute and chronic regimens in Phase 2 had a significant disruptive effect on temporal discrimination in the form of a flattening of the psychophysical curve and loss of accuracy. This type of disruption matches the disruption found in Experiment 1 that was caused by *d*-amphetamine, nicotine, and haloperidol. Both experiments provide an array of diverse conditions under which disruption, in the form of a flattening of the curve, occurs regardless of procedural group and regardless of type of disruptor.

Table 3-1. F values of mixed model ANOVAs with repeated measures during the Pre-Feed (PF) condition for parameters Range, Sd, Min, and PSE.

Parameter	Condition	Condition by Group	Group	Scheffe's test (d.f. = 32)	Analyses agreed
Range	5.8 (1,15) (0.28)*			C-95% (3.5)* C-100% (5.3)*	Y
Sd		2.6 (6,30) (0.34)*	22.1 (1,10) (0.85)*		Group (Y) Cond*Gr (N)
Min	4.5 (4, 32) (0.36)**				N
PSE	8.5 (1, 15) (0.36)*				N

* $p < .05$
** $p < .01$

Table 3-1. F values of mixed model ANOVAs with repeated measures during the Pre-Feed (PF) condition for parameters Range, Sd, Min, and PSE during Phase 2. Degrees of freedom (df.) are shown in parentheses, followed by Partial Eta squared values indicating effect size, also in parentheses. Only statistically significant effects are shown. Condition was the within-subject factor, while Group was a between-subject factor. A post-hoc Scheffe's test was run to determine differences between PF condition and Control (C). If no data is shown for Scheffe's test, no significant differences were found between doses. The final column shows for each significant main effects and interaction if the two methods of statistical analyses agreed on the significant effect.

Table 3-2. F values of mixed model ANOVAs with repeated measures during the Extinction (EXT) condition for parameters Range, Sd, Min, and PSE.

Parameter	Condition (d.f. = 2, 30)	Condition by Group (d.f = 4, 30)	Group (d.f. = 1, 15)	Scheffe's test (d.f. = 30)
Range	43.1 (0.74)**	2.9 (0.28)*		C-1st Block (3.5) C-2nd Block (9.2)
Sd			11.7 (0.61)**	
Min	15.7 (0.51)**			C-2nd Block (5.2)
PSE	4.4 (0.23)*			C-2nd Block (3.0)

* $p < .05$
** $p < .01$

Note: Table 3-2. F values of mixed model ANOVAs with repeated measures during the Extinction (EXT) condition for parameters Range, Sd, Min, and PSE. Degrees of freedom (df.) are shown in parentheses following the main effect or interaction. Partial Eta squared values indicating the effect size are shown following the F values. Only statistically significant effects are shown. Condition was the within-subject factors, while Group was a between-subject factor. A post-hoc Scheffe's test was run if significance was found for a main effect. If no data is shown for Scheffe's test, no significant differences were found between doses.

Table 3-3. F values of mixed model ANOVAs with repeated measures during the Free-feed (FF) condition for parameters Range, Sd, Min, and PSE.

Parameter	Condition (d.f. = 1, 12)	Group (d.f. = 1, 12)
Range	19.1 (0.61)**	6.1 (0.50)*
Sd		9.1 (0.60)**
Min	25.4 (0.68)**	
PSE		

* $p < .05$
** $p < .01$

Note: Table 3-3. F values of mixed model ANOVAs with repeated measures during the Free-feed (FF) condition for parameters Range, Sd, Min, and PSE. All other details are the same as in Table 3-2.

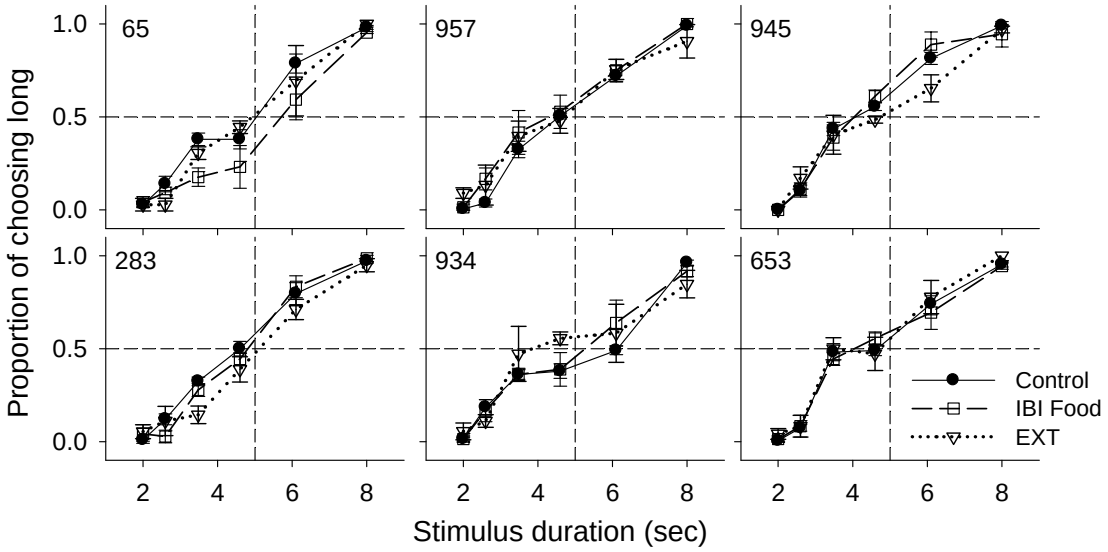

Figure 3-1. Psychophysical curves for IBI Food, EXT disruptors, and baseline sessions during Phase 1. The proportion of choosing the long alternative is shown as a function of stimulus duration. Closed circles represent control data; open squares represent the IBI Food condition; open triangles represent the Extinction (EXT) condition. Each curve represents the average of all baseline days, and the average of all presentations of each disruptor. Error bars represent standard error of mean.

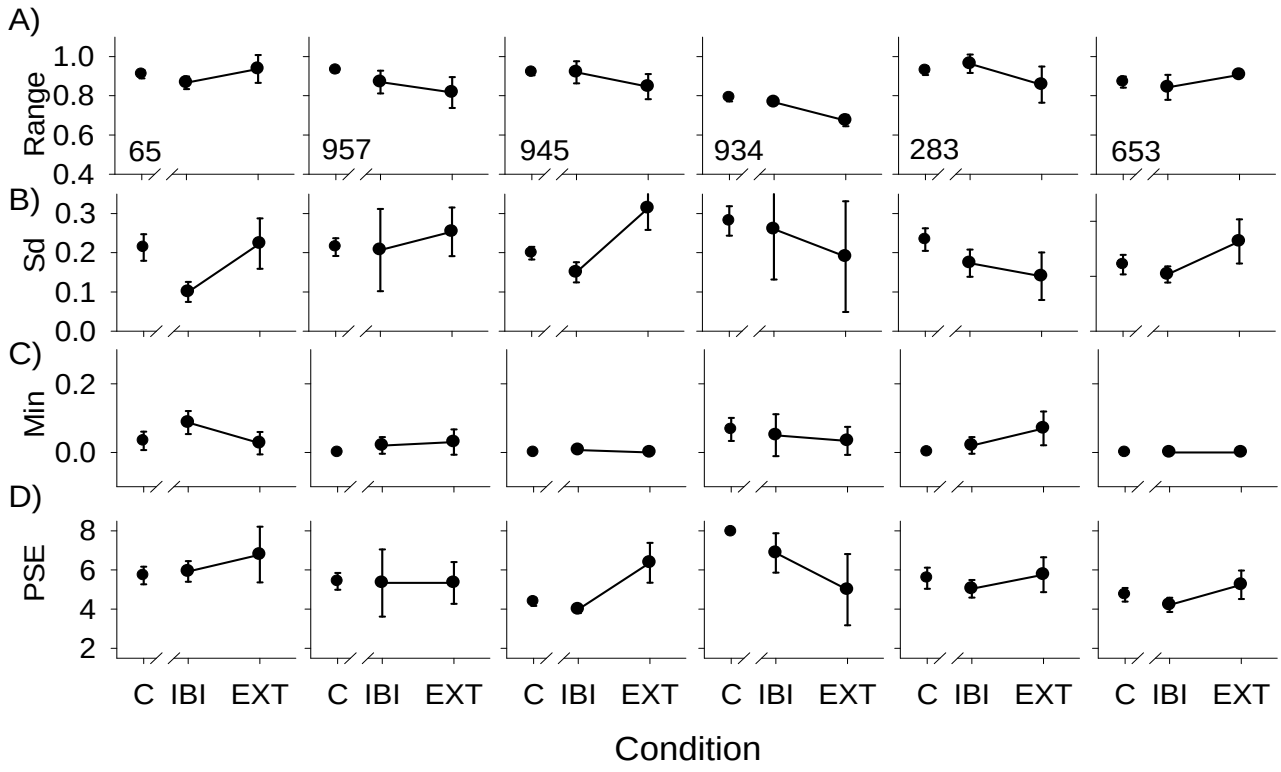

Figure 3-2. Parameters derived from Equation 2-1 for IBI Food and EXT. A) Range values. B) Sd values. C) Min values. D) PSE values. Averages are shown for Control, along with averaged values for each presentation of a disruptor. Error bars represent the standard error of the mean.

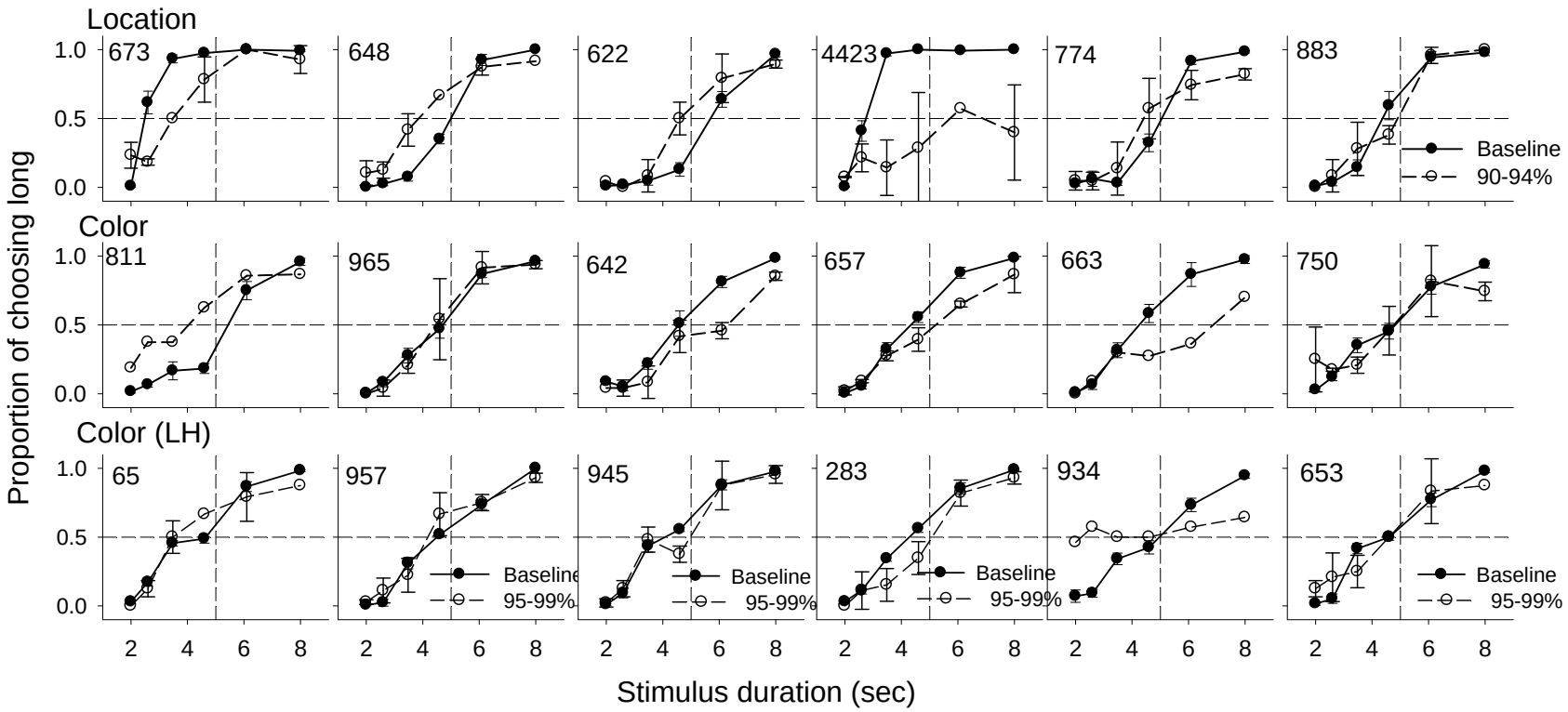

Figure 3-3. Psychophysical curves for the highest Pre-feed level given to each subject compared to Baseline sessions during Phase 2. The proportion of choosing the long alternative is shown as a function of stimulus duration. Closed circles represent baseline data; open circles represent the averaged psychophysical curve at the highest Pre-feed (PF) level. Baseline curves represent all sessions prior to PF sessions. PF averages represent all sessions in which the greatest amount of PF was given and responding was still maintained. All PF curves are for the level 100-105% of free feeding weight, unless otherwise stated in the legend. Error bars represent standard error of mean.

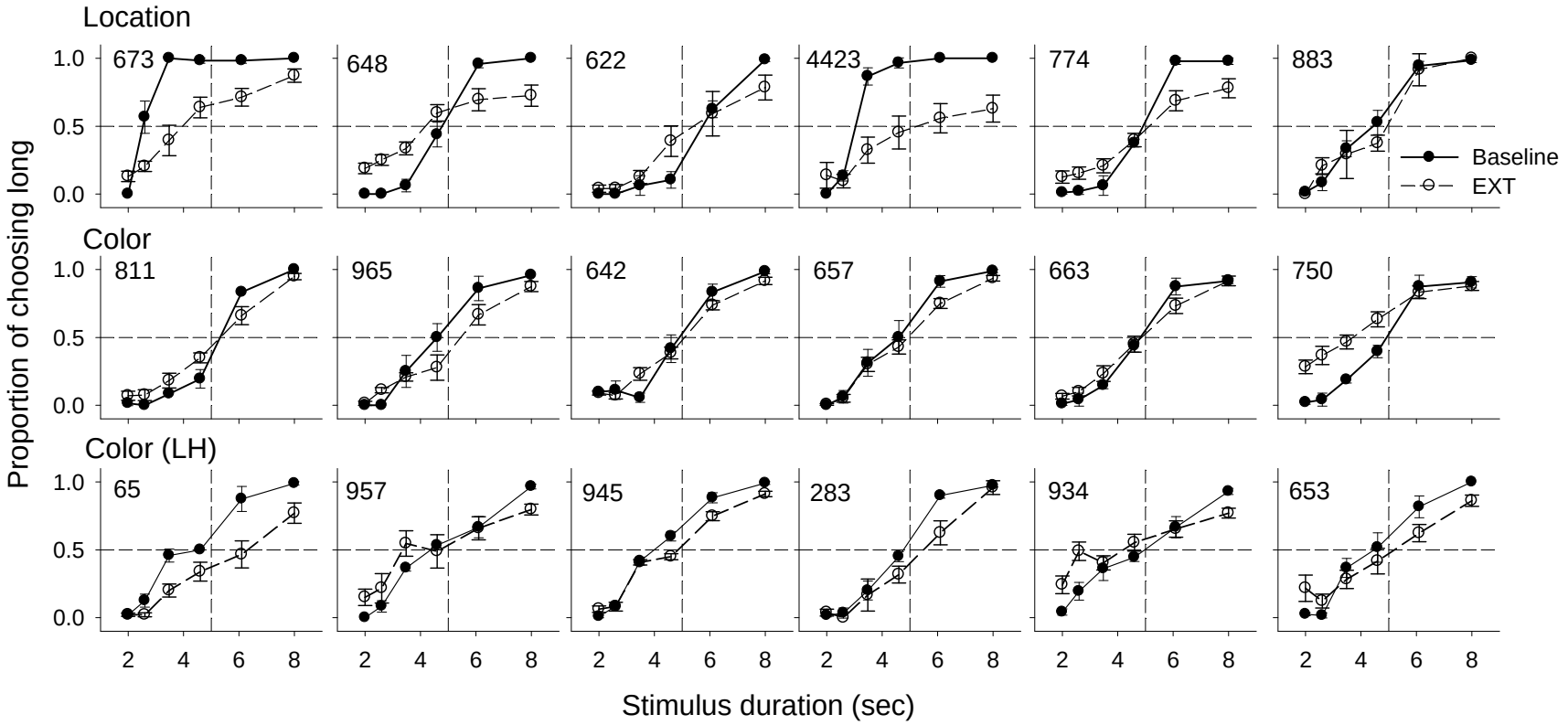

Figure 3-4. Psychophysical curves for all sessions during the Chronic Extinction (EXT) disruptor presentation during Phase 2. Closed circles represent Baseline data; open circles represent the averaged psychophysical curve for all EXT sessions. Baseline curves represent the average of three to five baseline sessions prior to the start of EXT sessions. EXT averages represent all EXT sessions in which the minimum trial requirement was reached. All other details are similar to Figure 3-3.

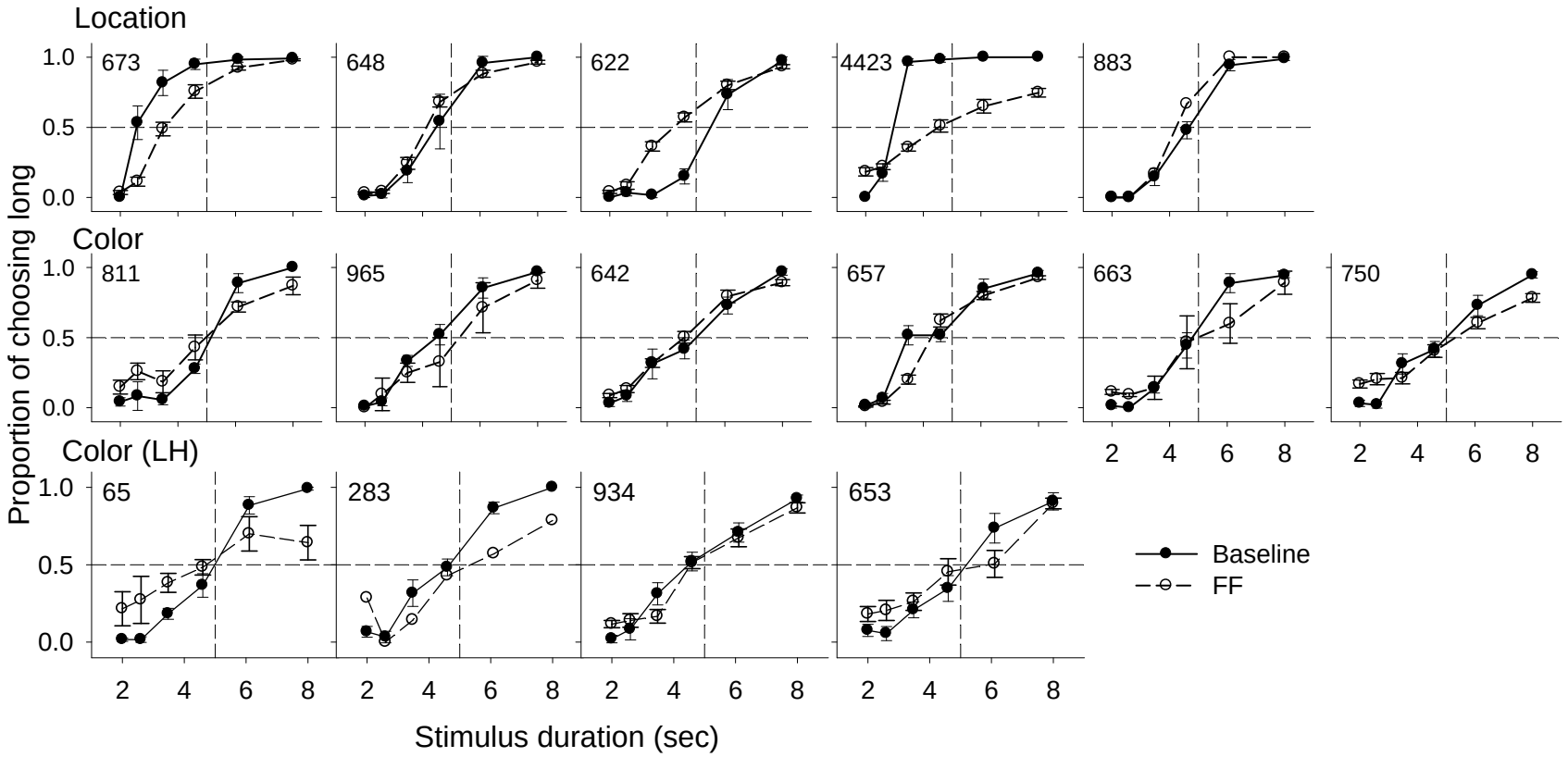

Figure 3-5. Psychophysical curves for all sessions during the Chronic Free-feed (FF) disruptor presentation during Phase 2. Closed circles represent Baseline data; open circles represent the averaged psychophysical curve for all FF sessions. Baseline curves represent the average of three to five baseline sessions prior to the start of FF sessions. FF averages represent all FF sessions in which the minimum trial requirement was reached. Two subjects in the Color (LH) group and one subject in the Location failed to complete the response requirement for any FF sessions, and so no panels are present for those birds. Sessions of FF range from 1-15 sessions. All other details are similar to Figure 3-4.

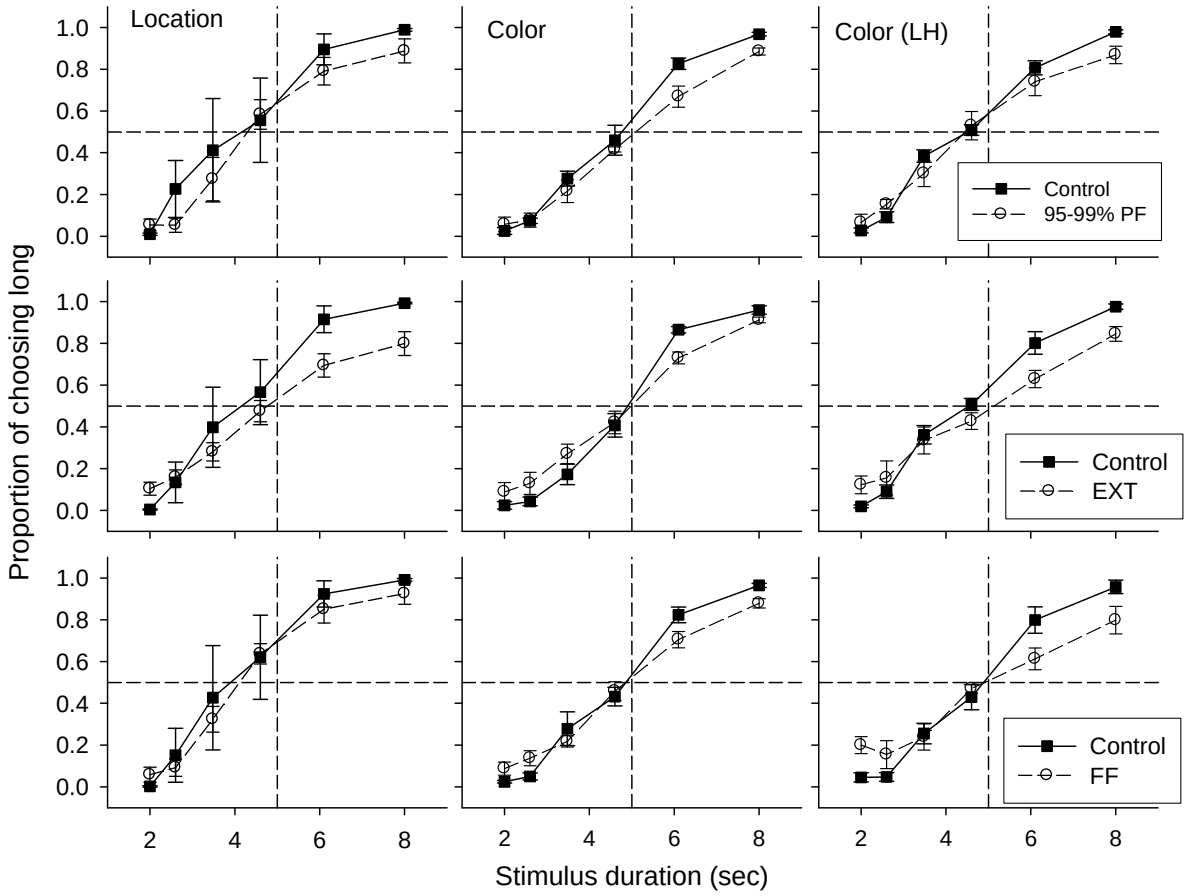

Figure 3-6. Averaged psychophysical curves between groups for disruptor presentations to all subjects with that procedural group. The highest PF dose is shown, along with averages from all subjects for consecutive disruptor presentations.

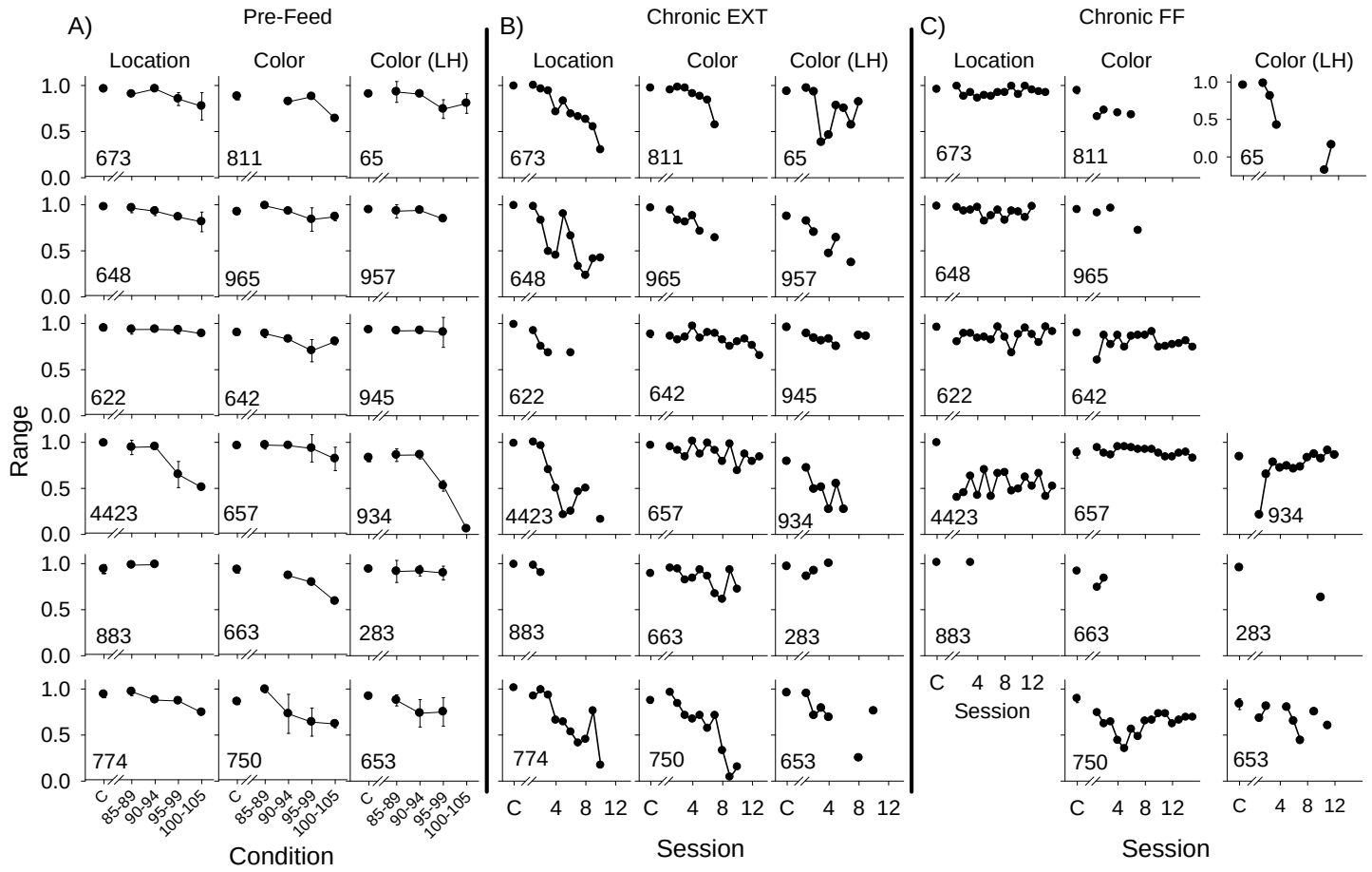

Figure 3-7. Range values during A) Pre-Feed (PF), shown as a function of condition. Each point represents the average of one to five presentations of that level of pre-feed. B) Chronic Extinction (EXT); all sessions in which the response requirement was reached are included. C) Chronic Free-feed (FF) disruptor conditions; missing subjects indicate those subjects did not meet the response requirement during any session of FF. Control values represent the average of control sessions prior to PF presentations, or three to five sessions prior to EXT or FF presentation. Error bars represent standard error of the mean. During EXT and FF conditions, each point represents the parameter value during that particular session. Note the difference in scale for Subject 65 during the Chronic FF condition. No panels exist for Subjects 957, 945, and 774 during FF due to suppression of all responding.

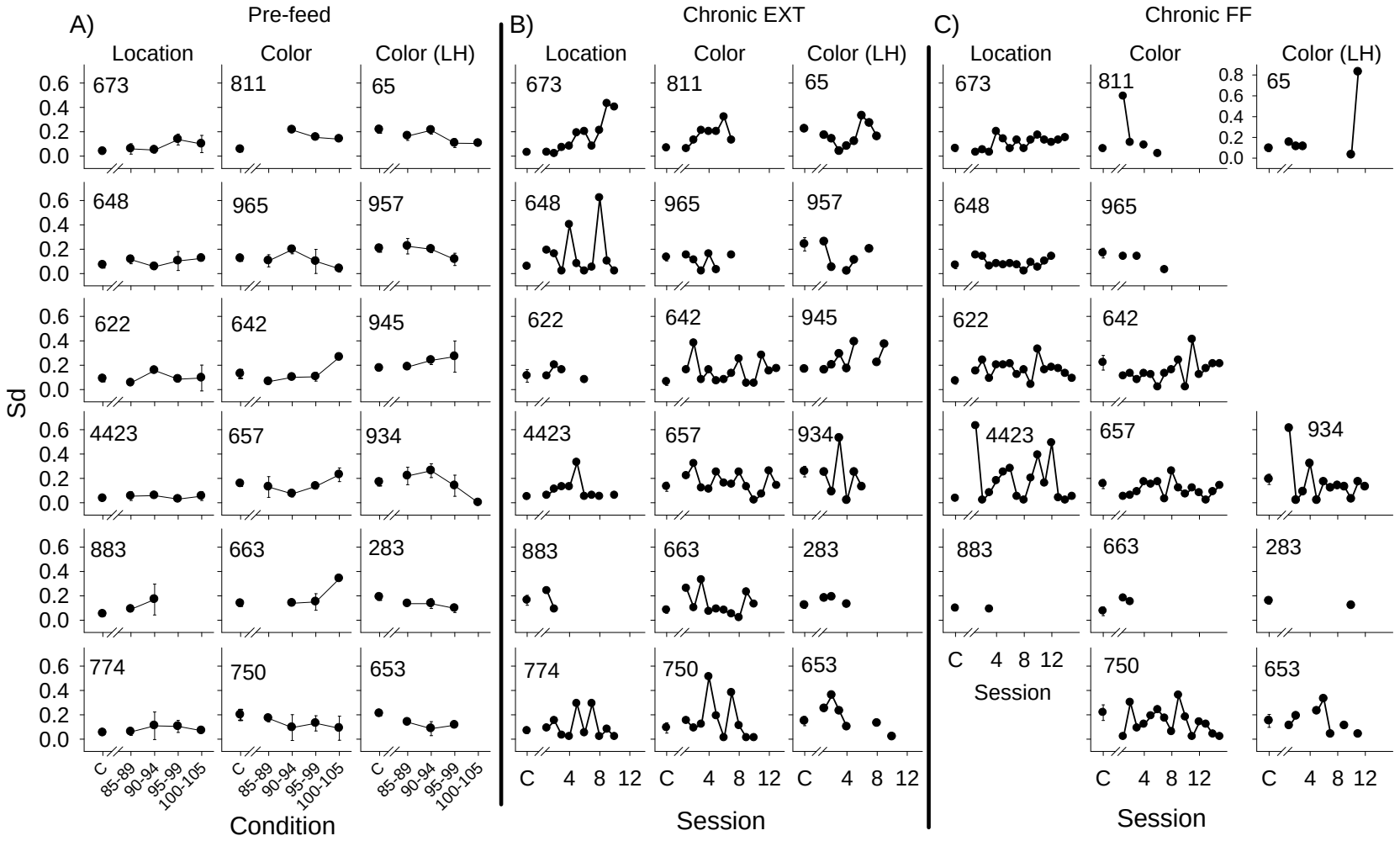

Figure 3-8. Sd values for all subjects during A) Pre-Feed. B) Chronic Extinction. C) Chronic Free-feed disruptor conditions. All other details are the same as in Figure 3-7. Note the difference in scale for Subject 65 during the Chronic FF conditio

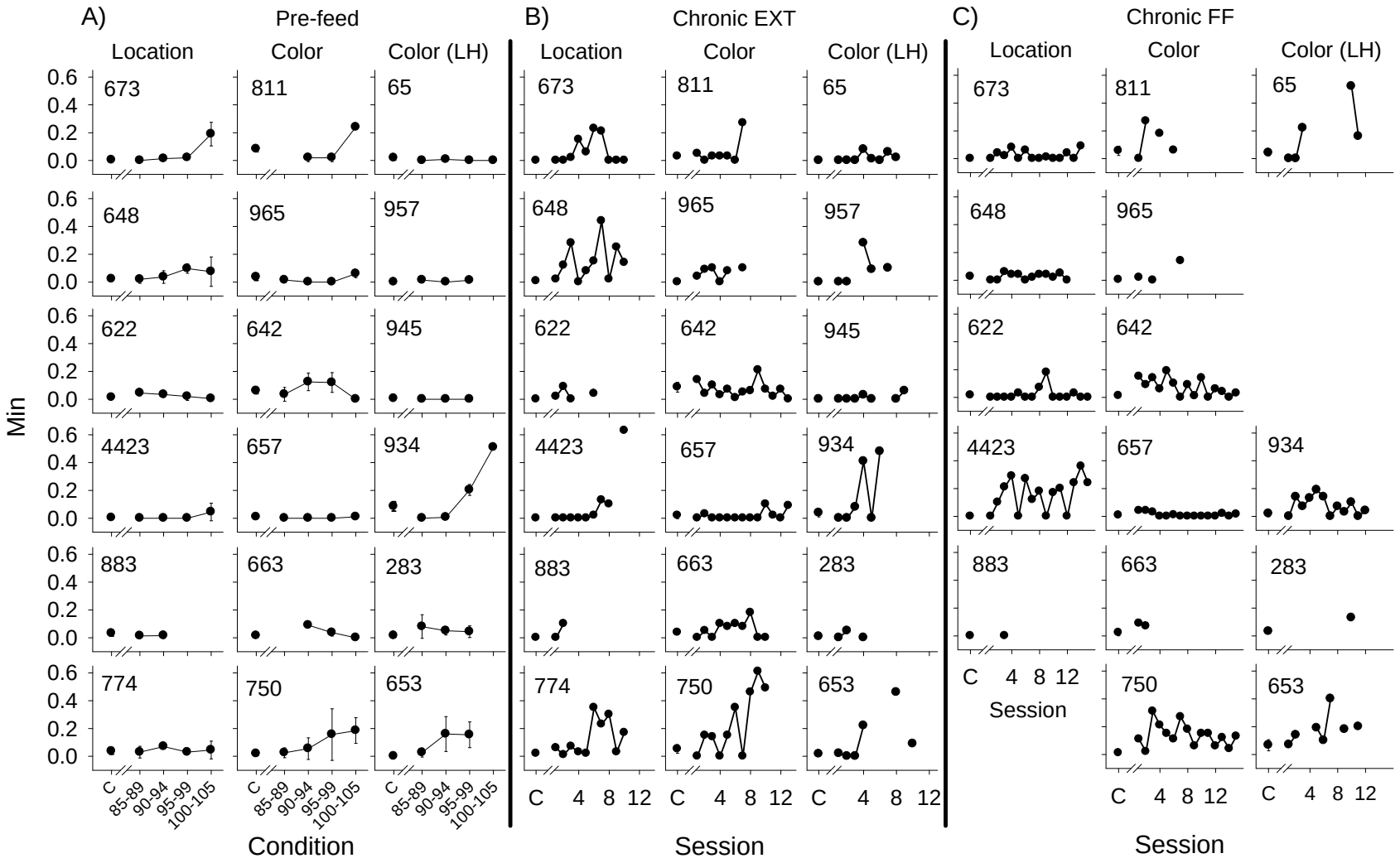

Figure 3-9. Min values for all subjects during A) Pre-Feed. B) Chronic Extinction. C) Chronic Free-feed. All other details are the same as in Figure 3-7.

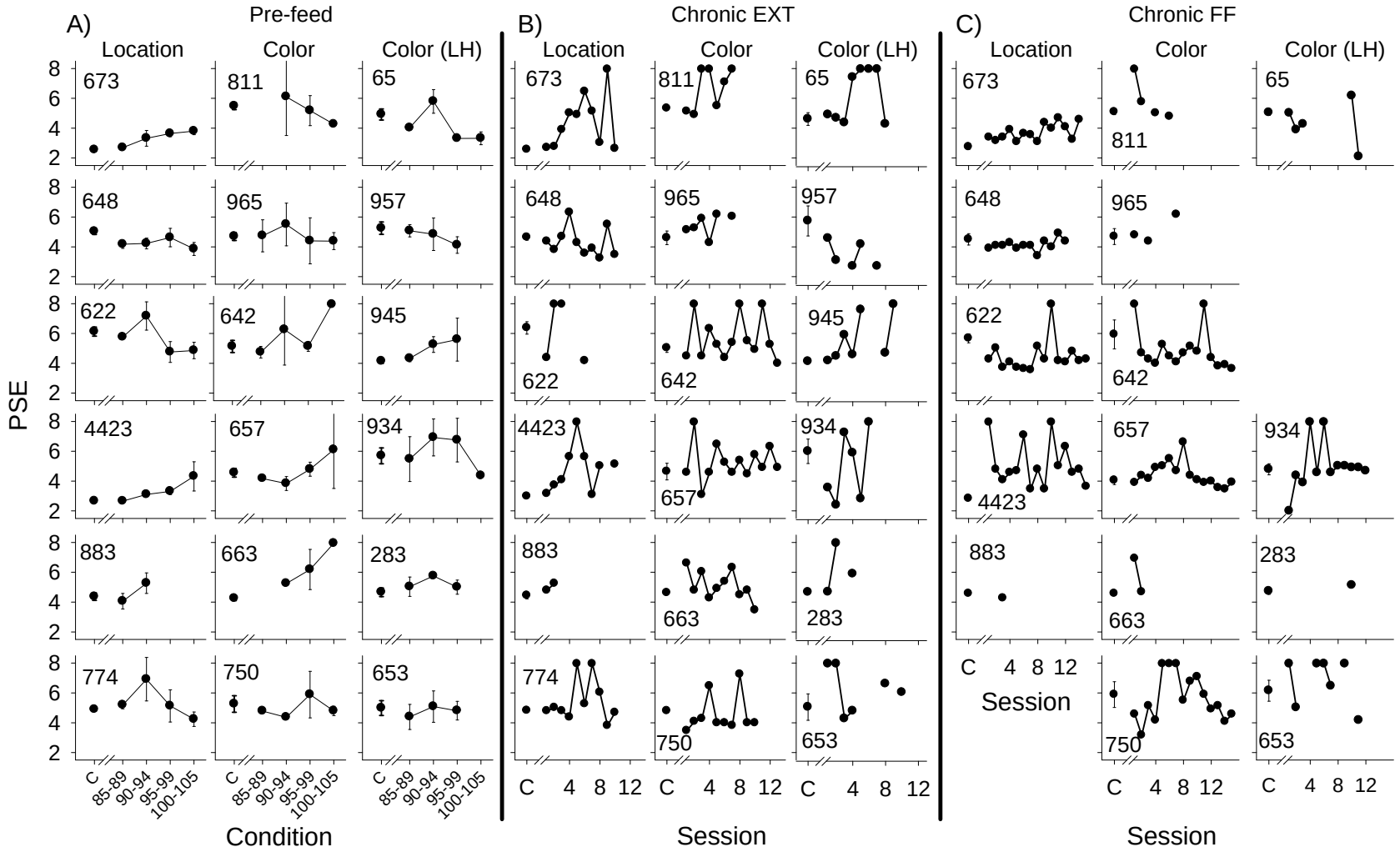

Figure 3-10. PSE values during A) Pre-Feed. B) Chronic Extinction. C) Chronic Free-feed. All other details are the same as in Figure 3-7

CHAPTER 4
GENERAL DISCUSSION

Results Summary

The results of Experiment 1, in which *d*-amphetamine, nicotine, and haloperidol were used to disrupt temporal discrimination, showed that the initial effects were similar across Color and Location procedural groups. All three drugs dose-dependently decreased Range values, while PSE values were not systematically or selectively impacted by these agents. The main difference found between drug types was in the Min parameter. Accuracy of classifying 2-s durations was disrupted more with *d*-amphetamine, than with either nicotine or haloperidol. The main difference found between procedural groups occurred during baseline and was found in the Sd parameter, indicating that the slope of the psychophysical curves was different across groups. Location subjects had lower Sd values compared to Color subjects. This difference occurred during baseline, but did not appear to lead to notable differences during drug administration.

Phase 1 of Experiment 2 used acute IBI food presentations and Extinction sessions to disrupt temporal discrimination. None of these disruptors led to any effect on the psychophysical curve or on temporal discrimination. Phase 2 utilized disruptors that included consecutive Extinction sessions, as well as acute Pre-feed and consecutive Free Feed conditions. The main result of Phase 2 was that Range decreased during all disruptor presentations. For acute Pre-Feed, Range decreased dependent upon increasing levels of food given prior to the experimental session. When PSE was affected, it was always accompanied by a decrease in Range, making selective effects on PSE rare. The differences between procedural groups were mostly found during baseline, and consisted of differences in Sd and Range values between groups. Just as in Experiment 1, those differences in baseline performance did lead to

differential disruption of temporal discrimination, but certain conditions surely exist in which they would make a difference.

The two main questions being asked in these experiments were 1) the extent of the impact of the procedural variation (Color or Location) on the disruptive effects of agents on temporal discrimination and 2) the importance of the type of disruptor being used to impact temporal discrimination. Both Experiments 1 and 2 showed that procedure and type of disruptor failed to explain differential disruptive results within the timing literature. There are differences between procedures, as evidenced by performance during baseline and level of stimulus control, but these differences most likely manifest in other ways rather than in the initial effects of pharmacological agents and the effects of non-pharmacological agents that affect motivation of the animal.

Procedural Variations

The literature to this point has shown that procedure is typically confounded with species. The Color (non-spatial) procedural variation has been typically used with pigeons and a flattening of the psychophysical curve has resulted from application of a variety of different disruptors (Stubbs and Thomas, 1974; Morgan *et al*., 1993; Bizo and White, 1994; Killeen *et al*., 1999; Odum, *et al*., 2002; McClure, *et al*., 2005; Ward and Odum, 2005, 2006, 2007; Odum and Ward, 2007; Ward *et al*., 2009; McClure *et al*., In Review (a,b,c)), whereas studies using rats have commonly employed the Location procedural variation and found lateral shifts in the psychophysical curve (Maricq, *et al*., 1981; Maricq and Church, 1983; Meck, 1983, 1986, 1996; Bizot, 1997; Kraemer, *et al*., 1995; Chiang, *et al*., 2000, Exp. 1; Cevik, 2003, Exp. 2; Cheng *et al*., 2007). The exceptions to this species rule have shown that flattenings of the psychophysical curve are possible with both rats and pigeons when the Location procedure is being used (Wilkie *et al*., 1988; Stanford and Santi, 1998; Chiang *et al*., 2000, Exp 2; Santi, *et al*., 2001; Cevik,

2003, Exp 1; Harper *et al*., 2006; Sanchez-Castillo, *et al*., 2007; Odum and Ward, 2007; McClure *et al*., In Review, a, b), and also occur when non-spatial arrangements are used with rats (Santi *et al*., 1995b). Lateral shifts appear to only be possible when the Location procedure is being used. Two studies that used increased stimulus intensity as a disruptor of temporal discrimination in a Color procedure with pigeons interpreted their results as lateral shifts of the psychophysical curves, yet both studies also showed decrements in accuracy in varying degrees (Wilkie, 1987; Kraemer *et al*., 1997). To this point, no studies have used a Color procedure or any non-spatial arrangement of temporal discrimination and shown exclusive lateral shifts of the curve. While the procedural variation in this study does not wholly explain the discrepancy in the literature, it does provide evidence that the Location procedure must be used in order to obtain lateral shifts of the psychophysical curve. We believe that the Color procedure will never be able to produce lateral shifts in isolation without decrements in accuracy.

Only one other published report has compared Color and Location procedural variations within the same study and species. This report showed similar conclusions as we have about the initial effects of *d*-amphetamine on temporal discrimination (Odum and Ward, 2007). There is evidence in the literature showing conditions under which procedural variations lead to differential disruption of temporal behavior. Previous results from our laboratory have shown that when increased stimulus intensity is used as a disruptor of temporal discrimination, subjects trained on the Color procedure are more disrupted than Location-trained subjects (McClure *et al*., In Review (c)). Furthermore, studies using *d*-amphetamine have shown slight differences in performance and disruption following chronic exposure to drug suggesting that differences in an animal's propensity to develop tolerance may exist based on these different procedures (McClure *et al*., In Review (b)). It appears that under certain conditions, differences do exist between the

resulting data of these procedural variations. This is a methodological concern that should not be overlooked when comparing studies within the timing literature.

Some studies have shown that the Color and Location variations are different in other respects. It has been shown that the Location version of the task is acquired more quickly and stability is reached faster as compared to the Color procedure, suggesting that it is an easier discrimination to learn (Chatlosh and Wasserman, 1987; Odum and Ward, 2007). The Location version of the task may be easier to learn than the Color version because the animal develops mediating behavior which aids in accurate timing. In the spatial variation of the task, it has been shown that animals can use their own behavior to indicate which alternative is correct based on the duration of the sample stimulus (Fetterman *et al*., 1998; Machado and Keen, 2003). This mediating behavior has been suggested to serve a useful function in helping the animal to accurately discriminate temporal intervals. Mediating behavior in these previous studies consisted of subjects beginning the interval in front of the short key and if the stimulus presentation continued, they would at some point move to the long key. The key they were standing in front of when the stimulus terminated seemed to be an accurate predictor of the choice alternative they chose. When mediating behavior is required during the experimental procedure in the form of responses on another lever or key, temporal discrimination is more accurate then when mediating responses are not required (Harper and Bizo, 2000). It could be the case that training on the Location procedure leads to the development of mediating behavior, perhaps making temporal discrimination more resistant to disruptors. The Color variation provides no such cue to aid in accurate temporal judgments, which may indicate that behavior on the Location variant is less likely to be disrupted than the Color variant.

Complexity of Procedure

Studies differ in the complexity of the procedure used, which could lead to differential levels of stimulus control of behavior by the relevant stimuli in the experimental preparation. Some procedures consist of a number of components, not just those that assess temporal judgments, and can presented in the same daily experimental sessions. It has been suggested that greater stimulus control on a procedure could lead to differing susceptibilities to disruptors (Laties, 1972; Ward and Odum, 2005; Odum and Ward, 2007; McClure *et al*., In Review (a)). Greater stimulus control could result from a relatively simple procedure with fewer components or an external stimulus providing a useful cue. On a complex procedure, stimulus control may break down more easily when disruptors are applied causing more severe disruption in behavior. Differential baseline performance in Sd and Range values were found in the current study for procedural groups, and could indicate that under certain conditions, the Location procedure would be less likely to be disrupted.

History Influences

Color and Location procedural groups were compared in Experiments 1 and 2, but Experiment 2 also added a group of subjects that were currently experiencing the Color procedural variation, but had previously been trained and tested with the Location variant. This group was added to determine if the effects of non-pharmacological agents were different for subjects experiencing the Color variant with no Location history versus subjects that had Location history. Previous studies from our laboratory have shown that subjects that experienced the Location variant followed by Color variant were less disrupted by *d*-amphetamine administration as compared to subjects that experienced Color first, and then Location (McClure *et al*., In Review (b)). There is reason to believe that history with the Location procedural variation leads to decreased disruptive effects of *d*-amphetamine, increased

tolerance to the drug, and a form of resistance to drug effects. This result had never previously been tested with non-pharmacological agents. Experiment 2 showed that a Location history did not provide any sort of resistance, as the Color (LH) group often showed the most severe disruption to non-pharmacological agents. Color (LH) subjects had lower Range values than other groups, as well as higher Sd values. These baseline values indicate that control by duration and discriminability was lowest for this procedural group, which most likely contributed to the most severe disruption of behavior of any group. It is unclear though why this group would have lower levels of discriminabilty compared to other groups.

Pharmacological and Non-pharmacological Disruptors

Pharmacological Agents

There is disagreement with the timing literature on how pharmacological agents disrupt timing. Given the mounting evidence that a number of pharmacological agents from *d*-amphetamine to nicotine flatten the psychophysical curve (Stubbs and Thomas, 1974; Rapp and Robbins, 1976; Stanford and Santi, 1998; Chiang *et al*. 2000 Exp. 2;, Popke *et al*., 2000; Santi, *et al*., 2001; Odum, *et al*., 2002; Cevik, 2003, Exp. 1; McClure, *et al*., 2005; Ward and Odum, 2005; Harper *et al*., 2006; Odum and Ward, 2007; Sanchez-Castillo, *et al*., 2007; Ward *et al*., 2009; McClure *et al*., In Review (a, b)), this result was not surprising in Experiment 1. *D*-amphetamine, nicotine, and haloperidol showed similar effects on temporal discrimination in the form of a flattening of the psychophysical curve in a dose-dependent manner and a decrease in Range. These results provide one side of a discrepancy, while the other side shows lateral shifts in the position of the psychophysical curve due to amphetamines, nicotine, and other dopaminergic agents (Maricq, *et al*., 1981; Maricq and Church, 1983; Meck, 1983, 1986; Chiang, *et al*., 2000, Exp. 1; Cevik, 2003, Exp. 2; Bizot, 1997; Cheng *et al*., 2006). Based on the current data set in Experiment 1, and previous reports, we conclude that diverse pharmacological

agents have the same effect on temporal judgments. Behavior is disrupted in the form of decreased accuracy of classifying temporal intervals, rather than exclusive lateral shifts in the curve. When exclusive lateral shifts did occur, they only occurred in the Location variant and were not consistent across all subjects within that procedural group.

There are a number of potential reasons for why our data are not consistent with previous reports using dopaminergic and cholinergic drugs. Rats have typically been used in neurophysiological studies of behavior with pharmacological agents, and when assessing duration discrimination, location alternatives are the standard. Over and underestimation of time in the form of lateral shifts of the psychophysical curve have never been shown in pigeons, without related decrements in accuracy. The non-spatial version of the temporal bisection task has been used with rats and pharmacological agents, and a flattening of the curve has been shown (Santi *et al*., 1995b). Based on these data, the species in the experiment does not appear to the relevant variable; however we are not ignoring the known anatomical and potential neurophysiological differences that exist between species. The neurophysiology of timing behavior has mostly been studied in rodents and humans, and findings using these techniques have not yet been well-established in pigeons. Differences exist in the visual systems between the avian and mammalian brains (Rogers *et al*., 2008), which could reveal variations in pharmacological effects on timing. The onset of the houselight signaled the stimulus to be timed, which served as a visually-detected stimulus in our study. By doing this we are making an assumption that the mechanisms responsible for accurate interval timing and their relations with the visual systems are the same in birds as they are in mammals. This assumption may not be correct however. Even though some rat studies have also failed to replicate over and underestimation of temporal intervals (Rapp and Robbins, 1976; Wilkie *et al*., 1988; Stanford

and Santi, 1998; Chiang *et al*., 2000, Exp 2; Santi, *et al*., 2001; Cevik, 2003, Exp 1; Harper *et al*., 2006; Sanchez-Castillo, *et al*., 2007), there are still known anatomical differences such as the mainly nuclear structure of the avian brain that we cannot ignore in our assessment of temporal disruption. Studies using lesions and electrophysiological recordings are required with pigeons to determine if bird species show similar neurophysiological actions during timing procedures compared to rodents and humans.

Another difference between our study and others was the range of drug doses used. Many studies assessing pharmacological effects on timing suggest using lower doses that will not disrupt other aspects of behavior, such as motor activity or attention (Maricq *et al*, 1981; Maricq and Church, 1983; Meck, 1983, 1986; Cheng *et al*., 2006). These studies used lower doses, and animals were never exposed to higher doses of drug, thus creating a potentially important distinction in methodology. We choose doses of drug that have been shown, in pigeons, to range from behaviorally inactive to almost completely suppressing responding. This allowed for parametric analysis of behavioral change based on dose and based on the neural actions of these drugs. The low doses we used did not reveal any consistent effects of PSE selectively (Figures 2-11 and 2-12). It is possible that a range of lower doses could produce certain temporal effects, without experience with higher doses. These possibilities should be explored in future empirical work.

Non-Pharmacological Agents

In Phase 1 of Experiment 2, intermittent presentations of an increased density of reinforcement during the session and extinction were apparently not powerful enough to produce disruption of temporal discrimination. In Phase 2, however, continuous Extinction, high levels of acute pre-feed, and free access to food led to disruption of the psychophysical curve in the form of a flattening of the psychophysical function and a decrease in Range. Similar results have

been found for non-contingent food given during the experimental session, pre-feed, extinction, and increased stimulus intensity (Wilkie *et al*., 1988; Morgan *et al*., 1993; Bizo *and* White, 1994; Killeen *et al*., 1999; Ward *and* Odum, 2006; McClure *et al*., In Review (c)). Though many non-pharmacological agents have produced similar disruption of temporal judgments, other studies have found lateral shifts in the psychophysical curve. These studies also showed decreases in accuracy to varying degrees (Wilkie, 1987; Kraemer, *et al*., 1995; Kraemer, *et al*., 1997).

The current results show that when using both Color and Location variants of the MTSD procedure, a diverse array of pharmacological and non-pharmacological disruptors cause similar disruptions of temporal behavior. The diversity of conditions under which a flattening of the psychophysical function for time is observed suggests the fundamental impact of these manipulations and a need for mechanisms of timing that adequately explain both.

Theories of Timing

Scalar Expectancy Theory (SET)/Oscillatory Networks

Meck (1983, 1986, 1996) extended Scalar Expectancy Theory (SET: Gibbon, 1977) to account for the effects of pharmacological agents on an internal pacemaker and the subsequent impacts on temporal judgments. Conceptualizations focusing on dopaminergic and cholinergic effects on the internal pacemaker and memory were based on empirical reports of over and underestimation of temporal intervals, either immediately or gradually, with the administration of these agents. In duration discrimination experiments, dopamine agonists such as amphetamine, cause the rate of the pacemaker to increase so that time intervals are overestimated and the psychophysical curve thus shifts to the left. Alternatively, dopamine antagonists should have the opposite effect, which should be a slowing down of the pacemaker and shift of the curve to the right.

In the current study, we show a flattening of the psychophysical curve as the overall trend across subjects. For a select number of subjects, lateral shifts with no decrease in accuracy did occur at certain doses. Most changes in temporal judgments were at high dose administrations, which are shown in Figures 2-1 through 2-3. Out of 18 total high dose administrations for all drugs, only five of those revealed exclusive lateral shifts. Four of the five showed shifts in the direction predicted by SET based on the pharmacology of the drug, while one did not move in the predicted direction. These lateral shifts, without decreases in Range, occurred for subjects on the Location variant of the task only. SET does not predict any changes in accuracy, which is the main effect in the current experiments. Thus, the general trend in our results does not agree with previous reports showing the overestimation or underestimation of time due to pharmacological action on an internal pacemaker.

Additions have been made to SET to account for changes in temporal behavior in terms of attention due to the administration of drug. An attentional mechanism has been implicated in the stop/reset process of the internal clock. Attention is responsible for opening a gate or switch that allows for pulses from the pacemaker to collect in the accumulator. The timing process typically begins at the onset of a stimulus when pulses start to accumulate, and ends when the stimulus is terminated (Buhusi and Meck, 2000, 2002). Disruption of attention would lead to the gate or switch being opened later, thus leading to less pulses in the accumulator, and an underestimation of time (Meck, 1984). Attention within this theory may be able to explain some decrements in accuracy, but a change in PSE would also need to be present in the predicted direction based on the drug. A short or long key bias would appear incongruent with this conceptualization of an attentional component. The results of the current study, which included decrements in accuracy which sometimes only occurred for short or long durations and no

consistent changes in PSE are difficult to incorporate into an SET conceptualization, with or without an attention component.

SET has not only dealt with pharmacological disruptors of timing, but has also incorporated non-pharmacological agents into the theoretical framework. Meck (1983) showed that a low level continuous shock and methamphetamine had similar effects on timing behavior and reasoned this was due to the neurological similarities in dopamine activation for both disruptors. Meck and Church (1987) also showed that certain nutrients given prior to session would influence maximal response rate on a peak procedure. Pre-feed which was high in protein increased levels of dopamine, leading to an increase in clock speed and an overestimation of time. Pre-feed which increased levels of acetylcholine caused an effect on temporal memory leading to a gradual shift in peak time as predicted by SET. These non-pharmacological disruptors are understood in terms of their physiological effects.

The pacemaker-accumulator model that SET is based on has recently been replaced with a new conceptualization of how neurophysiological processes lead to accurate timing. This cortico-striatal oscillatory network is based on empirical reports showing neural substrates and systems that contribute to timing behavior in non-human animals and humans (Keil *et al*., 2001; Bares *et al*., 2003; Matell *et al*., 2003; Nagai *et al*., 2004; Berke, 2005; Buhusi and Meck, 2005; Reuter *et al*., 2006; de Tommaso *et al*., 2007; Praamstra and Pope, 2007; Chiba *et al*., 2008). These reports reveal the pertinent areas that contribute to accurate timing, which Meck *et al*. (2008) used to develop a set of neural mechanisms of timing. Our data still consist of a set of effects that are not predicted by these models of timing. Regardless of the models, there is still disagreement concerning the nature of pharmacological impacts on temporal discrimination, and the reasons for that discrepancy must be clarified.

Behavioral Theory of Timing (BeT)

The Behavioral Theory of Timing (BeT) states that the rate of reinforcement will produce changes to the *arousal* of the animal, which then leads to a change in interpulse time (tau). Interpulse time is what pushes an animal through a series of behavioral states and influences the accuracy of temporal judgments. This theory makes predictions about how non-pharmacological agents will disrupt temporal accuracy and how that can be understood within a framework of changes in *arousal* of the animal, leading to increases or decreases in the interpulse time (tau) of a pacemaker based on the manipulation. BeT predicts that manipulations such as pre-feed and an increased rate of reinforcement during an experimental session should lead to increased *arousal*, which then leads to decreased levels of interpulse time. Alternatively, extinction is predicted to decrease *arousal*, and thus increase levels of interpulse time.

To determine how our results conform to the predictions made by BeT, we fit our data to this model and derived parameter estimates of tau (τ). While BeT has two main parameters, we focused on tau as this theory does not have a way to predict changes in *n* (see Killeen *et al*., 1999). Equation 4-1 is the probability that *n* pulses will be emitted at any given time *t* within the interval to be timed:

$$P[N(t) = n] = [(t/\tau)^n e^{-t/\tau}]\, n! \qquad (4\text{-}1)$$

Since BeT makes specific predictions about non-pharmacological disruptors, we determined measures of tau for conditions in Experiment 2, only for Phase 2. Phase 1 was not analyzed due to the lack of changes in temporal judgments due to disruptors. Data were pooled within procedural group for each condition. Curves were fit to pooled data, which led to one data point for control sessions, PF conditions, as well as one data point for each day of chronic EXT and FF. Measures of tau for Experiment 2, Phase 2 are shown in Figure 4-1. During PF

conditions, tau appears to increase slightly for all procedural groups during the highest level of pre-feed given. Measures of tau also increase during EXT for all procedural groups, with the only exception being the last session of EXT for the Color (LH) group, in which tau decreases. Variability was found for tau across FF sessions, but overall, when changes do occur, they are in the form of an increase, with the exception of two sessions for the Location group. The trend found for tau is that all non-pharmacological disruptors led to increases.

While the increases in tau during our PF and FF conditions seem at odds with BeT, others have found similar results (Plowright *et al*., 2000; Ward and Odum, 2006). Plowright *et al*. (2000) attempted to incorporate these results into BeT by suggesting that pre-feed may predict satiation during the session, which could decrease *arousal* levels, which would lead to increased levels of tau. Also, if satiation occurs prior to the experimental session due to large amounts of food, or free access to food, the same result could occur. Small amounts of pre-feed that do not lead to satiation would still increase *arousal* and decrease levels of tau.

BeT only makes predictions concerning disruptions of timing caused by non-pharmacological agents that affect the motivation of the animal to respond. It does not make predictions concerning the effect of pharmacological agents on interpulse time and *arousal*. Ward and Odum (2006) used BeT to fit temporal discrimination data disrupted by morphine and found increased levels of tau in a dose-dependent manner. This extension illustrates the potential generality of BeT to pharmacological disruptors. We conducted the same analysis with the disruption of temporal discrimination by pharmacological agents from Experiment 1. We again pooled the data across subjects within a procedural group for each dose of drug and vehicle. One curve was fit to those data. Measures of tau from Experiment 1 are shown in Figure 4-2. During *d*-amphetamine administration, both Color and Location groups showed an increase in tau, with

the Color group showing more of an increase in this measure. Increases in tau were also found for the Color group during nicotine and haloperidol administration, and slight increases were found for the Location group during haloperidol administration. When changes in tau did occur, they were in the form of dose-dependent increases for all three drug types.

All disruptors in the current set of experiments led to increases in tau. The increases due to non-pharmacological disruptors are easily incorporated into the predictions and conceptualization of timing by BeT. The changes in tau based on pharmacological disruptors are more difficult to incorporate. In terms of BeT conceptualization, it is not clear how the theoretical notion of *arousal* used as a variable in the explanation of the timing behavior could be understood in terms of the arousal that is known to be caused by certain pharmacological agents. Nicotine and *d*-amphetamine are typically thought of as stimulants, which would logically mean they should increase physiological or cognitive arousal at certain doses. If BeT's *arousal* is being used similarly in terms of physiological effects, then tau should decrease, and should alternatively increase with a drug like haloperidol which is thought of as a depressant. The theoretical concept of *arousal* used in BeT must be reconciled with physiological and neurological concepts of arousal of pharmacological agents if BeT is to be extended to this literature.

Stimulus Control and Attention

Other conceptualizations of timing behavior exist and have gained strength based on data that do not conform to other results in the literature. A way of interpreting results from the current data and previous research in timing is in terms of the disruption of stimulus control by non-pharmacological and pharmacological agents rather than any specific effects on timing. Timing is behavior that is under the control of the preceding or present stimulus, which in our

experiments was the presentation of the houselight, in which duration was a dimension. Many empirical reports and extensions from these reports are attempting to determine what is disrupted when the duration no longer controls behavior. Neurological actions have been shown to contribute to timing behavior, and must play a large role in accurate timing, and so the behavioral disruption that we show that does not appear to be specific to timing also has neurological mechanisms that are contributing to its presence. The importance of the environmental contingencies should also play a role in our analysis. The environment of the experimental session is a complex situation with a number of relevant stimuli. Any of those aspects of the procedure could be disrupted by a number of irregularities in the situation. This could then lead to disruption in temporal behavior, and to conclusions that ignore other behavioral disruption.

A number of studies have shown the presence of idiosyncratic response key biases that reliably accompany disruption of temporal behavior and a decrease in correctly categorizing short and long intervals by pharmacological and non-pharmacological agents (e.g. Rapp and Robbins, 1976; McClure *et al*., 2005; McClure *et al*., In Review (c)). These biases are not necessarily for the short or long keys, but appear to be random. Side biases have even been found when Color is the relevant property of the response alternative and side is unimportant (McClure *et al*., 2005; McClure *et al*., In Review (c)). This suggests that time does not appear to be moving more quickly or more slowly, but it could be that there is a disruption of the choice behavior, rather than a specific timing effect. Perhaps due to motoric effects induced by drug, animals remain in front of one key and respond almost exclusively on that key regardless of the preceding duration. The nature of the procedural variations would also change the resulting data based on a bias. Severe biases in the Color variant that are not to the short or long alternative

would result in equal decrements in accuracy at the extreme durations. However, only a side bias may develop in the Location variant, which would show in the form of a short or long bias. More work should be devoted into the kind of bias that develops based on disruptor presentation and why that occurs.

While the current data set and a number of previous reports have illustrated that drugs will disrupt temporal behavior, it also well-know that a variety of drugs can disrupt performance on non-temporal discrimination tasks (Berryman *et al*., 1962; Eckerman *et al*., 1978; Grilly *et al*., 1980; Koek and Slangen, 1983, 1984; Picker *et al*., 1987). If timing behavior is to be thought of as a type of discrimination learning and stimulus control, we must compare the disruption of temporal behavior to the disruption of non-temporal behavior for more information on common mechanisms contributing to both. It is a difficult, but possible task to separate the effects of drugs on temporal behavior compared to their disruptive effects on other non-temporal behavior.

One potential reason for the disruption of behavior due to a number of agents is based on attention to the external stimulus during its presentation. When disruption occurs, the duration is no longer controlling behavior, and this may be because there is disruption of attention to the stimulus, which leads to almost random responding and decreases in temporal accuracy. The disruption of attention to the sample stimulus has been used to account for decrements in accuracy in other studies (Heinemann *et al*., 1969; Santi *et al*., 1995b; Blough, 1996; Ward and Odum, 2009). It has also been suggested that attention may be diverted away from the stimulus presentation for more than half of the sample (3 to 4-sec of an 8-sec duration), which therefore leads the animal to choose the short alternative regardless of the actual duration that was presented (Ward and Odum, 2007). Thus, disruption of attention to the stimulus leads to a

choose-short effect, but temporal discrimination has not necessarily been exclusively affected, rather attention has been disrupted.

Two other studies directly assessed the possibility that temporal disruption is due to disruption of attention by including a non-temporal task within a temporal discrimination task. Both found disruptions of performance on the timing task, and concluded that attention was divided between the timing task and the non-temporal disruptor task (Lejeune *et al*., 1999; Sutton and Roberts, 2002). In those cases, attention was required for accurate timing, and when attention was divided, temporal behavior suffered. In most experiments, attention is difficult to operationalize. In MTSD procedures, the stimulus is the houselight which illuminates the entire experimental chamber, and it is therefore difficult to relate overt behavior and inattention. There have attempts to rectify this by analyzing response latencies to the choice alternatives following the termination of the stimulus to be timed. Presumably, if the animal is attending to the stimulus, it would respond more quickly to the correct choice alternative, and if attention to the stimulus has been disrupted, latencies to choice alternatives would increase. This possibility was examined in three studies, which did not find increases in response latency based on the presentation or administration of disruptive agents (Ward and Odum, 2007; Ward *et al*., 2009, McClure *et al*. (In Review, (c)). This however, does not mean that attention is not a key component to the disruption of temporal behavior. Attention is a variable that may be difficult to quantify empirically from a behavioral level, but not impossible and must surely have neurophysiological underpinnings that can be quantified and related to timing. To explain decrements in accuracy of temporal behavior, procedures will have to assess the specific aspects of behavior that are being disrupted, such as attention, key bias, motoric activity, etc. Only

demonstrations of those mechanisms will allow for their inclusion in a complete explanation of accurate timing.

Conclusions

The main methodological questions asked in these experiments concerning procedural variation and type of disruptor resulted in some interesting conclusions. The Color and Location procedural variations proved to be less important in explaining differential disruption of temporal discrimination caused by the initial effects of pharmacological agents and consecutive non-pharmacological agents. The conditions of the current experiments represent only a small subset of the conditions under which these procedural variations should be studied. The current data set provided useful information concerning differences in baseline performance based on the procedural variation, which could manifest in differential disruption under other disruptors or regimen conditions. Results from our laboratory have shown that the Location procedure is necessary for lateral shifts to occur (McClure *et al*, In Review (b)), and that differential propensities to develop tolerance may exist (McClure *et al*., In Review, (a)). These procedural variations are not minor and comparisons made across studies in which different variants are used should be done with caution while more work is dedicated to understanding their influence on temporal behavior.

The type of disruptors used in the current set of experiments proved to be diverse in form, but were functionally similar in the disruption of temporal judgments. The mechanisms that may be disrupted during administration of drugs or presentation of non-pharmacological agents are far reaching. These include attention to the stimulus and to the dimensions of the choice alternatives, as well as the neurological changes that occur during drug administration and may affect areas of the brain devoted to temporal processing. Disruption of any neurological or behavioral mechanisms of timing could lead to a variety of changes in behavior, such as response

key biases, decreases in accuracy, as well as changes in temporal or non-temporal behavior. It is possible that temporal and non-temporal behavior are not so unique and could be disrupted in a similar fashion based on the complexity and demands of the procedure.

The timing literature is filled with questions of a methodological and theoretical nature. For example, how is time represented to the animal and how are they able to respond to the passage of time with great accuracy? The answer to that question must take into account the neurological actions that are occurring at the time of temporal discrimination and how they are responsible for accurate timing. Behavioral contingencies and mechanisms also must be assessed to determine their role in accurate timing. As our understanding of the brain improves, and our technology increases in resolution we will have access to levels of activity not possible previously. An adequate and complete explanation of what is controlling timing behavior will need to include neurological and behavioral information. Therefore, incorporating neurophysiological data into behavioral assessments of temporal disruption will only provide a more complete understanding of the timing process.

Our suggestion is that timing behavior is not so no unique from other non-temporal behavior that is controlled by an external stimulus; it is merely one type of behavior. Neurophysiological data have revealed a wealth of information concerning the neural mechanisms responsible for timing but if timing also relies on attention, then those neural mechanisms can and should be studied in connection to timing. Reports have shown that there are neural areas that contribute to interval timing, but what other abilities are possible because of these areas? Also, the focus in timing research has been to study neurological activity during pharmacological presentation, but we have shown that non-pharmacological agents that influence motivation also have an effect on behavior. Non-pharmacological agents also result in

neural activity that should be studied in connection with timing. Our inclusion of neurophysiological data should not be specific to certain kinds of disruptors. Any disruptor of behavior must be mediated through the brain in some form and this deserves study. It has been recommended that the neurophysiological study of timing should also include information on the links between timing and memory processes, as well as learning (Staddon and Higa, 2006). Research in timing would only be improved with neurophysiological inquiry of memory, stimulus control, attention, and their links to timing.

The connections should not end there though. Take for example the procedural variations used in our study. One is based on non-spatial response alternatives, which requires accurate discrimination of color, while the other does not require this same ability and is spatial in nature. From a neurophysiological level, those procedural variations require diverse neural activity and substrates for spatial and color perception to be possible. How do those procedural variations translate into neural action and that can that be connected to timing? Do the visual cues as compared to spatial cues that define these procedures make a difference and how is this linked to neural activity? Neurophysiological contributions to timing are immense, but perhaps would be more complete with an understanding of how related processes and methodological manipulations are liked to temporal neural mechanisms.

Future Studies

Future studies using pharmacological agents and operant techniques can make use of drugs that are more specific in their neural mechanisms and specific substrates to isolate the relevant areas and understand the mechanisms responsible for accurate timing. Drugs of abuse are socially relevant, but can often times be widespread in their neurological effects, yet tend to have common effects on dopamine. Drugs that are more specific to interval timing-related neural substrates and systems are preferential for elucidating mechanisms and understanding the

processes of temporal judgments. Previous reports within the timing field provide information about where and how accurate timing is occurring. This body of literature can be expanded with future studies using pharmacological agents of a specific nature and neurophysiological techniques with rodents, humans, pigeons, and other species. Methodological consistency, such as procedural variations used to assess timing, and appropriate doses of drug, should be agreed upon. Also, future work should be devoted to the comparative study of timing mechanisms in other species. This will help to answer questions as to whether timing is a general neurophysiological process that has implications for an evolutionary understanding of this ability, or whether there are distinct systems involved in timing for different species.

Future research should also be devoted to characterizing and explaining the disruptive effects of non-pharmacological agents on temporal discrimination, taking into consideration the role played by the procedural variation used and specific conditions when modulating effects of disruptors are found. Future studies will have more information to provide clarification into the best way to conceptualize timing behavior. Only when the methodological issues within the timing literature have been clarified, can the theories of timing be adequately tested and supported. A theory explaining any phenomenon will persist when there is still some optimal level of data accounted for and until an alternative theory is proposed that is superior.

Concluding Remarks

Staddon and Higa (2006) stressed the importance of directing future research of interval timing to neurophysiological techniques that are focused on related processes to timing, such as memory, rather than focusing on a clock framework set forth by pacemaker-accumulator and coincidence-detection models. Recent data have isolated neural mechanisms for interval timing, as well as timing on different scales, such as circadian timing and millisecond timing. These data are interesting in their own right, and tend to be ignored when results are interpreted within

a specific theoretical framework. The data sets provide useful information concerning neural mechanisms of timing, regardless of their respective theoretical interpretations. It is clear that advances in the understanding the neurological mechanisms of timing are necessary for a more complete explanation of timing behavior.

Church (2002) notes that exploration of timing behavior during most the twentieth century was being conducted by investigators of human psychophysics, biological rhythms, and animal learning. However, these separate lines of research progressed independent on one another, with little to no knowledge of the work being done in the parallel areas, to the detriment of the entire enterprise. This same mistake should not be repeated currently. Those focusing on behavioral processes should not ignore advances in physiology, and in the same vein, those interested in physiology should not ignore the advances, as well as the fundamental questions that are being asked about timing by behavioral researchers. Neurophysiological and behavioral experiments and their questions should be guided by knowledge from both sides and the data should be focused on, not necessarily the theoretical interpretations. That is the only appropriate way for scientific inquiry to move forward. It is clear from all the work that has been done on timing, that this ability in animals must surely be possible due to a complex system of biochemical and electrophysiological oscillators within the central nervous system, which developed either specifically or as an epiphenomenon by differing evolutionary pressures across species and are modulated by current contingencies of the task and neurological manipulations used with a given species.

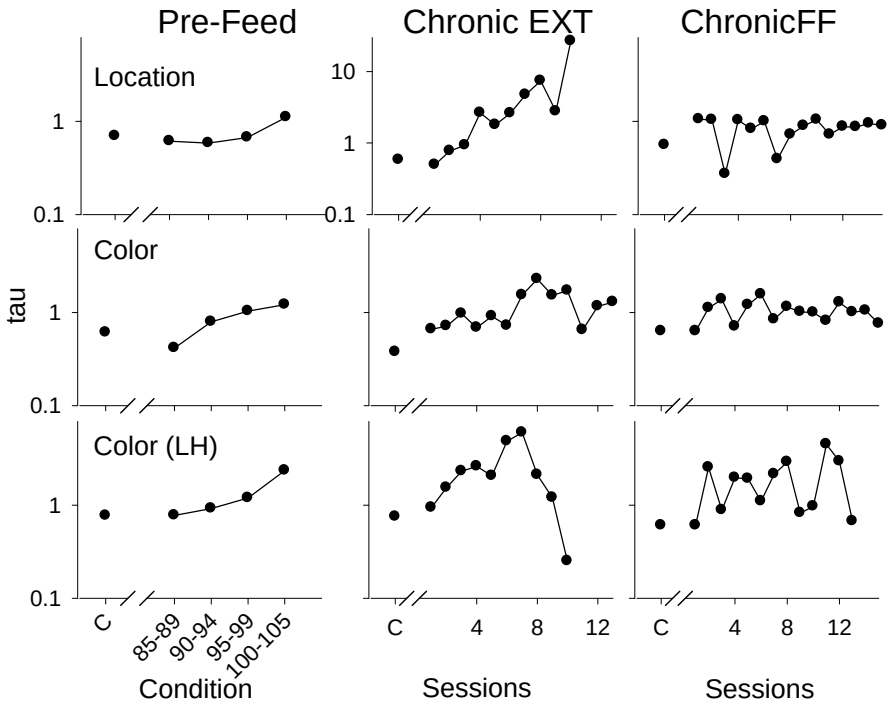

Figure 4-1. Parameter tau for PF conditions, and all sessions during EXT and FF. The scale for tau is logarithmic. Note the difference in scale for the Location group during the Chronic EXT condition.

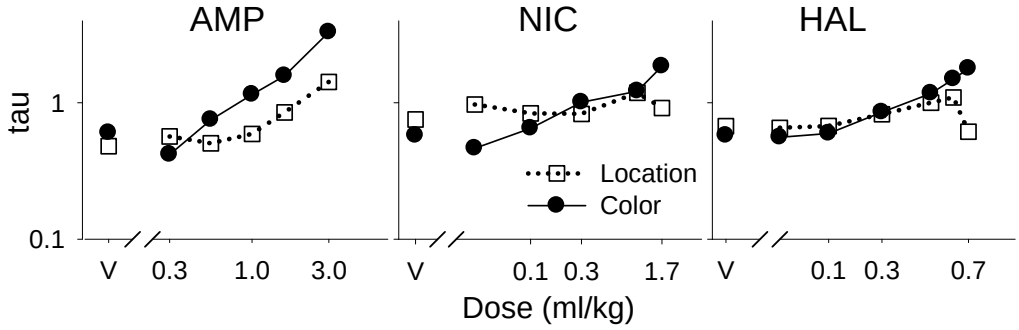

Figure 4-2. Parameter tau for *d*-amphetamine, nicotine, and haloperidol during Experiment 1.

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BIOGRAPHICAL SKETCH

Erin A. McClure's interest in psychology began before beginning her undergraduate work at Allegheny College. From a young age, she was always fascinated by human behavior and understanding the reasons for why people did the things they did. Her curiosity was not exclusive to human behavior, but rather was a more broad curiosity about how the world worked. Her desire to understand how and why phenomena occurred, along with her interest in human behavior led Erin to psychology as a major. She wanted to find a way in which she could contribute knowledge to the scientific community.

During Erin's undergraduate training at Allegheny College, she was introduced to the principles of behavior analysis as a subject matter and sub-field within psychology. She finally felt satisfied in what psychology had to offer. The principles of behavior analysis offered a way to look at behavior of the whole organism as a function of the environmental contingencies. These principles could be used to change complex human behavior, but it could also be studied in a basic laboratory with non-human animals. Behavior analysis offered a highly scientific and testable method for analyzing the behavior of organisms. Radical behaviorism offered a philosophy of science in which fundamentals and assumptions were made that then informed and shaped scientific inquiry. The theoretical and methodological aspects of behaviorism appealed to her and throughout her undergraduate training, she pursed research within the area of behavior analysis.

Erin conducted an independent study, and then a senior thesis with Dr. Rodney Clark and Dr. Jennifer O'Donnell at Allegheny College that assessed changes in avoidance behavior due to administration of oxycodone in rodents. The area of behavioral pharmacology appealed to her as a sub-field of behavior analysis, but also because of her interest in pharmacological agents for

their addictive and reinforcing properties. There is such a dynamic interaction between drugs and behavior, and she wanted to pursue this interest in the basic laboratory.

Along with her psychology training, Erin was also a double-major in neuroscience. She gained experience with the methodology by which neuroscientists study the brain and behavior. In the summer of 2002, Erin was awarded a research fellowship from the Center for Neuroscience at the University of Pittsburgh in which she worked on projects concerning portions of the brain responsible for hypertension and its treatment. This fellowship gave her experience in a new body of literature and with new techniques that she had not used before.

Upon completion of her B.S. degree in psychology and neuroscience from Allegheny College in May of 2003, Erin's interests were still grounded in behavior analysis and behavioral pharmacology, and she applied to the PhD program at the University of Florida with the hopes of being in a department that upheld the tenets of radical behaviorism and would foster the interests she had developed in this field. While at the University of Florida, under the instruction of Dr. Clive Wynne, Erin has worked in the area of pharmacological disruptors of timing behavior in pigeons. Much of her work has involved methodological and theoretical considerations within the timing literature and attempting to shed light on long-standing discrepancies among the literature. She has used a range of pharmacological agents, such as *d*-amphetamine, nicotine, and haloperidol, as disruptors of timing. She has also explored non-pharmacological disruptors of timing. Erin received her M.S. in psychology from the University of Florida in December of 2005, and became a doctoral candidate in April of 2007. Erin then received her PhD from the Department of Psychology at the University of Florida in August of 2009.

Erin enjoyed the work conducted in the basic behavioral pharmacology laboratory with non-human animals; however, her interests remained regarding the environmental contingencies

and the reinforcing and addictive power of drugs. Therefore, Erin's post-doctoral research was in the area of substance abuse treatment using behavioral techniques to change complex human behavior.