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Effects of cholinergic and dopaminergic drugs on number and time processing in rats

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Effects of Cholinergic and Dopaminergic Drugs on Number and Time Processing in Rats

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Abstract

This study describes the effects of cholinergic and dopaminergic drugs on time and number processing by rats. Rats were trained to discriminate discrete sound sequences. On number trials, the duration of the sound sequence was a constant 4 seconds and the number of sounds was 2 or 8. On time trials, the number of sounds was held constant at 4, and the duration of the sound sequence was either 2 or 8 seconds. Psychophysical functions for number and time were obtained by presenting unreinforced sequences of intermediate number and duration. Accuracy of performance was greater with temporal signals than with numerical signals. The general dopamine agonist methamphetamine (1.5 mg/kg) and the specific D2 agonist quinpirole (0.08 mg/kg) significantly reduced control by time and number without shifting the psychophysical functions leftward ($p<.05$). The cholinergic antagonist scopolamine (0.1 mg/kg) significantly reduced accuracy at longer durations and higher numbers, but not at lower values of time or number ($p<.05$). Under all three drugs, the psychophysical functions for time and number showed a decrease in signal discriminability. The cholinergic agonist nicotine (0.2 mg/kg) significantly shifted the psychophysical function rightward for time and number ($p<.05$). This similarity of the effect of each drug on both time and number processing is consistent with the idea that the same internal mechanism is used for timing and counting. However, the specific effect of each drug on timing and counting was not consistent with previous descriptions of the role of different neurotransmitter systems on the perception of time and number.

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Effects of Cholinergic and Dopaminergic Drugs on Number and Time Processing in Rats

Time and number perception are a basic guiding force in all of our lives. Numerical and temporal sensitivity requires the perception of a current signal and the memory of a past signal. Animals depend upon being sensitive to number and duration accurately in the wild. A properly functioning numerical and temporal mechanism enables the avoidance of predators, the capture of prey, the hunting and gathering of food, caring for the young, and providing a safe home. Sensitivity to number and duration is under neurobiochemical control, and these neurobiological and pharmacological mechanisms constitute the behavioural components of numerical and temporal sensitivity under investigation in this paper. This pharmacopsychological approach is aimed at discovering the neurobiological and neurochemical brain systems that mediate these behaviours.

Temporal Processing Methods

There are two methods commonly used in the study of temporal sensitivity: the bisection procedure (time perception) and the peak procedure (time production). The peak procedure is a discrete-trial variation of a fixed-interval schedule in which reinforcement is delivered for the first response that occurs after a fixed amount of time following the last reinforcer. Each trial is defined by the presentation of a stimulus (e.g., tone or light) and a specified duration after the onset of the trial stimulus, food is available and the subject can obtain it by making a response (e.g., pressing a lever). After the fixed-interval has been sufficiently learned, empty test trials are initiated in which the reward usually occurring at the fixed time is eliminated, thus,

responding on these trials goes unrewarded. Various measures are used to define estimation in the peak procedure, the most notable being the peak response rate (the maximal rate of responding) and the peak time (the time at which the greatest amount of responding occurs). The peak time on these empty trials is similar to the fixed-interval peak time, illustrating animals' ability to produce duration. This type of temporal estimation is also evident in humans. This behaviour is under cognitive control in humans whereby temporal judgements are affected by the amount of mental content, complexity of information, processing effort, and experience of change (Rammsayer, 1997).

The peak procedure is in contrast to the bisection procedure. In the bisection procedure, subjects are trained on a forced-choice task to respond to the stimulus presented (e.g., tone or light) that is either "short" or "long" in duration (e.g., 2s versus 8s), or "few" or "many" in number (e.g., 2 versus 8 events). Subjects are trained to respond in one manner (e.g., press the left lever) following a "short" or "few" stimulus, and to respond in an alternate manner (e.g., press the right lever) following a "long" or "many" stimulus. Once subjects have sufficiently acquired this task, durations and/or numbers intermediate to those presented during training are added (e.g., 3, 4, 5, and 6). Responding generates a psychophysical function which is a plot of the percentage of responding "many" or "long" as a function of stimulus value (number of events or duration of events). The bisection point, or point of subjective equality (PSE), is the point at which subjects choose "many" or "long" just as much as they do "few" or "short". In other words, the PSE is the point of indifference lying at 50% correct, representing the subjective middle between two reinforced values. The bisection procedure is followed in this

study. Two other important parts of a psychophysical function are the difference limen (DL) (one half of the range of signal values that the rat called "long" or "many" on 75% of the trials and the signal value that the rat classified as "long" or "many" on 25% of the trials) and the Weber fractions (WF) (the principle that for various stimulus intensities the difference threshold tends to be a constant fraction of the stimulus; DL/PSE).

Internal Clock Model

Current explanations of temporal and numerical sensitivity encompass a clock/counter information-processing system which was elaborated by Meck and Church (1983). A schematic representation of the internal clock/counter model is provided in Figure 1. As we can see in Figure 1, the internal clock/counter-model contains three main stages: a clock stage, a memory stage, and a decision stage. During the clock stage a pacemaker emits pulses at regular intervals. These pulses are gated by the status of a switch which alternates its mode of accounting for incoming duration or number. When closed, the switch passes the pacemaker pulses into an accumulator which records these pulses as a physical time interval. This accumulator value is transferred to working memory, which is occupied by temporarily relevant information (e.g., pulse count of the current trial). The working memory value is compared to a remembered accumulator value of duration and/or number which is gained from experience (e.g., current vs. past value comparison) and held in reference memory (Meck & Church, 1987a). The reference memory storage area is occupied by long term information (e.g., duration or number representation developed through repeated reinforced trials with similar duration or number). The value transferred from the accumulator to reference memory after a reinforced response is

the number of pulses in the accumulator multiplied by a theorized memory storage constant. The speed with which values are transferred from working memory to reference memory occurs via this memory storage constant. The Meck and Church (1983) model describes that under baseline conditions, animals have an average memory storage constant of 1.0. This value may increase or decrease with the administration of drugs, thus, altering the speed with which values are transferred from working memory to reference memory and the point at which animals will respond for reinforcement. The decision process occurs in the comparator, and involves the application of a response rule that is task-specific (Meck, Church,& Olton, 1984). If the response is correct, it is reinforced. The value in the accumulator is then transferred to reference memory via an encoding system for later retrieval and use in comparing remembered and current times (Meck & Church, 1987a).

An important aspect of the internal clock/counter model which accounts for the relevance of both duration and number is that both dimensions are deemed to have a mode switch, accumulator, and working and reference memory storage components. Meck and Church (1983) trained rats on a bisection procedure in which both temporal and numerical signals were presented. The number of sound segments varied (2, 3, 4, 5, 6, & 8 events of white noise) while duration of the segments was held constant, and the duration of the sound segments varied (2, 3, 4, 5, 6, & 8 seconds) while the number of segments was held constant. Because in sessions where number and duration stimuli were confounded (both were presented) rats gained both numerical and durational information and decided which to use, Meck and Church (1983) theorized that a single pacemaker but separate mode switches, accumulators, and memories were

used. Thus, it was hypothesized that the internal mode switch found between the pacemaker and accumulator runs in alternative modes depending upon the requirements made upon subjects. Pacemaker pulses are controlled accordingly. Figure 2 provides a diagram of three modes of operation of the switch of the internal clock/counter model. In the run mode, the switch operates (is closed) from stimulus onset until the end of the trial; in the stop mode the switch operates whenever the stimulus occurs and does not operate (is open) between the interstimulus intervals; and in the event mode, the switch closes for a fixed duration at each onset of the stimulus regardless of stimulus duration, allowing solely the number of segments independent of their duration to be counted. Thus, the event switch mode is used for counting events, and the run or stop switch modes are used for timing events (Meck & Church, 1983).

Number and Time Signals and the Internal Clock

Both number and duration have been found to be relevant stimulus attributes which rats classify. Meck and Church (1983) have reported that for rats, the PSE for time and number both rest at the geometric mean (the square root of the multiplied value of the two training values), and that the psychophysical functions for duration and number are similar. This shows that both number and time can serve as an effective stimulus for behaviour when all other cues are held constant.

This similarity in numerical and temporal judgement has also been found in pigeons. Pigeons were found to be able to discriminate two light flashes from eight light flashes, as well as flashes of light occurring within 2s of duration or 8s of duration in a procedure identical to that of Meck and Church (1983) (Roberts & Mitchell, 1994). Presenting the pigeons with lights that varied

only in duration tested their temporal processing while presenting the pigeons with lights that varied only in number tested their numerical processing (Roberts & Mitchell, 1994). When given explicit training on numerical discriminations, a light signal was presented for two flashes or eight flashes, and within each number of flashes the total duration of the sequence was 2, 4, or 8s. So, the six types of trials were as follows: 2 flashes in 2s; 2 flashes in 4s; 2 flashes in 8s; 8 flashes in 2s; 8 flashes in 4s; and 8 flashes in 8s. Both the 8 flashes in 2s and the 2 flashes in 8s were ambiguous sequences because whereas training occurred with 2 flashes in 2s and 8 flashes in 8s sequences, the new 8 flashes in 2s and 2 flashes in 8s sequences indicate different responses for number and duration. The pigeons performed significantly above chance with 8 flashes in 2s and 2 flashes in 8s sequences based on numerical discriminations. Because of this, Roberts and Mitchell (1994) suggested that the Meck and Church (1983) model must distinguish between numerical and temporal information in working memory stemming from separate numerical and temporal accumulators. A schematic representation of this updated internal clock/counter model is represented in Figure 3 (Roberts & Mitchell, 1994). Thus, according to Roberts and Mitchell (1994), subjects will use the stimulus attribute that is a more relevant or viable dimension along which to make predictive responses and gain reinforcement according to the needs of the task.

Roberts, Macuda, and Brodbeck (1995) partially support Meck and Church's (1983) mode control model of numerical and temporal sensitivity. It was shown that pigeons relegated to a number group exhibited a "choose-small" effect (subjects respond to stimuli associated with a "few" sample when "many" are presented and memory is assessed at a long delay) for various

numbers of samples with time held constant. This "choose-small" effect was equivalent to the "choose-short" effect (subjects respond to stimuli associated with a short sample at longer delays) usually found with temporal samples (Roberts et al., 1995). In those pigeons relegated to a time group however, a "choose-long effect" (subjects respond to stimuli associated with the long sample at longer delays) was observed, which was actually a numerical "choose-small effect". It was concluded that the pigeons in the time group made use of the recent flashes at the end of a flash sequence (recency effect) instead of the total duration of the sequence (Roberts et al., 1995). To test this, Roberts et al. (1995) placed the pigeons into a consistent and inconsistent transfer contingency paradigm in which the time group was shifted to a number discrimination, and the number group was shifted to a time discrimination. The pigeons were presented with contingencies that were consistent or inconsistent with the hypothesis that number was being attended to. For example, the time group learned to choose a red key after 4 flashes in 2s because a large number of flashes was remembered versus choosing a green key after 4 flashes in 8s because a small number of flashes was remembered. Thus, it was expected that the pigeons placed in the consistent group would exhibit "positive transfer" (performance above chance which lies at 50%) when transferred to number samples if the red key was correct after a "many" number sample (e.g; 8 flashes in 4s), and the green key was correct after a "few" number sample (e.g; 2 flashes in 4s). On the other hand, Roberts et al. (1995) expected that pigeons that received the same training and were placed in the inconsistent group would exhibit "negative transfer" (performance below chance which lies at 50%) if the colour contingencies were reversed (e.g., green key correct after the "many" number sample, 8 flashes in 4s; and the

red key correct after the "few" number sample, 2 flashes in 4s). The expectations for the group of pigeons transferred from the number discrimination to the time discrimination were the same.

Those pigeons placed in the consistent group showed "positive transfer" and performed significantly above chance, showing that the pigeons were attending to the number of flashes and thus, performed accurately. In contrast, those pigeons placed in the inconsistent group showed "negative transfer" and performed significantly below chance. This showed that the pigeons were basing their choices upon their previous training contingencies that were now reversed, indicative of attending to the number of flashes at the end of the sequence rather than the entire sequence (Roberts et al., 1995).

The research of Alsop and Honig (1991) supports the conclusion of Roberts et al. (1995). Alsop and Honig (1991) placed pigeons in a test of numerical discrimination between blue and red flashes of light. It was found that those stimuli occurring later in the sequence controlled the type of responses made by subjects more than stimuli occurring earlier in the sequence. These findings necessitated modification of the mode control model (Meck & Church, 1983). Rather than the total pulses in duration and number being transferred from the accumulator to working memory when the total of pulses are emitted and a signal has ended, perhaps pulses dwindle upon initiation of a sequence given that pigeons used the end of the flash sequences for their numerical discriminations (Alsop & Honig, 1991; Roberts et al., 1995). If so, the accumulation of pulses in working memory would be greater for the samples with shorter durations (e.g., 4 flashes present at the end of a 2s duration sequence versus 1 flash present at the end of an 8s duration sequence). Thus, with the presentation of a delay in which the pulse counts present

would diminish, pigeons would respond to the 2s sample as though it were an 8s sample because the "greater" number of pulses in the 2s sample would diminish over the delay interval and appear "small". Because the final 2s of the 8s sample would seem "small", the 8s sample key would be chosen following a long delay.

However, the equivalency between numerical and temporal bisection points does not always remain, questioning the validity of the claims of Meck and Church (1983). The inequalities found between numerical and temporal bisection points has necessitated further extension of the model by Meck and Church (1983). Fetterman (1993) reported that the PSE found for numerical and temporal tasks has not been uniform. While the temporal bisection point has been robustly documented to occur at the geometric mean the numerical bisection point has been found to be more variable. The numerical bisection point has been reported at the harmonic mean (the variance of the harmonic mean is proportional not to N, but to1/N) (Fetterman, 1993) and the geometric mean (Meck & Church, 1983). Furthermore, these differences in bisection point location vary with type of sample presentation. For example, the numerical bisection point was found to be at the harmonic mean for tones but at the geometric mean for food quantities (Martin-Iverson, Fibiger, & Wilkie, 1988), suggesting that the perception of food quantity depends on different processes than the perception of tone quantity. Perhaps the type of stimulus used alters the working of the clock differently between numerical and temporal tasks.

While previous work shows that animals do make decisions according to both numerical and temporal signals, the degree of control exerted by each signal type does not seem to be as equal as Meck and Church (1983) first described. It would seem reasonable that numerical and

temporal choices occur in different situations and in alternative forms. The three criteria which must be met to fulfill counting behaviour highlight this idea: 1) *the one-to-one principle* - a unique tag in the form of the accumulator value is applied to each event in a one-to-one correspondence; 2) *the stable-order principle* - the accumulated quantities are reliably ordered, and; 3) *the cardinal principle* - the final accumulator value is a tag that represents the numerosity of the entire event sequence (Breukelaar & Dalrymple-Alford, 1998). Breukelaar and Dalrymple-Alford (1998) performed an experiment identical to that described by Meck and Church (1983), where compound time-relevant and number-relevant cues occurred. Unlike the equal control of choice behaviour for both numerical and temporal cues found by Meck and Church (1983), rats were found to significantly and accurately discriminate signal duration but not signal frequency, and continued to respond on the basis of time when numerical cues were available (Breukelaar & Dalrymple-Alford, 1998).

Next, rats were trained on 2 and 8 time-relevant cues as well as 2 and 8 number-relevant cues separately, allowing the sensitivity to time and number to be compared. It was found that discrimination between numerical standards was poorer than discrimination between temporal standards, reflecting an advantage of temporal competence over numerical competence. In order to eliminate the possibility that the advantage of temporal cues was due to the fact that the temporal discrimination was learned first, the acquisition and psychophysical functions of the numerical and temporal discriminations by naive rats trained with concurrent 2 and 8 sec/event time and number signals was used as a comparison. It was found that the rate of acquisition and the asymptotic performance of numerical signals was poorer than the rate of acquisition and the

asymptotic performance of temporal signals. Furthermore, several rats failed to reach the acquisition criterion and showed a slower rate of learning on numerical trials. This was evidenced by higher DLs and WFS on numerical trials. This is in contrast to temporal trials where all rats met the acquisition criterion and showed a faster rate of learning.

Finally, Breukelaar and Dalrymple-Alford (1998) tested the last-resort hypothesis, the idea that even animals that have been trained to respond on the basis of number will not do so if other accurate cues to reinforcement are available. This hypothesis was tested by presenting rats with ambiguous signals (2 events in 8 seconds, and 8 events in 2 seconds) where the numerical and temporal choices demanded opposite lever responses. If the last-resort hypothesis is correct, then responding to these ambiguous signals should be based solely upon signal duration, whereas dependancy on both number and time would reveal lever choice according to both dimensions irrespective of the signal ambiguity (Breukelaar & Dalrymple-Alford, 1998). The results showed that while the rats' ability to discriminate cues according to numerical signals was not disrupted, they ignored the numerical cues and responded entirely on the basis of time. This occurred even when accurate, yet ambiguous, temporal cues were available, and even when numerical attributes of the signals were the most accurate.

Each of these experiments has led to an hypothesized addition to the mode-control model of Meck and Church (1983), and the separate working memory areas for numerical and temporal information made to it by Roberts and Mitchell (1994). Breukelaar and Dalrymple-Alford (1998) suggest that at the comparator stage, information is processed sequentially rather than simultaneously, with the most salient information being compared to values in reference

memory first. If time is more salient than number, and it is thus processed first, the subsequent processing of numerical information is at the expense of the control by time. Perhaps this would make numerical control more susceptible to error and less advantageous and possibly more affected by drug manipulations.

Dopamine and the Internal Clock Model

Site of action

Alongside the definition of the nature of numerical and temporal judgements in animals, the neurobiological and neurochemical makeup of the internal clock/counter has begun to be elucidated. More specifically, the striato-cortical loops have been identified as the site of the dopaminergic components of the internal clock/counter (Penney, Meck, & Holder, 1996). The substantia nigra secretes dopamine which enters the caudate-putamen (the accumulator) of the basal ganglia for temporal integration. The dorsal noradrenergic bundle (dopaminergic ventral tegmental area and substantia nigra) projects to the caudate-putamen which is rich in both D1 and D2 receptors (Penney et al., 1996). This postulates that the dorsal noradrenergic bundle determines whether pacemaker pulses are gated (closed switch) to the accumulator (Penney et al., 1996). The salience of these structures for timing events is highlighted by their identification in functional magnetic resonance images obtained during temporal tasks (Morell, 1996).

The importance of these structures is substantiated by rats' inability to discriminate among temporal signals which had been learned previously following lesions of the caudate-putamen or substantia nigra (Morell, 1996). Rats with caudate-putamen and substantia nigra lesions fail to express interval discriminations, a deficit which is restored with L-DOPA administration only in

the substantia nigra lesioned group (Meck, 1996). This suggests that the accumulation or gating process is dependent upon the caudate and putamen, while the generation of pulses or timekeeping is dependent upon the substantia nigra (Meck, 1996).

These findings support the theory that degradation of the dopamine centres in the mesostriatal substantia nigra in Parkinson's disease patients are associated with their timing deficiencies. Parkinson's disease patients show impaired temporal processing in a task where the time interval between two stimuli needed to perceive them as separate was prolonged (Hellstrom, Lang, Portin, & Rinne, 1997). This further supports the idea that the basal ganglia is the site of brief temporal control (Hellstrom et al., 1997). Furthermore, midbrain neurotoxin lesions produce symptoms akin to Parkinson's disease, including akinesia, catalepsy, and impaired time perception (Meck, 1996). Also, the basal ganglia is the site which mediates the motor side-effects of Parkinson's disease and tardive dyskinesia. Intact memory functioning is necessary for time perception, thus, temporal discrimination in a computerized test of tone duration discrimination using pairs of tones of 0.4-1.6s of duration is impaired by brain damage, senile dementia (Alzheimer's disease and vascular type), aging, and Parkinson's disease (Hellstrom et al., 1997).

Curve-shift paradigm

In order to differentiate the specific versus the non-specific effects of drugs on the functioning of the internal clock/counter model, the 'curve-shift' paradigm has been used to study the pharmacological bases of interval timing. In the study of numerical and temporal discriminations, the curve being 'shifted' is a psychophysical function relating the duration of a

stimulus or the number of stimuli to the probability of a certain response (Meck, 1996). Using the bisection procedure, if a pharmacological manipulation speeds up the numerical or temporal processing system, the resultant psychophysical function will shift horizontally to the left as the subject will classify "shorter" and "fewer" number of stimuli as being proportionally "longer" or "greater" than normal (Meck, 1996). An example of this can be seen with the use of the general dopaminergic agonist methamphetamine in the top portion of Figure 4. Contrarily, if a pharmacological manipulation slows down the temporal or numerical processing system, the psychophysical function will shift horizontally to the right as the subject will classify longer and a greater number of stimuli as being proportionally "shorter" or "fewer" than normal. An example of this can be seen with the use of the specific D1/D2 dopaminergic antagonist haloperidol in the lower portion of Figure 4 (Meck, 1983).

Dopamine

In addition to the neurophysiological identification of the site of the dopaminergic components of the internal clock/counter, the action of dopamine on the internal clock/counter is becoming more clear through such 'curve-shift' paradigms. It has been found that manipulation of dopamine concentrations via the administration of dopamine agonists and antagonists produces changes in behaviour which are interpreted as being the result of a change in clock speed. Increases in the synaptic level of dopamine increases the speed of the pacemaker, so that there is an increased number of pulses transmitted to the accumulator. Conversely, decreases in the synaptic level of dopamine decreases the speed of the pacemaker so that there is a decreased number of pulses transmitted to the accumulator. Ultimately, the match

between current accumulator and past reference memory times will occur at different points in physical time than before. These neurochemical alterations are exemplified in the changes in rats' numerical and temporal discriminations versus their baseline discriminations.

It is important to note that these "clock pattern" dopaminergic shifts are phasic in nature. This means that the shifts occur immediately following drug administration, the shifts disappear and re-normalize with repeated drug exposure as the subjects learn to rescale time, and the shifts occur in the opposite direction back to baseline levels when drug administration stops (rebound effect) (Meck & Church, 1987a). The immediate and drug-dependent nature of these shifts implicates changes in clock speed (e.g; the pacemaker) as the cause.

Dopaminergic phasic shifts have been found to occur in both numerical and temporal discrimination paradigms in rats. Increases in the effective level of brain dopamine with methamphetamine (DA agonist) causes rats to estimate time as "longer" and number as "more" to the same degree (10% leftward shift), evident by phasic horizontal leftward displacements of numerical or temporal judgements (Meck, 1983; Meck & Church, 1983). This suggests that the same pacemaker is responsible for both numerical and temporal discriminations. Similarly, decreases in the effective level of brain dopamine with haloperidol (DA antagonist) causes rats to estimate time as "shorter", evident by phasic horizontal rightward displacements of temporal psychophysical functions (Meck, 1983).

Pigeons tested in a temporal peak procedure paradigm have shown similar results when administered with d-Amphetamine (DA agonist). In particular, it was deemed important to integrate the pharmacological data from both bisection procedures and peak procedures in order

to more decisively say that the effects are due to an influence upon the timing process itself rather than merely influencing an animal's criterion for classifying a duration as short or long (Kraemer, Randall, Dose, & Brown, 1997). Pigeons were placed on a fixed interval schedule where the first response made after a signal duration of 30s was reinforced. When administered with d-Amphetamine, the pigeons showed a leftward shift in the peak of the response function and the mean peak duration was lower than under saline administration. This was attributed to an increase in the speed of the pacemaker, thus, an increase in the number of pulses in the accumulator. The results were not attributed to attentional or activity effects of the drug because the mean peck rate was not different between d-Amphetamine and saline trials. Thus, it was concluded that amphetamines exert a similar effect on timing among both rats and pigeons. Another set of pigeons was placed in the exact same paradigm but administered one of three increasing dosages of d-Amphetamine (0.3, 1.0 or 2.0 mg/kg). The results revealed that the peak duration differed as a function of the dose of d-Amphetamine: the performance under 0.3 mg/kg of d-Amphetamine was equal to that of saline, the mean peak duration was shorter under 1.0 mg/kg of d-Amphetamine, and shorter still under 2.0 mg/kg of d-Amphetamine. This d-Amphetamine dose-response curve shows that the degree to which responding occurs earlier during a temporal signal is a function of the dose of d-Amphetamine.

While the aforementioned work is limited to animal studies, it has been shown that the dopamine-antagonistic effects of haloperidol (D1 and D2 antagonist with greater affinity to D2 receptors) are the same in human subjects (Rammsayer, 1994). The dopamine-antagonistic effects of haloperidol are evident in patients suffering from schizophrenia and Tourette's

syndrome who show temporal discrimination deficits while under haloperidol administration in comparison to those patients who are not under haloperidol administration (Rammsayer, 1994). Furthermore, blocking serotonergic receptors with the 5-HT2 receptor blocker ritanserin increased time perception performance on a task in which subjects were to decide which of two auditory intervals ranging from 20ms to 80ms was longer (Rammsayer, 1994). This occurred possibly by enhancing dopaminergic activity by blocking serotonergic inhibition (Rammsayer, 1994). These findings support the contention that temporal processing of brief intervals relies upon the effective level of brain dopamine, especially within the basal ganglia (Rammsayer, 1994). However, the observed impairment of memory processes following midazolam (benzodiazepine - anxiolytic drug that activates benzodiazepine receptors coupled to GABA receptors on neurons, making the latter more sensitive to the neurotransmitter) administration in humans may have caused the decrease in performance on the time production task due to its amnesic and sedative properties, evident in a serial event-recall task (Rammsayer, 1994). Thus, the results of dopamine manipulation in animals has been interpreted as a modulation of clock speed while the interpretation of the results of dopamine manipulation in humans is more complicated. Either the processes in question are mediated differently between species, perhaps by different receptor subtypes or the action of alternative receptor combinations. Furthermore, the clock effect comparable to that in animals does not occur in humans, or the clock effect in humans was masked by memory effects.

D2 receptor

Because the dopaminergic antagonist alpha-methyl-*p*-tyrosine (AMPT) (an inhibitor of

tyrosine hydroxylase, one of the key elements in the biosynthesis of dopamine) fails to affect temporal processing like the dopaminergic antagonist haloperidol, it has been hypothesized that changes in pacemaker speed depends on changes in D2 receptor activity rather than on changes in the rate of dopamine synthesis, release of dopamine, or overall changes in the level of dopaminergic activity in the brain (Rammsayer, 1997). The effects of the striatal D1-D2 receptor blocker haloperidol and the selective D2 mesolimbic and mesocortical receptor blocker remoxipride on temporal discrimination of brief stimuli were analysed in human subjects (Rammsayer, 1997). It was found that time perception was impaired by haloperidol which produces motor side-effects consistent with certain neuroleptics, while time perception was unaffected by remoxipride which does not produce motor side-effects consistent with an atypical neuroleptic (Rammsayer, 1997). This suggested that the modulation of the internal clock depends on D2 receptor mediated dopamine antagonistic effects on the basal ganglia rather than on D2 receptor activity in the mesolimbocortical dopaminergic system (Rammsayer, 1997). This conclusion is drawn because if mesolimbocortical dopamine were involved in temporal processing of brief intervals, time perception performance should have been affected by both antagonists. However, only haloperidol had a deteriorating effect upon temporal processing when compared to remoxipride, suggesting that the timing mechanism underlying time perception depends on D2 receptor activity in the basal ganglia (Rammsayer, 1997).

The shift in temporal psychophysical functions following other D2 antagonists has also been examined. Meck (1986) administered five different neuroleptics (chlorpromazine, haloperidol, pimozide, promazine, and spiroperidol) that have variable affinities to both dopaminergic and

other aminergic receptors in rats (D1 or adenylate cyclase-linked; D2 or non-adenylate cyclase-linked; D3 or pre-synaptic; NE-α or alpha noradrenergic; 5HT-1; 5HT-2). It was found that these neuroleptics produced a 15-20% rightward horizontal shift in the PSE for the psychophysical bisection functions relating the percentage of "long" responses to signal duration (2-8s and 4-16s) (Meck, 1986). Meck (1986) concluded that the D2 receptor plays an integral role in temporal processing whereas other aminergic receptors (D1, D3, NE-α, 5HT-1, and 5HT-2) do not because D2 affinity alone predicted the shift. Affinity for the dopaminergic D2 receptor predicted neuroleptic potency in producing the shift of the timing functions, whereas affinity to other neural receptor sites did not. Thus, Meck (1986) concluded that neuroleptic drugs with increasing affinity for the D2 receptor increasingly affect temporal processing by decreasing the rate at which the pacemaker emits pulses. However, temporal processing may be affected by combining D2 receptor neuroleptics with specific D2 affinities with other receptor subtypes. In other words, greater D2 affinity may not simply translate into greater control over temporal processing.

Frederick and Allen (1996) partially supported the results of Meck and Church (1983) by illustrating that rats, in a peak procedure, administered with a D1 agonist (SKF 38393) and a D2 agonist (quinpirole) produced a significant leftward shift consistent with the overestimation of the passage of time, while administration of the D1 antagonist (SCH 23390) and the D2 antagonist (eticlopride) produced a nonsignificant rightward shift. A significant rightward shift would have been consistent with the underestimation of the passage of time. The non-significance of part of these results renders the possibility that dopaminergic compounds specific

to one receptor subtype may produce much different effects on timing behaviour than compounds with mixed affinities for both receptor subtypes (eg., haloperidol). Such nonspecific compounds may have equal affinities for multiple receptor subtypes or may have a greater affinity for one receptor subtype over another. Furthermore, such nonspecific compounds can not only increase or decrease clock speed, but do both. Claiming that general increases and decreases alters the speed of the clock may be too simplistic.

Stanford and Santi (in press) also used the specific D2 agonist quinpirole to test the hypothesis that rats treated with quinpirole would have temporal discrimination functions shifted leftward in a nonpermanent, phasic manner. They found that increases in dopamine levels did not increase the speed of the clock, evidenced by the lack of a leftward shift in the psychophysical function and decrease in the PSE. Instead, there was an increase in the PSE and disruption in the perception of the samples, measured by the difference limen (DL) and Weber fraction (WF). Stanford and Santi (in press) show that previous dopaminergic drug experience, the use of a psychophysical function to examine the mechanisms of the internal clock/counter, and response latency corrections do not account for the contradictions found between this study and that of Meck (1986). These findings question the idea that an increase in brain dopamine at D2 receptors shifts psychophysical functions leftward, indicating an increase in clock speed. Perhaps the dopamine receptor subtypes subserving agonistic (leftward shifts or increased clock speed) and antagonistic (rightward shifts or decreases in clock speed) synaptic interactions vary in isolation or combination. Again, explaining the observed psychophysical shifts via general increases or decreases in dopamine levels is too simplistic.

Attention and vigilance

While dopaminergic manipulation has been found to alter temporal discrimination performance, the degree to which this effect is due to attentional or vigilance modulation has also been examined. The effect of the tricyclic antidepressant general dopamine agonist amineptine upon temporal performance was assessed in rats placed in three separate schedules (differential reinforcement of low rate or DRL, fixed-interval or FI, and signalled continuous reinforcement or CRF-S) (Lejeune, Hermans, Mocaer, Rettori, Poignant, & Richelle, 1995). If dopamine enhancement via amineptine modulates attention or vigilance, increases or decreases in the latency to respond to stimuli would be expected in the CRF-S schedule alone (Lejeune et al., 1995). This is because the CRF-S schedule requires subjects to react to signals only as they occur. Conversely, if dopamine enhancement via amineptine modulates the temporal mechanism of the subjects, increases or decreases in the latency to respond to stimuli would be expected in the DRL and FI schedules alone (Lejeune et al., 1995). The results obtained were consistent with a role of dopamine enhancement via amineptine administration upon attention and vigilance of spontaneous motoric activity and acquired operant activity, and increased reactivity to extraneous significant stimuli rather than a timing mechanism per se (Lejeune et al., 1995). There was a dose-related increase in response rates in the FI and DRL schedules correlated with a dose-related impairment in the temporal regulation of performance evident in the temporal discrimination task. Lejeune et al. (1995), thus, argued against Meck and Church's (1983) contention that dopaminergic manipulation alters the speed of the internal clock. The effect observed upon attention or vigilance may be due to the effects of amineptine

upon those systems integral to arousal and attention, thus, masking the underlying temporal effects that may be occurring with dopamine manipulation using amineptine. Also, the tasks used by Lejeune et al. (1995) may not be able to illustrate the effects of increasing dopamine upon temporal judgements. Alternatively, the role of dopamine in timing may not always be consistent with that proposed by Meck and Church (1983).

The results of Santi, Weise, and Kuiper (1995) are also inconsistent with those of Meck and Church (1983). A time perception procedure was used where sample stimuli were 2s and 12s of tone or light. Time perception was analysed at a zero second delay and the memory for time was analysed at variable delays (1s, 3s, and 9s) (Santi et al., 1995). In both rats and pigeons, Santi et al. (1995) found that increasing the effective level of brain dopamine with systemic amphetamine administration did not increase the speed of the internal clock and produce a "choose-long" bias at the zero second delay. A "choose-long" effect was hypothesized because an increase in pacemaker speed would result in a greater number of pulses being transferred to working memory and ultimately compared with reference memory. Thus, subjects would judge the "short" stimuli as "long". Instead, there was reduced accuracy for all signal durations at the zero second delay, suggesting a general disruption of attention to temporal samples.

The results reported by Santi et al. (1995) are corroborated by other research. More specifically, Stubbs and Thomas (1974) placed pigeons in a psychophysical choice procedure whereby a stimulus was presented for 1 of 10 durations, followed by the illumination of two coloured choice keys. One choice was correct if the sample was between 1s and 5s, while the other choice was correct if the sample was between 6s and 10s. Following systemic d-

Amphetamine administration, discrimination accuracy dropped in a dose-dependent fashion over all stimulus durations, suggesting that accuracy was reduced at both shorter and longer durations. Stubbs and Thomas' (1974) results are akin to those of Santi et al. (1995) because they also failed to find a "choose-long" bias as would be expected if the clock was sped up. These results are also consistent with those of Rapp and Robbins (1976). Rapp and Robbins (1976) also failed to find a "choose-long" bias in a temporal discrimination task using rats administered with d-Amphetamine. Rather, Rapp and Robbins (1976) found a "choose-short" bias evidenced by a higher error rate for the 7s sample when using 3s and 7s tone durations as samples. Again, d-Amphetamine disrupted accuracy but did not selectively increase the speed of the clock.

Coyle (MA Thesis, 1997) administered methamphetamine to pigeons in a numerical delayed matching to sample task (matching a test sample with a previously shown sample cue following a delay). It was expected that a "choose-many" effect indicative of increased pacemaker speed would occur. A "choose-many" effect was hypothesized because an increase in pacemaker speed would result in a greater number of pulses being transferred to working memory and ultimately compared with reference memory. Thus, subjects would judge the "few" stimuli as "many". However, the pigeons actually exhibited a "choose-few" bias and performance on the "many" trials decreased. These data are inconsistent with Meck and Church's (1983) claim that increases in dopamine increases the speed of the pacemaker. Rather, these results corroborate those of others (Lejeune et al., 1995; Rapp & Robbins, 1976; Santi et al., 1995; Stanford & Santi, in press; Stubbs & Thomas, 1974) that increases in dopamine cause a general disruption

of attention.

Acetylcholine and the Internal Clock Model

Site of action

The neurophysiological site of cholinergic action of the internal clock/counter has also begun to be elucidated. Cholinergic effects upon the internal clock/counter are substantiated by the knowledge that the hippocampus is very rich in acetylcholine receptors and known to be an important site for working memory. Furthermore, it is known that brain cholinergic systems play an integral role in both learning and memory processes in various species and tasks (Aigner & Mishkin, 1986). More specifically, cholinergic mechanisms seem to be involved in the retention of recent transient events maintained in working memory, as well as in the retention of more long term information found in reference memory. This suggests that the cholinergic system originating in the magnocellular nuclei of the basal forebrain and projecting to the hippocampus is involved in the internal clock/counter.

Acetylcholine and the internal clock model

While dopaminergic manipulation changes clock speed, cholinergic manipulation via cholinergic agonists and antagonists has been reported to produce changes in the memory stage of the internal clock/counter model (Meck, 1996). Temporal memory processes are affected by the destruction or blockade of cholinergic areas including the nucleus basalis magnocellularis, fimbria-fornix, medial septal area, and the hippocampus (Meck, 1996). More specifically, increases in the synaptic level of acetylcholine increases memory storage speed, and hence, increases the speed with which values are transmitted from working memory to reference

memory. Conversely, decreases in the synaptic level of acetylcholine decreases memory storage speed, and hence, decreases the speed with which values are transmitted from working memory to reference memory. These neurochemical alterations are exemplified in the temporal discriminations that rats make.

It is important to note that these "memory pattern" cholinergic shifts are chronic in nature, opposite to the immediate "clock pattern" dopaminergic shifts. This means that they do not occur immediately but following a few sessions of drug administration. The shift increases its magnitude with repeated drug administration until a maximum or asymptote is reached. The shift is maintained as long as drug administration continues indicating that no rescaling of time occurs. The shift is maintained for a few sessions after drug administration has stopped before moving in the opposite direction back to baseline levels (Meck & Church, 1987a). The shifts are gradual in nature because the times stored in reference memory are those accumulated during baseline conditions of normal memory storage speed, so that initial sessions of drug administration do not show any changes. With continued training under drug administration, the values transferred to reference memory are "shorter/fewer" or "longer/greater" and begin to make up the content of the values found in reference memory. These altered reference memory values are then compared to current accumulator values derived from normal clock speed. The non-immediate nature of these shifts implicates changes in memory storage speed as the site of action.

Increases in acetylcholine via systemic physostigmine administration (Ach agonist which produces a carbamylated anticholinesterase enzyme that prevents the normal hydrolysis of Ach)

(Meck 1983; Meck & Church, 1987a) and choline nutrients (Meck & Church, 1987b) creates chronic leftward shifts indicating a decrease in the remembered times at reinforcement. Decreases in acetylcholine via systemic atropine administration (Ach antagonist) (Meck & Church, 1987a) and pyrithiamine (an antimetabolite of thiamine that inhibits Ach synthesis) (Meck & Angell, 1992) creates chronic rightward shifts indicating an increase in the remembered times at reinforcement, consistent with increases and decreases in memory storage speed respectively (Meck, 1983; Meck & Church, 1987a).

This view is supported by studies which have found that lesions of the fimbria-fornix in the hippocampus reduces the remembered time of reinforcement stored in reference memory and interferes with the internal control of information stored in working memory, while failing to affect sensitivity to stimulus duration (Meck et al., 1984; Meck, 1988). A group of rats were trained to discriminate between auditory signals whereby half of the rats were trained to discriminate between 2s or 8s and the remaining half were trained to discriminate between 2 or 16 cycles (Meck et al., 1984). Psychophysical functions were derived by presenting the rats with signals of intermediate duration and number following acquisition of these four extreme signal types. Half of the rats then received fimbria-fornix lesions and the remaining half received sham-lesions. Both operations decreased the PSE and permanently shifted the function, indicating a greater choice of responding to "long/many" and "shorter/lesser" numbers and durations. The same rats were then tested on a temporal peak procedure where the first response made following a 20s interval was reinforced. The rats with fimbria-fornix lesions had an earlier maximum response rate, exemplified as a leftward shift. This earlier maximum response

rate was earlier than the time of scheduled reinforcement (20s) which was the maximum response rate of rats with sham-lesions. Furthermore, when a 5s gap was placed into the peak procedure during the presentation of a signal, the normal rats stopped their clocks during the gap and summed the temporal signals before and after the gap. In contrast, the rats with fimbria-fornix lesions reset their clocks during the gap, evident by no retention of the temporal signal presented prior to the gap. This shows that values in the accumulator are only temporarily available following signal termination and that maintenance of this information requires an intact and functioning working memory. Thus, fimbria-fornix lesions impair temporal behaviour by disrupting the site and/or neurochemical integrity of working memory, evident in tasks where working memory is required (eg., the peak procedure). Taken as whole, these results show that fimbria-fornix lesions interfere with temporal memory. However, this interference is not accompanied by a disruption of sensitivity to time, evident through equivalent difference limens (DL) of the psychophysical functions relating the proportion of "long" responses to signal duration for normal and lesioned rats (Meck et al., 1984). The permanent leftward shifts found in the lesioned rats were interpreted as a decrease in memory storage speed rather than a change in clock speed because alterations in clock speed are accompanied by a relearning and rescaling of time, thus, preventing a permanent horizontal leftward shift (Meck, 1983). Rather, an increase in memory storage speed led to an underestimation of the remembered times of reinforcement evident by the permanent horizontal leftward shifts (Meck et al., 1984). It was concluded that fimbria-fornix lesions disrupt working memory, thus, produce impairments in temporal behaviour requiring working memory.

Berz, Battig, and Welzl (1992) provide results which they interpret as inconsistent with those of Meck and Church (1983). Rats were systemically administered with scopolamine hydrobromide dihydrate (a muscarinic cholinergic antagonist) and mecamylamine (a nicotinic cholinergic antagonist) in a temporal discrimination task. Pressing one lever was correct following a short light stimulus of 2s and pressing the alternate lever was correct following a long light stimulus of 8s. Rats injected with scopolamine reported both the short and the long stimulus as being shorter, suggesting that subjective time was slowed down assuming that the memory of the sample was not affected. Thus, when the 8s of the long stimulus was complete, the scopolamine-injected rats still had not counted the full 8s so that they considered the stimulus to be shorter than 8s. Mecamylamine similarly attenuated performance only when administered in high doses (8 mg/kg). Berz et al. (1992) interpret these results in terms of clock speed rather than as a memory effect. However, the possibility that the rats memory for the signals was affected in that the memory for the 8s signal had shortened under scopolamine administration is conceivable.

The representation of the internal clock/counter model by Meck and Church (1983) has again failed to account for the findings of subsequent research. For example, an inability to find any shifts in the psychophysical functions following decreases in acetylcholine with the same dose of atropine (0.45 mg/kg) in rats placed in a temporal bisection procedure with visual signals (Coppa, 1997a, unpublished). Instead, the atropine psychophysical functions were equal to saline baseline functions. These results do not replicate Meck and Church's (1983) results that cholinergic blockade via atropine increases the remembered duration at reinforcement and

decreases sensitivity to time by decreasing the rate with which values are transferred from working

memory to reference memory.

Acetylcholine and numerical processing

While the cholinergic modulation of timing via alterations in memory storage speed has been examined, the cholinergic modulation of numerical processing via alterations in memory storage speed has not. Pilot studies (Coppa 1997b, unpublished studies) involved placing rats into a numerical bisection procedure with visual signals under systemic atropine administration (0.15 & 0.45 mg/kg) using the same doses as Meck and Church (1987a). Again, there was no statistically significant movement in the psychophysical function, indicating that cholinergic blockade via atropine does not increase the remembered number of events at reinforcement by decreasing the rate with which values are transferred from working memory to reference memory. These results are inconsistent with those of Meck and Church (1987a). These same rats were placed into a concurrent numerical and temporal bisection procedure with visual signals following scopolamine (0.1 mg/kg) and physostigmine (0.15 mg/kg) administration. The results revealed no horizontal movements in the psychophysical function, only flattening indicative of decreased discrimination .

Attention and vigilance revisited

When examining the effects of physostigmine and scopolamine in rats in a temporal bisection procedure using both visual and auditory stimuli, it was found that two perceptual systems (subjective duration and loudness) were similarly affected (Shurtleff, Raslear, Genovese, &

Simmons, 1992). Physostigmine decreased discriminability without changing the bisection point while scopolamine also decreased discriminability but shortened the bisection point. This is inconsistent with the contentions of Meck and Church (1987a) who suggest that administration of a cholinergic antagonist shifts the bisection point rightward, or increases it. However, the antagonist used in the Meck and Church (1987a) study was atropine, positing the possibility that the difference in the results rests in the use of different cholinergic antagonists. This shows that these cholinergic agonists and antagonists affect perceptual processes regardless of sensory modality (Shurtleff et al., 1992). Therefore, the mode of stimulus representation does not alter the action of increasing or decreasing brain levels of acetylcholine upon temporal tasks.

Cholinergic-dopaminergic interactions

Hinton and Meck (1996) have examined the role of nicotine (nicotinic acetylcholine receptor agonist) administration upon the ability of rats to time short intervals. Rats were trained to discriminate 20s and 60s of auditory and visual signals and tested on the peak interval timing procedure for their ability to reproduce these durations. The results showed a significant horizontal leftward shift in the psychophysical timing functions (Hinton & Meck, 1996). This leftward shift occurred immediately following nicotine administration, it was renormalised on the second administration of nicotine, and it immediately shifted in the opposite direction to baseline levels when nicotine was withdrawn (Hinton & Meck, 1996). Here, rather than the cholinergic agonist nicotine producing a chronic leftward shift consistent with the "memory pattern" of interval timing, it produced a phasic leftward shift consistent with a dopaminergic "clock pattern". Hinton and Meck (1996) explain these results by stating that nicotine directly

stimulates the nigrostriatal dopamine system, thus, elicits increased dopamine efflux and parallels the effects of dopaminergic stimulants or agonists like methamphetamine. Hinton and Meck (1996) also state that because nicotinic receptors are functionally associated with D2 receptors, perhaps the nicotinic cholinergic receptor antagonist mecamylamine would yield temporal performance results comparable to those of the D1/D2 antagonist haloperidol. However, Berz et al. (1992) found that the administration of mecamylamine to rats in a temporal discrimination task attenuated performance only at high doses, suggesting the occurrence of nonspecific effects.

The nature of the neurochemical basis of temporal and numerical competence and functioning has met with mixed explanations, as has the underlying brain structures involved in these behavioural processes. Meck, Church, Wenk, and Olton (1987) hypothesized that the basal forebrain cholinergic system (BFChS) and certain limbic structures were integral to timing. Thus, rats were placed into a peak procedure following lesions of the medial septal area (MSA) and the fimbria fornix (FF) for the septo-hippocampal pathway (limbic structures), and the nucleus basalis magnocellularis (NBM) and the medial frontal cortex for the BFChS. The MSA and FF lesioned-animals expected the time of reinforcement to occur earlier, evidenced by a permanent leftward shift in their peak curves. Conversely, the NBM and medial frontal cortex lesioned-animals expected the time of reinforcement to occur later, evidenced by a permanent rightward shift in their peak curves and interpreted as a reference memory effect. Meck et al. (1987) thus, concluded that the frontal cortex was functionally similar to the NBM but different from the septo-hippocampal system, and that the BFChS and the septo-hippocampal system were

involved in timing behaviour.

However, the foundation which supports the Meck et al. (1987) study is oversimplified. Given that the neuroanatomy of the pre-frontal cortex (PFC) has recently been so elaborated, Dietrich, Frederick, and Allen (1997) wanted to use this new information to challenge the conclusion drawn by Meck et al. (1987). With regard to the temporal integration of behaviour, the PFC is thought to organize behaviour across time and provide a basis for a timing mechanism (Dietrich et al., 1997). It must be understood that the PFC exists amidst an array of interconnected pathways and nuclei that make the isolation of a singular timing mechanism questionable. Meck et al. (1987) based their experiment on the assumption that the septo-hippocampal and NBM-medial frontal pathways were two singular and isolated routes involved in timing behaviour. However, it is now known that these two routes are interconnected, they share projection sites, and the hippocampus innervates the PFC. The PFC is divided into: 1) the medial frontal cortex which receives input from the NBM and is thus rich in Ach, and 2) the ventral frontal cortex which receives input from the striate cortex and rostral areas of the ventral tegmental area (VTA) and is thus rich in DA. The PFC connects to the BFChS and to the limbic system (Dietrich et al., 1997). The basal forebrain nucleus of the BFChS receives afferent fibres from the PFC while the cholinergic fibres of the NBM projects to the PFC, particularly into the medial frontal cortex (Dietrich et al., 1997). The PFC also projects to the entorhinal and perirhinal cortical hippocampal inputs of the limbic system, which have efferent connections to the PFC in the medial frontal cortex (Dietrich et al., 1997). Due to all of this new information, Dietrich et al. (1997) tested whether subtotal PFC lesions impaired timing abilities in rats by

lesioning the medial frontal area and disrupting ACh concentration, and lesioning the ventral frontal area disrupting DA concentration. It was hypothesized that when in a peak procedure, medial lesions would result in chronic shifts due to the interruption of ACh, while ventral lesions would result in phasic shifts due to the interruption of DA. The results revealed no changes in the peak times with medial or ventral lesioned rats, showing that subtotal PFC lesions do not impair timing behaviour in rats. Following this, Dietrich et al. (1997) totally ablated the PFC and hypothesized that this lesion would impair the timing ability in rats evident by a shift in the peak curves. Consistent with Meck et al. (1987), the results supported the hypothesis that total PFC ablation disrupts timing ability evident by a chronic shift. However, unlike the chronic rightward shift apparent in the experiment of Meck et al. (1987), a chronic leftward shift in the peak curves indicative of a decrease in peak time was found. Dietrich et al. (1997) concluded that the amount of excised cortical tissue is related to the ability or inability to estimate the passage of time, so that rather than the ventral frontal or medial frontal area being involved in isolation, both are necessary for the accurate and complete behaviour of timing. Given that the PFC as a whole is thought to regulate temporal integration, perhaps certain subsections of the PFC contribute to timing in ways different to alternative subsections.

The preceding discussion clearly illustrates that the neurochemical and neuroanatomical mediation of the internal clock/counter model is not as simple as Meck and Church (1983) had originally proposed. General increases and decreases in the effective level of dopamine and acetylcholine seem to disrupt attentional processes, yet affect numerical and temporal processing when certain combinations of ACh and DA compounds are used. Thus, it is more likely that

specific dopaminergic and cholinergic manipulation will be more fruitful avenues of research, allowing us to pinpoint the drugs that do or do not manipulate numerical and temporal processing in rats.

Purpose of Present Study

The aim of this study is to use a concurrent numerical and temporal bisection procedure using drugs as research tools to elucidate the underlying psychopharmacological mechanisms of numerical and temporal processing in rats. Specifically, dopaminergic and cholinergic concentrations are manipulated and their effects upon numerical and temporal psychophysical functions was evaluated. The initial purpose is to increase the effective level of dopamine with the general dopaminergic agonist methamphetamine (Meck & Church, 1983) and the specific D2 agonist quinpirole (Stanford & Santi, in press) to see whether this leads to a phasic leftward shift in the psychophysical function and a decrease in the PSE for both number and time (Meck & Church, 1983) indicative of increased clock speed, or to a decrease in sample discriminability and sensitivity evident by a flattening of the psychophysical function (Lejeune et al., 1995; Stubbs & Thomas, 1974; Rapp & Robbins, 1976; Santi et al., 1995; Stanford & Santi, in press). Furthermore, because the effects of manipulating dopamine levels at D2 receptors has never been examined within a numerical task, it will be examined whether the effects of quinpirole in a temporal discrimination procedure are similar to the effects of quinpirole in a numerical discrimination procedure. It is hypothesized that increasing the level of dopamine will have the same effect on numerical processing as temporal processing.

Also, a concurrent numerical and temporal bisection procedure will be used to asses the

effect of decreasing the level of acetylcholine via administration of the cholinergic muscarinic receptor antagonist scopolamine (Shurtleff et al., 1992). It is hypothesized that decreasing the effective level of acetylcholine will lower sample discriminability and sensitivity evident by a flattening of the psychophysical function (Berz et al., 1992; Shurtleff et al., 1992; Coppa, 1997). Finally, the level of acetylcholine will be increased with the administration of the cholinergic nicotinic receptor agonist nicotine in an attempt to replicate the results of Hinton and Meck (1996) using a concurrent numerical and temporal bisection procedure (Meck & Church, 1983). It is hypothesized that increasing the effective level of acetylcholine with nicotine will increase the speed of the clock evident by a phasic horizontal leftward shift in the psychophysical function. The results from the temporal discrimination procedure will be compared to those from the numerical discrimination procedure, which has never been conducted before for cholinergic agents.

The results of this experiment will generate knowledge of the psychopharmacology of time and number perception in rats. Variations in performance following drug administration will be attributable to central changes in the dopamine and acetylcholine systems, indicating the importance of dopaminergic and cholinergic systems in the clock and memory stages of reinforcement.

Method

Participants

The participants were 24 experimentally naive male Long Evans rats (Charles River, Canada) approximately 225-267g in weight and 58-67 days in age when the experiment began. The rats

were individually housed in clear plexiglass shoebox cages in which water was continuously available. Fluorescent lights were illuminated on a 12 L:12 D (7am - 7pm) cycle in the colony room. The rats were food deprived to 85-90% of their ad libitum weight and at variable times were fed a daily ration of approximately 20g of Lab Diet for rodents (PMI Feeds).

Apparatus

Four Coulbourn modular operant test cages (Model E10-10) individually housed in isolation cubicles (Model E10-20) were used. Each cubicle was equipped with a ventilation fan and a baffled air intake exhaust system. The front wall of each chamber had two retractable levers (Model E23-07), approximately 3cm away from the grid floor of the cage and 14cm apart. Between the two levers there was a 45mg pellet feeder (Model E14-06) with an opening approximately 3cm from the floor of the chamber which allowed access to dustless precision pellets. A houselight (Coulbourn Model E11-01 with bulb #SL 1819X) was positioned 6.5cm above the pellet feeder with the light reflecting from the top of the cage. Each chamber was equipped with two 2.9-Khz tone module sonalerts (Model E12-02), each positioned approximately 10cm below the houselight. One was mounted directly above the left retractable lever, and the other directly above the right retractable lever. All events and subject responses were arranged and recorded by a microcomputer system located in the same room.

Procedure

Pretraining. Each rat first received 10-15 sessions of magazine and lever training. The houselight was continuously illuminated throughout all training sessions. Each session was comprised of 160 60-second trials in which the left or right lever was inserted into the chamber.

Responding to the available lever resulted in the immediate delivery of a food pellet which was accompanied by a 0.5s flash of light in the magazine, and the re-insertion of the left or right lever. The availability of the left or right lever was random with a probability of 0.5. During these sessions, a pellet of food was delivered at least once every 60 seconds.

Training. Four rats were tested at a time, and all rats were tested every day. Sound signals were produced by the simultaneous onset of both sonalerts (sound burst). There were two types of sound signals: count relevant and time relevant. In Figure 5 we can see a diagram of the training procedure. The count relevant signals were 4 seconds in duration and were either 2 or 8 cycles in number (2c/4s or 8c/4s). The time relevant signals were 4 cycles in number and were either 2 or 8 seconds in duration (4c/2s or 4c/8s). Half of the rats were trained to press the left lever following the 4c/2s and 2c/4s stimulus and to press the right lever following the 4c/8s and 8c/4s stimulus. The remaining half of the rats were trained with the opposite contingencies. The houselight was continuously illuminated throughout all sessions. Performing the correct response resulted in the delivery of a food pellet accompanied by a 0.5s flash of light in the magazine. If an incorrect response was made, no pellet was delivered and a correction procedure was initiated. The correction procedure consisted of a 5s delay prior to a re-presentation of the same signal. A correct response during a correction trial resulted in the delivery of a food pellet accompanied by a flash of light in the magazine and, the presentation of one of five intertrial intervals (ITI) (5, 10,15, 20, 25s), and initiation of the next trial.

The procedure was designed so that it would be impossible for the rats to use the duration of a single sound burst or the interval between two sound bursts to respond correctly. If the rats

were timing the duration of an individual sound burst, they could not differentiate the temporal signal of 4c/2s from the numerical signal of 8c/4s. This would be impossible because each individual sound burst has a duration of 0.25s, but each requires a different response for reinforcement to occur. More specifically, 4c/2s requires the left lever to be depressed to gain reinforcement while 8c/4s requires the right lever to be depressed to gain reinforcement. If the rats were timing the interval between sound bursts, they could not differentiate the temporal signal of 4c/8s from the numerical signal of 2c/4s. This would be impossible because each of these sequences has an inter-burst interval of 1s, but requires a different response for reinforcement to occur. More specifically, 4c/8s requires the right lever to be depressed to gain reinforcement while 2c/4s requires the left lever to be depressed to gain reinforcement.

Only the first response choice on each trial was included in the recorded data. Each session consisted of 160 trials (80 numerical trials and 80 temporal trials in random order) or was 120 minutes in length. This four-signal training continued until accuracy was at least 75% for numerical signals and 75% for temporal signals for all rats. The number of sessions needed to reach 75% accuracy varied for each rat. Four rats were eliminated from the study because they failed to reach 75% accuracy despite repeated sessions of training.

Testing with saline. The training conditions were maintained. All rats received saline testing for five daily sessions. Twenty minutes prior to each experimental session, all rats received an intraperitoneal (ip) injection of 0.9% physiological saline in a volume of 1 ml/kg. Each of the four extreme signals (2c/4s, 8c/4s, 4c/2s, and 4c/8s) were presented with a probability of 0.125 on each trial. On remaining trials, one of eight intermediate signals (3,4,5, or 6 cycles/seconds)

was presented, each with a probability of 0.0625 on each trial. There were two types of intermediate test signals: one set of signals held the number of cycles constant at 4 while varying total signal duration between 3 and 6 seconds; the other set of test signals held the total signal duration constant at 4s while varying the number of cycles between 3 and 6 cycles. See Figure 5 for a depiction of this procedure. On each trial, one signal was randomly presented and ITIs were variable and randomly presented. If the rat made a correct response following one of the four extreme signals a pellet of food was delivered. If the rat made an incorrect response following one of the four extreme signals, no pellet was delivered. Responses to the eight intermediate signals were unreinforced. There was no correction procedure. Each session consisted of 160 trials (80 numerical trials and 80 temporal trials) or 120 minutes in length. Each signal was randomly presented with the reinforced endpoints (2c/s and 8c/s) being presented 20 times per session, and the intermediate signals (3c/s, 4c/s, 5c/s, and 6c/s) being presented 10 times per session. A record was kept of the number of left and right responses following each of the two dimensional signals and the latency of each response. Each daily session began within 30 minutes of the same time each day.

Drug Testing. The conditions of saline testing were maintained. The rats were randomly assigned to three drug groups: methamphetamine (1.5 mg/kg) (Meck & Church, 1983), quinpirole (Research Biochemicals International, Natick, MA) (0.08 mg/kg) (Stanford & Santi, in press), and scopolamine (SIGMA) (0.1 mg/kg) (Shurtleff et al., 1992). Twenty minutes prior to each experimental session the rats received an ip injection of drug in a 0.9% saline vehicle in a volume of 1 ml/kg. Given that four rats were eliminated from the experiment due to poor

performance, the subject allocation across these three drug groups was counterbalanced, but not even in number. Six randomly assigned rats received methamphetamine (1.5 mg/kg) for 15 consecutive daily sessions, a separate six randomly assigned rats received scopolamine hydrobromide (0.1 mg/kg) for 15 consecutive daily sessions, and a separate eight randomly assigned rats received quinpirole hydrochloride (0.08 mg/kg) for 15 consecutive daily sessions. Upon completion of this, a pilot study was conducted. All 20 rats received saline for 5 daily sessions. Following this, all 20 rats received nicotine bitartrate (0.2 mg/kg) (Hinton & Meck, 1996) for six consecutive daily sessions, followed by saline for two daily sessions. The movement between saline and drug administration was always consecutive. The rats' mean percentage of "many" and "long" responding per session was following all injections was automatically recorded via a computer system.

Analyses

A data file was generated that included the date, rat, session, trial number, total number of trials presented in the session, sample presented, choice of many/long lever, and response latency for each trial. The number of responses to the lever associated with the many/long response and the total number of presentations of each sample were used to calculate the proportions required for the psychophysical functions. This was calculated because all rats did not complete all 160 trials within 120 minutes in each session. The psychophysical functions were calculated by plotting the percentage of "many" responding as a function of signal frequency for the number dimension, and the percentage of "long" responding as a function of signal duration for the time dimension. Points of subjective equality (PSE) were estimated from

the psychophysical functions for each rat by conducting linear regressions of the proportion of "many" and "long" responses for each of three adjacent signal frequencies (number dimension) and durations (time dimension). The regression equation with the greatest slope for each rat was used to estimate the PSE by calculating the signal frequency and duration associated with 50% of the "many" and "long" responses. The regression equations were also used to calculate difference limens (DL), which represent the average difference between the signal frequency and duration associated with 75% "many" and "long" responses and the signal frequency and duration associated with 25% "many" and "long" responses. The Weber fraction (WF) was calculated as DL/PSE. See Appendix A for details on sessions in which rats did not complete 160 trials within 120 minutes.

Results

Preliminary within-subjects repeated measures analyses of variance with two factors (signal: 2, 3, 4, 5, 6, and 8c/s; dimension: number and time) were conducted on all of the drug testing data: methamphetamine, quinpirole, scopolamine, and nicotine. These preliminary analyses were carried out in order to determine whether or not a significant difference in responding "many" or "long" occurred within blocks of the drug sessions. In other words, the drug testing sessions were divided into subunits and the proportion of "many/long" responding was compared between these subunits for methamphetamine, quinpirole, scopolamine, and nicotine. A significant difference between these subunits would indicate whether or not the occurrence of a phasic (immediate) or chronic (delayed) shift in the psychophysical function had occurred. The analyses for the methamphetamine group, the quinpirole group, and the scopolamine group

compared the 15 drug sessions in three blocks of five sessions each: block one was comprised of sessions 1-5, block two was comprised of sessions 6-10, and block three was comprised of sessions 11-15. The analysis for the nicotine testing compared the six drug sessions in two blocks of three sessions each: block one was comprised of sessions 1-3 and block two was comprised of sessions 4-6. These analyses revealed no significant effects of block [Fs<1]. Because there was no effect of block, each drug group was treated separately as a within-subjects repeated measures analyses of variance with three factors (signal: 2, 3, 4, 5, 6 and 8c/s; dimension: number and time; drug: pre-drug saline, drug, post-drug saline). Following these analyses, finer analyses with a partitioning of the three factors were conducted. All analyses were conducted with an alpha level of 0.05.

Methamphetamine (1.5 mg/kg)

The administration of methamphetamine did not affect the speed of the internal clock, but significantly reduced signal discriminability and accuracy. The graphs representing the numerical and temporal performance of the rats under methamphetamine administration are represented in Figure 6. The top portion of Figure 6 depicts variation in signal frequency while the lower portion of Figure 6 depicts variation in signal duration. The 15 days of methamphetamine administration are represented by the dashed function. It can be seen that the performance was better under temporal signals than for numerical signals, evident by a steeper psychophysical function for temporal stimuli. For both numerical and temporal signals, the probability of a "many" and "long" response significantly increased as a function of signal value. Performing an overall analysis on the pre-drug saline condition versus the methamphetamine

condition versus the post-drug saline condition revealed a significant main effect of signal [$F(5,25)=192.34$, $p<.001$] and drug [$F(2,10)=9.64$, $p<.01$], but no effect of dimension [$F<1$]. There was also a significant two-way interaction of dimension by signal [$F(5,25)=13.02$, $p<.001$] and drug by signal [$F(10, 50)=11.98$, $p<.001$], but no effect of dimension by drug or dimension by drug by signal [$Fs<1$].

Analyses of the rats' performance for each signal type (2, 3, 4, 5, 6, and 8c/s) was conducted. These ANOVAs revealed that the differences in the proportion of "many" and "long" responses between the pre-drug saline condition, the methamphetamine condition, and the post-drug saline condition showed a significant main effect of dimension at the reinforced endpoints: signal two [$F(1,5)=24.36$, $p<.005$] and eight [$F(1,5)=11.92$, $p<.05$]. These analyses also revealed a significant two-way interaction of dimension by drug for signal two [$F(2,10)=4.50$, $p<.05$].

An analysis collapsed across dimension revealed that the drug by signal interactions occurred as a result of a significant main effect of signal under the pre-drug saline condition [$F(5,25)=153.266$, $p<.001$], the methamphetamine condition [$F(5,25)=103.149$, $p<.001$], and the post-drug saline condition [$F(5,25)=41.29$, $p<.001$]. There was also a significant main effect of drug for signal two [$F(2,10)=8.00$, $p<.01$], four [$F(2,10)=8.42$, $p<.01$], five [$F(2,10)=11.73$, $p<.005$], six [$F(2,10)=37.84$, $p<.001$], and eight [$F(2,10)=18.43$, $p<.001$]. A separate analysis for the number and time dimension was undertaken in which the effect of drug condition was examined at each signal value. For number, there was a significant main effect of drug at the signal frequency of: two [$F(2,10)=4.83$, $p<.05$] where the rats made fewer "many" responses under the two saline conditions than under the methamphetamine condition; four [$F(2,10)=7.06$,

$p<.05$] where the rats made fewer "many" responses under the post-drug saline condition than under the pre-drug saline and methamphetamine conditions; six [$F(2,10)=29.13$, $p<.001$] where the rats made fewer "many" responses under the methamphetamine and post-drug saline conditions than under the pre-drug saline condition; and eight [$F(2,10)=8.52$, $p<.01$] where the rats made fewer "many" responses under the methamphetamine and post-drug saline conditions than under the pre-drug saline condition. For time, there was a significant main effect of drug at the signal duration of : two [$F(2,10)=11.21$, $p<.005$] where the rats made fewer "long" responses under the pre-drug saline condition than under the methamphetamine and post-drug saline conditions; five [$F(2,10)=12.57$, $p<.005$], six [$F(2,10)=12.16$, $p<.005$] and, eight [$F(2,10)=23.15$, $p<.001$] where the rats made fewer "long" responses under the methamphetamine and post-drug saline conditions than under the pre-drug saline condition. Further analyses of the pre-drug saline condition versus the methamphetamine condition, and the methamphetamine condition versus the post-drug saline condition can be seen in Appendix B.

The mean PSEs for the numerical and temporal dimension for the pre-drug saline, methamphetamine, and post-drug saline conditions can be seen in Table 1 at the end of the results section. Immediate increases in the PSE value would be indicative of a decrease in the speed of the clock, whereas immediate decreases in the PSE value would be indicative of an increase in the speed of the clock. For number, the pre-drug saline and methamphetamine PSE were not significantly different from the geometric mean of 4.00, while the post-drug saline PSE was significantly different from the geometric mean of 4.00 [$t(5)=+7.76$, $p<.05$]. For time, the pre-drug saline PSE was not significantly different form the geometric mean, while the

methamphetamine and post-drug-saline PSEs were [$t(5)=+3.02$, $p<.05$; $t(5)=+6.81$, $p<.05$].

An overall analysis of the PSE data comparing the pre-drug saline condition and the methamphetamine condition and the post-drug saline condition revealed a significant main effect of drug [$F(2,10)=8.05$, $p<.01$], but no effect of dimension or dimension by drug [$Fs<1$]. This significant drug effect occurred as a result of the PSE increasing from the pre-drug saline condition, to the drug condition, to the post-drug saline condition for both the number and time dimension. A Tukey's post-hoc test was performed which revealed no significant difference between the pre-drug saline and methamphetamine condition or the methamphetamine and post-drug saline condition. Rather, the overall significant main effect of drug was attributable to a significant difference between the pre-drug saline and post-drug saline conditions [$F(1,5)=10.00$, $p<.05$], without an effect of dimension or dimension by drug [$Fs<1$].

The DL was calculated to give an indication of the rats' ability to discriminate the range of samples they were presented with. The lower the DL values, the better the rats were in discriminating the range of samples presented; the higher the DL values, the worse the rats were in discriminating the range of samples presented. The mean DLs for the numerical and temporal dimension for the pre-drug saline, methamphetamine, and post-drug saline conditions can be seen in Table 1 at the end of the results section. In general, the mean DL was lower for time in all three drug conditions, indicating that the rats showed better discriminability of the temporal samples than the numerical samples. An overall analysis of the DL data comparing the pre-drug saline condition and the methamphetamine condition and the post-drug saline condition revealed a significant main effect of dimension [$F(1,5)=20.93$, $p<.01$] and drug [$F(2,10)=9.58$, $p<.01$], but

no effect of dimension by drug [F<1]. Tukey's post-hoc tests revealed a significant difference between the pre-drug saline and methamphetamine condition ($p<.05$). This significant drug effect was indicative of a significant increase in the DL from the pre-drug saline condition to the methamphetamine condition for both the number and time dimension, indicative of a decrease in sample discriminability and sensitivity under methamphetamine. The significant main effects of dimension occurred because the rats displayed an overall greater sensitivity to temporal samples than to numerical samples.

The WF was used to determine the rats' ability to discriminate differences over a range of samples in the modality used (ie: auditory). The lower the WF values, the better the rats were in discriminating the samples presented; the higher the WF values, the worse the rats were in discriminating the samples presented. The mean WFS for the numerical and temporal dimension for the pre-drug saline, methamphetamine, and post-drug saline conditions can be seen in Table 1 at the end of the results section. In general, the mean WF was lower for time in all three drug conditions, indicating better discriminability for temporal samples than for numerical samples. An overall analysis of the pre-drug saline condition versus the methamphetamine condition versus the post-saline condition revealed results akin to those of the DL. There was a significant main effect of dimension [$F(1,5)=9.48$, $p<.05$] and drug [$F(2,10)=7.25$, $p=.05$], but no effect of dimension by drug [F<1]. A Tukey's post-hoc test revealed a significant difference between the pre-drug saline and methamphetamine condition, and the methamphetamine and post-drug saline condition ($p<.05$). These significant drug effects are indicative of a significant increase in the WF from the pre-drug saline condition to the

methamphetamine condition indicating a decrease in sample discriminability under the methamphetamine condition, and of a significant decrease in the WF from the methamphetamine condition to the post-drug saline condition indicating an increase in sample discriminability, or recovery, in the post-drug saline condition. These comparisons show that the overall significant main effect of drug was due to an additive significant difference between the pre-drug saline condition and the methamphetamine condition, as well as the methamphetamine condition and the post-drug saline condition. The significant main effect of dimension occurred because the rats displayed an overall greater sensitivity to temporal samples than to numerical samples.

These analyses indicate that methamphetamine affected the quality of the numerical and temporal discriminations (DLs and WFS) without selectively increasing the speed of the internal clock (ie: lowering the PSEs).

Quinpirole (0.08 mg/kg)

The administration of quinpirole did not affect the speed of the clock, but significantly reduced sample discriminability and accuracy. The graphs representing the numerical and temporal performance of the rats under quinpirole administration are represented in Figure 7. The top portion of Figure 7 depicts variation in signal frequency while the lower portion of Figure 7 depicts variation in signal duration. The 15 days of quinpirole administration are represented by the dashed function. It can be seen that the performance was better under temporal signals than for numerical signals, evident by a steeper psychophysical function for temporal stimuli. For both numerical and temporal signals, the probability of a "many" and

"long" response significantly increased as a function of signal value.

Performing an overall analysis on the pre-drug saline condition versus the quinpirole condition versus the post-drug saline condition revealed a significant main effect of dimension [$F(1,7)=6.00$, $p<.05$], drug [$F(2,14)=9.37$, $p<.005$], and signal [$F(5,35)=41.94$, $p<.001$]. There was also a significant two-way interaction of dimension by signal [$F(5,35)=26.74$, $p<.001$] and drug by signal [$F(10,70)=19.29$, $p<.001$], but no effect of dimension by drug or dimension by drug by signal [$Fs<1$].

Analyses of the rats' performance collapsed across the three drug conditions for each signal type was conducted. These analyses revealed that the differences in the proportion of "many" and "long" responses between the pre-drug saline condition, the quinpirole condition, and the post-drug saline condition showed a significant main effect of dimension for signal two [$F(1,7)=12.47$, $p<.05$], three [$F(1,7)=25.39$, $p<.005$], five [$F(1,7)=9.63$, $p<.05$], six [$F(1,7)=30.30$, $p<.005$], and eight [$F(1,7)=24.45$, $p<.005$]. There were no dimension by drug interactions [$Fs<1$].

An analysis collapsed across dimension revealed that the drug by signal interactions occurred as a result of a significant main effect of signal under the pre-drug saline condition [$F(5,35)=119.34$, $p<.001$], the quinpirole condition [$F(5,35)=10.78$, $p<.001$], and the post-drug saline condition [$F(5,35)=17.70$, $p<.001$]. There was also a significant main effect of drug for signal two [$F(2,14)=11.37$, $p<.005$], four [$F(2,14)=4.82$, $p<.05$], five [$F(2,14)=21.25$, $p<.001$], six [$F(2,14)=27.27$, $p<.001$], and eight [$F(2,14)=48.20$, $p<.001$] A separate analysis for the number and time dimension was undertaken in which the effect of drug condition was examined at each

signal value. For number, there was a significant main effect of drug at the signal frequency of: two [$F(2,14)=6.17$, $p<.05$] where the rats made fewer "many" responses under the pre-drug saline condition than under the quinpirole and post-drug saline conditions; four [$F(2,14)=5.27$, $p<.05$], five [$F(2,14)=8.72$, $p<.005$], six [$F(2,14)=10.80$, $p<.005$], and eight [$F(2,14)=21.72$, $p<.001$] where the rats made fewer "many" responses under the quinpirole condition than under the two saline conditions. For time, there was a significant main effect of drug at the signal duration of: two [$F(2,14)=16.34$, $p<.001$] where the rats made fewer "long" responses under the pre-drug saline condition than under the quinpirole and post-drug saline conditions; five [$F(2,14)=26.23$, $p<.001$], six [$F(2,14)=23.02$, $p<.001$], and eight [$F(2,14)=28.96$, $p<.001$] where the rats made fewer "long" responses under the quinpirole condition than under the two saline conditions. Further analyses of the pre-drug saline condition versus the quinpirole condition, and the quinpirole condition and the post-drug saline condition can be seen in Appendix B.

Quinpirole lowered the accuracy of the rats' numerical discrimination such that they rarely completed 160 sessions within 120 minutes, and their level of accuracy dropped to 50-60%. Thus, for six of the eight rats it was not meaningful to estimate PSEs, DLs, and WFS, and their data for the number dimension was removed. Due to this, the numerical PSE, DL, and WF mean values are based on two subjects and no statistical tests for the number dimension were conducted. On the other hand, the data for the time dimension was based on all eight subjects and statistical tests were conducted on this data. The mean PSEs for the number and time dimension for the pre-drug saline, quinpirole, and post-drug saline condition can be seen in Table 1 at the end of the results section. For time, none of the PSEs were significantly different

from the geometric mean. For time an overall analysis of the PSE data comparing the pre-drug saline condition and the quinpirole condition and the post-drug saline condition revealed no significant effects [Fs<1].

The mean DLs for the number and time dimension for the pre-drug saline, quinpirole, and post-drug saline condition can be seen in Table 1 at the end of the results section. The mean DL value increased from the pre-drug saline condition to the quinpirole condition, indicative decreased sample discriminability under quinpirole. The mean DL decreased from the quinpirole condition to the post-drug saline condition, indicative of increased sample discriminability, or recovery, in the post-drug saline condition. An overall analysis of the DL data comparing the pre-drug saline condition and the quinpirole condition and the post-drug saline condition revealed a significant main effect of drug [$F(2,12)=29.60$, $p<.001$], indicative of a significant change in discriminability for temporal samples, seen by an increase then a decrease in the DL.

The mean WFS for the number and time dimension for the pre-drug saline, quinpirole, and post-drug saline condition can be seen in Table 1 at the end of the results section.. The mean WF value increased from the pre-drug saline condition to the quinpirole condition, indicative of a decrease in sample discriminability. The mean WF value decreased from the quinpirole condition to the post-drug saline condition, indicative of better sample discriminability, or recovery, in the post-saline drug condition. Analyses of the WF data revealed results akin to those of the DL. An overall analysis of the WF data comparing the pre-drug saline condition and the quinpirole condition and the post-drug saline condition collapsed across dimension revealed

no significant effects [Fs<1]. A temporal analysis revealed a significant main effect of drug [F(2,12)=5.94, p<.05], indicative of a significant change in discriminability for temporal samples Number and Timeseen by an increase then a decrease in the WF.

These analyses indicate that quinpirole affected the quality of both the numerical and temporal discriminations (DLs and WFS) without selectively increasing the speed of the internal clock (ie: lowering the PSEs).

Scopolamine (0.1 mg/kg)

The administration of scopolamine did not affect the memory components of the clock, but significantly reduced sample discriminability an accuracy. The graphs representing the numerical and temporal performance of the rats under scopolamine administration are represented in Figure 8. The top portion of Figure 8 depicts variation in signal frequency while the lower portion of Figure 8 depicts variation in signal duration. The 15 days of scopolamine administration are represented by the dashed function. It can be seen that the performance was better under temporal signals than for numerical signals, evident by a steeper psychophysical function for temporal stimuli. For both numerical and temporal signals, the probability of a "many" and "long" response significantly increased as a function of signal value. Performing an overall analysis of the pre-drug saline condition versus the scopolamine condition versus the post-drug saline condition revealed a significant main effect of drug [F(2,10)=6.33, p<.05] and signal [F(5,25)=267.06, p<.001], but no effect of dimension [F<1]. There was also a significant two-way interaction of dimension by signal [F(5,25)=23.97, p<.001] and drug by signal [F(10,50)=4.88, p<.001], but no effect of dimension by drug or dimension by drug by signal

[$F<1$].

Analyses of the rats' performance for each signal type was conducted. These analyses revealed that the differences in the proportion of "many" and "long" responses between the pre-drug saline condition, the scopolamine condition, and the post-drug saline condition showed a significant main effect of dimension for signal two [$F(1,5)=76.62$, $p<.001$], three [$F(1,5)=12.02$, $p<.05$], five [$F(1,5)=25.75$, $p<.005$], six [$F(1,5)=18.67$, $p<.01$], and eight [$F(1,5)=24.41$, $p<.005$]. There were no effects of dimension by drug [$Fs<1$].

An analysis revealed a significant main effect of drug for signal five [$F(2,10)=5.68$, $p<.05$], six [$F(2,10)=7.32$, $p<.05$], and eight [$F(2,10)=5.81$, $p<.05$]. A separate analysis for the number and time dimension was undertaken in which the effect of drug condition was examined at each signal value. For number, there was a significant main effect of drug for signal eight [$F(2,10)=4.60$, $p<.05$], where the rats made fewer "many" responses under the scopolamine and post-saline conditions than under the pre-drug saline condition. For time, there was a significant main effect of drug for signal: five [$F(2,10)=8.96$, $p<.01$], six [$F(2,10)=10.19$, $p<.005$], and eight [$F(2,10)=6.14$, $p<.05$], where the rats made fewer "long" responses under the scopolamine and post-drug saline conditions than under the pre-drug saline condition. Further analyses of the pre-drug saline condition versus the scopolamine condition, and the scopolamine condition versus the post-drug saline condition can be seen in Appendix B.

Scopolamine disrupted the accuracy of the number discrimination whereby responding "many" was below 50% at eight cycles so that for one of the six rats it was not meaningful to estimate the point of subjective equality. The mean PSEs for the number and time dimension for

the pre-drug saline, scopolamine, and post-drug saline conditions can be seen in Table 1 at the end of the results section. Although the PSEs for number and time were slightly higher under each subsequent drug condition (except from the scopolamine condition to the post-drug saline condition for the temporal dimension), none of these differences were statistically significant. For number, the pre-drug saline PSE was not statistically different from the geometric mean, while the scopolamine and post-drug saline PSEs were ($t(4)=+3.82$, $p<.05$ and $t(4)=+6.94$, $p<.05$) For time, the pre-drug saline and post-drug saline PSEs were not statistically different from the geometric mean, while the scopolamine PSE was ($t(4)=+3.95$, $p<.05$.

An overall analysis of the PSE data comparing the pre-drug saline condition and the scopolamine condition and the post-drug saline condition revealed no significant effects [Fs<1]. Given that one subject was removed from the number dimension, a separate analysis of the number dimension and time dimension collapsed across drug condition was performed, both to reveal no significant effects [Fs<1].

Difference limens were eliminated for the same subject in the numerical portion of the data as the PSE data set. The mean DLs for the number and time dimension for the pre-drug saline, scopolamine, and post-drug saline conditions can be seen in Table 1 at the end of the results section. The mean temporal DL values were lower for time than for number in all three drug conditions. An overall analysis of the DL data comparing the pre-drug saline condition and the scopolamine condition and the post-drug saline condition revealed a significant main effect of dimension [$F(1,4)=20.40$, $p<.05$] and drug [$F(2,8)=5.15$, $p<.05$], but no effect of dimension by drug [$F<1$]. Tukey's post-hoc tests revealed a significant difference between the pre-drug saline

and scopolamine condition ($p<.05$). This significant effect of drug is indicative of a significant increase in the DL from the pre-drug saline condition to the scopolamine condition for both the number and time dimension, illustrating a decrease in sample discriminability under scopolamine. Given that one subject was removed from the number dimension, a separate analysis of the number dimension and time dimension collapsed across drug condition was performed. While the numerical analysis revealed no significant effect of drug [$F<1$], the temporal analysis revealed a significant main effect of drug [$F(2,10)=8.01$, $p<.01$].

Weber fractions were eliminated for the same subject in the numerical portion of the data as the PSE and DL data. The mean WFS for the number and time dimension for the pre-drug saline, scopolamine, and post-drug saline conditions can be seen in Table 1 at the end of the results section. The mean WF value increased slightly from the scopolamine condition to the post-drug saline condition for number, but decreased from the scopolamine condition to the post-drug saline condition for time. An analysis of the WF data revealed results akin to those of the DL. An overall analysis of the WF data comparing the pre-drug saline condition and the scopolamine condition and the post-drug saline condition revealed a significant main effect of dimension [$F(1,4)=26.34$, $p<.01$] and drug [$F(2,8)=5.70$, $p<.05$], but no effect of dimension by drug [$F<1$]. Tukey's post-hoc tests revealed a significant difference between the pre-drug saline and scopolamine condition ($p<.05$). Thus, the overall significant main effect of drug was indicative of a significant increase in the WF from the pre-drug saline condition to the scopolamine condition for both number and time, illustrating a decrease in sample discriminability under scopolamine. Given that one subject was removed from the number

dimension, a separate analysis of the number dimension and time dimension was performed. While the numerical analysis revealed no significant effect of drug [$F<1$], the temporal analysis did [$F(2,10)=14.69$, $p<.005$]. This significant drug effect is indicative of a significant change in discriminability for temporal samples, seen as an increase then a decrease in the WF.

These analyses indicate that scopolamine affected the quality of the numerical and temporal discriminations (DLs and WFS) without selectively manipulating the memory components of the internal clock.

Nicotine (0.2 mg/kg)

The administration of nicotine did not increase the speed of the clock. Rather, the results suggest that nicotine reduced the speed of the clock. The graphs representing the numerical and temporal performance of the rats under nicotine administration are represented in Figure 9. The top portion of Figure 9 depicts variation in signal frequency while the lower portion of Figure 9 depicts variation in signal duration. The 6 days of nicotine administration are represented by the dashed function. It can be seen that the performance was better under temporal signals than for numerical signals, evident by a steeper psychophysical function for temporal stimuli. For both numerical and temporal signals, the probability of a "many" and "long" response significantly increased as a function of signal value. Performing and overall analysis on the pre-drug saline condition versus the nicotine condition versus the post-drug saline condition revealed a significant main effect of drug [$F(2,38)=12.87$, $p<.001$] and signal [$F(5,95)=159.40$, $p<.001$], but no effect of dimension [$F<1$]. There was also a significant two-way interaction of dimension by drug [$F(2,38)=3.69$, $p<.05$], dimension by signal [$F(5,95)=22.95$, $p<.001$], and drug by signal

[F(10,190)=7.04, p<.001], but no effect of dimension by drug by signal [F<1].

Analyses of the rats' performance collapsed across the three drug conditions for each signal type was conducted. These analyses revealed that the differences in the proportion of "many" and "long" responses between the pre-drug saline condition, the nicotine condition, and the post-drug saline condition showed a significant main effect of dimension for signal two [F(1,19)=46.11, p<.001], three [F(1,19)=16.37, p<.005], five [F(1,19)=13.51, p<.005], six [F(1,19)=26.55, p<.001], and eight [F(1,19)=43.10, p<.001].

An analysis collapsed across dimension revealed that the drug by signal interactions occurred as a result of a significant main effect of signal under the pre-drug saline condition [F(5,95)=132.14, p<.001], the nicotine condition [F(5,95)=88.35, p<.001], and the post-drug saline condition [F(5,95)=78.35, p<.001]. There was a significant main effect of drug for signal four [F(2,38)=38.97, p<.001], five [F(2,38)=12.46, p<.001], and six [F(2,38)=5.23, p<.05], and a significant two-way interaction of dimension by drug for signal two [F(2,38)=7.44, p<.005]. A separate analysis for the number and time dimension was conducted in which the effect of drug condition was examined at each signal value. For number, there was a significant main effect of drug at the signal frequency of: two [F(2,38)=4.01, p<.05], where the rats made fewer "many" responses under the post-drug saline condition than under the pre-drug saline or nicotine conditions; four [F(2,38)=24.64, p<.001] and five [F(2,38)=4.10, p<.05], where the rats made fewer "many" responses under the nicotine condition than under the pre-drug saline or post-drug saline conditions. For time, there was a significant main effect of drug at the signal duration of: four [F(2,38)=16.11, p<.001], five [F(2,38)=11.28, p<.001], and six [F(2,38)=5.55, p<.01], where

the rats made fewer "long" responses under the nicotine condition than under the pre-drug saline and post-drug saline conditions.

The dimension by drug interactions occurred because the rats showed better discrimination of temporal samples than numerical samples in all three drug conditions. An analysis collapsed across signals for the number data revealed a significant main effect of drug [$F(2,38)=15.19$, $p<.001$]. For number, a pre-drug saline versus nicotine ANOVA revealed a significant drug effect [$F(1,19)=8.50$, $p<.01$]. The nicotine versus post-drug saline ANOVA revealed no effect. The pre-drug saline versus post-drug saline ANOVA also revealed a significant effect of drug [$F(1,19)=15.34$, $p<.01$]. For time, a pre-drug saline versus nicotine ANOVA revealed a significant drug effect [$F(1,19)=23.70$, $p<.001$]. The nicotine versus post-drug saline ANOVA revealed a significant effect of drug [$F(1,19)=6.21$, $p<.05$]. The pre-drug saline versus post-drug saline test was also significant [$F(1,19)=16.01$, $p<.005$]. Further analyses of the pre-drug saline condition versus the nicotine condition, and the nicotine condition versus the post-drug saline condition can be seen in Appendix B.

Nicotine disrupted the accuracy of the number discrimination so that for one of the 20 rats it was not meaningful to estimate points of subjective equality. The mean PSEs for the number and time dimension for the pre-drug saline, nicotine, and post-drug saline conditions can be seen in Table 1 at the end of the results section. The numerical pre-drug saline PSE was slightly above the geometric mean while the temporal pre-drug saline PSE was at the geometric mean. Although the PSEs for number and time were slightly higher under nicotine than under the saline conditions, none of these differences were statistically significant. For number, the pre-drug

saline, nicotine, and post-drug saline PSEs were all significantly different from the geometric mean [$t(18)=+2.60$, $p<.05$; $t(18)=+32$, $p<.05$; and $t(18)=+15.20$, $p<.05$]. For time, the nicotine and post-drug saline PSEs were significantly different from the geometric mean [$t(18)=+34$, $p<.05$ and $t(18)=+9.80$, $p<.05$], while the pre-drug saline PSE was not.

An overall analysis of the PSE data comparing the pre-drug saline condition and the nicotine condition and the post-drug saline condition revealed a significant main effect of drug [$F(2,36)=15.73$, $p<.001$], but no effect of dimension or dimension by drug [$Fs<1$]. Tukey's post-hoc tests were performed which revealed a significant difference between the pre-drug saline and nicotine condition ($p<.01$), as well as between nicotine condition and the post-drug saline condition ($p<.05$). These analyses indicate that the overall significant main effect of drug was due to an additive significant difference between the pre-drug saline condition and the nicotine condition, as well as between the nicotine condition and the post-drug saline condition. This significant effect occurred as a result of the PSE increasing from the pre-drug saline condition to the nicotine condition, and decreasing from the nicotine condition to the post-drug saline condition. Given that one subject was removed from the numerical portion of the data, a separate analysis of the number dimension and time dimension collapsed across drug condition was performed. Both the numerical [$F(2,36)=11.29$, $p<.001$] and temporal [$F(2,38)=14.17$, $p<.001$] analyses revealed a significant main effect of drug. This significant drug effect is indicative of a significant change in discriminability for temporal samples, seen as an increase then a decrease in the PSE.

Difference limens were eliminated for the same subject in the numerical portion of the data

as the PSE data set. The mean DLs for the number and time dimension for the pre-drug saline, nicotine, and post-drug saline conditions can be seen in Table 1 at the end of the results section. In general, the DL changed in the same direction for both the numerical and temporal dimension. The DL increased from the pre-drug saline condition to the nicotine condition, and decreased from the nicotine condition to the post-drug saline condition. The DL was lower for time than for number in all three drug conditions, indicative of better sample discriminability with temporal samples. An overall analysis of the DL data comparing the pre-drug saline condition and the nicotine condition and the post-drug saline condition revealed a significant main effect of dimension [$F(1,18)=30.12$, $p<.001$] and drug [$F(2,36)=4.96$, $p<.05$]. There was also a significant two-way interaction of dimension by drug [$F(2,36)=4.67$, $p<.05$]. Tukey's post-hoc tests revealed a significant difference between the pre-drug saline and nicotine condition ($p<.05$). The mean DL value increased from the pre-drug saline condition to the nicotine condition for both number and time, indicative of a decrease in sample discriminability under nicotine. While not significant, the mean DL value decreased from the nicotine condition to the post-drug saline condition for both number and time, indicative of an increase in sample discriminability, or recovery, in the post-drug saline condition. The significant main effects of dimension occurred because the rats displayed an overall greater sensitivity to temporal samples than to numerical samples. Given that one subject was removed from the number dimension, a separate analysis of the number dimension and time dimension collapsed across drug condition was performed. While the temporal analysis revealed no significant main effect of drug [$F<1$],the numerical analysis did [$F(2,36)=8.08$, $p<.005$]. This significant drug effect is

indicative of a significant change in discriminability for numerical samples.

Weber fractions were eliminated for the same subject in the numerical portion of the data as the PSE and DL data set. The mean WFS for the number and time dimension for the pre-drug saline, nicotine, and post-drug saline conditions can be seen in Table 1 at the end of the results section. In general, for the numerical dimension, the WF increased from the pre-drug saline condition to the nicotine condition, and decreased from the nicotine condition to the post-drug saline condition. The opposite occurred in the temporal dimension where the WF decreased from the pre-drug saline condition to the nicotine condition, and increased from the nicotine to the post-drug saline condition. An overall analysis of the WF data comparing the pre-drug saline condition and the nicotine condition and the post-drug saline condition revealed a significant main effect of dimension [$F(1,18)=24.54$, $p<.001$], but no effect of drug or dimension by drug [$F<1$]. The significant main effects of dimension occurred because the rats displayed an overall greater sensitivity to temporal samples than to numerical samples. Given that one subject was removed from the number dimension, a separate analysis of the number dimension and time dimension collapsed across drug condition was performed. There was no significant main effect of drug for either the numerical or temporal dimension [$F<1$].

These analyses indicate that nicotine affected the quality of the numerical and temporal discriminations (DLs and WFS) and also decreased the speed of the internal clock (ie: increasing the PSEs).

Summary

Methamphetamine (1.5 mg/kg), Quinpirole (0.08 mg/kg), and Scopolamine (0.1 mg/kg)

The control by temporal samples was greater than the control by numerical samples under all drugs. This was evident by a sharper psychophysical function for temporal discriminations, including greater accuracy. The methamphetamine, quinpirole, and scopolamine psychophysical functions immediately and significantly flattened in comparison to the saline conditions. This was supported by increases in the DL and WF under drug administration. For methamphetamine and quinpirole, this was evident by an increase in "many/long" responding at "fewer" numbers and "shorter" durations, and a decrease in "many/long" responding at "greater" numbers and "longer" durations. For scopolamine, this was evident by an decrease in "many/long" responding at "greater" numbers and "longer" durations. This flattening of the functions suggests that a loss of sample discriminability and accuracy occurred, rather than an effect on the speed or the memory components of the internal clock/counter.

Nicotine (0.2 mg/kg)

The control by temporal samples was greater than the control by numerical samples. This was evident by a sharper psychophysical function for temporal discriminations, including greater accuracy. With nicotine administration, the position of the function at 2 c/s and 8 c/s reinforced endpoints did not change between the three drug conditions for temporal samples, and did not change at the 8c/s endpoint for numerical samples. Rather, the intermediate unreinforced signals immediately, significantly, and horizontally shifted to the right for both number and time. This rightward shift was supported by a significant increase in the PSE under nicotine administration. Post-drug saline testing resulted in a large degree of recovery to pre-drug saline levels, evident by a horizontal leftward shift in the psychophysical function. This

leftward shift was supported by a significant decrease in the PSE under post-drug saline testing. The initial immediate rightward horizontal shift in the psychophysical function suggests that nicotine administration decreased the speed of the internal clock/counter.

Table 1
Numerical and temporal PSEs, DLs, and WFS for the three drug conditions for each drug group

DRUG	# PSE	Time PSE	# DL	Time DL	# WF	Time WF
Met Pre	3.85	4.0	1.53	1.04	.39	.25
Drug	4.02	4.35*	2.96	2.16	.74	.48
Post	4.90*	4.79*	2.48	1.47	.52	.30
Quin+ Pre	3.31	3.78	1.05	.93	.31	.24
Drug	4.86	4.57	2.78	2.12	.57	.52
Post	3.92	4.06	1.36	1.25	.34	.31
Scop~ Pre	3.82	3.80	1.42	.88	.37	.22
Drug	4.60*	4.62*	2.53	1.73	.55	.36
Post	5.09*	4.49	2.96	1.33	.56	.28
Nic~ Pre	4.13*	4.01	1.40	.99	.34	.25
Drug	5.60*	5.70*	2.01	1.32	.35	.24
Post	4.76*	4.49*	1.55	1.31	.32	.28

PSE: point of subjective equality - point of indifference where subjects choose "few/short" as much as they do "many/long"

DL: difference limen - ½ (75% signals + 25% signals); increasing DL values represent decreasing discriminability, and vice versa

WF: Weber fraction - DL/PSE; increasing WF values represent decreasing discriminability in the modality used (auditory), and vice versa

+: The numerical discrimination was lowered so severely with the use of quinpirole so that for this dimension the PSE, DL, and WF were calculated only with 2 out of 8 rats.

~: The numerical discrimination was lowered with the use of scopolamine and nicotine so that for this dimension the PSE, DL, and WF were calculated only with 5 out of 6 subjects for scopolamine, and 19 out of 20 rats for nicotine

*: significantly different from the geometric mean of 4.0 ($p<.05$)

Discussion

Numerical and Temporal Processing

An important contribution of the current study is the finding that numerical and temporal auditory stimuli are not processed equally or to the same degree by rats placed in a bisection procedure. While Meck and Church (1983) found that rats' psychophysical classification of number and time was equivalent, the current study did not. Rather, this study bore data similar to that of Breukelaar and Dalrymple-Alford (1998), who found that rats placed in an identical procedure to that of Meck and Church (1983) gained strong control of responding via auditory temporal cues while control by numerical cues was weak. Perhaps temporal information is processed first, therefore, the processing of numerical information occurs later. Thus, numerical information may be processed through a system more suited to the processing of temporal information, leaving numerical processing subject to the processing of temporal information.

The probability of responding "many" and "long" significantly increased as a function of signal value for both number and time, resulting in an ogival psychophysical function for both dimensions. However, the sharpness of the psychophysical function was greater for the temporal function than for the numerical function in all drug conditions (pre-drug saline, drug, post-drug saline). This supports the conclusion that the rats were better able, or preferred, to use temporal attributes for choice responding than numerical attributes in order to gain reinforcement. The difference limen (DL) and Weber fraction (WF) measures of sample discriminability attest to this. Overall, the DLs and WFS were lower for numerical samples than for temporal samples in all conditions. These lower DL and WF values for the numerical dimension reveal that the rats

had poorer discrimination and sensitivity to numerical cues in comparison to temporal cues. While the temporal DLs and WFs decreased in saline trials following drug administration in all conditions, sometimes the numerical DLs and WFs increased in saline trials following drug administration. Perhaps this was due to a general loss of attention that occurred with the administration of drug, requiring that the rats relearn the paradigm in order to reach their previous pre-drug saline level.

The point of subjective equality (PSE) was not significantly different between number and time in all drug conditions. Because Meck and Church (1983) reported strong and equivalent control of both numerical and temporal cues, they suggested that both dimensions are processed equivalently by an internal clock/counter with the use of variable number and time switch mechanisms. This internal clock/counter has a pacemaker, accumulator, working memory storage area, reference memory storage area, and comparator. This mechanism was elaborated by Roberts and Mitchell (1994) to contain two separate accumulators and working memory storage areas for numerical and temporal information because subjects showed selective retrieval of information from each dimension. Given that the current experiment showed that both numerical and temporal information can guide and regulate the choice behaviour of animals, but that temporal cues do so to a greater degree and to a higher level of accuracy, necessitates further elaboration of the internal clock/counter mechanism.

Like the results reported by Breukelaar and Dalrymple-Alford (1998), while control by numerical and temporal cues differed in terms of strength, the manner of processing numerical and temporal cues was similar. This shows that both types of cues are processed by the same

internal mechanism, but that primary control is relegated to temporal cues. The performance of the rats show that rather than processing numerical stimuli as effectively as temporal stimuli, responding amidst numerical information is error-ridden and faulty. Thus, when accordance to numerical information occurs it is processed via the same mechanism as temporal information, but more poorly.

Methamphetamine and Quinpirole and the Internal Clock/Counter Model

A replication of one experiment from the Meck and Church (1983) study was conducted. In the Meck and Church (1983) study, rats were trained on a bisection procedure with concurrent numerical and temporal stimuli and administered with the general dopaminergic agonist methamphetamine (1.5 mg/kg). The rats showed a phasic horizontal leftward shift in both the numerical and temporal functions under methamphetamine in comparison to the baseline saline function. This leftward shift was accompanied by a decrease in the PSE, indicative of an increase in pacemaker speed for both number and time (Meck & Church, 1983). Consistent findings in pigeons were reported by Kraemer et al. (1997) who found evidence of an increasing leftward shift compared to baseline saline trials with increasing doses of d-Amphetamine (0.3, 1.0, and 2.0 mg/kg). These findings pointed to the equivalence of the effect of amphetamines, and therefore to increases in the level of dopamine, upon the processing of temporal information.

The Meck and Church (1983) study was also replicated with the use of the specific D2 agonist quinpirole used in the Frederick and Allen (1996) study. In the Frederick and Allen (1996) study, rats were trained on a peak procedure with temporal signals and administered with

the specific D2 agonist quinpirole (0.01 mg/kg). The rats showed a phasic leftward shift in the temporal function under quinpirole administration in comparison to the baseline saline function. This leftward shift was accompanied by a significant decrease in peak time and peak rate under quinpirole (Frederick & Allen, 1996). These results were interpreted as consistent with the hypothesis that specifically increasing dopaminergic levels at the D2 receptor increases the speed of the pacemaker, resulting in an overestimation of the passage of time. These results were consistent with those of Meck (1986) who administered five different D2 neuroleptics to rats in a temporal bisection procedure and found an increasing phasic horizontal rightward shift and increase in the PSE with increasingly selective D2 receptors.

In the current study, there was a significant phasic change in the probability of responding "many/long" from the pre-drug saline condition to the drug (methamphetamine and quinpirole) condition as with Meck and Church (1983) and Kraemer et al. (1997). However, the effect was not the expected horizontal leftward shift and decrease in the PSE for either the numerical or temporal dimension. Instead, the function significantly flattened. This flattening was indicative of a decrease in sample discriminability and sensitivity for both the numerical and temporal dimension. This loss of discriminability was further evidenced by a significant increase in the DL and WF under drug trials in comparison to baseline saline trials.

While there was no significant change from the drug condition to the post-drug saline condition, Figures 6 and 7 show partial recovery from drug and movement back to the original pre-drug saline function for both the numerical and temporal dimension. This is in contrast to the expected immediate recovery of performance to pre-drug saline levels during post-drug

saline testing. This recovery is supported by a decrease in the DL and WF from the drug function to the post-drug saline function, indicative of an increase in sample discriminability and sensitivity with the removal of drug and return of saline. However, the degree of recovery was greater for the temporal dimension than for the numerical dimension, exemplified by a greater decrease in the DL and WF in the post-drug saline condition for the temporal dimension.

These results conflict with those of Meck and Church (1983) and Frederick and Allen (1996), and do not support those of Meck (1986). Increases in dopamine levels did not culminate in a horizontal leftward shift in the psychophysical function and a decrease in the PSE. Thus, rather than the speed of the pacemaker increasing with increased levels of dopamine, the speed of the pacemaker was unadjusted. The occurrence of this flattening indicates that methamphetamine and quinpirole had a generally disruptive effect upon the numerical and temporal discriminations that the rats made. The animals suffered from a loss of attention stemming from an increase in dopaminergic levels. This finding is in accordance with previous reports (Berz et al., 1992; Coppa, 1997; Lejeune et al., 1995; Rapp & Robbins, 1976; Santi et al., 1995; Shurtleff et al., 1992; Stanford & Santi, in press; Stubbs & Thomas, 1974).

Another interesting finding of the current study is that while the initial change from the pre-drug saline condition to the drug condition was phasic, the change from the drug condition to the post-drug saline condition was not. Given that the initial dopaminergic shift in the psychophysical function was phasic, one would have expected a block effect to occur. In other words, it was expected that with the continuation of drug administration the psychophysical function would return to the original pre-drug saline function during drug administration itself.

This however, did not occur. The occurrence of an initially phasic transition culminating in a chronic-like transition while under the influence of the same pharmacological manipulation is unlike anything reported before. Aside from the possibility of empirical unreliability, the explanation may lie in the knowledge that dopaminergic receptors do not exist in isolation, but have connections with various sites that have different neurotransmitter receptors.

For example, the substantia nigra (SN) and ventral tegmental area (VTA) dopaminergic sites have direct connections to the lateral dorsal tegmental nucleus (LDT) and pedunculopontine tegmentum (PPT) cholinergic sites (Mesulam et al., 1990). Furthermore, cholinergic receptors exist directly on the cell bodies of the SN (Mesulam et al., 1990). Given the existence of the interconnections between dopaminergic and cholinergic sites, it is possible that the administration of a dopaminergic agonist initially manipulates the speed of the internal clock by increasing the level of dopamine. However, with repeated, consecutive, and long term administration of dopaminergic agonists and resultant dopamine efflux, the direct connections to various cholinergic sites become stimulated, resulting in an increase in cholinergic efflux. In other words, a combination of a clock effect and a memory effect may have occurred here. This would be evident in a bisection procedure when rats initially show a phasic shift under the administration of a dopaminergic agonist which is initially masked by attentional deficits. This phasic shift then culminates in a chronic-like shift linked to increased cholinergic efflux. This occurrence seems possible in the current study because the rats received 15 consecutive days of methamphetamine administration. Given the hypothesis that the chronic memory effects of increased acetylcholine administration are non-immediate and require repeated administrations

to occur (Meck & Church, 1983), a more long-term and consecutive schedule of drug administration may be necessary to allow the chronic cholinergic effect with administration of a dopaminergic agonist to occur.

Scopolamine and the Internal Clock/Counter Model

It has been stated that decreasing the central level of acetylcholine with the administration of cholinergic antagonists such as atropine (Meck & Church, 1987) and pyrithiamine (Meck & Angell, 1992) results in an increase in the remembered times of reinforcement in temporal peak production procedures. Meck and Church (1987) and Meck and Angell (1992) suggest that these effects occur because the effective level of acetylcholine sets the communication speed for the translation of durations measured by the internal clock into values stored in temporal memory. More specifically, decreasing the level of acetylcholine slows down the speed of memory storage so that information is transferred from the working memory storage area to the reference memory storage area at a slower rate. This is evidenced by a chronic rightward shift in comparison to a baseline saline function, and a corresponding increase in the PSE.

In contrast to these results, Shurtleff et al. (1992) tested rats in a perceptual bisection task with the use of increasing doses of the cholinergic antagonist scopolamine (0.075-0.422 mg/kg) and found that rats showed decreased discriminability and decreases in the PSE under scopolamine administration. Berz et al. (1992) tested rats in a delayed conditional time bisection task with the use of increasing doses of scopolamine (0.06, 0.25, and 1.0 mg/kg) and also found that the rats showed decreased discriminability and attention. An examination of manipulating cholinergic levels and testing rats' numerical processing has never been examined

before. Thus, Coppa (1997) placed rats in a numerical bisection task and administered atropine (0.15 & 0.45 mg/kg). The result was no horizontal movement in the psychophysical function. This was supported by further pilot work which also revealed no horizontal movement in the psychophysical function in a concurrent numerical and temporal bisection task using rats administered with scopolamine (0.1 mg/kg).

A replication of the Meck and Church (1983) numerical and temporal bisection experiment using the cholinergic muscarinic antagonist scopolamine (0.1 mg/kg) was conducted. There was a phasic shift in the psychophysical function from the pre-drug saline condition to the scopolamine condition exemplified as a significant main effect of drug. The effect was not a chronic horizontal rightward shift in the psychophysical function and increase in the PSE for either the numerical or temporal dimension. Instead, the function significantly and immediately flattened. This flattening was indicative of a decrease in sample discriminability and sensitivity for both the numerical and temporal dimension. This loss of discriminability was further evidenced by a significant increase in the DL and WF under scopolamine trials in comparison to baseline saline trials.

As can be seen in Figure 8, the post-drug saline data does not show any recovery back to pre-drug saline levels from scopolamine administration for either the numerical or temporal dimension. Rather, the post-drug saline function is equal to the scopolamine function, exemplified by no significant drug effect from the scopolamine condition to the post-drug saline condition. This lack of recovery in performance was accompanied by a further increase in the DL and WF for the numerical dimension, indicative of further decreases in sample

discriminability, and a minimal increase in the DL and WF for the temporal dimension, indicative of a small degree of recovery not significantly different from zero.

These results support those of Shurtleff et al. (1992), Berz et al. (1992), and Coppa (1997), but conflict with those of Meck and Church (1987) and Meck and Angell (1992). A decrease in cholinergic levels with scopolamine did not produce a chronic horizontal rightward shift in the function. Rather, the occurrence of an immediate shift implies that rather than the speed of the memory storage constant decreasing with decreased levels of acetylcholine, the speed of the memory storage constant was unadjusted. The occurrence of a flattening of the psychophysical function indicates that the animals suffered from a loss of attention rather than a change in the speed of the memory storage constant. The immediate nature of this disruption implies that the degree of attentional-deficiency was great enough to occur early on and mask any chronic shifts that may have occurred. The use of a smaller dose of scopolamine may remedy this, causing lesser degrees of disruption and therefore, allowing the occurrence of a chronic horizontal shift to become apparent, if it exists.

Another interesting finding of the current study was that while the initial change from the pre-drug saline condition to the scopolamine condition was immediate, there was no change from the scopolamine condition to the post-drug saline condition. Again, the occurrence of an initially phasic transition culminating in a chronic-like transition while under the influence of the same pharmacological manipulation is unlike anything reported before. It was expected that with the continuation of scopolamine administration the psychophysical function would remain shifted and not return to the original pre-drug saline function during scopolamine administration

itself. The shift back to the pre-drug saline function was expected to occur following a series of post-drug saline sessions, in chronic form. This did occur. The lack of a shift in the post-drug saline condition resembles the chronic movement back to pre-drug saline levels following a cholinergic manipulation reported by Meck and Church (1987) and Meck and Angell (1992). However, it must be reiterated that the shift in the current study is vertical rather than horizontal. It is possible that the original and immediate disruptive effects of the drug became more tolerable with the passage of physical time, and that the equivalence between the scopolamine and the post-drug saline conditions indicates the occurrence of a slower memory storage constant. If so, further post-drug saline testing should reveal eventual approximation of the pre-drug saline function.

In Figure 8 we can see another interesting finding under scopolamine administration. There was a disruptive effect of scopolamine exemplified as a decrease in "many/long" responding at higher numbers and longer durations. However, the psychophysical classification of "fewer" numbers and "shorter" durations was equivalent for the saline and scopolamine conditions. In other words, the drug function flattened only for higher numbers and longer durations. This in contrast to the dopaminergic results which showed a disruption at both the "few/short" and "many/long" psychophysical endpoints. Perhaps this "uneven" degree of decrement is due to the rats' positional biases. For example, the administration of scopolamine created a loss of discriminability, perhaps due to a loss of attention. This may have been accompanied by decreased movement, leading the rat to respond more frequently at one lever over another.

Nicotine and the Internal Clock/Counter Model

A replication of the Meck and Church (1983) bisection experiment was conducted with the use of the nicotinic receptor cholinergic agonist nicotine. Hinton and Meck (1996) administered nicotine (0.2 mg/kg) to rats in a peak procedure with temporal signals. The rats showed an immediate horizontal leftward shift in the temporal function with nicotine administration which was renormalized on the second nicotine injection session, and rebounded to pre-drug saline levels on the following session with a saline injection. This phasic leftward shift was accompanied by a significant decrease in peak time under the first nicotine session. These results were interpreted as an increase in pacemaker speed via nicotine-induced stimulation of the nigrostriatal and frontostriatal dopamine systems, thus, resembling the effects of dopamine stimulants such as methamphetamine. Hinton and Meck (1996) hypothesized that the observed effect with nicotine administration may be due to D2 receptor dopamine efflux, given that nicotinic receptors are functionally associated with D2 receptors. This theory would support that of D2 receptor modulation of the "clock pattern" (Meck, 1986). If so, the nicotinic cholinergic receptor antagonist mecamylamine should produce results compatible with those of the D1/D2 receptor antagonist haloperidol - namely, a phasic horizontal rightward shift (Hinton & Meck, 1996). However, Berz et al. (1992) found that mecamylamine produced only a performance attenuating effect and a reduction in response efficiency only at very high doses (8 mg/kg), not an effect consistent with the dopaminergic antagonist haloperidol.

In the current study, there was an immediate change in the psychophysical function from the pre-drug saline condition to the nicotine condition exemplified as a significant main effect of drug. However, the effect was not the expected immediate horizontal leftward shift and

decrease in the PSE for either the numerical or temporal dimension which would be consistent with the results of Hinton and Meck (1996). Instead, the function showed a significant, immediate, horizontal rightward shift for both the numerical and temporal dimension. This immediate horizontal rightward shift was accompanied by a significant increase in the PSE for both the numerical and temporal dimension.

Figure 9 shows that the post-drug saline testing allowed some degree of recovery from nicotine administration for both the numerical and temporal dimension. This recovery in performance was supported by a decrease in the DL for number and time and the WF for number from the nicotine function to the post-drug saline function, indicative of an increase in sample discriminability and sensitivity with the removal of nicotine and the return of saline. The PSE also significantly decreased from the nicotine condition to the post-drug saline condition for both the numerical and temporal dimension.

While a specific increase in acetylcholine levels with nicotine produced an immediate horizontal shift in the psychophysical function, it was rightward rather than leftward. Thus, rather than the speed of the pacemaker increasing with increased levels of acetylcholine, the speed of the pacemaker decreased. However, there was no effect of session block which would indicate a re-scaling of time consistent with a clock effect. Perhaps a greater number of nicotine sessions were required, or an alternative division of the session blocks for analysis would reveal this effect. The occurrence of the phasic shift may have been due to the stimulation of dopaminergic receptors via cholinergic connections, resulting in an alteration in pacemaker speed, akin to the results of Hinton and Meck (1996). The occurrence of a rightward shift

indicative of a decrease in pacemaker speed with increases in cholinergic and dopaminergic levels could be explained with the existence of dopaminergic autoreceptors. When stimulated, an autoreceptor will act to lower the amount of neurotransmitter of which it is a class of, in this case dopamine. So a dopaminergic autoreceptor will actually lower the level of dopamine which would explain the rightward shift and increase in the PSE under nicotine administration, similar to the action of other dopaminergic antagonists such as haloperidol.

Conclusions and Suggestions for Future Research

Overall, control by time was stronger than control by number. This finding replicates studies that the degree of control by numerical and temporal stimuli is not equal, and that the control by temporal stimuli is stronger (Breukelaar & Dalrymple-Alford, 1998). This finding is not consistent with the equal control by number and time reported by Meck and Church (1983). However, the psychophysical functions for number and time were both affected in a similar manner by each drug. This supports the idea that the same internal mechanism is used for numerical and temporal discriminations. It could also be that the drugs affected an internal process required for both numerical and temporal processing, but these processes themselves are controlled by separate mechanisms.

Yet, the specific effect of each drug on numerical and temporal discriminations was not consistent with previous descriptions of the role of different neurotransmitter systems on the perception of number and time (Frederick & Allen, 1996; Kraemer et al., 1997; Meck & Church, 1983; Meck & Angell, 1992). In other words, the effect of each drug was not consistent with the manipulation of clock speed or memory components of the internal clock/counter. Rather, the

current findings with methamphetamine, quinpirole, and scopolamine were consistent with previous findings that placing rats into a temporal discrimination task and manipulating dopaminergic and cholinergic levels leads to a decrement in discriminative performance (Berz et al., 1992; Coppa, 1997; Lejeune et al., 1995; Rapp & Robbins, 1976; Santi et al., 1995; Shurtleff et al., 1992; Stanford & Santi, in press; Stubbs & Thomas, 1974). This result was also apparent in the numerical discrimination task. In general, there was a loss of sample discriminability and sensitivity, possibly due to a loss of attention. The lack of a rebound to baseline performance during the post-drug saline testing may be due to the rats' need to relearn the task due to this loss of attention.

While nicotine did affect the speed of the internal clock/counter which was consistent with previous descriptions, the direction of the shift was not the same as that previously reported (Hinton & Meck, 1996). Nicotine significantly increased the PSE which could be interpreted as a decrease in the speed of the internal clock, causing the rats to classify greater and longer stimuli as "fewer" or "shorter" than normal. This was evident by a phasic horizontal rightward shift in the psychophysical function. An important aspect of nicotine is that it increases cholinergic levels by way of activating nicotinic cholinergic receptors, not muscarinic cholinergic receptors. Perhaps it is this nicotinic activation which manipulates the speed of the internal clock/counter, and perhaps it is the nicotinic pathways that are responsible for the stimulation of mesolimbic dopaminergic pathways. Future research would benefit from a direct examination of both nicotinic and muscarinic agonists and antagonists upon numerical and temporal processing. Perhaps the effect of each cholinergic receptor subtype contributes to a

different stage of the internal clock/counter.

This is an important contribution to the study of numerical and temporal processing because while dopaminergic and cholinergic influences upon temporal processing have been examined, studies of the dopaminergic influence upon numerical processing have been limited while studies of the cholinergic influence upon numerical processing have not been conducted. This is the first collective examination of dopaminergic and cholinergic manipulation upon numerical and temporal processing, which has allowed us to draw conclusions not only about the similarity of numerical and temporal processing, but of the effects of both dopamine and acetylcholine upon these systems.

Future research can benefit from lowering the doses of quinpirole and scopolamine in order to remedy the loss of accuracy and sample discriminability that occurred with the current doses. Perhaps any effects upon numerical and temporal processing will become apparent once this is done. The dose of methamphetamine, however, was identical to that of Meck and Church (1983) but did not replicate their results of an increase in clock speed. Thus, the comparison of numerical and temporal processing can be examined with an alternative general dopaminergic agonist in order to decipher whether the previous effects of increasing levels of dopamine were due to the use of methamphetamine specifically, or to a dopamine agonist in general. In addition to drug dosage, procedural details, and methods of analysis can not account for the different results in this study and that of Meck and Church (1983), given that they were identical in these parameters. Furthermore, Stanford and Santi (in press) showed that previous exposure to the drug, and discarding trials with latencies greater than a criterion amount also do not

account for these differences. Also, Coppa's (1997a, 1997b) use of a bisection procedure with visual signals showed that the differences can not be accounted for with the use of various stimuli. However, the strain, age, and sex of the rat may be important variables to look at and control in future research, given that there is some variation of these parameters in the related research..

The role of dopamine and acetylcholine upon numerical and temporal processing is more complex than previously believed. The hypothesis that dopamine singularly and selectively modulates the speed of numerical and temporal processing, while acetylcholine singularly and selectively modulates numerical and temporal memory is too simplistic. Perhaps certain dopamine receptors affect the switch of the internal clock/counter, while others affect the speed of the clock/counter. Perhaps certain cholinergic receptors affect working memory components of the clock/counter, while other cholinergic receptors affect reference memory components of the clock/counter. It must be recognized that studying more specific subtypes of receptors in isolation and combination with the use of various pharmacological agents at each level of the internal clock/counter model is required. Only such complex pharmacological studies will more directly pinpoint the role of dopamine and acetylcholine upon numerical and temporal processing.

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Figure Captions

Figure 1: Internal Clock Model elaborated by Meck and Church (1983).

Figure 2: Three mode switches of the internal clock model elaborated by Meck and Church (1983).

Figure 3: Internal Clock Model elaborated by Roberts and Mitchell (1994) with separate numerical and temporal accumulators and working memory storage areas.

Figure 4: The top figure represents a phasic horizontal leftward shift occurring following administration of the general dopaminergic agonist methamphetamine (1.5). The median proportion of a "long" response as a function of signal duration during training and testing is represented. The lower figure represents a phasic horizontal rightward shift occurring following administration of the D1/D2 antagonist haloperidol (0.12 mg/kg). The median proportion of a "long" response as a function of signal duration during the last three sessions of training is represented.

Figure 5: The top portion of the figure represents the test for time in which the number of sound bursts in a signal was constant at four while the duration of the signal varied from 2 to 8 seconds. Only the 2 and 8 training signals were reinforced while the 3 to 6 intermediate probe signals were not. The lower portion of the figure represents the test for number in which the duration of the signal was constant at four seconds while the number of sound bursts in a signal varied from 2 to 8 events. Only the 2 and 8 training signals were reinforced while the 3 to 6 intermediate probe signals were not. (Meck & Church, 1983)

Number and Time

Figure 6: These figures represent methamphetamine testing (n=6). The top portion represents methamphetamine (1.5 mg/kg) testing with numerical signals while the lower portion represents methamphetamine (1.5 mg/kg) testing with temporal signals. The graph depicts mean percentage of "many/long" responses as a function of signal value (frequency/duration). The solid functions represent the pre- drug saline and post-drug saline testing, while the open dashed function represents the 15 days of methamphetamine testing.

Figure 7: These figures represent quinpirole testing (n=8). The top portion represents quinpirole (0.08 mg/kg) testing with numerical signals while the lower portion represents quinpirole (0.08 mg/kg) testing with temporal signals. The graph depicts mean percentage of "many/long" responses as a function of signal value (frequency/duration). The solid functions represent the pre-drug saline and post-drug saline testing, while the open dashed function represents the 15 days of quinpirole testing.

Figure 8: These figures represent scopolamine testing (n=6). The top portion represents scopolamine (0.1 mg/kg) testing with numerical signals while the lower portion represents scopolamine (0.1 mg/kg) testing with temporal signals. The graph depicts mean percentage of "many/long" responses as a function of signal value (frequency/duration). The solid functions represent the pre-drug saline and post-drug saline testing, while the open dashed function represents the 15 days of quinpirole testing.

Number and Time

Figure 9: These figures represent nicotine testing (n=20). The top portion represents nicotine (0.2 mg/kg) testing with numerical signals while the lower portion represents nicotine (0.2 mg/kg) testing with temporal signals. The solid functions represent the pre-drug saline and post-drug saline testing, and the open dashed function represents the 6 days of nicotine testing.

Figure 1

Number and Time
LONG
SHORT
REFERENCE MEMORY
WORKING MEMORY
ACCUMULATOR
COMPARATOR
SIGNAL
SWITCH
PACEMAKER

Figure 2

Number and Time

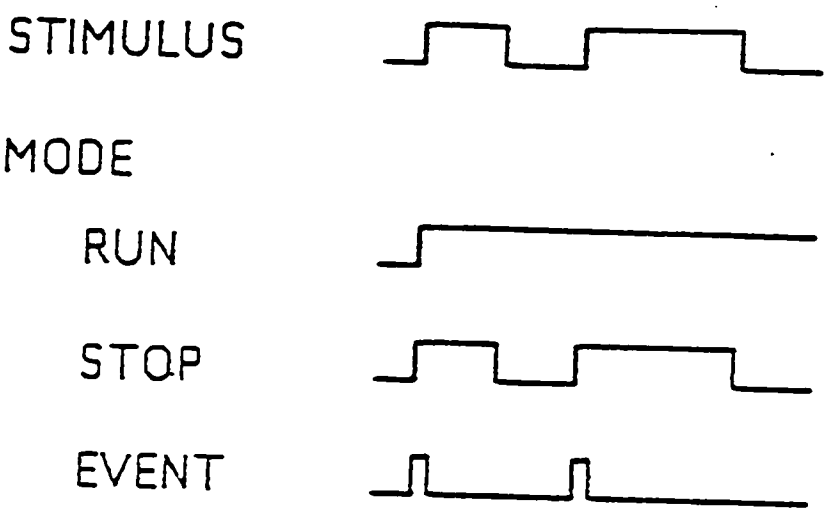
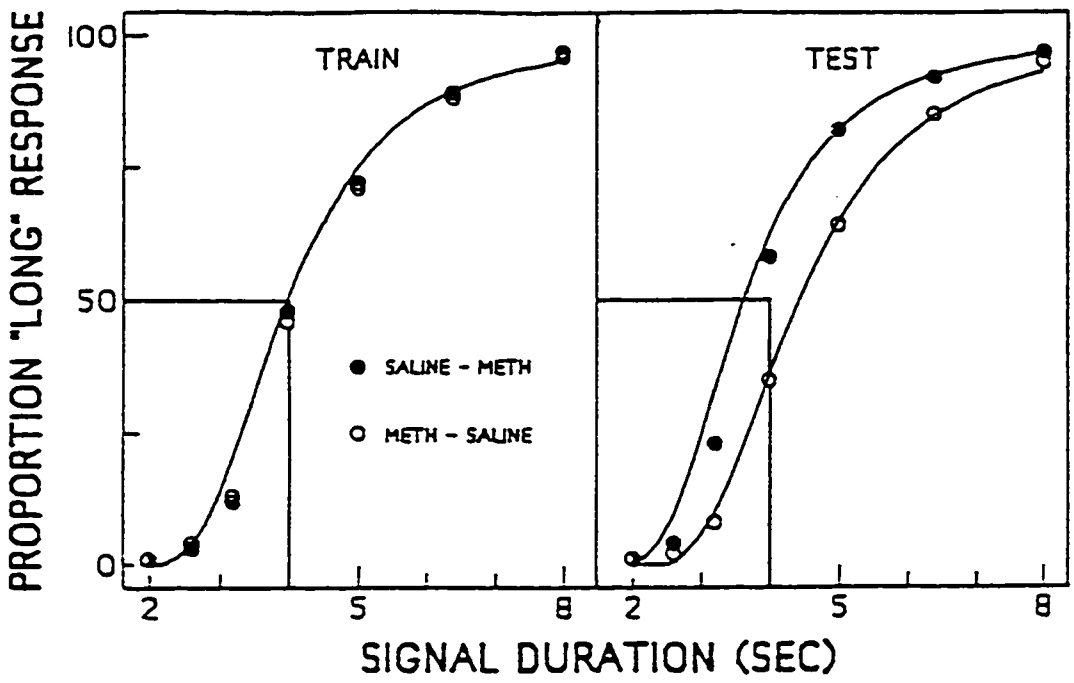


Figure 3

Number andTime
Response B
Response A
SIGNAL
PACEMAKER
Time Switch
Count Switch
Time Accum
Count Accum
WORKING MEMORY
Time Info
Number Info
REFERENCE MEMORY
COMPARATOR

Figure 4

Number andTime



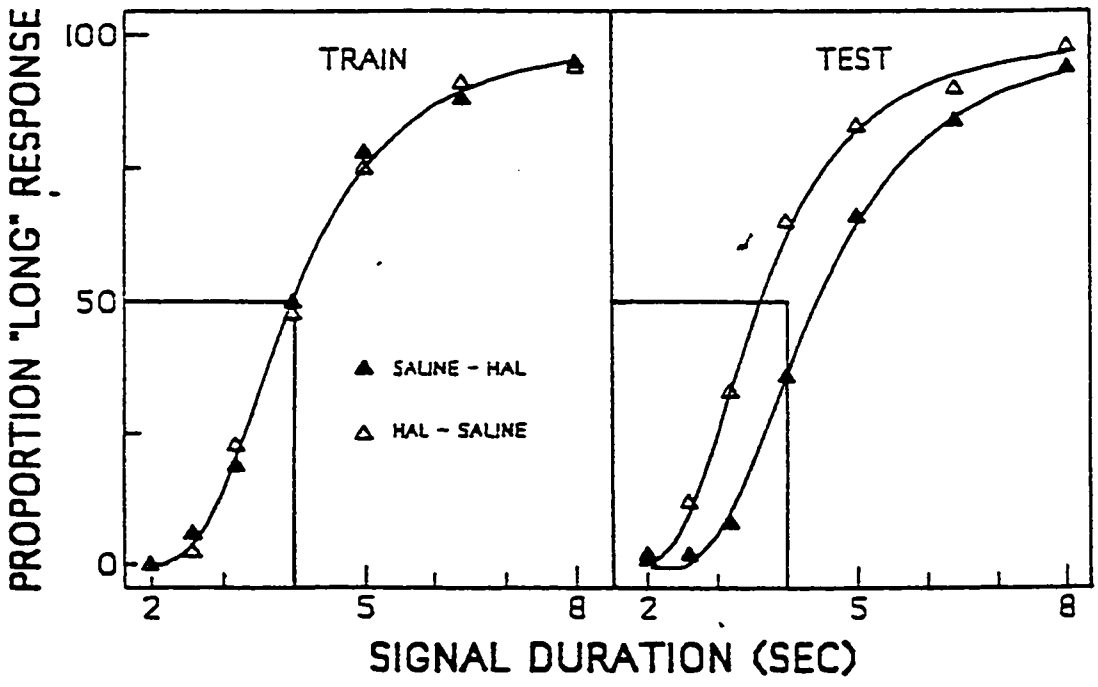
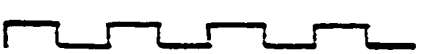


Figure 5

Number and Time

TEST FOR TIME

Number of Stimuli	Total signal Duration (sec)		Reinforced Response
4	2		Left
4	3		----
4	4		----
4	5		----
4	6		----
4	8		Right

TEST FOR NUMBER

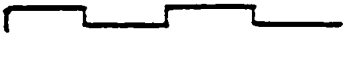
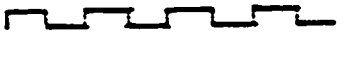
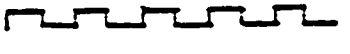
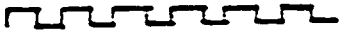
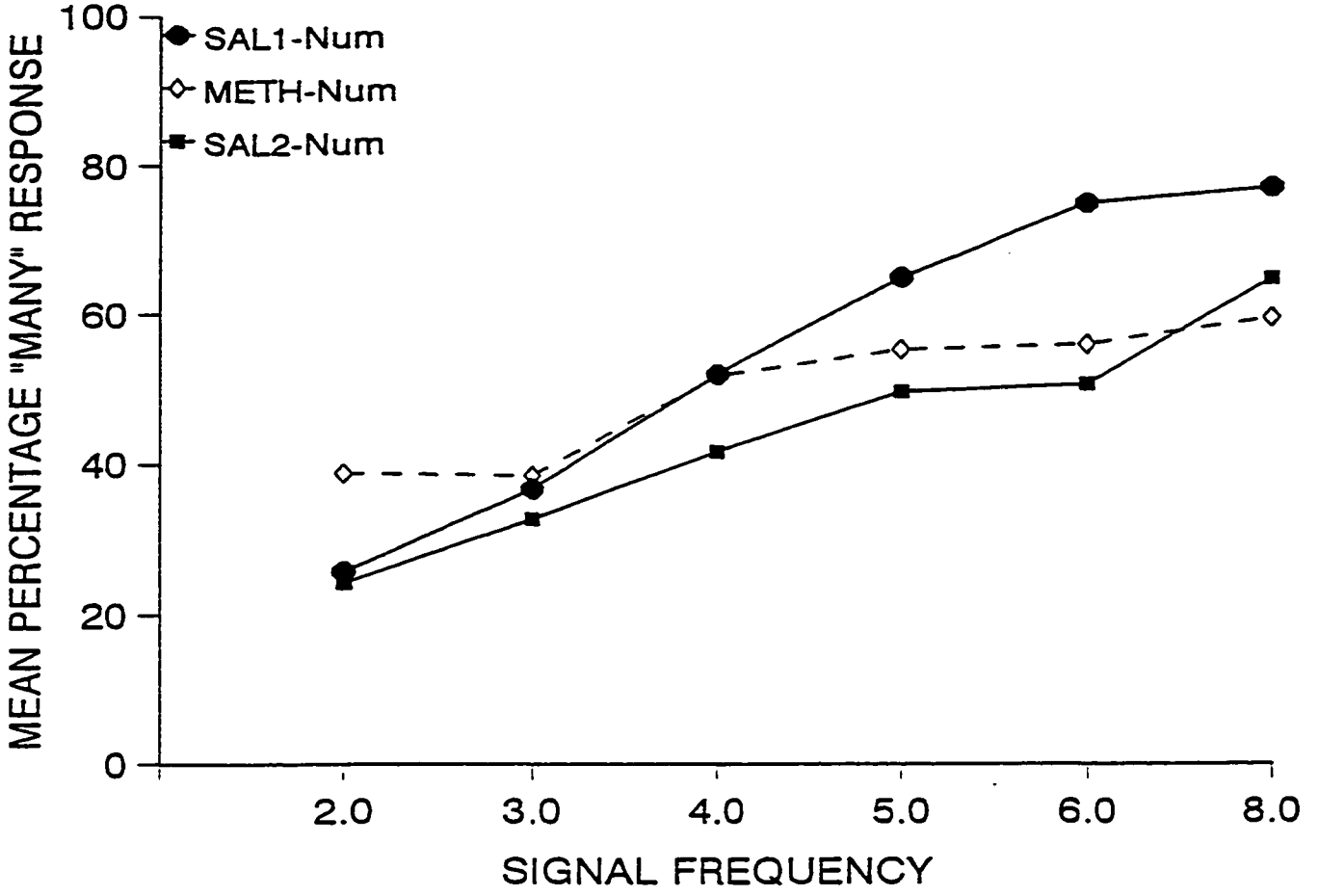
Number of Stimuli	Total Signal Duration (sec)		
2	4		Left
3	4		----
4	4		----
5	4		----
6	4		----
8	4		Right

Figure 6

Number and Time



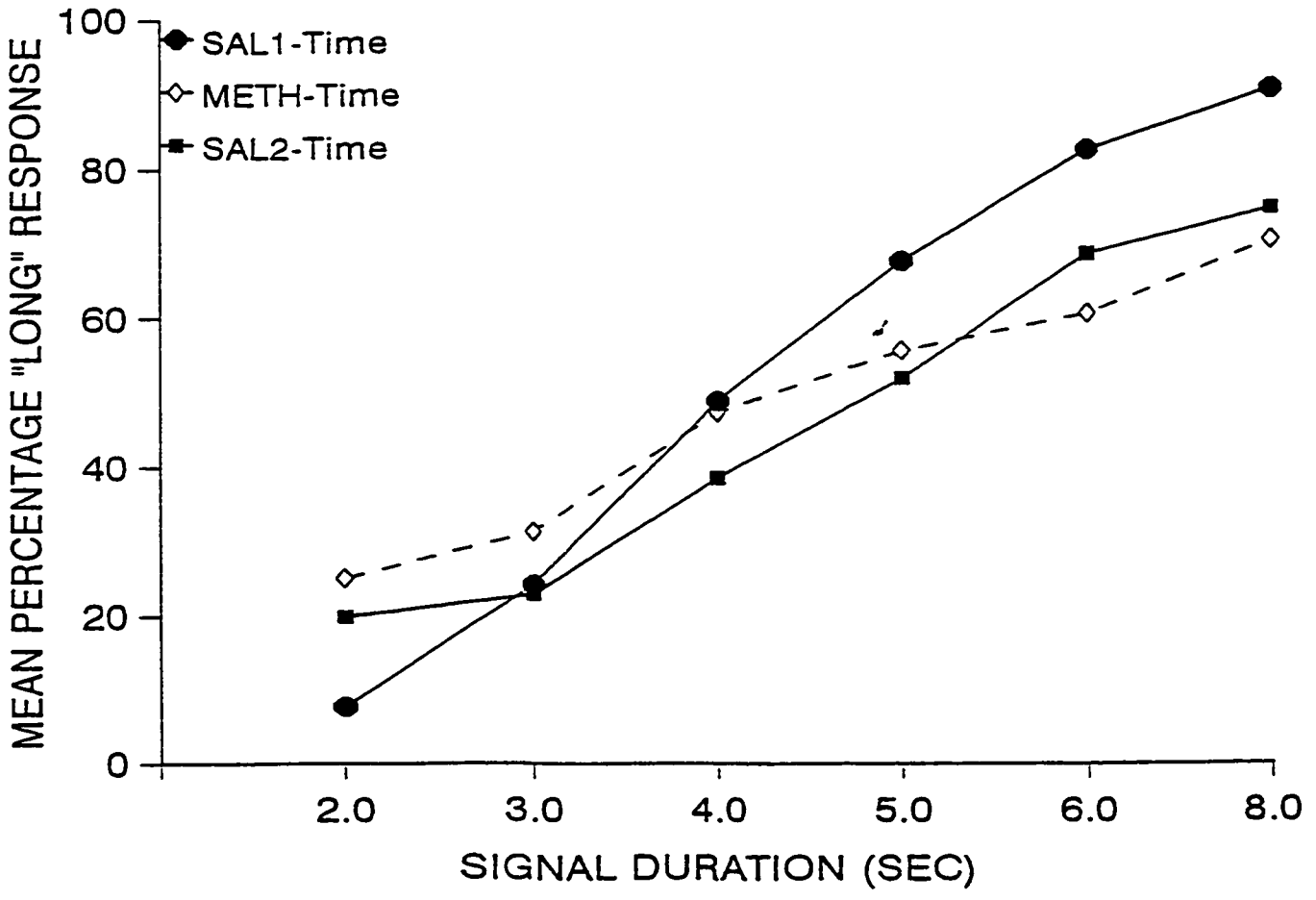
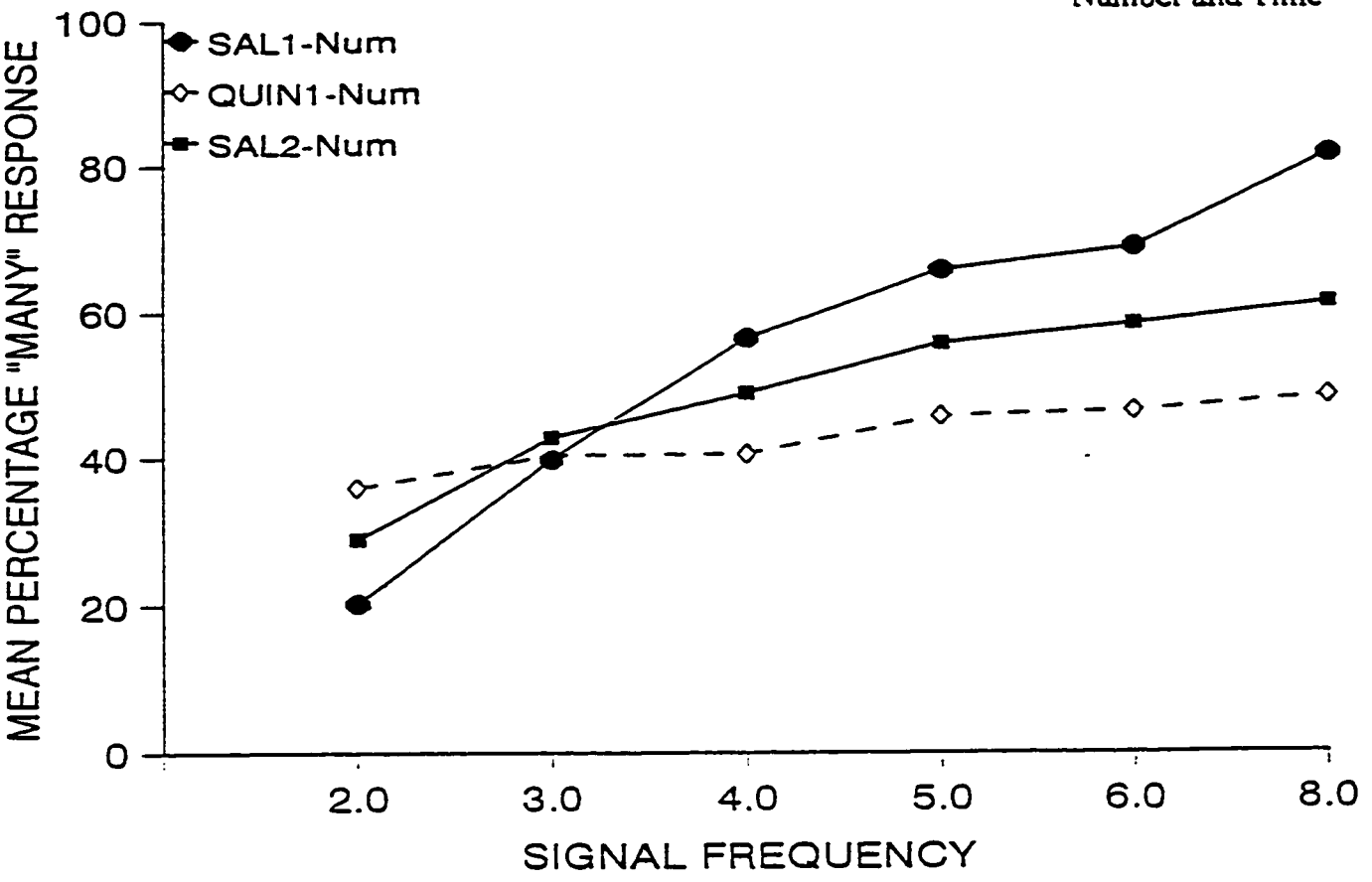
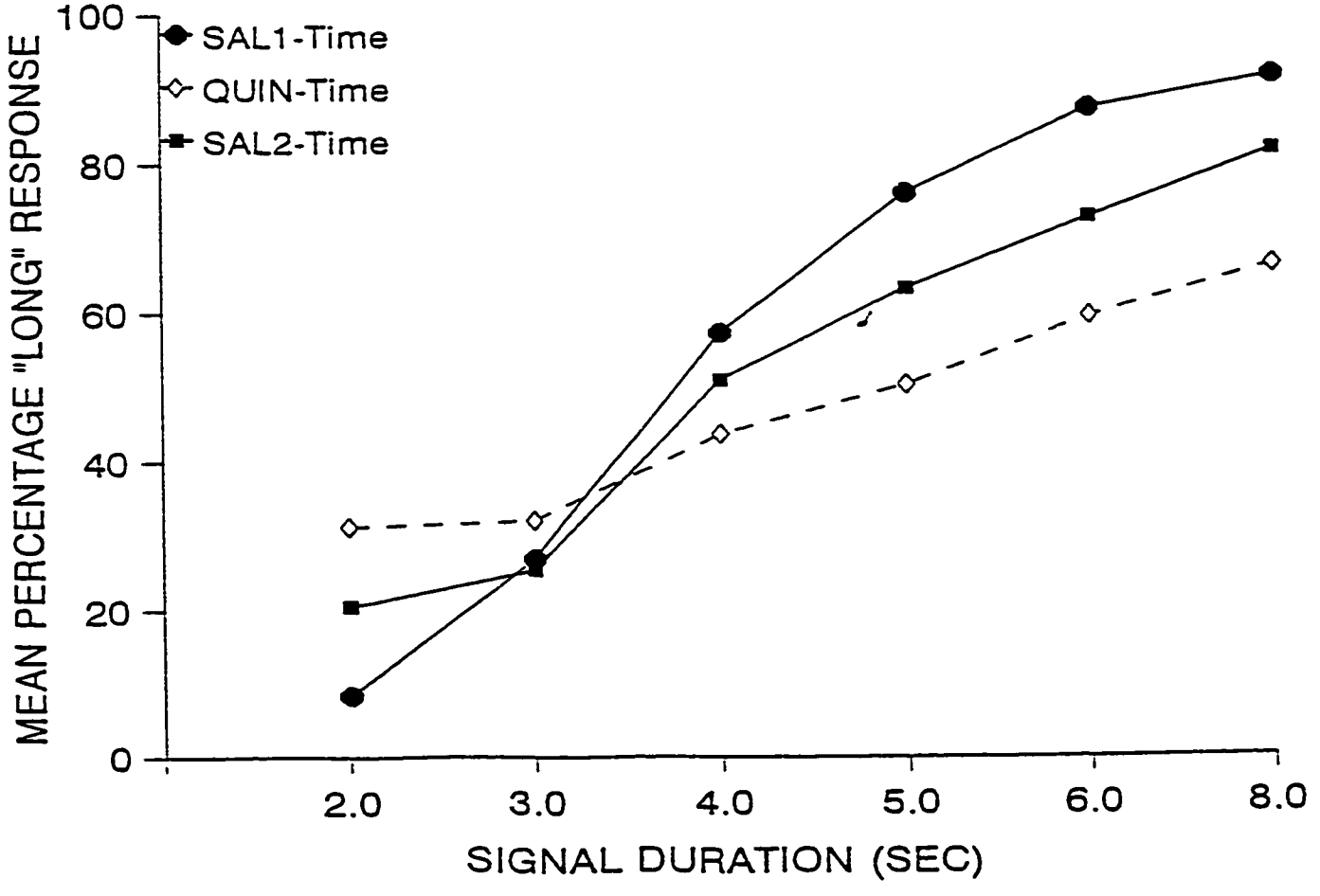
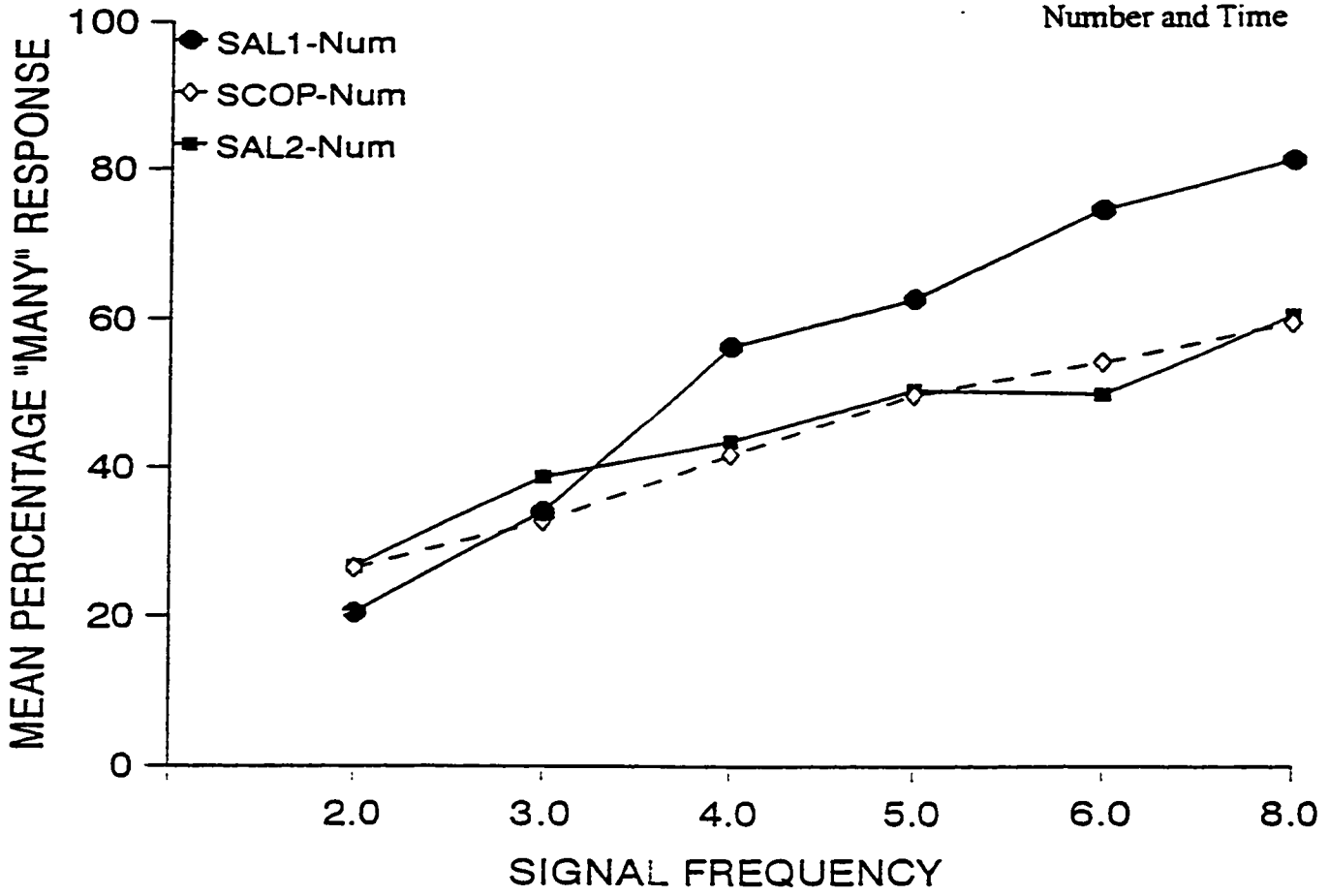


Figure 7

Number and Time






Number and Time
SAL1-Num
SCOP-Num
SAL2-Num
MEAN PERCENTAGE "MANY" RESPONSE
100
80
60
40
20
0
2.0
3.0
4.0
5.0
6.0
8.0
SIGNAL FREQUENCY

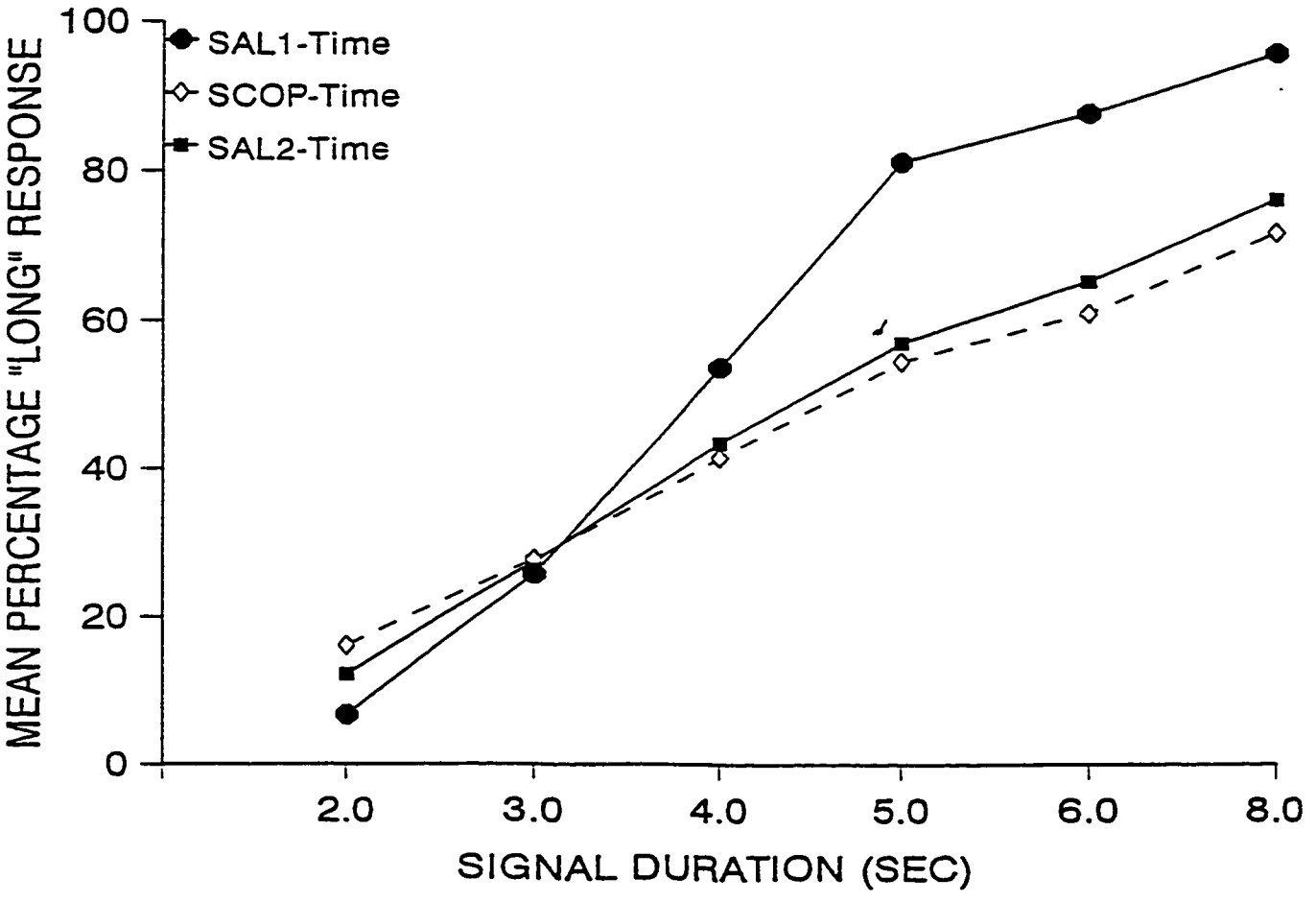
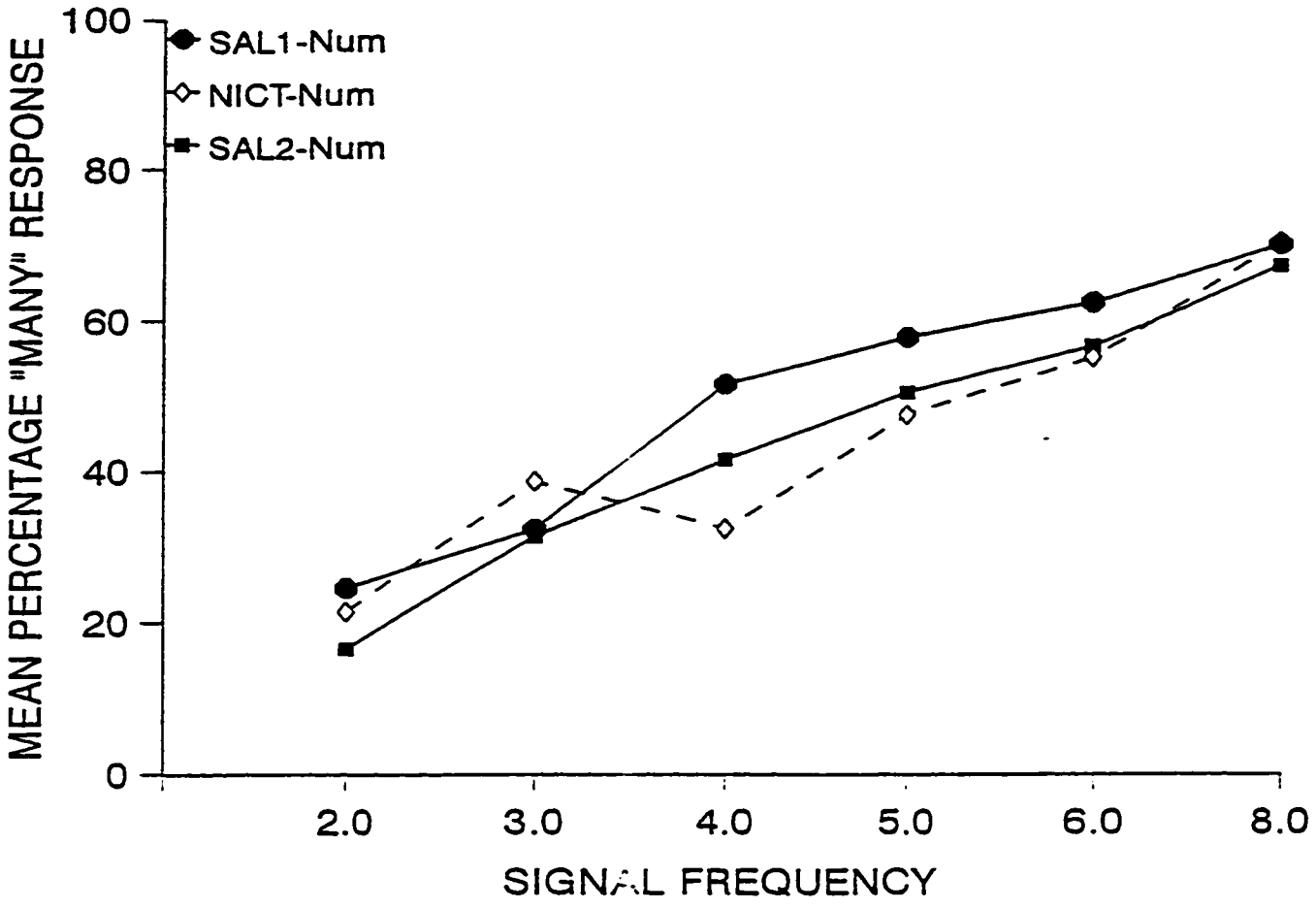
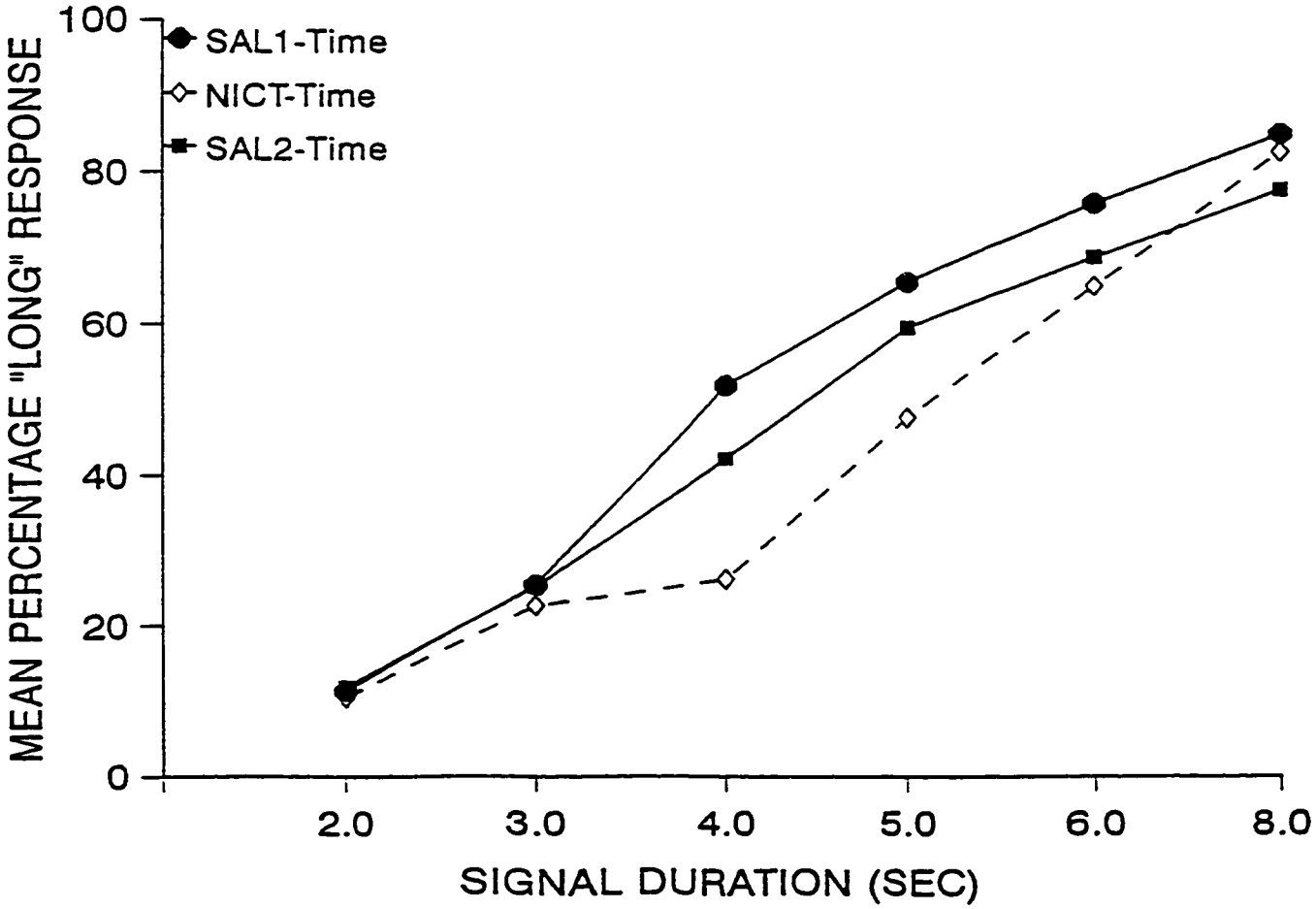

SAL1-Time
SCOP-Time
SAL2-Time
MEAN PERCENTAGE "LONG" RESPONSE
100
80
60
40
20
0
2.0
3.0
4.0
5.0
6.0
8.0
SIGNAL DURATION (SEC)

Figure 9

Number and Time





Appendix A
Responding for incomplete sessions

This appendix only includes sessions for which less than the programmed number of trials (ie: 160) were completed. The drug (S1 = pre-drug saline; S2 = post-drug saline; M = methamphetamine; Q = quinpirole; S = scopolamine; N = nicotine), rat number (R), session number (S), number of trials completed for each signal type (number trials: 2c, 3c, 4c, 5c, 6c, and 8c; time trials: 2s, 3s, 4s, 5s, 6s, and 8s), total number of trials completed (T), and the inclusion/exclusion of the session data [? - Y(yes)/N(no)] is outlined. If a rat completed less than half of the total number of trials presented during a session (ie: <80), his data for that session was omitted.

Number and Time

D	R	S	2c	3c	4c	5c	6c	8c	2s	3s	4s	5s	6s	8s	T	?
S1	9	1	18	9	9	9	9	18	18	9	9	9	9	18	144	Y
S1	9	2	13	7	7	6	6	13	14	6	7	6	7	13	105	Y
M	21	2	18	9	9	9	9	18	18	9	9	9	9	18	144	Y
M	21	4	16	8	8	8	8	16	17	8	8	8	8	16	129	Y
M	22	6	18	9	9	9	9	18	18	9	9	9	9	18	144	Y
M	22	10	12	5	5	5	5	10	11	5	5	5	5	10	83	Y
M	22	11	20	10	9	10	10	20	19	10	10	10	10	19	157	Y
M	22	13	13	7	6	6	7	13	12	6	6	7	6	14	103	Y
M	7	2	14	8	8	7	7	15	14	8	8	8	7	14	118	Y
M	7	3	10	5	5	6	5	11	10	5	5	6	5	10	83	Y
M	7	4													21	N
M	7	5	17	8	9	9	8	16	17	8	9	8	8	17	134	Y
M	7	8	12	6	6	7	6	13	13	6	7	7	7	12	102	Y
M	7	9	15	7	8	7	7	14	15	7	8	7	7	15	117	Y
M	7	11	16	9	8	9	9	17	17	8	9	8	9	17	136	Y
M	7	12	19	9	9	9	9	18	18	9	10	10	10	19	149	Y
M	7	14	14	7	7	7	6	14	14	7	7	6	7	14	110	Y
M	18	14	19	9	9	10	9	18	19	10	10	9	10	20	152	Y
Q	14	1	10	6	6	6	5	12	12	6	6	6	6	12	93	Y
Q	14	2	16	9	8	8	8	16	16	8	8	8	8	16	129	Y
Q	14	3	18	9	9	9	9	18	18	9	9	9	10	18	145	Y
Q	14	4	20	9	10	10	10	20	20	10	10	9	9	20	157	Y
Q	14	15	19	9	9	10	9	19	18	10	9	10	9	18	149	Y
Q	4	13	18	10	9	9	9	19	19	9	9	10	10	18	149	Y

Q	10	2	15	8	8	8	8	16	16	7	7	8	8	15	124	Y
Q	10	3	12	6	6	6	6	12	13	7	6	6	6	12	98	Y
Q	10	5	18	9	9	9	9	19	18	9	9	9	9	18	145	Y
Q	10	8	13	7	6	7	6	12	13	6	7	6	6	12	101	Y
Q	10	9	12	6	6	5	6	11	11	6	6	6	6	12	93	Y
Q	10	10	17	9	9	8	9	18	17	8	8	9	10	18	140	Y
Q	10	13	18	10	9	9	9	18	19	10	10	10	9	19	150	Y
Q	10	14	10	6	6	6	6	12	11	6	5	6	6	11	91	Y
Q	10	15	17	8	8	9	8	17	16	9	8	8	8	16	132	Y
Q	15	1	18	9	9	9	9	18	18	9	9	9	10	19	146	Y
Q	15	2	20	10	10	10	10	20	19	9	10	10	10	19	157	Y
Q	15	3	20	10	9	9	9	20	20	10	9	10	10	20	156	Y
Q	15	5	14	8	7	7	7	17	17	8	8	8	7	16	124	Y
Q	15	7	15	8	7	7	8	16	15	8	7	7	8	16	122	Y
Q	15	12	20	9	9	9	10	19	19	9	9	9	9	20	151	Y
S	9	7													13	N
S	2	7	18	9	9	9	9	18	18	9	9	9	8	18	143	Y
S	6	5	14	7	8	7	7	15	15	7	7	8	8	15	118	Y
S	6	7	19	9	9	9	9	18	18	9	9	9	9	19	146	Y
S	6	8	18	10	10	9	9	19	18	9	9	9	9	19	148	Y
S	12	12	13	7	6	7	6	14	13	6	7	7	6	12	104	Y
S	13	12	16	8	8	8	8	17	16	8	8	9	8	17	131	Y
S	13	13	16	8	8	8	8	16	16	8	8	8	8	16	128	Y
S	23	2	19	10	9	10	10	18	19	9	10	10	9	20	153	Y
N	14	3	18	9	9	9	9	18	19	9	9	9	10	19	147	Y
N	8	3	14	8	8	8	8	14	15	7	7	7	7	14	117	Y
N	8	4	17	9	9	8	9	16	18	9	8	8	9	18	138	Y
N	8	5	14	7	7	7	8	14	14	8	8	8	7	14	116	Y
N	8	6	15	7	7	8	7	14	16	7	7	8	7	14	117	Y

N	9	1													73	Y
N	9	2													68	Y
N	9	3	18	8	8	8	8	18	17	8	8	8	8	16	133	Y
N	9	4	12	6	6	6	7	13	12	6	7	6	7	13	101	Y
N	9	5	12	6	7	6	6	12	12	6	6	6	6	12	97	Y
S2	12	1	13	7	7	6	6	13	13	6	7	6	7	13	104	Y
S2	12	5	19	10	9	9	9	18	18	10	9	9	9	19	148	Y
S2	12	9	11	6	5	6	5	12	11	6	5	6	5	11	89	Y
S2	8	7	16	8	9	8	8	17	16	9	9	9	9	17	135	Y
S2	8	9	14	7	7	7	7	14	14	6	7	7	7	14	111	Y
S2	9	4	19	9	9	9	9	18	18	9	9	10	9	18	146	Y
S2	9	5	13	7	6	7	6	14	13	6	6	6	7	12	103	Y
S2	9	6	12	6	7	6	6	12	13	6	6	6	6	13	99	Y
S2	9	7	11	6	6	5	5	12	10	6	5	5	6	10	87	Y
S2	9	8	17	8	9	8	8	16	16	8	9	9	8	16	132	Y
S2	9	9													35	N
S2	9	10	18	9	9	9	9	18	18	9	9	9	9	18	144	Y
S2	6	9	16	8	8	8	8	17	16	8	8	8	9	16	130	Y
S2	8	1	18	9	9	9	9	18	18	9	9	9	9	18	144	Y
S2	13	2	18	9	9	10	10	18	20	10	9	9	10	20	152	Y
S2	9	1	10	5	5	6	5	10	10	5	5	5	5	10	81	Y
S2	9	2	18	10	9	9	10	18	18	10	10	10	10	19	151	Y

Appendix B
Additional analyses for methamphetamine (1.5 mg/kg), quinpirole (0.08 mg/kg), scopolamine (0.1 mg/kg), and nicotine (0.2 mg/kg)

Methamphetamine (1.5 mg/kg)

In order to determine between which drug conditions the significant main effect of drug had occurred, more specific ANOVAs were performed. An analysis of the pre-drug saline condition versus the methamphetamine condition revealed a significant main effect of drug [$F(1,5)=11.67$, $p<.05$] and signal [$F(5,25)=242.16$, $p<.001$], but no effect of dimension [$F<1$]. There was also a significant two-way interaction of dimension by signal [$F(5,25)=12.17$, $p<.001$] and drug by signal [$F(5,25)=31.59$, $p<.001$], but no effect of dimension by drug or dimension by drug by signal [$Fs<1$]. An analysis of the methamphetamine condition versus the post-drug saline condition revealed a significant main effect of signal [$F(5,25)=78.11$, $p<.001$], but no effect of dimension or drug [$Fs<1$]. There was also a significant two-way interaction of dimension by drug [$F(1,5)=7.80$, $p<.05$], dimension by signal [$F(5,25)=7.10$, $p<.001$] and drug by signal [$F(5,25)=5.04$, $p<.005$], but no effect of dimension by drug by signal [$F<1$].

Quinpirole (0.08 mg/kg)

In order to determine between which drug conditions the significant main effect of drug had occurred, more specific ANOVAs were performed. An analysis of the pre-drug saline condition versus the quinpirole condition revealed a significant main effect of dimension [$F(1,7)=6.91$, $p<.05$], drug [$F(1,7)=16.93$, $p<.005$], and signal [$F(5,35)=26.01$, $p<.001$] and drug and signal [$F(5,350=54.52$, $p<.001$], but not effect of dimension by drug or dimension by drug by signal

[Fs<1]. An analysis of the quinpirole condition versus the post-drug saline condition revealed a significant main effect of dimension [F(1,70=6.28, p<.05] and signal [F(5,35)=16.86, p<.001], but no effect of drug [F<1]. There was also a significant two-way interaction of dimension by signal [F(5,35)=23.69, p<.001] and drug by signal [F(5,35)=9.42, p<.001], but no effect of dimension by drug or dimension by drug by signal [Fs<1].

Scopolamine (0.1 mg/kg)

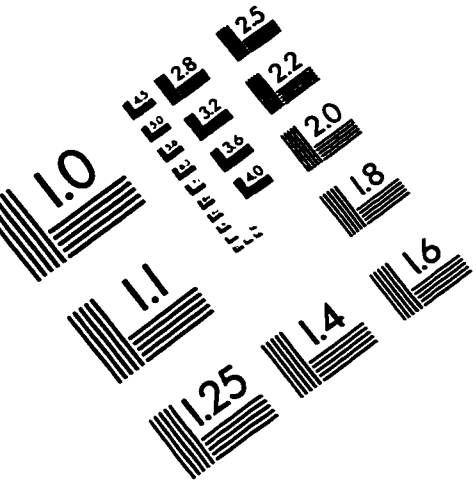
In order to determine between which drug conditions the significant main effect of drug had occurred, more specific ANOVAs were performed. An analysis of the pre-drug saline condition versus the scopolamine condition revealed a significant main effect of dimension [F(1,5)=6.86, p<.05], drug [F(1,5)=25.70, p<.005], and signal [F(5,25)=89.66, p<.001]. There was also a significant two-way interaction of dimension by signal [F(5,25)=16.21, p<.001] and drug by signal [F(5,25)=10.18, p<.001], but no effect of dimension by drug or dimension by drug by signal [Fs<1]. An analysis of the scopolamine condition versus the post-saline drug condition revealed a significant main effect of signal [F(5,25)=127.44, p<.001], but no effect of dimension or drug [Fs<1]. There was also a significant two-way interaction of dimension by signal [F(5,25)=15.53, p<.001], but no effect of dimension by drug, drug by signal, or dimension by drug by signal [Fs<1].

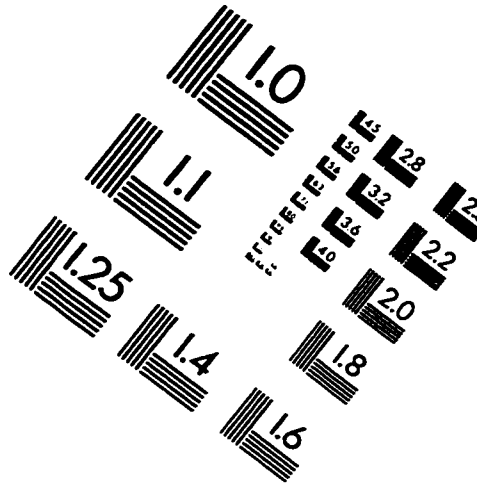
Nicotine (0.2 mg/kg)

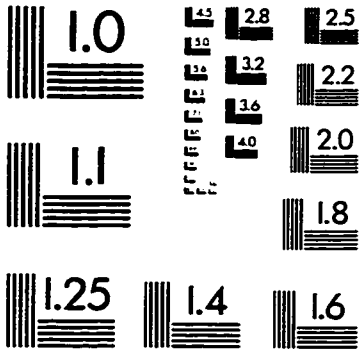
In order to determine between which drug conditions the significant main effect of drug had occurred, more specific ANOVAs were performed. An analysis of the pre-drug saline condition versus the nicotine condition revealed a significant main effect of drug [F(1,19)=18.94, p<.001]

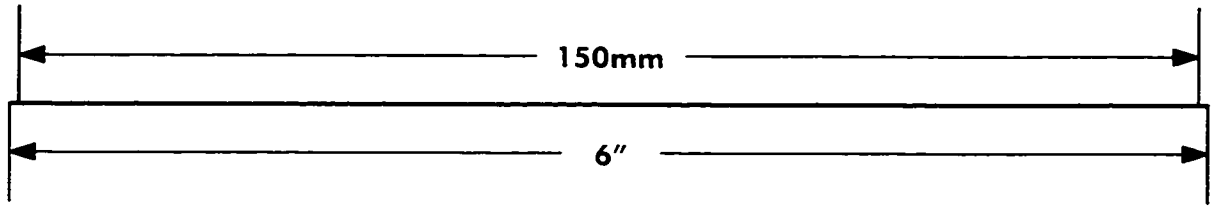
and signal [F(5,95)=135.20, p<.001], but no effect of dimension [F<1]. There was also a significant two-way interaction of dimension by drug [F(1,19)=5.37, p<.05], dimension by signal [F(5,95)=18.00, p<.001], and drug by signal [F(5,95)=17.47, p<.001], but no effect of dimension by drug by signal [F<1]. An analysis of the nicotine condition versus the post-drug saline condition revealed a significant main effect of signal [F(5,95)=111.91, p<.001], but no effect of dimension or drug [Fs<1]. There was also a significant two-way interaction of dimension by drug [F(1,19)=7.54, p<.05], dimension by signal [F(5,95)=21.79, p<.001], and drug by signal [F(5,95)=6,49, p<.001], but no effect of dimension by drug by signal [F<1].

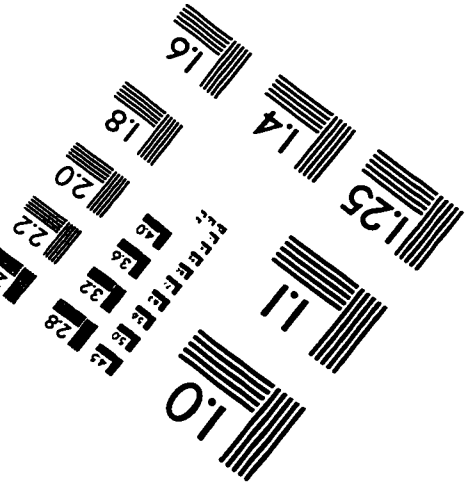
IMAGE EVALUATION TEST TARGET (QA-3)

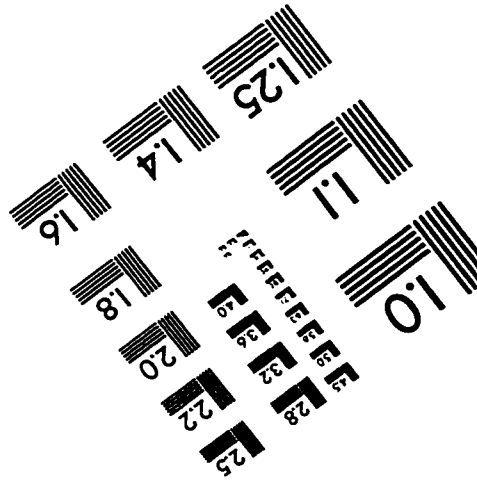












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