BEHAVIORAL AND PHARMACOLOGICAL MODIFICATION OF ATTENTIONAL PROCESSES INVOLVED IN PEAK-INTERVAL TIMING

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BEHAVIORAL AND PHARMACOLOGICAL MODIFICATION OF ATTENTIONAL PROCESSES INVOLVED IN PEAK-INTERVAL TIMING

BY

© TREVOR B. PENNEY

A thesis submitted to the School of Graduate Studies in partial fulfillment of the requirements for the degree of Master of Science

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September, 1993

St. John's Newfoundland

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ISBN 0-315-96057-4

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The involvement of attentional processes in interval timing was investigated, both behaviorally and pharmacologically, in rats trained on 10-sec and 30-sec peak-interval timing procedures. Three behavioral procedures were used: standard peak-interval, prior-entry, and prior-entry reversal. Brain levels of norepinephrine were manipulated using the α_2-agonist clonidine (0.025 mg/kg i.p.) and the α_2-antagonist idazoxan (2 mg/kg i.p.). In the prior-entry procedure a cue of the same modality as the signal to be timed preceded signal presentation, in the prior-entry reversal procedure the cue was of a different modality from the signal to be timed, and in the standard peak-interval procedure a cue was not presented. Relative to the peak-interval procedure the rats showed a horizontal rightward shift in their peak functions for the prior-entry reversal procedure. The α_2-agonist clonidine caused a rightward shift in peak functions for all behavioral procedures. The α_2-antagonist idazoxan also caused an unexpected horizontal rightward shift in peak functions. These horizontal shifts may be interpreted within the framework of an increase (rightward shift) in the latency to start the internal clock that is influenced both by the attentional demands of the task and the effective level of brain norepinephrine. The presentation of a cue directs the rat's attention toward a particular signal modality. If the cue directs attention to a different modality from the subsequently presented timing signal the rat takes longer to notice the signal. The effect of clonidine administration implicates the noradrenergic system in the attentional aspect of interval timing and also provides further support for the role of norepinephrine in general attentional processing.

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Temporal Processing

Time perception allows an animal to determine cause and effect, and to become more efficient in dealing with demands placed on it by the environment (Roberts & Holder, 1984a). When an animal learns that one event precedes another, the presence of the first event can allow the animal to predict and prepare for the second. An animal could also use the ability to time durations to make its foraging strategies more efficient. When an area is depleted of food it is in an animal's best interest not to return to that area immediately but rather to wait until the region has been replenished. If an animal is sensitive to the duration since its last visit, it can forage in a more optimal fashion thereby maximizing its food gain relative to energy and time lost. Animals also need to make use of a timing mechanism while in the food patch in order to decide whether or not to stay in the patch (Krebs & Kacelnik, 1984). If an animal is to determine whether or not its rate of gain in terms of energy is high enough to justify staying in the patch it must be able to average its energy intake and expenditure over time.

Animals, however, do not time all events in their environment. If time is viewed as a form of information (Michon & Jackson, 1984) then there must be an upper limit on the amount of such information that can be processed. Due to this upper limit on attentional capacity an animal must select certain events or stimuli from its environment that are relevant to the current task and exclude other events from processing. This suggestion is supported by work using the peak-interval procedure (Roberts, 1981) which demonstrated that rats time signals that predict important events but do not time non-predictive signals (Roberts & Holder, 1984b).

One procedure used to study timing is the peak-interval procedure which is similar to a discrete-trials fixed-interval procedure (Roberts, 1981). On some trials the animal is rewarded for the first response after a discriminative stimulus has been present for a fixed time whereas on other trials the stimulus remains on for a much longer duration and no reward is available. The responses are recorded during the non-rewarded trials to yield a response/time function. Following training with this procedure, mean response rate averaged across trials steadily increases until it reaches a maximum at about the time that food is normally given and then declines. Averaged over trials, a plot of responses through time yields a Gaussian response-rate function. The main measures of performance are peak-time, the time of maximum response rate measured from the start of the trial and peak-rate, the response rate observed at the peak time.

Within a certain range of time values peak-time and peak-rate are independent measures (Roberts, 1981). One can change peak-time without changing peak-rate and vice versa. Peak-time is sensitive to changes in the animal's internal representation of time and peak-rate is sensitive to the animal's motivational state. The results found with the peak-interval procedure have been confirmed by a number of other temporal discrimination procedures which rely on different assumptions (Roberts, 1982; Meck, Church, & Olton, 1984; Roberts & Holder, 1984b). This confirmation by other procedures provides strong support for the peak-interval procedure as a valid and sensitive measure of temporal discrimination.

A psychological model of the short-interval timing process identifies four major parts: the clock, working memory, reference memory, and comparator (Church, 1984; Gibbon, Church, & Meck, 1984). The clock is composed of a pacemaker, a switch and an accumulator. The pacemaker emits pulses that are switched into an accumulator. The latency to close the switch is influenced by the amount of attentional resources directed toward the modality of the signal which is to be timed. Working memory is used if the value in the accumulator needs to be stored temporarily in the absence of the timing signal. The number of pulses emitted during the current trial is compared to a reference memory store of the number of pulses preceding reinforcement on previous trials. The comparator has the role of comparing the value in the accumulator to the value in reference memory in order to determine whether a response should be made. If the two values are close enough, as determined by a response rule, a response is made. If a response is made and reinforced, the value is stored in reference memory.

Neural Substrates of Temporal Processing

The neural substrates of several aspects of the psychological model have been localized using pharmacological and lesion techniques. For example, methamphetamine and haloperidol alter timing functions in a characteristic manner (Maricq, Roberts & Church, 1981; Meck, 1983). The specific nature of the alteration indicates which aspect of the internal time representation has been affected by the manipulation. Methamphetamine administration immediately decreases peak-time whereas haloperidol causes an immediate increase. If administration is continued over a number of training days these effects gradually disappear. If the administration of either drug is then abruptly stopped there is an immediate rebound effect in the direction opposite to the initial effect. With continued

training peak-time gradually returns to its pre-drug value. This particular pattern of results has been interpreted as a change in the speed of the rat's pacemaker (Aronson & Meck, 1994; Meck, 1983). Methamphetamine causes the rat's pacemaker to operate faster than normal such that the criterion for responding is met earlier. Because the rat does not receive reinforcement at the expected time the rat's reference memory store (criterion value) is steadily adjusted so that it comes to accurately reflect the time of food availability given that clock speed has increased. When the methamphetamine is removed the pacemaker returns to its normal rate. As a consequence it now takes longer for the clock to meet the criterion value to release a response. Therefore peak-time occurs later than normal. Continued training with the pacemaker operating at the normal rate causes the reference memory store of the criterion value to be changed to reflect the number of pulses that now occur prior to earliest food availability. The drug haloperidol has the opposite effect of methamphetamine in that its initial presentation causes an increase in peak-time and that its removal after chronic administration causes a decrease in peak-time. This pattern is interpreted as haloperidol causing a decrease in pacemaker speed. Methamphetamine is a dopamine receptor agonist whereas haloperidol is a dopamine receptor antagonist. The effectiveness of these two drugs in changing clock speed implicates the dopaminergic system in control of clock rate. A study of drugs capable of causing a rightward horizontal shift in timing functions via changes in pacemaker speed indicated that the affinity of a drug for the dopamine D_2 receptor was the best predictor of a drug's ability to cause a shift (Meck, 1986).

These pharmacological results have received further support from neuroanatomical lesion studies of dopaminergic pathways. Rats that received substantia nigra (SN) or caudate putamen (CPu) lesions had severe impairments in their ability to either generate or accumulate the pulses required to quantify the temporal dimensions of stimulus events (Meck, 1994a). These results were interpreted as indicating that the SN and possibly the ventral tegmental area (VTA) send pacemaker signals to the CPu and other areas of the striatum where they can be integrated over time.

Pharmacological manipulations using physostigmine and atropine change peak-time in a manner which suggests changes to a different aspect of the rat's temporal representation. Within the framework of the psychological model of timing the value transferred from the accumulator to reference memory at the time of reinforcement is assumed to be the value in the accumulator times a memory storage constant (K*) (Church & Meck, 1988). Administration of physostigmine or atropine affects the comparison

between the output of the clock and the memory of reinforcement times by changing K* (Meck, 1983). Acute administration of these drugs does not alter peak-time, however, chronic administration results in a gradual shift in peak-time to a new value. When the drug is removed there is a gradual shift in peak-time to the original value. Unlike pacemaker effects there is no rebound to a value greater or less than the original value. Physostigmine, which increases the effective level of ACh in the brain, produces a leftward shift or decrease in peak-time. Atropine, which blocks ACh receptors, produces a rightward shift or increase in peak-time (Meck & Church, 1987). These effects are explained in terms of cholinergic drugs either facilitating or disrupting the memory storage of pacemaker values corresponding to reinforcement times. If the memory storage speed is increased then the reinforcement times will be systematically recorded as occurring earlier than they actually did. Alternatively, if memory storage speed is decreased reinforcement times will be recorded as occurring later than they actually did. The shifts are gradual because changes in the remembered store of reinforcement times depend on old values being replaced by newer ones. When the drugs are removed it takes more than one trial for the new temporal representations to dominate the old ones.

Lesion studies indicate that the frontal cortex is involved in the reference memory storage of temporal values although the frontal cortex itself may not be the site of storage (Meck, 1993b).

The frontal cortex has also been implicated as being involved in the divided attention component of a simultaneous temporal processing task. Rats that received lesions of the frontal cortex (FC) or the nucleus basalis magnocellularis (NBM) were able to time a single stimulus but could not time two stimuli presented simultaneously whereas rats that received control lesions could perform both tasks (Olton, Wenk, Church, & Meck, 1988).

The hippocampus has been implicated as the working memory storage site in temporal tasks which require the animal to hold the value of a stimulus duration during a gap in stimulus presentation and then add to this the value of the continuation of the stimulus presentation. (Meck, Church, Olton, 1984).

The nucleus accumbens is believed to be involved in the control of an animal's motivational state and therefore peak-rate. Peak-rate is sensitive to motivational factors and can be affected by changes in the probability of food (Roberts, 1981). The peak-interval procedure has the advantage of allowing one to determine whether pharmacological effects are due to processing (i.e. pacemaker, retrieval/storage or attentional processes) or to motivational factors. If motivation alone is affected then peak-rate but not peak-time might

change.

Attention and Temporal Processing

Within the framework of the information processing model of timing outlined above attention could be placed both at the level of the switch and at the level of the comparison process. Attention operating at the level of the switch would affect the latency to close the switch and begin timing a particular signal. The current research addresses this aspect of the attentional component of timing and is discussed in detail below. Attention operating at the level of the comparison process would be involved in simultaneous temporal processing or divided attention tasks and has been localized to the frontal striatal loops (Olton, Wenk, Church, & Meck, 1988).

Behavioral Manipulations

The present study investigated the behavioral modification of the attentional component of timing using the peak-interval, prior-entry, and prior-entry reversal procedures. The prior-entry and prior-entry reversal procedures are modifications of the peak-interval procedure and have demonstrated an attentional bias between modalities in animal time discrimination (Meck, 1984). The prior-entry method entails giving the subject a brief warning cue of the same modality as the subsequently presented timing signal. For example, rats were initially trained on the standard peak-interval procedure such that a stimulus of one modality (e.g. light) indicated that food might be primed 10-sec after signal onset and that a signal of another modality (e.g. sound) indicated that food might be primed 30-sec after signal onset. Subsequently rats were trained with the prior-entry method. Rats were given a 1-sec warning cue and then, after a short variable interval, a timing signal of the same modality as the warning cue was presented. As in the initial training, a timing signal of one modality indicated reinforcement was available after 10-sec and the other modality after 30-sec. During training the modality of the warning cue and timing signal were always the same. As a result rats could use the warning cue to predict which signal modality would occur next, allowing the rat to select the appropriate temporal criterion and response rule for the upcoming signal.

Following this training phase, the prior-entry reversal procedure was introduced. A random 25% of the prior-entry trials were not reinforced and the modality of the warning

cue and the modality of the timing signal were different. Meck found that the rats used the temporal criterion and response rule appropriate for a timing signal of the same modality as the warning cue rather than the criterion and response rule appropriate for the actual signal that was presented. For example, a rat trained to anticipate food availability 10-sec after the onset of light and 30-sec after the onset of sound would treat a sound stimulus as a light stimulus when it was preceded by a light cue and exhibit greatest anticipation of reinforcement after approximately 10-sec of the stimulus. Conversely when a sound cue was followed by a light stimulus the peak of responding would occur after approximately 30-sec. This result suggested that the consistent relation between the cue modality and the stimulus modality during training led rats to bias their attention toward the modality of the cue and to select in advance the temporal criterion and response rule to be used while timing the stimulus. The attentional bias produced by the cue apparently prevented the rats from attending to the modality of the stimulus and adjusting their temporal criterion and response rule to be appropriate for the modality of the stimulus being timed. The failure of the rats to update and correct the response rule and temporal criterion used during the stimulus presentation indicates that the rats take a single sample of the response rule and temporal criterion from reference memory on each trial.

The latency to time signals when they were unexpected (prior-entry reversal) was longer than when they were expected (prior-entry) although whether the signal is expected or unexpected may interact with the signal modality (Meck, 1984). The model of interval timing outlined above suggests that expected signals close the mode switch of the clock more rapidly whereas unexpected signals increase the latency to close the mode switch by requiring attention to be shifted from one modality to another.

The peak-interval procedure and the prior-entry and prior-entry reversal modifications of that procedure provide a method for examining the neural substrate of the attentional aspects of timing.

Physiological Basis of Attention

The noradrenergic system has been implicated in attention and as a consequence it may mediate attentional processes within timing tasks. In the present study, clonidine and idazoxan were used to manipulate the noradrenergic system in order to study an attentional component involved in timing. Clonidine is the most potent of the α_2 receptor agonists as it completely inhibits locus coeruleus (LC) neurons at extremely low doses (Svennson,

Bunney, & Aghajanian, 1975). Idazoxan is a highly selective α_2 receptor antagonist that enhances cell firing and NE release by blocking inhibitory autoreceptors on LC cell bodies and presynaptic receptors on nerve terminals (Sara, 1991; Richter-Levin, Segal, & Sara, 1991).

Central nervous system (CNS) norepinephrine (NE) may accentuate activity of neurons that are transmitting the presence of significant stimuli and inhibit the activity of other neurons (Kety, 1970). This could be interpreted as an improvement in the signal to noise ratio or an enhancement of selective attention. The locus coeruleus (LC) contains more than 40% of all NE neurons in the brain of the rat (Swanson & Hartman, 1975). In the rat the LC contains about 1500 neurons and is located bilaterally in the central gray of the isthmus on the floor of the fourth ventricle, medial to the mesencephalic tract of the trigeminal nerve (Grant & Redmond, 1981). The LC projection system is extremely global, innervating all major regions of the neuraxis. It provides the sole NE innervation of the cerebral, hippocampal and cerebellar cortices (Aston-Jones, 1985).

The hypothesis that selective attention was mediated by LC NE projections was initially based on the behavioral results of lesions to the dorsal noradrenergic bundle [DNAB] (Robbins, Everitt, Cole, Archer, & Mohammed, 1985; Mason, 1980). This pathway originates in the pontine LC and provides innervation to the spinal cord, cerebellum and many forebrain areas including the caudate-putamen (Mason, 1980). The LC may act as an important gating mechanism for determining the global level of attention to environmental stimuli, while the action of NE, in particular LC terminal sensory areas, could further specify the selectivity of such attention (Aston-Jones, 1985). Neural activity in the dorsal bundle could serve to filter out stimuli that are not relevant to the current task. If an animal is more efficient at detecting significant stimuli then this improvement might be demonstrated in behavioral tasks which require the animal to devote attention to the detection of stimuli. Pharmacological, physiological, and behavioral research supports the Kety hypothesis.

Microiontophoresis of NE onto cells in the auditory cortex of the squirrel monkey changed the pattern of firing to species-specific vocalizations; NE inhibited the background firing rate to a greater extent than the firing of cells driven by the preferred auditory stimuli (Foote, Friedman, & Oliver, 1975). NE applied to the visual cortex suppresses spontaneous background activity but enhances reactivity to some aspects of visual stimuli (Segal, 1985).

NE release induced by the α_2 receptor antagonist idazoxan (IDA) enhances the

evoked field potential recorded in the dentate gyrus after electrical stimulation of the perforant pathway (Sara, 1991). Since the perforant path is the main sensory input to the hippocampus Sara takes this result as evidence that NE modulates or gates sensory input to the perforant path thereby selecting, honing, and sharpening the information coming from the cortex to the hippocampus.

Electrical stimulation of the LC in the behaving rat enhanced the unconditioned inhibitory effect of an auditory tone on hippocampal firing and enhanced the excitatory effect of the same stimulus when it was predictive of food (Segal & Bloom, 1976). These results suggest an improvement in the signal to noise ratio of the evoked responses to salient environmental stimuli.

Activation of the noradrenergic system with IDA facilitated an attentional shift in the rat (Sara & Devauges, 1990). Rats were initially trained to solve a maze based on its spatial characteristics. When the rats had reached criterion, the task was changed such that they now had to solve the maze based on visual cues. Rats which received IDA on each training trial subsequent to the change from a spatial to a visual problem took significantly fewer trials to reach criterion than rats given saline. Control groups given IDA during the initial acquisition of the visual or spatial problem did not reach criterion faster than saline treated animals. This supports the contention that the drug effect was on the aspect of the task where the rat was required to notice a change in the significance of certain stimuli and use this new information to solve the task.

Depletion of cortical norepinephrine in rats widens the attentional span, impairing the acquisition of conditioning to an explicit stimulus while enhancing conditioning to contextual stimuli (Selden, Robbins & Everitt, 1990). Rats were exposed to pairings of an auditory CS and a shock US in a distinctive environment. Rats that were depleted of NE showed impaired fear conditioning to explicit cues but enhanced fear of contextual cues relative to controls. It was suggested that the coeruleal noradrenergic projections normally function to enable focusing of attention onto specific cues that predict reinforcement in preference to contextual cues.

As described earlier, Meck (1984) found evidence of attentional bias in time perception in the rat with the peak-interval, prior-entry, and prior-reversal procedures. Therefore, these procedures can be used to determine the involvement, if any, of NE in the attentional aspects of time perception.

General Method

Subjects. Subjects were 23 male albino Sprague-Dawley rats (Charles River Breeding Colonies, Montreal) about 70 days old at the start of the experiment. Rats were maintained on a 12:12 Light/Dark cycle for the duration of the experiment.

Apparatus. The rats worked in 8 similar lever boxes (Coulbourn E10-10) located in a separate room adjacent to the animal colony. The boxes' dimensions were 31(l) x 26(w) x 32.5(h) cm. Each floor consisted of 16 parallel stainless steel bars. The side walls were acrylic; the front and back walls and the roof were aluminum. Each box contained two stainless steel levers on the front wall. The levers measured 6 x 2 cm, projected 3.5 cm into the box and were 8 cm above the floor. The front lip of the lever was rounded. The force required to depress the lever was 27g. A response was recorded on the break of microswitch closure. In each box the pellet dispenser delivered a 45-mg Noyes sucrose pellet (Formula F). Pellets were delivered to a food tray located beneath and midway between the two levers. A 250ml water bottle was attached to the outside of the lever box such that the spout projected into the box from the right side at the back. The sound stimulus was a broad band increase in the noise level produced by a speaker located above the left lever. The light stimulus was the lever box houselight located above and midway between the levers. An isolating cubicle (Coulbourn E10-20) housed each box and each cubicle contained a ventilation fan that also helped mask extraneous noise.

Materials. Two drugs were used to test the involvement of the noradrenergic system in an attentional aspect of time perception. A dose of 0.025 mg/kg of clonidine was used. Pilot work by the author indicated that this dose level affects short-interval timing without sedating the animal to the point of motor inhibition. A dose of 2 mg/kg of idazoxan was used in the current experiment. This dose is close to one used in previous experiments using operant responding as the dependent measure (Sanger, 1988a; Sanger, 1988b). Rats were placed in the lever boxes 15-min after saline or drug injections.

Procedure. Throughout the experiment the rats had ad lib access to water but were on a restricted feeding schedule of 10 - 11g of standard lab chow per day initially, later increased to 14 - 15g of standard lab chow per day.

Rats were trained and tested in three shifts. Shift 1 started at 8:00 am, Shift 2 at 10:30 am, and Shift 3 at 1:00 pm. Sessions were two hr in duration and rats were trained and tested during the same shift throughout the entire experiment.

Pretraining (Sessions 1 - 14). Upon arrival at the animal colony the rats were given 20 days to habituate to their surroundings after which they were magazine trained and autoshaped to press levers in the presence of discriminative stimuli to obtain food rewards. For some rats left lever presses resulted in food only in the presence of a sound signal and right lever responses were only reinforced in the presence of a light signal whereas other rats received the left lever paired with light and the right with sound. The pairing of a particular signal modality with a particular response lever remained consistent for each rat throughout the experiment. During magazine training and autoshaping, signals were presented for either 10, 20, 30, or 40 seconds. The signal modality and duration used was determined randomly for each trial within a session. Each bar press on the appropriate signal-paired lever during the presence of the signal resulted in a 45 mg sucrose pellet, free food was also presented with a probability of 1/1000 calculated once each second of signal presentation. A criterion of 50 reinforced responses on one lever and at least 10 reinforced responses on the other was used. When rats reached this criterion magazine training was discontinued. All rats had reached criterion by Day 14.

Peak-interval (PI) training (Sessions 15 - 71). For half the rats the light signal indicated food availability after 10-sec and the sound signal indicated food availability after 30-sec. For the other half the light signal indicated food availability after 30-sec and the sound signal indicated food availability after 10-sec. Inter-trial intervals were a minimum of nine sec and had a 22% probability of ending after each subsequent second. During PI training 50% of trials were with light signals and 50% were with sound signals. Fifty percent of trials for both light and sound signals were reinforced and the other 50 percent were non-reinforced probe trials. Non-reinforced probe trials were trials in which the stimulus remained on for 120-sec and the rat was not rewarded for responding. Rats experienced about 20 trials of each of the four types during a session.

Three stages of behavioral testing were used in combination with administration of either the NE α_2 agonist clonidine or the antagonist idazoxan. The variants of the PI procedure were the standard PI procedure, the prior-entry procedure (PE), and the prior-entry reversal (PER) procedure. Figure 1 illustrates the temporal characteristics of the three

procedures. Figure 2 is a diagrammatic representation of the order of behavioral and pharmacological manipulations used in the current study.

Stage I. The standard PI procedure was used first (Sessions 15 - 71). All rats were injected with saline (1ml/kg, i.p.) prior to Session 60. Saline injections occurred on the day prior to drug manipulations for all rats and all drug manipulations. Saline was given in order to control for any effects of the actual injection procedure, effects of giving the vehicle alone, and also to reduce the likelihood of drug-ritual conditioning effects. For Session 61, 12 rats received injections of idazoxan (2mg/kg, i.p.), and 12 received clonidine (0.025mg/kg, i.p.). During Sessions 62 to 66 rats received the same operant training as during Sessions 15 to 59. All rats received saline injections prior to Session 67. For Session 68 those rats that received idazoxan before Session 61 received clonidine and those that received clonidine received idazoxan. For Sessions 69 to 71 rats were returned to regular PI procedure training. The rats were not run for a period of eight days between Sessions 71 and 72, however they remained on restricted food during this time.

Stage II. The second stage of Experiment 1 utilized the prior-entry method. Rats were trained on the prior-entry (PE) method of the PI procedure from Sessions 72 to 92. During the PE method rats received a 1-sec cue of the same modality as the signal prior to (a random interval between 2 and 15 sec) the onset of the signal. All rats received saline (1ml/kg, i.p.) prior to Session 93. For Session 94, 12 rats received idazoxan (1mg/kg, i.p.) and 12 received clonidine (0.025 mg/kg, i.p.). For Sessions 95 to 97 rats received the same prior-entry training as for Sessions 72 to 92. All rats received saline injections prior to Session 98. For Session 99 those rats that had received idazoxan for Session 94 received clonidine and those that had received clonidine received idazoxan. In order to counterbalance for the order of drug presentation, half of the rats received the same drug during Week 1 of Stage 2 as they received during Week 1 of Stage 1. The other half received the opposite drug during Week 1 of Stage 2 to the one they received during Week 1 of Stage 1. For Sessions 100 to 106 rats continued with standard prior-entry method training with the exception of Session 103 during which they were exposed to the prior-entry reversal procedure.

Stage III. Stage 3 involved the use of the prior-entry reversal (PER) method. For Sessions 103, 107, 116, 117, 123, and 124 the rats regular prior-entry training was changed such that on 50% of the trials the modality of the cue did not match the modality of the signal. All such reversed modality trials were nonreinforced trials. All rats were given saline (1ml/kg, i.p.) injections prior to Session 107. Technical difficulties at the end of

Session 107 resulted in the rats not being run for a period of 17 days. During this time all rats were placed on ad lib food. Rats were returned to their regular schedule of food restriction and PE procedure training at the end of this period, Session 108. Rats were not run for two days between Sessions 110 and 111 but were on a restricted feeding schedule for those two days. Prior to Session 116 all rats were given saline injections (1ml/kg, i.p.). For Session 117, 12 rats received idazoxan (1mg/kg, i.p.) and 12 received clonidine (0.025mg/kg, i.p.). Sessions 118 to 122 were PE sessions to allow the rats to return to baseline levels of responding. Prior to Session 123 all rats were injected with saline (1ml/kg, i.p.). For Session 124 rats which had received idazoxan for Session 117 received clonidine and those that had received clonidine received idazoxan. In order to counterbalance for order of drug presentation rats received the opposite drug during Week 1 of Stage 3 as they did during Week 1 of Stage 2.

Data Collection and Analyses

Each rat's responses were collected in 1-sec bins as a function of time since signal onset. Responses were collected for both fixed-interval and probe trials but only the probe data were analyzed. Responses were recorded for the first 60 seconds of stimulus presentation for the probe trials. Responses were collapsed across like trials within a session for each rat, divided by the total number of like trials run in the session, and multiplied by 60 in order to obtain an average response rate function in responses per minute.

The obtained average response-rate functions were fit with a Gaussian function with a background ramp component using the Peakfit program by Jandel. Peakfit, a general purpose non-linear fitting package which employs a graphical interpolation algorithm to determine the best fitting parameters, was used to provide an atheoretical analysis of the data and undoubtedly produces results very similar to iterative procedures (e.g. Roberts, 1981) and model fitting procedures (e.g. Gibbon, Church, & Meck, 1984). The background ramp function, consisting of y-intercept and slope, was included to account for some of the noise in the response functions not controlled by the timing system. The parameters of the Gaussian function provide a measure of peak-time (center), and spread (width). Prior to fitting with the Gaussian function the data were smoothed (20%) using a Fast Fourier Filter included in the Peakfit package. This filter converted the data to the Fourier domain and a window function was applied to filter out the high

frequency component. An inverse function then restored the data. Smoothing at this level did not affect the underlying parameter information and allowed data from more rats to meet the inclusion criterion outlined below.

Peak-rates were determined by taking the maximum of each rat's response-rate functions. Analyses of peak-rates were conducted on the logarithms of those peak-rates. Separate analyses were conducted to determine if behavioral procedure (PI, PE, PER) had an effect on peak-time and peak-rate and if pharmacological manipulation of NE affected peak-time and peak-rate.

Behavioral Effects Analysis

The data used to examine behavioral effects of the PI, PE, and PER procedures were collected on non drug administration days of each of the three experimental stages. Standard PI procedure data were obtained from Sessions 52 to 58, data from early PE training (PE1) were obtained from Sessions 72 to 79 with the exception of Session 74, and late PE training (PE2) data were obtained from Sessions 86 to 92. PER data were obtained from Sessions 103, 107, 116, 123. Session 103 was purely a behavioral manipulation whereas prior to Sessions 107, 116, and 123 the rats were administered saline. These sessions were included in order to increase the reliability of the PER response-rate functions.

Data were selected from 12 rats for the 10-sec Light functions, 11 rats for the 10-sec Sound functions, 11 rats for the 30-sec Light functions, and 12 rats for the 30-sec Sound functions.

The ANOVA's treated signal modality as a between-subjects factor and behavioral procedure as a repeated measure.

Figures only show comparisons of behavioral procedure (Figures 3-4). In this experiment each rat contributed seven sessions of data for the PI and PE procedures and four sessions of data for the PER procedure. Individual functions for each rat in each procedure were normalized, summed across rats and renormalized, smoothed and renormalized. Smoothing entailed calculating a running mean of five points for each point on the function with the exception of the first and last points which were running means of three points. Functions were normalized to ensure each rat's data contributed equally to the overall response function and to more readily allow comparisons between response functions.

The mean peak-times presented in all tables were calculated from the peak-times generated for individual rat's response-rate functions using the Peakfit software described above. The mean log peak-rates in all tables were calculated from the peak-rates generated from individual rat's response-rate functions.

Pharmacological Effects Analysis

Only data from those rats that demonstrated temporal discrimination (Curve fits with an r^2 value greater than 0.50) in all saline phases of each experiment were included in the data analysis. This means that if a rat failed to exhibit temporal discrimination on one saline day all the data from that rat for that particular signal modality were removed from the analyses of pharmacological effects. If a rat failed to exhibit temporal discrimination on a drug day the rat's saline day data were used in place of the drug data for statistical analyses. This approach assumed no effect of drug treatment for that rat on that particular behavioral manipulation but allowed the rat's data from the other behavioral manipulations to be included in the repeated measures design. If a rat's data were removed from the data analysis for one signal modality, its data for the other signal modality were included provided those data met the criterion for temporal discrimination. As a consequence of this requirement of consistent temporal discrimination, data were selected from 11 rats for the 10-sec Light functions, 11 rats for the 10-sec Sound functions, 6 rats for the 30-sec Light functions, and 5 rats for the 30-sec Sound functions.

Analyses of Variance (ANOVA's) were conducted to compare the effects of drug treatment on peak-time and peak-rate. Separate ANOVA's were conducted for the 10-sec and 30-sec data. The ANOVA's treated signal modality as a between-subjects factor and drug treatment and behavioral procedure as repeated measures.

In order to avoid unnecessary repetition in figure captions the data manipulation procedures used in figure and table preparation are described below. For the pharmacological effects the figures showing comparisons of saline and drug administration (Figures 5-6, 8-9, and 11-12) were obtained in the following manner. Rats' individual response rate functions were first normalized to percent of maximum response rate for each of the three behavioral procedures, the different procedural functions were summed, renormalized, summed across rats, renormalized, smoothed and then renormalized. Smoothing entailed calculating a running mean of five points for each point on the function with the exception of the first and last points which were running means of three points.

Functions were normalized to ensure each rat's data contributed equally to the overall response function and to more readily allow comparisons between response functions.

The mean peak-times presented in all tables were calculated from the peak-times generated for individual rat's response-rate functions using the Peakfit software described above. The mean log peak-rates in all tables were calculated from the peak-rates generated from individual rat's response-rate functions.

Results & Discussion

Behavioral Effects

Figures 3 and 4 suggest that the PER procedure caused a rightward shift in peak-time for the 10-sec signals, $F(3,63) = 4.20$, $p < 0.01$. However, a nearly significant modality x behavioral procedure interaction, $F(3,63) = 2.55$, $p = 0.06$, suggests that this effect is more pronounced for the 10-sec sound functions than for the 10-sec light functions. In the case of the 30-sec signals there was a rightward shift in peak-time for both the PE and the PER procedures relative to the PI procedure, $F(3,63) = 5.34$, $p < 0.01$. Table 1 shows the mean peak-times for both modalities and durations for each of the behavioral procedures.

There were no differences in peak-rate for the 10-sec signals due to the different behavioral procedures. In the case of the 30-sec signals, however, peak-rate was lower for the PI procedure than for the PE or PER procedures, $F(3,63) = 25.80$, $p < 0.01$. Peak-rates for the 10-sec and 30-sec signals are shown in Table 2.

The absence of a decrease in peak-time for any signal modality or duration when the signal was predicted by a cue in the PE procedure may be interpreted in a number of ways.

It may indicate there was no potential for improvement in attentional performance because the rats were already operating at maximal attentional capacity. If this were the case a modest decrease may have been too small to detect.

A second interpretation is that the rats, for one of two reasons, did not attend to the cues. They may not have learned that the cue predicted the modality of the stimulus. This is unlikely given the number of training trials the rats received. It is also possible that the cues were not salient enough in intensity or duration for the rat to notice and attend to them. If the cues were not noticed they could not serve to direct attention toward the correct signal

modality even though the target signals were noticed and timed correctly. It is likely that the duration of both cues was sufficient to be noticed because previous work has shown that cues 1 second in duration do affect responding in the peak procedure (Meck, 1984). Since the cues did have an effect in the PER procedure it is apparent the rats did notice and utilize the cues.

This shift supports the contention that the attentional component of time perception can be influenced by behavioral procedures. It also suggests that the rats were using the cues even though the cues did not cause a leftward shift in peak-time in the PE procedure.

The peak-rate increase for the 30 sec signals in both the PE and PER procedures may be due to the cues, whether correct or incorrect, increasing the probability the rat attended and responded during a given trial within the session thus increasing peak-rate relative to the PI procedure.

Pharmacological Effects

Clonidine

Figures 5 and 6 show a rightward shift in peak-time following clonidine administration for the 10-sec signals of both modalities. This increase in peak-time for both light and sound was supported statistically by a significant main effect of drug treatment $F(1,17) = 17.69$, $p < 0.01$. Figure 7 shows the increase in peak-time was present for all behavioral procedures and is supported by the absence of a significant drug by behavioral procedure interaction. As shown in Figures 8 and 9, drug treatment also increased peak-time for the 30-sec signals of both modalities $F(1,9) = 8.84$, $p < 0.05$. Figure 10 shows that for the 30-sec signals clonidine increased peak-time for the PI and PER procedures but not for the PE procedure. The clonidine-induced rightward shifts in response-rate functions for both modalities and durations, as indexed by peak-time, are presented in Table 3.

Administration of clonidine reduced peak-rate for the 10-sec signals for the PI and PER procedures but not for the PE procedure as indicated by a significant behavioral procedure by drug interaction $F(2,34) = 7.28$, $p < 0.01$. Table 4 shows that peak-rate was similar for the PI, PE and PER procedures following saline administration, but that peak-rate was reduced for the PI and PER procedures but not for the PE procedure following clonidine administration. Peak-rate was also greater for the sound signal than for the light

signal, $F(1,17) = 8.74$, $p < 0.01$.

Clonidine administration also reduced peak-rate for the 30-sec signals, $F(1,6) = 26.60$, $p < 0.01$. This effect is shown in Table 4.

An attentional aspect of a peak-interval timing task was apparently manipulated through pharmacological means for the 10-sec and 30-sec signals of both modalities.

Administration of the α_2 noradrenergic agonist clonidine caused a rightward shift in response-rate function, as indexed by an increase in peak-time, in all three behavioral procedures for the 10-sec signals of both modalities. This rightward shift is consistent with an increased latency to begin timing the signal, thereby reflecting an attentional deficit. However, there are a number of other possibilities that must also be addressed.

As described in the introduction decreases in pacemaker rate can produce rightward shifts in response-rate functions. There are two pieces of evidence which suggest the present effects are not due to an alteration of pacemaker rate. One would expect a pacemaker rate increase to change peak time by a constant proportion for both signal durations. In the present experiment the clonidine induced increase was 12% and 10% for 10-sec light and sound respectively and 7% and 4% for 30-sec light and sound respectively. Secondly, clonidine administration did not increase peak time in the PE procedure for the 30-sec signal. It is unlikely that the presentation of a cue would compensate for a drug-induced change in pacemaker rate. However, such an effect is consistent with an attentional hypothesis.

Another potential explanation of the clonidine effect involves an increase in memory storage speed (K*). As described in the introduction, memory storage speed refers to the storage in reference memory of accumulated duration corresponding to reinforcement times. Two reasons, however, make it unlikely that the clonidine effect was due to a disruption of memory storage speed. First, there was only a single administration of clonidine for each behavioral procedure. It is improbable that reference memory values could be changed enough within a single training session to yield significant K* effects within that session. Previous demonstrations of K* effects have required administration of pharmacological agents over many consecutive days (Meck and Church, 1987; Meck, 1983). Second, a decrease in memory storage speed should affect all modalities and durations of stimuli by a constant proportion. The differences following clonidine administration, however, were not equal for all modalities and durations.

Unlike pacemaker and K* effects, an attentional effect does not necessarily yield a

proportional difference for all stimulus durations and modalities. One might expect an attentional process operating at the level of initial switch closure to yield an absolute difference for all stimuli of the same modality. This is to say that the amount of time required to notice and begin timing a signal is independent of the duration of the signal. For example, if an average of one second is required to notice a signal, the duration of the signal should not matter as long as it is greater than the time required to be noticed. However it is possible that short and long durations within a session are not treated the same in terms of utilization of attentional resources. For the longer durations it takes longer for the animal to obtain food and therefore the rat may allocate less attentional resources to that signal modality as it is less valuable than the shorter duration signal modality.

The presence of a clonidine effect for the 10-sec signal in spite of the prior-entry cue is of interest because one may have expected the cue to compensate for the clonidine administration. If the prior-entry cue focuses the rat's attention on the correct signal the rat should have an advantage over the PI procedure in which both signals were equally likely and the rat had to divide attentional resources between the two modalities. When given a warning cue, the rat has only to focus attention on one modality. Therefore the rat could potentially compensate for the effect of clonidine when the signal was cued. Of course, if the rat normally uses the cues to focus attention upon a particular signal modality clonidine may interfere with its ability to notice the cue in the same manner that it interferes with its ability to notice the stimulus. Therefore, as the current data suggest, the rat would not be able to compensate for the effect of the clonidine.

There are at least three explanations for the decrease in peak-rate following clonidine administration.

It could be due to a motor impairment. If the clonidine dose was high enough to interfere with a rat's ability to move it would not have been able to respond at as high a rate. It should be noted, however, that motor inhibition should not affect peak-time because removing a constant proportion of responding from the entire response-rate function does not alter the peak of the function.

Clonidine may cause a decrease in the reward value of the sucrose pellets. Clonidine administration may have changed the rat's motivational state by making the rat ill or suppressing its appetite thereby reducing the value of the sucrose reward. Peak-rate decreased when normally food deprived rats were fed immediately prior to peak-interval procedure training (Roberts, 1981). The pre-feeding apparently reduced the intrinsic value of the reward pellets leading to a general reduction in the effort (i.e., bar presses) that the

rat expended to obtain the food.

If clonidine was producing motor impairment and/or decreasing the reward value of the food it should have reduced peak rate in the PE procedure. Because clonidine administration did not reduce peak rate for the 10-sec signals in the PE procedure these two explanations are not viable.

A more likely possibility is a generalized attentional deficit. On some proportion of trials within a session a rat fails to time the signal and responds at a fairly low constant rate throughout the entire trial. If clonidine increases the proportion of trials during which a rat fails to time the signal it will cause a decrease in peak rate. This is a consequence of how average response-rate functions were calculated. As outlined in the Data Analysis section, responses for each 1-second bin were summed across trials and divided by the number of trials. If there are more trials during which the rat either does not respond or responds at a low constant rate the average peak-rate will be reduced even though the rat's peak-rate on the trials that are attended to and timed may be normal. The finding that peak-rate for the 10-sec signals following clonidine administration was greater during the PE procedure than during the PI or PER procedure is consistent with this interpretation. The cue may have increased the probability the rat attended to and responded during a given trial within the session thus increasing the mean response-rate function and as a consequence increasing peak-rate. It is possible that a single trials analysis of the data would reveal whether or not a generalized attention deficit is present as it would allow one to determine the number of trials during a session that the rats attend and respond to the signals (Church, Meck, Gibbon, 1993).

Idazoxan

Figure 11 suggests that idazoxan administration increased peak-time for the 10-sec Light signal, whereas Figure 12 implies the effect is not present for the 10 sec Sound signal. This effect, as indicated by the interaction of signal modality and drug, approached but did not reach traditional levels of significance $F(1,17) = 4.22$, $p = 0.06$. Idazoxan treatment also did not alter peak-time for the 30-sec response-rate functions of either modality, $F(1,9) = 0.63$. The mean peak-time values are presented in Table 5.

Peak-rate was greater for the 10-sec sound signal than for the 10-sec light signal, $F(1,17) = 10.44$, $p < 0.01$. In the case of the 30-sec signals idazoxan administration

decreased peak-rate for the PI and PE procedures , but increased peak-rate for the PER procedure as indicated by a significant drug by behavioral procedure interaction $F(2,18) = 4.10$, $p < 0.05$. This effect is shown in Table 6.

Idazoxan administration was expected to improve the signal to noise ratio and as a consequence decrease peak-time. Surprisingly, however, idazoxan increased peak-time for the 10-sec signals of both modalities although not quite significantly. There is likely an optimal level of norepinephrine for maximum facilitation of attentional capacity and idazoxan administration may have increased NE levels beyond this optimal level thereby interfering with attentional processing and causing an increase in peak-time rather than a decrease.

General Discussion

The behavioral effect of PER supports the contention that allocation of attentional resources can be manipulated by behavioral procedures and measured by alterations in response-rate functions. Within the framework of the information processing model of timing this effect may be interpreted to be operating at the level of the switch component. The latency to close the switch and begin timing a signal can be increased or decreased depending upon whether attention is directed toward the correct or the incorrect stimulus modality.

The presence of a clonidine effect on timing functions, and the interpretation of this effect as attentional in nature provides further support for the role of the noradrenergic system, specifically the locus coeruleus, in selective attention. If CNS NE accentuates the activity of neurons that indicate the presence of significant signals while at the same time inhibiting the activity of other neurons then one may expect a reduction of CNS NE to result in a longer latency to notice the presence of stimuli that signal food. Clonidine increased peak-time and this increase may be interpreted as being due to an impairment of selective attention such that it took the rats longer to notice signal presentation and close the mode switch of the internal clock.

Some of the results of the present work differ from previous research. Meck (1984) found that when the modality of the cue did not match the modality of the signal the rat used a response criterion appropriate for the modality of the cue and not that of the signal. As a consequence it was posited that the rat retrieves only one criterion time from

reference memory and does not access reference memory again at a later point in the trial. In the present experiments, however, when the cue modality and the signal modality did not match, rats used the criterion time for the signal modality and not that of the cue modality. There are a number of possible explanations of this result.

It is quite likely that the sound and light signals were not of equal salience or intensity. The operant chambers were dark prior to presentation of the light signal. When signal onset occurred the chamber was illuminated completely, making it very likely the rat would notice its onset. In contrast, the white noise signal was not extremely loud and there was background noise provided by a fan in each isolation chamber. The difference between the auditory signal and background was not as great as that between the visual signal and background. The rats may have been able to determine that the signal was of a different modality from the cue, retrieve the correct criterion value and time the signal properly. If the signal had been of equal salience perhaps the rats would not have distinguished between the cue and signal modality and continued to time the signal using the criterion time appropriate for the cue modality. Retrieval of a new criterion value could potentially cause a delay in the commencement of timing and consequently an increase in peak-time, as was observed. Of course, as posited earlier, the delay could also be due to the rat failing to attend to the signal onset as it was focused on the incorrect signal modality.

Alternatively, the rats may not have been using the cue to determine which reference memory value to access and as a consequence mismatching had no effect. The absence of a decrease in peak-time for the PE procedure could be taken as support that the rats were not using the cue. If the rats had been using the cue to predict the signal modality and focus attention one would have expected a decrease in peak-time for PE relative to the standard PI procedure. However given the effect of PER it is very unlikely that the rats did not notice the cues. If they had not been using the cues to bias attention toward a particular modality then mismatching cue and signal modality would have had no effect. The increase in peak-time suggests that both cues were salient enough in terms of duration and intensity, to affect behavior. It is still possible that even though the rats may have used the cues to direct attention toward a particular stimulus modality they may not have retrieved the criterion value until the signal was presented.

Another possibility, and also the most likely explanation, is that the similarity of the ITI duration and the duration separating the cue and the signal interfered with the rat's ability to use the cue as a predictor of signal modality. If the PE method had caused a decrease in peak-time as expected it would have been because the cue focused the rat's

attention on the correct signal modality allowing it to notice signal presentation earlier than usual and/or the cue allowed the rat to retrieve the correct temporal criterion from reference memory in advance thereby saving processing time when signal onset occurred. Following an unreinforced probe trial the rat must reset its clock in order to be able to successfully time the next signal presentation. This reset must also erase the reference memory criterion value held temporarily in the comparator. Reset is not necessarily immediate upon termination of the signal, but may be a function of the similarity of signal offset to the ITI. Meck (1984) used an ITI of 130 seconds and a cue-signal gap that averaged 15 seconds. These two intervals are very different making it easy for the rat to distinguish between the ITI and the cue-signal gap. In the present experiment the ITI was a minimum of 9 seconds and had a 25% probability of ending after each subsequent second. The cue-signal gap ranged from 2 to 15 seconds. Assuming the cue initiated the retrieval of the criterion value, the similarity of these two intervals may have caused a reset of the criterion value in the comparator after each cue presentation. This reset would eliminate any enhancement of processing speed because it would force the rat to retrieve the correct criterion value from reference memory when signal onset occurred. The retrieval of the criterion time appropriate to the signal presented would result in a failure to replicate Meck's (1984) finding that the rat's use the criterion time appropriate for the modality of the cue. The reset of the timing system, however, does necessitate that the rat stops focusing attention on a particular sensory modality. The rat could still direct attention toward one modality and, therefore, not notice signal onset as quickly when the presented signal is of another modality. The results of the behavioral manipulations fit this pattern. The increase in peak-time for both 10-second signals when cue-stimulus pairings were reversed indicates that the rats were attending to the modality of the cue.

Another important difference was that unlike in previous work, in the present study the attentional effects were stronger for the sound modality as compared to the light modality. Previous work, as summarized in the introduction, suggested that sound signals are processed automatically and do not require the allocation of attention, whereas visual signals require the direction of attention toward the signal modality. One plausible explanation of this apparent discrepancy calls upon the suggestion, raised earlier in the General Discussion, that the light and sound signals were not of equal salience. Perhaps in previous work the light signals were less salient than the current light signal, whereas the sound signals may have been more salient than those used in the current experiment. It seems reasonable to suggest that whether a signal is difficult to detect and process is

governed by its salience in relation to other signals in its environment rather than a specific characteristic such as whether it is light or sound. Even if certain species have predispositions toward particular signal modalities there are likely circumstances under which those predispositions could be overridden.

Although there were some unexpected differences between the results of the current study and previous research these differences can be reasonably accounted for. The most important facets of the current research support and extend Meck's (1984) work on the attentional component of time perception and also provide further behavioral support for the role of NE in attention. It supports the contention that the attentional aspects of temporal processing can be manipulated with behavioral procedures. It extends the earlier work in that it localizes the attentional aspect of temporal processing to a specific neurotransmitter system. As summarized in the introduction, there is a range of evidence which suggests that the effective level of brain norepinephrine can enhance or interfere with attentional processing. More specifically, the dorsal noradrenergic bundle (DNAB), which originates in the pontine LC, is thought to act both as a gating mechanism for the global level of attention to environmental stimuli and also to mediate selective attention. The current data are consistent with both a specific deficit in selective attention and also a generalized attentional deficit. The administration of clonidine, which reduced NE levels, increased the rats' latency to notice signal onset which, in the framework of the psychological model of timing, corresponds to an increased latency to close the switch that could be due to a deficit in attending to specific signal modalities. Secondly, as was suggested in the discussion of clonidine effects, the decrease in peak-rate that occurred following clonidine administration may be interpreted as being due to a generalized attentional deficit.

The neuroanatomy of the DNAB is also consistent with the posited neural substrate of interval timing. Although only speculation as to the mechanism of action is possible from the current data, it is interesting to note that the DNAB does project to the caudate-putamen (CPu). The CPu is believed to be the accumulator (Meck, 1993a) so it is possible that the DNAB determines whether or not pulses from the pacemaker are gated to the accumulator (switch closure).

Finally it is important to test theories of the neurological basis of the components of cognition with several different behavioral procedures. It is especially important that those procedures have an extensive theoretical basis from which to interpret various aspects of the data. That manipulation of the noradrenergic system influenced the attentional aspects of temporal processing provides strong support for the involvement of NE in attention.

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Table 1. Group mean peak-times for each behavioral procedure in the absence of drug manipulations.

	10 Seconds				30 Seconds			
	PI	**PE 1**	**PE 2**	**PER**	**PI**	**PE 1**	**PE 2**	**PER**
Light	11.7 (0.4)	12.0 (0.4)	12.3 (0.6)	12.2 (0.4)	29.7 (1.3)	33.1 (1.4)	32.5 (1.0)	33.0 (1.1)
Sound	12.2 (0.37)	11.7 (0.69)	12.4 (0.76)	14.0 (0.59)	27.8 (1.71)	29.4 (1.2)	31.5 (0.9)	29.0 (1.2)

Table 2. Group mean log peak-rates for each behavioral procedure in the absence of drug manipulations.

	10 Seconds				30 Seconds			
	PI	**PE 1**	**PE 2**	**PER**	**PI**	**PE 1**	**PE 2**	**PER**
Light	1.54 (0.04)	1.58 (0.03)	1.56 (0.05)	1.54 (0.05)	1.45 (0.07)	1.48 (0.07)	1.58 (0.06)	1.62 (0.06)
Sound	1.62 (0.06)	1.62 (0.07)	1.67 (0.06)	1.70 (0.05)	1.42 (0.07)	1.46 (0.07)	1.50 (0.07)	1.51 (0.7)

Table 3. Group mean peak-times following saline or clonidine administration combined across behavioral procedures.

	10 Seconds		30 Seconds	
	Saline	**Clonidine**	**Saline**	**Clonidine**
Light	12.1 (0.4)	13.5 (0.4)	32.5 (1.0)	34.8 (1.4)
Sound	13.3 (0.6)	14.6 (0.5)	32.8 (1.2)	34.2 (1.6)

Table 4. Group mean log peak-rates for each behavioral procedure following saline or clonidine administration.

	10 Seconds			30 Seconds		
	PI	**PE**	**PER**	**PI**	**PE**	**PER**
Saline	1.73 (0.04)	1.76 (0.04)	1.70 (0.04)	1.72 (0.06)	1.82 (0.05)	1.84 (0.07)
Clonidine	1.55 (0.05)	1.74 (0.04)	1.46 (0.04)	1.57 (0.05)	1.72 (0.04)	1.66 (0.07)

Table 5. Group mean peak-times following saline or idazoxan administration combined across behavioral procedures.

	10 Seconds		30 Seconds	
	Saline	Idazoxan	Saline	Idazoxan
Light	12.0 (0.4)	13.6 (0.5)	32.3 (0.9)	33.6 (1.3)
Sound	13.8 (0.6)	13.8 (0.6)	30.4 (0.9)	27.5 (1.5)

Table 6. Group mean log peak-rates for each behavioral procedure following saline or idazoxan administration.

	10 Seconds			30 Seconds		
	PI	**PE**	**PER**	**PI**	**PE**	**PER**
Saline	1.73 (0.04)	1.75 (0.05)	1.68 (0.04)	1.76 (0.05)	1.78 (0.06)	1.75 (0.04)
Idazoxan	1.77 (0.04)	1.72 (0.04)	1.71 (0.03)	1.74 (0.07)	1.68 (0.06)	1.80 (0.04)

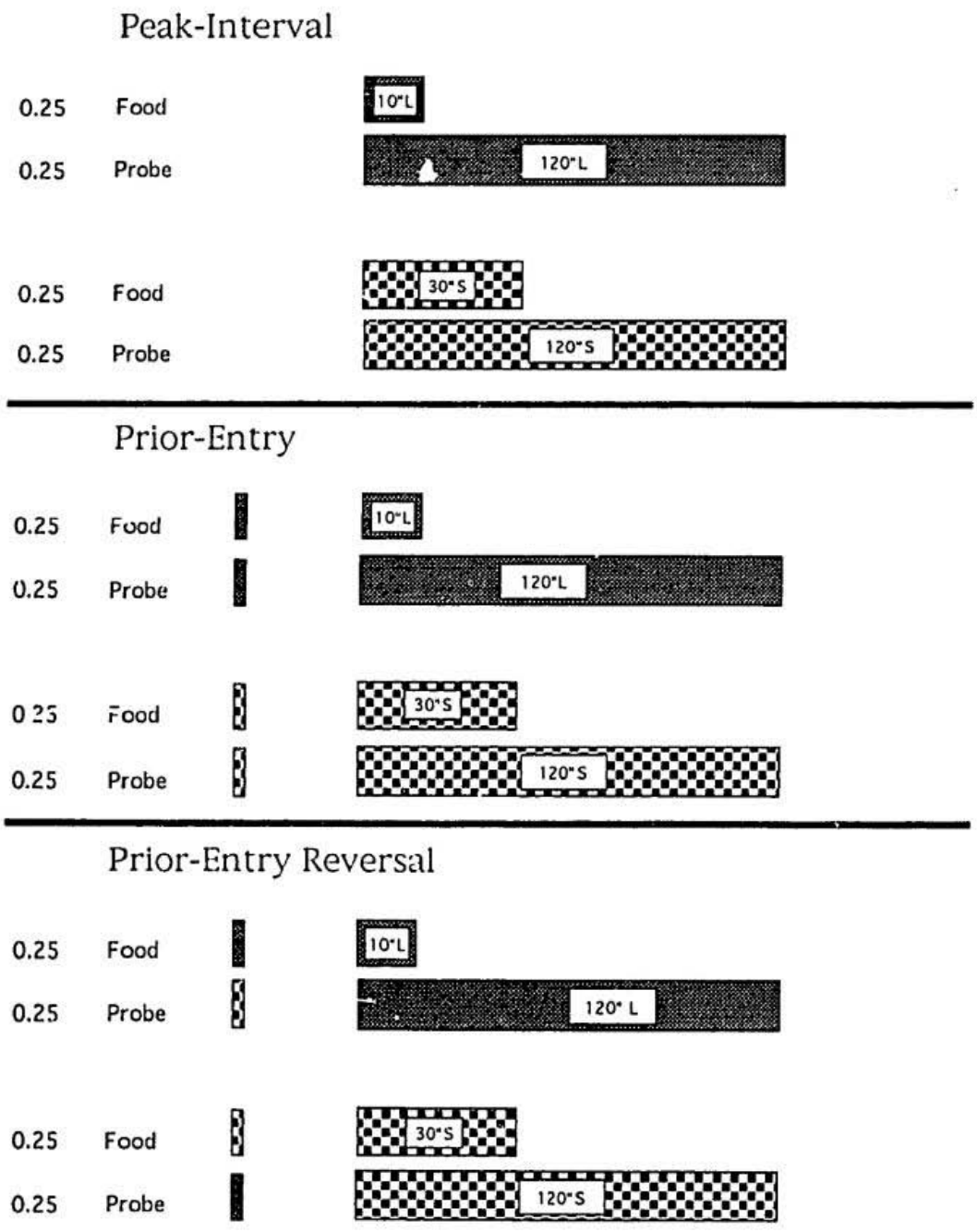
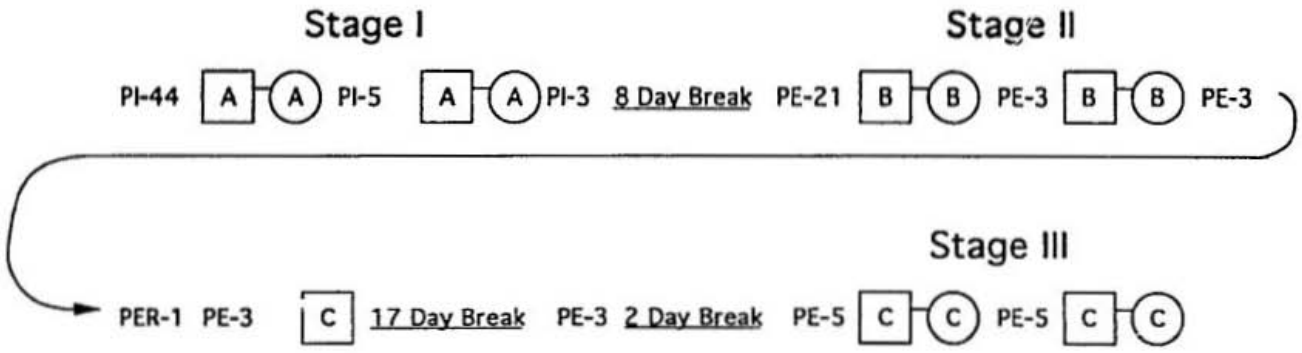


Figure 1. Example of the temporal characteristics of signals presented to a rat trained on a 10-sec light criterion and a 30-sec sound criterion. Ten-sec and 30-sec signals were equally probable as were food and probe trials. Cues in the prior-entry and prior-entry reversal conditions were 1-sec in duration.



PI = peak-interval procedure, PE = prior-entry method, PER = prior-entry reversal.

Digits refer to the number of training and/or test sessions within a condition.

A = 1 PI session, B = 1 PE session, C = 1 PER session.

= pairs of saline and drug test sessions.

Figure 2. Experimental flowchart illustrating the order of behavioral and pharmacological manipulations.

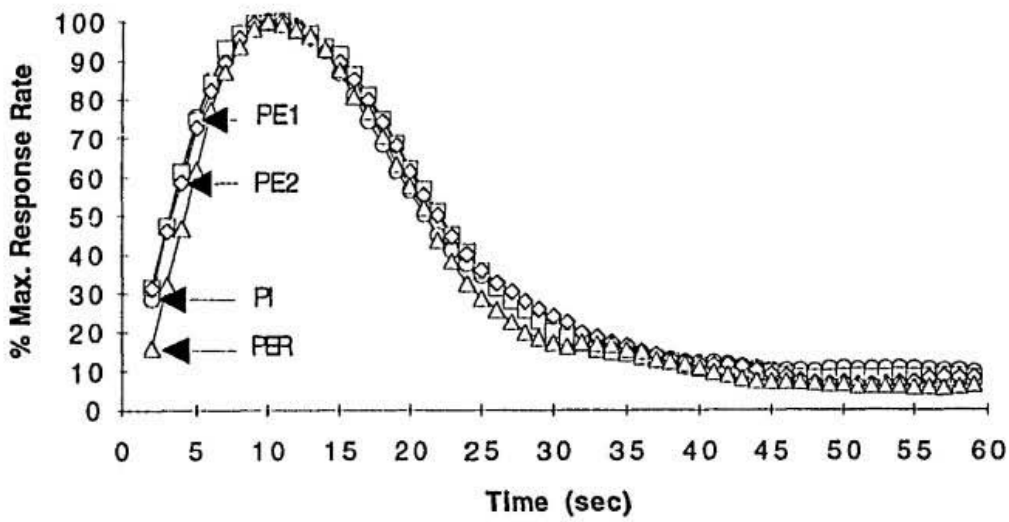


Figure 3. Mean response rate on probe trials for the peak-interval (open circle), prior-entry-1 (open square), prior-entry-2 (open diamond), and prior-entry reversal (open triangle) procedures, plotted as a function of time since signal onset. Rats were trained with a light signal and a criterion time of 10 seconds.

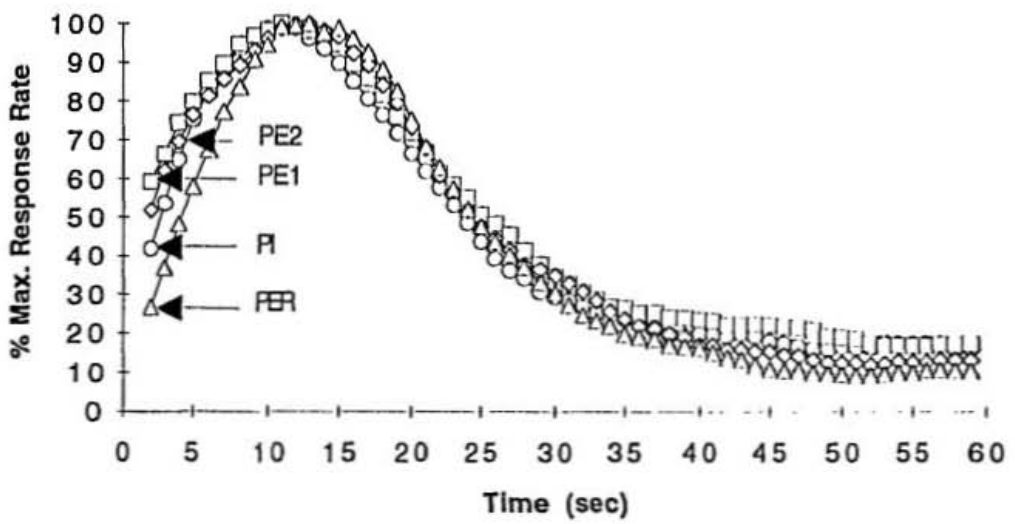


Figure 4. Mean response rate on probe trials for the peak-interval (open circle), prior-entry -1 (open square), prior-entry-2 (open diamond), and prior-entry reversal (open triangle) procedures, plotted as a function of time since signal onset. Rats were trained with a sound signal and a criterion time of 10 seconds.

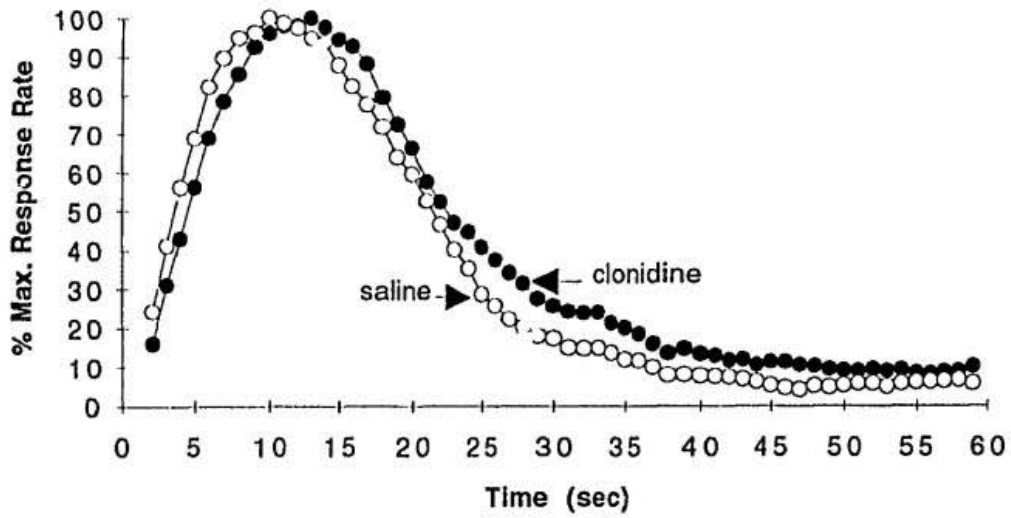


Figure 5. Mean response-rate on probe trials, following saline (open circles) and clonidine (closed circles) administration, plotted as a function of time since signal onset. Rats were trained with a light signal and a criterion time of 10 seconds.

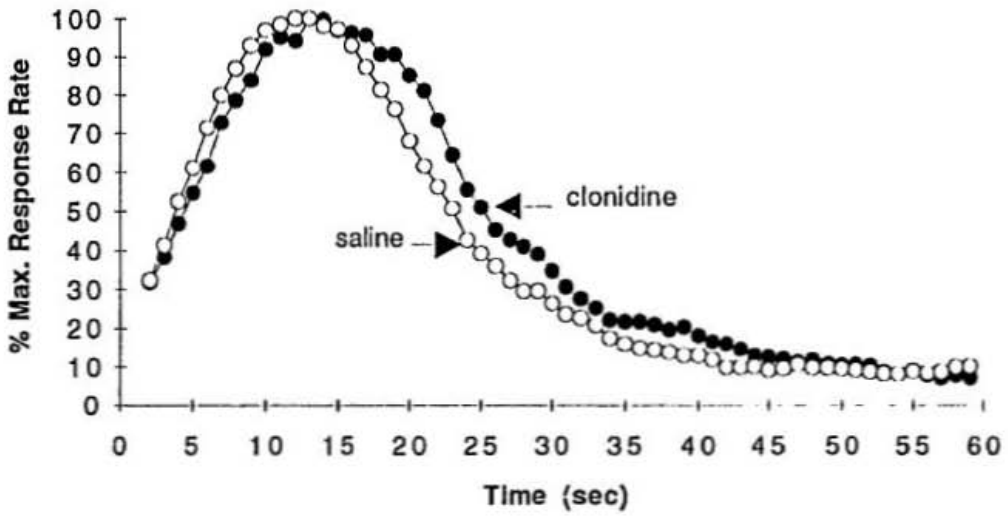


Figure 6. Mean response rate on probe trials, following saline (open circles) and clonidine (closed circles) administration, plotted as a function of time since signal onset. Rats were trained with a sound signal and a criterion time of 10 seconds.

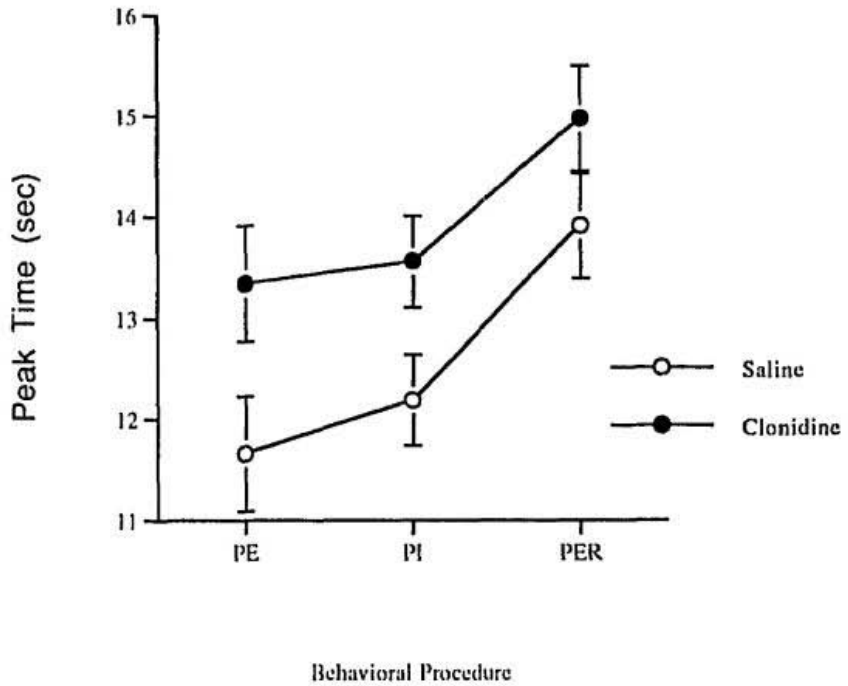


Figure 7. Peak-times for the 10-sec signals, combined over light and sound, as a function of drug administration for each of the behavioral procedures. Values plotted are means ± standard error.

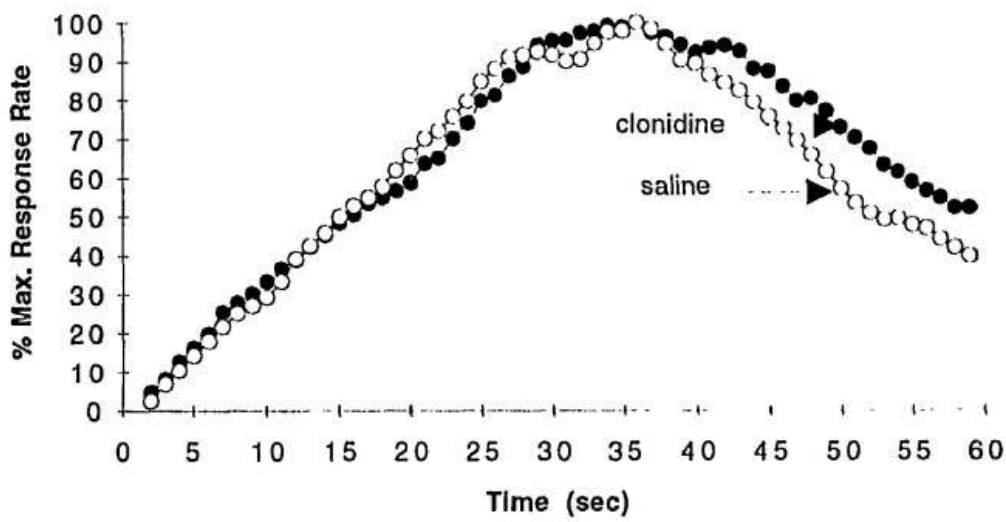


Figure 8. Mean response rate on probe trials, following saline (open circles) and clonidine (closed circles) administration, plotted as a function of time since signal onset. Rats were trained with a light signal and a criterion time of 30 seconds.

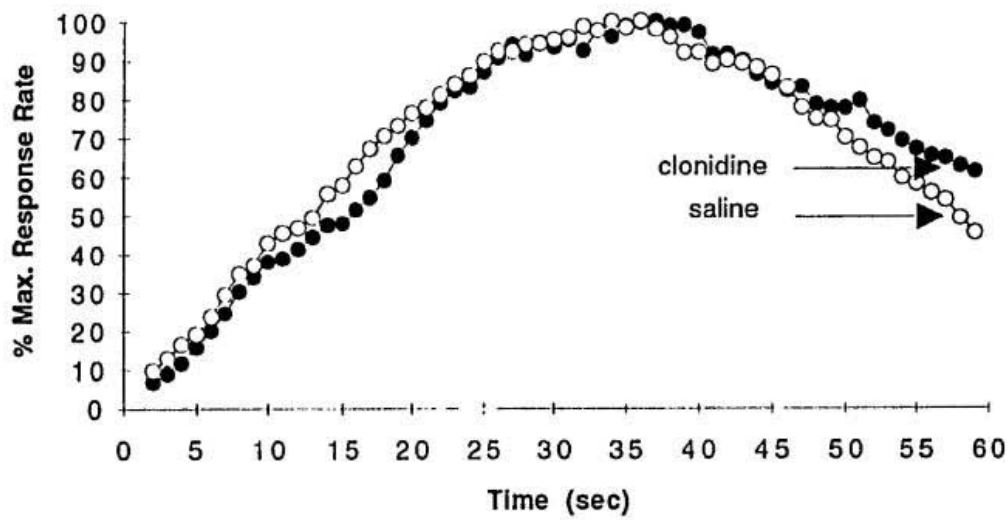


Figure 9. Mean response rate on probe trials, following saline (open circles) and clonidine (closed circles) administration, plotted as a function of time since signal onset. Rats were trained with a sound signal and a criterion time of 30 seconds.

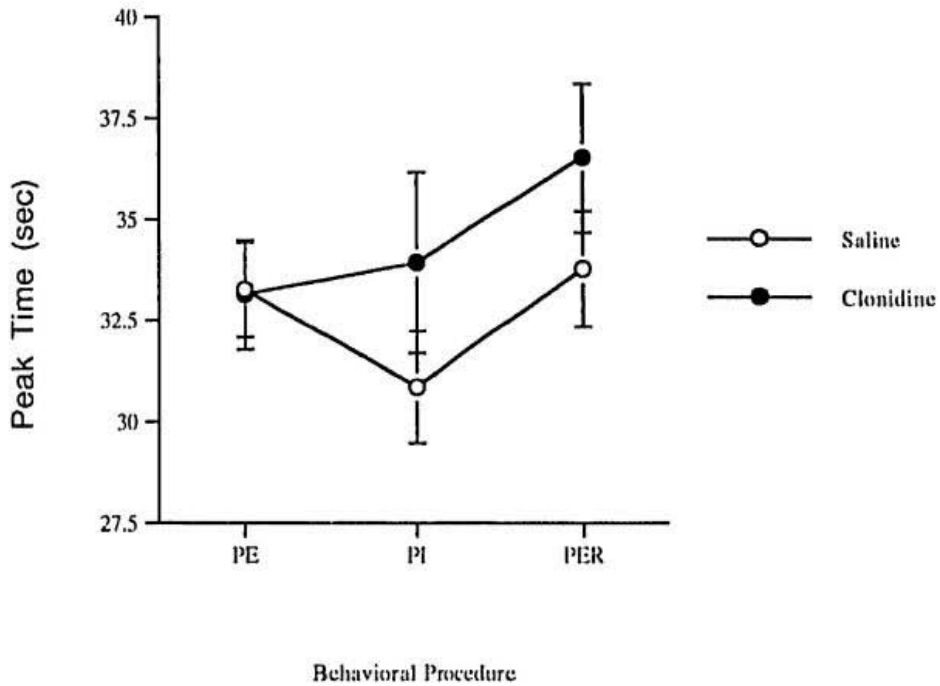


Figure 10. Peak-times for the 30-sec signals, combined over light and sound, as a function of drug administration for each of the behavioral procedures. Values plotted are means ± standard error.

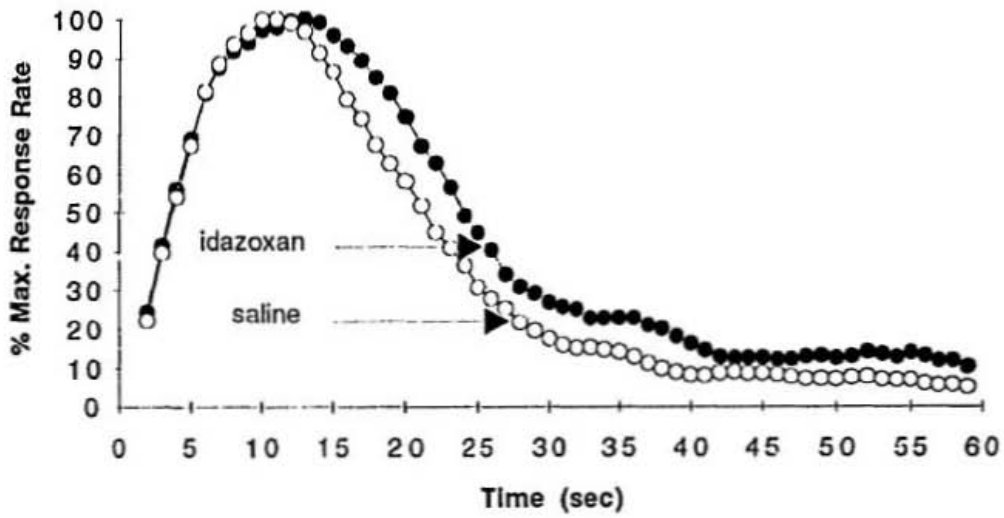


Figure 11. Mean response rate on probe trials, following saline (open circles) and idazoxan (closed circles) administration, plotted as a function of time since signal onset. Rats were trained with a light signal and a criterion time of 10 seconds.

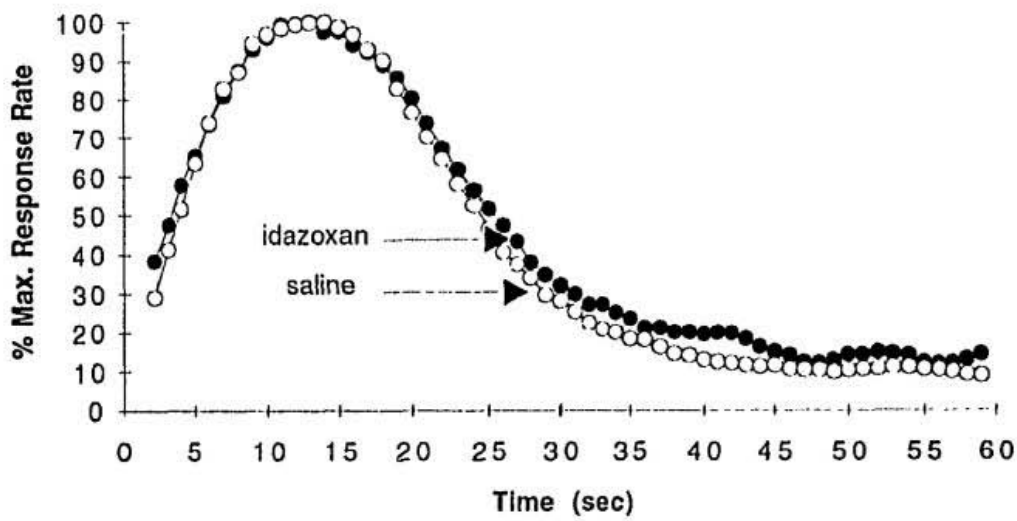


Figure 12. Mean response rate on probe trials, following saline (open circles) and idazoxan (closed circles) administration, plotted as a function of time since signal onset. Rats were trained with a sound signal and a criterion time of 10 seconds.