ASSESSMENT OF ATTENTION THRESHOLD IN RATS BY TITRATION OF VISUAL CUE DURATION DURING THE FIVE CHOICE SERIAL REACTION TIME TASK

Thomas J. Martin, **Amanda Grigg**, **Susy A. Kim**, **Douglas G. Ririe**, and **James C. Eisenach**

Pain Mechanisms Lab, Dept. of Anesthesiology, Wake Forest University Health Sciences, Medical Center Blvd, Winston-Salem, NC 27157, USA

Abstract

Background—The 5 choice serial reaction time task (5CSRTT) is commonly used to assess attention in rodents. We sought to develop a variant of the 5CSRTT that would speed training to objective success criteria, and to test whether this variant could determine attention capability in each subject.

New Method—Fisher 344 rats were trained to perform a variant of the 5CSRTT in which the duration of visual cue presentation (cue duration) was titrated between trials based upon performance. The cue duration was decreased when the subject made a correct response, or increased with incorrect responses or omissions. Additionally, test day challenges were provided consisting of lengthening the intertrial interval and inclusion of a visual distracting stimulus.

Results—Rats readily titrated the cue duration to less than 1 sec in 25 training sessions or less (mean ± SEM, 22.9 ± 0.7), and the median cue duration (MCD) was calculated as a measure of attention threshold. Increasing the intertrial interval increased premature responses, decreased the number of trials completed, and increased the MCD. Decreasing the intertrial interval and time allotted for consuming the food reward demonstrated that a minimum of 3.5 sec is required for rats to consume two food pellets and successfully attend to the next trial. Visual distraction in the form of a 3 Hz flashing light increased the MCD and both premature and time out responses.

Comparison with existing method—The titration variant of the 5CSRTT is a useful method that dynamically measures attention threshold across a wide range of subject performance, and significantly decreases the time required for training. Task challenges produce similar effects in the titration method as reported for the classical procedure.

Corresponding author: Thomas J. Martin, Ph.D., Pain Mechanisms Lab, Dept. Anesthesiology, Wake Forest University Health Sciences, Medical Center Blvd., Winston-Salem, NC 27157, Tel: (336)716-8554, FAX: (336)716-6744, tjmartin@wakehealth.edu.
No conflicts of interest to report.

Conclusions—The titration 5CSRTT method is an efficient training procedure for assessing attention and can be utilized to assess the limit in performance ability across subjects and various schedule manipulations.

1. INTRODUCTION

Treatment of attention disorders comprises a major use of psychotherapeutics throughout the world, particularly in adolescents and young adults. Several behavioral paradigms have been described to assess attention in rodents. The five choice serial reaction time task (5CSRTT) was developed by Robbins in the early 1980s for the study of attention in laboratory animals, based on the continuous performance task used in humans.[8] This procedure in rodents involves illuminating one of five nose poke holes located on one wall of the operant chamber for a set duration. If the subject pokes its nose in the illuminated hole, then a food pellet reward is delivered in a trough located on the opposite chamber wall. The animal must remain attentive to the 5 nose poke holes, one of which is illuminated at random for each trial, and choose the illuminated hole correctly in order to be rewarded with food. The length of time that the nose poke is illuminated (cue duration) is gradually decreased over many training sessions to make the task more challenging and to require a high level of attention processing for accuracy. The final stimulus cue duration used for most studies varies from 0.5 to 2 sec, with a typical required minimum accuracy of 60% to 80% across all trials with training durations ranging from 60 to 120 days depending on the stringency of final training criteria.[2, 6] The typical outcome measures used to indicate levels of attention are %correct responses and %omissions (trials in which the subject fails to respond with a nose poke in any hole within a given time limit). However, both measures are dependent on the final cue duration used for the study. Further, this method does not determine the duration at which, if any, the subjects are capable of attending to the stimulus cue. It is possible that some manipulations can reduce accuracy that can be overcome by increasing the stimulus duration, while others may not. To determine the interaction between stimulus duration, accuracy, and effects of experimental manipulations using traditional 5CSRTT methods would require an inordinate amount of time and animals.

Paradigms have been developed and utilized in rodents and nonhuman primates that titrate certain independent variables based on operant responses. One such paradigm is shock titration, in which the level of shock delivered to the tail (nonhuman primate) or feet (rodents) is altered systematically based on the performance of the subject.[3, 5] The level of shock is initially set to a low level and gradually increases in the absence of an operant response, typically a lever press. Once the shock reaches a noxious level the subject presses the lever, which turns off the shock and after a brief time-out resets the shock to the next lowest level. In this manner the operant behavior of the animal titrates the shock level throughout the session. From these data the median shock level is calculated, which is typically thought to be the threshold of noxious stimulation by electric shock and can be manipulated using strong analgesics such as opioids.[3]

In this paper, we applied this titration concept to visual cue duration in the 5CSRTT. Rats were initially trained using the traditional 5CSRTT method with a relatively long visual cue duration of 30 sec, which is rapidly attained and typically an initial phase of training for the classical procedure. We then used a paradigm in which the visual cue duration was made contingent upon trial outcome such that correct responses reduced the cue duration in the subsequent trial, while incorrect responses or omissions increased the cue duration in the subsequent trial. Using this method we demonstrate that rats rapidly titrate cue duration to under 1 sec within two weeks of access, and that the median cue duration (MCD) can be dynamically manipulated by altering other schedule parameters such as the intertrial interval or by providing a visual distractor as has been demonstrated using the classical procedure. [1] We propose that the MCD represents the attention threshold of each subject, and that the titration method provides not only an efficient method for training, but also a reproducible and dynamic measure to quantify attention performance throughout each session over a wide dynamic range of measurement.

2. MATERIALS AND METHODS

2.1. Animals

Male, Fisher 344 rats (N=34, 240–350 g, Harlan Laboratories, Indianapolis, IN) were used for all studies and kept on a reversed light:dark cycle (dark 05:00–17:00). Animals were housed in a temperature and humidity controlled room immediately adjacent to the laboratory, contained within an AALAC accredited facility. Rats were housed in pairs and allowed to acclimate for one week upon arrival at the laboratory during which time they were given ad lib access to standard rat chow and water. After this period, animals were singly housed and given ad lib access to rat chow until they attained a minimum body weight of 240 g. Animals were then reduced to 90% of their free feeding weight and given sufficient rat chow thereafter to maintain normal growth and increased weight gain while maintaining 90% of average free feeding weight for Fisher 344 rats based on published growth curves from the vendor for this strain. Animals were given ad lib access to water throughout the experiment except during experimental sessions. All procedures were in accordance with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health and were approved by the Institutional Animal Care and Use Committee of Wake Forest University Health Sciences (Winston-Salem, NC).

2.2. Behavioral procedures

2.2.1. Apparatus—All procedures were conducted in standard commercially available operant chambers controlled through a PC-compatible computer and interface using Med-PC IV software (Med Associates Inc., St. Albans, VT). Operant chambers (9.5″ W, 13″ L, 12″ H) contained one curved wall with a bank of 5 nose poke holes for the rat with LEDs located in the rear of each and an illuminated food trough with infrared head entry detection located on the opposite wall with a magazine type pellet dispenser for 45 mg food pellets. The standard clear lens cap provided by the vendor for the food trough lamp was replaced with a jeweled red lens cap (Allied Electronics Inc., Fort Worth, TX). At the top of the wall that contained the food trough was placed a standard stimulus lamp with a red lens cap

(house light) and an adjustable sonalert tone generator (Med Associates Inc.). Each operant chamber contained a standard stainless steel grid bar floor and was contained within an expanded PVC sound and light attenuating cubicle (Med Associates Inc.).

2.2.2. 5CSRTT training and titration of visual cue duration—All experiments were conducted during the dark phase of the light:dark cycle on weekdays only. Once body weight stabilized at 90% of free feeding weight, all animals were trained in 4 phases. Phase 1 consisted of training the animal to nose poke in the food trough for 45 mg chocolate flavored purified rat chow pellets (Bio-Serv Inc., Flemington, NJ). The food trough lamp was illuminated to indicate pellet availability. Each successful nose poke was reinforced by delivery of one pellet and accompanied by a 0.5 sec tone and turning off the food trough lamp for 0.5 sec. Sessions lasted for 30 min or until the animal obtained 100 pellets, whichever occurred first. Once animals obtained 100 pellets for a minimum of 2 consecutive sessions they graduated to the next phase of training.

Phase 2 consisted of training the animal to nose poke in the middle of the 5 nose poke holes located on the wall opposite of the food trough for food pellet reward. Sessions were initiated by delivery of two pellets into the food trough and illumination of the food trough light. Once the animal interrupted the head entry detector on the food trough, the trough lamp was turned off after 2 sec and the trials were initiated, signaled by illumination of the house light. Each trial consisted of the LED in the middle nose poke being illuminated for 30 sec (cue duration) during which time a nose poke resulted in the LED being turned off and the food trough light being illuminated and delivery of two food pellets. Head entry detection at the food trough initiated a 2 sec reward cycle timer, after which the food trough lamp was turned off and an inter-trial interval (ITI) timer of 5 sec was initiated. After the ITI the next trial began, signaled by illumination of the middle nose poke LED. If the animal responded in a nose poke other than the middle one (incorrect response) or did not respond within 30 sec (limited hold, omission of response), the LED was turned off and a 2 sec time-out period was initiated during which all lights were turned off. Responses in any of the nose pokes during this time-out period reset the 2 sec time-out timer. At the end of the time-out, the next trial was initiated, signaled by illumination of the house light and after the ITI, illumination of the middle nose poke LED. Responses during the ITI were recorded as premature responses and resulted in initiation of a time-out. Sessions consisted of 50 trials or 30 min whichever came first. Animals were required to complete all 50 trials with a minimum of 80% correct responses for 3 consecutive sessions before graduating to the third phase of training.

Phase 3 of training was identical to the second phase, with the exception that one of the five nose pokes was illuminated at random for each trial. The cue duration and limited hold were kept at 30 sec, the ITI at 5 sec, and the time-out and reward cycle at 2 sec during this phase of training and all other details of the procedure were identical to the second training phase. Animals were required to complete all 50 trials with a minimum of 80% correct responses for 3 consecutive sessions during the third phase of training before graduating to the final titration phase.

Phase 4 was the final titration phase of training and was identical to phase 3, except that the cue duration and limited hold were altered automatically using the Med-PC IV programming language based upon the outcome of each trial. The Med-PC program will be made available upon request by the corresponding author. Each session consisted of 100 trials or 30 min whichever came first. The cue duration was altered according to the series 30, 25, 20, 15, 10, 8, 6, 4, 2, 1, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, 0.1 sec. The limited hold was set to the cue duration or 5 sec, whichever was greater (i.e., the animal always had a minimum of 5 sec to respond or the entire cue duration if greater than 5 sec). The cue duration was initially set to 30 sec. If the animal made a correct response, the cue duration was decreased to the next lowest value in the series for the subsequent trial. If the animal made an incorrect response or an omission, the cue duration was increased to the next highest value in the series for the subsequent trial. If the animal made an incorrect response or omission when the cue duration was 30 sec, or made a correct response when the cue duration was 0.1 sec, the cue duration was not altered for the subsequent trial. The median cue duration (MCD) was calculated excluding the first 15 trials, during which animals were titrating down the cue duration. Once the MCD was stable (5 consecutive sessions during which the MCD did not vary by more than 15% from the mean) experimental manipulations were initiated as described below.

2.2.3. Manipulation of schedule parameters—The effect of altering the ITI, duration of the reward cycle, or both on performance in the titration paradigm was assessed in 24 animals. Once MCD was stable as described above, the ITI was changed from 5 to 0.1, 1, 2, 10, or 20 sec. in separate sessions. In additional sessions, the ITI was set to 1 sec and the reward cycle was changed from 2 to 0.5 or 1 sec.

2.2.4. Visual distractor stimulus—The effect of providing a visual distractor on performance in the cue duration titration procedure was determined in 10 animals. Once the MCD was stable a white stimulus lamp (Med Associates Inc.) was placed in the center of the Plexiglas chamber top. The lamp was illuminated at approximately 3 Hz (alternating 0.16 sec on, 0.16 sec off) during trials 26–75 of individual sessions.

2.3. Data analysis

The primary outcome measure related to attention was the median cue duration (MCD) that was calculated using Microsoft Excel from the cue durations for trials 15–100 for each session. For sessions including the visual distractor stimulus, the MCD was calculated in a similar manner from the cue durations before (trials 15–25), during (trials 26–75) and after (trials 76–100) presentation of the flashing light distractor. Other measures collected were the number of premature responses, perseverative responses, number of trials with a correct response, number of trials with an incorrect response, number of trials with no response (omission), and total number of trials completed. Additionally the latency to a correct response, incorrect response, or to retrieval of the food reward following a correct response was also obtained. MCD with respect to training session was analyzed using the Friedman non-parametric test, as the data were not normally distributed and the variances across training sessions were not equal. The effect of ITI duration on MCD, premature responses, total number of trials completed, or %omissions (number of omissions/total trials

completed) was analyzed using one-way repeated measures ANOVA. The effect of ITI and reward cycle duration on MCD was analyzed using one-way repeated measures ANOVA. Post-hoc comparisons were made using Dunnett's t-test for multiple comparisons with the control conditions stated for each analysis in the figure legends. Significance was indicated for all analyses by a p-value of 0.05 or less. The effect of the visual distractor stimulus was determined using t-tests with Welch's correction for unequal variances comparing the MCD between sessions with or without the distractor for trials 15–25, 26–75, or 76–100 separately. To correct for multiple comparisons a p-value of 0.017 (0.05/3) was considered statistically significant. The effect of the visual distractor stimulus on premature or time out responses was also determined across all trials using a paired t-test. All statistical analyses were performed using Prism 5 for MacIntosh (GraphPad Software, San Diego, CA).

3. Results

3.1. Training performance and duration of each training phase

The time required to meet the criteria for the individual phases of training was analyzed for 24 of the 34 animals and training data are shown in Figure 1. In phase 1, 17 of these 24 animals acquired nose poking for food pellet reward within 4 sessions, and the mean number of sessions required for all rats to attain criterion for graduating to the next phase of training was 5.7 ± 0.6 sessions (mean $\pm$ SEM). In phase 2, the % correct responses increased from 31.1 ± 4.3 in the first session to 95.3 ± 1.0 in the fifth session, and the average number of sessions required to reach criterion for graduating to phase 3 was 5.1 ± 0.1. The latency to correct responses also decreased from 11.4 ± 1.1 sec in the first session to 3.3 ± 0.2 sec in the fifth session of phase 2. In phase 3, the % correct responses increased from 86.3 ± 2.0 in the first session to 95.6 ± 1.0 in the fifth session, and the average number of sessions required to attain criterion for graduation to the final titration phase was 5.1 ± 0.2. The latency to correct responses decreased from 4.1 ± 0.4 sec in the first session to 2.7 ± 0.3 in the fifth session of phase 3. The MCD across the first 12 trials in phase 4 of training is shown in Figure 1. By the seventh session under the CD titration schedule, the MCD was stable with a mean $\pm$ SEM of 0.50 ± 0.04 sec. The total time required to train subjects under all 4 phases to the point of attaining a stable MCD under the final titration schedule was 22.9 ± 0.7 sessions, with a range across all 24 subjects of 19–25 sessions.

Typical CD titration curves for individual sessions are shown in Figure 2. To compare behavior across trials within single sessions, curves are also plotted using a log scale to accommodate the wide dynamic range of possible CDs. Subjects typically rapidly titrate down the CD to under 1 sec in the first 15 trials of the session and maintain the CD within a close range around the MCD for the remaining trials (Figure 2).

3.2. Effect of ITI and reward cycle duration on MCD, premature responses, trials completed, and %omssions

All training and baseline sessions for the titration procedure were conducted using an ITI of 5 sec and a reward cycle of 2 sec. In separate sessions, premature responses increased as a function of increasing the ITI to 10 or 20 sec (Figure 3). The MCD increased only when the ITI was increased to 20 sec however from 0.42 ± 0.03 sec at the baseline value of 5 sec to

0.81 ± 11 sec (Figure 3, upper panel). The number of trials completed decreased as a function of increasing the ITI, however the omission rate did not change (Figure 3, lower panel).

To determine the limits of the ability of subjects to maintain performance under the titration schedule, the ITI was set to 0.1 sec and the reward cycle was set to 2, 1, or 0.5 sec in separate sessions. The cumulative time between the initial nose poke into the food trough (reward cycle), the ITI, and the CD are depicted in Figure 4 for these manipulations, as well as for the sessions when the ITI was set to 1, 2, or 5 sec and the reward cycle was set to 2 sec. The MCD was a function of ITI and reward cycle duration [F(5,47)=10.2, p<0.0001] and increased relative to the baseline conditions when the ITI was lowered to 0.1 sec (Figure 4). The total cumulative time that elapsed between initiating food reward retrieval, beginning of the next trial, and successful titration of the stimulus duration was also a function of ITI and reward cycle duration [F(5,47)=28.9, p<0.0001] and reached an asymptote when the ITI and reward cycle duration were lowered (Figure 4). This cumulative time did not differ when the ITI was set to 0.1 sec for all reward cycle durations and when the ITI was set to 1 sec and the reward cycle was set to 2 sec. The mean ± SEM for this total cumulative time across these 4 conditions (indicated by 4 rightmost bars in Figure 4) was 3.56 ± 0.16 sec.

3.3 Effect of a visual distractor on the MCD

A flashing stimulus lamp during trials 26–75 significantly disrupted ongoing cue duration titration in the 10 animals tested (Figure 5). There was no difference between the MCD before (trials 15–25, p=0.45) or after (trials 76–100, p=0.09) presentation of the flashing distractor stimulus compared with baseline sessions (Figure 5). However the MCD was significantly increased from 0.56±0.6 sec during trials 26–75 in the absence of the flashing distracting stimulus to 3.9±1.0 sec (p=0.01) during trials 26–75 in the presence of the flashing distracting stimulus (Figure 5, upper panel). Representative CD titration curves are shown for one animal during separate sessions with the presence or absence of the flashing distractor stimulus during trials 26–75 (Figure 5, lower panels). Additionally, the number of premature responses increased from 3.2±1.0 at baseline to 7.0±1.7 in the presence of the flashing distractor (p=0.04), and the number of time out responses increased as well from 5.0±1.3 to 10.5±2.9 (p=0.04) in the absence or presence of the visual distractor, respectively.

4. Discussion

Titration of the visual cue duration based on individual subject performance in the 5CSRTT was found to be an efficient method of training this procedure to a task level consistent with optimal performance. Similar up-down methods of titration provide reliable and robust measures of behavioral sensitivity at or near the threshold of detection in small samples.[4] Here we propose applying the up-down method of titration to determine dynamic performance threshold in the 5CSRTT. We propose that the median cue duration derived from trials 15–100 is a measure of, or related to, attention threshold. Further, this method provides a wide dynamic range of visual cue durations associated with varying performance ability that can be used to assess the influence of either schedule parameters or distracting visual stimuli on attention threshold. Using a similar strategy and varying the ITI and reward

cycle duration, animals were found to compensate for these timing demands by increasing the MCD in a manner that suggests approximately 3.5 sec is the minimum amount of time that a rat can effectively consume two 45 mg food pellets and still be able to attend to the visual cues required for optimal task performance. Increasing the ITI in the titration paradigm altered behavioral endpoints associated with impulse control in a manner similar to that reported previously with the classical procedure.[1] Additionally, the presence of a 3 Hz flashing light diminished the ability of animals to perform the titration task, significantly increasing the MCD approximately 7-fold, while altering other endpoints similarly as has been described using the classical 5CSRTT method.[1]

The present series of studies utilized Fisher 344 rats, an albino strain. This would seem to confirm the efficiency of the titration method for training, as albino rat strains typically perform worse than non-albino strains in visual performance tasks. The time required for training to final criteria in the present study using Fisher 344 rats is similar to that reported for the classical 5CSRTT using hooded Lister rats, a non-albino strain[7]. As mentioned above, training times are typically much longer for the classical method and on the order of 60–120 sessions for albino strains. The reasons for differences between training times required for individual studies is not clear however in addition to the rat strain used, variables such as extent of food restriction, final training criteria, and visual inspection of individual subjects during the training phase may all have a role. Experience in our laboratory watching individual animals perform the classical procedure during various training phases indicated that behavior would rapidly extinguish if individuals subjects missed more than 4 or 5 visual cues consecutively. Manually increasing the cue duration upon omissions or decreasing the cue duration with correct responses proved to be more efficient than maintaining a fixed cue duration across all trials within a training session, however this process proved to be labor intensive and difficult to standardize across subjects and individual investigators. The present method was adapted to perform these manipulations of visual cue duration to optimize performance in an automated and standardized manner that does not require intervention by the investigator.

While these studies provide an initial description of this novel method and proof of concept by documenting the effects of procedural manipulations on behavior maintained by this paradigm compared to literature using the classical method, future studies determining the sensitivity of behavior maintained by the titration variant to manipulations of prefrontal cortex are warranted. Additional variants of the general titration theme are also possible, such as using the titration method to speed training and then switching to the classical paradigm, or possibly setting the CD to a fixed value for the remainder of the session once a predetermined number of titration trials have elapsed. The advantage of the latter two strategies is that the data generated would be similar to that generated by studies in the literature and perhaps more directly comparable. One disadvantage would be loss of a dynamic assessment of performance across the entire session. Clearly, many other permutations of this theme are possible, each with their own advantages and disadvantages.

5. Conclusions

The titration variant of the 5CSRTT is an efficient method of training a visual attention task to final, objective criteria and can be utilized to assess limits of visual attention performance in a dynamic, systematic, and automated manner.

Acknowledgments

ABBREVIATIONS

5CSRTT   5 choice serial reaction time task

ITI   intertrial interval

MCD   median cue duration

References

1. Amitai N, Markou A. Comparative effects of different test day challenges on performance in the 5-choice serial reaction time task. Behav Neurosci. 2011; 125:764–774. [PubMed: 21942437]

2. Berquist MD II, Mooney-Leber SM, Feifel D, Prus AJ. Assessment of attention in male and female Brattleboro rats using a self-paced five-choice serial reaction time task. Brain Res. 2013; 1537:174–179. [PubMed: 24055104]

3. Craft RM, Dykstra LA. Differential cross-tolerance to opioids in squirrel monkeys responding under a shock titration schedule. J Pharmacol Exp Ther. 1990; 252:945–952. [PubMed: 1969478]

4. Dixon WJ, Mood AM. A method for obtaining and analyzing sensitivity data. J Am Stat Assoc. 1948; 43:109–126.

5. Minor BG, Persson ML, Post C, Jonsson G, Archer T. Intrathecal noradrenaline restores 5-methoxy-N,N-dimethyltryptamine induced antinociception abolished by intrathecal 6-hydroxydopamine. J Neural Transm. 1988; 72:107–120. [PubMed: 3133452]

6. Pezze M, McGarrity S, Mason R, Fone KC, Bast T. Too little and too much: hypoactivation and disinhibition of medial prefrontal cortex cause attentional deficits. J Neurosci. 2014; 34:7931–7946. [PubMed: 24899715]

7. Pezze MA, Dalley JW, Robbins TW. Differential roles of dopamine D1 and D2 receptors in the nucleus accumbens in attentional performance on the five-choice serial reaction time task. Neuropsychopharmacology. 2007; 32:273–283. [PubMed: 16641946]

8. Robbins TW. The 5-choice serial reaction time task: behavioural pharmacology and functional neurochemistry. Psychopharmacology (Berl). 2002; 163:362–380. [PubMed: 12373437]

Highlights

- We report a novel variant of the 5CSRTT that systematically titrates the level of task difficulty.

- This variant of the 5CSRTT reduces the training period significantly compared to other methods.

- The median cue duration is sensitive to manipulations known to alter attention performance.

- This method is able to detect the performance limits for each subject in each daily session.
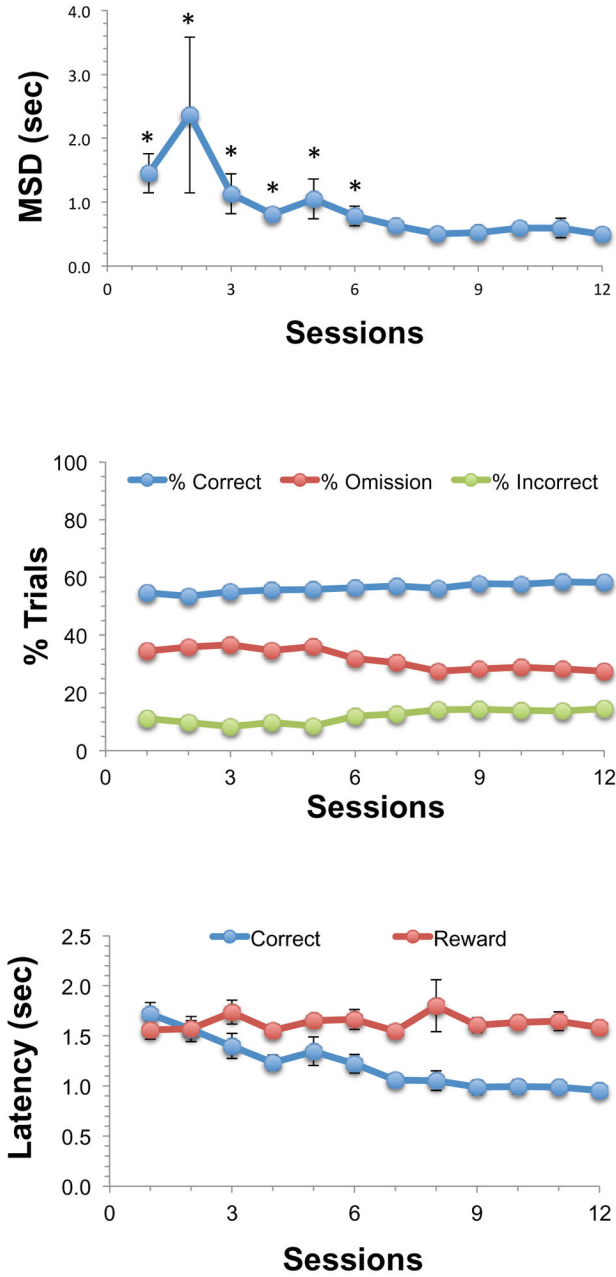
Figure 1. Stabilization of median cue duration (MCD) during training in the titration phase of the 5CSRTT titration procedure

The MCD (mean ± SEM, N=24) was calculated from trials 15–100 for each subject beginning on the first session of access to the titration procedure. The MCD (mean±SEM) across the first 12 sessions of access to the titration procedure is shown in the upper panel. MCD decreased as a function of training session [Friedman statistic = 135.2, $p<0.0001$]. *, significantly different from session 12, $p<0.05$. The number of % correct, % omission, and %incorrect trials (mean±SEM) from these same sessions are shown in the middle panel. The lower panel shows the latency to respond correctly (Correct) or to retrieve the food reward (Reward) following a correct response (mean±SEM).
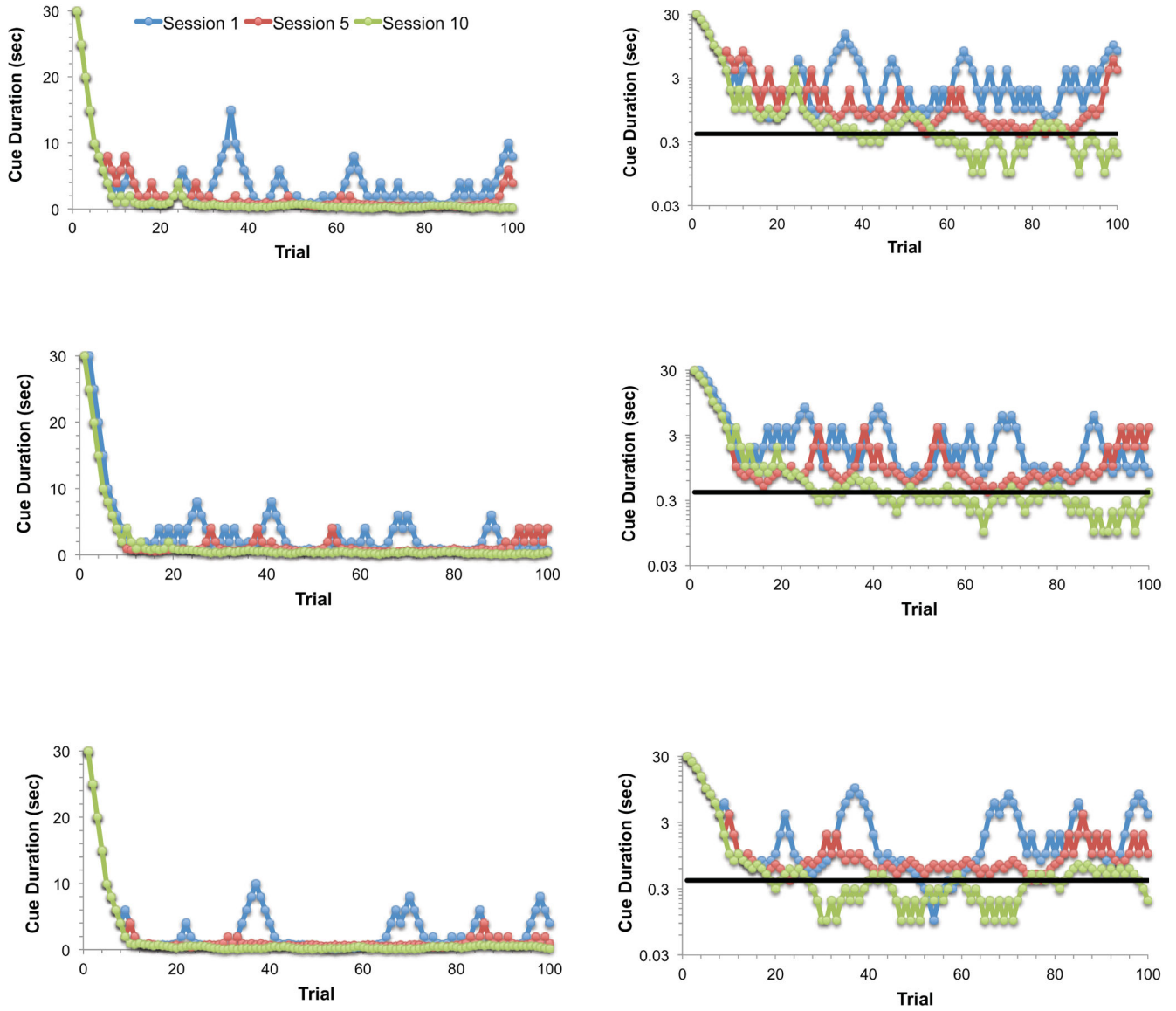
Figure 2. Cue duration titration curves during initial access to the 5CSRTT titration procedure
Representative cue duration titration curves are shown for 3 different animals during the first, fifth, and tenth sessions of initial access. To more clearly view the titration during the stable portion of the curves, the cue duration is plotted using a log scale in the graphs to the right. The black line indicates the MCD for the tenth session.
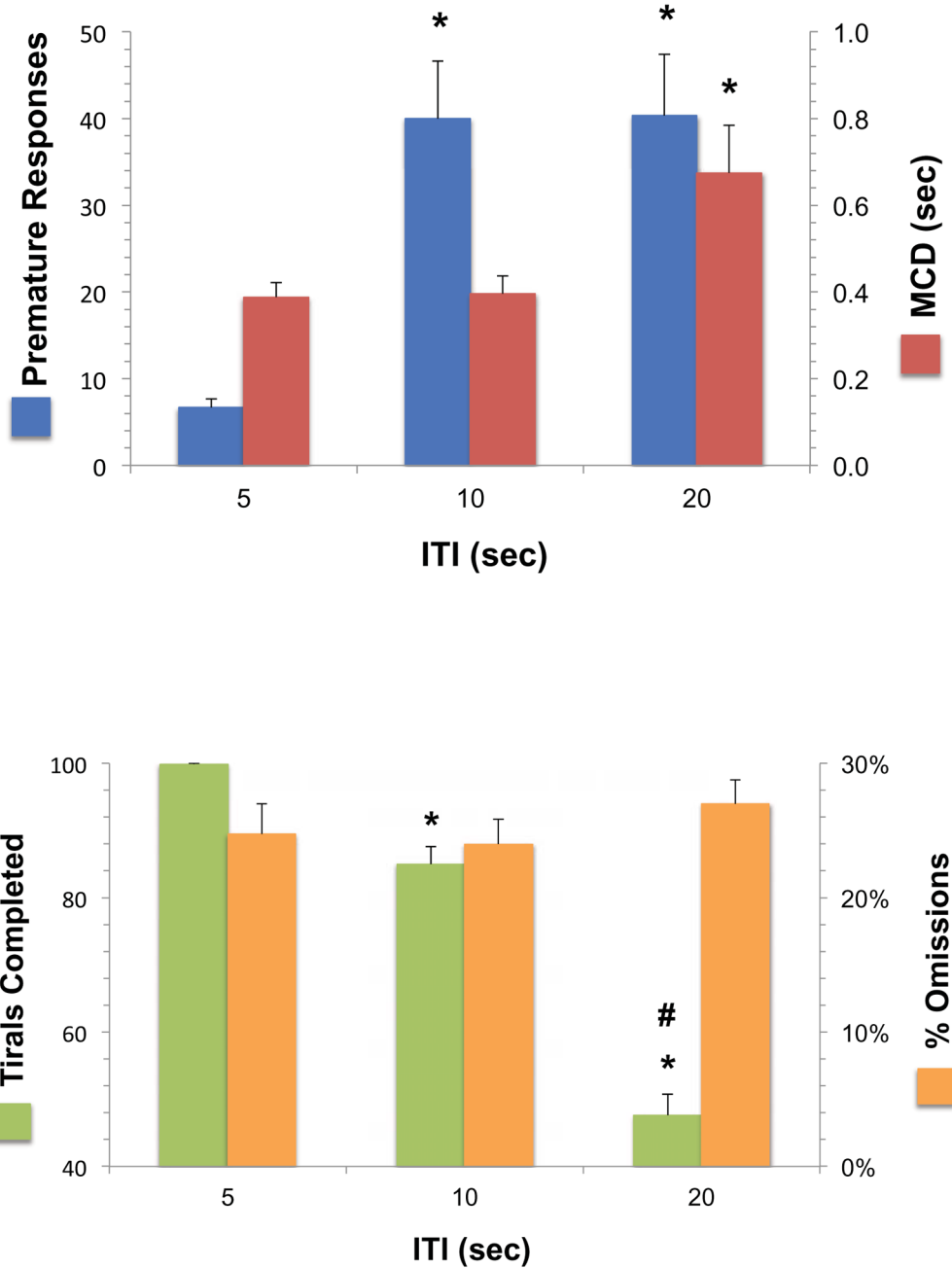
Figure 3. Premature responses, MCD, total trials completed, and %omissions as a function of ITI duration in the 5CSRTT titration procedure

The number of premature responses varied as a function of ITI duration [F(2,35)=16.2, p<0.0001], increasing above the normal baseline conditions (ITI=5 sec) at values of 10 or 20 sec (upper panel). The MCD also varied as a function of ITI duration [F(2,35)=5.2, p=0.014], and was increased only when the ITI was increased to 20 sec (upper panel: *, significantly different from ITI=5, p<0.05). The number of trials completed was significantly decreased when the ITI was increased from 5 to either 10 or 20 sec [F(2,35)=130.1, p<0.0001], but the omission rate was not changed [F(2,35)=0.6, p=0.5]

(lower panel: *, significantly different from ITI = 5 sec, p < 0.001. #, significantly different from ITI=10 sec, p<0.01.) N=12.
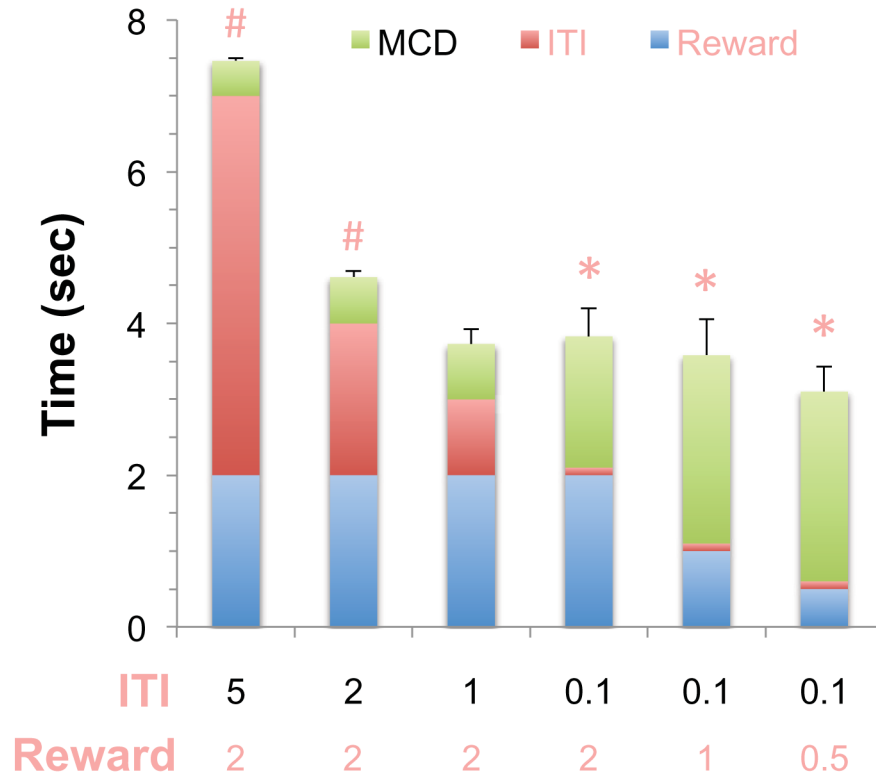
Figure 4. Effects of ITI and reward cycle duration on MCD

The cumulative time required to perform the titration task from initiation of reward retrieval to visual cue duration is shown for different ITI and reward cycle durations. As the ITI and reward cycle durations were constants under each condition, the error bars indicate the SEM for the MCD calculated for each subject for sessions in which the indicated ITI and reward cycle duration were in effect. The leftmost bar indicates the standard baseline condition where ITI = 5 sec and the reward cycle = 2 sec. #, MCD + ITI + reward significantly different from condition where ITI = 0.1 sec and reward = 0.5 sec (rightmost bar on graph), $p < 0.05$. *, MCD significantly different from baseline condition, $p < 0.05$. N = 8.
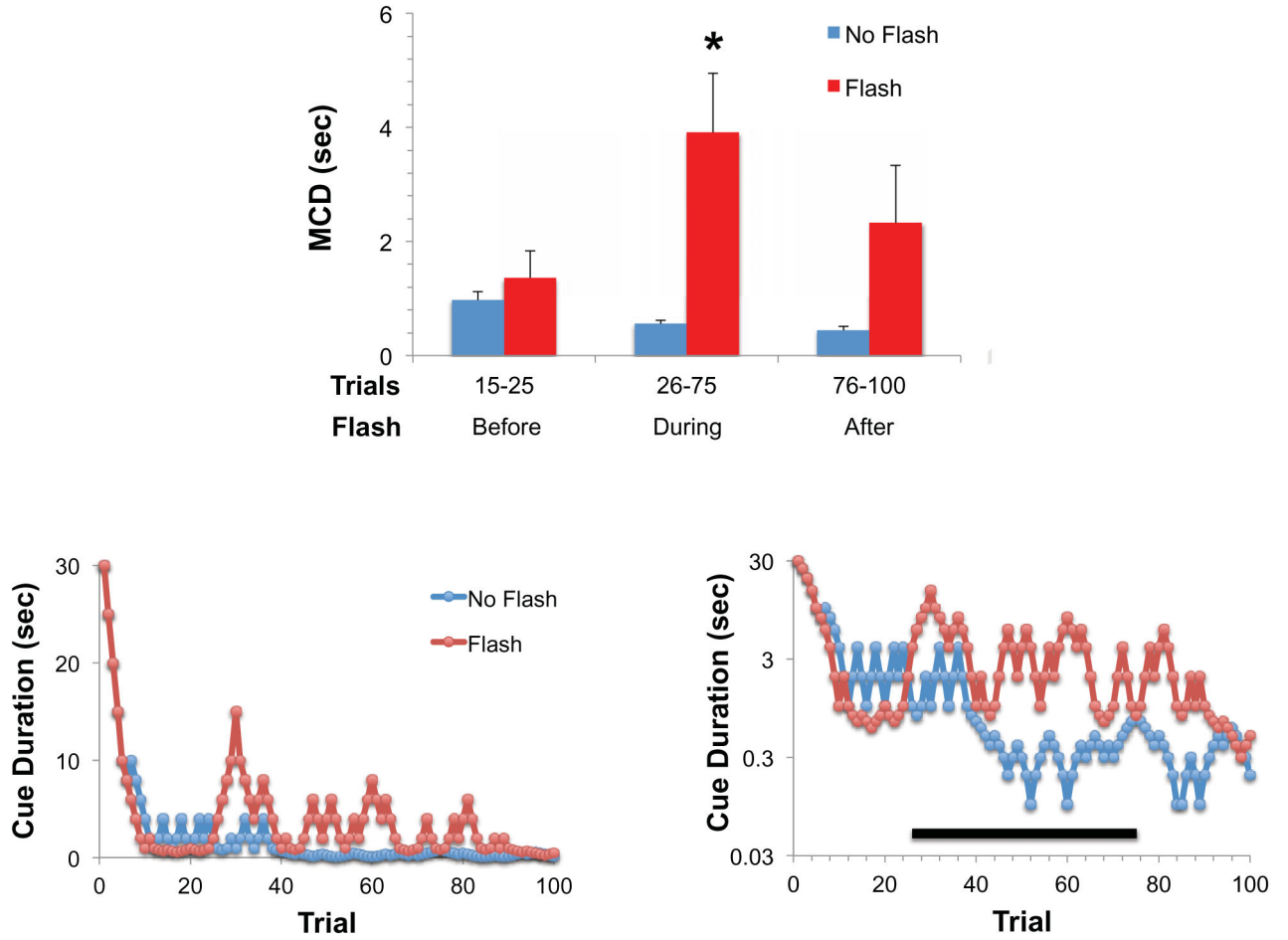
Figure 5. Effect of visual distractor on MCD

Visual distraction was provided during trials 26–75 only in the form of a 3 Hz flashing light as described in Methods. The MCD was increased during trials in which the visual distractor was present but not in other trials compared to a normal session without the distractor (top panel, * significantly different from No Flash, p<0.017). The two lower panels show representative CD titration curves from the same subject with or without the flash present (left panel, linear scale; right panel, log scale). The black bar in the lower right graph indicates the trials during which the flashing distractor stimulus was presented.