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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, James C. Eisenach

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

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.

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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 s 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 s 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.
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.

Abbreviations: 5CSRTT, 5 choice serial reaction time task; ITI, intertrial interval; MCD, median cue duration.

* Corresponding author. Tel.: +1 336 716 8554; fax: +1 336 716 6744.
E-mail address: tjmartin@wakehealth.edu (T.J. Martin).

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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 (Robbins, 2002). 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 s, with a typical required minimum accuracy of 60–80% across all trials with training durations ranging from 60 to 120 days depending on the stringency of final training criteria (Berquist Ii et al., 2013; Pezze et al., 2014). 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 (Craft and Dykstra, 1990; Minor et al., 1988). 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 (Craft and Dykstra, 1990).

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 s, 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 s 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 (Amitai and Markou, 2011). 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 s tone and turning off the food trough lamp for 0.5 s. Sessions lasted for 30 min or until the animal obtained 100 pellets, whichever