Rodent Model of Attention: The 5-Choice Serial Reaction Time Task

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ABSTRACT

The 5-choice serial reaction time task (5-CSRTT) is the most widely used test to measure attentional performance in rodents. The basic test design involves training animals to respond to a brief visual stimulus presented unpredictably in one of five locations. Once trained to stable performance levels, the effects of experimental manipulations on response speed and choice accuracy are measured and each are related to attentional performance. Increasingly, the test is also used to examine aspects of response control. Having been adapted from a human task, the test has also been successfully extended to the mouse and primate, thus highlighting its translational value. Increasingly this test is being applied in drug discovery efforts, primarily to identify novel drug treatments for conditions associated with attention deficits. *Curr. Protoc. Pharmacol.* 41:5.49.1-5.49.20.

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INTRODUCTION

In the 5-choice serial reaction time test (5-CSRTT) rodents are first trained to respond to a brief visual stimulus by performing a nose poke to obtain a food reward. Learning of the stimulus-reward association and acquiring stable (asymptotic) performance levels typically requires 20 to 30 training sessions. This is described for the rat in the Basic Protocol. Once trained, the effect of an experimental manipulation, such as a lesion or drug, can then be examined. This is also described in the Basic Protocol.

One of the strengths of the 5-CSRTT is the ability to manipulate various experimental conditions to tax animals' performance on aspects of the task. Such modifications to the basic test procedure are described in Alternate Protocol 1.

Rats are the most commonly used rodent species in this task, although mice can be reliably trained in this procedure. Training and testing procedures for the mouse are described in Alternate Protocol 2.

NOTE: All protocols using live animals must be reviewed and approved by an Institutional Animal Care and Use Committee (IACUC) or must conform to governmental regulations regarding the care and use of laboratory animals.

5-CHOICE SERIAL REACTION TIME TASK IN THE RAT

BASIC PROTOCOL

The test has training and testing components and there are a number of modifications that can be applied to this task. The basic procedure is presented below and variations are described in further detail in Alternate Protocol 1.

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Materials

200- to 250-g rats (typically a pigmented strain such as hooded Lister or Long Evans, see Troubleshooting)

Standard rodent diet

Transparent plastic cages (e.g., Macrolon 44 × 28 × 19–cm), containing wood shavings

Purpose-built operant conditioning chambers (approximate chamber dimensions 25-cm wide × 30-cm long; see Critical Parameters and Troubleshooting) and associated software for conducting 5-choice serial reaction time task

Permanent ink marker

Syringes for administration of compounds (e.g., Terumo type BS-025)

Needles for intraperitoneal or subcutaneous injections [e.g., 23-G × 1-in. (0.6 × 16–mm; Terumo]

Luer gastric probes with oval extremity (70-mm long × 1.5-mm diameter) for oral administration

Metric balance

Set up general housing and husbandry

1. House rats in cages containing wood shavings (paper bedding not recommended), and provide free access to tap water, assuming a food restriction regimen is used.

   IMPORTANT NOTE: Paper bedding is not recommended for animals on food restriction as they may feed on the bedding material.

   The number of animals housed per cage should be governed by IACUC guidelines and experimenter preference (see Critical Parameters and Troubleshooting).

2. Maintain general housing conditions at 21° ± 3°C on a standard (nonreversed) 12 hr light/dark cycle with, for example, lights on between 0700 and 1900 hr.

3. If rats are singly housed, then provide a preweighed amount of food at the end of the test day.

   In the event of group housing, such a procedure is inappropriate (see Critical Parameters and Troubleshooting) and a preferred method is to allow all animals equal access to unlimited food for a fixed amount of time at the end of test day.

   The level of food restriction used will be governed by IACUC guidelines and experimenter preference (see Critical Parameter and Troubleshooting). Because the 5-CSRTT is a food-reinforced procedure, a food restriction regimen needs to be adopted for animals to be sufficiently motivated to learn, and once learned, perform the task.

4. Transport animals to the experimental room on test days using the regular holding cages as used for overnight housing (recommended), or smaller shoebox-type cages for single housing for ease of transportation (see Critical Parameters and Troubleshooting).

   Training and testing are typically conducted 5 days/week for up to several months and so experimenter convenience and practicality are important considerations.

5. Clearly identify each animal throughout the course of training and testing, e.g., with tail marking using a permanent ink marker.

Set up basic protocol design

6. Set up test chambers.

   All testing is conducted within purpose-built test chambers, equipped with 5 niches, each with a centrally positioned light, a magazine well for food pellets, and a houselight which, except for timeout periods, illuminates the chamber for the duration of the test session (see Fig. 5.49.1A). Only a single animal is tested within a test chamber; multiple test chambers are necessary to allow several animals to be run concurrently.

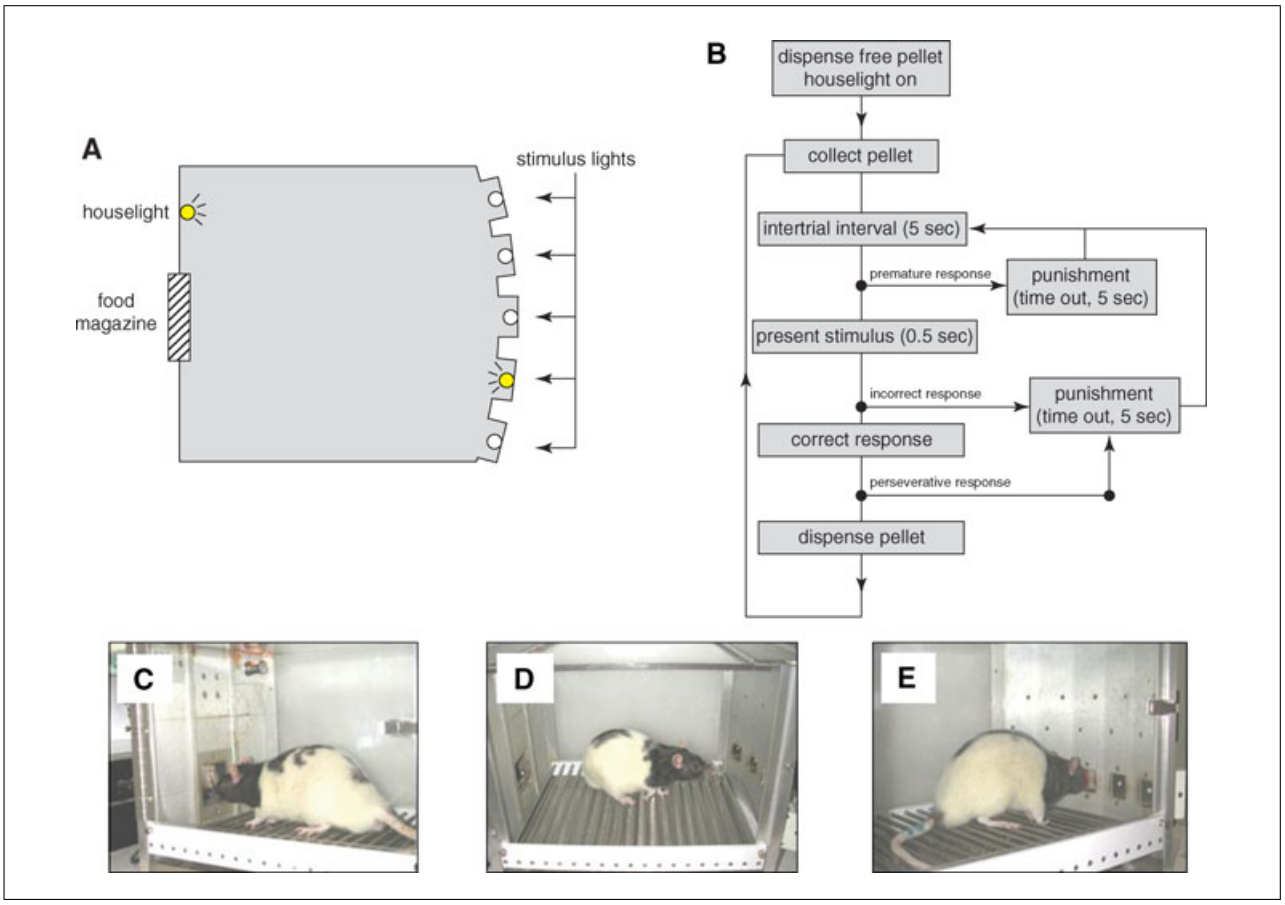

Figure 5.49.1 (**A**) General plan of the 5-choice serial reaction time test apparatus. On one wall a magazine well is situated, which dispenses food or liquid reward. On the opposite wall five niches are located, each of which contains a light stimulus. A houselight is also located in the test chamber. (**B**) Flow diagram to illustrate the general task requirements. The basic procedure requires the animal to attend to five niches located on one wall of the test chamber. A visual stimulus is briefly presented in one of the niches in a spatially unpredictable manner. Upon detection the animal is required to nose poke into the illuminated niche within a fixed time (limited hold, LH). If the nose poke is made into the correct niche, and within the LH period, a 45-mg food pellet is dispensed into a magazine tray. Food collection triggers the next trial where, after a fixed time period (intertrial interval, ITI, typically 5 sec), a visual stimulus is presented unpredictably in one of the five niches. In the event of the animal making an incorrect nose poke (i.e., into an unilluminated niche during the LH, an error of commission), the animal is punished by no food reward and a 5-sec time-out (TO) period typically signaled by the houselight being switched off. In the event of an animal making a nose poke prior to stimulus presentation, i.e., during the ITI, a premature response, the animal is punished by no food reward and a 5-sec TO. Further nose pokes into the stimulus niches after a correct or incorrect response has been registered (termed perseverative response) are also recorded and punished by a 5-sec TO. A failure to make any response during the ITI or the LH period, i.e., an error of omission, is punished by no food reward and a 5-sec TO. (C through E) are photographs taken to illustrate the positioning of the rat at (**C**) food collection, (**D**) orientation to the visual stimulus location, and (**E**) nose poke into the location of the visual stimulus.

7. A flow plan of the test protocol is illustrated in Figure 5.49.1B. The basic procedure requires the animal to pay attention to the five niches located on one wall of the test chamber. A visual stimulus is briefly presented (typically 0.5 to 1.0 sec after training) in one of the five niches in a spatially unpredictable manner. The animal is required to register that it has detected the stimulus by making a nose poke into the illuminated niche within a fixed period of time (called limited hold, LH). If the nose poke is made into the correct niche, and within the LH period, a food pellet is dispensed into a magazine tray located at the opposite wall. Consequently, the animal is required to turn to the magazine tray to collect the reward (Fig. 5.49.1C). Food collection triggers the next trial, where, after a fixed-time period (intertrial interval, ITI, typically 5 sec), a visual stimulus is presented unpredictably in one of the 5 niches. Again, the animal is required to turn 180° to attend to the niche wall in preparation to detect the next stimulus (see Fig. 5.49.1D). On presentation of the

next visual stimulus, the animal makes a nose poke (Fig. 5.49.1E) and, if correct, collects the food reward.

8. If the animal makes an incorrect nose poke (i.e., into a non-illuminated niche during the limited hold period, termed an "error of commission"), record the incorrect response and punish by providing no food reward and imposing a 5-sec time-out (TO) period typically signaled by the houselight being switched off.
9. If the animal makes a nose poke prior to stimulus presentation, i.e., during the ITI, termed a "premature response," record the premature response and punish by providing no food reward and imposing a 5-sec TO with the houselight off.
10. Record further nose pokes into the stimulus niches after a correct or incorrect response (termed a perseverative response) and punish by imposing a 5-sec TO.
11. If the animal fails to make any response during the ITI or the LH period, termed an "error of omission," record the lack of response and punish by providing no food reward and imposing a 5-sec TO.
12. Signal the end of the TO period by turning the houselight on, and allow the animal to trigger the next trial by making a nose poke into the magazine tray (however, with no food reward). See Figure 5.49.1B.
13. A typical session consists of 100 trials, i.e., 20 trials per stimulus location, which in well trained rats will take ~20 min to complete. At the end of each session determine and record the following:
    a. Total number of trials initiated. This includes correct (defined in step 7), incorrect (defined in step 8), and missed (defined in step 11) trials.
    b. Percentage of correct responses (% correct) defined as number of correct trials as percentage of total trials completed (i.e., correct and incorrect trials; this does not include missed trials).
    c. Total number of missed trials recorded over the test session.
    d. Latency to make a correct response, averaged for all correct trials recorded over the test session.
    e. Latency to make an incorrect response, averaged for all incorrect trials recorded over the test session.
    f. Latency to collect food reward (magazine latency) averaged for all food-reinforced trials recorded over the test session.
    g. Total number of premature responses (defined in step 9) recorded over the test session.
    h. Total number of perseverative responses (defined in step 10) recorded over the test session.

Train the animals

14. Initially, place a few 45-mg food pellets into each niche. Then place animals singly into the test chamber with all five response apertures illuminated. Extinguish the lights once the animal nose pokes into any of the apertures, then illuminate the food magazine light (houselight) and present a food reward. Leave the magazine light on until the pellet is collected, then extinguish the magazine light and start the next trial by illuminating all five response apertures. The duration of this session should be ~30 min.

    The purpose of this stage is to train the animal to associate the illumination of a niche with availability of food reward. If during the course of a single 30-min session the animal earns ≥50 rewards, then the animal can be moved to the next training stage (step 15).

15. Place each rat singly into an operant chamber. The general methodology is identical to that described in step 14, except present a single stimulus light. Set stimulus duration (SD) at 30 sec (LH also 30 sec) to provide the animal the opportunity to further learn the stimulus-reward association and make the appropriate response. At this point, introduce the intertrial interval (ITI) component, imposing a 5-sec delay between the collection of the food reward and presentation of the next visual stimulus.

    As a general rule of thumb, when the animals make >50 correct responses within a single session of a 30-sec SD, they are considered to have learned the association. In some animals steps 14 and 15 may be acquired within two sessions, while in others this may take up to 5 sessions or more.

16. Once the rat has learned the stimulus-reward association, gradually reduce the SD to 20 sec, 10 sec, and 5 sec over consecutive sessions, keeping the ITI fixed at 5 sec. Monitor each animal's performance over this period and, if it attains >70 correct responses at a given SD, use a shorter SD at the next session. Do not move animals to a lower SD when they are performing poorly (e.g., <50 correct/session) at the higher SD, as behavior may extinguish.

    The overall purpose is to have the animals responding reliably to the light stimulus presented for 5 sec. Attaining this level of performance generally takes 5 to 10 training sessions.

17. Decrease the SD from 5 to 2 to 0.5 sec, and LH from 30 to 2 sec over 10 to 20 additional training sessions until the animals perform reliably to the final test parameters of 0.5-sec SD, 2-sec LH, and 5-sec ITI, for 100 trials. Classify animals as trained and ready for experimentation when (1) % correct, number omissions, and premature/perseverative responses do not vary by >10% over five consecutive sessions, (2) do not show additional overall (improvement) trend, and (3) fall within acceptable criteria of >80% correct, $\leq$20 omissions/session, and $\leq$20 premature/perseverative responses/session.

    This decrease in SD places performance demands on the animal's attention and response control. Animals should tolerate the change in LH quite easily, but decreasing SD from 5 to 0.5 sec can be taxing for some animals and care has to be taken to monitor performance over each session.

Perform testing

Because of the time necessary to train the animals to appropriate performance levels, drug testing is typically conducted using a repeated measures design, i.e., each animal receives each treatment according to a Latin square design to control for treatment sequence. Animals continue to be run for 5 days/week with drug testing usually 2 days/week. Test days on Tuesdays and Fridays are recommended, because this allows collection of baseline data for each animal on the day prior to drug or vehicle pretreatment. This ensures no carryover effect of drug from the previous cycle on behavior.

18. One or two days before starting formal drug testing, familiarize animals with the injection procedure by administering 1 to 2 injections of vehicle by the intended route of administration for test article.

    Such injections should be made after running the animals in the 5-choice task. In this way, the baseline data are not potentially compromised by the animals' unfamiliarity with the injection procedure.

19. On each test day, weigh the animals and administer either the test drug or its vehicle. Following a predetermined pretreatment time, place the animals in the test chambers and run under standard conditions (i.e., 0.5-sec SD, 2-sec LH, 5-sec ITI, 100 trials).

20. Run animals under standard conditions on days between treatments to ensure performance returns to baseline on washout days. If performance has not returned to baseline by the next scheduled treatment day, include further washout days until baseline performance is achieved.

21. At the completion of study, with all animals receiving each treatment, compare the data from drug treatment to vehicle control using a repeated measures ANOVA.

ALTERNATE PROTOCOL 1

5-CHOICE SERIAL REACTION TIME TASK: EXPERIMENTAL MANIPULATIONS IN THE RAT

Once the animals are trained to stable performance (through step 17 of the Basic Protocol), in addition to testing the effect of an experimental manipulation on this baseline performance, manipulations to the basic task can often be made within a single test or 'challenge' session. Such manipulations can be made to SD, SI, ITI, trial number, and noise interpolation, among others. These are described in further detail in Critical Parameters and Troubleshooting. Figure 5.49.2 presents a summary of accuracy changes produced by within-session variations in SD, SI, and ITI. This figure also serves to

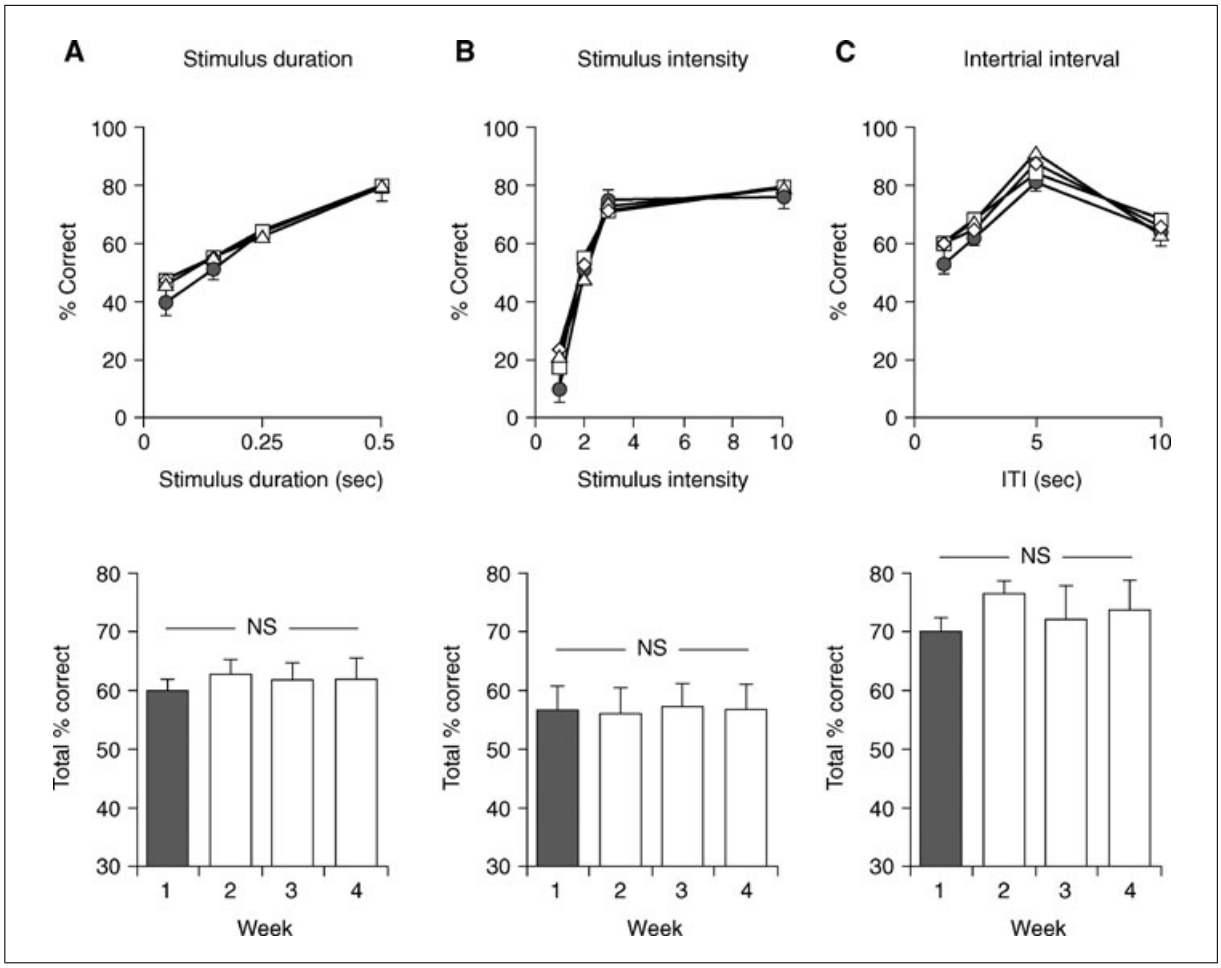

Figure 5.49.2 The effect of weekly challenges of (**A**) variable stimulus duration, (**B**) variable stimulus intensity, and (**C**) variable ITI on % correct measure in the 5-CSRTT. All experiments with parameter changes were run once weekly (Wednesday) for 4 weeks with rats tested under standard conditions (0.5-sec SD, 5-sec ITI, 10 SI) on each intervening day. All animals had been initially trained to criterion for at least 2 weeks prior to each challenge. N = 8 male, Lister hooded rats per challenge. The histobars present the total % correct collapsed across each variable. For SI experiment: 1 = 16 lux, 2 = 45 lux, 3 = 82 lux, 10 = 575 lux. ● = week 1, ◇ = week 2, △ = week 3, □ = week 4 (Higgins, Kirkby, and Jones, unpublished data). NS = not significant.

illustrate that, at least in terms of accuracy, these changes are reproducible over multiple sessions, and thus amenable to counterbalanced treatment designs. For materials see the Basic Protocol.

1. Train rats to stable performance under standard conditions of 0.5-sec SD, 5-sec ITI, 100 trials, as described in the Basic Protocol.

2a. *For variable ITI challenge:* Program a single session such that while SD and trial number remain at 0.5-sec and 100 trials respectively, the ITI is presented at one of 4 levels within the session (ITI = 5, 6, 8, and 10 sec). Employ a pseudo-random schedule such that each level of ITI is equally paired with each stimulus location, i.e., 5 pairings of 5-sec ITI with stimulus location 1 (5 × 5-sec ITI @1, 5 × 6-sec ITI @1, 5 × 8-sec ITI @1, 5 × 10-sec ITI@1, 5 × 5-sec ITI @2, etc.)

2b. *For variable stimulus duration (SD) challenge:* Program a single session such that while ITI and trial number remain at 5 sec and 100 trials, respectively, the SD is presented at one of 4 levels within the session (SD = 0.05, 0.1, 0.25, and 0.5 sec). Employ a pseudo-random schedule such that each level of SD is equally paired with each stimulus location, i.e., 5 pairings of 0.05-sec SD with stimulus location 1 (5 × 0.05-sec SD @1, 5 × 0.1-sec SD @1, 5 × 0.25-sec SD @1, 5 × 0.5-sec SD@1, 5 × 0.05-sec SD @2, etc.).

2c. *For variable noise distractor challenge:* Program a single session such that a burst of white noise (1-sec, 85 dB) is presented under one of 4 conditions within the session ITI, i.e., no noise distractor, 0-sec, 2.5-sec, and 5-sec ITI. With the 5-sec ITI the noise distractor is activated simultaneously with the visual stimulus presentation. Employ a pseudorandom schedule such that each condition is equally paired with each stimulus location.

3. On intervening days run the rats under standard test conditions as described in step 1 above.

4. Repeat challenge session pending the number of treatment levels. Ensure counterbalancing of treatment sequence across each session.

5-CHOICE SERIAL REACTION TIME TASK IN THE MOUSE

ALTERNATE PROTOCOL 2

Adaptation of the 5-CSRTT to the mouse was first reported by Humby et al. (1999). Subsequently, a number of reports have appeared in the literature documenting procedures for training mice in this task. Overall, the training protocols reported in these studies are similar to the original procedure (Humby et al., 1999). A sample protocol is presented below, although slight modification to test parameters may be necessary, partly to accommodate strain differences and satiation (see Critical Parameters and Troubleshooting).

5-CSRTT in the mouse is very similar to 5-CSRTT in the rat in terms of general housing and husbandry, and also the protocol itself (including design, training, and testing). Purpose-built test chambers for the mouse are necessary and several suppliers manufacture such chambers (see Critical Parameters and Troubleshooting). Typically, such chambers measure ~22 × 18 × 13–cm (length × width × height). Animals are run 5 days per week, one session of 100 consecutive trials per day (20 trials per stimulus location). Most commonly a liquid form of reinforcement is used, although solid food pellets are used by some groups (see Critical Parameters and Troubleshooting). The protocol below describes a procedure using 10 μl of 10% sucrose solution as each reward. For materials see the Basic Protocol.

1. Initially, place a mouse in an operant chamber with all five niches illuminated. Program the chamber such that a nose poke into any of the apertures extinguishes the

lights, illuminates the food magazine light, and results in the presentation of 10 µl of a 10% sucrose liquid reward. The magazine light remains illuminated until the reward is collected and is then inactivated to start the next trial.

These sessions allow general habituation and learning that liquid reward is dispensed after a nose poke into an illuminated niche (typically 1 to 3 days, depending upon individual performance).

2. Once the general learning in step 1 is stable, adjust conditions such that mice have to initiate the first trial by nose poking in the food magazine which starts a 5-sec ITI. At the end of the ITI, randomly present a light stimulus at one of the five possible locations. If the animal nose pokes in the niche in which the stimulus light has been presented, it is rewarded by sucrose reinforcement. Initially maintain stimulus duration and LH at 30 sec to provide opportunity to learn the stimulus-reward association. Incorrect responses or failure to respond within this period (omissions) results in a 5-sec time out (TO) period. In a similar manner, a premature response (responses made during the ITI) or a perseverative response, also result in a 5-sec TO.

3. After animals have stably learned the stimulus-reward association, reduce the SD through 15, 10, 5, 3, 2, 1.8, 1.6, 1.4, 1.2, to a final SD of 1 sec. Monitor animal performance on a daily basis. Once an animal achieves a criterion of $\geq$80% accuracy, $\leq$20% omissions, $\leq$20% premature/perseverative responses/session over two consecutive sessions then it can be moved to a shorter SD (step 4).

   Do not move animals to a shorter SD when they are already poorly performing to avoid extinction of behavior.

4. Train the animals until they reach stable performance at the final test parameters (e.g., 1-sec SD; 5-sec LH, 5-sec ITI, 100 trials).

   Animals are considered ready for experimentation when (1) % correct, number omissions, and premature/perseverative responses do not vary by 10% over 5 consecutive sessions, (2) they do not show further overall (improvement) trends, and (3) they fall within acceptable criteria of >80% correct, $\leq$20 omissions/session, $\leq$20 premature/perseverative responses/session.

   For possible experimental manipulations see Alternate Protocol 3.

ALTERNATE PROTOCOL 3

5-CHOICE SERIAL REACTION TIME TASK: EXPERIMENTAL MANIPULATIONS IN THE MOUSE

Experimental manipulations can also be applied to the mouse 5CSRTT (see Alternate Protocol 1). Indeed, once trained to stable performance, attentional load or motivational alterations can be achieved by manipulating the basic parameters of the task on a single session (also called challenge session). Such manipulations can be made to SD, ITI, trial numbers, SI, distractive noise interference, absence of reward when correct responses are made, or free access to food before testing. Each manipulation session is presented after three consecutive days of baseline performance. For materials see the Basic Protocol.

1. Train mice to stable performance under standard conditions of 1-sec SD, 5-sec ITI, and 100 trials as described in Alternate Protocol 2.

2a. *Example variable noise distractor challenge:* Program a single session such that a 0.5-sec burst of white noise (100-dB) is introduced at 0, 2.5, and 5 sec after the beginning of the ITI (the 5-sec presentation being simultaneous with the onset of the visual stimulus).

2b. *Example variable ITI challenge:* Program a single session such that while SD and trial number remain at 1 sec and 100 trials, respectively, the ITI is presented at one of 4 levels within the session (either short ITI = 2, 3, 4, 5 sec; or long ITI = 5, 6, 7, 8 sec).

For short-ITI challenge, employ a pseudo-random schedule such that each level of ITI is equally paired with each stimulus location, i.e., 5 pairings of 2-sec ITI with stimulus location 1 (5 × 2-sec ITI @ 1, 5 × 3-sec ITI @1, 5 × 4-sec ITI @ 1, 5 × 5-sec ITI @1, 5 × 2-sec ITI @ 2, 5 × 3-sec ITI @ 2, 5 × 4-sec ITI @ 2, 5 × 5-sec ITI @ 2, etc).

A similar experimental procedure can be applied for long ITI challenge.

2c. *Example variable stimulus duration (SD) challenge:* Program a single session such that while ITI and trial number remain at 5 sec and 100 trials, respectively, the SD is presented at one of 4 levels within the session (0.25, 0.5, 0.75, and 1 sec). Employ a pseudo-random schedule within the session such that each level of SD is equally paired with each stimulus location, i.e., 5 pairings of 0.25-sec SD with stimulus location 1 (5 × 0.25-sec SD @1, 5 × 0.5-sec SD @1, 5 × 0.75-sec SD @1, 5 × 1-sec SD@1, 5 × 0.25-sec SD @2, etc.).

3. On intervening days, run the mice under standard test conditions.

4. Repeat challenge session pending the number of treatment levels. Ensure counterbalancing of treatment sequence across each session.

COMMENTARY

Background Information

The first published report describing the rodent version of the 5-CSRTT was Carli et al. (1983). The task arose from a need to study attention in the rat and was adapted from an equivalent task in humans (see Robbins, 2002). Attention is not a unitary construct, there being distinct subcategories. One form of attention is selective attention, where an animal has to focus on a restricted set of stimuli, while ignoring the rest. A second form is divided attention, requiring the animal to simultaneously monitor two or more distinct ongoing sensory modalities. A third form is vigilance, a continuous allocation of resources for the detection of rare events. Vigilance deficits are typically observed towards the end of a long session, and thus are time-dependent. A central advantage of the 5-CSRTT is its flexibility; the experimenter is able to configure the test conditions in multiple ways. This allows one to theoretically probe these distinct aspects of attention using this task.

The seminal paper of Carli et al. (1983) demonstrated that manipulations to test parameters such as ITI and stimulus duration, produced robust and predictable changes in basal performance, which provided a valuable means to asses the impact of experimental manipulation on behaviors related to attention and response control [in this instance, lesions to a CNS noradrenergic (NA) system; see Figs. 5.49.2 and 5.49.3A]. These manipulations are discussed in more detail below in Anticipated Results. The initial research emphasis with the 5-CSRTT was to explore the roles of central cholinergic, serotonergic, dopaminergic, and noradrenergic systems, primarily through selective lesioning techniques. An important outcome from this research was to highlight the dissociable roles of each neurotransmitter system on attention, reaction time, and response control (reviewed in Robbins, 2002).

In 1999, Wilkinson and coworkers (Humby et al., 1999) reported that mice can reliably learn to perform the 5-CSRTT, thus opening up opportunities to study genetic strain differences and the impact of gene targeting on performance in this task. This initial study highlighted that task acquisition and performance of the mouse was similar to the rat, with the exception that task motivation in the mouse may be a more sensitive factor.

Over the last ∼10 years the 5-CSRTT has been increasingly used to study the impact of drugs on attention, reflecting a gradual adoption for applied pharmaceutical drug discovery, as well as academic based research. The emphasis of this applied research has been to identify therapeutics for conditions where attentional dysfunction is a significant clinical feature, such as Alzheimer's Disease, schizophrenia, and attention deficit/hyperactivity disorder (ADHD). In this context, the study of nicotine and nicotine receptor subtype-selective nicotine analogs provide a useful example of the versatility and application of this task, where variations to the basic task procedure have

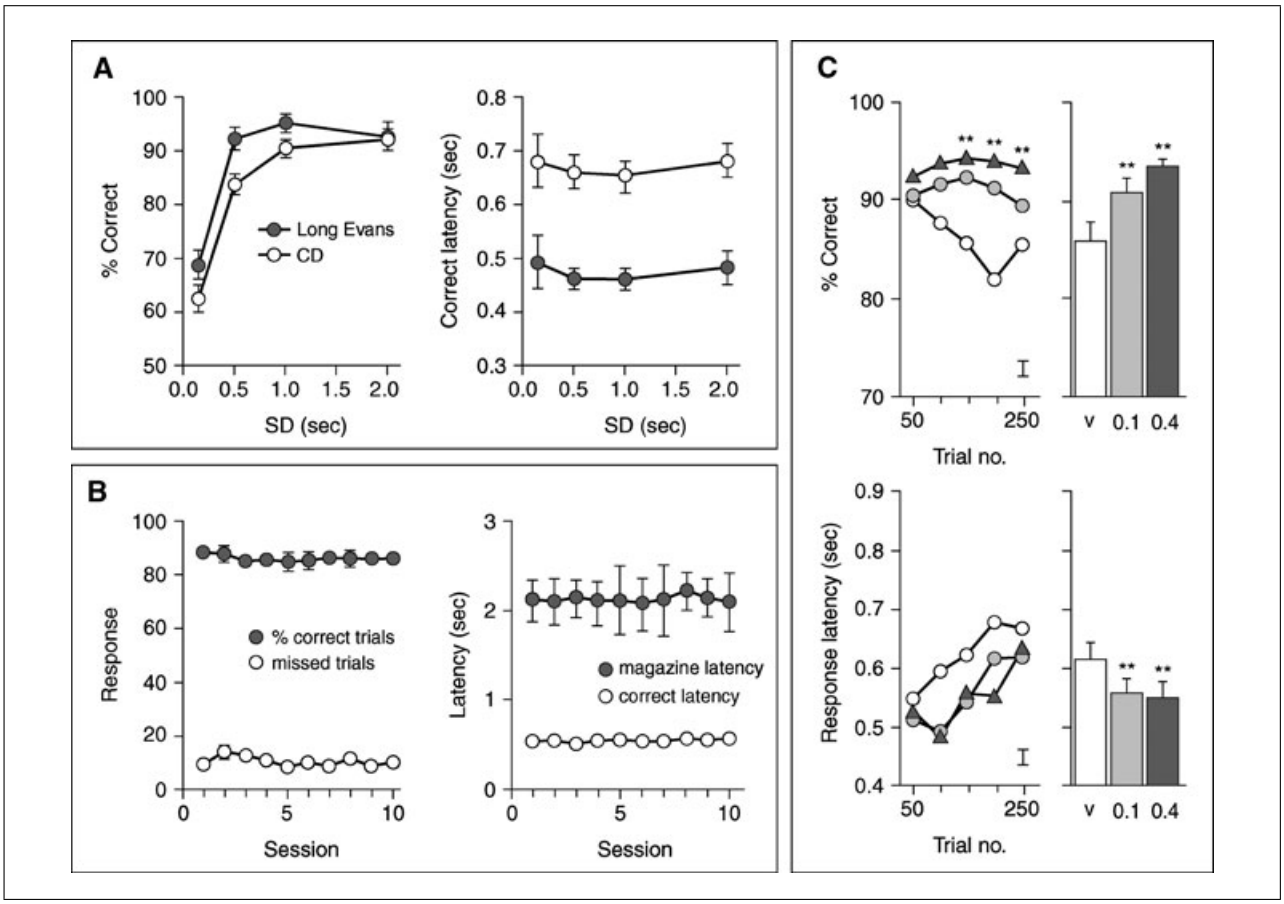

Figure 5.49.3 (**A**) Comparison of pigmented Long Evans (LE) and albino CD rat strains on % correct (left) and correct latency (right) over conditions of variable stimulus duration within a single 100-trial test session. Note at SD of 0.15 to 1 sec, the LE rats showed greater choice accuracy compared to CD strain, yet at a 2-sec SD both groups showed similar performance, suggesting differences at shorter SD did not reflect motivational differences. In terms of response speed, at all SD, the LE strain were faster than CD (adapted from Higgins et al., 2007). (**B**) Performance of adult male Lister Hooded rats over 10 consecutive days under standard test conditions of 5-sec ITI, 0.5-sec SD, 2-sec LH. Note the stable baseline for each measure over days (Higgins and Enderlin, unpublished data). (**C**) Effect of nicotine pretreatment (0.1 to 0.4 mg/kg) on performance in an extended 250-trials version of the 5-CSRTT. Data for % correct and correct response latency are presented as the total cumulative score over the overall session (right-hand panel), or by 50-trial bin (left-hand panel). ○ = vehicle, ● = 0.1 mg/kg, ▲ = 0.4 mg/kg, **represent $p < 0.01$ versus vehicle. Note the decline in accuracy and slowing of response speed in vehicle pretreated rats over successive trial bins, and the resistance to this decline following nicotine pretreatment (adapted from Grottick and Higgins, 2001).

revealed robust effects of nicotine on attention. The following example is given to highlight possible modifications to this task.

The well-documented effects of smoked nicotine on attention in humans, coupled with the elucidation of nicotine receptor subtypes at the molecular level, made identification of subtype-selective nicotine analogs an attractive therapeutic target. Using standard test conditions of 5-sec ITI, 0.5-sec SD, Muir et al. (1995) first demonstrated a subtle effect of nicotine to improve attention in rats with central cholinergic lesions, although performance in normal unlesioned rats was unaffected. However, by manipulating test conditions through introducing a low-event (ITI = 20 sec) schedule for test sessions only, and leaving premature responses unpunished, Mirza and Stolerman (1998) demonstrated reliable effects of nicotine on attentional accuracy in normal animals. Other studies reported further test variations to establish nicotine improvements in attention (Grottick and Higgins, 2000, 2002; Hahn et al., 2002a). For example, Grottick and Higgins (2002) adopted an extended-trials protocol (250 trials) where performance was tracked over the session course. Specifically, nicotine attenuated a performance decline seen at later trials which the authors attribute to a nicotine-induced improvement in vigilance (i.e., sustained attention; see Fig. 5.49.3C). In a further test variant, Blondel et al. (2000) reported that nicotine improved performance to the

less well attended stimulus locations. Having established test conditions to detect robust nicotine-induced improvements in performance, the same conditions were applied to study nicotine receptor subtype-selective agonists with the purpose of identifying compounds retaining the procognitive effects, but not some of the adverse effects, of nicotine (Grottick et al., 2000; Hahn et al., 2003).

Recently, a report describing the combination of a 5-CSRTT paradigm with a variable delay component enabled the simultaneous measurement of attention and memory using the 5-CSRTT test apparatus (Chudasama et al., 2004). These studies further highlight the flexibility and potential of the task. Extension of the task to computerized touch screen variants in rhesus monkey and marmoset primate species (Weed et al., 1999; Spinelli et al., 2004) and humans (e.g., Sahakian et al., 1993) highlight the translational capability of the 5-CSRTT.

Critical Parameters and Troubleshooting

Strain of animals

Because the 5-CSRTT relies on the detection of a visual stimulus, pigmented rat strains have been preferred to albino strains because of their better visual acuity (e.g., Prusky et al., 2002). Thus, the Lister hooded or Long Evans rats are the most frequently used strains in this task and may attain a discriminative accuracy approximating 90% under standard test conditions, such as 0.5-sec SD. However, albino strains such as Sprague-Dawley can reliably perform the test, and the lower discriminative accuracy demonstrated by these animals under equivalent SD can be exploited to test compounds predicted to improve accuracy (e.g., Mirza and Bright, 2001; see Fig. 5.49.3A). There are no clear data to suggest that rates of task acquisition differ significantly between pigmented and albino strains. Once trained, performance is stable and consistent across animals and over days (see Fig. 5.49.3B). Consequently, group sizes of ~12 are adequate for experimental study.

Different strains of mice have been tested in the 5-CSRTT with the main strains used for pharmacological manipulations being C57Bl/6 and DBA/2 (Humby et al., 1999; Greco et al., 2005; Fletcher et al., 2007). Transgenic mice phenotypes have also been assessed in the 5-CSRTT to investigate attentional performance in models of Alzheimer's disease (e.g., FTDP-17 tau_{v337M}; Labourne et al., 2007) or ADHD (e.g., XO mouse model; Davies et al., 2007). Group sizes of ~12 are generally adequate for experimental study.

Method of food restriction and reinforcement

Being a food-motivated task, it is important that all animals are placed on a defined level of food restriction throughout the course of the study. A typical regimen is to keep the animals at ~85% of their free-feeding weight. To achieve this, animals are frequently given a preweighed amount of food at the end of the day. If rats are singly housed this procedure is acceptable, with the caveat that social isolation has been reported to affect 5-CSRTT task performance compared to group-housed animals (see Dalley et al., 2002). The experimenter may consider these changes to be minor and acceptable within the overall context of the experiment. However, if group housing is preferred, it is strongly recommended not to place preweighed quantities of food in a cage containing two or more rats, as this will encourage hoarding and inter-animal aggression. One workable solution is to give all animals in a group cage free and unlimited access to food for a fixed time period at the end of the day. If the food hopper and cage design is such that all animals have ready access to food, this procedure reduces the potential for inter-animal aggression and all animals should show similar growth rates. On days when the animals are not run in the 5-CSRTT, then the access period should be increased slightly. Experimenters may wish to define their own access periods, but free food access for 45 to 50 min (60 min on test-free days) at the end of each day should keep rats at ~85% of their free-feeding weight.

In rats, 45-mg food pellets are typically used as reinforcement although liquid (e.g., 10% sucrose) is occasionally reported (e.g., Fletcher et al., 2007). The nature of food reinforcement does not seem to impact the test outcome. Mice, on the other hand, appear to be more sensitive to the nature of the food reward and the impact of satiation on test performance seems greater in this species compared to the rat (Humby et al., 1999). The majority of studies report the use of liquid reinforcement, either 10% sucrose or condensed milk, at volumes of 10 to 20 µl per reward (e.g., Humby et al., 1999; Greco et al., 2005; Fletcher et al., 2007; Lambourne et al., 2007). In the case of a solid food reinforcer, pellets of size 12 mg, 20 mg, and 25 mg have been described; however, in the case of the larger pellet size, the ITI may

have to be increased to offset satiation and to give the animals sufficient time to consume the pellets before continuing to the next trial (see de Bruin et al., 2006; Patel et al., 2006).

Test session design

Trial number. The 5-CSRTT is a discrete-trials procedure, with the final performance analysis being measured over all trials undertaken in the test session. Most commonly, a 100 trial per session design is used, which allows the visual stimulus to be presented equally at each location 20 times. In this instance, a cutoff time of 30 to 60 min is used since well-trained rats typically complete 100 trials within 30 min. However, rats of the Lister hooded strain can reliably perform many more trials before behavior becomes compromised by satiety, and test schedules of up to 250 trials have been reported (see Carli et al., 1983; Grottick and Higgins, 2002). An advantage of extended sessions is that performance deficits may emerge over the latter trials, perhaps reflecting a vigilance decrement. In the case of experimental challenges as described below it may also be preferable to increase overall number of trials to increase the number of replications of each challenge level. An alternative to a fixed-trials session design is to have the session duration fixed (e.g., see Mirza and Stolerman, 1998). One potential advantage of this design is that it may allow detection of experimental manipulations that speed performance without detracting from accuracy.

Variations to SD. Typically rats are trained to respond to a final SD of 0.5 or 1 sec. Increasing or decreasing the SD from this level serves as a reliable means to respectively reduce or increase the attentional demand to the animal. For example, increasing the SD from 1 to 5 sec restored accuracy performance of rats with central cholinergic lesions, confirming the deficits seen at the lower SD were attention-based, rather than, for example, reduced task motivation (Lehmann et al., 2003). Conversely, reducing SD from 0.5 to 0.25 sec reduces accuracy and offers a window for detecting a drug- or lesion-based improvement. A range of SD manipulations can be made within a single test session, or alternatively a single SD change can be applied to a single test session (see Figs. 5.49.2 and 5.49.3A).

Variations to SI. As with SD, it is also possible to vary the brightness of the visual stimulus typically within a single test session. Performance declines as a function of reduced SI (see Fig. 5.49.2). Differences between experimental groups across this change may reflect differences in visual sensory function.

Variations to ITI. An important distinction in the 5-CSRTT is between paced and unpaced versions of the task, the unpaced version placing more demand on attentional resources. Typically, the 5-CSRTT is run under a paced condition where the visual stimulus is programmed to occur after the animal makes a certain response. A fixed ITI of 5 sec indicates that, for each trial, the visual stimulus is presented 5 sec after the first magazine nose poke. A variable ITI removes this predictability and typically 4 levels of ITI may be presented randomly within a single test session. In practice, two such ranges of ITI tend to be used: a "short ITI," e.g., 2, 3, 4, 5 sec and a "long ITI," e.g., 5, 6, 8, 10 sec, although these can be mixed (e.g., see Fig. 5.49.2). Longer ITIs reduce the rate of stimulus presentation and tax vigilance processing (e.g., Mirza and Stolerman, 1998). Long ITIs also place greater demands on the animals' capacity to wait for the stimulus onset and, consequently, rates of premature responding tend to increase with increasing ITI. As such, long ITIs are frequently used to study experimental manipulations on motor impulsivity (e.g., Fletcher et al., 2007).

Interpolation of distractor stimuli. To assess whether an animal may be distracted by a stimulus in another distinct modality, brief ($\leq$1 sec) bursts of white noise can be introduced at various points within the ITI, including simultaneously with the visual stimulus itself, within a single test session. In normal, well-trained animals, such bursts of white noise do not appear to have a significant effect on discriminative performance, but in rats with cholinergic deficits, deficits may be revealed (e.g., Jones and Higgins, 1995).

Combinations. Under some experimental circumstances it may be useful to combine some of these experimental challenges. For example, Jones et al. (1995) employed a task variant of reduced SD and SI to lower baseline accuracy performance further than either manipulation alone.

Test apparatus

The original test apparatus reported by Carli et al. (1983) to run the 5-CSRTT was a nine-hole box. The nine-hole box was of aluminum construction (25-cm $\times$ 25-cm) with a curved rear wall, set into which were nine 2.5-cm square holes. Each hole had an infrared beam crossing the entrance and a standard 3-W light bulb set into the rear. Each hole could be

blocked by metal caps and, for the 5-choice task, alternate holes were blocked, allowing five open and equally spaced apertures. An advantage of the 9-hole system design is that alternate light configurations may be used to conduct tests other than the 5-choice task. For example, opening the three adjacent central apertures, while closing the remainder, enables a separate reaction time procedure to be conducted (e.g., see Carli et al., 1985). Both 5- and 9-hole test chambers for rat and mouse are available from suppliers such as Campden Instruments (*http://www.campdeninstruments.com*), Med Associates (*www.med-associates.com*), Lafayette Instruments (*http://www.lafayetteneuroscience.com*), and TSE Systems (*http://www.TSE-Systems.com*). Model examples for the rat include, but are not limited to, Standard 5/9 hole box (Campden Instruments), MED-NP5L-D1 (Med Associates), Model no. 80600A-CL (Lafayette Instruments).

The original test chambers described by Carli et al. (1983) also utilized a metal flap over the magazine tray. A magazine nose poke is registered by the animal opening the flap which operates a microswitch. A further advantage of the flap is that it conceals the magazine food tray. Consequently, the animal still readily makes a magazine nose poke to start the next trial in the event of a timeout period. An occasional, but significant, problem encountered with the magazine flap is animals catching their snout between the flap and tray, which can deter this behavior. Test chambers such as those provided by Med Associates are not routinely equipped with a magazine flap. Rather, entry into the magazine well is detected by a photocell beam placed across the well entrance. However, in the event of a timeout, the untrained animal is less inclined to nose poke as no food pellet is visible. To counter this, a stimulus light positioned within the magazine well is necessary to signal to the animal when a nose poke is required.

The advantage of LEDs for the visual stimulus rather than light bulbs is also worth highlighting. LEDs offer superior temporal control of the visual stimulus duration, as well as easier control of stimulus intensity. Thus, the authors recommend utilization of test chambers equipped with LEDs in each of the five niche locations.

A variant to the standard test configuration is the positioning of response levers below each stimulus light. Thus, registration of stimulus detection is by lever press rather than nose poke (e.g., Shannon and Eberle, 2006).

Anticipated Results

Baseline behavior. Once trained, performance of rodents in this task is very stable over extended periods of weeks to months (e.g., Fig. 5.49.3B). Also, changes in accuracy produced by parametric changes may also be consistent across repeated challenge sessions (see Fig. 5.49.2). This is important in the context of crossover design studies to study drug effects against such changes.

Test compound effects. A number of test compounds have been evaluated in the 5-CSRTT, and a selection of this data is summarized in Table 5.49.1 (see also Robbins, 2002). Probably the most widely studied drug classes in this test are psychostimulants, such as amphetamine, nicotine and nicotine analogs, and cholinergic antagonists such as scopolamine (see Robbins, 2002). At low doses, amphetamine reliably speeds reaction time (i.e., decreases correct latency) and, under some circumstances, can improve accuracy (e.g., Cole and Robbins, 1987; Grottick and Higgins, 2002). At higher doses, response control is impaired and premature responding is increased. At a certain point, the magnitude of this effect becomes sufficient to impair overall task performance. A number of reports have documented the effects of nicotine in this task (see Background Information and Table 5.49.1) and, like amphetamine, any performance-improving effect appears to follow an inverted U shape. This is an important point when evaluating any novel test compound in this task, with the potential to improve task performance. Careful attention needs to be paid not to overdose, and apparently subtle improvements seen at a relatively low dose level should not be ignored. Modifications to the test procedure may enable clearer expression of effect, as exemplified with nicotine.

Lesion effects. The most extensively characterized neurotransmitter system through neurotoxin lesion-based study is the cholinergic system. A variety of lesion approaches have been adopted, with the 192 IgG-saporin approach probably producing the most extensive and selective lesions to this system. 192 IgG-saporin lesions to the NbM brain region deplete cortical levels of choline acetyltransferase and acetylcholine, with the animals subsequently demonstrating profound deficits in discrimination accuracy to a standard test stimulus compared to sham lesion in this test (McGaughy et al., 2002; Lehmann et al., 2003).

Table 5.49.1 Summary of Pharmacology-Based Studies in the 5-Choice Serial Reaction Time Task[a]

System	Drug	Primary target	Dose	Result			References
				Accuracy	Reaction time	Response control	
Cholinergic	Nicotine	nAchR agonist	0.1-0.4 mg/kg s.c.	Improved	Faster	↔/↑ premature	Mirza and Stolerman (1998); Grottick and Higgins (2000; 2002); Blondel et al. (2000); Hahn et al. (2002a,b; 2003); Day et al. (2007)
	SIB1765F	nAchR (e.g., α4β2)	1-5 mg/kg s.c.	Improved	Faster	↑ premature	Grottick and Higgins (2000); Grottick et al. (2003)
	Epibatidine	nAchR (e.g., α4β2)	0.13-1 μg/kg s.c.	Improved	Faster	↓ premature	Hahn et al. (2003)
	AR-R17779	nAchR (α7)	1-24 mg/kg i.p.	↔	↔	↔	Grottick et al. (2000; 2003); Hahn et al. (2003)
	Aricept (E2020)	AchE inhibitor	0.3-1 mg/kg i.p.	↔[b]	↔	↔	Kirkby et al. (1996)
	Scopolamine	Muscarinic antagonist	0.01-0.1 mg/kg s.c.	Impaired	↔	↔/↑ premature	Jones and Higgins (1995); Mirza and Stolerman (2000); Ruotsalainen et al. (2000); Shannon and Eberle (2006)
	Mecamylamine	nAchR antagonist	0.3-3 mg/kg s.c.	Impaired	Slowed	↔	Grottick and Higgins (2000); Ruotsalainen et al. (2000); Mirza and Stolerman (2000)
	DHβE	nAchR antagonist	1-10 mg/kg s.c.	↔	↔	↔	Blondel et al. (2000); Grottick and Higgins (2000)

continued

Table 5.49.1 Summary of Pharmacology-Based Studies in the 5-Choice Serial Reaction Time Task[a], *continued*

System	Drug	Primary target	Dose	Result			References
				Accuracy	Reaction time	Response control	
Dopaminergic (DAergic)	Amphetamine	DA releaser	0.1-0.8 mg/kg s.c.	↔/Improved	Faster	↑ premature	Cole and Robbins (1987); Grottick and Higgins (2002); Bizarro et al. (2004)
	SCH23390	DA1/5 antagonist	0.003-0.1 mg/kg i.p.	↔	Slowed	↓ premature	Harrison et al. (1997); Shoaib and Bizarro (2005)
	Raclopride	DA2/3 antagonist	0.025-3 mg/kg s.c.	↔/Impaired	Slowed	↓ premature	Hahn et al. (2002b); Shoaib and Bizarro (2005)
	Haloperidol	DA2-like antagonist	0.03-0.1 mg/kg i.p.	↔	Slowed	↔	Carli and Samanin (1992); Millan et al. (2008)
	S33138	DA3 antagonist	0.04-2.5 mg/kg s.c.	↔	↔	↔	Millan et al. (2008)
Serotoninergic (5-HTergic)	8-OH DPAT	5-HT1A agonist	0.01-0.1 mg/kg s.c.	Impaired	Slowed	↑ premature	Carli and Samanin (2000)
	DOI	5-HT2A agonist	0.1-0.6 mg/kg s.c.	↔/Impaired	↔	↔/↑ premature	Koskinen et al. (2000); Fletcher et al. (2007)
	Ro 60-0175	5-HT2C agonist	0.1-0.8 mg/kg s.c.	↔	Slowed	↓ premature	Quarta et al. (2007); Fletcher et al. (2007)
	M100907	5-HT2A antagonist	0.01-1.0 mg/kg s.c.	↔	Slowed	↓ premature	Higgins et al. (2003b); Winstanley et al. (2004); Fletcher et al. (2007)
	SB242084	5-HT2C antagonist	0.02-0.5 mg/kg i.p.	↔	↔/Faster	↑ premature	Higgins et al. (2003b); Winstanley et al. (2004); Fletcher et al. (2007)
	Ondansetron	5-HT3 antagonist	0.01-1mg/kg sc	↔	↔	↔	Muir et al. (1995); Kirkby et al. (1996)

continued

Table 5.49.1 Summary of Pharmacology-Based Studies in the 5-Choice Serial Reaction Time Task[a], *continued*

System	Drug	Primary target	Dose	Result			References
				Accuracy	Reaction time	Response control	
Noradrenergic (NAergic)	ST-587	α1 agonist	0.1-1 mg/kg s.c.	Improved	↔	↓ premature	Puumala et al. (1997)
	Dexmedetomidine	α2 agonist	0.3-3 μg/kg s.c.	↔	↔	↓ premature	Ruotsalainen et al. (1997)
	Prazosin	α1 antagonist	0.1-0.3 mg/kg s.c.	Impaired	Slowed	↔	Puumala et al. (1997)
	Atipamezole	α2 antagonist	0.03-3 mg/kg s.c.	Improved	↔	↔	Sirvio et al. (1993); Ruotsalainen et al. (1997)
	Atomoxetine	NA reuptake inhibitor	0.6-3.0 mg/kg i.p.	↔	↔	↓ premature	Robinson et al. (2008)
Misc.	Modafinil	—	32-128 mg/kg oral	↔	↔	↑ premature	Waters et al. (2005)
	Caffeine	A1/A2a antagonist	3-20 mg/kg i.p.	↔/Improved	Faster	↑ premature	Grottick and Higgins (2002); Bizzaro et al. (2004); Higgins et al. (2007)
	SCH412348	A2a antagonist	0.03-1 mg/kg oral	↔	Faster	↑ premature	Higgins et al. (2007)
	Methylphenidate	DA/NA reuptake inhib.	2.5-10 mg/kg s.c.	Improved	Faster	↔	Bizzaro et al. (2004)
	Ciproxifan	H3 antagonist	0.3-3 mg/kg i.p.	Improved	↔	↓ premature	Ligneau et al. (1998); Day et al. (2007)

continued

Table 5.49.1 Summary of Pharmacology-Based Studies in the 5-Choice Serial Reaction Time Task[a], *continued*

System	Drug	Primary target	Dose	Result			References
				Accuracy	Reaction time	Response control	
	Dizocilpine	NMDA antagonist	0.01-0.25 mg/kg s.c.	Impaired	Slow/faster	↑ premature	Higgins et al. (2003a, 2005); Paine et al. (2007)
	Phencyclidine	NMDA antagonist	0.3-3 mg/kg s.c.	Impaired	Slowed	↑ premature	Le Pen et al. (2003); Amitia et al. (2007) (chronic treatment)
	Ro 63-1908	NR2B NMDA antagonist	0.3-10 mg/kg s.c.	Improved/↔	↔/Faster	↑ premature	Higgins et al. (2003a); Higgins et al. (2005)
	Sodium valproate	AED class	30-300 mg/kg i.p.	↔	Slowed	↔	Shannon and Love (2005)
	Prefeeding	—	—	↔	Slowed	↓ premature	Carli and Samanin (1992); Harrison et al. (1997); Grottick and Higgins (2000; 2002)

[a]This table is designed to give an overview of various pharmacology-based studies conducted in the rat version of the 5-CSRTT. This list is not intended to be complete but representative, and emphasis is given to systemic administration of drugs in this test. Where possible, data from multiple laboratories is given. Drug effects in the 5-CSRTT is summarized under three categories (i) discriminative accuracy [i.e., improved, impaired, or no effect (↔)], (ii) correct/incorrect response speed [i.e., faster, slower or no effect (↔)], (iii) response control based on drug effects on premature responding. Where findings are mixed, both effects may be highlighted.

[b]Reversed scopolamine (SCOP) deficit.

The effects of NbM lesions contrast with changes reported following central catecholaminergic (dopaminergic, noradrenergic) and serotonergic lesions in this test. For example, discriminative accuracy may actually be improved in rats with central serotonergic lesions, although the primary deficit is in measures of response control, with enduring increases in premature responding (Harrison et al., 1997). Indeed the 5-CSRTT has proved an effective means to highlight the differential roles of distinct neurotransmitter systems, as well as distinct subsystems of a particular neurotransmitter, on higher order behaviors such as attention and response control.

Time Considerations

In general from the start of autoshaping to asymptotic performance levels at final training condition, requires a time period of ~4 to 6 weeks, assuming training is 5 days/week. This time period is similar for rat and mouse species. At this point the experimental manipulation is usually undertaken and the overall study duration is governed by its extent. For example, testing a single test compound at three dose levels plus a vehicle control would take 2 weeks assuming two dosing cycles were run each week. However, much longer experimental periods are not uncommon, for example studying the effects of various parametric challenges and drug interactions to a specific lesion may extend this period to 6 months.

Literature Cited

Amitia, N., Semenova, S., and Markou, A. 2007. Cognitive-disruptive effects of the psychotomimetic phencyclidine and attenuation by atypical antipsychotic medications in rats. *Psychopharmacology* 193:521-537.

Bizarro, L., Patel, S., Murtagh, C., and Stolerman, I.P. 2004. Differential effects of psychomotor stimulants on attentional performance in rats: Nicotine, amphetamine, caffeine and methylphenidate. *Behav. Pharmacol.* 15:195-206.

Blondel, A., Sanger, D.J., and Moser, P.C. 2000. Characterization of the effects of nicotine in the five-choice serial reaction time task in rats: Antagonist studies. *Psychopharmacology* 149:293-305.

Carli, M., Evenden, J.L., and Robbins, T.W. 1985. Depletion of unilateral striatal dopamine impairs initiation of contralateral actions and not sensory attention. *Nature* 313:679-682.

Carli, M., Robbins, T.W., Evenden, J.L., and Everitt, B.J. 1983. Effects of lesions to ascending noradrenergic neurons on performance of a 5-choice serial reaction task in rats; implications for theories of dorsal noradrenergic bundle function based on selective attention and arousal. *Behav. Brain Res.* 9:361-380.

Carli, M. and Samanin, R. 1992. Serotonin2 receptor agonists and serotonergic anorectic drugs affect rats' performance differently in a five-choice serial reaction time task. *Psychopharmacology* 106:228-234.

Carli, M. and Samanin, R. 2000. The 5-HT1A receptor agonist 8-OH DPAT reduces rats' accuracy of attentional performance and enhances impulsive responding in a five-choice serial reaction time task: Role of presynaptic 5-HT1A receptors. *Psychopharmacology* 149:259-268.

Chudasama, Y., Dalley, J.W., Nathwani, F., Bouger, P., and Robbins, T.W. 2004. Cholinergic modulation of visual attention and working memory: Dissociable effects of basal forebrain 192-IgG-saporin lesions and intraprefrontal infusions of scopolamine. *Learn. Memory* 11:78-86.

Cole, B.J. and Robbins, T.W. 1987. Amphetamine impairs the discriminative performance of rats with dorsal bundle lesions on a 5-choice serial reaction time task: New evidence for central dopaminergic-noradrenergic interactions. *Psychopharmacology* 91:458-466.

Dalley, J.W., Theobald, D.E., Pereira, E.A., Li, P.M., and Robbins, T.W. 2002. Specific abnormalities in serotonin release in the prefrontal cortex of isolation-reared rats measured during behavioural performance of a task assessing visuospatial attention and impulsivity. *Psychopharmacology* 164:329-340.

Davies, W., Humby, T., Isles, A.R., Burgoyne, P.S., and Wilkinson, L.S. 2007. X-Monosomy effects on visuospatial attention in mice: A candidate gene and implications for turner syndrome and attention deficit hyperactivity disorder. *Biol. Psychiat.* 61:1351-1360.

Day, M., Pan, J.B., Buckley, M.J., Cronin, E., Hollingsworth, P.R., Hirst, W.D., Navarra, R., Sullivan, J.P., Decker, M.W., and Fox, G.B. 2007. Differential effects of ciproxifan and nicotine on impulsivity and attention measures in the 5-choice serial reaction time test. *Biochem. Pharmacol.* 73:1123-1134.

De Bruin, N.M.W.J., Fransen, F., Duytschaever, H., Grantham, C., and Megens, A.A.H.P. 2006. Attentional performance of (C57BL/6J × 129Sv)F2 mice in the five-choice serial reaction time task. *Physiol. Behav.* 89:692-703.

Fletcher, P.J., Tampakeras, M., Sinyard, J., and Higgins, G.A. 2007. Opposing effects of 5-HT2A and 5-HT2C receptor antagonists in the rat and mouse on premature responding in the five-choice serial reaction time test. *Psychopharmacology* 195:223-234.

Greco, B., Invernizzi, R.W., and Carli, M. 2005. Phencyclidine-induced impairment in attention and response control depends on the background genotype of mice: Reversal bt the mGLU2/3 receptor agonist LY379268. *Psychopharmacology* 179:68-76.

Grottick, A.J. and Higgins, G.A. 2000. Effect of subtype selective nicotine compounds on

attention as assessed by the five-choice serial reaction time task. *Behav. Brain Res.* 117:197-208.

Grottick, A.J. and Higgins, G.A. 2002. Assessing a vigilance decrement in aged rats: Effects of pre-feeding, task manipulation, and psychostimulants. *Psychopharmacology* 164:33-41.

Grottick, A.J., Haman, M., Wyler, R., and Higgins, G.A. 2003. Reversal of a vigilance decrement in the aged rat by subtype-selective nicotinic ligands. *Neuropsychopharmacology* 28:880-887.

Hahn, B., Shoaib, M., and Stolerman, I.P. 2002a. Nicotine-induced enhancement of attention in the five-choice serial reaction time task: The influence of task demands. *Psychopharmacology* 162:129-137.

Hahn, B., Shoaib, M., and Stolerman, I.P. 2002b. Effects of dopamine receptor antagonists on nicotine-induced attentional enhancement. *Behav. Pharmacol.* 13:621-632.

Hahn, B., Sharples, C.G.V., Wonnacott, S., Shoaib, M., and Stolerman, I.P. 2003. Attentional effects of nicotinic agonists in rats. *Neuropharmacology* 44:1054-1067.

Harrison, A.L., Everitt, B.J., and Robbins, T.W. 1997. Central 5-HT depletion enhances impulsive responding without affecting the accuracy of attentional performance: Interactions with dopaminergic mechanisms. *Psychopharmacology* 133:329-342.

Higgins, G.A., Ballard, T.M., Huwyler, J., Kemp, J.A., and Gill, R. 2003a. Evaluation of the NR2B-selective NMDA receptor antagonist Ro 63-1908 on rodent behaviour: Evidence for an involvement of NR2B receptors in response inhibition. *Neuropharmacology* 44:324-341.

Higgins, G.A., Enderlin, M., Haman, M., and Fletcher, P.J. 2003b. The 5-HT2A receptor antagonist M100,907 attenuates motor and 'impulsive-type' behaviours produced by NMDA receptor antagonism. *Psychopharmacology* 170:309-319.

Higgins, G.A., Ballard, T.M., Enderlin, M., Haman, M., and Kemp, J.A. 2005. Evidence for improved performance in cognitive tasks following selective NR2B NMDA receptor antagonist pretreatment in the rat. *Psychopharmacology* 179:85-98.

Higgins, G.A., Grzelak, M.E., Pond, A.J., Cohen-Williams, M.E., Hodgson, R.A., and Varty, G.B. 2007. The effect of caffeine to increase reaction time in the rat during a test of attention is mediated through antagonism of adenosine A2A receptors. *Behav. Brain Res.* 185:32-42.

Humby, T., Laird, F.M., Davies, W., and Wilkinson, L.S. 1999. Visuospatial attentional functioning in mice: Interactions between cholinergic manipulations and genotype. *Eur. J. Neurosci.* 11:2813-2823.

Jones, D.N.C. and Higgins, G.A. 1995. Effect of scopolamine on visual attention in rats. *Psychopharmacology* 120:142-149.

Jones, D.N.C., Barnes, J.C., Kirkby, D.L., and Higgins, G.A. 1995. Age associated impairments in a test of attention: Evidence for involvement of cholinergic systems. *J. Neurosci.* 15:7282-7292.

Kirkby, D.L., Jones, D.N.C., Barnes, J.C., and Higgins, G.A. 1996. Effects of anticholinesterase drugs tacrine and E2020, the 5-HT(3) antagonist ondansetron, and the H(3) antagonist thioperamide, in models of cognition and cholinergic function. *Behav. Pharmacol.* 7:513-525.

Koskinen, T., Ruotsalainen, S., and Sirvio, J. 2000. The 5-HT(2) receptor activation enhances impulsive responding without increasing motor activity in rats. *Pharmacol. Biochem. Behav*. 66:729-738.

Lambourne, S.L., Humby, T., Isles, A.R., Emson, P.C., Spillantini, M.G., and Wilkinson, L.S. 2007. Impairments in impulse control in mice transgenic for the human FTDP-17 tauV337M mutation are exacerbated by age. *Hum. Mol. Genet.* 16:1708-1719.

Lehmann, O., Grottick, A.J., Cassel, J.C., and Higgins, G.A. 2003. A double dissociation between serial reaction time and radial maze performance in rats subjected to 192 IgG-saporin lesions of the nucleus basalis and/or the septal region. *Eur. J. Neurosci.* 18:651-666.

Le Pen, G., Grottick, A.J., Higgins, G.A., and Moreau, J-L. 2003. Phencyclidine exacerbates attentional deficits in a neurodevelopmental rat model of schizophrenia. *Neuropsychopharmacology* 28:1799-1809.

Ligneau, X., Lin, J., Vanni-Mercier, G., Jouvet, M., Muir, J.L., Ganellin, C.R., Stark, H., Els, S., Schunack, W., and Schwartz, J. 1998. Neurochemical and behavioral effects of ciproxifan, a potent histamine H3-receptor antagonist. *J. Pharmacol. Exp. Ther*. 287:658-666.

McGaughy, J., Dalley, J.W., Morrison, C.H., Everitt, B.J., and Robbins, T.W. 2002. Selective behavioral and neurochemical effects of cholinergic lesions produced by intrabasalis infusions of 192IgG-saporin on attentional performance in a five-choice serial reaction time task. *J. Neurosci.* 22:1905-1913.

Millan, M.J., Loiseau, F., Dekeyne, A., Gobert, A., Flik, G., Cremers, T.I., Rivet, J-M., Sicard, D., Billiras, R., and Brocco, M. 2008. S33138 (N-[4-[2-[(3aS,9bR)-8-cyano-1,3a,4,9b-tetrahydro[1] benzopyrano[3,4-c]pyrrol-2(3H)-yl)-ethyl]phenyl-acetamide), a preferential dopamine D3 versus D2 receptor antagonist and potential antipsychotic agent: III. Actions in models of therapeutic activity and induction of side effects. *J. Pharmacol. Exp. Ther*. 324:1212-1226.

Mirza, N.R. and Stolerman, I.P. 1998. Nicotine enhances sustained attention in the rat under specific task conditions. *Psychopharmacology* 138:266-274.

Mirza, N.R. and Stolerman, I.P. 2000. The role of nicotinic and muscarinic acetylcholine receptors

in attention. *Psychopharmacology* 148:243-250.

Mirza, N.R. and Bright, J.L. 2001. Nicotine-induced enhancements in the five-choice serial reaction time task in rats are strain-dependent. *Psychopharmacology* 154:8-12.

Muir, J.L., Everitt, B.J., and Robbins, T.W. 1995. Reversal of visual attentional dysfunction following lesions of the cholinergic basal forebrain by physostigmine and nicotine but not by the 5-HT3 receptor antagonist, ondansetron. *Psychopharmacology* 118:82-92.

Paine, T.A., Tomasiewicz, H.C., Zhang, K., and Carlezon, W.A. Jr. 2007. Sensitivity of the five-choice serial reaction time task to the effects of various psychotropic drugs in Sprague-Dawley rats. *Biol. Psychiat.* 62:687-693.

Patel, S., Stolerman, I.P., Asherson, P., and Sluyter, F. 2006. Attentional performance of C57BL/6 and DBA/2 mice in the 5-choice serial reaction time task. *Behav. Brain Res.* 170:197-203.

Prusky, G.T., Harker, K.T., Douglas, R.M., and Whishaw, I.Q., 2002. Variation in visual acuity within pigmented, and between pigmented and albino rat strains. *Behav. Brain Res.* 136:339-348.

Puumala, T., Riekkinen, P., and Sirvio, J. 1997. Modulation of vigilance and behavioural activation by alpha-1 adrenoceptors in the rat. *Pharmacol. Biochem. Behav.* 56:705-712.

Quarta, D., Naylor, C., and Stolerman, I.P. 2007. The serotonin2C receptor agonist Ro-60-0175 attenuates effects of nicotine in the five-choice serial reaction time task and in drug discrimination. *Psychopharmacology* 193:391-402.

Robbins, T.W. 2002. The 5-choice serial reaction time task: Behavioural pharmacology and functional neurochemistry. *Psychopharmacology* 163:362-380.

Robinson, E.S.J., Eagle, D.M., Mar, A.C., Bari, A., Banerjee, G., Jiang, X., Dalley, J.W., and Robbins, T.W. 2008. Similar fffects of the selective noradrenaline reuptake inhibitor atomoxetine on three distinct forms of impulsivity in the rat. *Neuropsychopharmacology* 33:1028-1037.

Ruotsalainen, S., Haapalinna, A., Riekkinen, P.J. Sr., and Sirvio, J. 1997. Dexmedetomidine reduces response tendency, but not accuracy of rats in attention and short-term memory tasks. *Pharmacol. Biochem. Behav*. 56:31-40.

Ruotsalainen, S., Miettinen, R., MacDonald, E., Koivisto, E., and Sirvio, J. 2000. Blockade of muscarinic, rather than nicotinic, receptors impairs attention, but does not interact with serotonin depletion. *Psychopharmacology* 148:111-123.

Sahakian, B.J., Owen, A.M., Morant, N.J., Eagger, S.A., Boddington, S., Crayton, L., Crockford, H.A., Crooks, M., Hill, K., and Levy, R. 1993. Further analysis of the cognitive effects of tetrahydroaminoacridine (THA) in Alzheimer's disease: Assessment of attentional and mnemonic function using CANTAB. *Psychopharmacology* 110:395-401.

Shannon, H.E. and Eberle, E.L. 2006. Effects of biasing the location of stimulus presentation, and the muscarinic cholinergic receptor antagonist scopolamine, on performance of a 5-choice serial reaction time attention task in rats. *Behav. Pharmacol.* 17:71-85.

Shannon, H.E. and Love, P.L. 2005. Effects of antiepileptic drugs on attention as assessed by a five-choice serial reaction time task in rats. *Epilepsy Behav.* 7:620-628.

Shoaib, M. and Bizarro, L. 2005. Deficits in a sustained attention task following nicotine withdrawal in rats. *Psychopharmacology* 178:211-222.

Sirvio, J., Jakala, P., Mazurkiewicz, M., Haapalinna, A., Riekkinen, P. Jr., and Riekkinen, P.J. 1993. Dose- and parameter-dependent effects of atipamezole, an α2-antagonist, on the performance of rats in a five-choice serial reaction time task. *Pharmacol. Biochem. Behav*. 45:123-129.

Spinelli, S., Pennanen, L., Dettling, A.C., Feldon, J., Higgins, G.A., and Pryce, C.R. 2004. Performance of the marmoset monkey on computerized tasks of attention and working memory. *Cognitive Brain Res.* 19:123-137.

Waters, K.A., Burnham, K.E., O'Connor, D., Dawson, G.R., and Dias, R. 2005. Assessment of modafinil on attentional processes in a five-choice serial reaction time test in the rat. *J. Psychopharmacol.* 19:149-158.

Weed, M.R., Taffe, M.A., Polis, I., Roberts, A.C., Robbins, T.W., Koob, G.F., Bloom, F.E., and Gold, L.H. 1999. Performance norms for a rhesus monkey neuropsychological testing battery: Acquisition and long-term performance. *Cognitive Brain Res.* 8:185-201.

Winstanley, C.A., Theobald, D.E., Dalley, J.W., Glennon, J.C., and Robbins, T.W. 2004. 5-HT2A and 5-HT2C receptor antagonists have opposing effects on a measure of impulsivity: Interactions with global 5-HT depletion. *Psychopharmacology* 176:376-385.