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The 5 Choice Continuous Performance Test (5C-CPT): A novel tool to assess cognitive control across species

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Abstract

Background—Neurodevelopmental disorders including Tourette's syndrome (TS) and attention deficit hyperactivity disorder (ADHD) are characterized by significant impairment in attention and cognitive control. These cognitive deficits persist throughout development, contribute significantly to socio-occupational impairment, and are relatively impervious to available treatment. A critical challenge in pro-cognitive drug discovery is translatability of findings across species, underscoring the need for developing valid and reliable cross-species cognitive tasks.

New Method—Here we describe a cross-species 5 choice continuous performance task that was developed to measure cognitive control processes of attention, vigilance, and response inhibition, enabling the translation of findings for pro-cognitive drug discovery across species and delineate neural mechanisms underlying cognitive control construct.

Results—Construct validity of 5C-CPT has been verified by multiple cross-species studies. Several lines of evidence report consistent findings across species including, deficits resulting from 36-hour sleep deprivation studies, engagement of parietal cortex in human brain imaging and rodent lesion studies, and vigilance decrements over time.

Comparison with existing method—Unlike the widely used rodent 5 choice serial reaction time task (5CSRTT) and the sustained attention task (SAT), the rodent 5C-CPT includes both target and non-target stimuli that allow measuring of cognitive control elements including response inhibition, an ability to inhibit pre-potent response during non-target trials, detect vigilance decrement and calculate signal detection parameters in rodents analogous to human CPT.

Conclusion—The cross-species 5C-CPT is a robust translational tool to characterize the neurobiological substrates underlying cognitive control deficits in clinical population including, ADHD and TS and develop targeted pro-cognitive therapeutics.

Keywords

5C-CPT; Tourette's syndrome; cognitive control; cross-species; translational; cognition; ADHD

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Introduction

Neurodevelopmental disorders including, Tourette's syndrome (TS) and attention deficit hyperactivity disorder (ADHD) are characterized by significant deficits in cognitive control processes, particularly attention and response inhibition (Eddy et al., 2012; Willcutt et al., 2005). Cognitive control is a higher order cognitive process that allows a) goal selection, updating, representation and maintenance, b) response selection, inhibition or suppression and c) performance monitoring (weblink). Given its broad influence on cognition overall, cognitive control is essential for decision-making and daily functioning; impaired cognitive control is believed to negatively impact psychosocial functioning in TS and ADHD (Robertson, 2000; Seidman, 2006; Sergeant et al., 2002; Skogli et al., 2014; Watkins et al., 2005). Clinical trials of putative pro-cognitive agents have mostly yielded negative results, however (Bidwell et al., 2011). This failure to detect pro-cognitive control treatment in-part, reflects the limitation of cross-species translational testing (Young and Geyer, 2015), hence underscoring the need to utilize reliable neurocognitive tasks that measure cognitive control with high fidelity and validity in both animal models and human subjects.

The standard neurocognitive tasks that measure different cognitive control elements in humans include but are not limited to, the continuous performance test (CPT) for goal maintenance and updating, response selection and inhibition/suppression, and performance monitoring (Conners, 1985; Macdonald, 2008), stroop color word interference task for performance monitoring, response selection and suppression (Westerhausen et al., 2011), and Go/Nogo task for response inhibition (Smith et al., 2004). Although these tests have high reliability and validity to measure these elements accurately in humans, there is dearth of cross-species translational neurocognitive tasks to measure these cognitive control elements, posing significant challenges for translational drug discovery. Cross-species neurocognitive tasks including the 5 Choice serial reaction time task (5CSRTT) and the sustained attention task (SAT) with and without distractor have been studied widely and validated to measure sustained attention, response selection and suppression and waiting impulsivity/timing in rodents (Cope et al, 2016; Humby et al., 2005; Robbins, 2002; McGaughy and Sarter, 1995). While these tasks measure several of the cognitive control elements mentioned above they are limited in their ability to measure response inhibition. Response inhibition is a prefrontal cortex mediated process that requires inhibition of pre-potent response to stimuli, impaired in TS and ADHD. The rodent 5 Choice Continuous Performance Test (5C-CPT) developed as a cross-species neurocognitive task analogous to the human CPT includes both target (requiring response selection and suppression) and non-target (requiring response inhibition) stimuli that allow similar calculation of signal detection parameters in both rodents and humans (Barnes et al, 2012; Young et al., 2009), including both target (requiring response) and non-target (requiring response inhibition) stimuli. Initial validity for the 5C-CPT came from evidence of a vigilance decrement over time, consistent with other human CPTs (Riccio et al., 2001; Young et al., 2009). Across species translational potential of this task, stemmed from the development of the human 5C-CPT (McKenna et al., 2013; Young et al., 2013). Further evidence of construct validity for this task came from, 36-hour sleep deprivation studies in mice and humans showing similar cross-species impairment in task performance (van Enkhuizen et al., 2014), and human

fMRI studies demonstrating parietal cortical involvement (McKenna et al., 2013), mirroring lesions studies demonstrating the need for parietal cortices (van Enkhuizen et al., 2015). Here we review the rodent and human 5C-CPT, methodological challenges, adaptations, and applications of this task for potential TS and ADHD research.

Rodent 5C-CPT

The rodent 5C-CPT is an elaboration of the 5CSRTT (Young et al., 2009). It includes target stimuli (an individual light that could appear in any one of five apertures in 5-hole or touchscreen chambers) consistent with 5CSRTT, and additional non-target stimuli (all 5 lights appearing in all five locations; Figure 1) to measure response inhibition. These two stimuli types enable the calculation of signal detection parameters that are validated in human CPT research, for use in rodent studies.

The 5C-CPT protocol has been validated in various mouse and rat strains (Barnes et al., 2012; Young et al., 2009). The protocol involves habituation to the testing chambers, fixed-ratio reward habituation, and then fixed-ratio response training. Once responding reliably, rodents are trained to respond to single target stimuli and inhibit from responding to non-target stimuli (Cope and Young, 2017). Once fully trained, rodents can then be challenged in various conditions to assess different cognitive control processes (e.g., distractibility; Young et al., 2011), described in detail in Cope et al., (2016a), with further details below.

The training and testing apparatus originally involved 5-hole operant chambers (25 × 25 × 25 cm, Med Associates, St Albans, VT, USA). Each chamber consisted of an array of five square holes (2.5 × 2.5 × 2.5 cm) arranged horizontally on a curved wall 2.5 cm above the grid floor opposite a food delivery magazine (Lafayette Instruments, Lafayette, IN, USA) at floor level and a house light near the ceiling. The chamber is located in a sound-attenuating box, ventilated by a fan that also provides a low level of background noise. An infrared camera installed in each chamber enables monitoring of performance during training and testing. Animals are trained to respond with a nose-poke to an illuminated LED recessed into the holes. Responses are detected by vertically mounted infrared beams located 3 mm from the opening of the hole. Liquid reinforcement in the form of strawberry milkshake (Nesquik (Vevey, Switzerland) plus non-fat milk, 30 μl) is delivered by peristaltic pump (Lafayette Instruments) to a well, located in the magazine opposite the 5-hole wall. Magazine entries are monitored using horizontally mounted infrared beam located 5 mm from the floor and recessed 6 mm into the magazine. The presentation of stimuli and recording of responses are managed by a SmartCtrl Package 8-In/16-Out with additional interfacing by MED-PC for Windows (Med Associates) using custom programming.

Training in the 5C-CPT is normally conducted over 5 days per week. Animals are first trained to obtain reinforcement at the magazine as they are delivered every 15 seconds (s) for 20 minutes (min). Once the animals are collecting >50 rewards in each session for two consecutive sessions (accomplished normally in 3 sessions), they are moved to fixed ratio 1 (FR1) training. Each FR1 training session is 30 mins in duration or 150 trials, whichever is completed first. Each trial is initiated by the animal poking it’s nose then removing it from the magazine. After a 5-sec inter-trial interval (ITI), a light stimulus appears in each of the five apertures located opposite the magazine. A nose-poke in any of the lit apertures results

in those apertures being de-illuminated, a reward being delivered, and the magazine being illuminated. Once animals are responding for >70 trials per session for two consecutive sessions, they are moved onto 5CSRTT training. Training on 5CSRTT starts when the animal responds in the magazine, similar to the FR1. However, instead of all five lights being illuminated, only one aperture is illuminated for a prescribed stimulus-duration (SD) plus a 2-sec limited hold period. SD starts at 10 sec then is gradually moved to 8, 4, 2, and 1.5 secs. Responding in only the lit aperture results in a correct (Hit) response being registered and a reward being delivered to the magazine. A nose-poke in any other aperture over this period is registered as an incorrect response and results in a 4-sec timeout (TO). Failure to respond in any aperture during the SD + limited hold is registered as an omission and also results in a TO. Response in any aperture during the ITI is registered as a premature response and triggers a TO. Miss = incorrect + omission. Initiation of the next trial occurs when the animal enters and then exits the magazine. The SD is moved to each shorter SD, when the animal meets criterion for the mean correct latency (less than half the current SD) for two consecutive days. Once at 1.5 sec SD, animals are transferred to a variable ITI (3–7 s). Once performance is stabilized (~3 days), the animals are moved to 5C-CPT training (Figure 1). Initially, 80 trials are target trials, while 40 trials are non-target trials. Responses to non-target trials result in a false alarm being registered and a TO occurring. A correct rejection of the non-target trial (non-response) results in a reward delivery. Once responding at <0.5 of false alarms for all non-target trials, animals are moved to 100 target trials and 20 non-target trials. These non-target stimuli are interspersed pseudorandomly within the 100 target trials (maximum of 3 sequential non-target trials). Latencies for every response type are collected, including correct, incorrect, premature, and false alarms. Approximately, 45 training sessions are required from 5CSRTT to meeting 5C-CPT criterion (120 trials or 30 min duration with a 1.5 s SD).

Human 5C-CPT

Most human CPTs have either numbers or letters as target and non-target stimuli that limits their use across cultures and species. The human 5C-CPT is reverse-translated from rodent 5C-CPT to address this limitation and utilizes distinct non-cultural stimuli presented in a spatial array (Figure 2). The human 5C-CPT results in brain region-specific activation that is consistent with other CPTs (McKenna et al., 2013). In addition, sleep deprivation impairs 5C-CPT similarly to other CPTs (van Enkhuizen et al., 2014). More importantly, the 5C-CPT is clinically sensitive, as demonstrated by deficits in schizophrenia patients compared to healthy participants (Young et al., 2013), with biomarker signatures (Young et al., 2017).

Methods

A Dell PC with E-Prime2 software (Psychology Software Tools, Sharpsburg, PA, USA) is used for stimulus presentation and data acquisition. For this task, participants sit comfortably in a chair, holding an arcade joystick in their dominant hand, facing a 25” computer screen (60 cm away) placed at eye level. The joystick is spring-mounted so that after every response the joystick would return to center. Throughout the task 5 white lines (3 cm) in an arc on a black background (Figure 2) appear on the screen.

During “target trials” a white circle (2 cm diameter) appears adjacent to a line. During non-target trials, all 5 white circles appear adjacent to every line simultaneously. Subjects are instructed to respond to target stimuli by moving the joystick in the direction of the white circle and withhold from responding during non-target stimuli. After a joystick response, the line under the selected stimulus flashes to indicate that target was selected. Otherwise no other feedback is provided. Stimuli are presented for 100 ms and subjects receive an additional 1sec response window after stimulus offset. Stimuli are presented in a random order to reduce temporal predictability of stimuli and preclude a mediating strategy that could aid performance. Variable inter-trial intervals (ITI; 0.5, 1 or 1.5 s) occur in pseudorandom order so that no more than three identical ITIs are presented after sequential trials. Before performing the full task, subjects are given a practice session consisting of 12 trials (10 target and 2 non-target stimuli randomly presented). Participants must perform the practice block correctly before moving on to the full task. The full task consists of 270 trials, 225 target and 45 non-target stimuli, presented in a pseudorandom order so that no more than 3 presentations of a specific stimulus appear consecutively. The high ratio of target vs. non-target stimuli in the rodent 5C-CPT ensures maintenance of responding, and also induces responding as a prepotent response (Lustig et al., 2013). This ratio was maintained in the human 5C-CPT. Similar to the rodent 5C-CPT with extended sessions, the human 5C-CPT has an extended version with 648 trials, 540 target and 108 non-target stimuli, when conducting electroencephalography (EEG) techniques requiring higher trial presentations.

The responses are recorded and calculated to use in the analysis of performance. *Hit rate* is quantified as the proportion of appropriate responses vs. miss to target stimuli. *Miss* is quantified as sum of incorrect responses to target stimuli and a nonresponse (failure to respond) within the allotted response window to target stimuli. *False alarm rate* is quantified as the proportion of inappropriate responses vs. correct rejection to non-target stimuli. *Accuracy* is determined as the proportion of correct compared to incorrect responses (Table 1).

The sensitivity index (SI) provides a nonparametric assessment of sensitivity to appropriate responding (McNicol, 1972). Values for sensitivity index vary from −1 to +1, with +1 indicating that a response was made to all target stimuli and withheld for all non-target stimuli. A value of 0 indicates chance levels of distinguishing between target and non-target stimuli (Table 2). To mirror the use of sensitivity index, the nonparametric response bias measure, responsivity index was chosen to provide a measure of the ‘tendency to respond’ (bias), with lower numbers indicating a conservative response strategy, whereas higher numbers equating to liberal responding (Bushnell et al., 2003; Green and Swets, 1966; McNicol, 1972). Both sensitivity and responsivity indices are based on the same geometric logic and are appropriate for use with single choice procedures [that is, responding or not; (Frey and Colliver, 1973; Green and Swets, 1966)]. With sufficient trial numbers, parametric statistics can also be used to calculate the difference between probability of hit rate and probability of false alarm rate using D-prime. Like SI, D-prime provides a calculation of the degree of discrimination between target and non-target trials, but does so parametrically.

Methodological Challenges

In Rodents

1. Animals need to have intact motor function to effectively perform nose poke within task requirements. There are of course secondary measures that provide indicators of alterations to motor function, e.g., response latencies. These measures should be scrutinized as a part of the analyses of any data-set.
2. Mostly adult rodents (>P60) are used for this task. Young animals (<60) cannot be studied due to concerns of food restriction potentially interfering with growth. Additionally, the time that is taken to train animals in the task precludes testing animals <P60, hence precluding adolescent animals – a key demographic in ADHD and TS. Given that cognitive control deficits persist even in adult life in both ADHD and TS, animal studies have used adult rats to characterize various subtypes of ADHD based on their 5C-CPT performance (Tomlinson et al., 2014, 2015).
3. Visual acuity remains important in the task, although since it is traditionally run with lights off, the stimuli are highly salient and visual acuity issues are rarely a concern.
4. Testing and training of animals should always be timed during the animal's active (dark) cycle. Therefore, care must be taken to minimize exposure to extraneous ambient white light that can disrupt circadian rhythm of the animal. An ambient red light can be used instead to illuminate testing room to carry out the laboratory procedures.
5. Training animals to respond to a single target or to withhold response to non-target stimuli might pose challenges. When first training rats in the 5-to-1 target-to-non-target stimuli task, it was observed they did not differentiate target from non-target trials, responding to all stimuli (Barnes et al., 2012), in contrast with mice (Young et al., 2009). Hence, training in a 2-to-1 ratio was first required to make the non-target stimuli more salient and is recommended for use (Cope and Young, 2017).
6. Response rates will drop when animals are moved from the FR1 training to the 5CSRTT. If, response rate drops below 5 for 3 consecutive days then, rodents can be moved back to the FR1 in order to increase responding.

In Humans

1. The task is simple and easy to perform. This simplicity could be a limitation while testing healthy subjects who perform superior to clinical population. Using an extended-session version of this task can increase task difficulty level. Alternatively, adding a backward mask can provide a graded difficulty level of the task. In backward masking, perception of the target stimulus is impaired by the presentation of a second stimulus, the mask (a white screen) at varying intervals from stimulus onset. Shorter inter stimulus intervals demand superior attention and thus increase task difficulty level.

2. Motor abilities of the dominant hand should not be impaired in order to effectively move the joystick within task requirement. Practice sessions should be monitored to ensure competency.

Adaptations

The human 5C-CPT has been adapted to provide neural biomarkers of performance using neuroimaging techniques. These neuroimaging techniques include functional magnetic resonance imaging (fMRI; McKenna et al., 2013) and electroencephalogram (EEG) (Young et al., 2017). These techniques are effective in identifying underlying neural correlates of cognitive control and attentive processes. EEG studies are being conducted in rodents to determine the neurobiological correlates of 5C-CPT performance and compare with human EEG activation patterns. The adaptation of these neuroimaging techniques enable robust translation across species and will likely, hasten discovery of pro-cognitive therapeutics for neuropsychiatric disorders including ADHD and TS, as well as schizophrenia and bipolar disorder.

1. *Functional magnetic resonance imaging (fMRI):* The fMRI-based human 5C-CPT was first administered to a group of healthy subjects to evaluate the construct validity of the task and assess the neural correlates of cognitive control (McKenna et al., 2013). Consistent with other human CPTs (Conners, 1985; Macdonald, 2008) and Go/Nogo (Smith et al., 2004) paradigms, the 5C-CPT activated the premotor cortex, inferior parietal lobe, basal ganglia and thalamus during target trials, and the inferior frontal cortex, premotor cortex, pre-supplementary motor area and inferior parietal lobe during non-target trials. The fMRI-based 5C-CPT task is identical to the human 5C-CPT with the following modifications required for using a fiber-optic joystick (Figure 3):

    a. The stimuli are presented as 5 white circles with black centers displayed on a black background in a semi-circular array with equal distance between the stimuli.

    b. During target trials, the black center of one of the circles turns white for 250 milliseconds (ms) followed by a variable ITI (0.5 to 1.5 seconds). Participants respond during this ITI by moving the cursor using an MRI-compatible joystick from the starting location until the perimeter of the target circle is broken.

    c. During non-target trials, black centers of all five circles become solid white and participants are asked to withhold responding by not moving the joystick.

    d. Correct responses are followed by the word “correct” displayed on the screen after each trial, while incorrect responses are followed by a totally white screen with the word “incorrect” displayed in red for 4000 ms.

    e. The ratio between target and non-target trial is 5:1 with total of 120 target trials and 24 non-target trials across four runs of the task. Each

run consisted of 11 blocks and lasted for 5 minutes and 10 seconds. Each block lasted for 30 seconds followed by a 30 second fixation trial block where participants look at a crosshair in the center of the screen.

As mentioned above, the fMRI-based 5C-CPT has been validated for use in humans, but conducting such studies in rodents would prove difficult given the movement artifact inherent in rodent 5C-CPT and behavioral studies in general.

2. *EEG:* Unlike the fMRI studies, the EEG studies can be conducted in both humans (Young et al., 2017) and rodents (Brigman et al., 2013; Nagy et al., 2015). EEG adaptation for rodent models of disease however, first requires prior knowledge of the EEG response dynamics in clinical populations (Featherstone et al., 2015; Gandal et al., 2010). In humans, the extended-sessions 5C-CPT is adapted for EEG studies. The 5C-CPT testing apparatus and presentation is identical to the human 5C-CPT discussed above. The presentation of the target and non-target stimuli, and correct, incorrect, and other responses, are coded as event markers and time-locked with the EEG recording. EEG is recorded from 64 channel scalp electrodes using a BioSemi Active Two System (Takahashi et al., 2013; Young et al., 2017). During data acquisition the electrode offsets are kept below 25 mV and all channels are referenced to the system's internal loop (CMS/DRL electrodes). All data are collected using a 1048 Hz sampling rate utilizing a first-order anti-aliasing filter, and all preprocessing occurs offline using Brain Vision Analyzer 2.0 (Brain Products GmbH). The raw data with event markers are first exported, recoded using the recode file in DOS and imported back. Bad channels are interpolated using a spherical spline interpolation and re-referenced to the average reference. Data are digitally band pass filtered between .1–70 Hz (24 db/oct) using a Butterworth zero phase-shift filter with 48 db/octave rolloff, and eye movement artifacts are corrected using independent component analysis (ICA). Epochs are generated from −100–700ms post stimulus onset for correct trials. Only correct trials are used for ERP analysis due to the low number of task related errors. Epochs with additional EEG artifacts (adjacent sample amplitudes and/or max voltage changes exceeding +/− 70 μV/ms) are rejected and all remaining epochs are baseline corrected from −100–0 ms. Separate ERP waveforms are generated for target and non-target trials.

Similar to other CPT ERP studies, mean amplitude of electrodes centered on a midline scalp electrode and extending bi-laterally forming a strip of electrodes was used to calculate centroids (e.g., Centroid 3 = Mean of F_z, F_1, F_2, F_3, F_4) (Fallgater et al., 1997; Young et al., 2017). For statistical analysis, three distinct time windows during which subject-level ERP peaks (point with greatest absolute maxima within a time window) were selected: 1) 100–150 ms is believed to represent early sensory components (Herrmann and Knight, 2001), 2) a middle latency transitional peak (150–250 ms) post stimulus corresponds to response selection (Heslenfeld et al., 1997; Kenemans et al., 1993; Lindholm and Koriath, 1985) and 3) a later temporal window (300–575 ms) post stimulus is considered to represent response action and visual feedback processes (Fallgater et al., 2001). Behaviorally, response

inhibition is measured as a false alarm rate for non-target stimuli; its neurophysiological correlate is assessed by quantifying brain electrical field frontalization during correctly identified non-target stimuli (Fallgater et al., 1997; Young et al., 2017).

In a recent study, Young et al. (2017), found that schizophrenia patients had reduced P200 and N200 amplitudes to target and non-target stimuli respectively, compared with healthy comparison subjects. Given normal P100 amplitudes (likely reflecting sensory processing), these data reflect poorer sensory integration to response selection for both target and non-target trials. Perhaps unsurprisingly therefore, reduced P300 amplitudes to target and non-target stimuli are also observed.

Applications

The cross-species 5C-CPT has been used to i) characterize cognitive control deficits in rodent models of disorders (Cope et al., 2016b) and clinical population, ii) examine sensitivity to pro-cognitive control therapeutics and iii) guide drug discovery.

While some studies have used rodent 5C-CPT to identify rats with low attention and high impulsivity behavior to model the ADHD-combined subtype (Tomlinson et al., 2014; Hayward et al., 2016), others have used rodent 5C-CPT with visual distractors to characterize attentional deficits and behavioral disinhibition resulting from chronic intermittent alcohol exposure (Irimia et al., 2014).

Several variations and adaptations of 5C-CPT have been used towards developing targeted pro-cognitive treatment. Evidence that amphetamine improves human, rat, and mouse 5C-CPT performance similarly (enhanced hit rate-driven increases in d prime), indicate its utility in assessing pro-cognitive therapeutics across species (Young et al., 2016). In animal models of disorders, e.g., Sp4 hypomorphic model of schizophrenia/bipolar disorder, 5C-CPT with visual distractors was used to characterize specific cognitive control deficits (reduced response to target stimuli). Administration of putative pro-cognitive drug, glycine1 transporter inhibitor in these animals remediated such deficits and enhanced hit rate (Young et al., 2015), providing strong rationale for extending these findings in patients with reduced Sp4 expression. In another study, phencyclidine (PCP) treated rats showed impaired 5C-CPT performance with reduced attention and increased response disinhibition. Pre-treatment with a direct dopamine D1 receptor agonist, partially attenuated PCP-induced 5C-CPT deficits by reducing false alarms and improving response accuracy (Barnes et al., 2016).

The use of target and non-target stimuli in 5C-CPT allows distinction between motor impulsivity and response disinhibition, core symptoms of ADHD and TS. Evidence suggests that reduced dopamine D4 receptor (DRD4) expression/function is associated with ADHD and TS (Barr et al., 2000, 2001; Grice et al., 1996). Animal studies, revealed impaired 5C-CPT performance with increased response disinhibition and no effect on premature responding in mice with reduced DRD4 expression (Young et al., 2011), and administration of DRD4 agonist improved 5C-CPT performance by enhancing attention, vigilance and response inhibition in rats (Tomlinson et al., 2015). Collectively, these findings reveal the ability of 5C-CPT to distinguish cognitive control elements and allow symptom specific

treatment, for example DRD4 agonist may be useful in improving cognitive control deficits in specific subtype of ADHD patients. Unlike DRD4 agonist, nicotine consistently improved 5C-CPT performance in mice (Young et al., 2013) similar to improvement in human Conners' CPT performance (Levin et al., 1998), seen as enhanced responding to target stimuli improving overall d prime. Interestingly, tolcapone, a catechol-O-methyltransferase (COMT) inhibitor enhanced sustained attention via reduced response inhibition in female rats with low attention and high impulsivity (ADHD-C type) (Tomlinson et al., 2015). Given our observations that tolcapone similarly improved 5C-CPT performance by enhancing response inhibition and activated frontal scalp electrodes during correctly identified non-target trials in poorly performing healthy participants (Bhakta et al., 2014), COMT inhibitors may be useful targeted treatments for disorders with evidence of response disinhibition.

Overall, these preclinical findings support the robust translational potential of 5C-CPT and provide a strong basis for its use in developing pro-cognitive control therapeutics. Additionally, this task could be utilized to characterize the neurobiological substrates of cognitive control deficits in clinical population, leading to more targeted development of animal models for testing novel cognitive enhancing therapeutics.

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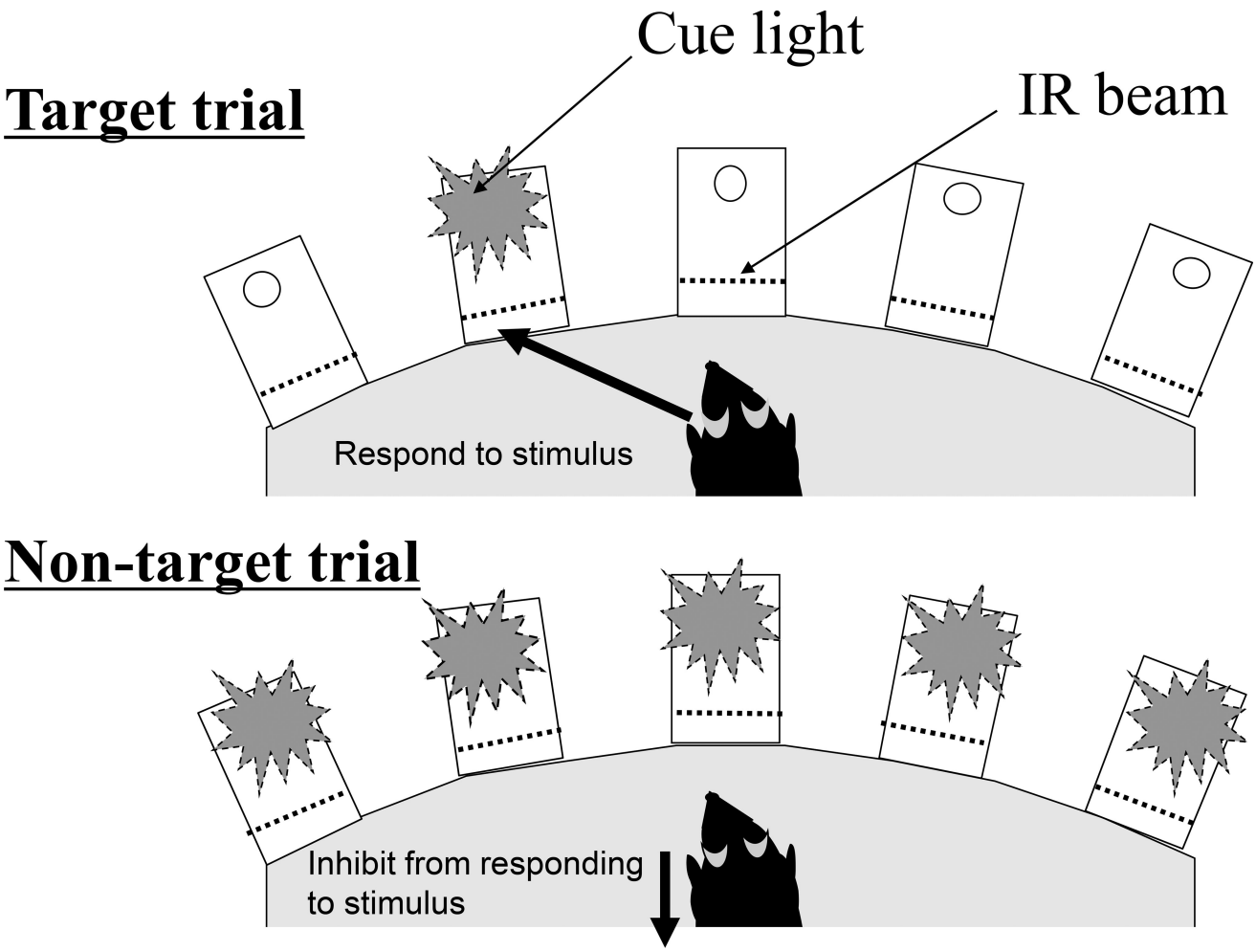


Figure 1.

Example of rodent 5C-CPT stimuli. Top represents target trials in which one aperture is illuminated, requiring a nose poke by the animal in that aperture for a 'hit' (correct response). Bottom image represents non-target stimulus in which all 5 apertures are illuminated, requiring the animal to withhold from responding in any aperture. Target trials generate hits and misses, culminating in the Hit Rate, Non-target trials generate correct rejections and false alarms, culminating in the False Alarm Rate. These two measures are combined using signal detection theory to generate D-prime, the sensitivity index (parametric and non-parametric indices of vigilance), and the responsivity index (a measure of bias), consistent with other human continuous performance tests.

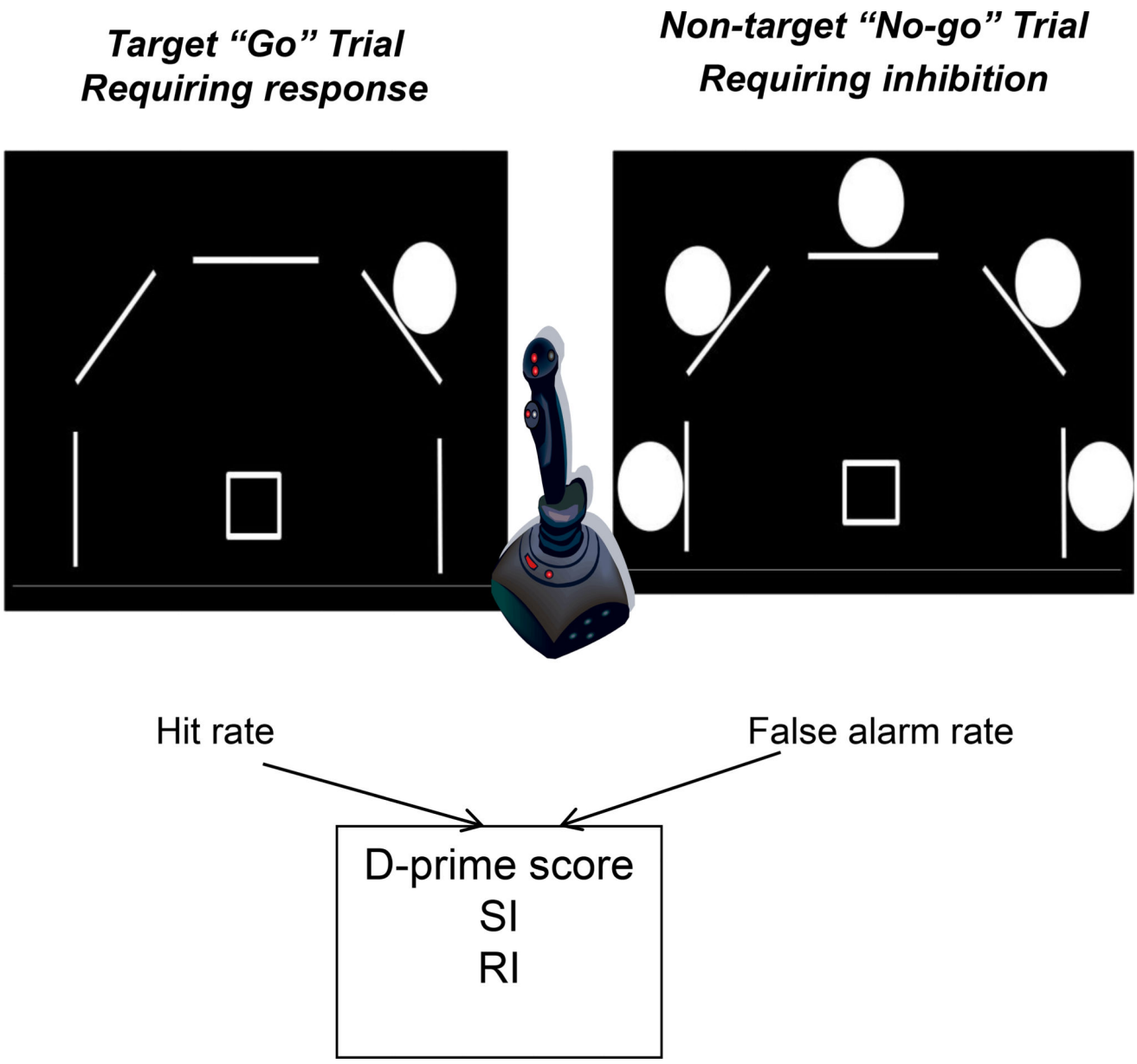


Figure 2.

Human 5C-CPT images with target stimuli requiring moving the arcade joystick in the direction where the white circle appears and non-target stimuli in which all 5 white circles appear requiring the individual to withhold from responding. Target trials generate hits and misses, culminating in the Hit Rate, Non-target trials generate correct rejections and false alarms, culminating in the False Alarm Rate. These two measures are combined using signal detection theory to generate D-prime, the sensitivity index (parametric and non-parametric indices of vigilance), and the responsivity index (a measure of bias), consistent with other human continuous performance tests.

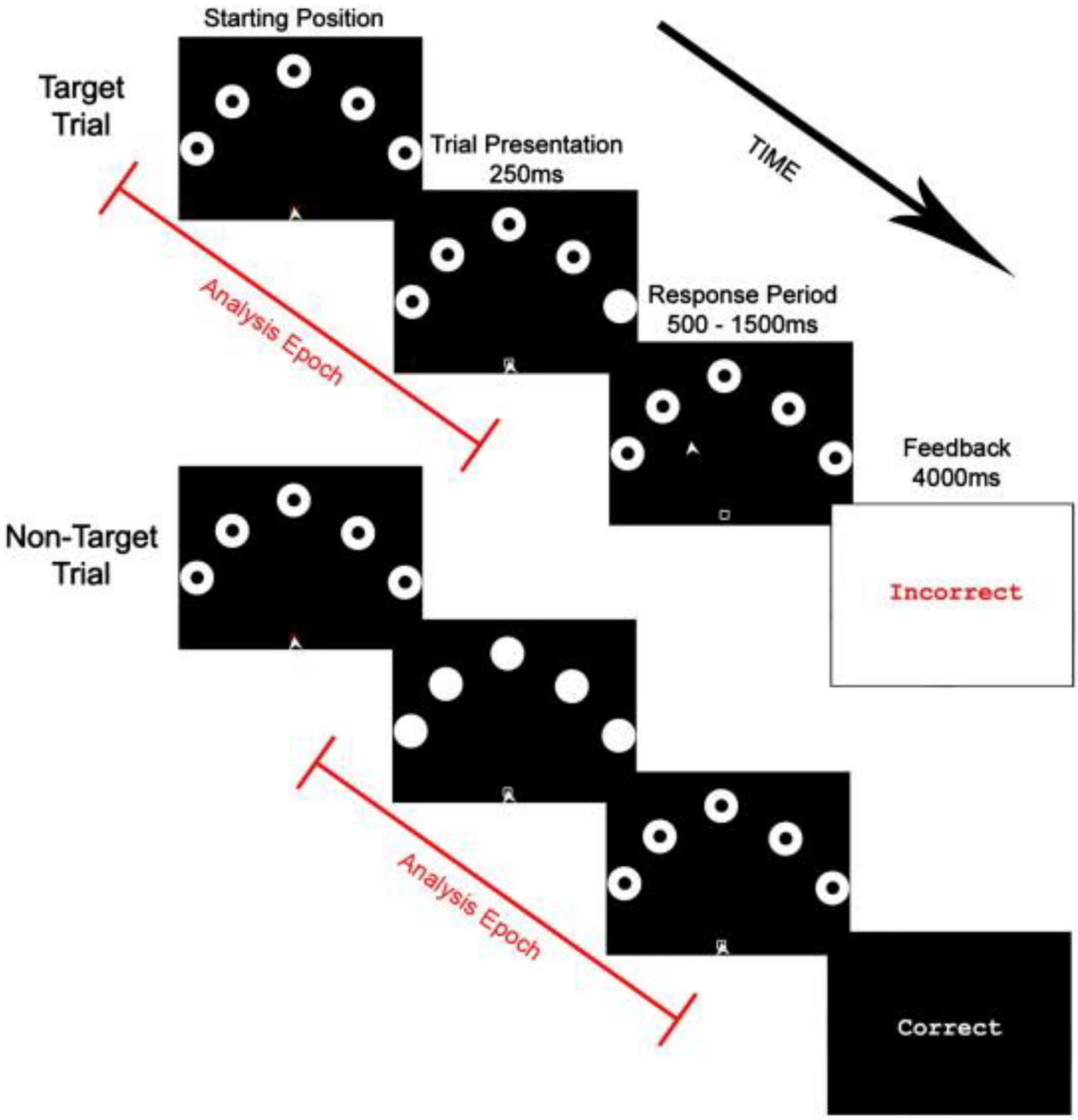
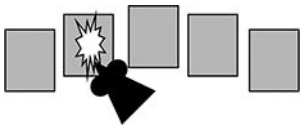
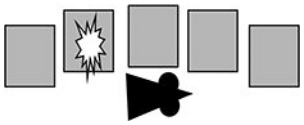
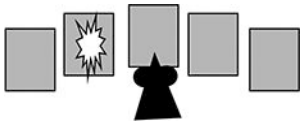
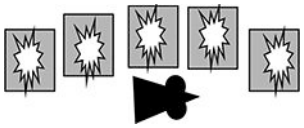
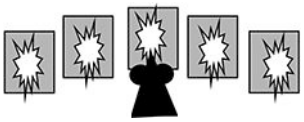
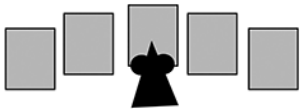


Figure 3.

fMRI based 5C-CPT (Mckenna et al., 2013). Obtained permission to include here. Top trial presents an incorrect response to target trial and bottom represents correct non-target trial. Response period and analysis epochs are represented, while distinct feedback is also provided.

Table 1

Description of 5C-CPT outcome measures

Outcome Measure	Calculation/Behavior	Description
Hits		Responding correctly to target stimuli.
Omission		Failure to respond to target stimuli.
Incorrect		Responding to target stimuli incorrectly.
Correct rejections		Withholding from responding to non-target stimuli.
False alarms		Responding to non-target stimuli by moving in one of the 5-lit positions.
Premature responses		Responding during inter-trial interval when no stimuli are presented.
Cumulative latencies	Time elapsed to respective action (millisecond)	Sum of all response latencies including, hits, incorrect, false alarm and premature.
Miss	**(Omission + Incorrect)**	Sum of failure to respond and responding incorrectly to target stimuli
Hit rate (HR)	$\frac{\mathbf{Hits}}{(\mathbf{Hits} + \mathbf{Miss}')}$	Proportion of correct responses vs. misses to target stimuli
False alarm rate (FAR)	$\frac{\mathbf{False\ Alarms}}{(\mathbf{False\ Alarms} + \mathbf{Correct\ Rejections})}$	Proportion of false alarms vs. correct inhibition to non-target stimuli
Sensitivity Index (SI) (vigilance)	$\frac{\mathbf{p(HR)} - \mathbf{p(FAR)}}{\mathbf{2[p(HR) + p(FAR)] - [p(HR) + p(FAR)]^2}}$	Non-parametric assessment of sensitivity to appropriate responding

Outcome Measure	Calculation/Behavior	Description
D-prime (d')	$\mathbf{z(p[HR]) - z(p[FAR])}$	Parametric assessment of sensitivity to appropriate responding
Responsivity Index (RI)	$\frac{\mathbf{p(HR) + p(FAR) - 1}}{\mathbf{1 - [p(FAR) - p(HR)]^2}}$	Non-parametric assessment of response bias
Accuracy	$\frac{\mathbf{Hits}}{\mathbf{(Hits + Incorrects)}}$	Proportion of correct vs. incorrect responses to target stimuli
% Omissions	$\left\{\frac{\mathbf{Omissions}}{\mathbf{(Omissions + Correct + Incorrect)}}\right\} * \mathbf{100}$	Percentage of misses to target stimuli

Table 2

Interpretation of Signal Detection Variables, SI and RI.

Sensitivity Index (SI)	Responsivity Index (RI)	Hit Rate	False Alarm Rate	Explanation of performance
+1	0	1.0	0.0	Optimal: accurate response to every target and inhibition of response to all non-target stimuli
0	+1	1.0	1.0	Chance Level: Response to every stimulus irrespective of target or non-target stimulus
	−1	0.0	0.0	Chance Level: Non-response to any stimulus irrespective of target or non-target stimulus
−1	0	0.0	1.0	Rule reversed: Inhibition of responding to all targets while response made to all non-target stimuli