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ORIGINAL INVESTIGATION

Profiling attention and cognition enhancing drugs in a rat touchscreen-based continuous performance test

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Abstract

Rationale A novel rodent continuous performance test (CPT) was developed as one of the goals of the NEWMEDS (Novel Methods leading to New Medications in Depression and Schizophrenia) consortium to improve its translatability to the CPT test used in human subjects.

Objectives The objective of the study is to investigate the effects of attention and cognition enhancing drugs in rodent CPT.

Methods A single cohort of rats were trained to asymptotic performance in the test. Pharmacological test sessions were then performed twice per week in a full crossover design with the following drugs tested: methylphenidate (0.3, 1, and 3 mg/kg), the α4β2 nicotinic agonist ABT-594 (0.0023, 0.007 and 0.023 mg/kg), modafinil (8, 16, and 32 mg/kg), atomoxetine (0.3, 1, and 3 mg/kg), donepezil (0.1, 0.3, and 1 mg/kg), and memantine (1.25, 2.5, and 5 mg/kg).

Results The stimulant-like drugs methylphenidate, ABT-594, and modafinil were found to increase measures of impulsivity and overall responding with generally no positive effects on d', a putative measure of attention, with the exception of ABT-594 which improved d' at the highest dose tested. Atomoxetine and the memory-enhancing drugs donepezil and memantine, on the other hand, were found to reduce measures of impulsivity and responding and had either negligible or worsening effects on d'.

Conclusions Our results suggest rodent CPT can detect changes in impulsivity resulting from drugs known to improve attention in rodents and humans. However, additional work is needed to assess the sensitivity and validity of this assay for assessing effects on attention.

Keywords Attention · Cognition · Touchscreen operant chamber · Continuous performance test · Methylphenidate · ABT-594 · Modafinil · Atomoxetine · Donepezil · Memantine

Introduction

Attention is critical for daily functioning and underlies effective processing of many cognitive domains, such as learning and memory and executive function. Deficits in attention are observed in patients with a variety of neuropsychiatric and neurological disorders, including Alzheimer's disease, schizophrenia, depression, and attention deficit hyperactivity disorder (ADHD) (Callahan and Terry 2015). Attention may be an important therapeutic target in these disorders and attention and cognition enhancing drugs could offer important benefits to these patients. However, there has been a relative lack of success of developing effective new treatments for deficits in attention and cognition in neuropsychiatric and neurological patients. New approaches are necessary, including new preclinical research strategies.

The standard test of attention in the clinic has been a variation of the continuous performance test (CPT). The original CPT developed by Rosvold et al. (1956) required subjects to attend to a visual field, responding to target stimuli (any letter) while inhibiting responses to non-target stimuli (the letter X). Although multiple variations of CPT now exist, each task requires both responses to target and the inhibition of responding to non-target stimuli. Human CPT has been used successfully to detect attention deficits across a variety of

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cognitive disorders such as Alzheimer's disease, schizophrenia, and ADHD. For pre-clinical work, the commonly used rodent five-choice serial reaction time task (5-CSRTT) is a useful measure of attention function, but lacks the ability to measure responding to non-target stimuli. The five-choice continuous performance task (5C-CPT) was developed to overcome this limitation of the 5-CSRTT, thus increasing its potential translational value to human research (Young et al. 2009). In both the 5-CSRTT and 5C-CPT, animals scan a horizontal array of possible locations where the target might be presented, thereby requiring spatially divided attention. More critically, the 5-CSRTT and 5C-CPT only require that the subject respond to the detection (e.g. presence or absence) or spatial location (e.g. which aperture is lit) of a simple light stimulus. However, common human CPTs require discrimination of sequentially presented, visually patterned 'target' and 'non-target' stimuli at a single location (Kim et al. 2015). The added difficulty of having to discriminate and remember target patterns has been demonstrated to be a key variable for observing vigilance decrements in perceptual sensitivity within the human CPT paradigm (Parasuraman 1979).

One of the goals of the NEWMEDS (Novel Methods leading to New Medications in Depression and Schizophrenia) consortium was to develop a rodent touchscreen-based cognitive battery for use in drug discovery. As part of this battery, a novel rodent CPT task was developed by Adam Mar and colleagues at the University of Cambridge. The stimulus presentation at a single location and response requirements (responding to a rewarded stimulus and withholding responses to an unrewarded stimuli) are highly similar to the human version of the CPT described above. Task validation studies confirmed detrimental effects on the discriminability index d' resulting from variable event rate, reduced stimulus duration (SD) and reduced stimulus contrast. Moreover, rats showed performance decrements toward the latter trials of the session suggestive of taxing vigilance processes (Mar et al. 2013).

The touchscreen-based CPT provides an objective assessment of attention performance that can be used across species from rats to non-human primates to humans, potentially offering translational value. However, little work has been done in evaluating attention and cognition enhancing drugs in rat CPT. The present experiments explored the effects of attention and cognition enhancing drugs in the rat CPT assay. The drugs investigated were the dopamine/norepinephrine reuptake inhibitor methylphenidate (0.3, 1, and 3 mg/kg), the α4β2 nicotinic agonist ABT-594 (0.0023, 0.007 and 0.023 mg/kg), modafinil (8, 16, and 32 mg/kg), the norepinephrine reuptake inhibitor atomoxetine (0.3, 1, and 3 mg/kg), the cholinesterase inhibitor donepezil (0.1, 0.3, and 1 mg/kg), and the N-Methyl D-Aspartate (NMDA) receptor antagonist memantine (1.25, 2.5, and 5 mg/kg). With the exception of ABT-594, all of the drugs tested are currently approved for human use. ABT-594 is an analog of ABT-894, which demonstrated efficacy in an adult ADHD trial (Bain et al. 2013). In addition, ABT-594 has previously been found to be efficacious in the 5-CSRTT (Mohler et al. 2010).

Methods

Subjects

A single cohort of 48 male Lister-Hooded rats, obtained from Harlan (UK), were used for all studies presented here. Rats weighed 180–200 g upon arrival and were allowed to acclimate to the facility for 1 week. Water was available ad libitum, except during experiments. Rats were food-restricted to 85% of their free-feeding weight during experiments through a combination of standard chow in the home cage and food rewards during the experiments. Animals were tested in the light phase of a 12-h light:12-h dark schedule (lights on 0600 h). All experiments were in compliance with the AbbVie Institutional Animal Care and Use Committee in a facility accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care.

Equipment

Bussey-Saksida Touchscreen Systems for rats were obtained from Lafayette Instruments (Lafayette, Indiana). The chamber consisted of 38 cm touchscreen (768 × 1024 resolution) and 34.5 cm tall walls forming a trapezoid, with total environmental area of 368 cm^2. The chambers were controlled through the Whisker control system and CPT testing employed a proprietary program by Adam Mar (currently at New York University, NY). This rCPT program is now commercially available from Lafayette Instruments. Rats received 45 mg sucrose pellets in a reward magazine opposite the touchscreen.

Continuous performance test (CPT)

The present experiments used a CPT protocol developed by the NEWMEDs consortium for Touchscreen chambers (Mar et al. 2013; Kim et al. 2015) (see Table 1). Rats were trained to respond to a single rewarded stimulus (S+), for food reward (see Fig. 1a). Four unrewarded stimuli (S-) required a rat to withhold responding. Trials with an S+ stimulus are referred to a "Signal Trials." Trials with an S- stimulus are referred to as "Non-signal Trials." Stimuli were presented in a randomized order with a 50% probability of S+ presentation. A trial was counted when one of the following four response options occurred: hit (correct response on signal trial), miss (failure to respond on a signal trial), false alarm (incorrect response on a nonsignal trial), and correct rejection (correctly withholding response on a non-signal trial (see Fig. 1b and c). Rats had up to 2 s after the stimulus appeared to make a response, followed

Table 1 Training stages of the rat CPT paradigm. Rats were trained 4 days a week to asymptotic performance on stage 5. All 48 rats that started training successfully learned the task

Initial training	Rats were habituated to the touchscreen box for 2 days. This was followed by five stages of touch training.
Stage 1 (initial touch)	Rats received sucrose pellets for touching a white box on the screen.
	Criterion: Earn 100 rewards in a single session. At a group level, rats took approximately 1 week to meet the criterion.
Stage 2 (S+ training)	Rats touched their assigned stimulus (horizontal OR vertical bars) to get sucrose pellets.
	Criterion: Earn 100 rewards in a single session. At a group level, rats took approximately 1 week to meet the criterion.
Stage 3 (addition of S-)	Similar to stage 2 with the addition of an S- stimulus (snowflake) that did not result in food reward on half of the trials. Incorrect responses resulted in correction trials.
	Criterion: d' > 0.8. At a group level, rats took approximately 1 week to meet the criterion.
Stage 4 (main CPT)	Similar to stage 3 with four different S-. The stimuli varied in length were from 500 to 1500 msec. Probability of S+ presentation was 50%. Incorrect responses resulted in correction trials.
	Criterion: Stable performance in d', Hit Rate, and False Alarm Rate achieved in at least 3 consecutive session. At a group level, rats took approximately 2 weeks to meet the criterion.
Stage 5 (challenge)	Similar to stage 4 with stimuli presented at multiple stimulus durations (typically 100, 400, and 700 msec). Probability of S+ presentation was 50%.
	Criterion: Stable performance in d', Hit Rate, and False Alarm Rate achieved in at least 3 consecutive session. At a group level, rats took approximately 4 weeks to meet the criterion.

by a 2–3 s inter-trial interval. After receiving a reward (single sucrose pellet), the rat had to wait 2 s, and then nose-poke in the food magazine to restart the trial sequence. For stages 3 and 4 of training, rats received correction trials for incorrect responses (False Alarms), which consisted of a repetition of the previous S- stimuli until no response was made. The session ended after 150 food rewards were received or 60 min had elapsed (whichever came first). All 48 rats were able to learn the CPT task and meet the training criteria of asymptotic performance in stage 5.

Treatment

Drugs tested were methylphenidate (0.3, 1, and 3 mg/kg), ABT-594 (0.0023, 0.007 and 0.023 mg/kg), modafinil (8, 16, and 32 mg/kg), atomoxetine (0.3, 1, and 3 mg/kg), donepezil (0.1, 0.3, and 1 mg/kg), and memantine (1.25, 2.5, and 5 mg/kg). Doses were chosen based on those reported in the literature to produce procognitive or attention-enhancing effects in rodents. All drugs were measured as the weight of the salt and dissolved in saline except modafinil, which was prepared as a nano-suspension in 2% super low viscosity grade hydroxypropylcellulose (HPC-SL) and 0.2% sodium dodecyl sulfate (%weight/volume). Rats received i.p. injections of vehicle or drug 30 min before the testing session. Drugs (methylphenidate, ABT-594, modafinil, atomoxetine, donepezil, and memantine, investigated in that order) were tested in a Latin Square design with all rats receiving all doses. There was a 2-week washout period between different drugs. Detailed analysis of performance among the vehicle-treated group across the course of these experiments found no appreciable differences in CPT measures thereby indicating stable performance across time.

Statistical methods

Measures of interest were hit rate [hits/(hits + misses)], false alarm rate [false alarms/(false alarms + correct rejections)], number of blank touches, correct and incorrect latency response, response bias (C score) [−(Z(hit rate) + Z(false alarm rate))/2], and the discriminability index (d') [Z(hit rate) − Z(false alarm rate)] (Green and Swets, 1966). Response bias or C score indicates the willingness of the subject to respond during the test with high values indicating high responsivity and low values indicating low or more conservative responsivity (Kim et al. 2015). The discriminability index (d') is a representation of the strength of responses to S+ and S- trials. An inability to discriminate will result in low d' value while good discriminative abilities will result in a higher d' value. Due to limitations of the analysis software correct and incorrect response latency were pooled for all SDs. All data were analyzed by repeated-measures ANOVA with comparison of drug performance to vehicle performance using Dunnett's post hoc test.

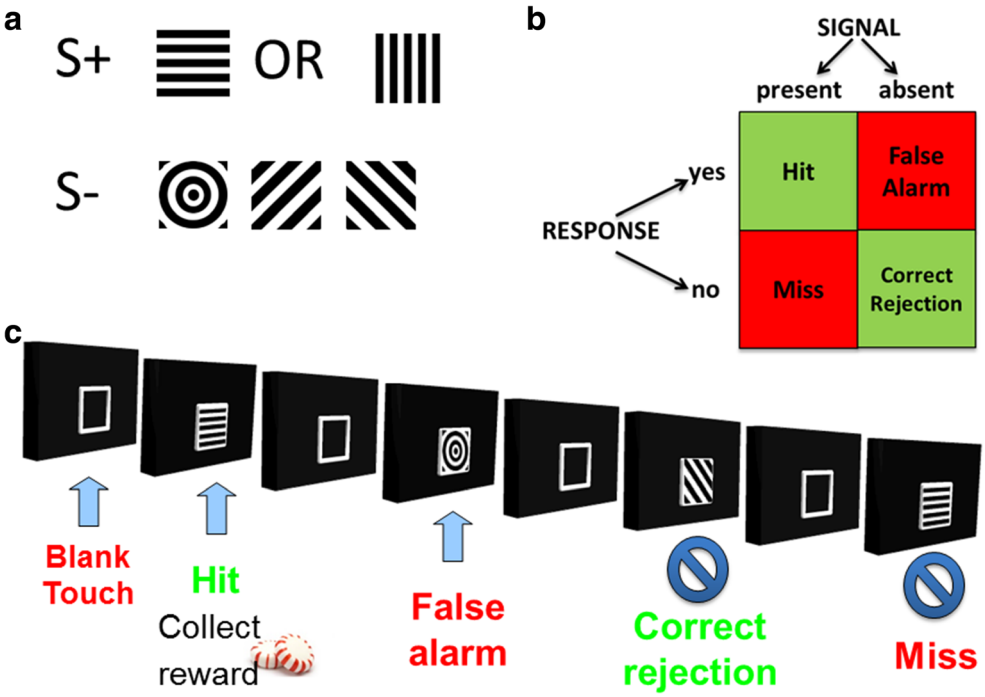

Fig. 1 **a** Examples of rewarded stimuli (S+) and non-rewarded stimuli (S-). S+ were counterbalanced so approximately half of the rats received horizontal bars and half of the rats received vertical bars as the reward stimuli. There were a total of four S- stimuli (either horizontal or vertical bars along with the other three stimuli). **b** The CPT is a signal detection task, and there are consequently four possible outcomes based on the presence or absence of a signal and the rat's response. **c** An example of a typical trial sequence. A blank touch is responding to a blank screen. **a** Hit results in food reward while a correct rejection does not

Results

General

Hit rate, false alarm rate, C score, and the discriminability index d' were strongly influenced by stimulus duration (SD). Hit rate and d' increased with longer SDs, while false alarm rate and C score decreased with longer SDs.

Methylphenidate

Rats treated with methylphenidate demonstrated an increased hit rate, $F(3, 141) = 10.40$, $p < 0.001$, with the 1 and 3 mg/kg doses statistically differing from vehicle for all three SDs, (all $p < 0.001$), and with the 0.3 mg/kg dose differing from vehicle for the 700 ms SD ($p < 0.01$) (see Fig. 2a). Treatment with methylphenidate also increased the false alarm rate, $F(3, 141) = 23.16$, $p < 0.001$, with the 0.3, 1, and 3 mg/kg doses differing from vehicles for all SDs ($p < 0.001$ for 1 and 3 mg/kg at all SDs; $p < 0.01$ for 0.3 mg/kg at 100 and 700 ms, and $p < 0.001$ at 400 ms) (Fig. 2b). Not surprisingly, the response bias, or C score, was significantly reduced by methylphenidate $F(3,141) = 21.09$, $p < 0.001$, with significant reductions observed across all doses tested ($p < 0.01$–$p < 0.001$; see Fig. 2d). Methylphenidate treatment worsened the discrimination index measure d', $F(3, 141) = 4.135$, $p < 0.01$,with the 3 mg/kg dose differing from vehicle at the 100 milliseconds (ms) ($p < 0.001$) and 400 ms ($p < 0.01$) SDs (Fig. 2c). Rats receiving methylphenidate demonstrated increased overall blank touches, $F(3, 141) = 16.75$, $p < 0.001$ (see Fig. 2e) and decreased overall correct response latencies, $F(3, 141) = 3.245$, $p < 0.05$, with only the 3 mg/kg dose differing from vehicle rats ($p < 0.001$ for blank touches and $p < 0.05$ for correct response latency. Incorrect response latency was not affected by methylphenidate treatment, $p > 0.05$.

ABT-594

Rats receiving ABT-594 demonstrated increased hit rate, $F(3, 141) = 16.43$, $p < 0.001$, with 0.007 and 0.023 mg/kg doses differing from vehicle for all SDs (both doses $p < 0.001$) and 0.0023 mg/kg differing from vehicle at only 100 ms ($p < 0.01$; see Fig. 3a). ABT-594 also increased false alarm rate, $F(3, 141) = 6.275$, $p < 0.001$, with the 0.007 and 0.023 mg/kg doses differing from vehicle for all SDs (all $p < 0.001$ for 0.007 mg/kg; all $p < 0.001$ for 0.023 mg/kg, Fig. 3b); the lowest dose of 0.0023 mg/kg also significantly increased false alarm rate at 100 ms and 400 ms SDs as well ($p < 0.01$ and $p < 0.05$, respectively, see Fig. 3b). ABT-594 treatment reduced C score $F(3,141) = 11.77$, $p < 0.001$, with 0.007 and 0.023 mg/kg doses reducing C score across all SDs ($p < 0.001$) and 0.0023 at 100 and 400 ms SDs only ($p < 0.01$ and $p < 0.001$, respectively; see Fig. 3d). Rats receiving ABT-594 demonstrated improved discrimination of stimuli as measured by d', $F(3, 141) = 7.947$, $p < 0.001$ with the 0.023 mg/kg dose differing from vehicle at all SDs ($p < 0.05$ for 100 ms, $p < 0.001$ for 400 and 700 ms, Fig. 3c). ABT-594 also increased blank touches, $F(3, 141) = 10.89$, $p < 0.001$ (Fig. 3e) with significant effects observed across all doses tested ($p < 0.01$ for 0.0023 and $p < 0.001$ for 0.007 and

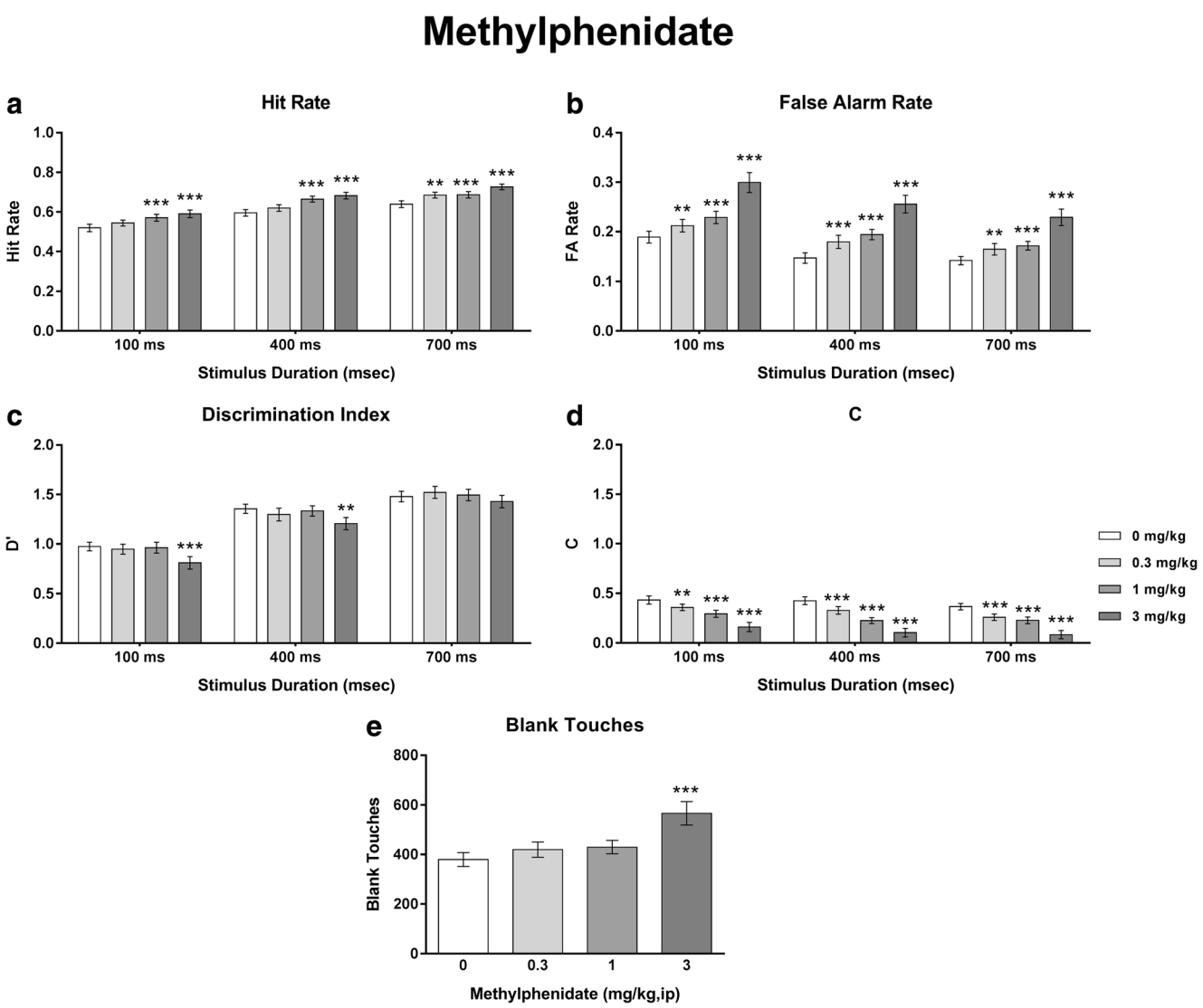

Fig. 2 Effects of methylphenidate in rat CPT. Methylphenidate increased hit rate (**a**) and false alarm rate (**b**) in a dose-dependent manner across all SDs. The highest dose of 3 mg/kg significantly reduced d' at 100 and 400 ms SDs (**c**). Dose-dependent reductions in C score were also observed with methylphenidate (**d**) while only the high dose of 3 mg/kg significantly increased blank touches (**e**). $N = 48$ rats per treatment group. Data are expressed as mean ± SEM. $^{**}p < 0.01$ and $^{***}p < 0.001$ vs. vehicle-treated group

0.023 mg/kg), and decreased incorrect response latency, $F(3, 141) = 7.495$, $p < 0.001$. Statistically significant reductions in incorrect response latency were observed for 0.007 and 0.023 mg/kg doses ($p < 0.01$ for both). There was no effect on correct response latency, $p > 0.05$.

Modafinil

Modafinil treatment increased hit rate, $F(3, 141) = 8.133$, $p < 0.001$, with the 32 mg/kg dose differing from vehicle for all SDs ($p < 0.001$, see Fig. 4a). Rats receiving modafinil also demonstrated increased false alarm rate, $F(3, 141) = 27.28$, $p < 0.001$, with the 16 and 32 mg/kg doses differing significantly from vehicle for all SDs ($p < 0.05$–$p < 0.001$, Fig. 4b). C scores were lowered by treatment with modafinil $F(3,141) = 19.09$, $p < 0.001$. The high dose of 32 mg/kg significantly reduced C score across all SDs ($p < 0.001$) while the 16 mg/kg dose reduced C score at only 100 and 400 ms SDs ($p < 0.01$ and $p < 0.001$, respectively; see Fig. 4d). Modafinil treatment impaired discrimination of stimuli as measured by d', $F(3, 141) = 3.647$, $p < 0.05$, with the 32 mg/kg dose differing from vehicle at 100 and 700 ms SDs ($p < 01$ and $p < 0.05$, respectively, see Fig. 4c). Rats receiving modafinil demonstrated increased overall blank touches $F(3, 141) = 15.98$, $p < 0.001$ (Fig. 4e), and decreased correct response latencies, $F(3, 141) = 5.067$, $p < 0.01$, with the 32 mg/kg dose differing from vehicle-treated rats for both measures ($p < 0.001$ for blank touches and $p < 0.01$ for correct response latency). Incorrect response latency was not affected by treatment with modafinil.

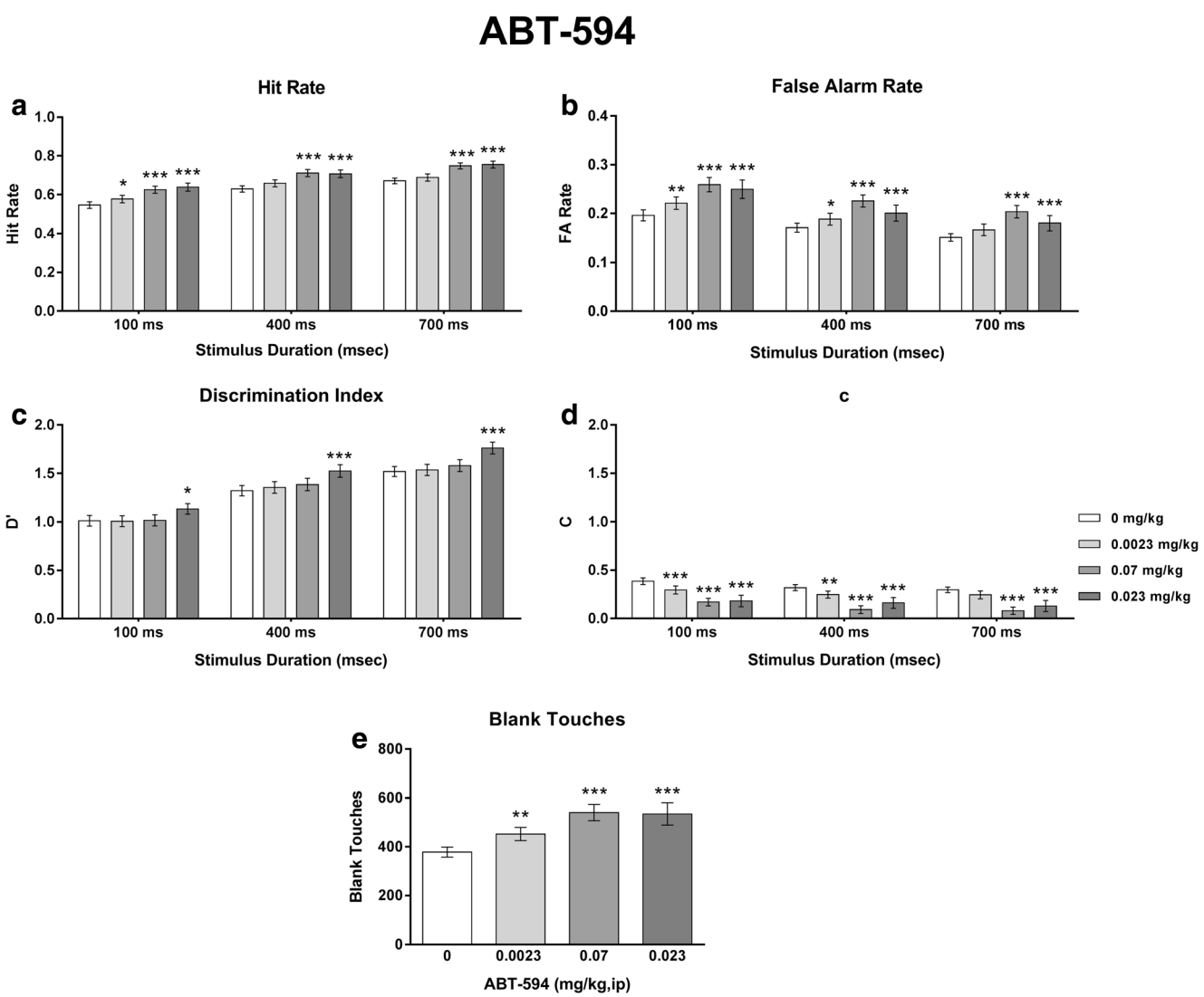

Fig. 3 Effects of ABT-594 in rat CPT. ABT-594 increased hit rate (**a**), false alarm rate (**b**), and d' (**c**) in a dose-dependent manner across all SDs. C score was reduced by ABT-594 (**d**) while blank touches were significantly increased (**e**). $N = 48$ rats per treatment group. Data are expressed as mean ± SEM. $*p < 0.01$, $**p < 0.01$, and $***p < 0.001$ vs. vehicle-treated group

Atomoxetine

Atomoxetine treatment decreased hit rate, $F(3, 141) = 10.70$, $p < 0.001$, with 1 and 3 mg/kg doses differing from vehicle for all SDs ($p < 0.05$–$p < 0.001$) and the 0.3 mg/kg dose differing from vehicle only at the 100 ms SD ($p < 0.05$, see Fig. 5a). Rats receiving atomoxetine also had a decreased false alarm rate, $F(3, 141) = 15.02$, $p < 0.001$, with the 3 mg/kg dose differing from vehicle at all SDs (all $p < 0.001$, Fig. 5b) and the middle dose of 1 mg/kg differing from vehicle at 100 ms and 700 ms SD only ($p < 0.05$ and $p < 0.01$, respectively). Atomoxetine treatment had no effect on the discrimination index, $p > 0.05$ (Fig. 5c), but did significantly increase response bias or C score ($F(3,141) = 17.51$, $p < 0.001$). Atomoxetine at 1 and 3 mg/kg increased C score across all SDs ($p < 0.001$) while the low dose of 0.3 mg/kg increased C score at only 100 and 400 ms ($p < 0.05$; see Fig. 5d). Rats treated with atomoxetine had decreased overall blank touches, $F(3, 141) = 11.75$, $p < 0.001$ (Fig. 5e), and increased correct response latencies, $F(3, 141) = 3.449$, $p < 0.05$, with the 3 mg/kg dose differing from rats receiving vehicle ($p < 0.001$ for blank touches and $p < 0.01$ for correct response latencies). There was no effect of atomoxetine on incorrect response latency ($p > 0.05$).

Donepezil

Donepezil decreased hit rate, $F(3, 141) = 5.506$, $p < 0.01$, with the 1 mg/kg dose differing from vehicle at all SDs ($p < 0.05$–$p < 0.01$) and 0.3 mg/kg differing from vehicle at 400 and 700 ms SD ($p < 0.001$ and $p < 0.01$ respectively; see Fig. 6a). Rats treated with donepezil had a decreased false alarm rate, $F(3, 141) = 3.130$, $p < 0.05$, with 1 mg/kg differing

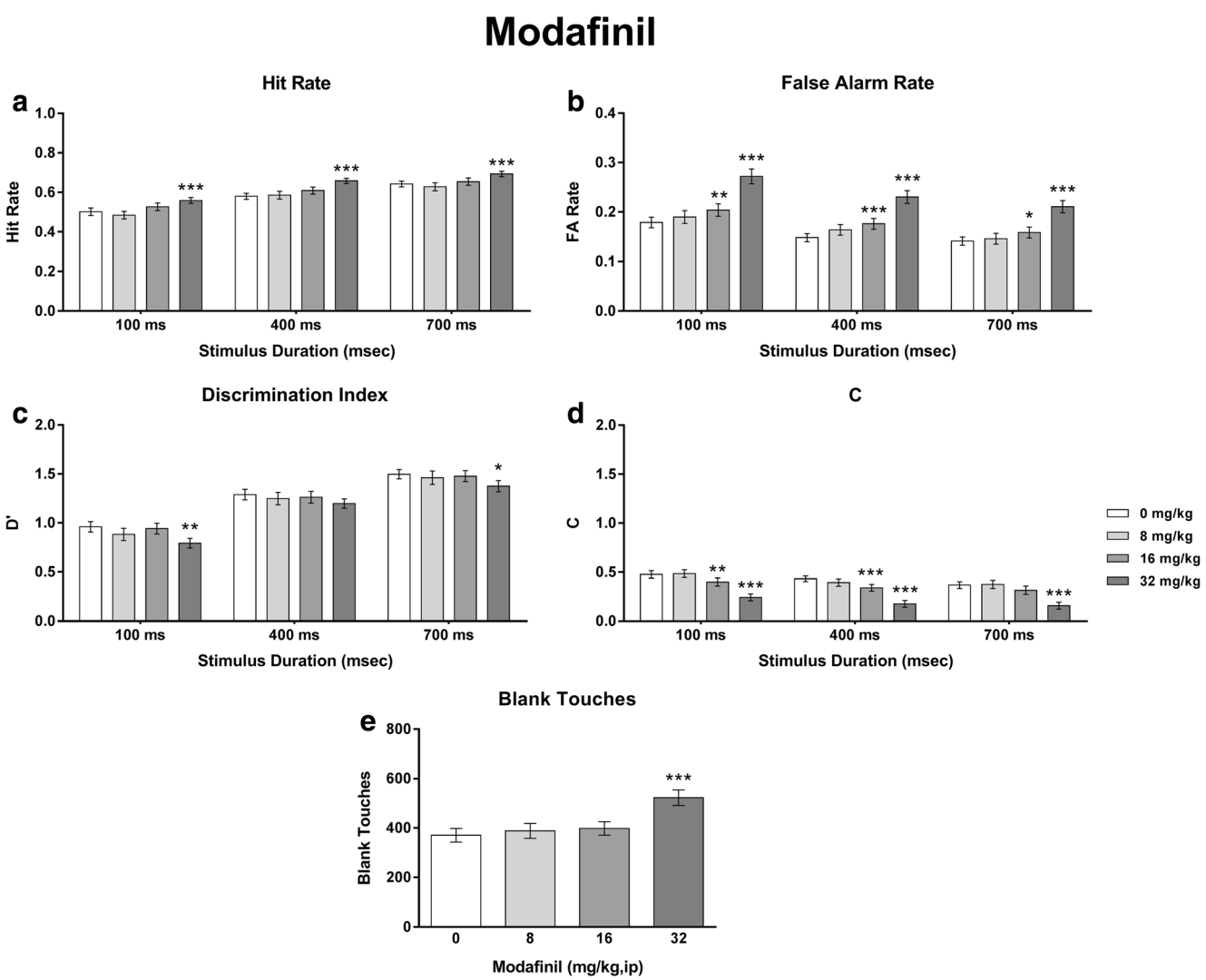

Fig. 4 Effects of modafinil in rat CPT. Modafinil increased hit rate (**a**) and false alarm rate (**b**) in a dose-dependent manner across all SDs. Both d' (**c**) and C score were reduced by ABT-594 (**d**). Blank touches (**e**) were significantly increased by the high dose of 32 mg/kg. $N = 48$ rats per treatment group. Data are expressed as mean ± SEM. $^{*}p < 0.01$, $^{**}p < 0.01$, and $^{***}p < 0.001$ vs. vehicle-treated group

from vehicle at the 100 ms SD ($p < 0.01$,Fig. 6b). The rats treated with donepezil demonstrated no differences on the discrimination index d' (Fig. 6c), correct response latencies, or incorrect response latencies (all $p > 0.05$). Donepezil treatment increased C score, $F(3,141) = 6.019$, $p < 0.001$, and decreased blank touches, $F(3, 141) = 6.60$, $p < 0.001$. The high dose of 1 mg/kg significantly increased C score at 100 and 400 ms ($p < 0.001$ and $p < 0.05$, respectively; see Fig. 6d) and decreased blank touches ($p < 0.05$, see Fig. 6e), while the middle dose of 0.3 mg/kg increased C score at 400 and 700 ms only ($p < 0.001$ and $p < 0.05$, respectively) with no effects on blank touches.

Memantine

Memantine decreased the hit rate, $F(3, 141) = 123.2$, $p < 0.001$, with the 2.5 and 5 mg/kg doses differing from vehicle at all SDs (all $p < 0.001$, Fig. 7a). Rats treated with memantine had a decreased false alarm rate, $F(3, 141) = 43.74$, $p < 0.001$), with the 5 mg/kg dose differing from vehicle at all SDs (all $p < 0.001$) and the 2.5 mg/kg dose differing from vehicle at the 100 and 700 ms SD ($p < 0.05$ and $p < 0.001$, respectively, see Fig. 7b). Response bias or C score was significantly increased by memantine treatment $F(3,141) = 75.51$, $p < 0.001$) with effects observed for doses of 2.5 and 5 mg/kg across all SDs ($p < 0.001$, see Fig. 7d). Memantine also decreased the discrimination index d', $F(3, 141) = 42.31$, $p < 0.001$, with the 5 mg/kg dose differing from vehicle at all SDs ($p < 0.01$ for 100 ms, $p < 0.001$ for 400 and 700 ms, Fig. 7c). Rats treated with memantine also had decreased blank touches, $F(3, 141) = 23.89$, $p < 0.001$ (Fig. 7e), increased correct response latency, $F(3, 141) = 28.27$, $p < 0.001$, and increased incorrect response latency, $F(3, 141) = 11.03$, $p < 0.001$, with the 5 mg/kg dose differing from

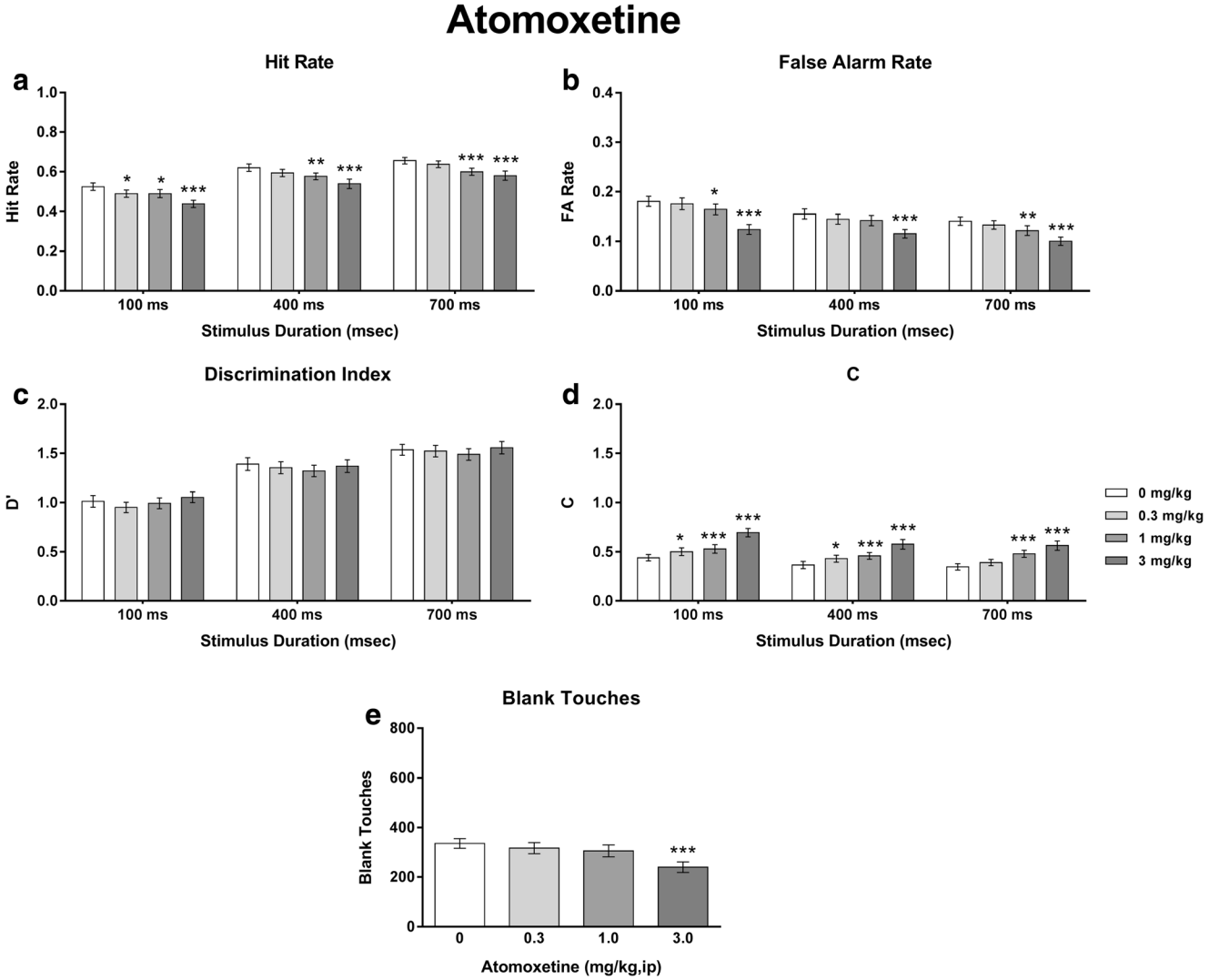

Fig. 5 Effects of atomoxetine in rat CPT. Atomoxetine decreased both hit rate (**a**) and false alarm rate (**b**) in a dose-dependent manner across all SDs. There was no effect of atomoxetine on d' (**c**). C score was dose-dependently increased by atomoxetine (**d**). Only the high dose of 3 mg/kg significantly reduced blank touches (**e**). $N = 48$ rats per treatment group. Data are expressed as mean ± SEM. $*p < 0.01$, $**p < 0.01$, and $***p < 0.001$ vs. vehicle-treated group

vehicle for all measures (all $p < 0.001$), and the 2.5 mg/kg dose differing from vehicle for correct response latency ($p < 0.01$).

Discussion

In this study, we examined five clinically approved attention- and cognition-enhancing drugs and one preclinical tool compound in rat CPT. In general, drugs with stimulant-like properties (Methylphenidate, ABT-594, modafinil) increased hit rate, false alarm rate, response bias (C score), and blank touches while non-stimulants (atomoxetine, donepezil, and memantine) decreased the same measures (see Table 2). The best subject maximizes hit rate and minimizes false alarms; and thus the larger the difference between hit rate and false alarms, the better the subject's sensitivity. The statistic d' ("d-prime") is a measure of this difference. Nearly all of these drugs had either no effect or worsened the discrimination index. ABT-594 was the sole exception in that d' was improved at the highest dose tested, but the specificity of this finding as it relates to attention is unclear given the increase in response bias (or low C score) also produced by this drug.

Methylphenidate

Methylphenidate (dopamine/norepinephrine reuptake inhibitor) increased both hit rate and false alarm rate across all doses tested. Blank touches were increased, correct response latencies were decreased, and the discriminability index worsened at the highest dose tested. These findings are consistent with literature reports of Methylphenidate increasing hit rate and

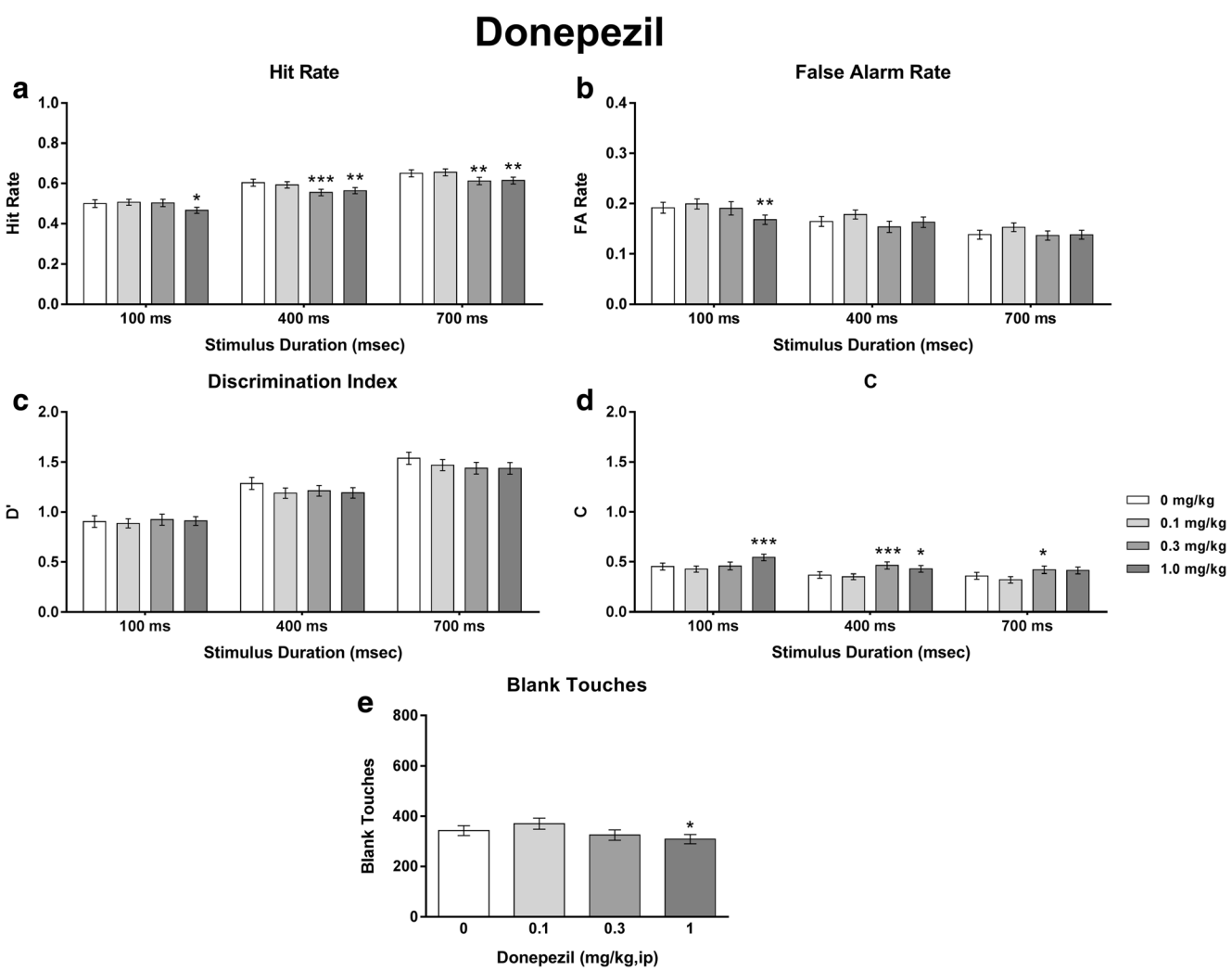

Fig. 6 Effects of donepezil in rat CPT. Hit rate (**a**) was significantly decreased by donepezil at 0.3 and 1 mg/kg while false alarm rate (**b**) was decreased by 1 mg/kg only at 100 ms SD. There was no effect of donepezil on d' (**c**). C score was increased by 0.3 and 1 mg/kg depending on SD (**d**). Only the high dose of 1 mg/kg reduced blank touches (**e**). Data are expressed as mean ± SEM. $*p < 0.01$, $**p < 0.01$, and $***p < 0.001$ vs. vehicle-treated group

blank touches while reducing response latency in both adult and aged rats (for review, see Callahan and Terry 2015). Methylphenidate increased false alarm responding to non-targets in addition to target stimuli. This response disinhibition to irrelevant (non-target) stimuli was accompanied by behavior suggestive of increased impulsivity as measured by blank touches (with no stimuli present). This suggests poorer inhibitory control or inattentiveness in rats when exposed to methylphenidate. In light of these findings it is likely that the increased impulsivity-like behavior observed in the present studies, and by those reported by Navarra et al. 2008 in the 5CSRT test, may be due to an increase in striatal dopamine caused by this drug. Indeed, for inhibitory control in tasks such as the 5-CSRT task, a range of noradrenergic drugs improved impulse control whereas psychostimulants (methylphenidate and amphetamine) invariably made impulse control worse (Eagle and Baunez 2010).

ABT-594

The α4β2 nicotinic agonist ABT-594 increased hit rate, false alarm rate, and blank touches and decreased incorrect response latencies at the two highest doses. Furthermore, response bias (C score) was also significantly reduced by ABT-594, suggesting an overall increase in responding and possible impulsivity induced by this drug. ABT-594 was the only drug tested were a significant improvement in the discrimination index was observed, but the nonspecific effects on overall responding and increases in measures of impulsivity confound the interpretation of this finding. ABT-594 has previously been shown to improve attention in the 5-choice serial reaction time task (5-CSRTT), but only under specific conditions whereby task difficulty and dosing paradigms were manipulated (Mohler et al. 2010). In the present study, normal subjects demonstrated sensitivity to ABT-594 under normal

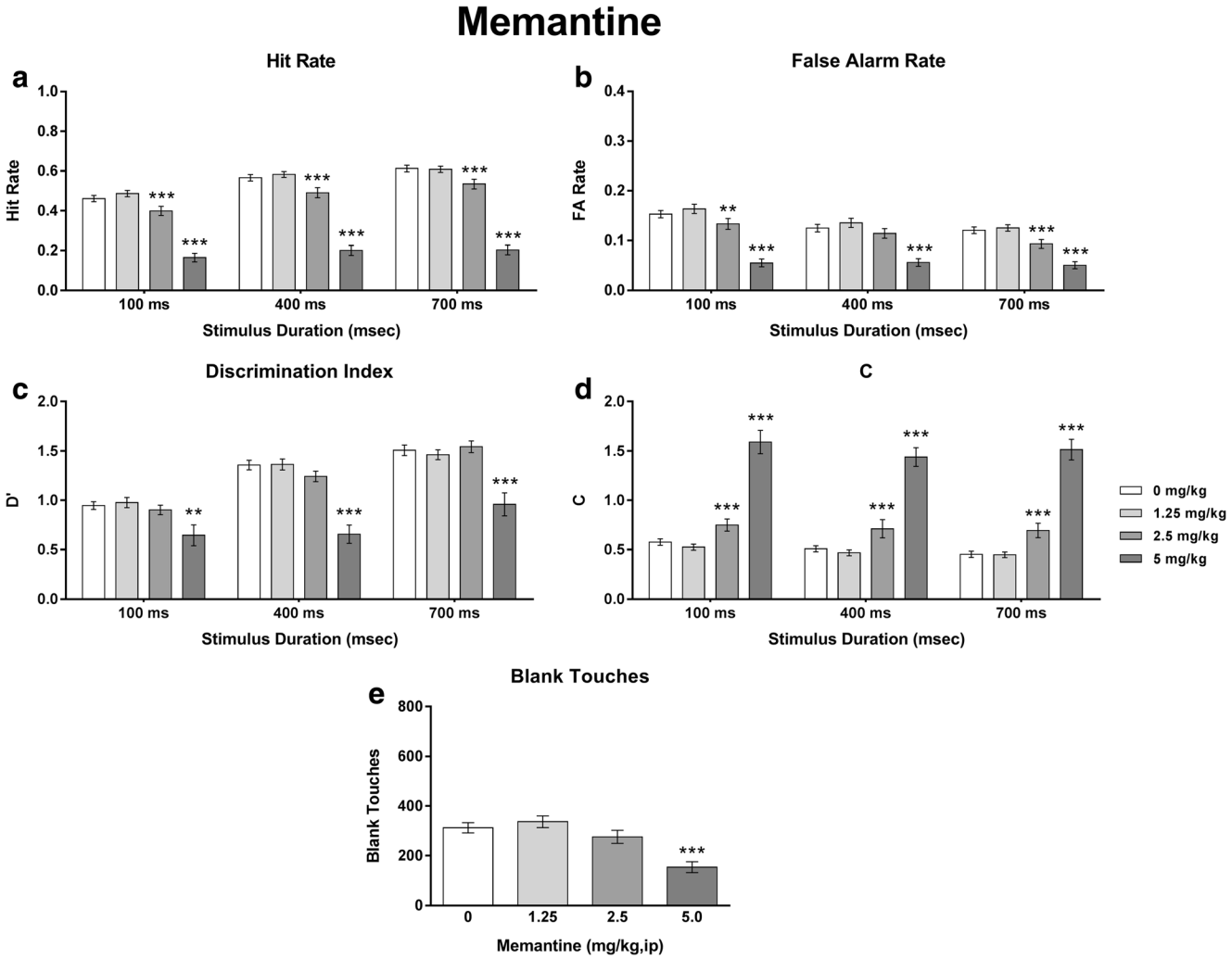

Fig. 7 Effects of memantine in rat CPT. Memantine dose-dependently decreased hit rate (**a**), false alarm rate (**b**), and d' (**c**) across all SDs. C score was dose-dependently increased by memantine (**d**) while blank touches were significantly reduced by 5 mg/kg only (**e**). Data are expressed as mean ± SEM. $*p < 0.01$, $**p < 0.01$, and $***p < 0.001$ vs. vehicle-treated group

task conditions in the rat CPT. The increased sensitivity to ABT-594 effects in rCPT likely reflects the increased difficulty and attentional demands of this task compared to the standard, self-initiated trials used by Mohler et al. 2010 in 5-CSRTT where no acute effects with ABT-594 were observed. Task conditions were important for distinguishing ABT-594's effects in CPT as well as improvements in d' were primarily observed at stimulus durations of 400 and 700 ms. Furthermore, the within-subjects design of this study allowed subjects to acclimate to the effects of ABT-594 treatment as a single pre-exposure to the drug has been found to improve its tolerance (Mohler et al. 2010). In humans, ABT-894 (analog

Table 2 Summary of main findings on d', C (or response bias), hit rate, false alarm rate, blank touches, and response latency

Drug	Mechanism	d'	C	Hit rate	False alarm rate	Blank touches	Response latency
Methylphenidate	DA & other	↓	↓	↑	↑	↑	↓
ABT-594	Nicotinic	↑	↓	↑	↑	↑	↓
Modafinil	Various	↓	↓	↑	↑	↑	↓
Atomoxetine	NRI	↔	↑	↓	↓	↓	↑
Donepezil	Cholinesterase	↔	↑	↓	↓	↓	↔
Memantine	NMDA	↓↓	↑	↓↓	↓↓	↓↓	↑

of ABT-594) significantly reduced ADHD symptoms in adults (Bain et al. 2013) and nicotine has been shown to improve attentional processing in humans (Sahakian et al. 1989; White and Levin 1999; Min et al. 2001).

Modafinil

The wake-promoting effects of modafinil in humans have been well documented (Wesensten et al. 2002) and modafinil may have clinical utility for the treatment of cognitive impairments associated with ADHD (Turner et al. 2004) and schizophrenia (Scoriels et al. 2012). Despite clinical interest in modafinil, few studies have characterized its effects in rodent attention studies and previous work has shown mixed results. For example, in a 3-choice task, modafinil improved attention, inhibitory control, and reaction time in healthy, 18–20 month old female rats (Morgan et al. 2007). In contrast, studies using the 5-CSRTT have found increased premature responses with little effect on other task parameters (e.g., Waters et al. 2005). In the present study, modafinil increased hit rate, false alarm rate, and blank touches at the highest dose, as well as decreased response bias, suggesting an overall increase in responding. Moreover, modafinil impaired the discriminability index at 100 and 700 ms SDs and decreased correct response latency at the highest dose. Based on the current findings in CPT and previous findings in the 5-CSRTT, it appears modafinil effects on attention may be specific to the task used. For example, modafinil significantly decreased the stop-signal reaction time with little effect on go-trial reaction time but only in rats with slow baseline SSRTs (Eagle et al. 2007). This is also found in human subjects, as modafinil treatment results in improvements on a stop-signal task but not the rapid visual information processing task in the CANTAB battery (Turner et al. 2003). In addition, modafinil improved attention for well-rested individuals (Repantis et al. 2010b), improved performance in a test of sustained attention in healthy and methamphetamine-dependent participants (Dean et al. 2011), and improved response inhibition in alcohol-dependent subjects with poor baseline response inhibition whereas response inhibition was decreased in better performing participants (Schmaal et al. 2013).

Atomoxetine

The norepinephrine reuptake inhibitor atomoxetine decreased hit rate, false alarm rate, and blank touches and increased response bias (C score) and correct response latency without affecting the discriminability index. This profile suggests atomoxetine may have promoted inhibitory control, but with the confound of concomitant reductions in overall responding, as indicated by the increase in C score. Others have reported atomoxetine reduced impulsivity as measured by premature responding, but only observed improved choice accuracy under challenging conditions or in poorly performing subjects (Navarra et al. 2008; Robinson 2012; Tomlinson et al. 2015). The most robust effects of atomoxetine in rodent tasks are improved inhibitory control (reducing SSRT, premature responding, and impulsive choice; for review, see Eagle and Baunez 2010). Similarly, atomoxetine improves response inhibition in both healthy adults and ADHD patients (Chamberlain et al. 2006; Sahakian et al. 2015), but had no effect on measures of learning and memory.

Donepezil

Donepezil decreased hit rate at the highest two doses, and decreased false alarm rate (100 ms only) and blank touches with the highest dose tested. Responding was also decreased by donepezil, as indicated by an increase in C score. No effect was observed on the discriminability index or response latencies. This is consistent with the literature where cholinesterase inhibitors have failed to alter sustained attention (McGaughy and Sarter 1998; Rezvani et al. 2012), 5-CSRTT performance (Mirza and Stolerman 2000; Romberg et al. 2011), and rCPT performance in C57 mice (Kim et al. 2015). However, donepezil has been efficacious in reversing MK-801 impairments (Rezvani et al. 2012), suggesting effects may be observed in subjects with compromised attention under certain circumstances. In healthy human subjects, researchers reported no effect of donepezil on visual attention in the non-sleep deprived condition (Chuah and Chee 2008) and on involuntary attention (Rokem et al. 2010). In a sleep deprivation trial, donepezil reduced the memory and attention deficits resulting from 24 h of sleep deprivation (Repantis et al. 2010a). In Alzheimer's disease, treatment with donepezil attenuated a decline in tests assessing attention and executive functions (Bracco et al. 2014), but the long-term benefit of donepezil treatment in patients is questionable.

Memantine

The NMDA antagonist memantine significantly decreased hit rate, false alarm rate, general responding (increased C score), and blank touches in a dose-dependent manner. Increased response latencies were observed as well. The discrimination index was also impaired at the highest dose, consistent with a general performance decrement in the task induced by memantine. Previous studies have shown accuracy and latency impairments with higher doses (3.0 mg/kg) of memantine in the 5-CSRTT task (Smith et al. 2011; Benn and Robinson 2014). No effects of memantine have been found in healthy adults on measures of attention or temporal discrimination (Rammsayer 2006). Memantine-induced improvements in choice reaction time have been observed in patients with

Dementia with Lewy Body and Parkinson's disease dementia (Wesnes et al. 2015), but these represent fairly impaired subjects.

Summary

Overall, these findings extend those of Kim et al. (2015) and suggest that the rodent Touchscreen-based CPT is sensitive to pharmacological manipulations on measures related to impulsivity and response bias. In particular, the rodent CPT is sensitive to the effects of stimulant-like drugs, as indicated by the dose-dependent increases in hit rate, false alarm rate, responsivity (decreased C score), and blank touches produced by methylphenidate, ABT-594, and modafinil. In addition, correct and incorrect response latency measures were decreased, but not as consistently as the above measures. Pharmacological effects on blank touches tracked closely with C score, indicating it to be measure of responsivity as well. The discriminability index d' was only improved by one of the drugs tested, ABT-594, but the nonspecific effects on overall responding and increases in measures make the interpretation of this finding unclear.

This is the first study to our knowledge to profile attention- and cognition-enhancing drugs in a rat touchscreen-based CPT. The data presented here suggests that the CPT test can be used to differentiate stimulant from non-stimulant pharmacotherapies on measures related to impulsivity. Rats were capable of discriminating sequentially presented, visually patterned 'target' and 'non-target' stimuli at a single location, analogous to the commonly performed human CPT tests. All drugs that decreased false alarms and blank touches also decreased hit rate, with corresponding decreases in response bias (increased C score), suggesting these particular drugs (atomoxetine, donepezil, and memantine) produced an overall reduction in general activity or responsivity, rather than a specific improvement on inhibitory control. Although our results suggest rat CPT is sensitive to detecting changes in measures related to responsivity and impulsivity, the validity of this test for assessing specific changes on attention remains unclear and requires further exploration. The advantage of using rCPT compared to established rodents assays of attention, like 5-CSRTT or SSRT, is also unclear as our understanding of the preclinical effects of these drugs on aspects of attention were not greatly advanced here despite the increased translational similarities of the rCPT task.

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