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ORIGINAL INVESTIGATION

The use of reaction time distributions to study attention in male rats: the effects of atomoxetine and guanfacine

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Abstract

Rationale Norepinephrine (NE) is involved in the control of sustained attention. Studies of sustained attention in humans include measures of reaction time (RT) and RT variability (RTV). The present study tested the role of NE using components of the RT distribution in rats in a manner thought to be similar to human studies of RTV.

Objectives This study tested the effects of increased synaptic NE (atomoxetine (ATX)) and α-2 receptor binding (guanfacine) on attentional lapses in rats.

Methods Male Sprague-Dawley rats ($n = 20$) were trained and tested in a two-choice RT task (2CRTT). Atomoxetine dose (saline, 0.1, 0.5, 1.0 mg/kg, i.p.), guanfacine dose (saline, 0.01, 0.1, 0.3 mg/kg, i.p.), and distractors were manipulated in three experiments. RT was divided into initiation time (IT) and movement time (MT). Analyses of distribution mode (peak) and deviation from the mode (skew) were then performed.

Results ATX and guanfacine had no effect on IT mode, reduced IT devmode, and increased MT mode. When distractors were introduced, ATX again improved devmode, but a lack of interaction between ATX and distractor indicated that ATX did not prevent distractor-induced impairments.

Conclusions IT devmode is a measure of distribution skew thought to reflect lapses of attention. The effects of ATX on IT devmode suggest that increased synaptic NE reduces attentional lapses. These findings are consistent with human reports of reduced RTV after ATX administration. The same pattern of results with guanfacine suggests that the effects of increased NE are due in part to binding at α-2 noradrenergic receptors.

Keywords Norepinephrine · α-2 noradrenergic receptors · Atomoxetine · Guanfacine · Rat · Lapses of attention · Distribution skew · Reaction time variability · ADHD · Distractors

Individuals with attention-deficit/hyperactivity disorder (ADHD) experience increased attentional lapses in tests of sustained attention (Leth-Steensen et al. 2000) and children in particular often struggle in school and other social contexts (Barkley 2006). Norepinephrine (NE) plays a critical role as a neuromodulator in cortical networks that promote sustained attention (Aston-Jones and Cohen 2005; Corbetta and Shulman 2002).

Atomoxetine (ATX), a selective NE reuptake inhibitor (Bymaster et al. 2002), reduces inattention based on parent assessments of children (Kratochvil et al. 2002; Michelson et al. 2002) and self-reports in adults with ADHD (Michelson et al. 2003). The continuous performance task (CPT) and the attention network task have been used to evaluate the effects of ATX on behavior. In the majority of studies, ATX improved sustained attention, increasing target discrimination or decreasing omissions (Fan et al. 2017; Gau and Shang 2010; Kratz et al. 2012; Lin and Gau 2016; Ni et al. 2013; Shang and Gau 2012; Wehmeier et al. 2011; Wehmeier et al. 2012); however, see Chamberlain et al. (2007) and Ni et al. (2016) who report no change in discrimination or omissions respectively. Mean reaction time (RT) is also measured in the CPT and attention network task. Findings are mixed with some studies reporting decreased RT (Fan et al. 2017; Gau and Shang 2010; Kratz et al. 2012; Wehmeier et al. 2011;

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Wehmeier et al. 2012) and others reporting no effects (Bédard et al. 2015; Ni et al. 2013; Ni et al. 2016; Shang and Gau 2012) after ATX treatment.

Sustained attention is measured in rodents using choice RT tasks and, more recently, CPTs. ATX improved accuracy (Navarra et al. 2008), particularly in low-performing animals (Caballero-Puntiverio et al. 2019; Robinson 2012; Tomlinson et al. 2014) and when preparatory intervals were increased (Baarendse and Vanderschuren 2012; Jentsch et al. 2008). On the other hand, the majority of studies reported no effects on accuracy or discrimination measures (Blondeau and Dellu-Hagedorn 2007; Ding et al. 2018; Fernando et al. 2012; Hauser et al. 2017; Koffarnus and Katz 2011; Liu et al. 2015; Paterson et al. 2011; Paterson et al. 2012; Robinson et al. 2008; Sun et al. 2012; Tsutsui-Kimura et al. 2009). The effects of ATX on RT in rodents are mixed. In contrast with effects in humans, however, ATX *increased* choice or discrimination RT (Baarendse and Vanderschuren 2012; Benn and Robinson 2017; Blondeau and Dellu-Hagedorn 2007; Caballero-Puntiverio et al. 2019; Ding et al. 2018; Fernando et al. 2012; Jentsch et al. 2008; Robinson 2012; Sun et al. 2012) or had no effect (Koffarnus and Katz 2011; Liu et al. 2015; Paterson et al. 2011; Paterson et al. 2012; Robinson et al. 2008; Tsutsui-Kimura et al. 2009) in rats. RT in rodent tasks has a substantial movement component; therefore, in addition to attention, RT could reflect motor, motivational, or sedative factors (Robbins 2002; see "Discussion").

In addition to accuracy and mean RT, intraindividual RT variability (RTV) is also used to measure sustained attention in humans and is thought to reflect lapses in attention (Kofler et al. 2013; Leth-Steensen et al. 2000; Tamm et al. 2012). RTV includes measures of standard deviation, as well as ex-Gaussian τ, an index of distribution skew. Increased RTV is associated with ADHD across a range of tasks (Kofler et al. 2013; Tamm et al. 2012). ATX reduced RTV in individuals with ADHD (Kratz et al. 2012; Ni et al. 2016; Shang and Gau 2012; Wehmeier et al. 2011; Wehmeier et al. 2012); however, several studies reported no effects in healthy (Nandam et al. 2011) or impaired individuals (Bédard et al. 2015; Chamberlain et al. 2007; Posey et al. 2006).

One aim of the present study was to test the effect of ATX on attentional lapses in rats. This approach used a two-choice reaction time task (2CRTT) and separated the movement time (MT) in rat RT from the initiation time (IT). We evaluated lapses of attention by separating IT distribution peak from skew in a manner that parallels the ex-Gaussian model (Richards et al. 2011; Sabol et al. 2003). In preliminary work, we found that ATX reduced IT distribution skew. The primary goals of experiment one were to extend these findings and determine if results from the rat model parallel results of ATX's effects on ex-Gaussian τ in humans (Ni et al. 2016). Experiment two addressed whether ATX would also protect against environmental distractors. This animal model of attentional lapses may then be useful for testing the efficacy of other drugs for the treatment of attention-related disorders in humans.

Guanfacine is a selective α-2 NE agonist (Jarrott et al. 1982; Timmermans et al. 1982) which is also used to treat ADHD (Bidwell et al. 2010). However, effects on behavioral measures have been mixed. Guanfacine decreased omissions or enhanced discrimination scores in children with ADHD (Scahill et al. 2001), monkeys (Decamp et al. 2011), and low-performing mice (Caballero-Puntiverio et al. 2019). On the other hand, no effects were reported in healthy adults (Jäkälä et al. 1999) and rats (Milstein et al. 2007; Pillidge et al. 2014; Sagvolden 2006). A third result was also reported, as guanfacine impaired choice accuracy in rats (Fernando et al. 2012). Regarding RT, guanfacine had no effect in monkeys (Decamp et al. 2011) and rodents (Caballero-Puntiverio et al. 2019; Milstein et al. 2007); however, increased RT was reported in other rodent studies (Fernando et al. 2012; Pillidge et al. 2014). Effects on RTV have not been reported in clinical or animal studies. Therefore, experiment three explored the effect of guanfacine on attentional lapses in rats.

We hypothesized that ATX would decrease attentional lapses in rats performing a 2CRTT and prevent increased attentional lapses caused by visual distractors. We also predicted that guanfacine would decrease attentional lapses.

Methods

Subjects

Male Sprague-Dawley rats ($n = 22$) were acquired from Envigo (Indianapolis, USA). Rats weighed 250–275 g upon arrival and were pair housed in a climate-controlled environment with 12-h light/dark cycle (lights on at 0700). All procedures were conducted during the light phase. Food was provided ad libitum to rats in home cages. Water was provided freely until 1 week prior to training then access for experimental rats ($n = 20$) was restricted to 30 min per day with a continuous 24-h access period once per week. Seven weeks into training, daily water access was decreased to 20 min. Weekly 24-h access periods continued throughout training and testing. Body weights were compared daily to free drinking controls ($n = 2$) to detect potential adverse effects from water restriction. Data for one rat were dropped from all analyses for experiments two and three due to low number of trials completed. All procedures were approved by the Institutional Animal Care and Use Committee of the University of Mississippi.

Apparatus

Rats were tested in four boxes enclosed within chambers to dampen external light and sound. Testing boxes had

aluminum front and rear panels, plexiglass side panels and tops, and wire floors. Front panels had three nose poke apertures. Left and right apertures were centered 1.5 cm above the floor and the middle aperture was centered 4.5 cm above the floor. The lateral apertures were centered 5.5 cm to either side of the center of the middle aperture. All nose poke apertures contained photobeams to measure entries and exits. Left and right apertures contained water dispensers. Lights were mounted above each aperture. A house light at the top of the rear panel was connected to a potentiometer, allowing adjustment of ambient light levels. A small fan was installed in the wall of each chamber to provide ventilation and a consistent, low level of ambient noise. Boxes were connected to a 486 computer using an interface by MED Associates Inc. (Fairfax, VA, USA). Experimental contingencies were programmed using the MED-PC programming language.

Training

After 1 week of water restriction, rats began training on the 2CRTT under salient conditions (house light off). Sessions began when the rat entered the central nose poke aperture. The rat was then required to hold its nose in the central aperture for a period referred to as the foreperiod (initially 0.1 s). After the foreperiod, the left or right stimulus light was illuminated. The illumination of left or right stimulus lights was randomized between trials. A 50 μl water droplet was dispensed when the rat broke the photobeam in the aperture under the illuminated light. The next trial was started when the rat returned to the central aperture (Fig. 1). Hand shaping with a water dropper was used in some cases to orient rats toward apertures. Training continued until all rats completed 100 trials within 30 min with at least 70% accuracy. This occurred during the second week of training.

Maximum foreperiod was then increased to 1.0 s. Foreperiods on individual trials were selected at random in 0.3-s intervals. Rats that exited the central nose poke aperture prematurely were able to complete a foreperiod in multiple trips. The maximum foreperiod length was increased by 1.0 s each day to the final maximum of 6.0 s. An adjusting time limit for responses was implemented the following day. This limit increased after every incorrect or slow response and decreased following two consecutive, correct, and timely responses (see Sabol et al. 2003). House lights were illuminated on the next testing day to reduce stimulus salience. Training was continued under these parameters until 70% accuracy was achieved and daily average IT and session length were stable (Speaker, unpublished). This occurred after 9 weeks of training.

Drugs

Atomoxetine hydrochloride and guanfacine hydrochloride were obtained from Sigma-Aldrich (St. Louis, USA) in solid form. Drugs were dissolved in physiological saline. Doses of ATX (0.1, 0.5, and 1.0 mg/kg) and guanfacine (0.01, 0.1, 0.3, and 1.0 mg/kg) were selected based on prior work with rats (Fernando et al. 2012; Navarra et al. 2008). These doses were mixed using freebase calculations. Drugs were administered via intraperitoneal injection 30 min prior to testing. Dosing schedules were counterbalanced using a Latin square procedure.

Procedure

Drug administration began after stable performance was reached. Drug administration was conducted on Tuesday

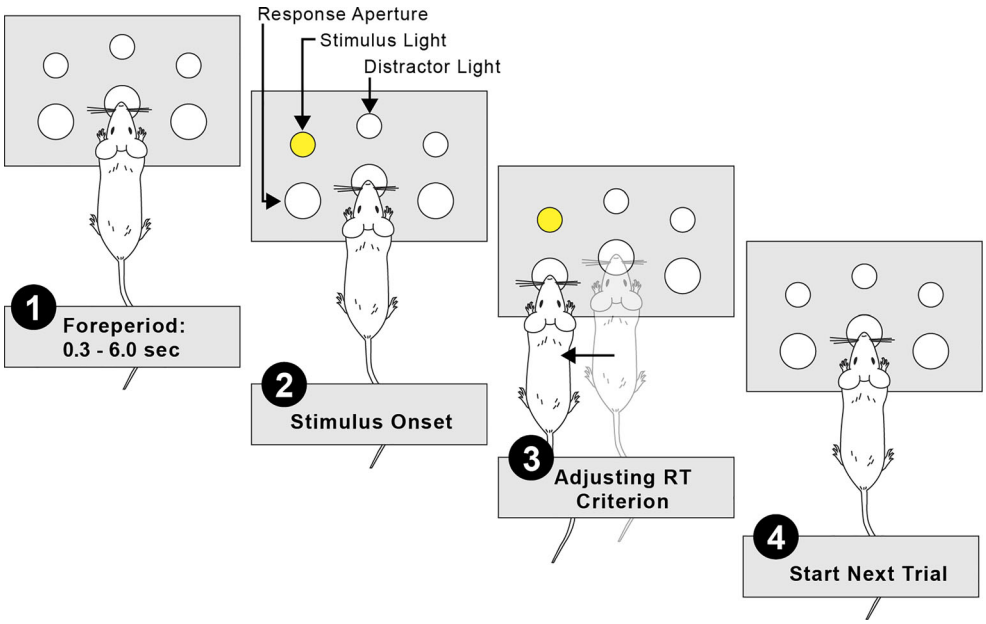

Fig. 1 Schematic depicting the task contingencies for the 2CRTT

and Friday each week. Experiment one tested the effects of ATX dose (saline, 0.1, 0.5, 1.0 mg/kg). House lights were turned on during testing to reduce stimulus salience.

Rats began trials by entering the center nose poke hole. Rats were required to hold this position for a foreperiod of 0.3 to 6.0 s (0.3-s intervals) that varied randomly between trials. After the foreperiod, a stimulus light was illuminated above one of the lateral nose poke holes until a response was completed. Rats were awarded 50 μl water droplets for responses under the illuminated light within an adjusting RT limit (described above). Slow responses and incorrect responses were not rewarded. Premature responses were not punished. Rats entered the central nose poke aperture to begin additional trials. At the end of testing (30 min or 100 trials completed), the house lights were extinguished, leaving the boxes in darkness.

Rats were allowed continuous access to water for a week after experiment one. Re-training was then started under salient conditions in preparation for experiment two. Re-training continued for 2 weeks when both IT averages and session lengths had re-stabilized for all rats. Experiment two tested ATX dose (saline, 0.1, 0.5, 1.0 mg/kg) and the presence of flashing light distractors during the foreperiod. The stimulus light above the middle aperture functioned as the distractor light. House lights were turned off during testing, making both distractors and stimuli more salient. Preliminary work showed these distractors significantly impaired attentional performance (Damico, unpublished). Three groups of four rats received distractors during the first half of the experiment and no distractors during the second half. The other two groups of four rats were tested under the reverse arrangement.

Rats were allowed continuous access to water for a week after experiment two. Re-training was then started under non-salient conditions in preparation for experiment three. Re-training continued for 2 weeks until both IT averages and session lengths had re-stabilized for all rats. Experiment three tested the effects of guanfacine dose (saline, 0.01, 0.1, 0.3, 1.0 mg/kg) on 2CRTT performance. Testing was again conducted with house lights on to reduce stimulus salience. House lights were extinguished when testing was completed, leaving the boxes in darkness.

In summary, drug administration for experiment one began on week 10 of the study and testing was completed on week 13. Animals were given a week of free access to water and re-trained for 2 weeks. Drug administration for experiment two began on week 17 and testing was completed on week 24. Animals were given a week of free access to water and re-trained for 2 weeks. Drug administration for experiment three began on week 28 and testing was completed on week 31 (see Table 1).

Dependent variables

Initiation time was defined as the time from stimulus onset until the rat removed its nose from the central aperture. Frequencies of ITs (measured in csec) were calculated for overlapping blocks of time (e.g., 1–5 csec, 2–6 csec, …, 196–200 csec). *IT mode* was recorded as the IT in the center of the block with the highest frequency. Modal IT for each rat was subtracted from mean IT to calculate *IT devmode*. All latency measures were converted to seconds for reporting. Omissions were recorded on trials with IT greater than 2.0 s. These abnormally long ITs were not factored into calculations of IT mode or IT devmode. The number of omissions was divided by the total number of trials in a session to determine *omission percentage*. Notably, the stimulus light remained illuminated until the rat completed a response.

Movement time was defined as the time from the end of the IT until the rat broke the photobeam in a lateral aperture. Calculation of *MT mode* and *MT devmode* followed the procedure detailed above for IT distributions. The *number of trials completed* was also recorded for each rat.

A premature initiation was recorded when a rat exited the central aperture prior to the presentation of the stimulus. *Premature initiation rates* were calculated by dividing the number of premature initiations by the sum of all foreperiod lengths in the session. A premature response was recorded when a rat exited the central aperture and entered one of the side apertures prior to the presentation of a stimulus. *Premature response rates* were calculated by dividing the number of premature responses by the sum of all foreperiod lengths in the session.

Data analysis

Each rat underwent two complete dose-response determinations in experiments one and three, yielding up to 200 trials per dose of drug in each experiment. In experiment two, all rats received two complete dose-response determinations for each of the two distractor conditions, yielding up to 200 trials per level of ATX dose for each distractor condition. In experiment three, data from the highest dose of guanfacine (1.0 mg/kg) were removed due to low number of trials completed (see "Results"). Data were analyzed using repeated measures ANOVA with drug dose and foreperiod block (0.3 - 1.5 s, 1.8 - 3.0 s, 3.3 - 4.5 s, and 4.8 - 6.0 s) as within-subject factors in each experiment and distractor as an additional within-subject factor in experiment two. Data for the foreperiod block factor are not reported here as no significant interactions were found for the variables of interest in this study. When data did not meet the assumption of sphericity, the Greenhouse-Geisser correction was used. Post hoc comparisons were performed using the Bonferroni technique to correct for family-wise error. All comparisons were made against vehicle.

Results

In addition to the information provided below, descriptive statistics are reported for mean latencies (RT, IT, MT),

Table 1 Two-choice RT task: training and testing procedure. Sessions ended after 100 trials were completed, or 30 min elapsed

Phase	Week	Max foreperiod	Response criterion	House lights	Distractor
Response acquisition	01–02	0.1 s	None	Off	None
Foreperiod increase	03–04	+ 1 s/day	None	Off	None
Baseline training	04–09	6.0 s	Adjusting	On	None
Experiment 1	10–13	6.0 s	Adjusting	On	None
Water holiday	14				
Re-baseline	15–16	6.0 s	Adjusting	Off	None
Experiment 2	17–24	6.0 s	Adjusting	Off	Flashing light
Water holiday	25				
Re-baseline	26–27	6.0 s	Adjusting	On	None
Experiment 3	28–31	6.0 s	Adjusting	On	None

accuracy, and premature initiation and response rates to allow comparison with other published reports (see Table 2). Figure 2 includes relative frequency distributions of ITs in 0.2-s bins for the saline control dose and the highest effective dose in experiment one (ATX) and experiment three (guanfacine).

Experiment one—ATX dose under non-salient conditions

Initiation time and omission percentage There was no effect of ATX dose on IT mode $F(3, 57) = 1.837$, $p > 0.05$ (Fig. 3a). There was a significant effect of ATX dose on IT devmode $F(3, 57) = 6.92$, $p < 0.001$ (Fig. 3b). Post hoc analysis indicated that IT devmode was reduced at the 1.0 mg/kg dose of ATX ($p < 0.05$) relative to vehicle (the 0.5 mg/kg dose was borderline, but not significant). There was no effect of ATX dose on omission percentage $F(3, 57) = 1.136$, $p > 0.05$ (Fig. 3e).

Movement time and completed trials There was a significant effect of ATX dose on MT mode $F(3, 57) = 4.385$, $p < 0.05$ (Fig. 3c); however, post hoc analysis revealed no significant differences relative to vehicle after Bonferroni correction. There was no effect of ATX dose on MT devmode $F(3,$

Table 2 Supplemental descriptive statistics. Data for each variable indicate mean (SEM). RT, IT, and MT data are reported in seconds; accuracy is reported as percentages

	RT mean	IT mean	MT mean	Accuracy	Premature initiation rate	Premature response rate
Experiment 1: atomoxetine						
Saline	0.803 (0.045)	0.371 (0.012)	0.432 (0.013)	97.4 (0.297)	1.108 (0.081)	0.226 (0.018)
0.1 mg/kg	0.792 (0.042)	0.369 (0.013)	0.423 (0.011)	97.5 (0.362)	1.092 (0.083)	0.235 (0.019)
0.5 mg/kg	0.751 (0.032)	0.327 (0.009)	0.424 (0.010)	98.5 (0.277)	0.970 (0.073)	0.201 (0.017)
1.0 mg/kg	0.769 (0.030)	0.320 (0.008)	0.449 (0.010)	98.4 (0.288)	1.066 (0.093)	0.205 (0.019)
Experiment 2: atomoxetine						
	No distractor	No distractor	No distractor	No distractor	No distractor	No distractor
Saline	0.613 (0.015)	0.233 (0.006)	0.379 (0.006)	98.8 (0.277)	0.832 (0.070)	0.132 (0.020)
0.1 mg/kg	0.604 (0.014)	0.219 (0.005)	0.384 (0.006)	98.6 (0.220)	0.844 (0.073)	0.127 (0.018)
0.5 mg/kg	0.619 (0.017)	0.221 (0.005)	0.398 (0.008)	99.0 (0.226)	0.700 (0.051)	0.130 (0.019)
1.0 mg/kg	0.603 (0.015)	0.207 (0.004)	0.396 (0.007)	98.8 (0.354)	0.778 (0.065)	0.149 (0.023)
	Distractor	Distractor	Distractor	Distractor	Distractor	Distractor
Saline	0.741 (0.025)	0.346 (0.008)	0.395 (0.008)	98.6 (0.237)	0.872 (0.045)	0.198 (0.019)
0.1 mg/kg	0.719 (0.027)	0.318 (0.009)	0.401 (0.009)	98.7 (0.194)	0.919 (0.057)	0.192 (0.020)
0.5 mg/kg	0.720 (0.020)	0.306 (0.008)	0.413 (0.008)	98.9 (0.242)	0.861 (0.042)	0.180 (0.018)
1.0 mg/kg	0.717 (0.023)	0.292 (0.009)	0.426 (0.008)	99.3 (0.193)	0.959 (0.058)	0.202 (0.021)
Experiment 3: guanfacine						
Saline	0.746 (0.032)	0.326 (0.010)	0.420 (0.009)	98.2 (0.259)	1.154 (0.092)	0.200 (0.019)
0.01 mg/kg	0.729 (0.032)	0.311 (0.009)	0.418 (0.010)	97.9 (0.357)	1.068 (0.090)	0.188 (0.017)
0.1 mg/kg	0.728 (0.031)	0.297 (0.009)	0.431 (0.009)	98.2 (0.357)	1.097 (0.099)	0.173 (0.018)
0.3 mg/kg	0.727 (0.032)	0.271 (0.009)	0.456 (0.010)	98.9 (0.217)	1.101 (0.092)	0.186 (0.018)

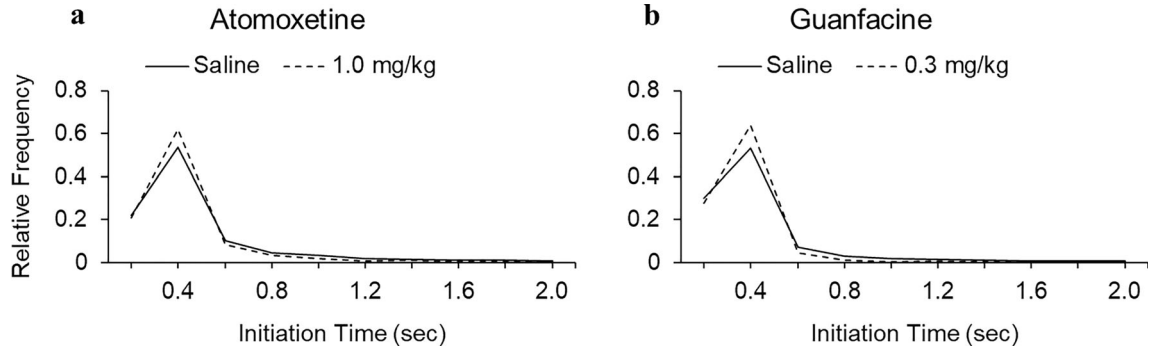

Fig. 2 Relative frequency distributions for initiation times in 0.2-s bins. Saline is compared with the highest dose of ATX (1.0 mg/kg) in experiment one (**a**) and guanfacine (0.3 mg/kg) in experiment three (**b**)

57) = 2.209, $p > 0.05$ (Fig. 3d). There was a significant effect of ATX on the number of trials completed $F(3, 57) = 10.194$, $p < 0.001$ (Fig. 3f). Post hoc analysis revealed that the number of trials completed was reduced at the 0.5 mg/kg dose ($p < 0.05$) and the 1.0 mg/kg dose ($p < 0.01$) relative to saline.

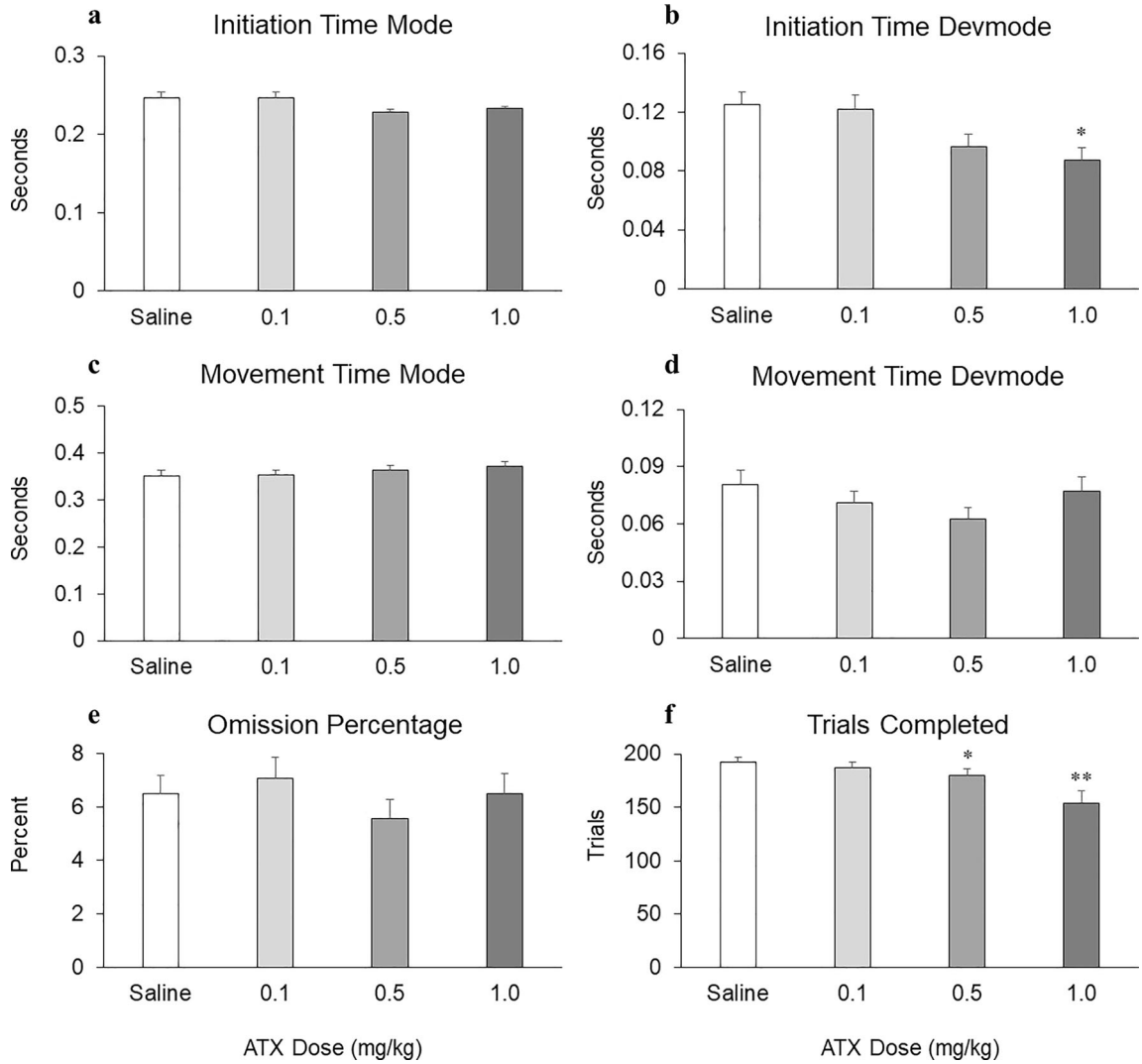

Fig. 3 **a**–**f** Effects of ATX dose (saline, 0.1, 0.5, 1.0 mg/kg, i.p.) on 2CRTT performance under non-salient conditions. ATX reduced IT devmode and trials completed. Data are shown as mean ± SEM, $n = 20$, ATX post hoc comparisons $^{*}p < 0.05$, $^{**}p < 0.01$. Post hoc tests to explore the effect on IT devmode revealed a significant reduction at the 1.0 mg/kg dose (**b**) and revealed a non-significant, borderline p value for the 0.5 mg/kg dose

Premature initiation rate and premature response rate There was no effect of ATX dose on premature initiation rate $F(3, 57) = 1.519$, $p > 0.05$. There was a significant effect of ATX dose on premature response rate $F(3, 57) = 4.417$, $p < 0.01$. Post hoc analysis revealed no significant differences relative to vehicle. Descriptive statistics for premature initiation and response rates are provided in Table 2.

Experiment two—distractor × ATX dose under salient conditions

Initiation time and omission percentage There was a significant main effect of distractor on IT mode $F(1, 18) = 96.513$, $p < 0.001$ (Fig. 4a); however, there was no main effect of ATX dose on IT mode $F(3, 54) = 1.318$, $p > 0.05$ (Fig. 4a). There was no interaction between distractor and ATX dose for IT mode $F(3, 54) = 0.905$, $p > 0.05$. There was a significant main effect of distractor on IT devmode $F(1, 18) = 47.284$, $p < 0.001$ (Fig. 4b) and there was a significant main effect of ATX dose on IT devmode $F(3, 54) = 15.909$, $p < 0.001$ (Fig. 4b). Post hoc analyses revealed that IT devmode was reduced at the 0.1 mg/kg dose ($p < 0.01$), the 0.5 mg/kg dose ($p < 0.001$), and the 1.0 mg/kg dose ($p < 0.001$) relative to saline. There was no interaction between distractor and ATX dose for IT devmode $F(3, 54) = 1.941$, $p > 0.05$. There was a significant main effect of distractor on omission percentage $F(1, 18) = 4.503$, $p < 0.05$ (Fig. 4e); however, there was no main effect of ATX dose on omission percentage $F(3, 54) = 0.776$, $p > 0.05$ (Fig. 4e). There was no interaction between distractor and ATX dose $F(3, 54) = 0.549$, $p > 0.05$.

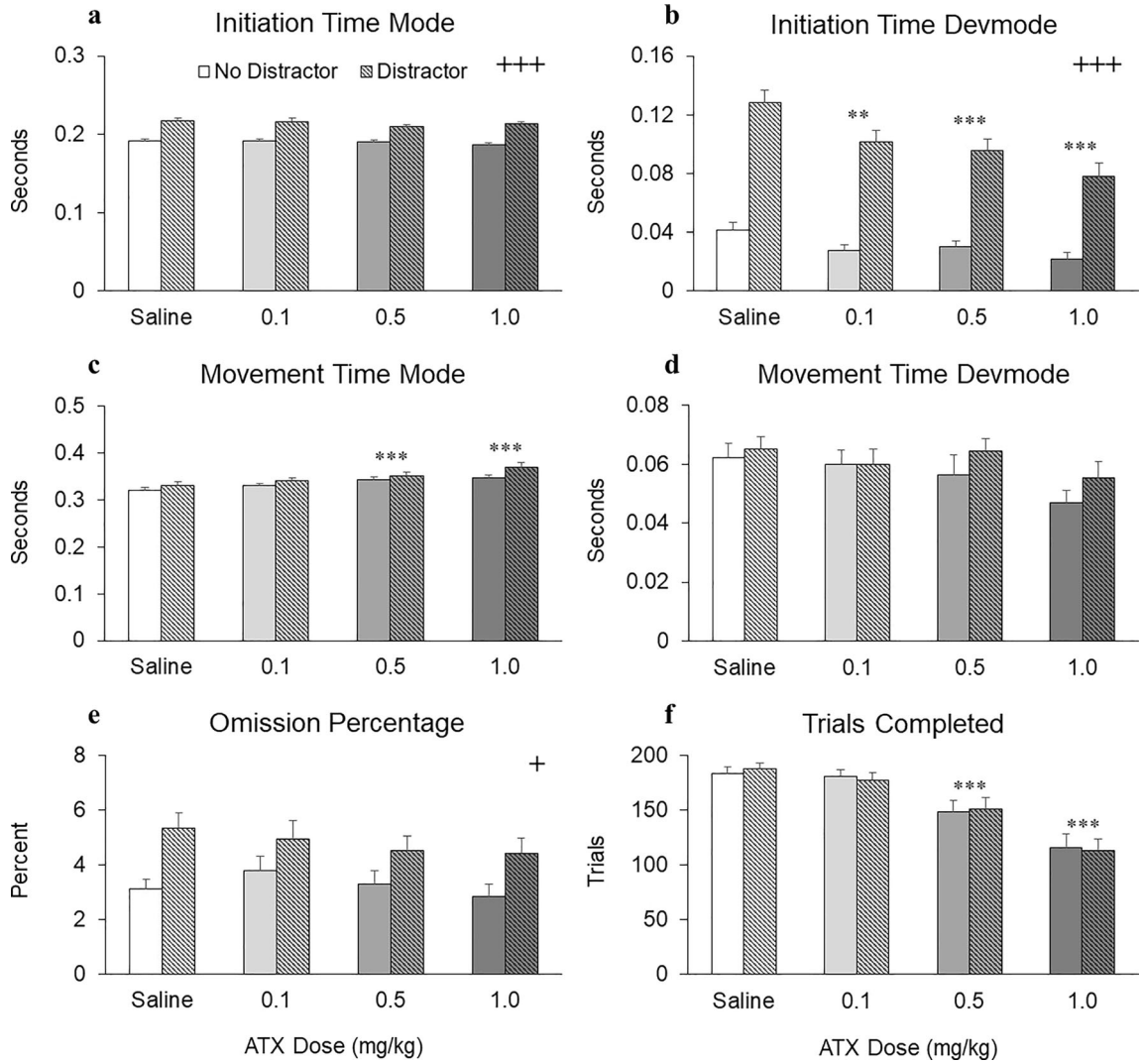

Fig. 4 **a**–**f** Effects of ATX dose (saline, 0.1, 0.5, 1.0 mg/kg, i.p.) and flashing light distractors on 2CRTT performance under salient conditions. ATX reduced IT devmode and trials completed. ATX increased MT mode. Distractors increased IT mode, IT devmode, and omission percentage. Data are shown as mean ± SEM, $n = 19$, ATX post hoc comparisons $^{**}p < 0.01$, $^{***}p < 0.001$, distractor main effects $^{+}p < 0.05$, $^{+++}p < 0.001$

Movement time and completed trials There was no main effect of distractor on MT mode $F(1, 18) = 3.516$, $p > 0.05$ (Fig. 4c); however, there was a significant main effect of ATX dose $F(3, 54) = 21.726$, $p < 0.001$ (Fig. 4c). Post hoc analyses revealed that MT mode was increased at the 0.5 mg/kg dose ($p < 0.001$) and the 1.0 mg/kg dose ($p < 0.001$) relative to saline. There was no interaction between distractor and ATX dose $F(3, 54) = 1.51$, $p > 0.05$. There were no main effects on MT devmode: distractor $F(1, 18) = 1.03$, $p > 0.05$; ATX dose $F(3, 54) = 1.431$, $p > 0.05$ (Fig. 4d). There was no interaction between distractor and ATX dose $F(3, 54) = 0.007$, $p > 0.05$. There was no main effect of distractor on the average number of trials completed $F(1, 18) = 0.051$, $p > 0.05$ (Fig. 4f); however, there was a significant main effect of ATX dose $F(3, 54) = 48.939$, $p < 0.001$ (Fig. 4f). Post hoc analyses revealed that the number of trials completed was reduced at the 0.5 mg/kg dose ($p < 0.001$) and the 1.0 mg/kg dose ($p < 0.001$) relative to saline. There was no interaction between distractor and ATX dose $F(3, 54) = 0.528$, $p > 0.05$.

Premature initiation rate and premature response rate There were no main effects on premature initiation rate: distractor $F(1, 18) = 3.824$, $p > 0.05$; ATX dose $F(3, 54) = 2.746$, $p > 0.05$. There was no interaction between distractor and ATX dose $F(3, 54) = 2.351$, $p > 0.05$. There was a significant main effect of distractor on premature response rate $F(1, 18) = 64.584$, $p < 0.001$; however, there was no main effect of ATX dose $F(3, 54) = 2.449$, $p > 0.05$. There was no interaction between distractor and ATX dose $F(3, 54) = 0.571$, $p > 0.05$. Descriptive statistics for premature initiation and response rates are provided in Table 2.

Experiment three—guanfacine dose under non-salient conditions

Initiation time and omission percentage There was no effect of guanfacine dose on IT mode $F(3, 54) = 1.297$, $p > 0.05$ (Fig. 5a). There was a significant effect of guanfacine dose on IT devmode $F(3, 54) = 15.75$, $p < 0.001$ (Fig. 5b). Post hoc analyses indicated that 0.1 ($p < 0.05$) and 0.3 mg/kg ($p < 0.001$) doses of guanfacine reduced IT devmode relative to saline. There was a significant effect of guanfacine dose on omission percentage $F(3, 54) = 5.312$, $p < 0.01$ (Fig. 5e); however, post hoc analysis revealed no significant differences relative to vehicle after Bonferroni correction (the 0.3 mg/kg dose was borderline, but not significant).

Movement time and completed trials There was a significant effect of guanfacine dose on MT mode $F(3, 54) = 19.022$, $p < 0.001$ (Fig. 5c). Post hoc analyses revealed that MT mode was increased at the 0.1 mg/kg dose ($p < 0.05$) and the 0.3 mg/kg dose ($p < 0.001$) relative to saline. There was no effect of guanfacine dose on MT devmode $F(3, 54) = 2.352$, $p > 0.05$ (Fig. 5d). There was a significant effect of guanfacine on the average number of trials completed $F(3, 54) = 42.645$, $p < 0.001$ (Fig. 5f). Post hoc analyses revealed that the number of trials completed was reduced at the 0.3 mg/kg dose ($p < 0.001$) relative to saline. The highest dose of guanfacine (1.0 mg/kg) severely reduced the number of trials completed (average of 16.6 trials out of a possible 200 trials); therefore, data for this dose were not included in analyses or figures.

Premature initiation rate and premature response rate There was no effect of guanfacine dose on premature initiation rate $F(3, 54) = 0.584$, $p > 0.05$. There was no effect of guanfacine dose on premature response rate $F(3, 54) = 1.532$, $p > 0.05$. Descriptive statistics for premature initiation and response rates are provided in Table 2.

Discussion

Networks of cortical and subcortical structures regulate sustained attention (Langner and Eickhoff 2013) in part by facilitating perception of and responding to relevant stimuli (Corbetta and Shulman 2002). Frontal and parietal nodes of these attention networks are innervated by NE projections from the locus coeruleus (Jones and Moore 1977) by which this neuromodulator affects top-down control over sustained attention (Aston-Jones and Cohen 2005; Corbetta and Shulman 2002; Petersen and Posner 2012). The present study used a mode/devmode analysis to explore the effects of two NE drugs on attentional lapses in rats performing a 2CRTT. These drugs included ATX, a NE reuptake inhibitor with secondary effects on dopamine reuptake in the prefrontal cortex, and guanfacine, a selective agonist for the α-2 NE receptor subtype.

The mode/devmode analysis used in this study was developed by Sabol et al. (2003) to separate effects on the peak (mode) and the skew (devmode) of RT distributions (similar to the ex-Gaussian model used in clinical studies). RT was divided into two measures to isolate attentional processes (IT) from factors related to movement, sedation, and/or motivation (MT). Mode and devmode were calculated for the IT and MT distributions produced by each rat. Notably, IT devmode reflects the occurrence of slow initiations which cause distributions to be more positively skewed. In human research, measures of RTV, especially those which reflect distribution skew, are thought to reflect lapses in sustained attention (Leth-Steensen et al. 2000). IT devmode could have translational value considering the increased RTV that is characteristic of individuals with ADHD (Kofler et al. 2013).

Experiment one tested the effects of ATX dose on 2CRTT performance under non-salient conditions. Experiment two tested the effects of distractors and ATX dose under salient

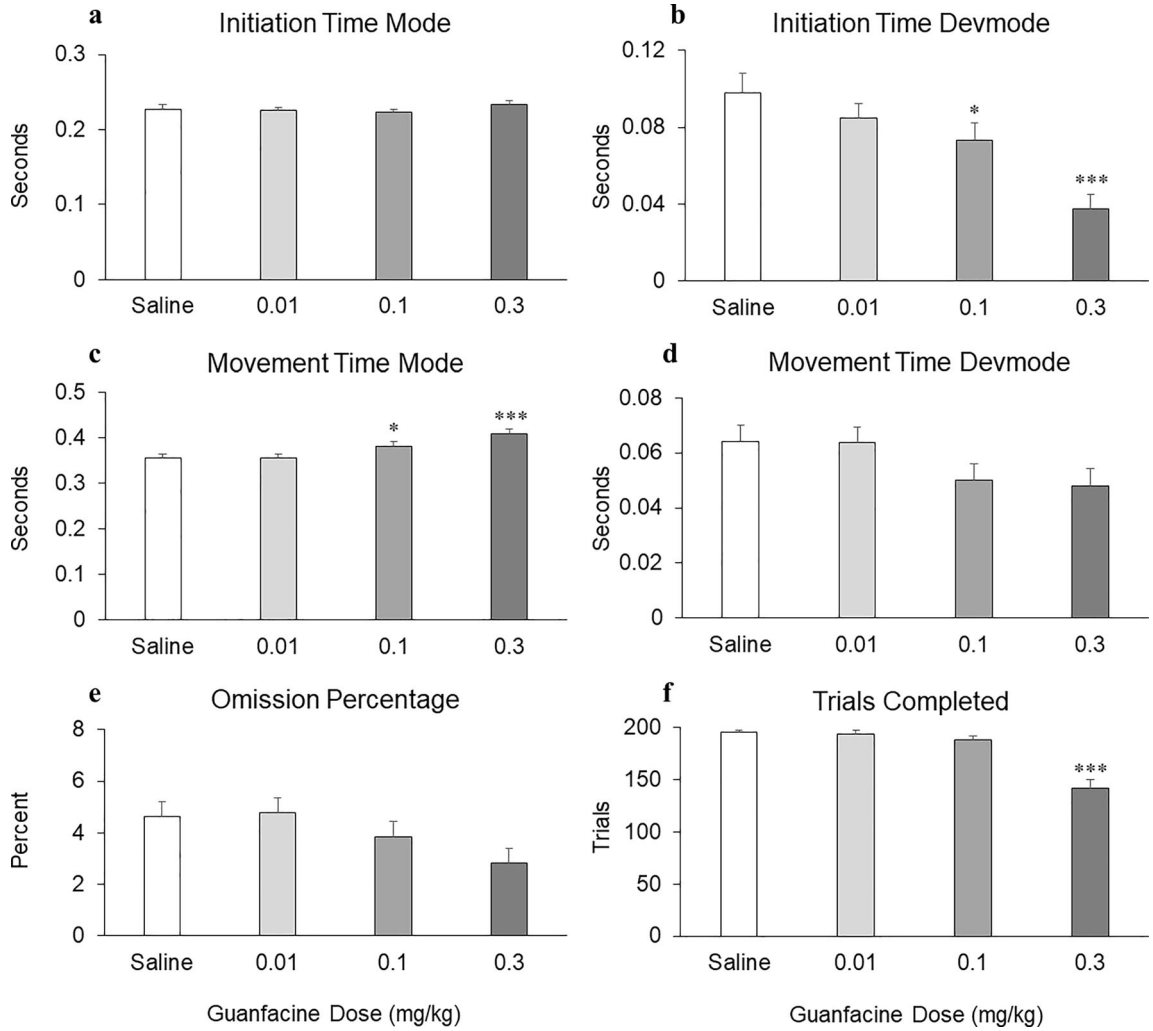

Fig. 5 **a**–**f** Effects of guanfacine dose (saline, 0.01, 0.1, 0.3 mg/kg, i.p.) on 2CRTT performance under non-salient conditions. Guanfacine reduced IT devmode and trials completed. Guanfacine increased MT mode. Data are shown as mean ± SEM, $n = 19$, guanfacine post hoc comparisons $^{*}p < 0.05$, $^{***}p < 0.001$. Post hoc tests revealed no significant effects on omission percentage (**e**); however, a borderline p value was found for the 0.3 mg/kg dose

conditions. Experiment three tested the effects of guanfacine under non-salient conditions.

Sensorimotor processing speed when rats are attentive: IT mode

Neither ATX nor guanfacine affected IT mode under the conditions tested in the present study. These results suggest that increased synaptic NE and α-2 receptor activation do not affect sensorimotor processing speed when rats are attentive to the task. In apparent contrast to this thinking, one clinical study (Ni et al. 2016) reported that ATX increased the mean of the Gaussian distribution in adults with ADHD performing Conners' CPT, despite responses requiring only small movements (discussed below). The reason for this discrepancy will require further research.

Lapses in attention: IT devmode

Atomoxetine dose-dependently reduced IT devmode in experiments one and two, suggesting that increased synaptic NE levels reduce attentional lapses. These findings are consistent with clinical reports of decreased RTV in children with ADHD performing the attention network task (Kratz et al. 2012) or CPTs (Shang and Gau 2012; Wehmeier et al. 2011; Wehmeier et al. 2012). Additionally, ATX decreased RTV in adults with ADHD performing a CPT (Ni et al. 2016). In contrast, other studies found no effects on RTV in children with attention deficits performing CPTs (Bédard et al. 2015; Posey et al. 2006) or in healthy (Nandam et al. 2011) and impaired adults performing stop-signal tasks (Chamberlain et al. 2007). Although findings are mixed, a large number of reports show ATX-induced decreases in RTV. In addition, ATX's effects on devmode (present study) and τ, but not RT standard error (Ni

et al. 2016) support the use of distribution skew as an indicator of inattention. This thinking is also supported by the finding that increased RT distribution skew characterizes children with ADHD relative to age-matched controls (Leth-Steensen et al. 2000).

Guanfacine dose-dependently reduced IT devmode in experiment three, suggesting that activation of α-2 NE receptors reduces attentional lapses in rats. These findings are consistent with the explanation that ATX's effects in experiments one and two are due in part to increased NE binding at α-2 receptors. Reduced IT devmode could be due to increased excitability in networks of task-related prefrontal cortex neurons (Wang et al. 2007) which facilitates the perception of expected stimuli (Corbetta and Shulman 2002). Additionally, ATX and guanfacine produced a similar pattern of results, suggesting that ATX's inhibition of dopamine reuptake in the prefrontal cortex (Bymaster et al. 2002) is not necessary for these improvements in sustained attention.

Distinction between IT mode and IT devmode

The ex-Gaussian model extracts Gaussian and exponential measures from RT distributions, and these measures represent distinct processes involved in sustained attention (Hohle 1967; Leth-Steensen et al. 2000). We make a similar distinction between mode and devmode measures (Richards et al. 2011; Sabol et al. 2003). Prior research using this approach showed that both IT mode and IT devmode are sensitive to environmental manipulations such as stimulus salience (Sabol et al. 2003). Methamphetamine also affected both measures in this initial report; therefore, neither manipulation dissociated IT mode and IT devmode. Subsequent research, however, found that prenatal alcohol exposure increased RT devmode with no effect on RT mode (Hausknecht et al. 2005). Furthermore, the present research dissociated IT measures, as both ATX and guanfacine reduced IT devmode without affecting IT mode. These findings support the use of a mode/devmode analysis to measure distinct phenomena within IT distributions.

Omission percentage

Atomoxetine did not affect omission percentage in the present study. These findings are consistent with other reports of ATX's effects in adults with ADHD performing CPTs (Bédard et al. 2015; Ni et al. 2016) and rats performing choice RT tasks (Hauser et al. 2017; Liu et al. 2015; Paterson et al. 2011; Paterson et al. 2012; Robinson et al. 2008; Robinson 2012; Tsutsui-Kimura et al. 2009). On the other hand, our findings are not consistent with the decreased omissions in children with ADHD performing CPTs (Shang and Gau 2012; Wehmeier et al. 2011; Wehmeier et al. 2012). Our findings are also inconsistent with a third outcome, in which ATX increased omissions in rats performing choice RT tasks (Baarendse and Vanderschuren 2012; Benn and Robinson 2017; Blondeau and Dellu-Hagedorn 2007; Fernando et al. 2012; Jentsch et al. 2008; Sun et al. 2012).

Guanfacine did not affect omission percentage in experiment three. The omnibus test of guanfacine's effect was significant; however, post hoc tests revealed no difference in omission percentage at any dose compared to saline (the 0.3 mg/kg dose was borderline). These guanfacine effects contrast with reduced omissions in children with impaired attention (Scahill et al. 2001) and monkeys (Decamp et al. 2011) performing CPTs. On the other hand, the present results also contrast with increased omissions in rats (Fernando et al. 2012) and mice (Pillidge et al. 2014) performing choice RT tasks.

The interpretation of omission measures is likely to be affected by differences between tasks, across species, and within species. For example, stimulus lights in the 2CRTT used in the present report remain active until a response is made, which clearly differs from other rodent tasks.

Movement time

In experiment one, the omnibus test of ATX's effects on MT mode was significant; however, post hoc analyses revealed no differences relative to saline after correcting for family-wise error rate. However, ATX and guanfacine dose-dependently increased MT mode in experiments two and three respectively. These findings suggest that enhanced NE function results in movement slowing due to activation of α-2 receptors.

Two components of RT distributions are analyzed in this report (IT and MT). Of these, MT may better represent the choice RT reported in most rodent tests of sustained attention. The increased MT mode found in the present study is consistent with reports that ATX increased choice RT (Baarendse and Vanderschuren 2012; Benn and Robinson 2017; Blondeau and Dellu-Hagedorn 2007; Fernando et al. 2012; Jentsch et al. 2008; Robinson 2012; Sun et al. 2012) and discrimination RT (Caballero-Puntiverio et al. 2019; Ding et al. 2018) in rodents. Similarly, guanfacine increased choice RT in rats (Fernando et al. 2012) and mice (Pillidge et al. 2014). In contrast, ATX reduced RT in several clinical studies in which participants executed simple key press responses (Fan et al. 2017; Gau and Shang 2010; Kratz et al. 2012; Wehmeier et al. 2011; Wehmeier et al. 2012). This difference between *increased* RT (and MT) in rats and *decreased* RT in humans may be related to differences in task requirements: whole body movement for rats compared to a simple key press for humans. This view is supported by the finding of Shang and Gau (2012) in which ATX increased choice RT in humans when the response required an additional arm movement. This view also suggests that the increased RT (and MT) is due to movement slowing.

A third pattern of results is reported, however, in which ATX had no effect on RT in children or adults with ADHD performing CPTs (Bédard et al. 2015; Ni et al. 2013; Ni et al. 2016) and no effects on choice RT in rats (Koffarnus and Katz 2011; Liu et al. 2015; Paterson et al. 2011; Paterson et al. 2012; Robinson et al. 2008; Tsutsui-Kimura et al. 2009). Additionally, no effects of guanfacine were reported in monkeys (Decamp et al. 2011) or mice (Caballero-Puntiverio et al. 2019) performing CPTs.

Some of the discrepancies in these reports may be related to the nature of the response requirement as discussed above; however, they may also be related to sedation or decreased motivation. Sedation has been reported during ATX and guanfacine treatment. A linear trend across doses of ATX was reported in adults' self-reports of sedation on two distinct sedation scales (Heil et al. 2002). Similarly, guanfacine caused sedation in humans (Wilens et al. 2015) and monkeys (Arnsten et al. 1988) and a clinical meta-analysis reported somnolence, sedation, and drowsiness in some children (Ruggiero et al. 2014). However, contrary to a sedation explanation, NE is known to be related to arousal (Aston-Jones and Cohen 2005) and intraventricular infusions of NE increased free-field activity levels in rats (Geyer et al. 1972).

Motivation is another potential influence on MT mode. In choice RT tasks, reduced motivation can be inferred from increased collection latency if rats also perform more omissions (Robbins 2002). Consistent with this view, ATX increased collection latencies and omissions in rats performing choice RT tasks (Benn and Robinson 2017; Blondeau and Dellu-Hagedorn 2007; Jentsch et al. 2008; Sun et al. 2012). Additionally, guanfacine increased collection latencies and omissions in rats performing choice RT tasks (Pillidge et al. 2014). On the other hand, several studies reported no effects of ATX (Fernando et al. 2012; Liu et al. 2015; Paterson et al. 2011; Paterson et al. 2012; Robinson et al. 2008; Tsutsui-Kimura et al. 2009) or guanfacine (Fernando et al. 2012) on collection latencies in rats performing choice RT tasks. While the evidence is mixed, most reports indicate that ATX and guanfacine increase omissions and magazine latencies.

In conclusion, the above findings suggest that movement slowing, sedation, and/or motivation could each be related to increased MT mode in the present study; however, sedation and reduced motivation appear to be inconsistent with our IT devmode findings. At the 1.0 mg/kg dose of ATX and 0.3 mg/kg dose of guanfacine, we found both decreased lapses of attention (IT devmode) and increased MT. Therefore, the present results suggest that ATX and guanfacine increase MT mode due to movement slowing rather than increased sedation or reduced motivation. More research will be needed to determine whether sedation or decreased motivation (as suggested by the literature) may be related to higher doses in the context of the task/analysis used in this report.

Trials completed

Atomoxetine and guanfacine dose-dependently decreased the number of trials completed in all present experiments. Similar to effects on MT mode (described above), the 1.0 mg/kg dose of ATX and the 0.3 mg/kg dose of guanfacine decreased lapses of attention (IT devmode) and decreased trials completed, suggesting that these doses do not lead to sedation or reduced motivation. For guanfacine, the 1.0 mg/kg dose dramatically reduced the number of trials completed to an average of 16.6 trials out of a possible 200. We did not include these data in our statistical analyses, but they suggest that sedation or decreased motivation may have contributed to this high-dose effect. As with MT mode, further research will be needed to clarify the decrease in trials completed.

Premature responses

Neither ATX nor guanfacine affected premature response rates in the present study under any of the salience or distractor conditions tested. The present findings are consistent with a lack of ATX effects on commission errors in children with ADHD performing Conners' CPT (Bédard et al. 2015; Posey et al. 2006). Guanfacine also did not affect commission errors in monkeys performing a CPT (Decamp et al. 2011).

In contrast, numerous studies report improvements in impulsivity measures after treatment with these drugs. For example, ATX (Kratochvil et al. 2002; Michelson et al. 2002) and guanfacine (Sallee et al. 2009; Sallee et al. 2012) are associated with reduced hyperactivity/impulsivity in children rated on the ADHD Rating Scale IV. ATX is also associated with reduced hyperactivity/impulsivity in adults rated on Conners' Adult ADHD Rating Scale (Michelson et al. 2003). Behaviorally, ATX reduced commission errors in children (Shang and Gau 2012; Wehmeier et al. 2011; Wehmeier et al. 2012) and adults (Chamberlain et al. 2007; Ni et al. 2016) with ADHD performing CPTs. Guanfacine also reduced commission errors in children with ADHD performing a CPT (Scahill et al. 2001). Finally, both ATX (Baarendse and Vanderschuren 2012; Benn and Robinson 2017; Blondeau and Dellu-Hagedorn 2007; Ding et al. 2018; Jentsch et al. 2008; Liu et al. 2015; Paterson et al. 2011; Paterson et al. 2012; Robinson et al. 2008; Robinson 2012; Sun et al. 2012; Tsutsui-Kimura et al. 2009) and guanfacine (Fernando et al. 2012; Milstein et al. 2007; Pillidge et al. 2014; Sagvolden 2006) reduced premature responding in rodent studies.

Lack of effects on impulsivity in the present study could be related to task characteristics. For example, animals are punished with a time-out for premature responses in the five-choice serial RT task (Robbins 2002). On the other hand, rats are not punished for premature responses in the present 2CRTT and are not likely to experience the same pressures to withhold these responses. Additionally, effects of ATX and

guanfacine appear to depend on baseline impulsivity in some cases. For example, ATX reduced premature responding only in high-impulsive mice (Caballero-Puntiverio et al. 2019) and rats (Fernando et al. 2012; Tomlinson et al. 2014). Similarly, guanfacine reduced premature responses in high-impulsive mice and increased premature responses in low-impulsive mice in a rodent CPT (Caballero-Puntiverio et al. 2019). Animals in the present study, however, were not split according to baseline impulsivity, possibly obscuring selective effects in low- and high-impulsive animals. Future research will be needed to explore the contribution of baseline impulsivity levels in this paradigm.

Distractors

Flashing light distractors during the foreperiod increased IT mode, IT devmode, omission percentage, and premature response rate in experiment two. ATX reduced IT devmode under both no-distractor and distractor conditions. However, lack of interaction indicates that dose of ATX and distractor condition affected IT devmode independently. Despite the finding that ATX does not moderate the effect of distractors on sustained attention, it is worth emphasizing that ATX attenuated lapses of attention even when distractors were presented during the foreperiod.

Atomoxetine was expected to moderate the effects of distractors as this drug blocks NE reuptake transporters, increasing synaptic NE and dopamine levels in the prefrontal cortex (Bymaster et al. 2002). Higher NE levels increase excitability in frontal networks (Wang et al. 2007) that are responsible for attentional set control (Corbetta and Shulman 2002) and dopamine inhibits irrelevant inputs to these task-oriented networks (Durstewitz et al. 2000). Distractors were made highly salient in the present study to increase the likelihood of attentional impairment; however, this could overshadow a real protective effect of ATX against increased IT devmode (attentional lapses) at lower levels of distractor salience. Additionally, similarities between distractor and target stimuli in this study could lead to inadequate inhibition of distractors. In other words, facilitation of attention to targets based on their expected characteristics (Corbetta and Shulman 2002) could also facilitate the detection of distractors with the same physical characteristics. Future studies will need to test distractor stimuli in different sensory modalities to explore this possibility.

Conclusion

This study manipulated the NE system to explore effects on sustained attention in rats. A mode/devmode analysis was applied to IT and MT distributions, revealing several key findings. (1) Neither ATX nor guanfacine affected IT mode, suggesting no effects on sensorimotor processing speed when animals were attentive to the task. (2) On the other hand, both drugs reduced IT devmode, suggesting that increased synaptic NE reduces attentional lapses by activating α-2 receptors in attention network areas. The use of IT devmode, a measure of RTV that reflects distribution skew (similar to the ex-Gaussian τ), allows direct comparison with human studies. A large number of these human studies report ATX-induced decreases in RTV that are consistent with the present findings. (3) These results support the use of a mode/devmode analysis by dissociating effects on IT mode and IT devmode. These results also support the use of this animal model for the testing of treatment drugs for attention-related disorders in humans. (4) Furthermore, ATX and guanfacine increased MT mode in experiments two and three (no significant post hoc differences in experiment one). Findings from experiments two and three are consistent with increased choice RT in other rat studies and increased movement RT in humans. The available evidence suggests that motor slowing, rather than sedation and/or reduced motivation, increased MT mode in the present study. Parallel ATX and guanfacine effects suggest that increased NE acting at α-2 sites is partially responsible. (5) Finally, when ATX and distractors were manipulated together, both resulted in main effects: ATX decreased attentional lapses and distractors increased them. However, there was no interaction between the two variables, suggesting that ATX improved attention, but did not counteract the effect of the distractors. Alternatively, a protective effect could have been obscured by high distractor salience and/or high physical similarity between distractors and target stimuli in this study.

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Compliance with ethical standards

All procedures using animals were approved by the University of Mississippi Institutional Animal Care and Use Committee.

Conflict of interest The authors declare that they have no conflicts of interest.

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