Pharmacology, Biochemistry and Behavior 199 (2020) 173069

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Measuring attention in rats with a visual signal detection task: Signal intensity vs. signal duration

Zade Holloway, Reese Koburov, Andrew Hawkey, Edward D. Levin *

Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, United States of America

ARTICLE INFO

Keywords:
Attention
Signal detection
Rats
Scopolamine
Dizocilpine
MK-801

ABSTRACT

Measurement of attentional performance in animal behavioral research allows us to investigate neural mechanisms underlying attentional processes and translate results to better understand human attentional function, dysfunction and drug treatments to reverse dysfunction. One useful method to measure attention in experimental animal studies is to use an operant visual signal detection paradigm, consisting of two levers and the rapid flashing of a cue lamp to signal a reward. In this study, we tested the relative sensitivity of this task when using different variants of the stimulus signal, varying brightness or duration of the light cue. To investigate roles of different neural systems underlying attentional processes, we assessed the sensitivity of attentional performance with these two different cue variations with blockade of muscarinic acetylcholine and NMDA glutamate receptors with scopolamine and MK-801 (dizocilpine). Operant signal detection was tested using a signal light that varied in intensity (0.027, 0.269, 1.22 lx) of the signal light or in a paradigm which varied the duration (0.5 s, 1 s, 2 s) of the signal light. Both methods of assessing attention showed construct validity for producing gradients of accuracy for signal detection; the dimmest cue led to less accurate responding compared to the brighter cues, and the shortest duration led to less accuracy compared to the longer durations. However, the tests differed in their sensitivity to pharmacological disruption. With the duration test, the high dose of MK-801 along with co-exposure of scopolamine and MK-801 caused a significant reduction of hit and rejection accuracy. Conversely, the intensity variation test did not show significant differences as a function of drug exposures. These data suggest that changes in signal duration, rather than signal intensity, during operant signal detection may have higher sensitivity to detecting drug effects and be a more useful technique for examining pharmacological interventions on attentional behavior and performance.

1. Introduction

Mechanisms of attention are fundamental to cognitive function, and any malfunction in these mechanisms can lead to a host of impairments. Indeed, once the abilities to detect relevant stimuli, process them, and filter out irrelevant stimuli are disrupted, individuals experience difficulties in many aspects of life and may be diagnosed with neurocognitive disorders including autism, attention deficit hyperactivity disorder (ADHD), Alzheimer's disease and schizophrenia (Barr, 2001; Corbett and Constantine, 2006; Huntley et al., 2017). Experimental animal models are crucial to developing better mechanistic understanding of attentional function, dysfunction and developing treatments to reduce dysfunction. In particular, measuring sustained attention in rodents through operant visual signal detection has been an important avenue of exploration for translational neuropsychiatric research. Sustained attention is the ability to report the occurrence of rare or unpredictable events over extended periods of time (Bushnell & Strupp, 2009). Equivalent functions in non-human animals rely on the ability to measure changes in choice behaviors based on the presence or absence of a brief, unpredictable discriminative stimulus, with correct responses following a stimulus presentation providing evidence for successful signal detection. A common method for signal detection has been developed for rodents using a standard operant chamber, and this method has been modified and utilized in studies concerning various topics, including drug addiction, developmental toxicity, neuropharmacology and cognitive neuroscience (Hawkey et al., 2020; Pardey et al., 2009; Rezvani and Levin, 2003).

In recent years there has been an increase in research designed to understand the neurophysiological systems underlying sustained attention, a cognitive function underlying other cognitive domains, such as

* Corresponding author at: Department of Psychiatry and Behavioral Sciences, Box 104790, Duke University Medical Center, United States of America.
E-mail address: edlevin@duke.edu (E.D. Levin).

https://doi.org/10.1016/j.pbb.2020.173069
Received 14 July 2020; Received in revised form 13 October 2020; Accepted 30 October 2020
Available online 2 November 2020
0091-3057/

learning and memory. This form of attention differs from other attentional domains by the duration of the required activity. Petersen and Posner (2012) found there to be three subsystems involved in this process. The first are networks that orient to sensory events, which are dorsal networks associated with rapid strategic eye movements and a ventral network that is responsive to incoming stimuli across different modalities (Fisher, 2019). The second is an alerting network which is involved in maintaining sensitivity to incoming stimuli; this system includes thalamic and fronto-parietal regions. The last is an executive control network specializing in the detection of signals for conscious processing that utilizes fronto-parietal and cingulo-opercular systems, which are involved in the maintenance of task goals across trials. To date, the rodent version of a sustained attention test has been applied to sustained attention in a very general way, and its relevance to some of these different processes and substrates underlying attention remains unclear. The visual signal detection operant test for measuring sustained attention in rats was developed by Bushnell et al. (1994). This signal detection paradigm involves an animal being trained to press one of two retractable levers; with one pressed in response to a visual cue light that is illuminated (signal), and the other in response to nonoccurrence of a signal light (blank). In a "signal" trial, a press on the lever associated with the illumination of a cue light results in the delivery of a food pellet reward. If the press is made on the opposite lever, a short timeout period with no food occurs instead. For the "blank" trial, the contingency is the same, except that the positions of the "correct" and "incorrect" levers are reversed. There are usually equal numbers of "signal" and "blank" trials in each test session to prevent response bias. Reinforced responses are coded as either "hits", defined as correct choices on the signal trials, or "correct rejections", defined as correct choices on blank trials.

The stimulus parameters used in sustained attention tasks are critical to their validity and sensitivity. As stated, there are different variations in experimental set-ups to measure attention with operant equipment, and although all versions aim to test sustained attention, methodological differences may influence their sensitivity and interpretation. Key factors found to play an important role in examining the validity of a technique are the physical characteristics of the stimuli itself, the discriminability of stimuli, the sensitivity to detecting drug exposure, and the variability of stimuli presentation (Bushnell, 1999; Echevarria et al., 2005; Frey and Colliver, 1973; Levin et al., 2011). An effective demonstration of the validity of each method is provided by a signal detection gradient, where the signal light presentation can consist of three or more levels of advancing difficulty, usually by altering the brightness or duration of the signal light. Changes in the accuracy of choices across this gradient allow the researcher to assess the accuracy of the animal in discrimination of stimuli. One would expect that as stimuli become more difficult to detect, there will be a decrease in accuracy or an increase in errors of commission. The hardware and software used to run these tasks allow a small number of parameters to be manipulated in order to generate a signal detection gradient, although which of these features is selected may have meaningful effects on the interpretation of the task.

In previous work, drug-induced effects have been used to demonstrate the construct validity of operant attention tasks, as well as to assess the pharmacological systems that underlie cognitive processes, such as attention, short-term memory and reaction time, either by interrupting or enhancing performance. This approach has identified multiple systems which mediate signal detection and operant performance (Bushnell et al., 1997; McGaughy and Sarter, 1998; Nelson et al., 2002; Newman and McGaughy, 2008; Rezvani et al., 2009). Among these systems are the omnipresent excitatory neurotransmitter glutamate, which regulates excitatory tone across many attention-relevant areas of the brain, and the cholinergic system, which exerts more selective effects in relevant circuitry through populations of nicotinic and muscarinic receptors. As models of attentional impairment, two compounds of particular interest are the cholinergic muscarinic antagonist scopolamine and glutamatergic NMDA antagonist dizocipline (MK-801), both of which are found to disrupt attentional processes through separate mechanisms (Celikyurt et al., 2011; Khakpai et al., 2012). MK-801 has dissociative effects at pharmacologically relevant doses, acting as a noncompetitive inhibitor of the NMDA receptor, which has long been studied for learning and memory, and there is convincing evidence that hypofunction of NMDA receptors plays a primary role in pathophysiology of schizophrenia, which is characterized by attentional problems among its many symptoms (Riedel et al., 2003; Tsai and Coyle, 2002). Acute administration of MK-801 leads to a selective disruption of performance in the signal detection task (Rezvani and Levin, 2003), as does another NMDA-antagonist, ketamine (Nelson et al., 2002). Scopolamine is frequently used due to its disruptive effects on the muscarinic cholinergic system, which are prominent in maintaining efficient sustained and selective attentional performance, particularly through cholinergic projections to the hippocampus and frontal cortex (Dekosky et al., 2002; Jones and Higgins, 1995; Semmler et al., 2007; Newman and McGaughy, 2008). Blockade of cholinergic transmission via scopolamine has been associated with impaired sensory discrimination, short-term memory, and attention (Klinkenberg and Blokland, 2010; Ahmed and Gilani, 2009; Bajo et al., 2015; Ramos Reis et al., 2013). Moreover, in a signal-detection task it is expected that as exposure to these drugs increases, scopolamine leads to a greater disruption in choice accuracy and errors of commission at all levels of the stimuli presentation (Presburger and Robinson, 1999).

The current study was conducted to assess whether the type of signal manipulation (signal duration vs. signal intensity) used in an operant signal detection task would affect the sensitivity of the task to a drug challenge, and to determine if the relevant neuropharmacological systems differ depending on the type of stimulus gradient provided. Specifically, comparisons were made between variants using a signal light with variable intensity (dim, moderate, bright; 0.027, 0.269, 1.22 lx) during discrimination and one with variable duration (500 ms, 1 s, 2 s) of the signal light. It has been suggested that these two manipulations differ in nature from one another, and may utilize separate neurophysiological processes and demands (Muir, 1996). A reduction in the intensity of the stimulus (e.g. brightness of a cue light) would reduce detection by minimizing the salience of the stimulus (i.e. its recruitment of attentional focus). This is related to sustained attention, but would generally be unrelated to one defining feature of it, which is the duration of time that is allocated to the cue light. On the other hand, reducing the length of the cue presentation would be sensitive to differences in the duration of time allocated to the cue location, but not to the likelihood of a given cue being detected when it is within the focus of the animal when presented. Given that these cognitive differences may also implicate different neurobiological substrates, such as specific utilization of glutamatergic or cholinergic networks, additional work is needed to clarify whether such variants of the task are interchangeable tests of sustained attention or represent conceptually separate assays. To test this hypothesis and detect differences in the neuropharmacology of these tasks, the present study compared of the performance of adult, female rats in each of these methods at baseline and when challenged by acute doses of scopolamine, MK-801 or their combination prior to testing. Females were used to assess neuropharmacological differences between these two methods because investigation of attentional processes has typically focused on males. Although, a few studies have shown clear sex differences in certain aspects of attention. Specifically, males have been shown to exhibit heightened sustained attention on the five choice serial reaction time task (5-CSRT) and were more vigilant in a response inhibition task (Bayless et al., 2012; Hammerslag et al., 2014). Additionally, we have previously shown MK-801 has an influence on sustained attention in females and others have suggested that females are more susceptible to the deleterious effects of MK-801 than males (Hammerslag et al., 2014; Rezvani and Levin, 2003). Further research on females during a sustained attention task will strengthen our understanding of sex-differences in the field.

2. Methods

2.1. Subjects

The following experiments were performed with 24 female Sprague Dawley rats which were group-housed at a density of 2–3 rats per cage. Of these, 12 rats were assigned to the cue duration experiment and 12 to the cue intensity experiment. Within the cue duration experiment, two rats were excluded from the drug phase due to repeated failures to advance through the training sequence. All rats were housed in a temperature controlled room under a normal 12-h light- dark cycle. Behavioral testing occurred Monday through Friday. Throughout testing, rats were kept on a restricted diet to maintain their body weight at ~85% of free feeding body weight. This was done to ensure proper appetitive behavior during testing. Ad libitum access to water was maintained throughout the study.

2.2. Operant visual attention task

The visual signal detection attention test was conducted as described in detail previously (Hall et al., 2016). The training sequence consisted of multiple training phases completed over multiple weeks (minimum 2, typical 4–5 weeks), leading to the final version of the task used below. Briefly, each rat was placed in an operant chamber and trained to press one of two retractable levers in response to a visual cue light that was illuminated for a duration of 0.5 s. If the cue-light became illuminated ("signal" trial), the animal needed to press the lever designated as the "signal" lever to receive a 20 mg food pellet reward. If the cue-light was not illuminated ("blank" trial), the animal needed to press the opposite lever in the chamber to receive the reward. The position (left, right) of "signal" and "blank" levers was randomized across the rats. If the rat made no response within 5 s of insertion of the response levers into the chamber, both levers retracted and a response "failure" was recorded. During test sessions, there were equal numbers of "signal" and "blank" trials in summing to a total of 240 trials within each session. Additionally during the test sessions, rats in the Intensity group were shown a light cues (randomized across trials) of one of three different intensities (dim, moderate, bright, 0.027, 0.269, 1.22 lx) during "signal" trials that were chosen based on our previous studies (Rezvani and Levin, 2004). Rats in the Duration group were shown light cues of one of three different signal durations (0.5 s, 1 s, 2 s). The measure of interest was response accuracy, analyzed separately for "hits" and "correct rejections". "Hit" responses were defined as correct choices on the signal trials while "correct rejection" responses were correct choices on blank trials. Percent correct hit and percent correct rejection per session were the primary dependent measures on this attention task, while cue type and drug exposure were the independent variables. Analysis was conducted of the choice accuracy data including these factors as well as scopolamine and MK-801 exposure (Table 1).

2.3. Drug preparation and dosing

The drug doses were chosen based upon previous studies where they were shown to disrupt attentional performance in similar operant paradigms (Presburger and Robinson, 1999; Rezvani et al., 2012). Both scopolamine and MK-801 (Sigma, St Louis, Mo., USA) were prepared in a saline solution. Twenty minutes before each test session, rats received two subcutaneous (S.C.) injections (1 ml/kg volume) to deliver any combination of the following: control vehicle (saline), MK-801 (0.05 mg/kg, 0.10 mg/kg), or scopolamine (0.02 mg/kg, 0.04 mg/kg). All rats received all possible treatment combinations. The order of treatments were counterbalanced across rats. Between each drug test session, rats were given 24 h without treatment to avoid carry-over effects of the drugs. The elimination half-life of MK-801 in rat plasma at 2 mg/kg is 1.9 h (Vezzani et al., 1989). The half-life for scopolamine has been shown to be relatively short as well (Lyeth et al., 1992).

Table 1
Omissions and latencies after treatment with saline, scopolamine, or MK-801 (mean ± SEM).

	Mean	S.E.M.		Mean	S.E.M.
Duration omissions			Duration latency (ms)		
Saline	2.1	1.8	Saline	64.5	5.1
ScopLow	3.4	1.8	ScopLow	85.2	11.2
ScopHigh	4.9	3.2	ScopHigh	104.3	14.4
MK801Low	0	0	MK801Low	61.6	5.5
MK801High	14.1	7.4	MK801High	159.0	34.6
	Mean	S.E.M.		Mean	S.E.M.
Intensity omissions			Intensity latency (ms)		
Saline	5.8	4.9	Saline	87.8	10.7
ScopLow	3.5	2.7	ScopLow	117.7	23.7
ScopHigh	4.1	2.8	ScopHigh	121.7	16.5
MK801Low	0.3	0.3	MK801Low	85.8	14.0
MK801High	6.5	6.0	MK801High	87.7	13.1

2.4. Data analysis

The choice accuracy and rejection data were assessed by the analysis of variance for between and within subjects factors (IBM SPSS Statistics 24). The between subjects factor was cue type or testing with light intensity vs. light duration as a test of attentional function. Within subjects factors were the levels of intensity or duration of the light signal and drug treatment. The threshold for significance was $p < 0.05$, two-tailed. Post hoc tests were performed using Tukey's test for multiple comparisons of the treated conditions to control.

3. Results

In the operant visual signal detection test of attentional function, accuracy on the test was examined using percent correct hits. Fig. 1 shows the main effect of cue type as a function of drug exposure was significant ($F(1,17) = 9.46$, $p < 0.01$) with rats in the duration group having significantly lower percent correct hits (78.9 ± 2.36) than rats in the intensity group (89.53 ± 2.49). There was also a significant main effect of cue type ($F(1,17) = 10.85$, $p < 0.01$) on percent correct rejections (Fig. 2), with rats in the duration group showing less accuracy (79.3 ± 2.49) than rats in the intensity group (91.2 ± 2.62).

There was a significant interaction between cue type and drug exposure ($F(8,136) = 4.25$, $p < 0.01$) that prompted further analysis of the simple main effects of cue type within each drug exposure (percent hit and percent correct rejection). This further analysis (Fig. 1) showed that the high dose of MK-801 caused a significant decrease in hit performance ($F(1,17) = 5.51$, $p < 0.05$) for the duration group (Duration = $75.4 \pm 8.06\%$; Intensity = $93.1 \pm 1.58\%$).

Following up on the aforementioned interaction between cue type and drug exposure, rats that were co-administered the high dose of MK-801 with the low dose of scopolamine showed a significant reduction in percent hits ($F(1,17) = 6.382$, $p < 0.05$) if they were in the duration group (Duration = $60.2 \pm 7.29\%$; Intensity = $86.9 \pm 7.69\%$), but exhibited no significant differences for correct rejection performance. Lastly, rats that were co-administered the high dose of both scopolamine and MK-801 showed a significant reduction in percent hits ($F(1,17) = 11.30$, $p < 0.01$) if they were in the duration group (Duration = $57.5 \pm 6.87\%$; Intensity = $91.1 \pm 7.24\%$). Percent correct rejection accuracy for this drug administration were also found to be significantly reduced ($F(1,17) = 14.981$, $p < 0.01$) for rats in the duration group (Duration = $57.0 \pm 6.65\%$; Intensity = $94.4 \pm 7.0\%$).

Fig. 3. shows the percent hit performance as a function of stimulus duration for saline, scopolamine and MK-801. For all drugs including saline, accuracy of hit performance increased significantly as the duration of the stimulus was lengthened (Saline: ($F(2,18) = 15.04$, $p < 0.01$);

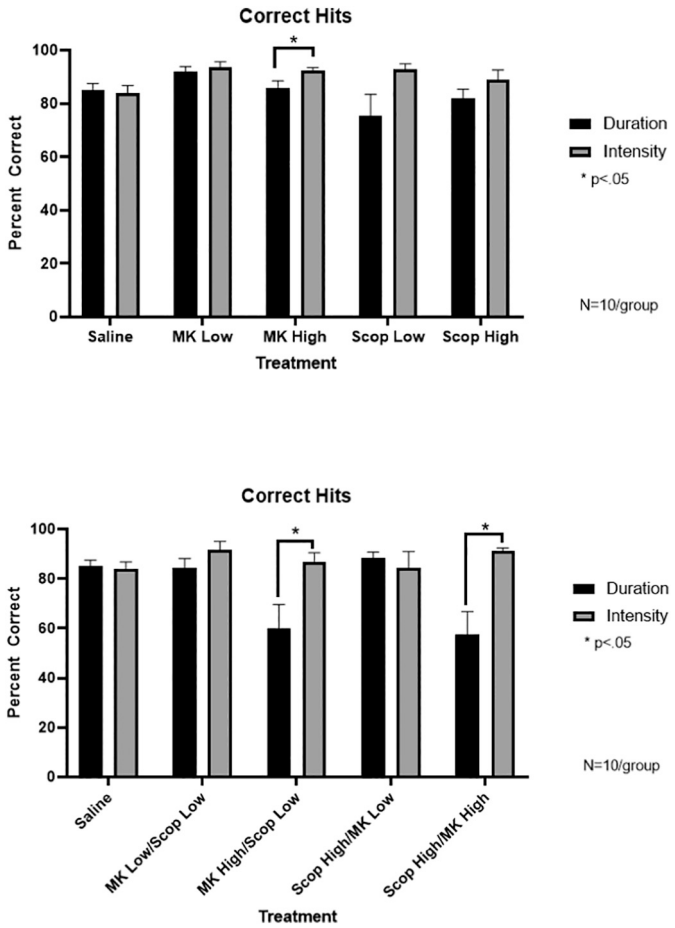

Fig. 1. Percent hit after treatment with scopolamine and MK-801 alone and in combination (mean ± SEM).

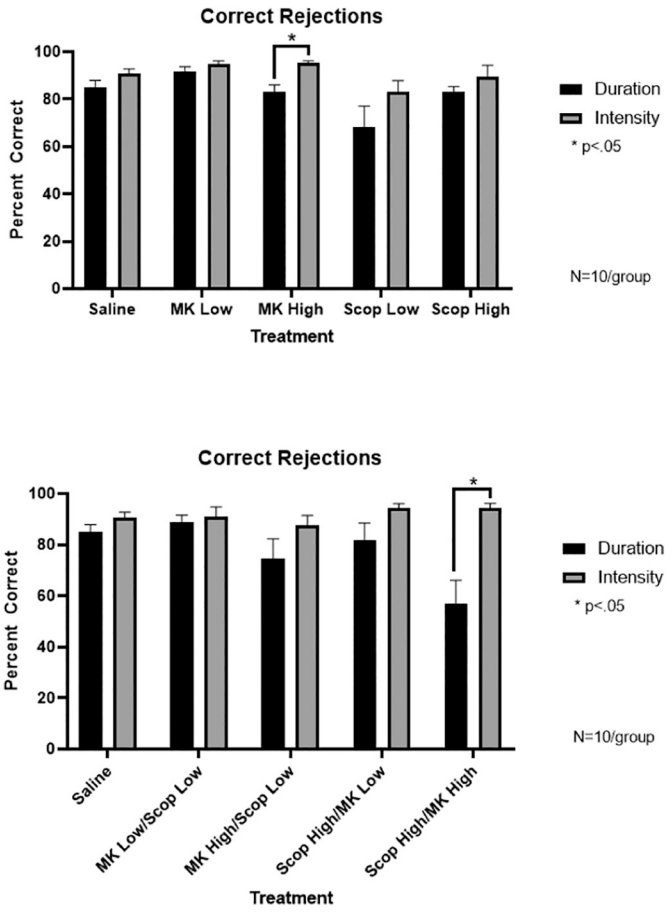

Fig. 2. Percent correct rejection after treatment with scopolamine and MK-801 alone and in combination (mean ± SEM).

MK-801 Low ($F(2,18) = 6.29$, $p < 0.01$); Scopolamine Low ($F(2,18) = 24.08$, $p < 0.01$); MK-801 High ($F(2,18) = 3.87$, $p < 0.05$); Scopolamine High ($F(2,18) = 16.08$, $p < 0.01$)).

Fig. 4. shows percent hit performance as a function of stimulus intensity for saline, scopolamine and MK-801. For all drugs, accuracy of hit performance increased significantly as the intensity of the stimulus was brightened or made more visible (Saline: ($F(2,20) = 7.68$, $p < 0.01$); MK-801 Low ($F(2,22) = 6.46$, $p < 0.01$); Scopolamine Low ($F(2,20) = 9.94$, $p < 0.01$); MK-801 High ($F(2,22) = 6.92$, $p < 0.05$); Scopolamine High ($F(2,22) = 7.68$, $p < 0.01$)).

4. Discussion

The two main goals of the current experiments were 1) to compare variations of visual stimulus intensity vs. duration as a way to assess attention in rats, and 2) to determine if the relevant neuropharmacological systems differ depending on the type of stimulus gradient provided. Specifically, this study assessed differences between two operant signal detection tests designed to measure attention at baseline and when performance was challenged by scopolamine or MK-801, two drugs known to disrupt attention and performance, or their combination. Use of these drugs by themselves and in combination allowed for assessment of how glutamatergic and cholinergic system blockade may affect performance in these two sustained attention tasks.

For both of these methods to exhibit validity of measuring attentional function, reductions in hit accuracy should be observed as either the duration of the signal becomes shorter, or the intensity of the signal becomes dimmer. Indeed, the saline, scopolamine, and MK-801 data (Fig. 3) all show that rats in the duration experiment typically performed less accurately when the stimuli with the shortest duration was presented. The same was seen for rats in the intensity experiment (Fig. 4), with the dimmest stimuli leading to less accurate responding compared to the brighter stimuli. Thus, both methods of assessing attention appear to have validity with the discriminability of stimuli.

However, when we examined each method's sensitivity to detecting drug exposure, we saw varying results between the two. It is expected that as rats were exposed to drugs, percent correct hits and correct rejections would be negatively affected in each the duration and intensity set-up. Exposure to MK-801 and scopolamine have been shown to reduce the discriminability of stimuli in signal detection tasks, leading to poor discrimination accuracy and increased errors of commission (Presburger and Robinson, 1999; Rezvani et al., 2011; Shannon and Yang, 2007; Slawecki and Roth, 2005). For the duration test, the high dose of MK-801, along with co-exposures of MK-801 and scopolamine, similarly led to significant reductions in accuracy for hits and rejections. The same was not shown for the method altering stimuli intensity. There were clear differences in accuracy between the dimmest signal and the brightest signal and rats did relatively well (>80%) on these dimensions (Figs. 1 and 2) in all exposure scenarios. This suggests that the intensity method may rely sufficiently on pharmacological mechanisms other than muscarinic acetylcholine and NMDA glutamate receptors for accuracy to remain high at doses which impair performance on the duration-based method. By contrast, the duration-based method appears to strongly rely upon these systems, with the glutamatergic mechanism standing as a clear candidate within the dose ranges examined in this study, based on the MK-801 data.

These data suggest that both methods (intensity, duration) are valid measures for measuring attentional function in rats due to the decreases

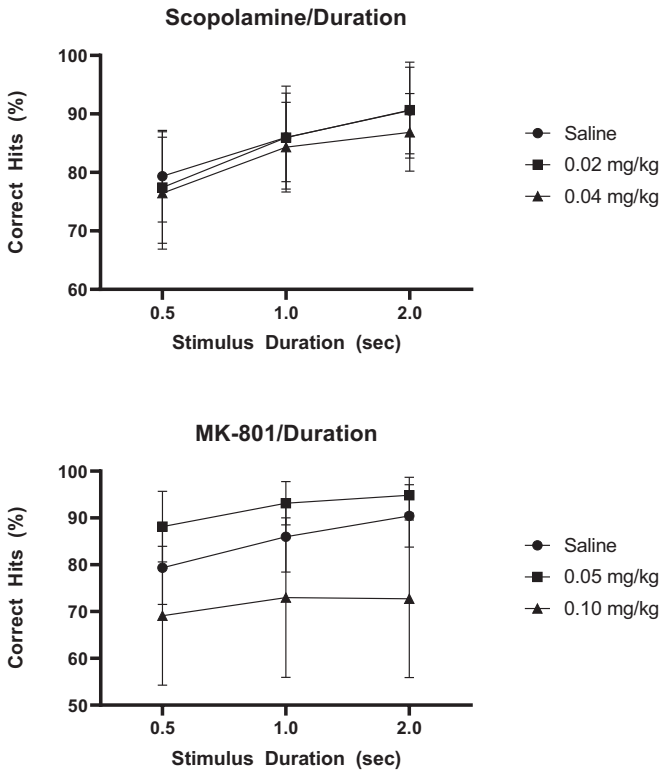

Fig. 3. Duration-effect function and percent hit response with scopolamine and MK-801 challenge (mean ± SEM).

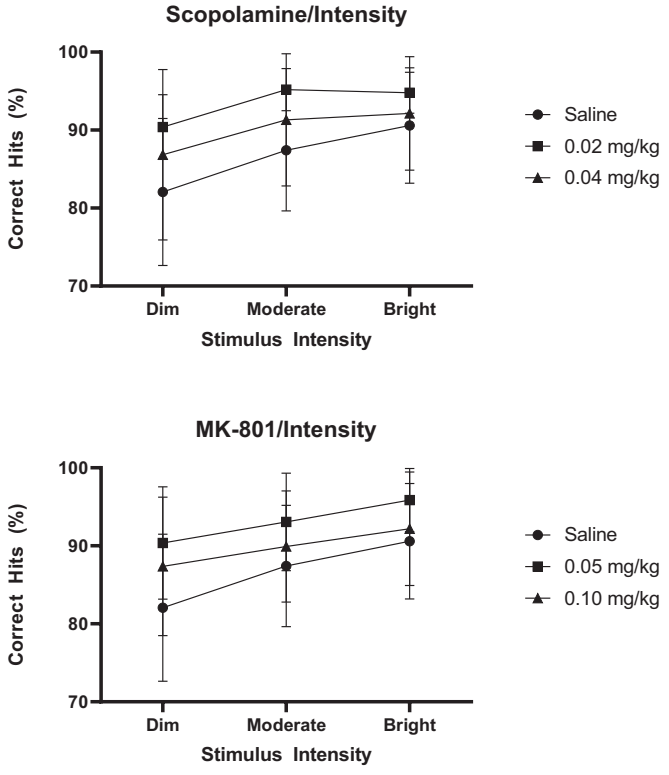

Fig. 4. Intensity-effect function and percent hit response with scopolamine and MK-801 challenge (mean ± SEM).

in accuracy seen as stimuli intervals became more difficult, likely requiring more focused attention or effort to detect them. Thus, both models may be useful for studying the neurobiological foundation of attention. However, it was expected that exposure to scopolamine and MK-801 would have effects on sensory-attentional and motivational processes leading to significantly more errors in accuracy and correct rejections. These errors were prevalent in the method that altered duration of stimuli but were absent in the intensity method. The inability of these drugs to impair performance accuracy under standard conditions may stem from differences in task difficulty between the two methods or in the neural systems required to complete the task (Fig. 5).

It is known that cholinergic innervation of the medial prefrontal cortex (mPFC) is crucial for attentional performance and there is evidence that increases in acetylcholine efflux may be related to increases in attentional effort (Bloem et al., 2014; Himmelheber et al., 2000). Importantly, cue-evoked glutamate bursts from thalamo-cortical neurons are necessary to generate these cholinergic transients in the cortex (Parikh et al., 2008). Thus, the interplay of cholinergic and glutamatergic systems is required for accurate detection in these tasks. It is

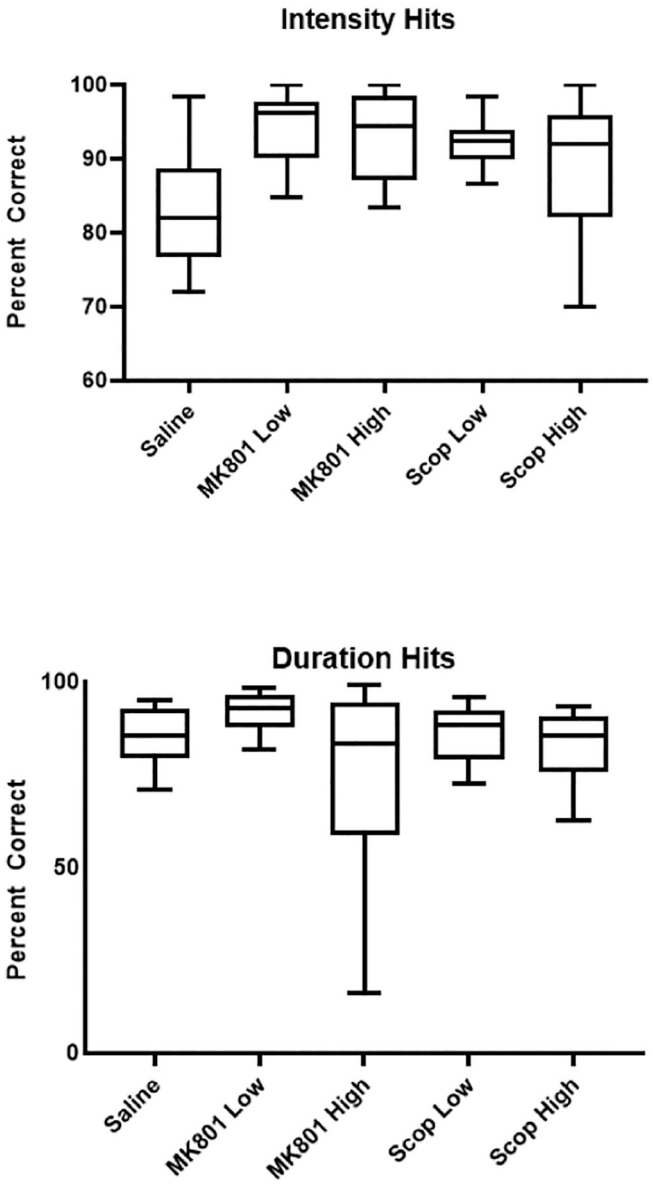

Fig. 5. Box and whisker plot of percent hit treatment effects on the duration vs. intensity methods.

possible that alterations in the brightness of the signal are simply easier to detect or require less attentional effort in the presence of these exposures than changes in duration. Additionally, scopolamine is a cholinergic inhibitor of muscarinic receptors and one cognitive process that depends on cholinergic circuits is interval timing, a task which requires subjects to estimate an interval of several seconds by making a motor response (Buhusi and Meck, 2005). Further, interval timing in rodents has been shown to be reliably impaired when exposure to scopolamine is present (Balci et al., 2008; Zhang et al., 2019). Of the two methods used in the current study, only the duration method requires the animal to rely on temporal precision, which may explain why errors were seen prominently with this method. In conclusion, changes in signal duration or temporal predictability may be a more useful technique for understanding the effects of disruptive drugs, environmental toxins, or pharmacological intervention on attentional behavior and performance.

Acknowledgments

This research was supported by the National Institute of Environmental Health Sciences at the National Institutes of Health, Superfund Research Program (ES010356).

References

Ahmed, T., Gilani, A.H., 2009. Inhibitory effect of curcuminoids on acetylcholinesterase activity and attenuation of scopolamine-induced amnesia may explain medicinal use of turmeric in Alzheimer's disease. Pharmacol. Biochem. Behav. 91 (4), 554–559.

Bajo, R., Pusil, S., López, M.E., Canuet, L., Pereda, E., Osipova, D., Maestu, F., Pekkonen, E., 2015. Scopolamine effects on functional brain connectivity: a pharmacological model of Alzheimer's disease. Sci. Rep. 5 (1), 1–6.

Balci, F., Ludvig, E.A., Gibson, J.M., Allen, B.D., Frank, K.M., Kapustinski, B.J., Fedolak, T.E., Brunner, D., 2008. Pharmacological manipulations of interval timing using the peak procedure in male C3H mice. Psychopharmacology 201 (1), 67–80.

Barr, W.B., 2001. Schizophrenia and attention deficit disorder: two complex disorders of attention. Ann. N. Y. Acad. Sci. 931 (1), 239–250.

Bayless, D.W., Darling, J.S., Stout, W.J., Daniel, J.M., 2012. Sex differences in attentional processes in adult rats as measured by performance on the 5-choice serial reaction time task. Behav. Brain Res. 235 (1), 48–54.

Bloem, B., Poorthuis, R.B., Mansvelder, H.D., 2014. Cholinergic modulation of the medial prefrontal cortex: the role of nicotinic receptors in attention and regulation of neuronal activity. Frontiers in Neural Circuits 8, 17.

Buhusi, C.V., Meck, W.H., 2005. What makes us tick? Functional and neural mechanisms of interval timing. Nat. Rev. Neurosci. 6 (10), 755–765.

Bushnell, P.J., 1999. Detection of visual signals by rats: effects of signal intensity, event rate, and task type. Behav. Process. 46 (2), 141–150.

Bushnell, P.J., Barbara, J., 2009. Strupp Assessing Attention in Rodents. Chapter 7. In: Buccafusco, J.J. (Ed.), Methods of Behavior Analysis in Neuroscience, 2nd edition. CRC Press/Taylor & Francis, Boca Raton, FL.

Bushnell, P.J., Kelly, K.L., Crofton, K.M., 1994. Effects of toluene inhalation on detection of auditory signals in rats. Neurotoxicol. Teratol. 16, 149–160.

Bushnell, P.J., Oshiro, W.M., Padnos, B.K., 1997. Detection of visual signals by rats: effects of chlordiazepoxide and cholinergic and adrenergic drugs on sustained attention. Psychopharmacology 134 (3), 230–241.

Celikyurt, I.K., Akar, F.Y., Ulak, G., Mutlu, O., Erden, F., 2011. Effects of risperidone on learning and memory in naive and MK-801-treated rats. Pharmacology 87 (3–4), 187–194.

Corbett, B.A., Constantine, L.J., 2006. Autism and attention deficit hyperactivity disorder: assessing attention and response control with the integrated visual and auditory continuous performance test. Child Neuropsychology 12 (4–5), 335–348.

DeKosky, S.T., Ikonomovic, M.D., Styren, S.D., Beckett, L., Wisniewski, S., Bennett, D.A., Mufson, E.J., 2002. Upregulation of choline acetyltransferase activity in hippocampus and frontal cortex of elderly subjects with mild cognitive impairment. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology*. Society 51 (2), 145–155.

Echevarria, D.J., Brewer, A., Burk, J.A., Brown, S.N., Manuzon, H., Robinson, J.K., 2005. Construct validity of an operant signal detection task for rats. Behav. Brain Res. 157 (2), 283–290.

Fisher, A.V., 2019. Selective sustained attention: a developmental foundation for cognition. Curr. Opin. Psychol. 29, 248–253.

Frey, P.W., Colliver, J.A., 1973. Sensitivity and responsivity measures for discrimination learning. Learn. Motiv. 4 (3), 327–342.

Hall, B.J., Cauley, M., Burke, D.A., Kiany, A., Slotkin, T.A., Levin, E.D., 2016. Cognitive and behavioral impairments evoked by low-level exposure to tobacco smoke components: comparison with nicotine alone. Toxicol. Sci. 151 (2), 236–244.

Hammerslag, L.R., Waldman, A.J., Gulley, J.M., 2014. Effects of amphetamine exposure in adolescence or young adulthood on inhibitory control in adult male and female rats. Behav. Brain Res. 263, 22–33.

Hawkey, A., Pippen, E., White, H., Kim, J., Greengrove, E., Kenou, B., Holloway, Z., Levin, E.D., 2020. Gestational and perinatal exposure to diazinon causes long-lasting neurobehavioral consequences in the rat. Toxicology 429, 152327.

Himmelheber, A.M., Sarter, M., Bruno, J.P., 2000. Increases in cortical acetylcholine release during sustained attention performance in rats. Cogn. Brain Res. 9 (3), 313–325.

Huntley, J.D., Hampshire, A., Bor, D., Owen, A.M., Howard, R.J., 2017. The importance of sustained attention in early Alzheimer's disease. International Journal of Geriatric Psychiatry 32 (8), 860–867.

Jones, D.N.C., Higgins, G.A., 1995. Effect of scopolamine on visual attention in rats. Psychopharmacology 120 (2), 142–149.

Khakpai, F., Nasehi, M., Haeri-Rohani, A., Eidi, A., Zarrindast, M.R., 2012. Scopolamine induced memory impairment; possible involvement of NMDA receptor mechanisms of dorsal hippocampus and/or septum. Behav. Brain Res. 231 (1), 1–10.

Klinkenberg, I., Blokland, A., 2010. The validity of scopolamine as a pharmacological model for cognitive impairment: a review of animal behavioral studies. Neurosci. Biobehav. Rev. 34 (8), 1307–1350.

Levin, E.D., Bushnell, P.J., Rezvani, A.H., 2011. Attention-modulating effects of cognitive enhancers. Pharmacol. Biochem. Behav. 99 (2), 146–154.

Lyeth, B.G., Ray, M., Hamm, R.J., Schnabel, J., Saady, J.J., Poklis, A., Jenkins, L.W., Gudeman, S.K., Hayes, R.L., 1992. Postinjury scopolamine administration in experimental traumatic brain injury. Brain Res. 569 (2), 281–286.

McGaughy, J., Sarter, M., 1998. Sustained attention performance in rats with intracortical infusions of 192 IgG-saporin-induced cortical cholinergic deafferentation: effects of physostigmine and FG 7142. Behav. Neurosci. 112 (6), 1519.

Muir, J.L., 1996. Attention and stimulus processing in the rat. Cogn. Brain Res. 3 (3–4), 215–225.

Nelson, C.L., Burk, J.A., Bruno, J.P., Sarter, M., 2002. Effects of acute and repeated systemic administration of ketamine on prefrontal acetylcholine release and sustained attention performance in rats. Psychopharmacology 161 (2), 168–179.

Newman, L.A., McGaughy, J., 2008. Cholinergic deafferentation of prefrontal cortex increases sensitivity to cross-modal distractors during a sustained attention task. J. Neurosci. 28 (10), 2642–2650.

Pardey, M.C., Homewood, J., Taylor, A., Cornish, J.L., 2009. Re-evaluation of an animal model for ADHD using a free-operant choice task. J. Neurosci. Methods 176 (2), 166–171.

Parikh, V., Man, K., Decker, M.W., Sarter, M., 2008. Glutamatergic contributions to nicotinic acetylcholine receptor agonist-evoked cholinergic transients in the prefrontal cortex. J. Neurosci. 28 (14), 3769–3780.

Petersen, S.E., Posner, M.I., 2012. The attention system of the human brain: 20 years after. Annu. Rev. Neurosci. 35, 73–89.

Presburger, G., Robinson, J.K., 1999. Spatial signal detection in rats is differentially disrupted by Δ-9-tetrahydrocannabinol, scopolamine, and MK-801. Behav. Brain Res. 99 (1), 27–34.

Ramos Reis, P.M., Eckhardt, H., Denise, P., Bodem, F., Lochmann, M., 2013. Localization of scopolamine induced electrocortical brain activity changes, in healthy humans at rest. J. Clin. Pharmacol. 53 (6), 619–625.

Rezvani, A.H., Levin, E.D., 2003. Nicotinic–glutamatergic interactions and attentional performance on an operant visual signal detection task in female rats. Eur. J. Pharmacol. 465 (1–2), 83–90.

Rezvani, A.H., Levin, E.D., 2004. Nicotine–antipsychotic drug interactions and attentional performance in female rats. Eur. J. Pharmacol. 486 (2), 175–182.

Rezvani, A.H., Kholdebarin, E., Brucato, F.H., Callahan, P.M., Lowe, D.A., Levin, E.D., 2009. Effect of R3487/MEM3454, a novel nicotinic α7 receptor partial agonist and 5-HT3 antagonist on sustained attention in rats. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 33 (2), 269–275.

Rezvani, A.H., Cauley, M., Sexton, H., Xiao, Y., Brown, M.L., Paige, M.A., McDowell, B. E., Kellar, K.J., Rose, J.E., Levin, E.D., 2011. Sazetidine-A, a selective α4β2 nicotinic acetylcholine receptor ligand: effects on dizocilpine and scopolamine-induced attentional impairments in female Sprague–Dawley rats. Psychopharmacology 215 (4), 621–630.

Rezvani, A.H., Cauley, M.C., Johnson, E.C., Gatto, G.J., Levin, E.D., 2012. Effects of AZD3480, a neuronal nicotinic acetylcholine receptor agonist, and donepezil on dizocilpine-induced attentional impairment in rats. Psychopharmacology 223 (3), 251–258.

Riedel, G., Platt, B., Micheau, J., 2003. Glutamate receptor function in learning and memory. Behav. Brain Res. 140 (1–2), 1–47.

Semmler, A., Frisch, C., Debeir, T., Ramanathan, M., Okulla, T., Klockgether, T., Heneka, M.T., 2007. Long-term cognitive impairment, neuronal loss and reduced cortical cholinergic innervation after recovery from sepsis in a rodent model. Exp. Neurol. 204 (2), 733–740.

Shannon, H.E., Yang, L., 2007. A non-spatial, stimulus-comparison working memory task in rats and disruption by scopolamine. Neuroscience 145 (3), 955–962.

Slawecki, C.J., Roth, J., 2005. Assessment of sustained attention in ad libitum fed Wistar rats: effects of MK-801. Physiol. Behav. 85 (3), 346–353.

Tsai, G., Coyle, J.T., 2002. Glutamatergic mechanisms in schizophrenia. Annu. Rev. Pharmacol. Toxicol. 42 (1), 165–179.

Vezzani, A., Serafini, R., Stasi, M.A., Caccia, S., Conti, I., Tridico, R.V., Samanin, R., 1989. Kinetics of MK-801 and its effect on quinolinic acid-induced seizures and neurotoxicity in rats. J. Pharmacol. Exp. Ther. 249 (1), 278–283.

Zhang, Q., Jung, D., Larson, T., Kim, Y., Narayanan, N.S., 2019. Scopolamine and medial frontal stimulus-processing during interval timing. Neuroscience 414, 219–227.