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Effects of NMDA antagonist dizocilpine (MK-801) are modulated by the number of distractor stimuli in the rodent odor span task of working memory

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Abstract

The rodent odor span task (OST) uses an incrementing non-matching to sample procedure in which a series of odors is presented and selection of the session-novel odor is reinforced. An OST is frequently used to test the effects of neurobiological variables on memory capacity as the number of odors to remember increases during the course of the session. In this regard, one important finding has been that NMDA receptor antagonists selectively impair OST performance at doses that spare accuracy on control tasks. However, in many versions of the odor span task the number of stimuli to remember is confounded with the number of distractor odors presented to the rat on each trial. The present study compared the effects of the NMDA antagonist dizocilpine when the number of choices was held constant at two (one novel odor—S+ and one previously presented distractor odor—S-) and when the number of choice stimuli was permitted to increase up to 10 (one S+ and 9 S-). Dizocilpine impaired OST accuracy at doses that had no effect on a reference memory control task in both 2-choice and 10-choice conditions; however, the dose-response function was shifted to the left in the 10-choice tests. The impairments produced by dizocilpine were exacerbated as the memory load increased in both 2- and 10-choice conditions. These findings support the hypothesis that NMDA antagonism reduces the number of stimuli that rats can remember accurately, but the interaction between the effective DZP dose and the number of distractors shows that drug effects on OST performances may involve attentional factors in addition to memory capacity. The findings also demonstrate that variations in number of OST distractors can be used to alter sensitivity of the task.

Keywords

NMDA antagonist; odor span task; working memory; MK-801

Delayed matching- and non-matching to sample tasks are among the most frequently used procedures to study drug effects on working memory in nonhuman animals (Baron &

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Wenger, 2001; Steckler, Sahgal, Aggleton, & Drinkenburg, 1998), but, perhaps surprisingly, most of these studies have found delay-independent effects. That is, most drugs, even those considered to possess amnesic effects, disrupt overall performance, but do not alter the forgetting function (see Galizio, 2016; Steckler et al., 1998; White, 2013). However, a limitation of delayed matching is the focus on retention of a *single* item which may fail to address important aspects of memory processes. This point is well-recognized in the human memory literature which includes countless studies of memory for lists, passages and episodes. Indeed, the construct of working memory in humans is typically characterized not only as *short-lived*, affected by the delay interval, but also as of *limited capacity*, affected by the number of items to be remembered (Gathercole, 2009). Procedures have been developed to study memory capacity in nonhuman animals using a variety of list learning and memory span procedures (e.g., Dudchenko, 2004; Wright, 2007).

In rats, the most successful of these procedures has been the odor span task (OST) for rodents developed by Dudchenko, Wood, and Eichenbaum (2000). In their procedure, rats were placed in a large arena in which cups filled with scented sand were presented. Digging in cups with a session-novel odor led to a food reward, but when an odor was repeated in the session, no reinforcement was provided. On each trial a new odor baited with food was introduced to the arena along with odors previously presented which were not baited. The procedure is characterized as an *incremental* non-matching to sample task with each trial increasing the number of sample stimuli to remember. Dependent measures include span length (the number of consecutive correct choices minus one—as there is nothing to remember on the first trial) and overall percent correct. Several studies with rodents have reported span lengths ranging between 8-10 odors and decreased accuracy with increased memory load (Dudchenko et al., 2000; Galizio, Deal, April, & Hawkey, 2013; Hawkey, April & Galizio, 2014; MacQueen, Bullard & Galizio, 2011; Young et al., 2007).

A growing literature using the OST to analyze drug effects is beginning to identify the neurobiological and pharmacological determinants of performance on this task. For example, OST performance is not affected by hippocampal lesions (Dudchenko et al., 2000), but is impaired by inactivation of the medial prefrontal cortex (Davies, Greba, & Howland, 2013; Davies et al., 2017). Further, the OST was nominated as a benchmark procedure to model working memory capacity in rodents by the CNTRICS group (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia; Dudchenko, Talpos, Young & Baxter, 2013). Indeed, guided by the NMDA hypofunction hypothesis of cognitive impairment in schizophrenia, much of the early work on the behavioral pharmacology of the OST focused on NMDA antagonists. The hypothesis asserts that core psychotic and cognitive symptoms in schizophrenia are based on NMDA receptor hypofunction, and predicts that administration of NMDA receptor antagonists to non-humans should produce symptoms that model those observed in schizophrenia (Gilmour et al., 2012).

As the hypothesis would predict, several studies have shown that these compounds impair OST performances in rats. In early work from our laboratory, we found that the noncompetitive NMDA antagonist dizocilpine/MK-801 (DZP) impaired span length and overall OST accuracy at doses that had no effect on a simple discrimination task that

controlled for drug effects on sensorimotor function, motivation, and reference memory (Galizio et al., 2013; MacQueen et al., 2011). More recently we found that two additional non-competitive NMDA antagonists, phencyclidine (PCP) and methoxetamine (MXE), selectively impaired OST accuracy, although the low-efficacy NMDA antagonist ketamine was less selective (Galizio et al., 2016; Mathews, Mead, & Galizio, 2018). Other laboratories have shown that the competitive NMDA antagonist 3-(2-carboxypiperazin-4-yl) propyl-1-phosphonic acid (CPP) produced effects that were similarly selective to OST performance, as did the GluN2B-selective antagonist Ro 256981 (Davies et al., 2013, 2017; MacQueen, Dalrymple, Drobos & Diamond, 2016). Interestingly, these effects generally depend on the number of stimuli to remember. That is, effects were minimal when the memory load was low, but impairment of accuracy accelerated as the number of odors to remember increased during the session (Galizio et al., 2013; MacQueen et al., 2011; Mathews et al., 2018). In summary, findings from multiple laboratories have converged to find that NMDA antagonists interfere with memory capacity in the OST. Importantly, other drugs have generally not produced selective effects in the OST, but rather disrupted OST performance only at doses that impaired overall responding on a control task that did not place demands on working memory (Galizio, 2016). However, the conditions that make the OST uniquely sensitive to NMDA antagonists are yet to be determined.

Although the OST is generally viewed as a measure of working memory capacity, variables other than the number of odors to remember may affect OST accuracy. For example, in the original study by Dudchenko et al. (2000) and in many subsequent studies, the number of comparison cups in the arena incremented on each trial so that there was a confound between the memory load and number of distractor stimuli present in the arena. April, Bruce & Galizio (2013) conducted a study in which the number of distractors was held constant as the number of stimuli to remember incremented. In this study, rats were first given brief OST training using the standard incrementing comparison procedure, but then the subjects were moved to a procedure in which the number of comparison stimuli was limited to 10, 5, or 2 as the memory load increased. Trials after the distractor limit was reached always included one novel odor presented along with either 9, 4, or 1 distractor odors drawn randomly from those previously presented during the session. April et al. (2013) found that both span and overall percent correct were highest when the number of comparison stimuli was lowest (two) and that performance degraded somewhat as the number of distractors increased.

There is wide variation in procedures across drug studies using the OST, and in many, the number of distractors has been permitted to increase with the memory load (e.g., Rushforth, Steckler, & Shoaib, 2010; Rushforth, Allison, Wonnacut, & Shoaib, 2011). However, in our studies of NMDA antagonists using the modified OST procedure, the number of comparison stimuli was limited to five (Galizio et al., 2013, 2016; MacQueen et al., 2011 with DZP and ketamine) or two (Mathews et al., 2018 with PCP, methoxetamine and ketamine). These studies showed selective, memory-load dependent effects of DZP, methoxetamine and PCP when the number of distractors was held constant. However, even with as few as five comparisons, it is possible that drug effects may depend to some extent on confusion among distractors. No experiments are currently available that permit direct comparison of drug effects as a function of the number of distractors in the OST.

The purpose of the present study was to determine the extent to which NMDA antagonist effects are altered by a potential interaction between the number of distractors and the memory load. Rats were studied under two OST conditions: one with a limit of two comparison stimuli (always one novel odor and one previously presented odor) and the other with a limit of 10 comparison stimuli (one novel odor and up to 9 previously presented odors). Unlike April et al. (2013), training on each condition was continued until stable, asymptotic accuracy levels were reached. Then the effects of DZP, which had previous been studied only using a 5-choice OST, were determined under both 2-Choice and 10-Choice conditions. The hypothesis was that impairment of remembering by DZP would be exacerbated in the 10-Choice condition.

Method

Subjects

Six male Sprague-Dawley rats were 90 to 150 days old when training began. Rats were housed individually in self-ventilating Plexiglas cages measuring 34.5 cm L x 18 cm W x 24.5 cm H and were maintained on a 12:12 reverse dark/light cycle. A food-restricted diet (Purina Lab Diet 5001 Rodent Diet--PMI Nutrition International, INC Brentwood, MO) was used to maintain animals at 85% of free feeding weight with *ad lib* water access. Procedures and animal care were approved by the UNC Wilmington IACUC.

Apparatus

Circular open-field arenas (94 cm in diameter) surrounded by 32 cm high metal baffling (described previously by Galizio, et al., 2017; Mathews, et al., 2018) were used for this experiment. The floor of the arenas included 18 holes, spaced 13.3 cm apart in two concentric circular arrangements with 12 holes in the outside ring and 6 in the inner ring. Plastic cups (60 ml) were placed snugly in each of the 18 holes. Each arena was located in a small testing room with a video camera positioned in the ceiling for digital recording of each session and a video display monitor located beside the arena. To prevent cueing, the experimenter observed the rat's performance on the monitor while remaining outside the rat's field of view. White noise (70 dB) was presented for the duration of the session.

Stimuli

Odorants were delivered by covering the cups with opaque polystyrene lids (Fabri-Kal) that were scented by storing in plastic containers containing aromatic oils and spices. Lids were suspended above oils or spices during storage, rather than directly in the odorants, so that the concentration of odorant was relatively consistent, and lids were stored at least 2 weeks prior to initial use. The spices and oils in the storage containers were refreshed every two weeks. Odorants used were acai, allspice, anise, apple, banana, bay, black walnut, bubblegum, caramel, caraway, carob, celery, cherry, chocolate, cinnamon, clove, coconut, coriander, cumin, dill, fennel, fenugreek, garlic, ginger, honey, lilac, maple, marjoram, marshmallow, mustard, nutmeg, onion, oregano, pecan, pine forest, pumpkin, root beer, rosemary, sage, savory, spinach, sumac, thyme, and watermelon; all were purchased from Nature's Garden, McCormick, Sigma Aldrich, or Great American Spice Co. To control for scent marking on

lids during the session, lids were used only once per session and were replaced with one of the same odor each time that scent was presented.

Procedure

Preliminary OST Training.—Sessions were conducted 5 days per week (Monday-Friday). Subjects were first habituated to the apparatus with all stimulus locations filled with uncovered cups, each baited with a .45 mg sugar pellet (Noyes). When animals were reliably consuming pellets, trials began in which only one cup in the arena was baited per trial. As rats became successful in retrieving pellets, unscented lids that partially covered the cups were introduced and gradually covered more of the cup until rats had learned to remove lids that completely covered the cups. Rats then began training on the OST incrementing non-match-to-sample procedure (see Galizio, et al., 2017; Mathews et al., 2018). Scented lids now covered the cups and a session-novel odorant was presented during each trial along with odorants from previous trials. Removal of the novel scented lid (correct responses) resulted in food reinforcement, but removal of any previously presented lid (errors) was not reinforced. Following an error, the animal remained in the arena until a correct response was made or until 2 min elapsed. If a correct response was not made within 2 min, the rat was placed just above the correct lid by the experimenter to assure that it had been exposed to that odor. Initially, the number of cups in the arena incremented on each trial, but as accurate performances developed, all rats were trained on a 2-choice procedure. In the 2-choice procedure, the number of comparison stimuli in the arena was held constant at two: a new baited odor each trial (+) and an unbaited odor (-) which was randomly selected from any of the previously presented odors. Sessions were 25 trials in duration with an inter-trial interval of approximately 30 s. When a criterion of 80% correct for two consecutive sessions was met, the baseline procedure which included a combined OST and simple discrimination control condition (SDC) was introduced. Initial training on the above procedures required between 13 and 29 sessions (mean = 20.5 sessions).

Combined OST/SDC Baseline.—As in our previous OST studies, a simple discrimination task was trained to serve as a control for drug effects on reference memory as well as non-mnemonic drug effects (sensorimotor effects, motivational changes, etc.). For each rat, two odors were selected to serve in the SDC task. These odors were never used in the OST for that rat and one odor was always associated with reward (S+) and the selection of the other was never reinforced (S-) throughout the remainder of the study. Initially, six SDC trials were presented following 25 OST trials conducted as above. After rats responded with 100% accuracy to the six SDC trials during at least one session, the SDC trials were pseudo-randomly interspersed throughout the session during the remainder of the experiment.

An additional control procedure was applied when the OST and SDC were combined. An unbaited control procedure was added in six OST trials distributed throughout the session on at least one session per week. In these trials, neither stimulus cup contained a reinforcer, but a sugar pellet was manually placed in the S+ cup immediately following a correct response. This control procedure allowed for verification that the odor of the lid, and not the scent of the sugar pellet, controlled responding. Performances on these unbaited trials was

comparable to that for regular trials on these sessions and no animals showed significantly lower accuracy on unbaited trials.

All rats were trained on the combined OST and SDC tasks until meeting a stability criterion which required a minimum of 10 sessions. The criterion was met when the difference in percent correct between the mean of the most recent five sessions and the five preceding sessions was less than 10% of the grand mean of those ten sessions. Between 18 and 40 sessions were required for rats to meet this criterion (mean = 26 sessions). At this point, three of the rats began the drug study to determine the effects of DZP on the 2-choice OST. The remaining three rats were trained to stability on a 10-choice OST task with SDC. The procedures for the 10-choice task were the same as above except that the number of comparison lids presented in the arena was permitted to increment up to 10 (SDC trials continued as a 2-choice task). When these animals met criterion on the 10-choice task, they also began the drug study. When the drug study was complete, the baseline schedule was changed such that 2-choice rats were now trained on the 10-choice baseline and *vice versa*. Thus, order of exposure to the 2- and 10-choice conditions was counterbalanced. Because performances were similar regardless of order, data from all six rats are combined below.

Drug Protocol

DZP (MK-801 maleate hydrogen, Sigma) was dissolved in .09% saline solution and delivered in a volume of 1ml/kg. Intraperitoneal injections were administered 30 min prior to session onset three days per week. Saline was delivered on Thursdays as an injection control, while active drug was administered on Tuesdays and Fridays. Administered doses were 0.03, 0.056, 0.1, 0.18 and 0.3 mg/kg. Two or three determinations of each dose were given for each rat and order of administration was random without replacement; each dose in a set of determinations was administered prior to the second and third rounds of doses. Experimenters remained blind to the dose administered. Animals were tested without injections on Mondays and Wednesdays.

Data Analysis

The main dependent variables analyzed were span (number of correct responses made until the first error in the session, excluding Trial 1 with only one odor), longest run (highest number of correct consecutive responses in the session regardless of when the run occurred) and percent correct. If a subject failed to respond within 2 minutes, the trial was scored as an omission; omitted trials were not included in the percent correct calculation. The omitted trial was repeated so that the rat had experience with the S+ odor which could be a distractor odor in later trials. If this trial was also omitted, the rat was placed adjacent the S+ cup to assure contact with the S+ odor. Within session analysis of percent correct was conducted in order to evaluate changes in accuracy as a function of the number of stimuli to remember which ranged from 1-24 as the session continued.

Results

Percent correct is shown in Figure 1 with the left panel showing the dose-effect functions that were obtained when rats were tested with two comparison stimuli in the arena and the

right panel showing the 10-choice functions. In both graphs, black circles show mean accuracy on the OST and white circles show the SDC task accuracy. Vertical bars indicate percentage of trials on which no lid removal response was made during the 2 min trial (omissions). Figure 1 shows dose-dependent decreases in accuracy across all conditions, but note that OST accuracy was impaired at lower doses of DZP that did not affect SDC accuracy. The effect at such doses was selective in that the working memory (OST), but not the reference memory (SDC), task is impaired. In the 2-Choice conditions, OST accuracy was above 90% under saline, but dropped significantly to about 80% at the 0.1 mg/kg dose of DZP, a dose that had no effect on the SDC task. OST accuracy declined further at the 0.18 and 0.3 mg/kg doses, but SDC accuracy showed a decline and omissions became frequent at those doses as well; the effects were less clearly selective to the OST.

Similar results are apparent in the 10-Choice condition, but the OST dose-response function was shifted to the left along with a larger DZP effect size. Note that a significant decline in OST accuracy is apparent at the 0.056 mg/kg dose, as well as at higher doses. No effects of DZP on SDC accuracy were evident until the 0.3 mg/kg dose under 10-choice conditions, although a high rate of omissions emerged at the 0.18 mg/kg dose. In sum, DZP produced selective impairments of OST accuracy in both 2- and 10-choice conditions, but there was greater sensitivity with 10-choices, with selective effects evident at the 0.056 and 0.1 mg/kg doses, whereas a selective effect was only observed at the 0.1 dose in the 2-Choice condition.

A Dose X Choice (10 vs. 2) X Task (OST vs. SDC) ANOVA confirmed the above observations through a significant 3-way interaction [$F(4,20)=5.86$, $p<.01$]. Simple main effects and post-hoc pair-wise tests (Tukey) were conducted; points marked with asterisks in Figure 1 (0.056 mg/kg in the 10-Choice condition and 0.1 mg/kg in both 2- and 10-Choice conditions) were those at which a significant OST decrement relative to saline was obtained without a significant reduction in SDC accuracy ($p<.05$). Finally, a significant Choice X Task interaction [$F(1,5)=13.33$, $p<.05$] confirmed that overall OST accuracy, but not SDC accuracy, was lower under the 10-choice conditions. However, although OST accuracy under saline was somewhat lower in the 10-choice condition, this difference failed to reach statistical significance ($p>.05$).

A within-session analysis was conducted to determine how the effects of DZP under both 2- and 10-choice conditions depended on the number of odors to remember. Figure 2 shows this analysis comparing the dose of DZP that was selective for both 2- and 10-choice conditions (0.1 mg/kg, white circles) to the saline control (black circles) across the OST (3 bins of 8 trials--left half of x-axis) and the SDC trials (three bins of two trials--right half of x-axis). Focusing on the OST functions in both 2- and 10-choice panels, note that accuracy decreased as a function of memory load in both cases, but that DZP produced a much steeper decline. When the memory load was relatively low (1-8 odors to remember), accuracy was high in all conditions with DZP performance only slightly lower than saline performance across choice conditions. As the memory load increased, accuracy decreased only slightly in the saline 2-choice condition, remaining at over 90% correct even with 17-24 odors to remember. The saline 10-choice condition appeared to decline a bit more with the memory load, but, even here, accuracy remained at nearly 80% at the highest memory load.

In contrast, note the steep declines apparent after 0.1 DZP. In the 2-choice condition, there was a drop from near 90% with 1-8 odors to remember to about 70% at the high memory load, and in the 10-choice condition a drop from just above 80% at the low memory load to below 40% at the highest load. A Dose X Choice X Load ANOVA showed a significant Dose X Load interaction [$F(2,10)=5.83$, $p<.05$] which supports the claim that the effects of DZP depended on the number of stimuli to remember, but neither the main effect nor any of the interactions involving Choice reached significance. Thus, the rate of forgetting was not altered significantly by the number of distractors in the arena. Finally, a within-session breakdown for the SDC trials (right side functions in both panels of Figure 2) is added simply to show that performance on this reference memory task was not affected by the 0.1 DZP dose and did not change during the course of the session.

Two additional measures frequently used in OST research are mean odor span (Figure 3, left panel) and longest run (Figure 3, right panel) here shown as a function of DZP dose under 2-choice (black circles) and 10-choice (white circles) testing conditions. Although there was considerable variability with both of these measures, a dose-dependent decrease in both span and longest run was evident regardless of the number of choices. A within-subject Dose X Choice ANOVA confirmed this observation showing a significant main effect for dose on both measures [span: $F(5,25)=6.78$, $p<.01$; longest run: $F(5,25)=12.36$, $p<.01$]. Span was slightly lower under saline and low dose conditions with 10 choices, but the main effect for Choice was not significant, nor was there a significant interaction ($p>.05$). Longest run was also somewhat lower in the 10-choice condition at every point along the dose-response function, but variability was high and the main effect for Choice only approached statistical significance [$F(1,5)=5.80$, $p=.06$]. In summary, these measures of consecutive correct responding showed a clear dose-dependent impairment produced by DZP, but high variability on these measures may have obscured effects of the number of choices in the arena.

Discussion

The major findings of the present study were that DZP produced selective effects on OST accuracy that depended on the number of stimuli to remember under both 2- and 10-choice testing conditions. Under both choice conditions, DZP impaired OST accuracy at doses that spared performance on the SDC task confirming previous finding of selective within-session/working memory impairments produced by DZP (Galizio, et al., 2013; MacQueen et al., 2011). Those earlier studies also showed memory-load dependent effects of DZP, but they used a 5-choice task and the present study is the first to demonstrate that these selective, load-dependent effects of DZP occur with minimal distractors (i.e., under 2-choice conditions). That being said, the number of choices did modulate the effects of DZP. The dose-response function was shifted to the left in the 10-choice condition with selective effects observed at a lower dose (0.056 mg/kg) than was evident in the 2-choice condition. The magnitude of effects on OST accuracy was greater in the 10-choice condition as well. OST accuracy never dropped below 60% in the 2-choice condition, but reached a low of near 40% correct with 10 choices. Finally, more omissions were observed at the higher doses of DZP in the 10-choice condition. In sum, sensitivity to the effects of DZP was enhanced by the increased number of distractors in the 10-choice condition.

April et al. (2013) found that baseline span and percent correct were higher in 2-choice, relative to 5- or 10-choice conditions. In the present study, there were some trends toward higher accuracy, span and longest run in the 2-choice baseline conditions, but none of these reached statistical significance. One issue here is that our small sample size may have lacked sufficient power given this relatively small effect size. Another explanation for this difference is that the April et al. (2013) study used a multi-element design in which rats were randomly assigned to conditions daily beginning very early in training. In the present study, subjects were trained more extensively until stable performance accuracies were reached and this may have permitted rats to learn to ignore the distractors in the 10-choice condition. Interestingly, although the function relating accuracy and memory load was steeper with DZP administration, the slope of that function did not differ significantly between the 2- and 10-choice conditions (see Figure 2). In sum, the effect of the number of distractors was mainly to alter sensitivity to DZP effects; the number of distractors did not exert much effect on remembering under baseline conditions. Indeed, the ability of rats to accurately select the session-novel stimulus from an array of 10 stimuli under control conditions seems to us quite remarkable; for example, consider that chance performances in the 2-choice conditions is 50% compared to 10% in the 10-choice conditions.

The selective disruption of the OST performances by DZP is also noteworthy. Although the selective impairments produced by DZP were more pronounced in the 10-choice condition, it is important to note that such impairments were also observed in the 2-choice condition. Similar effects have been observed in 2-choice OST experiments for other non-competitive NMDA antagonists including PCP and MXE (Mathews et al., 2018) and competitive NMDA antagonist CPP (MacQueen et al., 2016). Taken together, these studies support the claim that the selective effects of NMDA antagonists on OST accuracy occur even when the number of distractors are minimized; this is consistent with a within-session or working memory interpretation of the effects. Still, the increased sensitivity to DZP observed in the 10-choice conditions of the present study shows that number of distractors can alter the dose-effect function and complicate interpretation.

In summary, these findings point out that OST outcomes may depend on attentional variables in addition to the memory load. This point is of both methodological and theoretical significance. From a methodological standpoint, if the focus in a particular study is primarily on the effects of neurobiological variables on memory capacity, the present results suggest use of the 2-choice version of the task to minimize the impact of the number of distractors on OST performances. On the other hand, increasing the number of distractors might be employed to raise the OST ceiling in studies of cognitive enhancing effects (e.g., Galizio, et al., 2016). Further, multiple comparison stimuli might be considered to enhance the procedure as model of the combined challenges of memory load and distraction in schizophrenia.

From a theoretical standpoint, one implication is that the variation in number of distractors across laboratories using the OST should be taken into consideration when comparing OST outcomes across studies. For example, Rushforth, et al. (2010) found that scopolamine decreased span length using an OST in which the number of distractor cups in the arena was permitted to increase across trials. In contrast, Galizio, et al. (2013) failed to find selective

effects of scopolamine using an OST in which the number of distractors was limited to five. The discrepancy in outcome between these studies may well reflect effects of scopolamine on susceptibility to distraction, rather than on memory capacity.

Finally, the present findings have implications for the status of the OST as a benchmark model of working memory capacity deficits in schizophrenia (see Dudchenko et al., 2013). Several studies have found evidence that diminished working memory capacity (as opposed to working memory duration or precision) is a significant marker of schizophrenia (Erickson et al., 2015; Gold et al., 2010; Lee & Park, 2005). Thus, the findings of selective impairment of working memory capacity by NMDA antagonists in the OST have been taken as support for the glutamatergic theory of working memory deficits in schizophrenia (e.g., MacQueen et al., 2016; Mathews et al., 2018). The impairment of OST capacity by DZP observed in the present study is consistent with such an account, but what about the modulation of that effect by the number of distractors? Several studies have found that schizophrenics are more likely than controls to show impaired performance when distractors are added to working memory tasks, particularly when the distractors are highly salient (Hahn, et al., 2010; Moritz, Woodward, Jelinek & Klinge, 2008; Oltmanns & Neale, 1975). The present findings may be viewed as modeling this vulnerability to distractors by showing that DZP impairment is modulated both by the number of items to remember and the number of distractors. It will be important to study additional NMDA manipulations under conditions that vary both memory load and distraction to further test the role of NMDA receptor hypoactivity as a model of cognitive deficits in schizophrenia.

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Highlights

- NMDA antagonist dizocilpine selectively impaired accuracy on the odor span task.
- Drug effects were exacerbated by increases in memory load and distraction.
- Both attentional and capacity deficits in schizophrenia are modeled in the task.

Figure 1.

Percent correct is shown as a function of DZP dose for the OST (black circles) and SDC (white circles) in the 2- (left panel) and 10-choice (right panel) conditions. Bars indicate percentage of trials on which no response occurred within 2 min (omissions) for OST (black) and SDC (white). Vertical lines indicate SEM. Stars highlight data points at which DZP significantly reduced OST accuracy relative to saline (SAL), but did not reduce SDC accuracy or increase omissions.

Figure 2.

Within session graphs show the effects of 0.1 DZP (open circles) and Saline (closed circles) on OST and SDC percent correct across the session in bins of 8 for the OST and 2 for the SDC. Vertical lines indicate SEM.

Figure 3.

Consecutive correct responses is shown as a function of DZP dose for the 2- (black circles) and 10-choice (white circles) tasks. The left panel shows the mean odor span (correct response until the first error) and the right panel shows the longest run of correct responses obtained during the session.