Psychopharmacology (2017) 234:211–222
DOI 10.1007/s00213-016-4451-2

ORIGINAL INVESTIGATION

MK-801-induced impairments on the trial-unique, delayed nonmatching-to-location task in rats: effects of acute sodium nitroprusside

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Received: 12 June 2016 / Accepted: 25 September 2016 / Published online: 10 October 2016

Abstract
Rationale The cognitive symptoms observed in schizophrenia are not consistently alleviated by conventional antipsychotics. Following a recent pilot study, sodium nitroprusside (SNP) has been identified as a promising adjunct treatment to reduce the working memory impairments experienced by schizophrenia patients.
Objective The present experiments were designed to explore the effects of SNP on the highly translatable trial-unique, delayed nonmatching-to-location (TUNL) task in rats with and without acute MK-801 treatment.
Methods SNP (0.5, 1.0, 2.0, 4.0, and 5.0 mg/kg) and MK-801 (0.05, 0.075, and 0.1 mg/kg) were acutely administered to rats trained on the TUNL task.
Results Acute MK-801 treatment impaired TUNL task accuracy. Administration of SNP (2.0 mg/kg) with MK-801 (0.1 mg/kg) failed to rescue performance on TUNL. SNP (5.0 mg/kg) administration nearly 4 h prior to MK-801 (0.05 mg/kg) treatment had no preventative effect on performance impairments. SNP (2.0 mg/kg) improved performance on a subset of trials.
Conclusion These results suggest that SNP may possess intrinsic cognitive-enhancing properties but is unable to block the effects of acute MK-801 treatment on the TUNL task. These results are inconsistent with the effectiveness of SNP as an adjunct therapy for working memory impairments in schizophrenia patients. Future studies in rodents that assess SNP as an adjunct therapy will be valuable in understanding the mechanisms underlying the effectiveness of SNP as a treatment for schizophrenia.

Keywords Schizophrenia · NMDA receptor · Nitric oxide donor · Working memory · Pattern separation

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Introduction

Schizophrenia affects approximately 0.7 % of the population (McGrath et al. 2008) and is characterized by positive, negative, and cognitive symptoms (Carbon and Correll 2014). The cognitive symptoms are distinct, core characteristics associated with the disease (Bozikas et al. 2004; Aquila and Citrome 2015), and their severity influences patient functional outcome (Bhagyavathi et al. 2015). Although these symptoms are experienced by the majority of patients, they remain largely unresolved by available antipsychotics (Palmer et al. 1997; Marder and Fenton 2004; Vingerhoets et al. 2013; Carbon and Correll 2014). Working memory deficits are emphasized as key impairments in schizophrenia by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative (Marder and Fenton 2004). These impairments are robust and highly prevalent among patients (Mesholam-Gately et al. 2009). Their severity is highlighted by the collection of working memory vulnerabilities, including the inability to maintain information across a delay or protect it from interference (Fleming et al. 1995; Kim et al. 2004; Fatouros-Bergman et al. 2014). Another cognitive domain impaired in schizophrenia is pattern separation, the ability to keep separate patterns as distinct internal representations. Although this domain is less frequently studied, patient impairments are observed in reduced accuracy on tasks that require face matching, matching-to-sample, or the spatial

discrimination of sound (Perrin et al. 2010; Soria Bauser et al. 2012). The trial-unique, delayed nonmatching-to-location (TUNL) task simultaneously measures working memory and pattern separation in rodents. The high cross-species translatability of this task makes it a promising and unique platform to study potential treatment of cognitive impairment in schizophrenia (Bussey et al. 2012). To date, only one study has examined TUNL task performance in a rodent model of schizophrenia (Kumar et al. 2015) and none have attempted to reverse any observed impairments.

NMDA receptor dysfunction is a pathophysiological change implicated in the symptoms of schizophrenia (Greene 2001). Human controls who received a noncompetitive NMDA receptor antagonist, such as ketamine or phencyclidine, present with a schizophrenia-like phenotype that is indistinguishable from symptoms exhibited by schizophrenia patients (Krystal et al. 1994; Adler et al. 1999). Further, these drugs exacerbate symptoms in diagnosed patients (Malhotra 1997). Noncompetitive NMDA receptor antagonism in rats has demonstrated face validity as model of schizophrenia (Moghaddam and Krystal 2012). Specifically, impaired working memory performance has been observed as MK-801 administration in rodents reduced performance on the TUNL task (Kumar et al. 2015). Sodium nitroprusside (SNP) is a nitric oxide donor that is traditionally used to treat hypertensive crisis by rapidly inducing vasodilation (Hottinger et al. 2014). Recently, SNP has been investigated as an adjunct treatment to reduce symptom severity in schizophrenia. Intravenous administration of SNP to schizophrenia patients taking antipsychotics significantly reduced the positive, negative, and cognitive symptoms experienced (Hallak et al. 2013; Maia-de-Oliveira et al. 2015a). Of particular importance, patient performance on working memory and selective attention tasks improved 8 h after SNP administration (Maia-de-Oliveira et al. 2015a). Although cognitive changes were not examined in a subsequent follow-up, positive and negative symptoms were reduced up to 4 weeks following the single SNP infusion (Hallak et al. 2013). This suggests that SNP may alleviate schizophrenia symptoms over long-term periods and improve patient quality of life. Although the mechanisms underlying these changes are not fully understood, SNP has reduced the schizophrenia-like phenotype produced by noncompetitive NMDA receptor antagonism in rodent studies. In these studies, administration of SNP in conjunction with ketamine or phencyclidine attenuated locomotor behavior, social behavior, and novel object recognition abnormalities. These measurements are believed to be rodent analogs of the positive, negative, and cognitive symptoms of schizophrenia (Bujas-Bobanovic et al. 2000; Maia-de-Oliveira et al. 2015b; Trevlopoulou et al. 2016). This alleviation has been observed up to 1 week following SNP administration, further supporting its long-term efficacy (Maia-de-Oliveira et al. 2015b).

The primary aim of this study was to explore MK-801-induced working memory and pattern separation impairments in the TUNL task in order to further characterize its pharmacological validity as a rodent model of schizophrenia. As mentioned, the TUNL task possesses high translational potential, making it an ideal platform to study validity (Bussey et al. 2012). The secondary objective was to explore the therapeutic potential of SNP alone using the MK-801 model in the TUNL task. Adjunct treatment with SNP reduces working memory impairments in schizophrenia patients (Maia-de-Oliveira et al. 2015a), while SNP alone has rescued ketamine-induced impairments in rodent cognitive tasks (Kandratavicius et al. 2015; Maia-de-Oliveira et al. 2015b). Therefore, as a first step, we chose to administer SNP alone in an attempt to block the acute effects of MK-801 on the TUNL task.

Materials and methods

Subjects

Forty-three male Long Evans rats were trained on the TUNL task in two separate cohorts, referred to as squad 1 (n = 23; Charles River Laboratories, Quebec, Canada) and squad 2 (n = 20; Charles River Laboratories, NY, USA). All subjects were housed in clear, ventilated plastic cages and contained within a temperature-controlled vivarium. Animals were given in-cage enrichment consisting of a plastic tube and maintained on a 12:12-h light-dark cycle, with all experimental procedures performed during the light phase. Subjects were food restricted in order to maintain 85 % of their free-feeding weight. Water was available ad libitum, except during testing. All experiments were approved by the University of Saskatchewan Animal Research Ethics Board and were conducted in accordance with the standards of the Canadian Council on Animal Care.

Training apparatus

All experimental training and testing occurred within eight touchscreen-equipped operant conditioning chambers (Lafayette Instruments, Lafayette, IN, USA). Each chamber was trapezoidal in shape, with the face of the wide edge comprised of a touchscreen (Fig. 1). The touchscreen was covered by a black polycarbonate mask with 14 small squares (2 cm × 2 cm) arranged in a 7 × 2 pattern. The lower part of the mask was covered by a spring-loaded "response shelf" that rats must use to touch the exposed touchscreen. On the opposite end of the chamber was a food magazine that dispensed odorless reward pellets (Dustless Precision Pellets, 45 mg, Rodent Purified Diet; BioServ, Frenchtown, NJ). The food magazine also contained a reward light and an infrared nosepoke detector. The floor of the chamber was composed of metal mesh, and the roof was a plastic lid. Each chamber was located on a sliding shelf at the base of a sound-

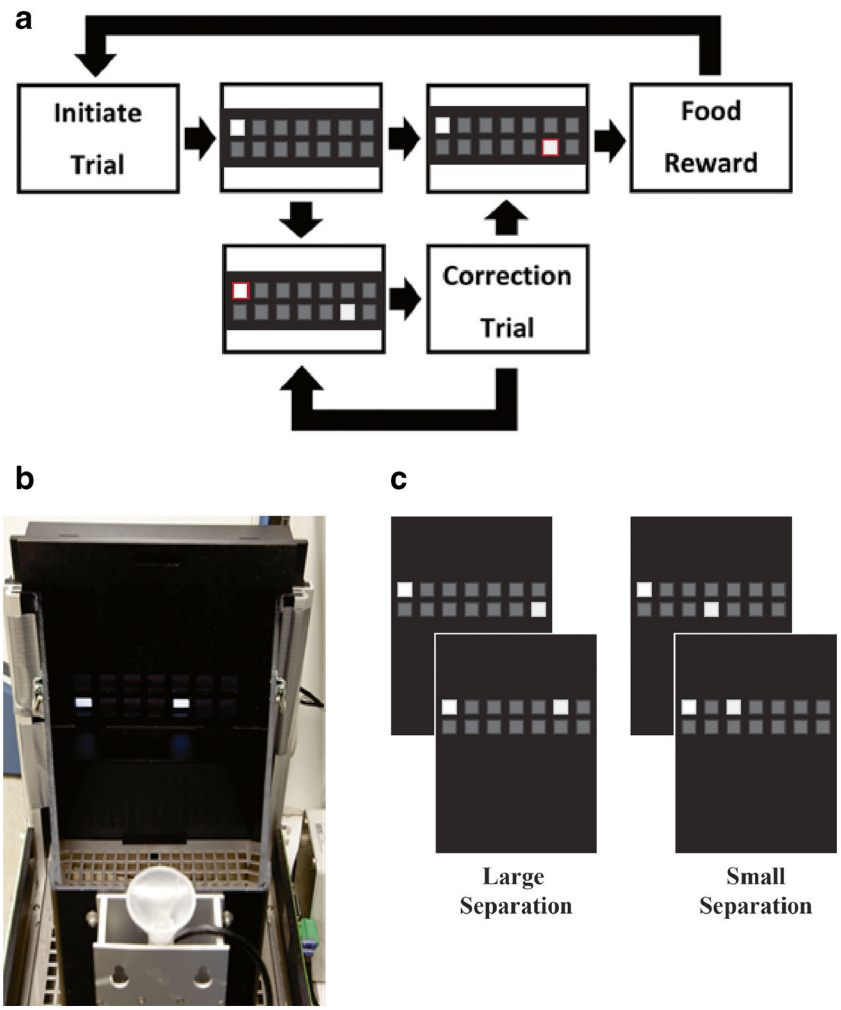

Fig. 1 Touchscreen-equipped operant conditioning chamber and task schematic. **a** Flow chart depicting TUNL trial procedure and outcome. Each trial began when a rat poked its nose into the reward magazine and initiated the sample phase where 1 of 14 squares was lit. Once the lit square was touched, the stimulus was removed from the screen and a 2-s delay began. In 33 % of trials, a reward pellet was dispensed in order to maintain motivation. Following the delay, a rat was required to poke its nose into the reward magazine to start the choice phase. During this phase, the sample square and a novel square were illuminated simultaneously. A correct response was made when a rat nonmatched to the sample square and touched the novel square. Correct responses were rewarded with reward pellet and followed by a 20-s ITI. A new "selection trial" began at the end of the ITI, with different stimuli from the previous trial. If an incorrect response was made, with the rat selecting the sample square, the house light turned on for 5 s and no reward was dispensed. This timeout was followed by a 20-s ITI, and the proceeding trial was identical to the previous one. Trials that repeat the most recent selection trial were termed "correction trials" and were presented until the correct response was made. **b** Photograph of the touchscreen apparatus and stimuli presentation corresponding to the choice phase of the task. **c** Samples of the two categories of pattern separations (large and small)

attenuating wooden box. Boxes contained a pellet dispenser, video camera, small ventilation fan, and a house light that was activated following incorrect responses.

Handling and habituation

Rats were undisturbed in the vivarium for a minimum of 5 days following their arrival. Rats were individually handled for 3 consecutive days and familiarized with the route of transportation from the vivarium to the touchscreen room. Rats were habituated following handling. On the first day of habituation, rats were left in the touchscreen room for 1 h with all technology turned on (2 computers and 8 chambers). Ten reward pellets were placed in each home cage to familiarize them with the food reward. On subsequent test days, rats were left undisturbed in the touchscreen room for 15 min prior to being placed in the chambers. Rats were run in groups of 8, and an effort was made to consistently put rats into the same chamber throughout training and testing. During the second and third days of habituation, rats were placed into the chambers with no stimuli present for 30 min with 10 pellets in the food reward port. All behaviors were recorded and an external monitor presented a live video feed of each rat's activity.

TUNL pretraining

The pretraining protocol followed a modified version of the instructions and software provided by Lafayette, and each phase was repeated until a specified criterion was reached. TUNL pretraining involved 4 stages: Initial Touch, Must Touch, Must Initiate, and Punish Incorrect. Initial Touch Training introduced the relationship between touchscreen stimuli and food reward. During each trial, 1 of 14 squares was illuminated. If a rat touched the illuminated square, 3 reward pellets were immediately dispensed. If the square was not touched after 30 s, the stimulus was removed and a single reward pellet was dispensed. A 20 s intertrial interval (ITI) separated sequential trials. Must Touch Training was similar to Initial Touch Training, but the square remained illuminated until it was touched by a rat, dispensing a single reward pellet. The subsequent Must Initiate Training required a rat to poke its nose in the food magazine to initiate trials identical to those in Must Touch Training. Criterion for completion of these 3 phases was 100 trials in 60 min. The final pretraining stage was Punish Incorrect Training, which built upon Must Touch Training in that if the rat touched an unilluminated square, a timeout began. During a timeout, no reward pellet was dispensed and the house light turned on for 5 s followed by an ITI. The previous trial was then repeated until the rat correctly selected the stimulus; these repeated trials were termed "correction trials." Criterion was the completion of 100 trials within 60 min with >80 % accuracy on two consecutive days.

TUNL task acquisition

Once a rat completed pretraining, it immediately began learning the standard TUNL task (Fig. 1). In brief, during a sample phase, 1 of 14 squares was illuminated. Once this square was touched by a rat, the stimulus was removed and a delay began. Following the delay, the sample square and a novel square were illuminated simultaneously. In order to receive a food reward and initiate the ITI, the novel square had to be touched. A new "selection trial" began following the ITI with stimuli different from the previous trial. If the rat incorrectly selected the sample square, a "correction trial" was presented. Correction trials repeated the stimuli of the incorrectly completed selection trial and were presented until a correct response was made. During a single TUNL session, rats were exposed to a variety of pattern separations in a randomized fashion, with stimuli ranging from 2 to 6 squares apart. During training, 2 s delays were used and accuracy was determined by the percent of correct responses made during selection trials. Rats were initially trained to complete 40 trials with >75 % correct in 35 min. Following this, the second criterion required 70 trials with >75 % correct in 60 min. Rats treated with SNP and MK-801 received additional training that included 2 and 6 s delays with criterion set at 75 % accuracy during a session over two consecutive days. Each session contained both delay lengths, which were presented in a pseudo-randomized order such that a single delay was not presented for more than three consecutive trials. Once the last criterion was met, rats were left undisturbed in the vivarium while the remaining rats were trained to criterion. Rats were given reminder training sessions once a week to maintain performance until testing began (Oomen et al. 2013). Once all rats completed training, they were reintroduced to daily testing for at least 3 days to collect baseline measurements prior to drug treatment. Animals that failed to reach criterion were not used for subsequent testing.

Drug treatments

The order of treatments was counterbalanced using a within-subjects design. Rats receiving MK-801 and SNP were quasi-randomly assigned such that MK-801 was not administered on 2 consecutive treatment days. Doses chosen for dose-response curve data were given in ascending order with the initial treatment counterbalanced across rats. MK-801 (Abcam, Cambridge, MA) and SNP (Sigma-Aldrich, St. Louis, MO) were dissolved in saline, and drugs were protected from light to prevent photodecomposition (Bisset et al. 1981). MK-801 and SNP doses were determined using existing literature and previously published touchscreen data collected within our lab (Gourgiotis et al. 2012; Kandratavicius et al. 2015; Maia-de-Oliveira et al. 2015b; Kumar et al. 2015; Lins et al. 2015; Lins and Howland 2016). Dose-response curve data were collected following administration (1.0 mL/kg; i.p.) of MK-801, SNP, or saline 25 min prior to TUNL task initiation. Treatment-free days were allowed between treatments, and baseline performance measurements were collected prior to each treatment day to ensure a sufficient washout period. Five rats (1 from squad 1 and 4 from squad 2) did not reach criterion or receive treatment. Rats trained in squad 1 were used for the MK-801 dose-response curve (n = 10; 0.05, 0.075, and 0.1 mg/kg), SNP dose-response curve (n = 10; 0.5, 1.0, 2.0, and 4.0 mg/kg), and the reversal experiment (n = 12; rats treated with SNP (2.0 mg/kg) 5 min prior to MK-801 administration (0.1 mg/kg)). MK-801 and SNP doses were chosen based on the collected dose-response curve performance data. The 0.1 mg/kg dose of MK-801 was used because it produced the most robust impairment in TUNL task without increasing latency. The 2.0 mg/kg dose of SNP was the highest tested dose that did not impair TUNL performance or dramatically increase latency. Due to the extensive training required to learn the task, squad 1 animals were used in the collection of data for multiple experiments within this study. The breakdown of squad 1 animals (n = 22) was as follows: SNP dose-response curve only (n = 7), reversal only (n = 5), SNP and MK-801 dose-response curves (n = 3), and MK-801 dose-response curve and reversal (n = 7). Squad 2 rats (n = 16) were used to test the preventative effect of SNP, as a previous study examined the potential of SNP to prevent the cognitive impairments observed in an NMDA dysfunction model of schizophrenia (Maia-de-Oliveira et al.

2015b). Therefore, we tested whether earlier pretreatment with SNP would enable it to block the effects of MK-801 on the TUNL task. To maximize the chances of observing an effect, we chose the lowest dose of MK-801 (0.05 mg/kg) from the dose-response curve that impaired performance of TUNL. Kumar et al. (2015) also noted that this dose impaired TUNL. SNP was administered 3 h and 35 min prior to MK-801 (0.05 mg/kg) or saline and 4 h prior to TUNL task initiation. Given this longer delay, we used a higher dose of SNP (5.0 mg/kg) that has been used previously to prevent behavioral effects in models of NMDA receptor hypofunction (Bujas-Bobanovic et al. 2000; Kandratavicius et al. 2015).

Statistical analysis

The fully automated nature of the touchscreen procedure eliminates the potential for researcher bias. All graphs present the data as group means plus the standard error of the mean (SEM). The dependent measures analyzed include overall accuracy (% correct on selection trials), accuracy on 2 s delay trials, accuracy on 6 s delay trials, accuracy on large separation trials (Fig. 1c; minimum of 4 unilluminated squares between sample and choice stimuli), accuracy on small separation trials (Fig. 1c; 1 or 2 unilluminated squares between stimuli), number of selection trials completed, number of correction trials completed, number of total trials completed (selection trials plus correction trials), mean reward collection latency, mean correct response latency, and mean incorrect latency. Statistics were calculated using Statistical Package for the Social Sciences (SPSS) version 21. MK-801 and SNP dose-response data were analyzed using a one-way repeated measures ANOVA. Post hoc analysis was performed with simple contrast tests, making comparisons only to saline. Two-way repeated measures ANOVA were used to analyze all other datasets (MK-801 + SNP). One rat failed to complete any trials when treated with 4.0 mg/kg of SNP and was removed from dose-response curve analysis and further testing. Therefore, performance of 9 rats was included in SNP dose-response curve analysis. Sphericity violations, as indicated by Mauchly's test, were corrected using Greenhouse-Geisser corrections. Partial η^2 was calculated as a measure of effect size and represents the total variability in each dependent variable that can be attributed to the intervention. Partial η^2 values of 0.01, 0.06, and 0.14 are considered small, medium, and large effect sizes respectively.

Results

MK-801 impaired TUNL performance in a dose-dependent manner

MK-801 (0.05, 0.075, and 0.1 mg/kg) or saline was administered 25 min prior to TUNL testing. Overall accuracy was altered following MK-801 treatment (Fig. 2a; $F(3,27) = 4.28$, $p = 0.014$, partial $\eta^2 = 0.322$) with post hoc analysis identifying reduced performance following 0.1 mg/kg of MK-801 compared to saline treatment. MK-801 impaired performance on large distance trials (Fig. 2b; $F(3,27) = 3.83$, $p = 0.021$, partial $\eta^2 = 0.299$). Although MK-801 impaired accuracy on small distance trials, the effect was not significant (Fig. 2b; $p = 0.058$, partial $\eta^2 = 0.239$). The number of selection trials completed was unaffected by MK-801 (Fig. 2c; $p > 0.05$), but a main effect was observed for correction trials (Fig. 2d; $F(3,27) = 4.13$, $p = 0.016$, partial $\eta^2 = 0.315$) and total trials (Fig. 2e; $F(3,27) = 3.39$, $p = 0.032$, partial $\eta^2 = 0.274$). Post hoc analysis revealed significant increases in correction and total trials completed following 0.05 and 0.1 mg/kg of MK-801 compared to saline treatments. Reward latency was altered following MK-801 treatment (Fig. 2f; $F(3,27) = 6.59$, $p = 0.002$, partial $\eta^2 = 0.423$), with post hoc analysis revealing all MK-801 treatments reduced latency compared to saline. The time to make a correct selection did not vary among the treatments (Fig. 2f; $p > 0.05$). MK-801 reduced incorrect latency (Fig. 2f; $F(3,27) = 3.98$, $p = 0.018$, partial $\eta^2 = 0.307$), with rats treated with 0.05 and 0.1 mg/kg of MK-801 being significantly faster than saline-treated rats.

SNP impaired performance on the TUNL task in a dose-dependent manner

SNP (0.5, 1.0, 2.0, and 4.0 mg/kg) or saline were administered 25 min prior to TUNL task initiation. SNP impaired performance on overall accuracy (Fig. 3a; $F(2.10, 16.81) = 6.64$, $p = 0.007$, partial $\eta^2 = 0.454$), with post hoc analysis revealing a significant difference between saline and 4.0 mg/kg of SNP. SNP did not alter accuracy on large separation trials (Fig. 3b; $p > 0.05$), while there was a main effect of SNP on small separation trial accuracy (Fig. 3b; $F(4,31) = 4.67$, $p = 0.004$, partial $\eta^2 = 0.368$) such that 4.0 mg/kg of SNP treatment impaired performance compared to saline treatment. SNP reduced the number of selection trials completed (Fig. 3c; $F(1.10, 8.81) = 15.98$, $p = 0.003$, partial $\eta^2 = 0.666$), with fewer trials completed following 4.0 mg/kg of SNP (post hoc, $p < 0.05$). No significant effect of SNP was observed for correction trials (Fig. 3d; $p > 0.05$). SNP significantly affected the number of total trials completed (Fig. 3e; $F(1.28, 10.22) = 12.33$, $p = 0.004$, partial $\eta^2 = 0.606$). Subsequent post hoc analysis revealed significantly fewer total trials were completed after 4.0 mg/kg of SNP compared to saline treatment. A main effect of SNP on reward latency (Fig. 3f; $F(1.90, 15.27) = 10.38$, $p = 0.002$, partial $\eta^2 = 0.565$) and correct latency (Fig. 3f; $F(2.06, 23.06) = 5.56$, $p = 0.014$, partial $\eta^2 = 0.410$) was confirmed with a difference between saline and treatment with 2.0 or 4.0 mg/kg of SNP on both. SNP also increased incorrect

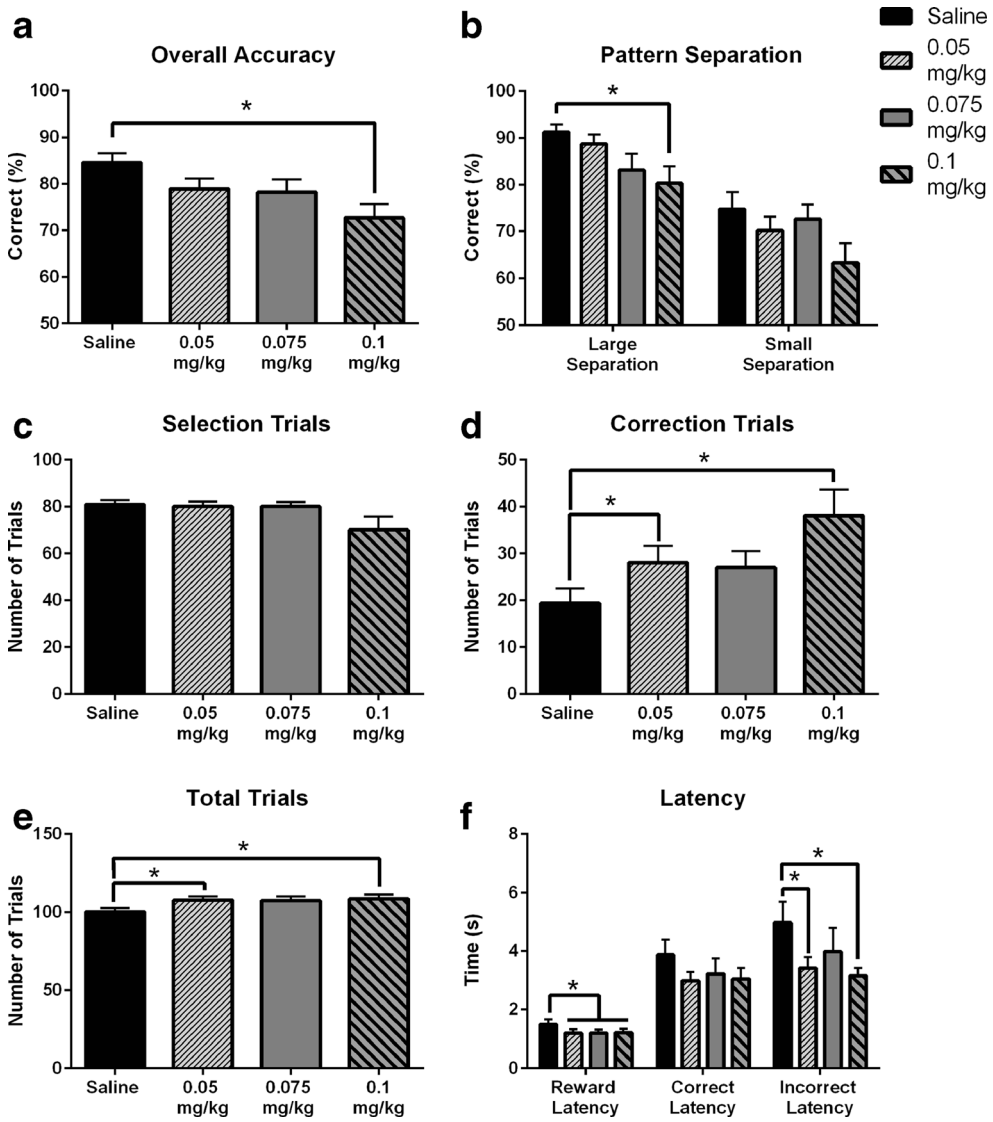

Fig. 2 Effects of MK-801 (0.05, 0.075, and 0.1 mg/kg) on TUNL. **a** Accuracy as measured by the percentage of selection trials correctly completed. **b** Accuracy broken down according to the difficulty of pattern separation. Separate repeated measures ANOVAs were completed for each pattern. **c** Number of unique trials completed by the rats. **d** Number of correction trials completed by rats. **e** Sum of selection and correction trials completed by the rats. **f** Response latencies for reward collection, correct trials, and incorrect trials. Separate ANOVAs were used for each latency. *$p < 0.05$ between groups as indicated

latency (Fig. 3f; $F(2.03, 16.22) = 4.10$, $p = 0.036$, partial $\eta^2 = 0.339$) with a significant difference between saline and 4 mg/kg SNP treatments.

SNP improved pattern separation but failed to alleviate MK-801 impairments on the TUNL task

SNP (2.0 mg/kg) or saline was administered 5 min prior to MK-801 (0.1 mg/kg) or saline to observe whether SNP would rescue TUNL performance. A 2 (MK-801, saline) by 2 (SNP, saline) repeated measures ANOVA revealed no significant interactions between MK-801 and SNP treatment on any of the variables (statistics not shown). There was a main effect of MK-801 ($F(1,11) = 15.63$, $p = 0.002$, partial $\eta^2 = 0.587$) but not SNP ($p > 0.05$) on overall accuracy (Fig. 4a). Trials were further divided according to delay (2 and 6 s) or separation (large, small). MK-801 impaired trials that contained a 2-s delay (Fig. 4c; $F(1,11) = 7.21$, $p = 0.021$, partial $\eta^2 = 0.396$), 6-s delay (Fig. 4c; $F(1,11) = 14.36$, $p = 0.003$, partial $\eta^2 = 0.566$), or large separation (Fig. 4b; $F(1,11) = 26.83$, $p < 0.001$, partial $\eta^2 = 0.709$), while SNP did not affect these variables ($p > 0.05$). In contrast, SNP trended toward improving performance during small separation trials (Fig. 4b; $p = 0.058$, partial $\eta^2 = 0.288$), while MK-801 had no effect ($p > 0.05$). MK-801 significantly reduced the number of selection trials completed by the rats (Fig. 4e; $F(1,11) = 11.47$, $p = 0.006$, partial $\eta^2 = 0.510$). Furthermore, MK-801 increased the number of completed correction trials (Fig. 4f; $F(1,11) = 23.00$, $p = 0.001$, partial $\eta^2 = 0.676$) and total trials (Fig. 4g; $F(1,11) = 12.84$, $p = 0.004$, partial $\eta^2 = 0.539$). SNP did not alter the number of selection trials, correction trials, or total trials completed (Fig. 4e–g; $p > 0.05$). Analysis of latencies showed that MK-801 decreased reward (Fig. 4h; $F(1,11) = 9.73$, $p = 0.010$, partial $\eta^2 = 0.469$), correct (Fig. 4h; $F(1,11) = 14.41$, $p = 0.003$, partial $\eta^2 = 0.567$), and incorrect latencies (Fig. 4h; $F(1,11) = 9.67$, $p = 0.010$, partial

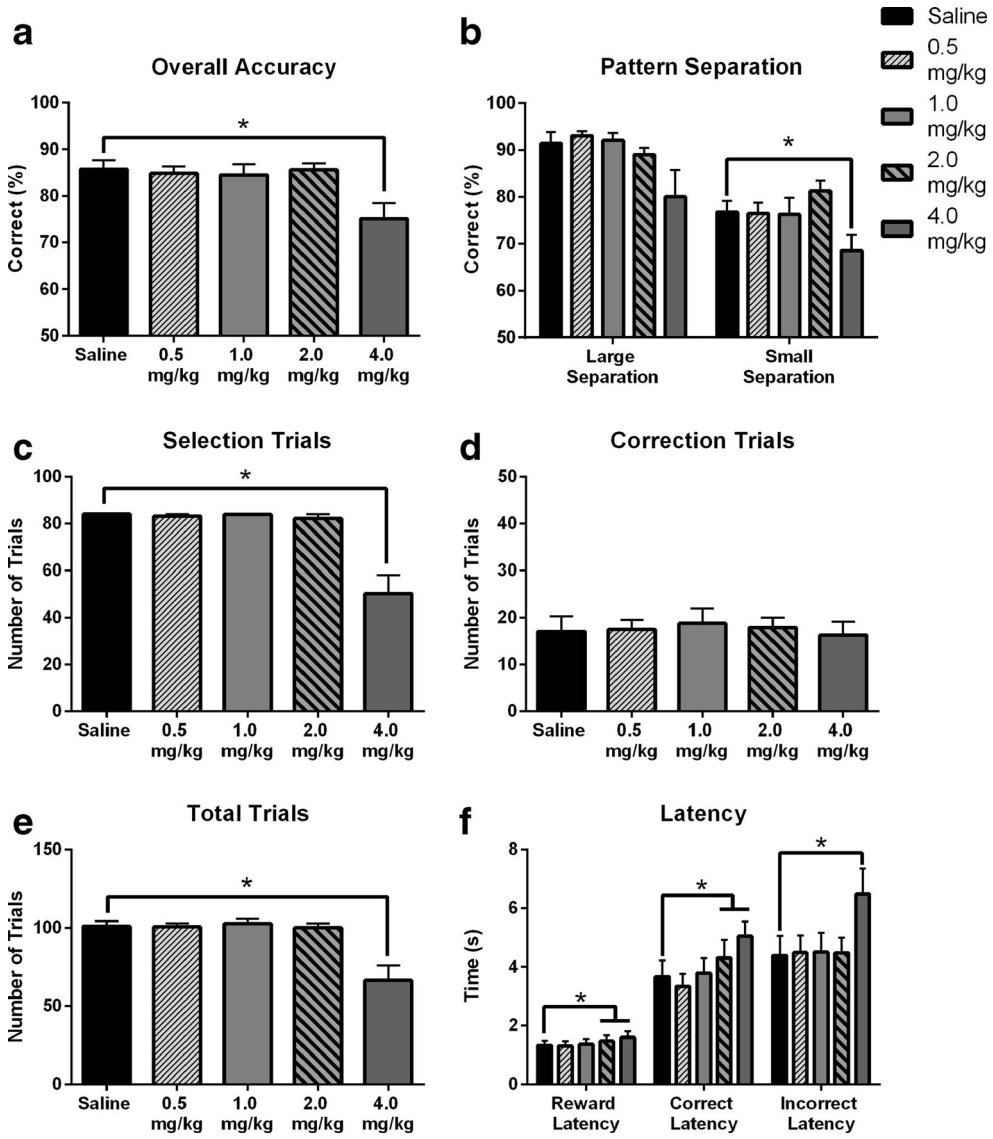

Fig. 3 Effects of SNP (0.5, 1.0, 2.0, and 4.0 mg/kg) on TUNL. **a** Accuracy as measured by the percentage of selection trials correctly completed. **b** Accuracy broken down according to the difficulty of pattern separation. Separate repeated measures ANOVAs were completed for each pattern. **c** Number of unique trials completed by the rats. **d** Number of correction trials completed by rats. **e** Sum of novel and correction trials completed by the rats. **f** Response latencies for reward collection, correct trials, and incorrect trials. Separate ANOVAs were used for each latency. *$p < 0.05$ between groups as indicated

$\eta^2 = 0.468$). In contrast, SNP increased reward (Fig. 4h; $F(1,11) = 35.35$, $p < 0.001$, partial $\eta^2 = 0.763$) and incorrect latencies (Fig. 4h; $F(1,11) = 6.94$, $p = 0.023$, partial $\eta^2 = 0.387$) but did not influence correct latency (Fig. 4h; $p > 0.05$).

To further investigate the effects of SNP on the TUNL task, trials were categorized into four groups based on their delay and separation. MK-801 significantly impaired performance at the 6 s delay regardless of whether the separation was large (Fig. 4d; $F(1,11) = 18.64$, $p = 0.001$, partial $\eta^2 = 0.629$) or small (Fig. 4d; $F(1,11) = 5.93$, $p = 0.033$, partial $\eta^2 = 0.350$). MK-801 also reduced accuracy on 2 s delay and large separation (Fig. 4d; $F(1,11) = 10.60$, $p = 0.008$, partial $\eta^2 = 0.491$) but not 2 s delay and small separation trials ($p > 0.05$). In contrast, SNP did not affect trials with a 2 s delay and large separation, 6 s delay and large separation, or 6 s delay and small separation but facilitated performance on trials with a 2 s delay and small separation (Fig. 4d; $F(1,11) = 7.79$, $p = 0.018$, partial $\eta^2 = 0.414$).

SNP does not prevent MK-801-induced impairments in the TUNL task

In this experiment, SNP (5.0 mg/kg) was administered 3 h and 35 min prior to MK-801 (0.05 mg/kg) or saline and 4 h prior to TUNL task initiation. No interactions were significant following a 2 (MK-801, saline) by 2 (SNP, saline) repeated measures ANOVA (statistics not shown). MK-801 reduced overall accuracy on the TUNL task (Fig. 5a; $F(1,15) = 10.14$, $p = 0.006$, partial $\eta^2 = 0.404$). After grouping trials according to separation, MK-801 was noted to impair performance on small (Fig. 5b; $F(1,15) = 8.38$, $p = 0.011$, partial $\eta^2 = 0.359$) but not large separation trials (Fig. 5b; $p = 0.061$, partial

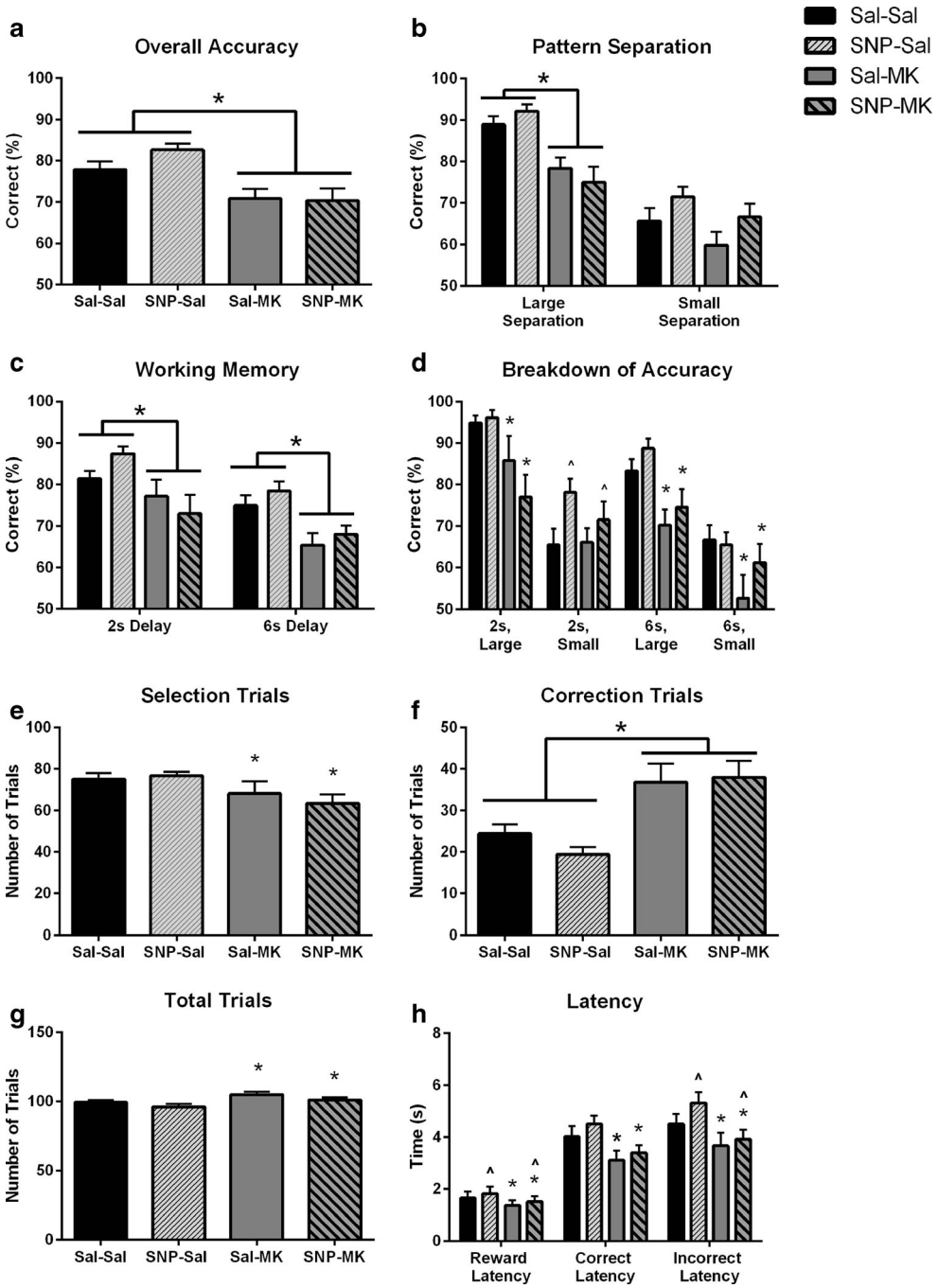

Fig. 4 Effects of SNP (2.0 mg/kg) and MK-801 (0.1 mg/kg) on TUNL. **a** MK-801 significantly reduced accuracy, while SNP had no effect. **b** MK-801 reduced accuracy when the stimuli had a large separation and had no effect when they were closer together. SNP did not alter performance for large separations but facilitated performance for small separation trials ($p = 0.058$). **c** MK-801 reduced the number of correct responses at the 2 and 6 s delay, while SNP had no effect. **d** Trials were broken down according to separation and delay. MK-801 impaired performance on 2 s delay and large separation, 6 s delay and large separation, and 6 s delay and small separation trials. SNP significantly improved performance on trials with a 2 s delay and small separation. **e** MK-801 reduced selection trials completed while SNP had no effect. MK-801 increased the number of correction (**f**) and total (**g**) trials completed while SNP did not change the number of completed trials. **h** MK-801 reduced reward, correct, and incorrect latencies while SNP increased reward latency and incorrect latency but did not affect correct latency in this sample. *Significant effect of MK-801 ($p < 0.05$). ^Significant effect of SNP ($p < 0.05$)

$\eta^2 = 0.215$). Impaired performance was observed whether the delay was 2 s (Fig. 5c; $F(1,15) = 7.75$, $p = 0.014$, partial $\eta^2 = 0.341$) or 6 s (Fig. 5c; $F(1,15) = 5.52$, $p = 0.038$, partial $\eta^2 = 0.256$). SNP did not influence performance on accuracy, pattern separation, or working memory (Fig. 5a–c; $p > 0.05$). Neither SNP nor MK-801 influenced the number of selection trials completed (Fig. 5d; $p > 0.05$). However, MK-801 increased the number of correction trials (Fig. 5e; $F(1,15) = 18.38$, $p < 0.001$, partial $\eta^2 = 0.551$) and total trials (Fig. 5f; $F(1,15) = 40.65$, $p < 0.001$, partial $\eta^2 = 0.730$). There was no main effect of SNP on total trials (Fig. 5f; $p > 0.05$), but the completion of fewer correction trials trended toward significance (Fig. 5e; $p = 0.063$, partial $\eta^2 = 0.212$). MK-801 significantly reduced reward (Fig. 5g; $F(1,15) = 18.35$, $p < 0.001$, partial $\eta^2 = 0.550$), correct (Fig. 5g; $F(1,15) = 26.78$, $p < 0.001$, partial $\eta^2 = 0.641$), and incorrect latencies (Fig. 5g; $F(1,15) = 38.31$, $p < 0.001$, partial $\eta^2 = 0.719$). SNP did not influence reward or correct latencies (Fig. 5g; $p > 0.05$) but significantly increased incorrect latency (Fig. 5g; $F(1,15) = 8.70$, $p = 0.010$, partial $\eta^2 = 0.367$).

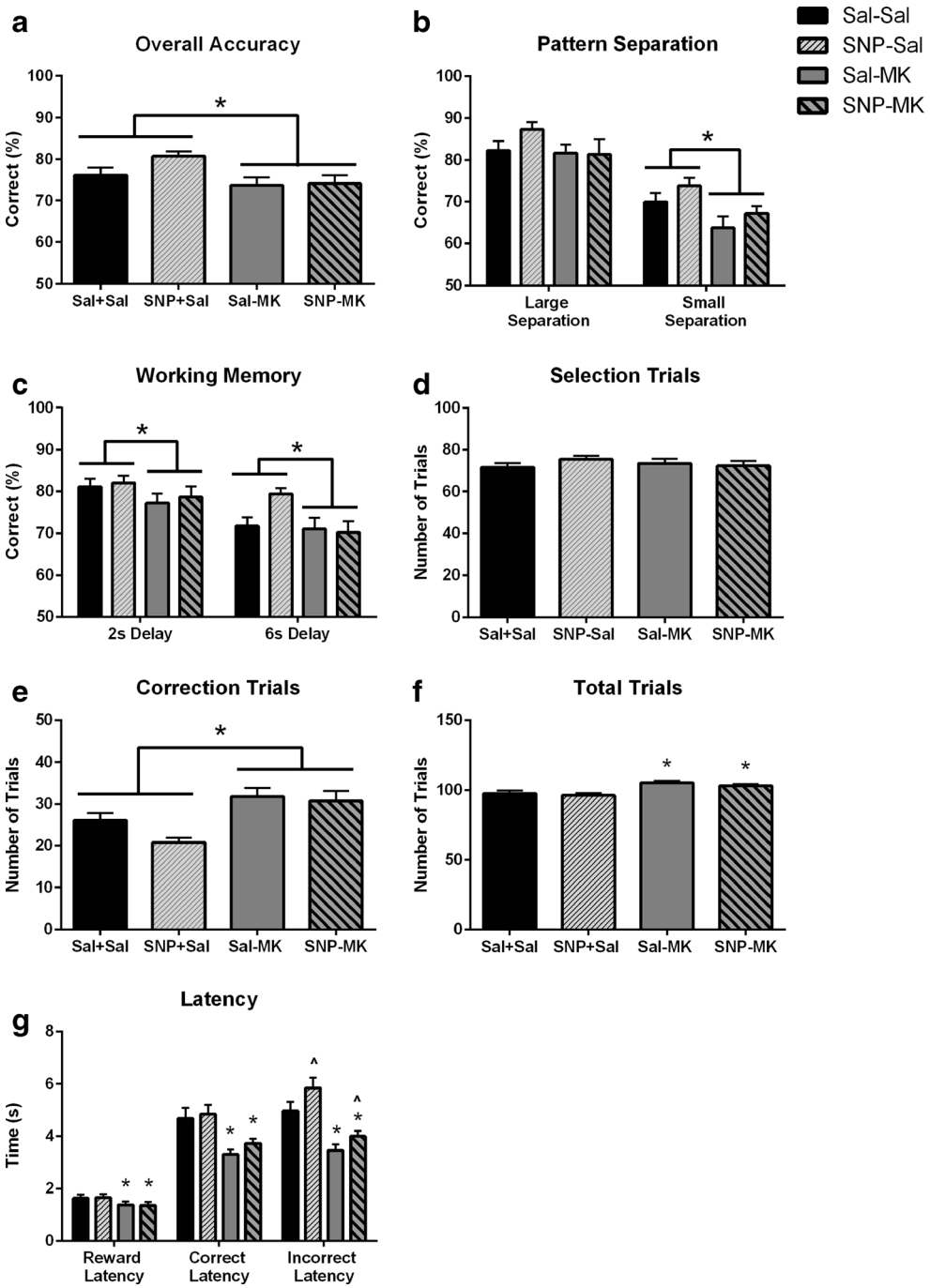

Fig. 5 Effects of SNP (5.0 mg/kg) when administered prior to MK-801 (0.05 mg/kg) on TUNL. **a** MK-801 significantly reduced overall accuracy across all selection trials but SNP had no effect. **b** MK-801 impaired performance on small separation trials but did not influence performance on large separation trials. SNP did not affect performance regardless of pattern separation. **c** MK-801 impaired performance on both delays but SNP had no effect. **d** Drug treatment did not affect the number of selection trials completed. MK-801, but not SNP, increased the number of correction (**e**) and total (**f**) trials completed. **g** MK-801 reduced reward, correct, and incorrect latencies while SNP only affected incorrect latency by increasing it. *Significant effect of MK-801 ($p < 0.05$). ^Significant effect of SNP ($p < 0.05$)

Discussion

The cognitive symptoms of schizophrenia are not consistently alleviated by conventional antipsychotics (Marder and Fenton 2004). Recently, SNP has demonstrated promise as an adjunct treatment to reduce these symptoms (Maia-de-Oliveira et al. 2015a). In the present experiments, we examined the effects of SNP on the acute MK-801-induced disruption of the TUNL task. MK-801 impaired TUNL performance by reducing accuracy and increasing the number of correction trials completed. SNP did not attenuate or prevent the effects of MK-801 but, interestingly, it improved accuracy on trials with small pattern separations when administered alone.

MK-801-induced disruption of TUNL

NMDA receptor dysfunction likely contributes to the symptoms of schizophrenia (Adell et al. 2012; Coyle 2012). Acute MK-801 treatment in rodents has face validity as a model of schizophrenia as its administration produces behavioral

changes similar to those observed in the disorder (Nestler and Hyman 2010). To date, only one study has assessed the effects of acute MK-801 (0.05 mg/kg) in TUNL, evaluating working memory performance using 1 and 20 s delays (Kumar et al. 2015). In the present study, delays with less variability (2 and 6 s) were used in order to detect subtle changes in working memory performance. We observed that, regardless of delay, MK-801 (0.05 and 0.1 mg/kg) reduced overall accuracy compared to saline. This suggests that the TUNL task is vulnerable to NMDA receptor antagonism regardless of working memory demand. Similar to these delay-independent impairments, patients with schizophrenia demonstrate working memory deficits whereby the degree of impairment is not affected with delays greater than 1 s (Lee and Park 2005). In Kumar et al. (2015), TUNL task accuracy following a 20 s delay was only examined using large pattern separations. In contrast, the present study included large and small separations during both delays. Overall, we observed that MK-801 (0.05 mg/kg) reduced performance on large and small separation trials. Surprisingly, trials with a 2 s delay and small pattern separation were not impaired following MK-801 in the first experiment (Fig. 4d), which may be a result of variability between animals. The present study is the first to analyze the effects of MK-801 on correction trials. Previous studies utilizing touchscreen tasks in rodents suggest correction trials are a measure of perseveration (Lins et al. 2015; Lins and Howland 2016), a behavior frequently observed in schizophrenia (Szoke et al. 2008; Ortuño et al. 2009). We observed MK-801 treatment increased the number of correction trials, suggesting it hindered the ability of rats to inhibit incorrect response selection. These findings are consistent with MK-801-induced perseveration and decreased inhibition in other rodent behavioral paradigms (Cohn et al. 1992; Tuplin et al. 2015; Lins et al. 2015).

It has been previously reported that MK-801 (0.075 mg/kg) increases reward and correct latencies on the TUNL task (Kumar et al. 2015). However, MK-801 (0.05 and 0.1 mg/kg) reduced reward, correct, and incorrect latencies in our studies. Reduced latency may be indicative of increased impulsive behavior following acute MK-801 treatment. It is unlikely that the observed MK-801-induced impairments were a consequence of impeded physical abilities as the total number of correction trials was increased. It is important to note that MK-801 does not impair visual perception at doses similar to those used here (Talpos et al. 2012); thus, it is unlikely that performance deterioration was a consequence of perceptual changes. However, future studies assessing performance of TUNL using a 0-s delay condition or following withdrawal from a subchronic treatment regime of ketamine or MK-801 would alleviate concerns regarding the short-lasting effects of acute MK-801 administration. The present experiment suggests acute MK-801 administration in rodents is capable of reducing the ability to resolve spatial patterns, maintain information across a delay, and may increase perseverative behavior as well as impulsivity. These behavioral impairments are similar to those that are expected in patients with schizophrenia, providing additional support for the face validity of MK-801 model of schizophrenia (Mesholam-Gately et al. 2009; Das et al. 2014; but see also Martinelli and Shergill, 2015).

SNP did not block MK-801-induced impairments but improved pattern separation

No available antipsychotics consistently alleviate the cognitive symptoms of schizophrenia. The lack of a positive control has limited the assessment of predictive validity in rodent models of schizophrenia, impeding the translatable development and evaluation of treatments for these symptoms (Markou et al. 2009). However, when SNP was administered as an adjunct treatment to patients with schizophrenia, working memory impairments on the n-back task were reduced (Maia-de-Oliveira et al. 2015a). Ketamine-induced cognitive deficits have been reduced by SNP in rodent studies (Trevlopoulou et al. 2016). In the present study, SNP neither rescued (Fig. 3) nor prevented (Fig. 4) MK-801-induced impairments in the TUNL task. The inability of SNP to reduce MK-801-induced impairments is inconsistent with previous reports of reduced cognitive impairments in ketamine-treated rats following SNP (Trevlopoulou et al. 2016). Like other rodent studies, our procedure did not test the effect of adjunct treatment with SNP. As adjunct treatment was used in the clinical studies, the assessment of predictive validity is limited with our design (Maia-de-Oliveira et al. 2015a). Future rodent experiments should administer SNP with antipsychotics and over a more varied time frame.

To the best of our knowledge, this is the first study to explore the effect of SNP on pattern separation and perseverative behaviors. When SNP (2.0 mg/kg) was administered 30 min prior to TUNL task initiation, accuracy on small separation trials increased. Although the p value failed to meet the threshold for significance ($p = 0.058$), the large effect size ($\eta = 0.288$) suggests the lack of significance may be a result of a small sample size. When small separation trials accounted for delay, facilitated pattern separation appeared to be driven by significantly improved performance during 2-s delays and small separation trials. Large separation trials were unaffected by SNP, perhaps due to a ceiling effect. In our experiment, saline-treated rats performed with 89 % accuracy on large separation trials. This level of performance is unmatched in previous reports (Talpos et al. 2010; McAllister et al. 2013; Oomen et al. 2013; Kumar et al. 2015; Svensson et al. 2015). Interestingly, the administration of SNP 4 h prior to the TUNL task trended toward reducing the number of correction trials ($p = 0.063$, $\eta = 0.212$), suggesting that SNP may reduce perseverative behaviors (Lins et al. 2015; Lins and Howland 2016). Taken together, this study is the first to demonstrate SNP may have intrinsic properties that facilitate pattern separation and reduce perseveration. The mechanisms underlying

SNP's antipsychotic and cognitive properties are poorly understood but may include its role in the mediation of tissue plasminogen factor (Hoirisch-Clapauch and Nardi 2015), involvement in the guanylyl cyclase signaling pathway (Gattaz et al. 1983; Friederich and Butterworth 1995), and/or modulation of the dopamine system (Maia-de-Oliveira et al. 2014). Further, c-fos expression resulting from phencyclidine is reduced by SNP treatment in a variety of cortical regions, including the frontal cortex (Bujas-Bobanovic et al. 2000). Future research should explore the effects of SNP on perseveration and pattern separation as well as determine the mechanism underlying SNP's cognitive properties.

Conclusion

The results of this study indicate that acute MK-801 administration impairs performance on the TUNL task. Treatment with SNP did not reduce MK-801-induced accuracy impairments, which is inconsistent with previous studies testing the ketamine-induced impairment of other cognitive tasks. SNP trended toward improving pattern separation and reducing perseveration but future research is required to support this assertion.

Acknowledgments This research was supported by an operating grant from the Canadian Institutes for Health Research (CIHR; #125984) and a Discovery Grant from the Natural Sciences and Engineering Research Council of Canada (NSERC). JGH is a CIHR New Investigator. JLH and WNM received salary support from the College of Medicine at the University of Saskatchewan. GBB received salary support and grant funding from the University of Alberta.

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

References

Adell A, Jimenez-Sanchez L, Lopez-Gil X, Romon T (2012) Is the acute NMDA receptor hypofunction a valid model of schizophrenia? Schizophr Bull 38:9–14. doi:10.1093/schbul/sbr133

Adler CM, Malhotra AK, Elman I et al (1999) Comparison of ketamine-induced thought disorder in healthy volunteers and thought disorder in schizophrenia. Am J Psychiatry 156:1646–1649. doi:10.1176/ajp.156.10.1646

Aquila R, Citrome L (2015) Cognitive impairment in schizophrenia: the great unmet need. CNS Spectr 20:32–40. doi:10.1017/S109285291500070X

Bhagyavathi HD, Mehta UM, Thirthalli J et al (2015) Cascading and combined effects of cognitive deficits and residual symptoms on functional outcome in schizophrenia—a path-analytical approach. Psychiatry Res 229:264–271. doi:10.1016/j.psychres.2015.07.022

Bisset WI, Butler AR, Glidewell C, Reglinski J (1981) Sodium nitroprusside and cyanide release: reasons for re-appraisal. Br J Anaesth 53:1015–1018

Bozikas VP, Kosmidis MH, Kioperlidou K, Karavatos A (2004) Relationship between psychopathology and cognitive functioning in schizophrenia. Compr Psychiatry 45:392–400. doi:10.1016/j.comppsych.2004.03.006

Bujas-Bobanovic M, Bird DC, Robertson HA, Dursun SM (2000) Blockade of phencyclidine-induced effects by a nitric oxide donor. Br J Pharmacol 130:1005–1012. doi:10.1038/sj.bjp.0703406

Bussey TJ, Holmes A, Lyon L et al (2012) New translational assays for preclinical modelling of cognition in schizophrenia: the touchscreen testing method for mice and rats. Neuropharmacology 62:1191–1203. doi:10.1016/j.neuropharm.2011.04.011

Carbon M, Correll CU (2014) Thinking and acting beyond the positive: the role of the cognitive and negative symptoms in schizophrenia. CNS Spectr 19(Suppl 1):38–52 . doi:10.1017/S1092852914000601 quiz 35–37, 53

Cohn J, Ziriax JM, Cox C, Cory-Slechta DA (1992) Comparison of error patterns produced by scopolamine and MK-801 on repeated acquisition and transition baselines. Psychopharmacology 107:243–254

Coyle JT (2012) NMDA receptor and schizophrenia: a brief history. Schizophr Bull 38:920–926. doi:10.1093/schbul/sbs076

Das T, Ivleva EI, Wagner AD et al (2014) Loss of pattern separation performance in schizophrenia suggests dentate gyrus dysfunction. Schizophr Res 159:193–197. doi:10.1016/j.schres.2014.05.006

Fatouros-Bergman H, Cervenka S, Flyckt L et al (2014) Meta-analysis of cognitive performance in drug-naïve patients with schizophrenia. Schizophr Res 158:156–162. doi:10.1016/j.schres.2014.06.034

Fleming K, Goldberg TE, Gold JM, Weinberger DR (1995) Verbal working memory dysfunction in schizophrenia: use of a Brown-Peterson paradigm. Psychiatry Res 56:155–161

Friederich JA, Butterworth JF (1995) Sodium nitroprusside: twenty years and counting. Anesth Analg 81:152–162

Gattaz WF, Cramer H, Beckmann H (1983) Low CSF concentrations of cyclic GMP in schizophrenia. Br J Psychiatry J Ment Sci 142:288–291

Gourgiotis I, Kampouri NG, Koulouri V et al (2012) Nitric oxide modulates apomorphine-induced recognition memory deficits in rats. Pharmacol Biochem Behav 102:507–514. doi:10.1016/j.pbb.2012.06.013

Greene R (2001) Circuit analysis of NMDAR hypofunction in the hippocampus, in vitro, and psychosis of schizophrenia. Hippocampus 11:569–577. doi:10.1002/hipo.1072

Hallak JEC, Maia-de-Oliveira JP, Abrao J et al (2013) Rapid improvement of acute schizophrenia symptoms after intravenous sodium nitroprusside: a randomized, double-blind, placebo-controlled trial. JAMA Psychiatry 70:668–676. doi:10.1001/jamapsychiatry.2013.1292

Hoirisch-Clapauch S, Nardi A (2015) Improvement of psychotic symptoms and the role of tissue plasminogen activator. Int J Mol Sci 16:27550–27560. doi:10.3390/ijms161126053

Hottinger DG, Beebe DS, Kozhimannil T et al (2014) Sodium nitroprusside in 2014: A clinical concepts review. J Anaesthesiol Clin Pharmacol 30:462–471. doi:10.4103/0970-9185.142799

Kandratavicius L, Balista P, Wolf D et al (2015) Effects of nitric oxide-related compounds in the acute ketamine animal model of schizophrenia. BMC Neurosci 16. doi:10.1186/s12868-015-0149-3

Kim J, Glahn DC, Nuechterlein KH, Cannon TD (2004) Maintenance and manipulation of information in schizophrenia: further evidence for impairment in the central executive component of working memory. Schizophr Res 68:173–187. doi:10.1016/S0920-9964(03)00150-6

Krystal JH, Karper LP, Seibyl JP et al (1994) Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry 51:199–214

Kumar G, Olley J, Steckler T, Talpos J (2015) Dissociable effects of NR2A and NR2B NMDA receptor antagonism on cognitive flexibility but not pattern separation. Psychopharmacology 232:3991–4003. doi:10.1007/s00213-015-4008-9

Lee J, Park S (2005) Working memory impairments in schizophrenia: a meta-analysis. J Abnorm Psychol 114:599–611. doi:10.1037/0021-843X.114.4.599

Lins BR, Howland JG (2016) Effects of the metabotropic glutamate receptor 5 positive allosteric modulator CDPPB on rats tested with the paired associates learning task in touchscreen-equipped operant conditioning chambers. Behav Brain Res 301:152–160. doi:10.1016/j.bbr.2015.12.029

Lins BR, Phillips AG, Howland JG (2015) Effects of D- and L-govadine on the disruption of touchscreen object-location paired associates learning in rats by acute MK-801 treatment. Psychopharmacology 232:4371–4382. doi:10.1007/s00213-015-4064-1

Maia-de-Oliveira JP, Lobão-Soares B, Baker GB et al (2014) Sodium nitroprusside, a nitric oxide donor for novel treatment of schizophrenia, may also modulate dopaminergic systems. Schizophr Res 159:558–559. doi:10.1016/j.schres.2014.08.020

Maia-de-Oliveira JP, Abrao J, Evora PR et al (2015a) The effects of sodium nitroprusside treatment on cognitive deficits in schizophrenia: a pilot study. J Clin Psychopharmacol 35:83–85. doi:10.1097/JCP.0000000000000258

Maia-de-Oliveira JP, Lobão-Soares B, Ramalho T et al (2015b) Nitroprusside single-dose prevents the psychosis-like behavior induced by ketamine in rats for up to one week. Schizophr Res 162:211–215. doi:10.1016/j.schres.2014.12.035

Malhotra MDA (1997) Ketamine-induced exacerbation of psychotic symptoms and cognitive impairment in neuroleptic-free schizophrenics. Neuropsychopharmacology 17:141–150. doi:10.1016/S0893-133X(97)00036-5

Marder SR, Fenton W (2004) Measurement and treatment research to improve cognition in schizophrenia: NIMH MATRICS initiative to support the development of agents for improving cognition in schizophrenia. Schizophr Res 72:5–9. doi:10.1016/j.schres.2004.09.010

Markou A, Chiamulera C, Geyer MA et al (2009) Removing obstacles in neuroscience drug discovery: the future path for animal models. Neuropsychopharmacology 34:74–89. doi:10.1038/npp.2008.173

Martinelli C, Shergill SS (2015) Clarifying the role of pattern separation in schizophrenia: the role of recognition and visual discrimination deficits. Schizophr Res 166:328–333

McAllister KAL, Saksida LM, Bussey TJ (2013) Dissociation between memory retention across a delay and pattern separation following medial prefrontal cortex lesions in the touchscreen TUNL task. Neurobiol Learn Mem 101:120–126. doi:10.1016/j.nlm.2013.01.010

McGrath J, Saha S, Chant D, Welham J (2008) Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev 30:67–76. doi:10.1093/epirev/mxn001

Mesholam-Gately RI, Giuliano AJ, Goff KP et al (2009) Neurocognition in first-episode schizophrenia: a meta-analytic review. Neuropsychology 23:315–336. doi:10.1037/a0014708

Moghaddam B, Krystal JH (2012) Capturing the angel in "angel dust": twenty years of translational neuroscience studies of NMDA receptor antagonists in animals and humans. Schizophr Bull 38:942–949. doi:10.1093/schbul/sbs075

Nestler EJ, Hyman SE (2010) Animal models of neuropsychiatric disorders. Nat Neurosci 13:1161–1169. doi:10.1038/nn.2647

Oomen CA, Hvoslef-Eide M, Heath CJ et al (2013) The touchscreen operant platform for testing working memory and pattern separation in rats and mice. Nat Protoc 8:2006–2021. doi:10.1038/nprot.2013.124

Ortuño F, Arbizu J, Soutullo CA, Bonelli RM (2009) Is there a cortical blood flow redistribution pattern related with perseverative error in schizophrenia? Psychiatr Danub 21:283–289

Palmer BW, Heaton RK, Paulsen JS et al (1997) Is it possible to be schizophrenic yet neuropsychologically normal? Neuropsychology 11:437–446

Perrin MA, Butler PD, DiCostanzo J et al (2010) Spatial localization deficits and auditory cortical dysfunction in schizophrenia. Schizophr Res 124:161–168. doi:10.1016/j.schres.2010.06.004

Soria Bauser D, Thoma P, Aizenberg V et al (2012) Face and body perception in schizophrenia: a configural processing deficit? Psychiatry Res 195:9–17. doi:10.1016/j.psychres.2011.07.017

Svensson M, Grahm M, Ekstrand J et al (2015) Effect of electroconvulsive seizures on pattern separation: ECS, neurogenesis, and pattern separation. Hippocampus 25:1351–1360. doi:10.1002/hipo.22441

Szoke A, Meary A, Trandafir A et al (2008) Executive deficits in psychotic and bipolar disorders – implications for our understanding of schizoaffective disorder. Eur Psychiatry 23:20–25. doi:10.1016/j.eurpsy.2007.10.006

Talpos JC, McTighe SM, Dias R et al (2010) Trial-unique, delayed nonmatching-to-location (TUNL): a novel, highly hippocampus-dependent automated touchscreen test of location memory and pattern separation. Neurobiol Learn Mem 94:341–352. doi:10.1016/j.nlm.2010.07.006

Talpos JC, Fletcher AC, Circelli C et al (2012) The pharmacological sensitivity of a touchscreen-based visual discrimination task in the rat using simple and perceptually challenging stimuli. Psychopharmacology 221:437–449. doi:10.1007/s00213-011-2590-z

Trevlopoulou A, Touzlatzi N, Pitsikas N (2016) The nitric oxide donor sodium nitroprusside attenuates recognition memory deficits and social withdrawal produced by the NMDA receptor antagonist ketamine and induces anxiolytic-like behaviour in rats. Psychopharmacology 233:1045–1054. doi:10.1007/s00213-015-4181-x

Tuplin EW, Stocco MR, Holahan MR (2015) Attenuation of MK-801-induced behavioral perseveration by typical and atypical antipsychotic pretreatment in rats. Behav Neurosci 129:399–411. doi:10.1037/bne0000066

Vingerhoets WAM, Bloemen OJN, Bakker G, van Amelsvoort TAMJ (2013) Pharmacological interventions for the MATRICS cognitive domains in schizophrenia: what's the evidence? Front Psychiatry. doi:10.3389/fpsyt.2013.00157