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ORIGINAL INVESTIGATION

The pharmacological sensitivity of a touchscreen-based visual discrimination task in the rat using simple and perceptually challenging stimuli

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Abstract
Rationale Cognitive testing with touchscreen-equipped operant boxes ('touchscreens') is becoming increasingly popular. Tasks, such as paired associate learning or reversal learning of visual stimuli, have the discrimination of visual stimuli as a fundamental component. However, the effect of drugs commonly used in the study of cognitive mechanisms has yet to be described in a visual discrimination.
Objective The objective of the study was to profile a range of psychoactive agents (glutamatergic, dopaminergic, and cholinergic agonists and antagonists) known to be important in cognitive processing on visual discrimination performance using a touch sensitive computer monitor.
Methods Male Lister Hooded rats were trained to a stable level of performance in a simple visual discrimination. In Experiment 1, the effect of MK-801, phencyclidine, memantine, dextroamphetamine sulphate (D-amphetamine) and scopolamine was assessed. In Experiment 2, the stimuli were blended together resulting in a perceptually more demanding discrimination and a reduction in accuracy. The rats used in Experiment 1 were then retested with these 'morphed' stimuli under the influence of the above compounds.
Results MK-801, PCP, and D-amphetamine induced selective deficits in accuracy in both versions of the task. In contrast, scopolamine and memantine produced non-selective deficits in accuracy. Morphing the stimuli reduced accuracy, but did not alter the observed behavioural profile after compound administration.
Conclusion These data improve our understanding of the basic neuropharmacology of a visual discrimination in cognitive tests employing touchscreens and will aid in the interpretation of pharmacological studies with more cognitively demanding methodologies.

Keywords MK-801 · PCP · D-Amphetamine · Scopolamine · Memantine · Rat · Touchscreen · Visual discrimination · Schizophrenia · Perception

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Introduction

Visual discrimination (VD), i.e. the requirement for an animal to discriminate a correct from an incorrect visual stimulus, is at the heart of many behavioural paradigms in many different species. The stimuli include single or multiple point sources of light that may vary in terms of brightness or frequency of illumination, two dimensional shapes, or solid objects (for examples, see Winters et al. 2004; Ennaceur and Aggleton 1997; McDonald et al. 2007; Reading et al. 1991). Furthermore, the variety of behavioural paradigms and the heterogeneity of the stimuli used make it difficult to reconcile pharmacology effects across studies. Moreover, the effect of a compound on the VD itself is often not considered.

Visual discrimination is also an essential component of a technique that is growing in popularity: operant testing with touchscreen-equipped operant boxes ('touchscreens') using rats or mice as subjects (Bussey et al. 1997; Bussey et al. 2001). In the last decade, numerous procedures for this apparatus have been published including transverse patterning

(Bussey et al. 1998), reversal learning (Brigman et al. 2009), visual conditional responding (Bussey et al, 1996), serial reaction time (Steckler and Sahgal 1995), spatial pattern separation (McTighe, et al. 2009), spatial search task (Talpos et al. 2008) paired-associate learning (Talpos et al. 2009), and trial unique non-match to location (Talpos et al. 2010). Numerous studies have been published investigating the effects of genetic manipulations on acquisition and reversal of a visual discrimination. For example, NR2A receptor knockout mice (Brigman et al. 2009) and GLAST knockout mice (Karlsson et al. 2009) both show impairments in acquisition of a visual discrimination, whereas GluA1 and M1 receptor knockout mice were shown to have no impairments in acquisition (Barkus et al. 2011; Bartko et al. 2011a, b). Despite these studies reporting the influence of genetic manipulations on the acquisition of a visual discrimination, surprisingly little is known about the influence of common acute pharmacological models of disease in a simple visual discrimination at steady state performance. Such data is crucial for the interpretation of more complex tasks that may have a visual discrimination at its core (paired-associate learning, reversal learning, transverse patterning, etc).

The primary goal of this work was to elucidate the effects of five compounds, commonly used to study cognition, on their ability to influence behaviour in a visual discrimination. In this study, two experiments were carried out. In Experiment 1, rats were trained to discriminate two contrasting stimuli (Fig. 1) to an accuracy of greater than 80% correct per training session. The effects of compound administration on task performance were then measured. In Experiment 2, the same compounds were tested in a visual discrimination using five different levels of 'morphed' (blended) stimuli in which the rewarded stimulus (S+) and the non-rewarded stimulus (S−) were merged to generate stimuli that had overlapping features which makes them more perceptually difficult to compare (Fig. 1). This manipulation circumvented a 'ceiling effect' by systematically lowering accuracy while also allowing a condition where the interactions between task difficulty and drug treatments could be considered. A failure to see an interaction with task difficulty would suggest that any pharmacologically induced performance deficits are less likely to be due to selective impairments on visual perceptual processing (within the perirhinal cortex for instance) and more likely related to a deficit in response selection, although the reason for such a deficit could be multi-fold. Interestingly, it has recently been shown that impairing visual discrimination performance through morphing the stimuli may make the task sensitive to enhancement by the acetylcholinesterase inhibitor, donepezil (McCarthy et al. 2011), although the procedure used differed from the one here.

Five compounds commonly used to study cognitive mechanisms (phencyclidine hydrochloride (PCP), MK-801, dextroamphetamine sulphate (D-amphetamine), scopolamine, and memantine) were examined. PCP and MK-801 are both N-methyl D-aspartate (NMDA) receptor antagonists that are frequently used preclinically to model aspects of psychosis and cognitive impairment (Gilmour et al. 2011). Memantine was also included because of its different mode of action on the NMDA receptor (Johnson and Kotermanski 2006) and its different behavioural profile compared to MK-801 and PCP (Gilmour et al. 2009; Dix et al. 2010; Smith et al. 2011). As memantine is an approved therapy for moderate to severe Alzheimer's disease, it is not only an important translational tool but also has the potential to reveal pro-cognitive effects, making it an especially interesting compound to test in the morph condition (McKeage 2010; Danysz and Parsons 2003). The indirect dopamine receptor agonist, D-amphetamine,

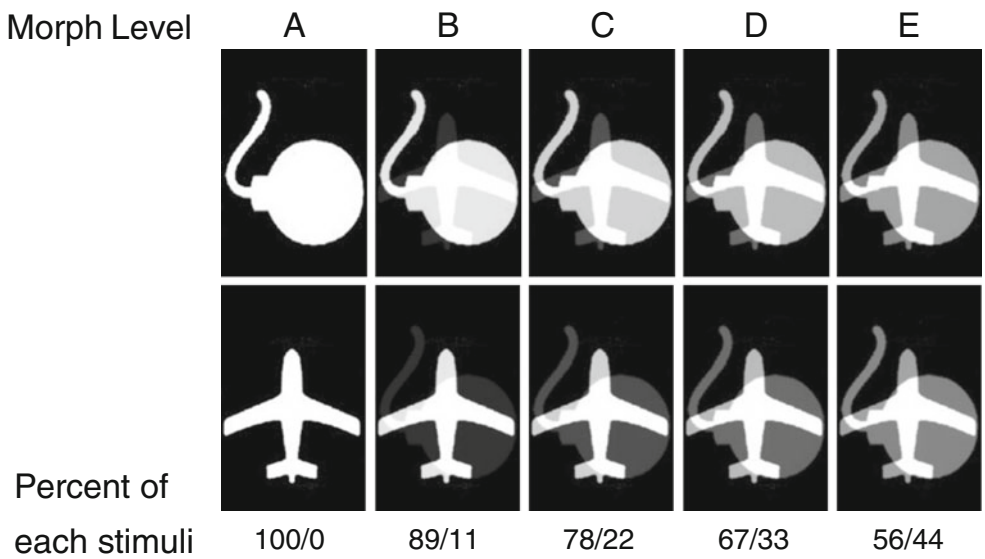

Fig. 1 Examples of images used in Experiments 1 and 2. Only *pair A* was used in Experiment 1, whereas all pairs were used in Experiment 2.

was included as it has been reported to impair learning and memory (e.g. Robbins 1978; Zeeuws et al. 2010; Hampson et al. 2010) as well as to model aspects of schizophrenia (e.g. Sarter et al. 2009; Pietrzak et al. 2010; Hijzen et al. 1991). Finally, the cognitive disrupter and muscarinic receptor antagonist, scopolamine (for a review, see Klinkenberg and Blokland 2010), was also included. Scopolamine is well established as a cognitive disruptor and a long standing acute pharmacological model of some aspects of Alzheimer's disease (Ebert and Kirch 1998).

Materials and methods

Subjects

Sixty-four male Lister hooded rats (Harlan, UK) were housed in groups of four in plastic individual ventilated cages containing sawdust. The animals were maintained on a food-restricted diet with ad libitum access to water under a 12-h light/dark cycle with lights on at 7 am. The experiments were conducted during the same part of the light phase each day (between 11:00 and 16:30). Food was given immediately following training or testing in an amount that maintained body weight at about 85% of their free feeding weight. All experimentation was conducted in accordance with the UK Animals (Scientific Procedures) Act 1986.

Compounds

In Experiment 1, MK-801 hydrogen maleate was administered 30 min prior to testing at 0.05, 0.1, and 0.25 mg/kg, subcutaneous (s.c.). PCP was also administered 30 min prior to testing, but at a concentration of 0.5, 1.0 and 2.5 mg/kg, s.c. Memantine hydrochloride (2.5, 5.0, and 10 mg/kg) was administered 60 min prior to testing via the intra-peritoneal (i.p.) route. D-Amphetamine (0.1, 0.3, 0.9, 1.8; s.c.) was administered 60 min prior to testing, and finally, scopolamine hydrobromide (0.03, 0.06, 0.09; i.p.) was administered 30 min prior to testing. Treatment conditions for the NMDA antagonists were based on a series of published behavioural studies performed onsite (Gilmour et al. 2009; Dix et al. 2010; Smith et al. 2011). Doses of D-amphetamine were determined from internal historical data but correspond with those used in the literature in general (for a review on D-amphetamine doses, see Grilly and Loveland 2001). Scopolamine concentrations were based on previous unpublished studies by one of the authors also using the touchscreen method (JT).

In Experiment 2, treatments were left the same except that lower concentrations were used in some instances (MK-801 hydrogen maleate, 0.025, 0.05, 0.1 mg/kg; PCP, unchanged; memantine hydrogen chloride, 1.25, 2.5, 5.0, 10 mg/kg; D-amphetamine, 0.1, 0.3, 0.9; and scopolamine hydrobromide, 0.015, 0.03, 0.06). Doses were modified when the highest concentration administered caused a clear suppression of behavioral responding, resulting in data not suitable for consideration of changes in accuracy. Moreover, the increase in difficulty could have made the task more sensitive to disruption, again supporting the use of lower compound concentrations.

All compounds were purchased from Sigma-Aldrich (UK) except memantine HCl (Tocris, UK). All compounds were administered in a volume of 1 ml of vehicle/kg of body weight. 5% glucose was used as vehicle for all experiments. Compound was prepared fresh for each test day. All compounds were tested for pH after formulation and adjusted to physiological levels with 1 M NaOH or 1 M HCl, as appropriate. Each compound was tested against the vehicle control. Testing was typically carried out twice a week (Tuesday and Friday).

Apparatus

Rats were tested in stainless steel five-bay modular test chambers (Med Associates, VT USA; 30.5 cm*L*×39.4 cm *W*×29.2 cm *H*). The grid flooring in these chambers was constructed from stainless steel rods (4.8 mm in diameter), 1 cm apart and 1.5 cm above a sawdust-filled tray. At the rear of the chamber, there was a pellet receptacle containing a light and an infrared nose-poke detector, a house-light (3 w), and a small speaker. On the other side, the stainless steel panels had been removed and were replaced by the touch-sensitive computer monitor (IT150-IR, Craft Data Ltd, Chesham UK; 30×22.5 cm) in a stainless steel housing which secured the monitor to the operant box. Positioned 9 cm above the grid floor, a 'window' (30×18 cm) was cut into the steel housing revealing the touchscreen monitor. This 'window' left 5.25 cm of housing between each side of the screen and the corner of the chamber, as well as approximately 9 cm between the top of the screen and the top of the chamber. Just below the window (1.5 cm), a metal flap (30×5 cm) was attached at a 90° angle to the housing. This flap was attached by a hinge so that it could swing downwards 90°, and was counter-weighted in order to automatically return to position. This caused the rats to slow down upon approach to the touchscreen, potentially allowing them more time to attend to stimuli on the screen before responding. The housing was designed so that different plastic cut-out inserts could be placed between the housing and the screen, limiting the available response area. For these experiments the inserts were made of black Perspex. At regular intervals, four windows (6×9 cm) were cut out of the insert. These were 1 cm above the top of the window in the housing and spaced 1.5 cm apart from each

other. There was 1 cm of space between the insert and the touchscreen monitor. The testing chamber was housed in a sound-attenuating cubicle. The operant chambers and touchscreens were run with custom-developed .NET application written in C# using the Microsoft .NET 3.0 framework, Microsoft SQL Server database, and SQL Server Reporting Services.

Behavioural testing and training

Training for this experiment comprised five stages: (1) habituation and screen touching, (2) rewarded responding towards any part of the screen, (3) selective rewarded responding to specific portions of the screen, (4) introduction of incorrect trials, and (5) VD task acquisition. Once stable performance had been achieved, animals would start Experiment 1 in which the effect of the drugs was assessed. In Experiment 2, the drugs were again profiled using the morphed stimuli.

1. Habituation

Prior to the first day of habituation, rats were placed on food restriction and had a mixture of peanut butter and reward pellets (40 mg Noyes formula 'P' chow pellets, Sandown Scientific) smeared on the inside of their home cage. The next day rats were placed into operant chambers with the fans running, but all other components turned off. Light was provided by a partially opened cubical door. Small amounts of a mixture of peanut butter and reward pellets were placed on the front and rear of the flap, the screen cover, and the screen itself. Rats remained in the chamber for approximately 45 min. This process was continued until all of the peanut butter had been eaten for two sessions in a row (three sessions to reach criteria).

2. Rewarded responding to the screen

The goal of this stage of testing was to train rats to touch any portion of the touchscreen for a reward pellet. A trial would begin with the food receptacle illuminated. Once a rat nose-poked to the receptacle, the light would be extinguished and white squares would appear in each of the four locations on the touchscreen. A response at any of these locations would trigger the reward tone (0.5 s beep), delivery of a reward pellet, and illumination of the pellet receptacle. Once the pellet was collected, the reward light would be deactivated and a 5-s inter-trial interval (ITI) would begin. Once the ITI had passed, the pellet receptacle was illuminated, signalling the start of a new trial. A nose-poke would then start the next trial. This continued for 60 trials or 45 min, whichever occurred first. During these sessions, the house light was kept on. Animals reached criterion (completion of 60 trials in 45 min) in three sessions.

3. Selective rewarded responding to the screen

This stage was included to avoid the development of a position bias. This stage of training was as above, except that only one location on the monitor would become illuminated. Only responses at the illuminated location would trigger a reward. The illuminated location would pseudorandomly change between one of four positions across trials. Responses at all non-illuminated locations were non-rewarded. Rats were trained on this schedule until they could complete 60 trials in 45 min. During these trials, the house light was kept on. Rats were able to reach criterion in one session.

4. Introduction of incorrect trials

This stage was the same as above, except that if a response was made at a location other than the S+, the screen was deactivated, the house light was deactivated, no reward was delivered, and reward tone did not sound. Five seconds after the incorrect response (the 'time-out' period), the reward light would again be illuminated. Further pokes to the incorrect location would result in the trial being repeated until it was successfully completed. Animals reached criteria in six sessions (completion of 60 trials in 45 min).

5. Discrimination task training

In this stage of testing, rats were required to learn to discriminate between a stimulus associated with reward (S+) and one associated with an absence of reward (S−). A trial would begin with the illumination of the pellet receptacle with the house light on. Once the rat had nose-poked at the pellet receptacle, two stimuli were displayed in separate positions upon the screen; the locations varied across trials. A response at the correct stimulus (S+) triggered the reward tone, the delivery of a pellet, the removal of the stimuli from the screen, and the illumination of the reward light. Once the pellet was collected, a short ITI would occur (5 s) and the reward light would be deactivated. When the ITI had passed, the reward light would again become illuminated, signalling the beginning of the next trial. If the subject selected the stimulus (S−), then a time-out period would occur for 10 s. The reward light was then activated, ready for a nose-poke into the pellet receptacle. When this happened, the house light would be activated, the reward light would be extinguished, and the ITI would begin. Once the ITI had passed, the reward light would again be illuminated, and a poke at the illuminated receptacle would trigger the next trial—a correction trial. The next trial would be the same as the previous, but not counted towards the total completed nor would it be considered towards the total number of correct or incorrect trials. Correction trials would be repeated until the S+was correctly selected. Each rat was maintained on the same S+/S−pairing across sessions. The locations of the S+and S−varied randomly between trials. Training consisted of 80 trials per daily session.

Experiment 1 Once animals had reached stable levels of performance, the effects of the chosen compounds were studied. Baseline behaviour was examined the day before testing, and animals showing abnormal behaviour, greater than 10% decrease when compared to their five previous baseline days, were excluded from the subsequent day's testing. However, these excluded animals would be considered for future inclusion if their behaviour would later be seen to be stable. All treatment groups were randomised between studies. Animals did not undergo training the day after drug administration. The testing session consisted of 80 trials.

Experiment 2 Testing in stimulus-morphing experiments was similar to the simple discrimination described above, except that the S+and S−were 'morphed' using FantaMorph version 4.0 (Abrosoft, Beijing, China) to create stimuli with varying levels of ambiguity (see Fig. 1). Each trial consisted of the same S+and S−pairing which the animal had previously learned as part of the simple VD, morphed to create five levels of increasing difficulty (A–E). In order to maintain the integrity of the stimulus representation, trials with non-morphed stimuli (n=33) were given more often than the other four trial types (n=17). Trials were presented in a blocked fashion (17 blocks) with each block beginning and ending with a non-morphed trial; the other four trial types were randomly dispersed throughout the block. This resulted in a total of 102 trials per session. Animals were only tested under the morph condition on treatment days to maintain the difficulty-dependent impairment. Finally, there were no correction trials during the morph drug test days.

Measures and statistics The basic measures taken were as follows: percent correct (number of correct trials / number trials completed excluding correction trials multiplied by 100), total trials completed (the number of trials completed excluding correction trials), magazine latency (the log time taken for the rat to nose-poke in the food magazine following illumination for collection of reward), correct response latency (the log time taken for a correct response to be recorded following presentation of stimuli on the touchscreen), and incorrect response latency (the log time taken for an incorrect response to be recorded following presentation of stimuli on the touchscreen). Each measure was subject to an appropriate mixed analysis of variance (ANOVA). Significant main effects and interactions were followed by appropriate planned comparisons (least squares means) against the vehicle control group. In Experiment 2, morph level was used as a within-subject factor. Owing to the lack of interactions, morph level was dropped as a factor for subsequent planned comparisons. In Experiment 1, any animal failing to complete at least 10 trials was excluded from all statistical analyses with the exception of trials completed. In Experiment 2, animals were required to perform a minimum of 48 trials, allowing at least eight trials at every level of morph. The relative 'weights' of the morph levels were determined by pilot work in order to give a consistent difference between levels and to ensure a suitable difficulty-dependent performance curve.

Results

Experiment 1. Simple visual discrimination task

MK-801 induced a significant decrease in the number of trials completed (F(3, 60)=186.8, p<0.001), with significant changes from vehicle occurring at doses of 0.1 mg/kg and 0.25 mg/kg (see Fig. 2). No subjects completed an adequate number of trials to include the highest dose of MK-801 tested (0.25 mg/kg), so this group was removed from further analysis. There was a main effect of treatment on accuracy (F(2, 45)=28.3, p<0.001) such that both 0.05 mg/kg and 0.1 mg/kg impaired performance. Significant main effects were seen on all latencies (magazine latency: F(2, 45)=17.5, p<0.001); incorrect response latency: F(2, 45)=24.9, p<0.001; and correct response latency: F(2, 45)=49.5, p<0.001). In each instance, significant differences were only seen against vehicle-treated rats following the dose of 0.1 mg/kg. Thus, MK-801 reduced choice accuracy in the absence of measureable side effects at a dose of 0.05 mg/kg.

PCP at the highest dose tested significantly decreased the number of trials completed (2.5 mg/kg, F(3, 60)=11.95, p< 0.001), and four animals were excluded from this group for the following analyses (see Fig. 3). There was a main effect of PCP on accuracy in the simple discrimination task (F(3, 56)=16.9, p<0.001). Compared to vehicle-treated rats, accuracy was decreased following treatment with PCP at doses of 1.0 and 2.5 mg/kg. There was a significant main effect of PCP on magazine latency (F(3, 56)=6.6, p<0.001), and planned comparisons indicated a significant increase in magazine latency at 2.5 mg/kg. Both the incorrect (F(3, 56)= 8.2, p<0.001) and correct (F(3, 56)=13.9, p<0.001) response latencies were significantly increased by PCP. This increase was only significant at 2.5 mg/kg. However, PCP also produced a significant decrease in the response latency on correct trials at the lowest dose of 0.5 mg/kg (p<0.05). Thus, PCP selectively reduced choice accuracy in the absence of measureable side effects at a dose of 1.0 mg/kg.

Memantine decreased the number of trials completed (F(3, 56)=31.7, p<0.001), but the effect was restricted to the highest dose (10 mg/kg, p<0.001, see Fig. 4). Three animals were excluded (all treated with 10 mg/kg memantine) from further analysis. Memantine induced a significant impair-

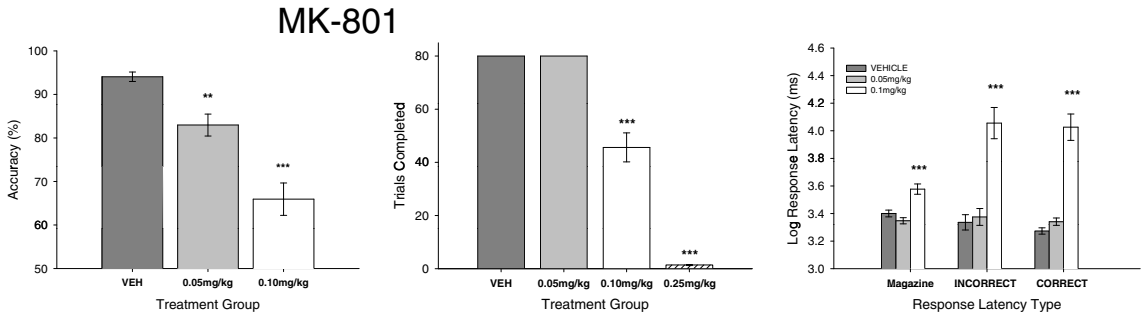

Fig. 2 MK-801. Data represented the mean value, and *error bars* are ±1 standard error of the mean (s.e.m). *$p<0.05$, **$p<0.01$, ***$p<0.001$

ment in accuracy ($F(3, 56)=16.3$, $p<0.001$), but the effect was significant compared to vehicle-treated rats only at the highest dose tested (10 mg/kg, $p<0.001$). Magazine latency ($F(3, 56)=4.14$, $p<0.05$), incorrect ($F(3, 53)=33.2$, $p<0.001$) and correct ($F(3, 56)=67.2$, $p<0.001$) response latencies were all significantly increased by memantine (magazine 10 mg/kg $p<0.05$; incorrect 5.0 mg/kg $p<0.001$, 10.0 mg/kg $p<0.001$; correct 5.0 mg/kg $p=0.001$, 10.0 mg/kg $p<0.001$). Thus, memantine reduced choice accuracy but only at doses that also produced evidence of other behavioural changes.

D-Amphetamine reduced the number of trials completed ($F(4, 59)=47.3$, $p<0.001$), however this effect was limited to the highest dose tested (1.8 mg/kg, $p<0.001$; see Fig. 5). Eight animals from this group failed to reach the inclusion criterion and were excluded from further analysis. D-Amphetamine had a significant effect on accuracy ($F(4, 51)=8.1$, $p<0.001$), with significant reductions from vehicle-treated rats observed at 0.9 mg/kg and 1.8 mg/kg. No significant effects of D-amphetamine were seen on magazine latency ($F(4, 51)=1.1$, $p>0.1$) or incorrect response latency ($F(4, 51)=1.1$, $p>0.1$). A significant effect of treatment was seen on correct response latency ($F(4, 51)=3.3$, $p<0.05$); interestingly, subsequent planned comparisons indicated a significant decrease in response latency at 0.9 mg/kg. Hence, the effects of the lowest dose of D-amphetamine tested on accuracy appear to be relatively specific and not a consequence of a general, non-specific impairment.

Scopolamine induced a decrease in trials completed ($F(3, 60)=38.9$, $p<0.001$; see Fig. 6). Both 0.06 mg/kg and 0.09 mg/kg reduced the trials completed, resulting in 19 animals being excluded. As with all of the other compounds tested, scopolamine produced a significant effect on accuracy ($F(3, 41)=17.7$, $p<0.001$). Subsequent analysis indicated that significant differences existed at doses of 0.06 mg/kg and 0.09 mg/kg. Main effects were seen on all latency measures (magazine latency: $F(3, 41)=12.4$, $p<0.001$; incorrect response: $F(3, 39)=11.2$, $p<0.001$; and correct response: $F(3, 41)=31.5$, $p<0.001$). Additional analyses indicated significant differences in magazine latency against vehicle-treated rats at 0.06 mg/kg and 0.09 mg/kg ($p=0.001$). Differences compared to vehicle-treated rats were seen at all doses for incorrect response latency as well as correct response latency. Thus, while scopolamine reduced task accuracy, there was no evidence at the doses tested that this effect was not a consequence of other behavioural changes.

Experiment 2. Morphed stimulus visual discrimination task

MK-801 significantly reduced the number of trials completed ($F(3, 59)=11.7$, $p<0.001$; see Fig. 7). Planned comparisons against the vehicle group revealed a significant reduction at the highest dose only; three animals from this group were removed from further analysis. The ANOVA on the accuracy data showed a significant main effect of treatment ($F(3, 56)=4.0$, $p<0.05$), morph level (F

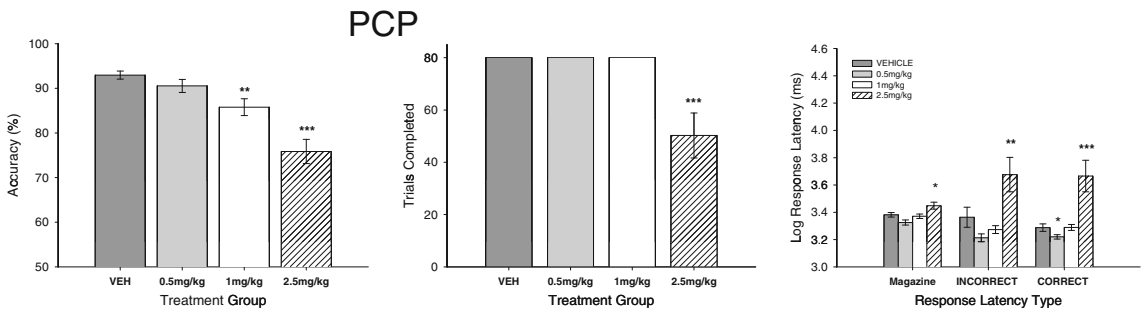

Fig. 3 PCP. Data represented the mean value, and *error bars* are ±1 standard error of the mean (s.e.m). *$p<0.05$, **$p<0.01$, ***$p<0.001$

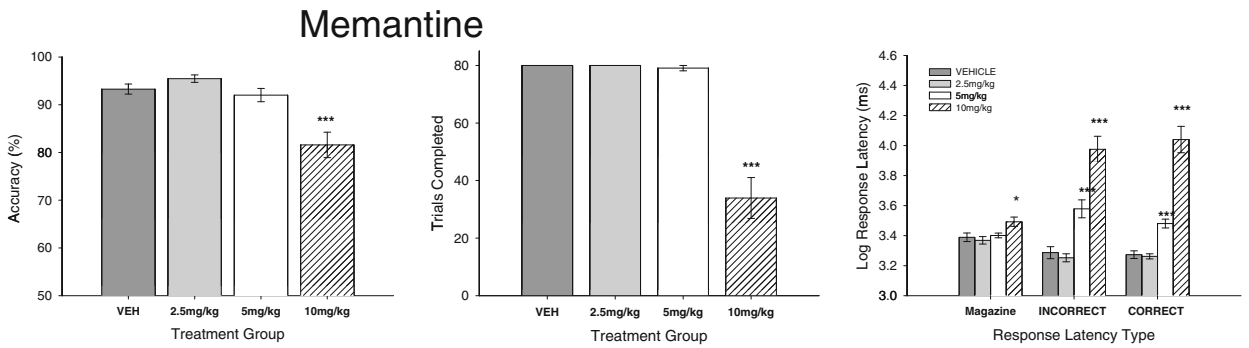

Fig. 4 Memantine. Data represented the mean value, and *error bars* are ±1 standard error of the mean (s.e.m). *$p<0.05$, **$p<0.01$, ***$p<0.001$

(4, 224)=80.6, $p<0.001$), and an interaction between the two ($F(12, 224)=2.0$, $p<0.05$), likely caused by a floor effect at morph level E. Planned comparisons against the vehicle control group are shown in Fig. 7 and revealed significant effects at both 0.05 and 0.1 mg/kg. The effect of the treatment on the magazine latency was also significant ($F(3, 56)=14.8$, $p<0.001$). Planned comparisons against the vehicle control group suggested that the animals in the lowest treatment group were faster (0.025 mg/kg), while animals treated with 0.1 mg/kg were slower to make a magazine entry ($p<0.001$). There was no main effect of morph level on the magazine latency ($F(4, 224)=1.0$, $p>0.1$), but there was an interaction between treatment and morph level ($F(12, 224)=2.1$, $p<0.05$). Planned comparisons showed significant effects at the highest dose at all morph levels and the effect of the 0.025 mg/kg dose at morph levels of B, D and E only (all $p<0.05$). The ANOVA on the correct response latency revealed significant main effects of the treatment ($F(3, 56)=32.63$, $p<0.001$) and the morph level ($F(4, 224)=4.68$, $p<0.01$), but no interaction between the two factors ($F(12, 224)=1.2$, $p>0.3$). Planned comparisons showed a significant increase in response latency at the highest dose only ($p<0.001$). The effect of the morph level was due to an increase in response latency at morph level E relative to all other morph levels.

PCP (2.5 mg/kg) induced non-specific deficits such that there was a main effect of treatment on the number of trials completed ($F3, 56=9.6$, $p<0.001$; see Fig. 8). Five animals treated with 2.5 mg/kg PCP were excluded from subsequent analyses for failing to complete 48 trials. Significant main effects of treatment ($F(3, 51)=3.7$, $p<0.05$) and morph level were seen on accuracy ($F(4, 204)=101.0$, $p<0.001$). However, no interaction between the two was observed ($F(12, 204)=0.7$, $p>0.1$). Planned comparisons against the vehicle control group revealed significant disruption at 1.0 mg/kg and 2.5 mg/kg. Analysis of the magazine latency data revealed a significant main effect of treatment ($F(3, 51)=4.1$, $p<0.05$), but none at morph level ($F(4, 204)<1$) and no interaction between the main factors ($F(12, 204)<1$). However, planned comparisons of each treatment against the vehicle control group revealed no significant effects. There was also a significant main effect of treatment ($F(3, 51)=27.0$, $p<0.001$) and morph condition ($F(4, 204)=3.71$, $p<0.01$) on correct response latency, but there was no interaction between them ($F(12, 204)<1$). Planned comparisons against the vehicle group following the main effect of treatment revealed a small increase in response latency at 1.0 mg/kg ($p<0.05$) and a marked increase at 2.5 mg/kg ($p<0.001$).

Memantine induced a significant decrease in the number of trials completed ($F(4, 58)=7.7$, $p<0.001$) which is evident at

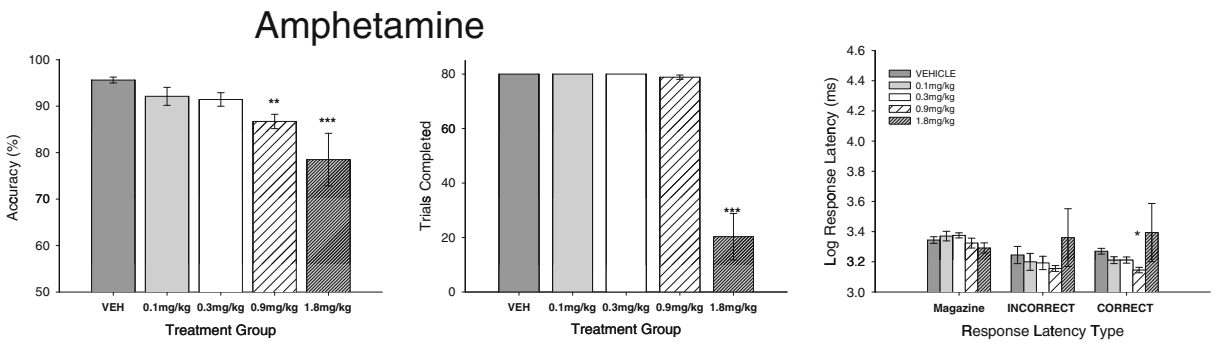

Fig. 5 Amphetamine. Data represented the mean value, and *error bars* are ±1 standard error of the mean (s.e.m). *$p<0.05$, **$p<0.01$, ***$p<0.001$

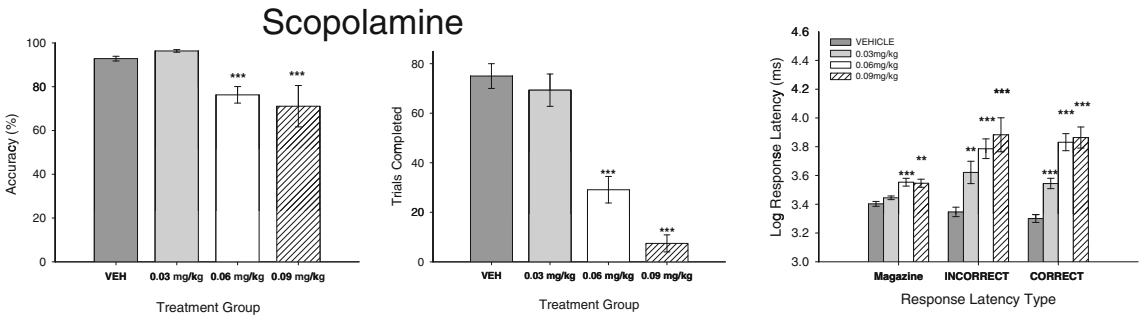

Fig. 6 Scopolamine. Data represented the mean value, and *error bars* are ±1 standard error of the mean (s.e.m). *$p<0.05$, **$p<0.01$, ***$p<0.001$

the highest dose only (see Fig. 9). No animals were excluded for failing to complete 48 trials. A main effect of treatment ($F(4, 58)=13.0$, $p<0.001$) and morph level ($F(4, 232)=139.2$, $p<0.001$) was seen on accuracy, but no interaction between these variables was seen ($F(16, 232)<1$). Planned comparisons against the vehicle control group showed a decrease in accuracy in animals treated with the highest dose (10 mg/kg) only. A main effect of treatment was seen on magazine latency ($F(4, 58)=2.8$, $p<0.05$). Planned comparisons revealed an increase in magazine response latency at the highest dose (10 mg/kg) only. There was neither a main effect of morph level nor interaction of this factor with the treatment (both $F<1$). There was a highly significant main effect of memantine on the latency to make a correct response ($F(4, 58)=49.3$, $p<0.001$); this was evident at the highest dose only ($p<0.001$). The treatment interacted with the morph level ($F(16, 232)=1.8$, $p<0.05$); planned comparisons showed a highly significant effect of 10 mg/kg memantine only at each morph level. There was a main effect of the morph level ($F(4, 232)=4.8$, $p<0.001$). This was due to an increase in response latency at morph level E relative to all other morph levels (Newman Keuls, all $p<0.05$).

D-Amphetamine produced a near significant decrease in trials completed ($F(3, 57)=2.7$, $p=0.056$; see Fig. 10, it is important to note that lower doses were used here when compared to the first study). Two animals (one from 0.1 mg/kg and one from 0.9 mg/kg group) failed to complete 48 trials and were excluded from further analysis. There was a main effect of D-amphetamine on accuracy ($F(3, 55)=4.3$, $p<0.01$); planned comparisons showed a loss of accuracy at both 0.3 and 0.9 mg/kg. There was a main effect of morph level ($F(4, 12)=98.5$, $p<0.001$); this effect was not dependent on the treatment administered ($F(12, 220)<1$). An ANOVA indicated a significant main effect of treatment on magazine latency ($F(3, 55)=4.2$, $p<0.01$) such that the highest two doses decreased the time to retrieve food from the magazine. However, there was no main effect or interaction involving the morph level (both $F<1$). The ANOVA on the correct response latency data revealed a highly significant main effect of the treatment but no interaction with ($F(12, 220)=1.0$, $p>0.1$) nor main effect of morph level ($F(4, 12)=1.7$, $p>0.1$). Planned comparisons against the vehicle group showed a dose-dependent increase in the speed of accurate responding.

Scopolamine produced a significant dose-dependent deficit in the number of trials completed ($F(3, 59)=46.4$, $p<0.001$; see Fig. 11). Three animals treated with 0.03 mg/kg and eight animals treated with 0.06 mg/kg scopolamine failed to complete the minimum of 48 trials and were therefore excluded from subsequent analyses. Significant main effects were seen on accuracy ($F(3, 48)=5.0$, $p<0.01$) and morph level ($F(4, 192)=62.0$, $p<0.001$), and there was an interaction between the two main factors ($F(12, 192)=2.0$, $p<0.05$). Scopolamine impaired accuracy at the highest dose administered (0.06 mg/kg). This effect was evident at morph levels A and C only. No significant main effects on

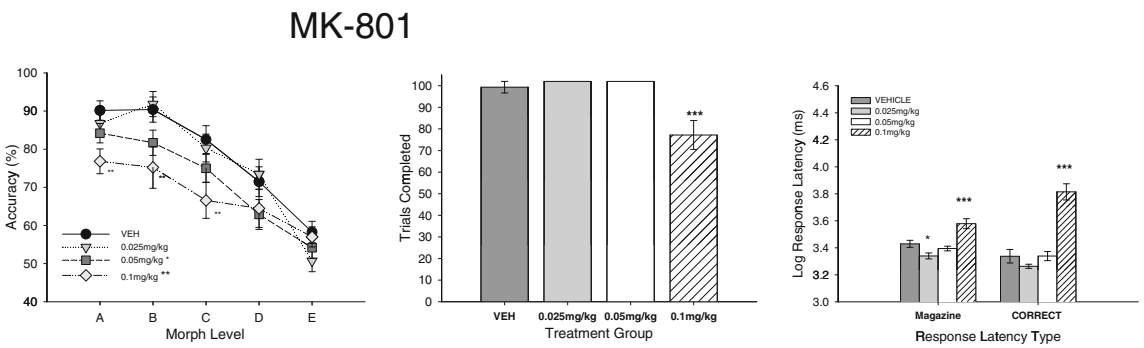

Fig. 7 MK-801. Data represented the mean value, and *error bars* are ±1 standard error of the mean (s.e.m). *$p<0.05$, **$p<0.01$, ***$p<0.001$

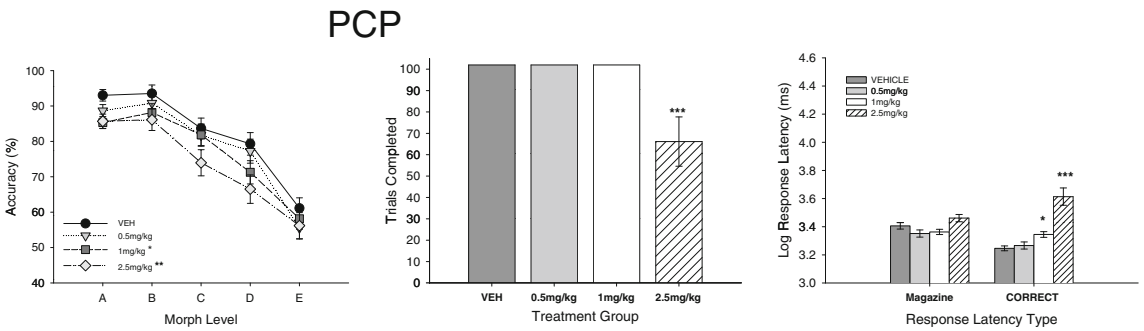

Fig. 8 PCP. Data represented the mean value, and *error bars* are ±1 standard error of the mean (s.e.m). *$p<0.05$, **$p<0.01$, ***$p<0.001$

magazine latency were seen involving treatment ($F(3, 48)=1.6$, $p>0.1$) or morph level ($F(4, 12)<1$), nor was there an interaction between the two ($F(12, 192)<1$). This contrasted with the highly significant main effects of treatment ($F(3, 48)=42.7$, $p<0.001$) on the correct response latency. Scopolamine dose dependently increased the time taken to make a correct response. There was also a significant main effect of morph level ($F(4, 192)=3.6$, $p=0.01$) which did not interact with the treatment ($F(12, 192)=1.1$, $p>0.1$). Post hoc analysis revealed that animals were slower to make a correct response to morph level D over morph level B (Newman Keuls).

Discussion

The aim of this study was to profile five drugs that are commonly used to study mechanisms of cognition in two variants of a visual discrimination paradigm in touchscreen-equipped operant chambers. In the first experiment, rats were required to perform a discrimination with simple visual stimuli. Impairments in accuracy were evident after treatment with MK-801 and PCP at doses having no measurable effect on response latency or the number of trials completed. At higher doses, more substantial reductions in accuracy were apparent, concomitant with increases in response and magazine latency as well as reductions in the number of trials completed. This pattern of effects is consistent with a dose-dependent intensification and 'globalisation' of functional disruption and is reminiscent of the effects of these compounds in two-lever operant discrimination paradigms (Gilmour et al. 2009; Dix et al. 2010, Smith et al. 2011).

A decreased in accuracy was also seen with D-amphetamine, but this was concomitant with shortened incorrect response latency, potentially indicative of a failure in response inhibition. In contrast, the reduction in accuracy induced by memantine and scopolamine could not be dissociated from changes in latency or trials completed. It seems likely that effects only on accuracy reflect disruption of mechanisms either involved in pattern recognition at the level of the perirhinal cortex (Winters et al. 2010; Bussey et al. 2002; Bussey and Saksida 2002) or by interference with the S–R association, possibly in the striatum (McDonald and White 1993; Packard et al. 1989; Squire 1994; Broadbent et al. 2007). It is entirely possible that similar mechanisms are disturbed also by memantine and scopolamine but only at doses that also induce motor confounds; there seems no logical reason why increased response latencies or number of trials completed could not occur without a decrease in accuracy. However, it is also possible that with higher doses of MK-801, PCP, and D-amphetamine and all active doses of memantine and scopolamine, the (greater) decrease in accuracy is a direct consequence of (increased) motor or motivational impairment.

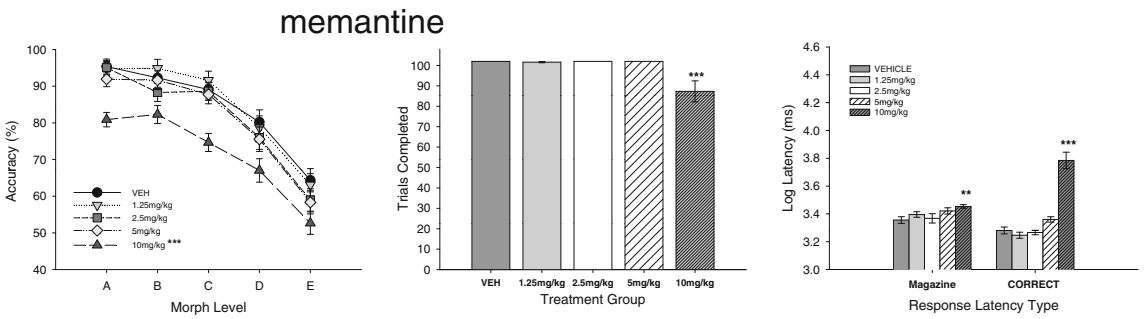

Fig. 9 Memantine. Data represented the mean value, and *error bars* are ±1 standard error of the mean (s.e.m). *$p<0.05$, **$p<0.01$, ***$p<0.001$

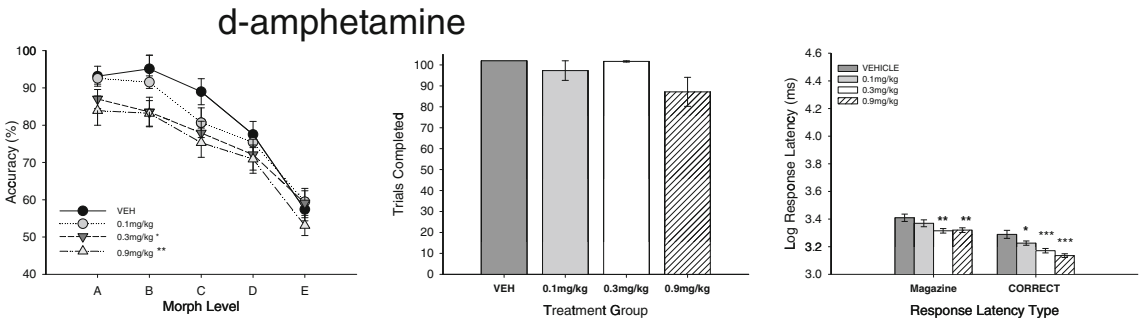

Fig. 10 D-amphetamine. Data represented the mean value, and *error bars* are ±1 standard error of the mean (s.e.m). *$p<0.05$, **$p<0.01$, ***$p<0.001$

If drug-induced decrements in accuracy are a consequence of selective disturbance within the pattern recognition system, it was hypothesised that gradual morphing of the two stimuli would increase the perceptual load and decrease accuracy synergistically with a pharmacological challenge. As expected, accuracy decreased with increasing similarity of the stimuli, consistent with the findings of McCarthy et al. (2011). However, there was no evidence that any of the drug treatments used impaired accuracy in a difficulty-dependent manner. On the whole, the morph-level–accuracy relationships under different doses of each drug were essentially parallel with gradients slightly changed, even with doses of compounds that impaired accuracy without change in response latency or the number of trials completed. These findings argue against the impairment in accuracy induced by MK-801 and PCP being a reflection of selective engagement of perceptual processes. It should be noted that within these studies, these animals were tested numerous times and could be considered 'over-trained'. However, the NMDA antagonists PCP and MK-801 were tested on more than one occasion (data not presented), and the behavioural effects remained remarkably consistent. While 'over-training' may have influenced the results seen, we have no reason to believe this is the case. If the high degree of training did influence behaviour, then the window to test 'trained' animals versus 'over-trained' animals is likely very small.

Schizophrenics, as well as healthy human volunteers subjected to the NMDA antagonist, ketamine, may experience fundamental disturbances within the visual system (Morgan et al. 2009b; Hutton and Ettinger 2006) and demonstrate impairments in visual learning and memory (Morgan et al. 2004, 2009a, 2010; Kalkstein et al. 2010). If the deficits seen after administration of the lower doses of PCP or MK-801 used here in rats are related to similar changes in both volunteers and schizophrenic patients, then NMDA receptor antagonism used in conjunction with touchscreen-based visual discrimination might have utility as a model and assay relevant to schizophrenia research. However, additional work will be required in a clinical setting to better describe these deficits in patients, as well as in the pre-clinical setting to determine whether the current findings have any relevance for use in drug discovery (Gilmour et al. 2011).

Scopolamine is widely used as a model of cognitive impairment even though peripheral effects can be observed at very low doses (see Klinkenberg and Blokland 2010 for a comprehensive review of the topic). Critical for this study, scopolamine has been shown to cause ocular pupil dilation at doses less than 0.01 mg/kg (Niemegeers et al. 1982; Jones and Higgins 1995), which is lower than the lowest dose used within this study. Indeed, the dramatic selective increase in correct response latency induced by scopolamine in the absence of any effects on magazine latency may be due to the higher, and potentially aversive, light intensity emitted by

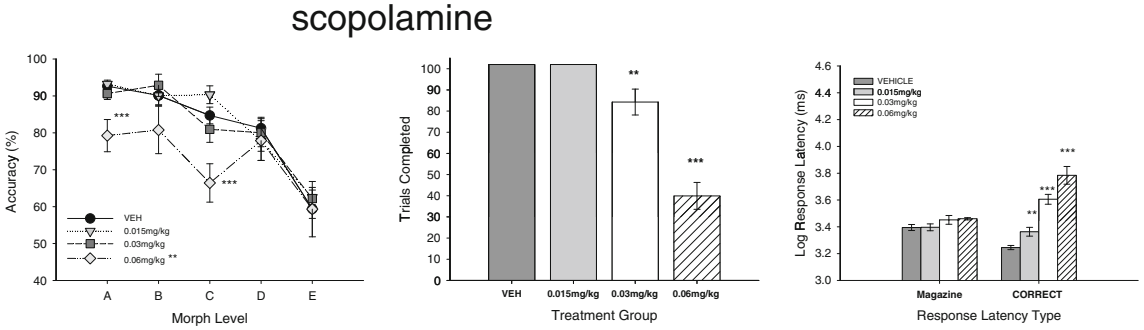

Fig. 11 Scopolamine. Data represented the mean value, and *error bars* are ±1 standard error of the mean (s.e.m). *$p<0.05$, **$p<0.01$, ***$p<0.001$

the screen being perceived in contrast to the lower light levels associated with the reward magazine. Similar effects of scopolamine on response latencies and number of trials completed were seen in rats trained to discriminate a bright from a dull visual stimulus in a two-lever operant box (Andrews et al. 1992). These effects were mimicked by the non-brain penetrant methylated form of scopolamine. Indeed, higher doses of scopolamine are tolerated in lever-based operant tasks where light intensity levels are often low in comparison (Klinkenberg and Blokland 2010). These data presented here strongly suggest that scopolamine may not be appropriate to use as a model of cognitive impairment with rats in touchscreen-based tasks. Bartko et al. (2011a, b) recently reported scopolamine-induced deficits in a touchscreen paired-associate task in mice; significant impairments in choice accuracy only occurred at the higher doses tested (0.2 and 2 mg/kg, i.p.), concomitant with large increases in touchscreen response latencies and smaller increases in magazine response latencies. However, equivalent doses (milligram per kilogram, not freebase) of scopolamine and methylated-scopolamine resulted in disparate results, suggesting that much of the non-specific effects are centrally mediated in the mouse. Additional work will be required to assess potential species differences in response to scopolamine.

These data present a clear role for the glutamatergic and dopaminergic systems in performance of learned visual discrimination. Involvement of the glutamatergic system is not entirely novel as genetic manipulations of the system (Brigman et al. 2009; Karlsson et al. 2009) and direct administration of selective antagonists have both been found to block acquisition of a visual discrimination. However, this work now extends the involvement of the glutamatergic system to recall and also supports the potential role of dopamine in recall of a visual discrimination. It is important to note that PCP and D-amphetamine are well established psycho-stimulants that can influence impulsivity. Accordingly, it is difficult to determine if the effects seen are true effects on recall of the discrimination or are indicative of increased basal impulsivity or hyperactivity. Additional work will be required to determine if this is a true 'cognitive' deficit or rather a 'pre-cognitive' deficit not specific to discrimination learning. At this time, it is difficult to make any clear comments about the role of the cholinergic system in this task. Bartko et al. (2011a, b) did report a cholinergic deficit in paired-associates learning after administration of scopolamine in the mouse. However, we were unable to find a concentration of scopolamine that reduced accuracy without influencing other behavioural measures. Moreover, a report by McCarthy et al. (2011) suggests that donepezil could enhance performance of a morphed discrimination; however, the procedure used may have allowed additional learning to occur, making it unclear if this is a case of cholinergic involvement in discrimination recall or acquisition. Similar difficulties arise when trying to interpret donepezil induced facilitation in reversal learning as observed by Chen et al. (2009). As such, the contribution of the cholinergic system to recall of a visual discrimination remains uncertain.

As cognitive tasks using touchscreens become more sophisticated and complex, it seems most likely that putative cognitive disruptors such as PCP, MK-801, and scopolamine will be examined. It is clear from the present work that it will be important to plan carefully the doses used in touchscreen-based tasks and take into account the possibility that changes associated with drug administration may not reflect a specific action on the cognitive construct under evaluation. Touchscreen technology represents an ideal methodology for studying behaviour across species including humans, non-human primates, rats, and mice (for examples, see Blackwell et al. 2004; Taffe et al. 2004; Talpos et al. 2009; Clelland et al. 2009). There is, therefore, unequivocal potential for the use of this technology to be the basis of translational paradigms that can use virtually identical stimuli and test parameters across multiple species making it particularly relevant for the study of disease (Bussey et al. 2011). The use of acute pharmacological challenges to impair touchscreen-based task performance will, however, be very limited unless agents and/or experimental manipulations that can selectively impair the psychological construct of interest can be found. Accordingly, we hope this will aid in the basic understanding of the neuropharmacology of cognition in touchscreens as well as in the development of pharmacological models of disease in this unique test environment.

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