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# Pre-training in a radial arm maze abolished anxiety and impaired habituation in C57BL6/J mice treated with dizocilpine

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**HIGHLIGHTS**

- C57BL/6J mice demonstrated low anxiety in a 3-dimensional maze.
- Dizocilpine produced a high level of anxiety over 7 test sessions.
- Three days pre-training under saline prevented dizocilpine to produce anxiety.
- In pre-trained mice, dizocilpine produced sustained non-habituating hyperactivity.

ABSTRACT

Familiarity can imply a reduction of fear and anxiety, which may render learning and memory performance insensitive to NMDA receptor antagonism. Our previous study indicates that MK-801 (dizocilpine), NMDA antagonist, increased anxiety and prevented the acquisition of a spatial memory task. Here, weexaminedwhetherMK-801 will produce anxiety in mice that were familiar with the test environment.

Male C57BL/6J mice were exposed, one session a day for 7 days, to a 3D maze, which consisted of nine arms attached to upward inclined bridges radiating from a nonagonal platform. In this maze, high anxiety mice avoid the arms in the first sessions. One group of mice received saline (SAL) while a second group received MK-801 (MKD1), both on day one. A third group received saline in the first 3 sessions, and MK 801 in subsequent sessions (MKD4). Saline and MK-801 (0.1 mg/kg) were administered intraperitoneally 30 min before the test.

MKD4 mice demonstrated an increase in bridge and arm visits, and reached arm/bridge entries ratio close to 1 in session 5. SAL mice also crossed frequently onto the arms, and reached a comparable ratio, but this was achieved with a lower number of arm visits. MKD1 mice demonstrated a reduced number of arm visits in each session compared to SAL and MKD4 mice.

Dizocilpine produced anxiety in mice treated from day 1 of the test, but not in those treated from day 4. It also impaired habituation in animals familiar with the test environment; it produced sustained non-habituating hyperactivity.

Keywords:

Anxiety; NMDA; Learning; Familiarity; Habituation; Sensitization

## 1. Introduction

The first evidence of the role of NMDA receptor in spatial memory using the water maze [67] was challenged in subsequent research studies in which familiarity with the test environment appeared to prevent the impairing effects of NMDA antagonists [9,10,14,58,70,81,85,87,88,92,100]. This effect of familiarization was shown to occur in other behavioral conditioning paradigms [14,81,85,97,111,118]. However, familiarity can imply a reduction of fear and anxiety, which may render learning and memory performance insensitive to NMDA receptor antagonism.

When exposed for the first time to a radial arm maze, mice and rats explore the proximal and avoid venturing into the distal segment of an arm. In the 3D maze (Fig. 1), which is a modification of the classic radial maze [69], animals need to climb onto an upwardly inclined bridge (proximal segment) attached to a central platform in order to access an arm (distal segment). During the first sessions, mice and rats were observed to reach the end of a bridge, then withdraw and return to the central platform; they do not continue into an arm. This avoidance of the distal segment, which is reflected by a low number of arm entries, is used as an indicator of fear and anxiety in mice. C57BL/6J and CD-1 mice demonstrated low anxiety compared to BALB/c J mice [28]. The latter made one or no visits during the first 3 sessions and required 5 sessions to make 8 arm visits whereas C57BL/6J and CD-1 mice made 8 arm visits in the second and third session, respectively. Repeated exposures to the test apparatus can lead to a reduction in anxiety. Hence, the arm/bridge entries ratio increase progressively to approach 1; this indicates that animals are no longer hesitant to cross onto the arms. The hesitation responses, which are indicated by a low arm/bridge entries ratio, reflect fear and anxiety in animals that have yet to make more than eight arm visits. They can also reflect impaired learning and memory performance in animals that had already made more than eight arm visits.

## 2.2. Drug treatment

Following 2 weeks acclimatization to the husbandry conditions, all mice were food-deprived, but had water ad libitum, and kept at 85–90% of their pre-test body weight throughout testing. They were randomly assigned to three groups (n = 8 per group) using a computer generated randomization software [QuickCalcs, GraphPad Software, Inc., La Jolla, CA]. The first group (SAL) received saline while the second group (MKD1) received MK-801 (0.1 mg/kg). The third group (MKD4) received saline in the first 3 days then MK-801 (0.1 mg/kg) in the remaining 4 days. Each group received intraperitoneal injection of its respective treatment 30 min before each test session, one session a day for 7 days. MK-801 (Sigma, UK) was dissolved in normal saline (0.9% NaCl). It was freshly prepared, and administered in a volume of 0.1 ml per 10 g body weight of mice.

### 2.3. Apparatus

The maze (Fig. 1) was made from grey PVC (5mmthick). It consisted of nine arms (35 cm × 11.2 cm, each) connected to bridges (15.2 cm × 11.2 cm, each) radiating from a nonagonal shaped central platform. Mice can access an arm by crossing a bridge. The bridges can be level with the arms providing a standard radial maze configuration. They can also be tilted upward or downward providing a maze with a raised or a lowered arm configuration, respectively. A1 cm diameter food well was located 1.5 cm from the end of each arm. Underneath this well, and separated by a small grid, there was another food well (3 cm diameter and 1 cm deep) containing inaccessible fresh food pellets. All parts of the maze apparatus were unprotected; hence, mice were exposed to a complete open space. In the present experiment, the bridge to each arm formed a slope, which was inclined upward by about 40°. The floor of the bridges was covered with wire-mesh grid, which can be easily removed for cleaning or swapped places. Each entry to a bridge was narrowed either on the left or on the right side by short wire mesh wall (width 5 cm × height 5 cm). The narrowing of the entries in and exits from the bridges were designed to prevent mice relying on sequential arm visits. In this setting, most mice did not choose more than one adjacent arm in a test session. The end of each arm was extended with panels of identical size (20.2 × 11.2 cm). These panels were used for holding intra-maze cues made of distinctive pattern drawings designed on plastic adhesive material and attached to a PVC board (18 × 11.2 cm). The maze was surrounded by a heavy pale beige-colored curtain, and it was placed in a sound attenuated room with a masking white noise of 68 dB. The illumination on the surface of the central platform was 180 Lux.

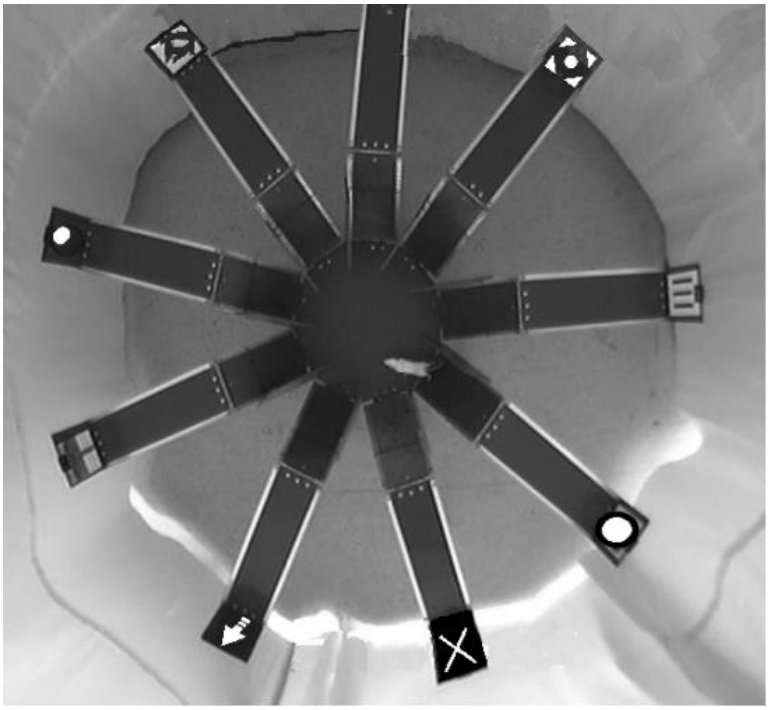


**Figure 1.** Picture of a 9-arms 3-Dimensional maze

### 2.4. Test procedure

Behavioral testing was conducted between 09:00 h and 15:00 h. All mice received their respective treatment in a counterbalanced order 30 min before each test session. A mouse was removed from its cage and placed in a small plastic beaker in which it was weighed. After an i.p. injection of saline or dizocilpine, a mouse was returned to its home cage where it was left for 30 min, then transported in the beaker to the test apparatus. The beaker was tilted gently over the central platform of the maze for the release of the mouse. In each test session, mice were left to explore for 10 min, and each food well contained a single food pellet [20 mg, Precision Pellets, Bio-Serv, UK] and was not replenished once depleted. During the test, mice were observed on a screen monitor connected to a video camera suspended above the test arena. Using an in-house computer program [EventLog] we recorded in sequential order the start and end of each entry to the different parts of the maze. This record provided a variety of measures including frequency, latency, duration, and the sequence order of each visit to the bridges and arms of the maze. An entry onto a bridge or an arm was recorded whenever a mouse crossed with all four paws the line that delimits these areas. After each test, the surface of the platform was cleaned to minimize the effects of lingering olfactory cues. Any feces and urine on the maze were removed with paper towels, then cleaned with ethanol, and left to dry before the introduction of the next mouse.

### 2.5. Statistical analysis

This was performed using Statistica [StatSoft Inc., Tulsa, OK]. All data are presented as mean and standard error of the mean (±SEM). Differences among group mean values for each measurement were tested for significance with two-way ANOVA, with group as a between- and sessions as within-subjects factors. This was followed up with Newman-Keuls post-hoc comparisons. Results were considered significant when $p \leq 0.05$.When p N 0.05 and $p \leq 0.10$, the p value was reported as nonsignificant, and rounded up to the nearest value.

## 3. Results

### 3.1. Latency to first bridge and arm entry

Overall ANOVA revealed significant differences between groups [$F_{2,21}$= 13.95 and 46.71 respectively, $p<0.0001$] and between sessions [$F_{6,126}$= 7.40 and 6.16 respectively, $p<0.0001$] for both parameters, and significant interactions between groups and sessions for the latency to the first arm [$F_{12,126}$= 2.55, $p<0.005$] but not to the first bridge [$F_{12,126}$= 0.80, $p>0.10$] entry. Post-hoc comparisons indicates that MKD1 took longer time to cross for the first time onto a bridge compared to SAL and to MD4 in sessions 2-7 [$p<0.01$, Fig. 2A]. MKD1 took also a longer time to cross for the first time onto an arm compared to SAL [$p<0.02$, Fig. 2B] and to MKD4 [$p<0.05$, Fig. 2B].

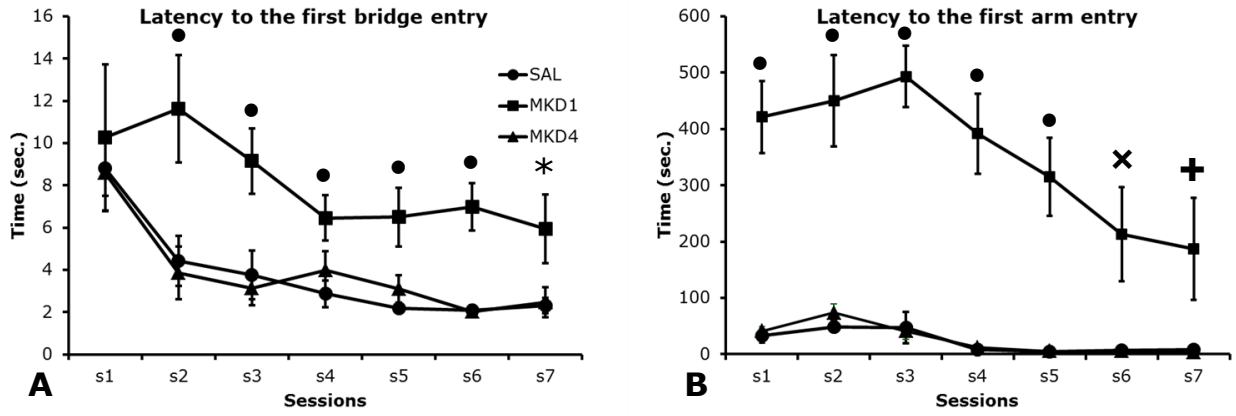
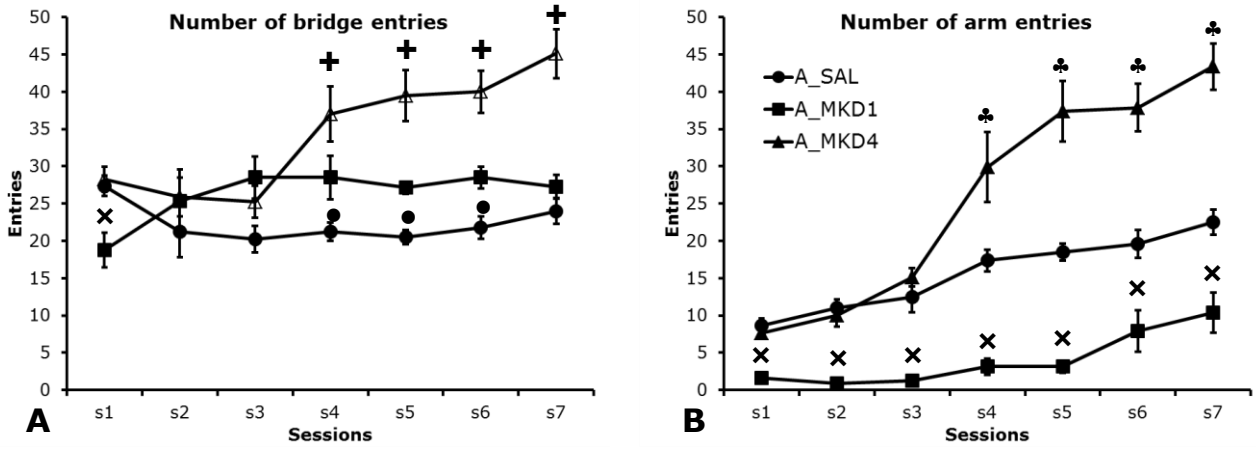



**Figure 2.** Latency of first entry on a bridge (A) and on an arm (B) of the maze. All data are shown as means ± SEM; n=8 in each group. (**A**) •compared to SAL and to MKD4 [p<0.01]; (**B**) •compared to SAL and to MKD4 [p<0.0002]; ×compared to SAL and to MKD4 [p<0.02]; +compared to SAL and to MKD4 [p<0.05].

### 3.2. Total number of bridge and arm entries, and arm/bridge entries ratio

Overall ANOVA revealed significant differences between groups [F2,21= 14.23, 69.98 and 121.61, respectively, p<0.001], between sessions [F6,126= 4.11, 51.42 and 63.05 respectively, p<0.0001] and significant interactions between groups and sessions [F12,126= 6.42, 11.92 11.92 and 6.40 respectively, p<0.0001]. Post-hoc comparisons [Fig. 3A] revealed that in session 1, MKD1 made fewer bridge entries than SAL and MKD4 [p<0.003] whereas in sessions 4-6, they made more bridge entries than SAL [p<0.04]. In sessions 4-7, MKD4 made more bridge crossings than SAL [p<0.002] and MKD1 [p<0.001]. Post-hoc comparisons [Fig. 3B] also show that MKD1 made fewer entries onto the arms than SAL [p<0.005] and MKD4 [p<0.0002] in sessions 1-7, and MKD4 made more entries than SAL [p<0.007] in sessions 4-7. The arm/bridge entries ratio [Fig. 3C] was significantly low in MKD1 compared to SAL [p<0.003] and to MKD4 [p<0.001] in each test session. There were no significant differences between saline and MKD4 groups [p>0.10].



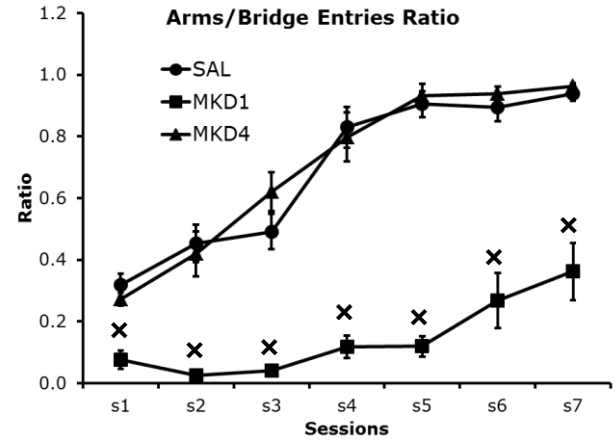
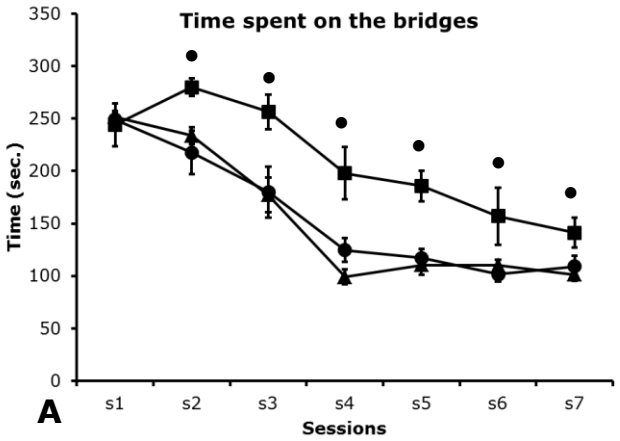
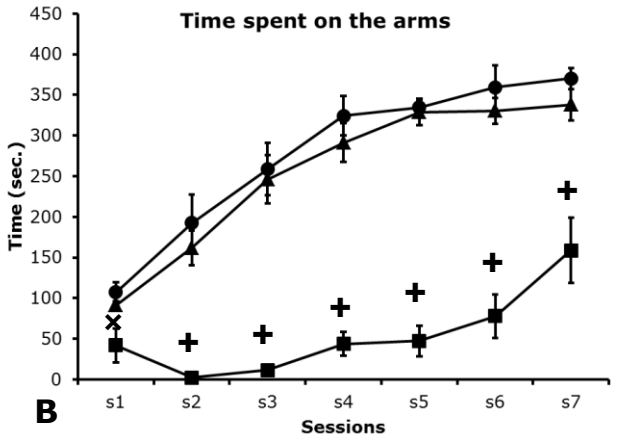



**Figure 3.** Number of entries on the bridges (A), the arms (B) of the maze, and bridge arm entries ratio (C). All data are shown as means ± SEM; n=8 in each group. (**A**) ×compared to SAL and MKD4 [p<0.003]; •compared to SAL [p<0.04]; ✚compared to SAL [p<0.002] and MKD1 [p<0.001]. (**B**) ×compared to SAL [p<0.005] and to MKD4 [p<0.0002]; ♣compared to SAL [p<0.007] (**C**) ×compared to SAL [p<0.003] and to MKD4 [p<0.001].

### 3.3. Total time spent on the bridges and on the arms of the maze, and arms/bridges ratio

Overall ANOVA revealed significant differences between groups [F2,21= 16.60, 88.89, and 33.12 respectively, p<0.0001], between sessions [F6,126= 52.58, 46.60 and 47.77 respectively, p<0.001] and significant interactions between groups and sessions [F12,126= 2.00, 5.71 and 7.05 respectively, p<0.03]. Post-hoc comparisons show that the time spent on the bridges [Fig. 4A] was significantly high in sessions 2 to 7 in MKD1 compared to SAL and MKD4 [p<0.05]. The time spent on the arms [Fig. 4B] was however lower in MKD1 than in the two other groups in session 1 [p<0.02] and sessions 2 to 7 [p<0.002]. The arms/bridges time ratio [Fig. 4C] was significantly low in MKD1 compared to SAL and MKD4 in sessions 2-7 [p<0.005].



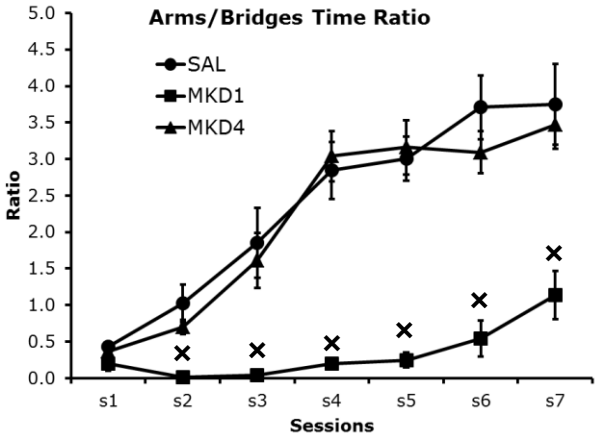



**Figure 4.** Time spent on the bridges (A), the arms (B) of the maze, and bridge/arm time ratio (C). All data are shown as means ± SEM; n=8 in each group. (**A**) •compared to SAL and MKD4 [p<0.05]; (**B**) ×compared to MKD4 and Saline [p<0.02] ✚compared to MKD4 and Saline [p<0.002]; (**C**) ×compared to SAL and MKD4 [p<0.005].

### 3.4. Number of unique arms and time spent up to the 9th arm visit

Overall ANOVA revealed significant differences between groups [F2,21= 62.83 and 50.75 respectively, p<0.0001], between sessions [F6,126= 6.586 and 49.42 respectively, p<0.0001] and significant interactions between groups and sessions [F12,126= 2.60 and 6.72 respectively, p<0.001]. Post-hoc comparisons show that MKD1 made significantly fewer unique arm visits in sessions 1 to 7 [p<0.04, Fig. 5A], and required less time to make these visits in sessions 2 to 7 [p<0.03, Fig. 5B] than SAL and MKD4.

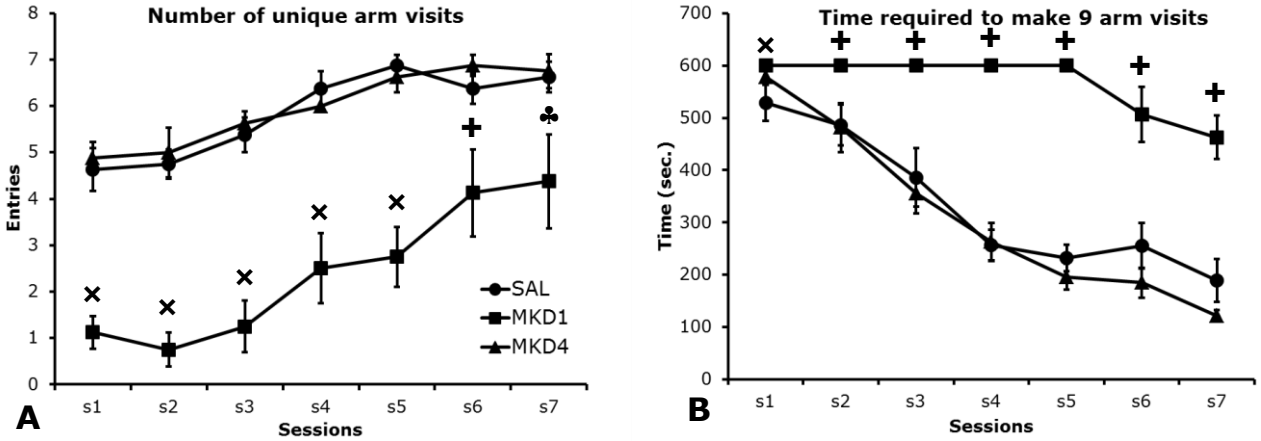



**Figure 5.** Number of unique arm visits (A) and time required to make 9 arm visits (B). All data are shown as means ± SEM; n=8 in each group. (**A**) ×compared to SAL and MKD4 [p<0.0002]; ✚compared to SAL [p<0.02] and to MKD4 [p<0.008]; ♣compared to SAL [p<0.02] and to MKD4 [p<0.04]; (**B**) ×compared to SAL and MKD4 [p<0.03]; ✚compared to SAL and MKD4 [p<0.0006].

## 4. Discussion

In the present study, C57 mice treated with dizocilpine from day 1 (MKD1) of the test demonstrated a very low number of arm entries in each test session compared to saline treated mice. They had also a high number of bridge entries, which led to a significantly low

arm bridge ratio in each test session. These results indicate that MK-801 treatment, which was started from day 1 of the test, produced anxiety in C57 mice and, this was maintained throughout the 7 sessions.

The introduction of dizocilpine after 3 days of exposure to the maze under saline treatment (MKD4) produced a significant high number of bridge and arm entries compared to saline treated mice. This increase in bridge and arm entries reached a ratio close to 1 from session 5 [group average 0.9 ±0.04]. Saline treated mice also reached a comparable bridge/arm entries ratio, but this was achieved with a low number of arm entries [SAL 18.5 ±1.2 vs MKD 37.4 ±4.1]. Treatment with dizocilpine from day 4 of the test did not produce anxiety; rather, it facilitated and increased significantly the number of crossings onto the arms. This does not imply that dizocilpine produced anxiolysis as MKD4 mice did show reduced anxiety before the start of the treatment; they made far more than 8 arm visits in the third session [Fig. 3A].

The present results seem to indicate that dizocilpine produced a psychomotor stimulation; this is more evident in MKD4 mice than in MKD1 mice. An increase in locomotor activity and impulsive response by dizocilpine, and other NMDA antagonists have been reported in the literature [Benn and Robinson 2014; Cottone et al., 2013; Fletcher et al., 2011; Gilmour et al., 2009; Hauber 1993; Higgins et al., 2003; Martin et al., 1997; Paine et al., 2007; Paine and Carlezon 2009; Sanger and Joly 1991; Scorza et al., 2010]. Such an increase in locomotor activity may confound the effects of anxiolytic and anxiogenic drugs [Dawson et al., 1995; Sanger and Joly 1991; Weiss et al., 1998]. However, this cannot account for the anxiety level in MKD1 and MKD4 mice in the 3D maze. In MKD1, an increase in motor activity was limited to the bridges; it did not extend to the arms. In MKD4, anxiety was already low before the administration of MK-801, and it is unlikely that hyperactivity alone could have produced a consistent high number of unique arm visits in the first 9 arm choices. Hence, in MKD1 mice, the increase in bridge entries, though not as dramatic as the one shown with MKD4 mice, appears to be opposed by a high level of anxiety, which prevented mice from crossing onto the arms.

MKD1 mice show a significant increase in entries and time spent in the arms, and a significant decrease in the latency of first arm visit in sessions 6 and 7 compared to the previous sessions. It seems likely that, with further exposures to the maze, the differences between MKD1 and saline treated mice would have been abolished or significantly reduced. In our previous study [Ennaceur et al., 2011], MK-801 treated C57BL/6J mice required 10 sessions of exposures to the maze to reach a high number of arm entries comparable to that of saline treated mice. This suggests that the anxiogenic effect of dizocilpine is not long lasting. It may be overcome through habituation and leaning processes.

The behavior of MKD1 mice contrasts with that of MKD4 mice, the latter demonstrated an increase in bridges and arm entries. MKD4 mice had already low basal level of anxiety at the start of the test, and with three pre-training session, it is unlikely that such level of anxiety could be decreased further. They were already moving freely in all parts of the maze with a group average of 15 arm entries and 0.62 arm/bridge entries ratio in session 3. MK-801

treatment seems to impair habituation in animals that were familiar with the test environment; it produced sustained non-habituating hyperactivity. This phenomenon have been reported for NMDA antagonists [Carey et al., 1988; Klamer et al., 2004; Réus et al., 2008; Venâncio et al., 2011] and genetic models of NMDA hypo-function [Ballard et al., 2002; Bickel et al., 2008; Duncan et al., 2006]. Hyperactivity and deficit in habituation were also observed in animals reared in social isolation [Geyer et al., 1990; 1993; Weiss et al., 2000; see Marsden 2011] and in dopamine transporter knockout mice [Zhuang et al 2001].

It has been reported that a number of drugs produces behavioral sensitization, which refers to long-lasting and progressive enhancement of locomotor and motivational responses following repeated or intermittent administration of psychostimulant drugs [Kalivas and Stewart 1991]. Behavioral sensitization was demonstrated with psychostimulant drugs such as amphetamine [Pierce and Kalivas 1997; Segal and Mandell 1974; Stöhr et al 1998; Kuczenski and Segal 2001], cocaine [Carey et al., 1995; Miserendino and Nestler 1995; Post and Rose 1976; Pierce and Kalivas 1997], methylphenidate [Crawford et al., 1998; Gaytan et al 1997; Kuczenski and Segal 2001], and also with dizocilpine [Vanderschuren et al 1997; Carey et al 1995; Jessa et al 1996; Xu and Domino 1994a; Wedzony and Czyrak 1994; Wedzony et al 1993; Wolf and Khansa 1991; Wolf et al 1993] and phencyclidine [Johnson et al 1998; Xu and Domino 1994b,c; Scalzo and Holson 1992]. The non-habituating hyperactivity observed in MKD4 seems to indicate that MK-801 induced progressive sensitization to its psychomotor stimulant effects.

In MKD1 mice, the time spent in the bridges was higher and the time spent in the arms was lower than that of saline and MKD4 mice; the latter two groups were indistinguishable from one another. Both saline and the two MK-801 treated groups demonstrated a significant decrease between sessions in the time spent on the bridges, and an increase in the time spent on the arms. However, in MKD1 the arm/bridge time ratio reached 1 in the last test session, while in the other two groups it exceeded that ratio much earlier, in session 3. These results indicate that from session 3 onward, saline and MKD4 mice were no longer fearful to venture into and explore the arms. In session 3, saline and MKD4 mice spent more than 41% of the test session in the arms compared to 30% in the bridges, and in session 7 they spent more than 60% of the test session in the arms compared to 18% on the bridges. In MKD1 mice, the time spent in the arms in session 3 was 0.02% compared to 43% in the bridges, and in session 7 it was 26% in the arms and 24% on the bridges.

Examination of the first 9 arm visits in each test session revealed that MKD1 made a high number of bridge entries (except in session 1), and made a very few unique arm visits compared to saline and MKD4. The latter two groups were not different from each other; they demonstrated a significant increase in unique arm visits in sessions 4 to 7 compared to the first 3 sessions, which suggest a reduction in arm repeats. In MKD1 mice, these arm repeats were still high in the last test sessions, which suggests a slower acquisition of a win-shift strategy in this group compared to saline and MKD4 mice. The behavior of MKD1 mice is similar to that observed in our previous study in which C57BL/6J mice received MK-801 on day

1 of the acquisition of a working memory task [Ennaceur et al., 2011]. In this previous experiment, the number of arm visits [6.5 ±1.4] and the number of unique arm visits [4.4 ±1] in MK-801 treated mice were significantly low compared to that of saline [9 ±0 and 7.1 ±0.4, respectively] in session 7.

The results of the present study add to a long-standing debate concerning the specific role of NMDA receptors in memory encoding [Cain et al., 1997; Caramanos and Shapiro 1994; Keith and Rudy 1990; Saucier and Cain 1995; Shapiro and Connor 1992]. NMDA receptors are considered essential to many of the activity-dependent changes in synaptic strength and connectivity, which are thought to underlie the formation of memory. Saucier et al. [1996] suggested that NMDA antagonists produce sensory-motor disturbances, which explain the memory encoding deficit observed in the water-maze. Non-spatial pre-training reduces the severity of these sensorimotor disturbances to the point where animals can acquire the task normally. Since then, numerous studies from these authors and others have been performed in various learning and memory paradigms; they demonstrated that familiarity with the test environment prevented the impairing effects of NMDA antagonists [Cain 1997; Caramanos and Shapiro1994; Chan and McNally 2009; Roesler et al., 1998; Shapiro and O'Connor 1992]. Hence, it appears that NMDA receptor-dependent synaptic plasticity is not necessary in all forms of learning.

MK-801 at 1 and 0.05 mg/kg have been reported to induce alterations in both sensory processing and motor performance that interfere with learning [Ahlander et al., 1999; Ford et al., 1989; Hargreaves and Cain 1992; Whishaw and Auer 1989]. In the present study, these sensory-motor disturbances were not apparent though our data revealed that pre-trained mice were hyperactive. It is possible that the wide range of motor disturbances observed with MK-801 and other NMDA antagonists are specific to the water-maze and resulted from the high level of stress associated with this test [Aguilar-Valles et al., 2005; Harrison et al., 2009; Hölscher 1999; Patil et al., 2009]. In the radial maze and operant conditioning, hyperactivity is the most common nonspecific effect that has been reported [Clissold et al., 1991; Caramanos and Shapiro 1994]. The results of the present study indicate that MK-801 produces anxiety in the 3D maze, hence it is possible that a similar effect occurred with NMDA antagonists in the water-maze. Anxiety could account for the abnormal pattern of behavior described in the literature. When first placed in the maze, mice and rats try to find a way to escape before they discover that there is a platform hidden in the water that they can climb to take refuge. With an increase in anxiety, mice and rats may show high swimming activity, increased thigmotaxis or wall hugging, inability to climb onto and to remain on the platform.

A number of studies reported that MK-801 and other NMDA antagonists exert anxiolytic effects in a number of anxiety tests [Clineschmidt et al., 1982; Criswell et al., 1994; Dunn et al., 1989; Engin et al., 2009; Fraser et al., 1996; Jessa et al., 1996; Kuribara et al., 1990; Plaznik et al., 1994; Sharma and Kulkarni 1991; Soderpalm et al., 1995; Wieronska et al., 2003; Xie and Commissaris 1992; see, Cryan and Dev 2008]. However, most of these studies reported an increase in motor activity indicating non-specific locomotor stimulation.

Furthermore, there are other studies which reported anxiogenic [Hetzler and Wautlet 1985; Ho et al., 2005; Mansbach et al., 1991; Mutlu et al., 2011; Rung et al., 2005; Silvestre et al., 1997; Vasar et al., 1993; Wiley et al., 1998] or no effect [Criswell et al., 1994; Haj-Mirzaian et al., 2015; Hill et al., 2015; Hliňák and Krejčı´1998; Ho et al., 2005; Padovan et al., 2000; Sanger and Joly 1991; Trevlopoulou et al 2016] of NMDA antagonists. The above results were observed in a number of anxiety tests, the plus-maze in particular, which suffer major methodological flaws as discussed in our recent reviews [Ennaceur 2014; Ennaceur and Chazot 2016].

As indicated in the introduction, the 3D maze is a complete open space with no shelter or a wall against which animals can hide. Animals exposed for the first time to this maze demonstrate high level of exploration of the bridges (proximal segments); they climb frequently up to the far end of the bridges and withdraw with a few or no crossing onto the arms (distal segments). However, in subsequent sessions the number of crossings onto the arms does progressively increase though some strains of mice (e.g. BALB/cJ) requires more sessions than other strains (C57BL/6J and CD-1); the former are considered highly anxious than the latter [Ennaceur et al., 2006; Ennaceur 2011]. Hence, in the 3D maze, the effect of an anxiogenic intervention is expected to maintain, or increase and prolong anxiety over a large number of sessions, and the effect of an anxiolytic intervention is not expected to decrease with repeated exposures to the test. This behavioral profile of animals exposed to the 3D maze differs considerably from that observed in the current tests of unconditioned anxiety. For instance, in the plus-maze, animals are reported to display an aversion of the open-arms on the first exposure to the maze and, this aversion is increased further in subsequent sessions [Arabo et al., 2014; Casarrubea et al., 2013; Espejo 1997; Holmes and Rodgers 1998; Rosa et al., 2000; Treit et al., 1993]. In addition, a single previous experience of the plus-maze or light/dark box has been reported to reduce or abolish the effects of both anxiolytic and anxiogenic drugs [Dawson et al., 1994; Escarabajal et al., 2003; Holmes and Rodgers 2003; Rodgers and Shepherd 1993]. Hence, their lack of sensitivity makes it very difficult to predict the therapeutic potential of a drug, especially for chronic use, as it is possible that an initial reaction to a drug differs from its effects on subsequent uses [de Wit and Phillips 2012; Cole and Pieper 1973; Abuhamdah et al., 2015].

The present study suggests that dizocilpine produces anxiety and impairs habituation in a spatial navigation task in C57BL6/J mice that were unfamiliar but not in mice that were familiar with the test environment. Elevated anxiety and impaired habituation may account for the acquisition deficit reported in various learning and memory tests.

## References


[1] R.M. Abuhamdah, M.D. Hussain, P.L. Chazot, A. Ennaceur, Effects of chronic fluoxetine treatment on anxious behaviour of BALB/c mice in a 3-dimensional maze, Stress 18 (2015) 677–685.

[2] A. Aguilar-Valles, E. Sánchez, P. de Gortari, I. Balderas, V. Ramírez-Amaya, F. Bermúdez-Rattoni, P. Joseph-Bravo, Analysis of the stress response in rats trained in the water-maze: differential expression of corticotropin-releasing hormone, CRH-R1, glucocorticoid receptors and brain-derived neurotrophic factor in limbic regions Neuroendocrinology 82 (2005) 306–319.

[3] M. Ahlander, I. Misane, P.A. Schött, S.O. Ogren, A behavioral analysis of the spatial learning deficit induced by the NMDA receptor antagonist MK-801 (dizocilpine) in the rat, Neuropsychopharmacology 21 (1999) 414–426.

[4] A. Arabo, C. Potier, G. Ollivier, T. Lorivel, V. Roy, Temporal analysis of free exploration of an elevated plus-maze in mice, J. Exp. Psychol. Anim. Learn. Cogn. 40 (2014) 457–466.

[5] T.M. Ballard, M. Pauly-Evers, G.A. Higgins, A.M. Ouagazzal, V. Mutel, E. Borroni, J.A. Kemp, H. Bluethmann, J.N. Kew, Severe impairment of NMDA receptor function in mice carrying targeted point mutations in the glycine binding site results in drug-resistant non habituating hyperactivity, J. Neurosci. 22 (2002) 6713–6723.

[6] A. Benn, E.S.J. Robinson, Investigating glutamatergic mechanism in attention and impulse control using rats in a modified 5-choice serial reaction time task, PLoS One 9 (2014), e115374.

[7] S. Bickel, H.P. Lipp, D. Umbricht, Early auditory sensory processing deficits in mouse mutants with reduced NMDA receptor function, Neuropsychopharmacology 33 (2008) 1680–1689.

[8] D.P. Cain, Prior non-spatial pretraining eliminates sensorimotor disturbances and impairments in water maze learning caused by diazepam, Psychopharmacology 130 (1997) 313–319.

[9] D.P. Cain, D. Saucier, F. Boon, Testing hypotheses of spatial learning: the role of NMDA receptors and NMDA-mediated long-term potentiation, Behav. Brain Res. 84 (1997) 179–193.

[10] Z. Caramanos, M.L. Shapiro, Spatial memory and N-methyl-D-aspartate receptor antagonists APV and MK-801: memory impairments depend on familiarity with the environment, drug dose, and training duration, Behav. Neurosci. 108 (1994) 30–43.

[11] R.J. Carey, H. Dai, M. Krost, J.P. Huston, The NMDA receptor and cocaine: evidence that MK-801 can induce behavioral sensitization effects, Pharmacol. Biochem. Behav. 51 (1995) 901–908.

[12] R.J. Carey, H. Dai, J. Gui, Effects of dizocilpine (MK-801) on motor activity and memory, Psychopharmacology 137 (1998) 241–246.

[13] M. Casarrubea, V. Roy, F. Sorbera, M.S.Magnusson, A. Santangelo, A. Arabo, Temporal structure of the rat's behavior in elevated plus maze test, Behav. Brain Res. 237 (2013) 290–299.

[14] W.Y. Chan, G.P. McNally, Conditioned stimulus familiarity determines effects of MK-801 on fear extinction, Behav. Neurosci. 123 (2009) 303–314.

[15] B.V. Clineschmidt, M. Williams, J.J.Witoslawski, P.R. Buting, E.A. Risley, J.A. Totaro, Restoration of shock-suppressed behavior by treatment with (+)-5-methyl-10-11-dihydro-5H dibenzo[a,d]cyclohepten-5,10-imine (MK 801), a substance with potent anticonvulsant, central sympatho-iminetic, and apparent anxiolytic properties, Drug Dev. Res. 2 (1982) 147–163.

[16] D.B. Clissold, J.W. Ferkany, M.J. Pontecorvo, Competitive and noncompetitive Nmethyl-D-aspartate (NM DA) antagonists, haloperidol, and scopolamine impair performance in a nonspatial operant discrimination task, Psychobiology 19 (1991) 332–338.

[17] J.M. Cole, W.A. Pieper, The effects of N,N-dimethyltryptamine on operant behavior in squirrel monkeys, Psychopharmacologia 29 (1973) 107–112.

[18] P. Cottone, A. Iemolo, A.R. Narayan, J. Kwak, D. Momaney, V. Sabino, The uncompetitive NMDA receptor antagonists ketamine and memantine preferentially increase the choice for a small, immediate reward in low-impulsive rats, Psychopharmacology 226 (2013) 127–138.

[19] C.A. Crawford, S.A. McDougall, T.L. Meier, R.L. Collins, J.B.Watson, Repeated methylphenidate treatment induces behavioral sensitization and decreases protein kinase

A and dopamine-stimulated adenylyl cyclase activity in the dorsal striatum, Psychopharmacology 136 (1998) 34–43.
[20] H.E. Criswell, D.J. Knapp, D.H. Overstreet, G.R. Breese, Effects of ethanol, chlordiazepoxide, and MK-801 on performance in the elevated-plusmaze and on locomotor activity, Alcohol. Clin. Exp. Res. 18 (1994) 596–601.
[21] J.F. Cryan, K.K. Dev, The glutamatergic system as a potential therapeutic target for the treatment of anxiety disorders, Handbook of Behavioral Neuroscience 17 (2008) 269–301.
[22] G.R. Dawson, S.P. Crawford, K.J. Stanhope, S.D. Iversen, M.D. Tricklebank, One-trial tolerance to the effects of chlordiazepoxide on the elevated plus-mazemay be due to locomotor habituation, not repeated drug exposure, Psychopharmacology 113 (1994) 570–572.
[23] G.R. Dawson, S.P. Crawford, N. Collinson, S.D. Iversen, M.D. Tricklebank, Evidence that the anxiolytic-like effects of chlordiazepoxide on the elevated plus maze are confounded by increases in locomotor activity, Psychopharmacology 118 (1995) 316–323.
[24] H. de Wit, T.J. Phillips, Do initial responses to drugs predict future use or abuse? Neurosci. Biobehav. Rev. 36 (2012) 1565–1576.
[25] G.E. Duncan, S.S. Moy, J.A. Lieberman, B.H. Koller, Typical and atypical antipsychotic drug effects on locomotor hyperactivity and deficits in sensorimotor gating in a genetic model of NMDA receptor hypofunction, Pharmacol. Biochem. Behav. 85 (2006) 481–491.
[26] R.W. Dunn, R. Corbett, S. Fielding, Effects of 5-HT1A receptor agonists and NMDA receptor antagonists in the social interaction test and the elevated plus-maze, Eur. J. Pharmacol. 169 (1989) 1–10.
[27] E. Engin, D. Treit, C.T. Dickson, Anxiolytic- and antidepressant-like properties of ketamine in behavioral and neurophysiological animal models, Neuroscience 161 (2009) 359–369.
[28] A. Ennaceur, Omission of the habituation procedure in the acquisition of a working memory task — evidence from Balb/c, C57BL/6J, and CD-1 mice, Behav. Brain Res. 223 (2011) 203–210.
[29] A. Ennaceur, Tests of unconditioned anxiety — pitfalls and disappointments, Physiol. Behav. 135 (2014) 55–71.
[30] A. Ennaceur, P.L. Chazot, Preclinical animal anxiety research — flaws and prejudices, Pharma. Res. Per. 4 (2016), e00223.
[31] A. Ennaceur, S. Michalikova, R. van Rensburg, P.L. Chazot, Models of anxiety: responses of mice to novelty and open spaces in a 3D maze, Behav. Brain Res. 174 (2006) 9–38.
[33] A. Ennaceur, S. Michalikova, R. van Rensburg, P.L. Chazot, MK-801 increases the baseline level of anxiety in mice introduced to a spatial memory task without prior habituation, Neuropharmacology 61 (2011) 981–991.
[34] M.D. Escarabajal, C. Torres, C.F. Flaherty, The phenomenon of one-trial tolerance to the anxiolytic effect of chlordiazepoxide in the elevated plus-maze test is abolished by previous administration of chlordiazepoxide or buspirone, Life Sci. 73 (2003) 1063–1074.
[35] E.F. Espejo, Effects of weekly or daily exposure to the elevated plus-maze in male mice, Behav. Brain Res. 87 (1997) 233–238.
[36] P.J. Fletcher, Z. Rizos, K. Noble, G.A. Higgins, Impulsive action induced by amphetamine, cocaine and MK801 is reduced by 5-HT(2C) receptor stimulation and 5-HT(2A) receptor blockade, Neuropharmacology 61 (2011) 468–477.
[37] L.M. Ford, A.B. Norman, P.R. Sanberg, The topography of MK-801-induced locomotor patterns in rats, Physiol. Behav. 46 (1989) 755–758.
[38] C.M. Fraser, M.J. Cooke, A. Fisher, I.D. Thompson, T.W. Stone, Interactions between ifenprodil and dizocilpine on mouse behaviour in models of anxiety and working memory, Eur. Neuropsychopharmacol. 6 (1996) 311–316.
[39] O. Gaytan, S. Al-Rahim, A. Swann, N. Dafny, Sensitization to locomotor effects of methylphenidate in the rat, Life Sci. 61 (1997) PL101–PL107.
[40] M.A. Geyer, N.R. Swerdlow, R.S. Mansbach, D.L. Braff, Startle response models of sensorimotor gating and habituation deficits in schizophrenia, Brain Res. Bull. 25 (1990) 485–498.
[41] M.A. Geyer, L.S. Wilkinson, T. Humby, T.W. Robbins, Isolation rearing of rats produces a deficit in prepulse inhibition of acoustic startle similar to that in schizophrenia, Biol. Psychiatry 34 (1993) 361–372.
[42] G. Gilmour, E.Y. Pioli, S.L. Dix, J.W. Smith, M.W. Conway, W.T. Jones, S. Loomis, R. Mason, S. Shahabi, M.D. Tricklebank, Diverse and often opposite behavioural effects of

NMDA receptor antagonists in rats: implications for "NMDA antagonist modelling" of schizophrenia, Psychopharmacology 205 (2009) 203–216.
[43] A. Haj-Mirzaian, S. Amiri, N. Kordjazy, M. Rahimi-Balaei, A. Haj-Mirzaian, H. Marzban, A. Aminzadeh, A.R. Dehpour, S.E. Mehr, Blockade of NMDA receptors reverses the depressant, but not anxiogenic effect of adolescence social isolation in mice, Eur. J. Pharmacol. 750 (2015) 160–166.
[44] E.L. Hargreaves, D.P. Cain, Hyperactivity, hyper-reactivity, and sensorimotor deficits induced by low doses of the N-methyl-D-aspartate non-competitive channel blocker MK801, Behav. Brain Res. 47 (1992) 23–33.
[45] F.E. Harrison, A.H. Hosseini, M.P. McDonald, Endogenous anxiety and stress responses in water maze and Barnes maze spatial memory tasks, Behav. Brain Res. 198 (2009) 247–251.
[46] W. Hauber, Clozapine improves dizocilpine-induced delayed alternation impairment in rats, J. Neural Transm. Gen. Sect. 94 (1993) 223–233.
[47] B.E. Hetzler, B.S. Wautlet, Ketamine-induced locomotion in rats in an open-field, Pharmacol. Biochem. Behav. 22 (1985) 653–655.
[48] G.A. Higgins, M. Enderlin, M. Haman, P.J. Fletcher, The 5-HT2A receptor antagonist M100, 907 attenuates motor and 'impulsive-type' behaviours produced by NMDA receptor antagonism, Psychopharmacology 170 (2003) 309–319.
[49] X.L. Hill, A. Richeri, C. Scorza, Measure of anxiety-related behaviors and hippocampal BDNF levels associated to the amnesic effect induced by MK-801 evaluated in the modified elevated plus-maze in rats, Physiol. Behav. 147 (2015) 359–363.
[50] Z. Hliňák, I. Krejči, Concurrent administration of subeffective doses of scopolamine and MK-801 produces a short-term amnesia for the elevated plus-maze in mice, Behav. Brain Res. 91 (1998) 83–89.
[51] Y.J. Ho, L.S. Hsu, C.F.Wang, W.Y. Hsu, T.J. Lai, C.C. Hsu, Y.F. Tsai, Behavioral effects of D-cycloserine in rats: the role of anxiety level, Brain Res. 1043 (2005) 179–185.
[52] A. Holmes, R.J. Rodgers, Responses of Swiss-Webster mice to repeated plus-maze experience: further evidence for a qualitative shift in emotional state? Pharmacol. Biochem. Behav. 60 (1998) 473–488.
[53] A. Holmes, R.J. Rodgers, Prior exposure to the elevated plus-maze sensitizes mice to the acute behavioral effects of fluoxetine and phenelzine, Eur. J. Pharmacol. 459 (2003) 221–230.
[54] C. Hölscher, Stress impairs performance in spatial water maze learning tasks, Behav. Brain Res. 100 (1999) 225–235.
[55] M. Jessa, M. Nazar, A. Bidzinski, A. Plaznik, The effects of repeated administration of diazepam, MK-801 and CGP 37849 on rat behavior in two models of anxiety, Eur. Neuropsychopharmacol. 6 (1996) 55–61.
[56] K.M. Johnson, M. Phillips, C. Wang, G.A. Kevetter, Chronic phencyclidine induces behavioral sensitization and apoptotic cell death in the olfactory and piriform cortex, J. Neurosci. Res. 52 (1998) 709–722.
[57] P.W. Kalivas, J. Stewart, Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity, Brain Res. Rev. 16 (1991) 223–244.
[58] G.J. Kant,W.L. Wright, T.N. Robinson 3rd, C.P. D'Angelo, Effects ofMK-801 on learning and memory as assessed using a novel water maze, Pharmacol. Biochem. Behav. 39 (1991) 479–485.
[59] J.R. Keith, J.W. Rudy, Why NMDA-receptor-dependent long-term potentiation may not be a mechanism of learning and memory: reappraisal of the NMDA-receptor blockade strategy, Psychobiology 18 (1990) 251–257.
[60] D. Klamer, E. Pålsson, A. Revesz, J.A. Engel, L. Svensson, Habituation of acoustic startle is disrupted by psychotomimetic drugs: differential dependence on dopaminergic and nitric oxide modulatory mechanisms, Psychopharmacology 176 (2004) 440–450.
[61] R. Kuczenski, D.S. Segal, Locomotor effects of acute and repeated threshold doses of amphetamine and methylphenidate: relative roles of dopamine and norepinephrine, J. Pharmacol. Exp. Ther. 296 (2001) 876–883.
[62] H. Kuribara, S. Fujiwara, H. Yasuda, S. Tadokoro, The anticonflict effect of MK-801, an NMDA antagonist: investigation by punishment procedure in mice, Jpn. J. Pharmacol. 54 (1990) 250–252.

[63] R.S. Mansbach, J. Willetts, S.A. Jortani, R.L. Balster, NMDA antagonists: lack of antipunishment effect in squirrel monkeys, Pharmacol. Biochem. Behav. 39 (1991) 977–981.
[64] C.A. Marsden, M.V. King, K.C. Fone, Influence of social isolation in the rat on serotonergic function and memory—relevance to models of schizophrenia and the role of 5-HT6 receptors, Neuropharmacology 61 (2011) 400–407.
[65] P. Martin, N. Waters, S. Waters, A. Carlsson, M.L. Carlsson, MK-801-induced hyperlocomotion: differential effects of M100907, SDZ PSD 958 and raclopride, Eur. J. Pharmacol. 24 (335) (1997) 107–116.
[66] M.J. Miserendino, E.J. Nestler, Behavioral sensitization to cocaine: modulation by the cyclic AMP system in the nucleus accumbens, Brain Res. 674 (1995) 299–306.
[67] R.G. Morris, E. Anderson, G.S. Lynch, M. Baudry, Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonists, AP5, Nature 319 (1986) 774–776.
[68] O. Mutlu, G. Ulak, I.K. Celikyurt, F.Y. Akar, F. Erden, P. Tanyeri, Effects of olanzapine, sertindole and clozapine on MK-801 induced visual memory deficits in mice, Pharmacol. Biochem. Behav. 99 (2011) 557–565.
[69] D.S. Olton, R.J. Samuelson, Remembrance of places passed: spatial memory in rats, J. Exp. Psychol. Animal. Behav. Process 2 (1976) 97–116.
[70] M.K. Otnaess, V.H. Brun, M.B. Moser, E.I. Moser, Pretraining prevents spatial learning impairment after saturation of hippocampal long-term potentiation, J. Neurosci. 19 (1999) RC49.
[71] C.M. Padovan, E.A. Del Bel, F.S. Guimarães, Behavioral effects in the elevated plus-maze of an NMDA antagonist injected into the dorsal hippocampus: influence of restraint stress, Pharmacol. Biochem. Behav. 67 (2000) 325–330.
[72] T.A. Paine,W.A. Carlezon Jr., Effects of antipsychotic drugs on MK-801-induced attentional and motivational deficits in rats, Neuropharmacology 56 (2009) 788–797.
[73] T.A. Paine, H.C. Tomasiewicz, K. Zhang, W.A. Carlezon Jr., Sensitivity of the fivechoice serial reaction time task to the effects of various psychotropic drugs in Sprague-Dawley rats, Biol. Psychiatry 62 (2007) 687–693.
[74] S.S. Patil, B. Sunyer, H. Höger, G. Lubec, Evaluation of spatial memory of C57BL/6J and CD1 mice in the Barnes maze, the multiple T-maze and in the Morris water maze, Behav. Brain Res. 198 (2009) 58–68.
[75] R.C. Pierce, P.W. Kalivas, A circuitry model of the expression of behavioral sensitization to amphetamine-like psychostimulants, Brain Res. Rev. 25 (1997) 192–216.
[76] A. Plaznik,W. Palejko,M. Nazar, M. Jessa, Effects of antagonists at the NMDA receptor complex in two models of anxiety, Eur. Neuropsychopharmacol. 4 (1994) 503–512.
[77] R.M. Post, H. Rose, Increasing effects of repetitive cocaine administration in the rat, Nature (London) 260 (1976) 731–732.
[79] G.Z. Réus, S.S. Valvassori, R.A.Machado,M.R. Martins, E.C. Gavioli, J. Quevedo, Acute treatment with low doses of memantine does not impair aversive, non-associative and recognition memory in rats, Naunyn Schmiedeberg's Arch. Pharmacol. 376 (2008) 295–300.
[80] R.J. Rodgers, J.K. Shepherd, Influence of prior maze experience on behaviour and response to diazepam in the elevated plus-maze and light/dark tests of anxiety in mice, Psychopharmacology (Berlin) 113 (1993) 237–242.
[81] R. Roesler, M. Vianna, M.K. Sant'Anna, C.R. Kuyven, A.V. Kruel, J. Quevedo, M.B. Ferreira, Intrahippocampal infusion of the NMDA receptor antagonist AP5 impairs retention of an inhibitory avoidance task: protection from impairment by pretraining or preexposure to the task apparatus, Neurobiol. Learn. Mem. 69 (1998) 87–91.
[82] V.P. Rosa, N. Vandresen, A.V. Calixto, D.F. Kovaleski, M.S. Faria, Temporal analysis of the rat's behavior in the plus-maze: effect of midazolam, Pharmacol. Biochem. Behav. 67 (2000) 177–182.
[84] J.P. Rung, A. Carlsson, K. Rydén Markinhuhta, M.L. Carlsson, (+)-MK-801 induced social withdrawal in rats; a model for negative symptoms of schizophrenia, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 29 (2005) 827–832.
[85] M.J. Sanders, M.S. Fanselow, Pre-training prevents context fear conditioning deficits produced by hippocampal NMDA receptor blockade, Neurobiol. Learn. Mem. 80 (2003) 123–129.

[86] D.J. Sanger, D. Joly, The effects of NMDA antagonists on punished exploration in mice, Behav. Pharmacol. 2 (1991) 57–63.
[87] D. Saucier, D.P. Cain, Spatial learning without NMDA receptor-dependent long term potentiation, Nature 378 (1995) 186–189.
[88] D. Saucier, E.L. Hargreaves, F. Boon, C.H. Vanderwolf, D.P. Cain, Detailed behavioral analysis of water maze acquisition under systemic NMDA or muscarinic antagonism: nonspatial pretraining eliminates spatial learning deficits, Behav. Neurosci. 110 (1996) 103–116.
[89] F.M. Scalzo, R.R. Holson, The ontogeny of behavioral sensitization to phencyclidine, Neurotoxicol. Teratol. 14 (1992) 7–14.
[90] M.C. Scorza, A. Castañé, A. Bortolozzi, F. Artigas, Clozapine does not require 5-HT1A receptors to block the locomotor hyperactivity induced by MK-801 Clz and MK-801 in KO1A mice, Neuropharmacology 59 (2010) 112–120.
[91] D.S. Segal, A.J. Mandell, Long-term administration of D-amphetamine: progressive augmentation of motor activity and stereotypy, Pharmacol. Biochem. Behav. 2 (1974) 249–255.
[92] M.L. Shapiro, C. O'Connor, N-methyl-D-aspartate receptor antagonist MK-801 and spatial memory representation: working memory is impaired in an unfamiliar environment but not in a familiar environment, Behav. Neurosci. 106 (1992) 604–612.
[93] A.C. Sharma, S.K. Kulkarni, MK-801 produces antianxiety effect in elevated plus-maze in mice, Drug Dev. Res. 22 (1991) 251–258.
[94] J.S. Silvestre, R. Nadal, M. Pallares, N. Ferre, Acute effects of ketamine in the holeboard, the elevated-plus maze, and the social interaction test in Wistar rats, Depress Anxiety 5 (1997) 29–33.
[95] A.K. Soderpalm, O. Blomqvist, J.A. Engel, B. Soderpalm, Characterization of the anticonflict effect of MK-801, a non-competitive NMDA antagonist, Pharmacol. Toxicol. 76 (1995) 122–127.
[96] T. Stöhr, D. Schulte Wermeling, I. Weiner, J. Feldon, Rat strain differences in openfield behavior and the locomotor stimulating and rewarding effects of amphetamine, Pharmacol. Biochem. Behav. 59 (1998) 813–818.
[97] K.K. Tayler, E. Lowry, K. Tanaka, B. Levy, L. Reijmers,M. Mayford, B.J.Wiltgen, Characterization of NMDAR-independent learning in the hippocampus, Front. Behav. Neurosci. 5 (2011) 28.
[98] D. Treit, J. Menard, C. Royan, Anxiogenic stimuli in the elevated plus-maze, Pharmacol. Biochem. Behav. 44 (1993) 463–469.
[99] A. Trevlopoulou, N. Touzlatzi, N. Pitsikas, 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 (2016) 1045–1054.
[100] T. Uekita, H. Okaichi, NMDA antagonist MK-801 does not interfere with the use of spatial representation in a familiar environment, Behav. Neurosci. 119 (2005) 548–556.
[101] L.J. Vanderschuren, A.N. Schoffelmeer, T.J. De Vries, Does dizocilpine (MK-801) inhibit the development of morphine-induced behavioural sensitization in rats? Life Sci. 61 (1997) PL427–P433.
[102] E. Vasar, J. Harro, A. Lang, A. Soosaar, T. Oopik, S. Koks, S. Sihver, V. Volke, Anti-exploratory effect of N-methyl-D-aspartate in elevated plus-maze. Involvement of NMDA and CCK receptors, Eur. Neuropsychopharmacol. 3 (1993) 63–73.
[103] C. Venâncio, A. Magalhães, L. Antunes, T. Summavielle, Impaired spatial memory after ketamine administration in chronic low doses, Curr. Neuropharmacol. 9 (2011) 251–255.
[104] K.Wedzony, A. Czyrak, The role of corticosteroids in the acquisition of sensitization to locomotor stimulant effects of MK-801, Brain Res. 657 (19) (1994) 351–356.
[105] K.Wedzony, K. Golembiowska, V. Klimek, MK-801-induced symptoms of sensitization. The lack of correlation with the extracellular concentration of dopamine in the rat prefrontal cortex, Brain Res. 625 (1993) 333–336.
[106] S.M. Weiss, G. Wadsworth, A. Fletcher, Utility of ethological analysis to overcome locomotor confounds in elevated maze models of anxiety, Neurosci. Biobehav. Rev. 23 (1998) 265–271.

[107] I.C.Weiss, L. Di Iorio, J. Feldon, A.M. Domeney, Strain differences in the isolation-induced effects on prepulse inhibition of the acoustic startle response and on locomotor activity, Behav. Neurosci. 114 (2000) 364–373.
[108] I.Q. Whishaw, R.N. Auer, Immediate and long-lasting effects of MK-801 on motor activity spatial navigation in a swimming pool and EEG in the rat, Psychopharmacology 98 (1989) 500–507.
[109] J.M.Wieronska, B. Szewczyk, A. Palucha, P. Branski,M. Smialowska, Involvement of CRF but not NPY in the anxiety regulation via NMDA receptors, Pol. J. Pharmacol. 55 (2003) 1119–1124.
[110] J.L. Wiley, A.D. Compton, J.D. Holcomb, S.E. McCallum, S.A. Varvel, J.H. Porter, R.L. Balster, Effects of modulation of NMDA neurotransmission on response rate and duration in a conflict procedure in rats, Neuropharmacology 37 (1998) 1527–1534.
[111] B.J. Wiltgen, A.N.Wood, B. Levy, The cellular mechanisms of memory are modified by experience, Learn. Mem. 18 (2011) 747–750.
[112] M.E.Wolf, M.R. Khansa, Repeated administration ofMK-801 produces sensitization to its own locomotor stimulant effects but blocks sensitization to amphetamine, Brain Res. 562 (1991) 164–168.
[113] M.E. Wolf, F.J. White, X.T. Hu, Behavioral sensitization to MK-801 (dizocilpine): neurochemical and electrophysiological correlates in the meso-accumbens dopamine system, Behav. Pharmacol. 4 (1993) 429–442.
[114] Z. Xie, R.L. Commissaris, Anxiolytic-like effects of the noncompetitive NMDA antagonist MK 801, Pharmacol. Biochem. Behav. 43 (1992) 471–477.
[115] X. Xu, E.F. Domino, Asymmetric cross-sensitization to the locomotor stimulant effects of phencyclidine and MK-801, Neurochem. Int. 25 (1994) 155–159.
[116] X. Xu, E.F. Domino, Genetic differences in the locomotor response to single and daily doses of phencyclidine in inbred mouse strains, Behav. Pharmacol. 5 (1994) 623–629.
[117] X. Xu, E.F. Domino, Phencyclidine-induced behavioral sensitization, Pharmacol. Biochem. Behav. 47 (1994) 603–608.
[118] A. Zemanova, A. Stankova, V. Lobellova, J. Svoboda, K. Vales, K. Vlcek, S. Kubik, I. Fajnerova, A. Stuchlik, Visuospatial working memory is impaired in an animal model of schizophrenia induced by acute MK-801: an effect of pretraining, Pharmacol. Biochem. Behav. 106 (2013) 117–123.
[119] X. Zhuang, R.S. Oosting, S.R. Jones, R.R. Gainetdinov, G.W. Miller, M.G. Caron, R. Hen, Hyperactivity and impaired response habituation in hyperdopaminergic mice, Proc Natl Acad Sci U S A. 98 (2001) 1982–1987.