Neuropharmacology 63 (2012) 710–718

Contents lists available at SciVerse ScienceDirect

Neuropharmacology

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

Dopaminergic modulation of hippocampus-dependent learning: Blockade of hippocampal D1-class receptors during learning impairs 1-trial place memory at a 30-min retention delay

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ARTICLE INFO

Article history:
Received 23 April 2012
Received in revised form
21 May 2012
Accepted 22 May 2012

Keywords:
Hippocampus
Dopamine
Spatial learning
Watermaze
Early LTP
Rat

ABSTRACT

Consistent with the requirement of D1-class dopamine receptors for the induction of late (>3 h) hippocampal long-term potentiation (LTP), hippocampus-dependent 1-trial memory at long retention delays (>6 h) requires hippocampal D1-class receptors during learning. Hippocampal D1-class receptors also modulate the induction and magnitude of early LTP (<1–3 h). However, a corresponding modulation of the formation of hippocampus-dependent early (<1 h) memory remains to be revealed. We addressed this conceptually important issue, using a novel modification of the watermaze delayed-matching-to-place (DMP) test with an improved measure of hippocampus-dependent 1-trial place memory. On the DMP test, rats learn the novel location of a hidden escape platform on trial 1 of every day, so that 1-trial place memory can be measured on trial 2. Our new task modification includes the measurement of search preference for the correct location on trial 2 – a very sensitive index of hippocampus-dependent place memory. We examined the effects of hippocampal D1-class receptor blockade or stimulation during learning on memory at a 30-min retention delay. Bilateral hippocampal infusion of the D1-class receptor antagonist SCH23390 (1 or 5 μg/1 μl/side) before trial 1 dose-dependently impaired such early memory: rats infused with the higher dose showed reduced search preference for the correct location and took longer paths to reach this location. Infusion of the D1-class partial agonist SKF38393 (1 or 5 μg/1 μl/side) did not affect measures of 1-trial place memory. Our data reveal a behavioural correlate of the dopaminergic modulation of early LTP, thereby supporting the close correspondence between hippocampal LTP and hippocampus-dependent learning.

1. Introduction

The hippocampus is innervated by midbrain dopamine neurons (Gasbarri et al., 1997; Swanson, 1982; Verney et al., 1985). These are activated by surprising, novel, aversive and rewarding events (Bromberg-Martin et al., 2010; Redgrave and Gurney, 2006; Schultz, 2007), i.e. relevant events that may be worth learning about. Activation of these neurons has recently also been revealed in response to a change in reward location (Puryear et al., 2010), i.e. in a situation that may require hippocampus-dependent learning of a new place. Currently, there is great interest in the idea that hippocampal dopamine may facilitate learning about relevant events by facilitating synaptic mechanisms of hippocampus-dependent learning, such as place and episodic learning (Lisman et al., 2011; Shohamy and Adcock, 2010).

Long-term potentiation (LTP)-like mechanisms at hippocampal synapses are considered to play a key role in hippocampus-dependent learning (Bliss and Collingridge, 1993; Martin et al., 2000; Morris, 2006; Nakazawa et al., 2004). Hippocampal LTP consists of two stages: early LTP that lasts up to 3 h from induction, is protein synthesis-independent and thought to underlie memories lasting a few minutes to hours; and late LTP that persists beyond 3 h, is protein synthesis-dependent and may underlie memories lasting many hours (Matthies, 1989; Reymann and Frey, 2007). Dopamine, acting mainly on D1-class (D1/5) receptors that are highly expressed in the hippocampus (Hersi et al., 1995), is important for both early and late LTP (Lisman et al., 2011). D1-class receptor activation during induction facilitates induction and increases the magnitude of early LTP (Granado et al., 2008; Hamilton et al., 2010; Ito and Schuman, 2007; Kusuki et al., 1997;

Abbreviations: DMP, delayed-matching-to-place; LTP, long-term potentiation.

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doi:10.1016/j.neuropharm.2012.05.036

Lemon and Manahan-Vaughan, 2006; Li et al., 2003; Ortiz et al., 2010; Otmakhova and Lisman, 1996; Roggenhofer et al., 2010; Stramiello and Wagner, 2008; Zhang et al., 2009) and is necessary for late LTP (Frey et al., 1991, 1990; Huang and Kandel, 1995; O'Carroll and Morris, 2004; Sajikumar and Frey, 2004; Swanson-Park et al., 1999; Wang et al., 2010).

If LTP-like mechanisms are important for hippocampal learning (Bliss and Collingridge, 1993; Martin et al., 2000; Morris, 2006; Nakazawa et al., 2004), the role of D1-class receptors in LTP suggests that blockade of these receptors during learning may decrease the strength of hippocampus-dependent memory at short retention intervals (corresponding to the dopaminergic modulation of early LTP) and abolish the persistence of such memory beyond 3 h (corresponding to the requirement of D1-class receptors for late LTP). These possibilities were examined in two recent studies from our laboratory, which combined hippocampal infusions of the D1-class receptor antagonist SCH23390 with behavioural tests of hippocampus-dependent 1-trial memory at short (20–30 min) and long retention delays (>6 h). Hippocampal D1-class receptor blockade during learning abolished 1-trial memory at the long delays, but did not significantly affect memory at the short delays (Bethus et al., 2010; O'Carroll et al., 2006). These findings offer behavioural correlates for the role of hippocampal D1-class receptors in the induction of late LTP. However, previous behavioural studies left a conceptually important gap: what is the behavioural correlate of the dopaminergic modulation of early LTP?

Given the emerging consensus from electrophysiological studies that hippocampal D1-class receptors play a moderate modulatory role in early LTP (Lisman et al., 2011), blockade of these receptors during learning may not completely block memory at short retention delays, but only moderately reduce memory strength. Interestingly, one of the two studies from our laboratory, using the watermaze delayed-matching-to-place (DMP) task, showed a trend for hippocampal D1-class receptor blockade during learning to impair 1-trial place memory at a short retention delay (20 min), as indicated by increased path lengths to the correct location on trial 2, the key retrieval trial ($0.1 > P > 0.05$) (O'Carroll et al., 2006). We have recently developed a new improved modification of the DMP task that includes the measurement of search preference for the correct location on trial 2 (Bast et al., 2009; Jackson et al., 2011). Search preference is a more sensitive measure of 1-trial place memory than path lengths or latencies; this is demonstrated, for example, by the higher sensitivity of search preference to increasing retention delays (Bruno da Silva, Tobias Bast, Richard G.M. Morris, unpublished findings, manuscript in preparation) and to small partial hippocampal lesions (Bast et al., 2009). In the present study, we used the modified watermaze DMP test with a search-preference measure, to re-examine if hippocampal D1-class receptor blockade, by SCH23390 (O'Boyle et al., 1989), during learning would significantly impair 1-trial place memory at a 30-min retention delay, thereby providing a behavioural correlate of the dopaminergic modulation of early LTP. Additionally, we examined the effect of D1-class receptor stimulation, by the partial agonist SKF38393 (O'Boyle et al., 1989), during learning.

2. Materials and methods

2.1. Subjects

Thirty-eight male adult Lister hooded rats (Charles River UK) weighing 280–330 g and approximately 10–13 weeks old at the start of the experiment (i.e., at surgery) were used. They were housed in cages of four, under temperature (20–23 C)- and humidity (40–55%)-controlled conditions with a 12 h-light–12 h-dark cycle (lights on 7 AM to7 PM). Food and water were provided *ad libitum*. Rats were habituated to handling by the experimenters before the start of any experimental procedures. Experimental procedures were conducted during the light phase as far as possible. All procedures were conducted in accordance with the requirements of the UK Animals (Scientific procedures) Act 1986. All efforts were made to minimise animal suffering and to reduce the number of animals used.

2.2. Implantation of hippocampal infusion guide cannulae

Before any watermaze training, rats were implanted with hippocampal infusion guide cannulae. One day before until 3 days after the surgery, rats received analgesic in their drinking water (Rimadyl Large Animal Solution; 2 ml/L). Rats were anesthetised using isoflurane delivered in oxygen (induction: 4–5%; maintenance: 1–3%). They were secured in a stereotaxic frame where bregma and lambda were aligned horizontally. Infusion guide cannulae (26 gauge) with stylets (33 gauge; Plastics One, Bilaney, UK) projecting 0.5 mm from the end of the guides were implanted through small holes drilled in the skull. The stylet tips were aimed at the following coordinates in the posterior dorsal hippocampus: 4.5 mm posterior, 3.3 mm lateral from bregma and 3.5 mm ventral from the skull. These coordinates were used in previous studies from our laboratory that examined the role of hippocampal neurotransmission, including dopamine transmission, on 1-trial place memory (Bast et al., 2005; O'Carroll et al., 2006; Steele and Morris, 1999; Wang et al., 2010). Cannulae were secured to the skull with dental acrylic and stainless-steel screws. After surgery, the rats were allowed at least 5 days of recovery before watermaze training. During the recovery period, rats were checked daily and habituated to the manual restraint necessary for the drug microinfusions.

2.3. Watermaze apparatus

Behavioural testing was carried out in an open field watermaze, 2 m in diameter and filled with water at 25 ± 1 °C. The water was made opaque by the addition of 200 ml of latex solution. The pool was located in the middle of a room containing large three-dimensional extramaze cues that were arranged at various distances from the pool and visible from the water surface, so as to serve as efficient allocentric orientation cues for the rats. To start a trial, rats were released from one of four start positions (N, E, S, W) around the pool. The rats' only escape route from the water was via a single escape platform of 12-cm diameter. The platform was hidden from the rats' sight 1–2 cm below the water surface. We used a so-called Atlantis platform (Spooner et al., 1994), which can be withheld at >30 cm below the water surface, inaccessible for the rats, by a computer-controlled electromagnet for a predetermined time, before rising to its normal position. This allowed us to run rewarded probe trials during which the rats' search preference for the zone containing the platform location was first monitored for 60 s before the platform was made available to reinforce spatially focussed searching. The rats' swimming behaviour was recorded via a system of a video camera connected to a computer in a control room adjacent to the watermaze room. The computer ran custom-written Watermaze software (Actimetrics, Wilmette, IL) that digitizes the path taken by the rats and computes various behavioural measures. Using the Watermaze programme the following measures were taken: escape latency, path length, swim speed and search preference as indicated by the '% time spent in the correct zone' (see 2.5. Measures of 1-trial place memory).

2.4. Delayed-matching-to-place (DMP) task

On the DMP task (Steele and Morris, 1999) rats receive 4 trials a day. The platform is hidden in a novel location on trial 1 of each day and then remains in this place for trials 2–4, on which rats can use rapidly-encoded place memory to reach the escape platform efficiently. All four start positions are used daily in arbitrary sequence to discourage egocentric strategies. Analysis focuses on trial 2 of each day, on which performance relies on place memory encoded within a single trial, while trials 3 and 4 are run to reinforce the win-stay rule of the task. Whereas the original DMP task relies exclusively on escape latencies to measure performance, we used a novel task modification where trial 2 is occasionally run as rewarded probe trial (Bast et al., 2009; Jackson et al., 2011). On these rewarded probe trials, the platform is not made accessible for the rat until after 60 s, enabling the measurement of the rats' search preference for the zone containing the platform location (compare 2.5.2. Search preference; Fig. 1A,B).

Each trial began with the rat being gently placed into the pool facing the side wall at one of the four start positions. Rats had a maximum of 120 s to search for the platform. Rats failing to locate the platform within this time were guided to the platform by the experimenter. Once rats had reached the platform, they were given 30 s to remain on the platform and encode the spatial location using the surrounding visual cues. The centre of the escape platform was either located on an inner (0.8 m) or outer (1.4 m) ring concentric with the pool. Rats were tested with a novel location each day: as each experiment involved 20 days of training or testing, respectively (eight days of pretraining plus two series of six days during which the effects of hippocampal drug infusions were tested, see 2.6 and 2.8), 20 different locations were used (Fig. 1C).

2.5. Measures of 1-trial place memory

2.5.1. Latencies and path lengths

Latencies and path lengths to reach the platform perimeter were recorded for all trials. Steep latency/path length reductions between trials 1 and 2, so-called

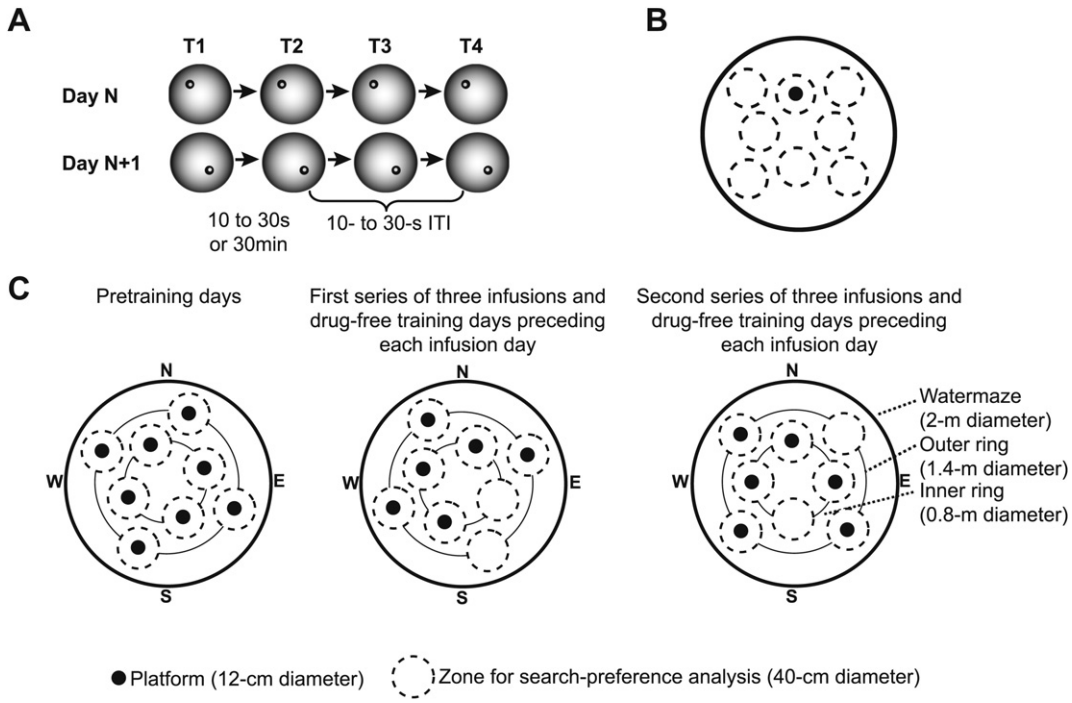

Fig. 1. The watermaze delayed-matching-to-place (DMP) task with a search preference measure. A. The DMP task consists of four daily trials (T1–T4). The hidden platform (dot) remained in the same location during a day, but was moved to a novel location at the start of each day. Thus, rats could rapidly learn the platform location during trial 1 (T1) of each day and use this place memory for efficient performance on trial 2 (T2) and the subsequent trials of this day. The retention delay between T1 and T2 was 10–30 s for the first four days of pretraining and 30 min on all other training and testing days. All other inter-trial intervals (ITIs) within a day were always 10–30 s. Trial 2 was occasionally run as a probe, with the platform not coming up for 60 s, during which search preference for the area containing the platform location could be measured. B. Zone analysis of search preference during probe trials: eight 40-cm diameter zones (stippled circles) were defined within the 2-m diameter surface of the watermaze, including the 'correct' zone, which was concentric with the location of the platform (black dot) on T1 of the day. Zones were arranged, so that they were non-overlapping, evenly spaced and symmetrically distributed across the watermaze surface. The time rats spent in the eight zones during the 60 s of the probe trial was measured, and the percentage of time spent in the correct zone was calculated as: (time in the correct zone [s]/time in all eight zones [s]) × 100%. C. Platform locations used during the three different stages of the two experiments; the zones used for analysis of search preference are also indicated. N, E, S and W indicate the four possible start positions around the pool.

'savings', indicate rapid one-trial place learning. Path lengths have the advantage over latencies that they are independent of swim speed. Because the dopaminergic hippocampal infusions in the present study affected swim speed (see Results; also compare (O'Carroll et al., 2006)), path lengths instead of latencies were analysed in the part of the study that involved hippocampal infusions.

2.5.2. Search preference

In addition, search preference for the vicinity of the platform location when trial 2 was run as a probe trial was used to measure rapid place learning that had taken place during trial 1 (Bast et al., 2009; Jackson et al., 2011). To measure search preference, eight 40-cm diameter 'virtual' zones were defined on the inner and outer ring of the pool, so that one zone, the 'correct' zone, was concentric with the platform location, and all eight zones were non-overlapping, evenly spaced and symmetrically arranged (Fig. 1B,C). The time spent in each of these eight zones during the 60-s probe trial was determined automatically using the Watermaze Software. From these measures, the '% time spent in the correct zone' was calculated as: (time in 'correct zone' [s]/time in all eight zones [s]) × 100%. By chance, this value should be 100%/8 = 12.5%, while higher values indicate a search preference for the correct zone.

2.6. Pretraining on the DMP task

Similar to previous studies, rats were given 8 days of pretraining with 4 trials per day to reach asymptotic performance levels (Bast et al., 2009; Jackson et al., 2011; O'Carroll et al., 2006), before the effects of hippocampal drug microinfusions were tested. During pretraining the platform was in one of eight possible locations, which were never repeated, i.e. a novel platform location was used every day (Fig. 1C, left panel). Rats were randomly split in two batches to be trained with one of two different sequences of daily platform locations, so that each day two different platform locations were used for training; the purpose of this was to reduce the possibility that a day's performance measures are biased by the properties of specific platform locations. After the rat had completed 30 s on the platform, the inter-trial interval (ITI) between trial 1 and 2 was 10–30 s (i.e., as short as possible for convenience) for the first four days of training and 30 min for the remaining days. The ITIs for trials 2–4 were always 10–30 s for convenience. Between trials, rats were placed in cages located in the control room adjacent to the watermaze. On pretraining days 6 and 8, trial 2 was run as probe. In addition, rats received a mock infusion before the start of testing on either day 6 or 8 in order to habituate them to the infusion procedure (see below). Half of the rats received the mock infusion on day 6, the other half on day 8, with start positions and platform locations counterbalanced between the mock-infusion and no-mock-infusion condition.

2.7. Infusion procedure and drugs

Infusions were made in the control room adjacent to the watermaze before trial 1 of the DMP task. Rats were gently restrained, the stylets were removed and 33-gauge injectors (Plastic Ones Bilaney, UK) were bilaterally inserted into the guide cannulae. The injector tips extended 0.5 mm below the guides into the posterior dorsal hippocampus, and the injector ends were connected through polyethylene tubing to 5-μl syringes mounted in a microinfusion pump. A volume of 1 μl per cannula was infused bilaterally over 2.5 min. An additional 1 min was allowed for drug absorption by the brain tissue, before the injectors were replaced by the stylets. The movement of an air bubble, which was included in the tubing, was monitored to verify that liquid was successfully infused into the brain. After completion of the infusion, the rats were kept in their cages for an extra 15 min before being subjected to the DMP task (as in (O'Carroll et al., 2006)). The mock infusions on day 6 or 8 of pretraining were performed like the actual infusions, except that the injection system was not filled with liquid.

The D1-class receptor antagonist SCH23390 and partial agonist SKF38393 (O'Boyle et al., 1989) (Tocris, Bristol, UK) were dissolved at doses of 1 and 5 μg per 1 μl in 0.9% saline and kept frozen and protected from light until use. Saline was used for control infusions. The higher dose (5 μg per side) was chosen based on previous studies examining the effects of SCH23390 (O'Carroll et al., 2006) and SKF38393 (Packard and White, 1991) on hippocampus-dependent learning and memory, and the lower dose (1 μg per side) was included to assess dose–response relations.

2.8. Testing the effects of hippocampal D1-class receptor blockade (Experiment 1) or stimulation (Experiment 2) during encoding on 1-trial place memory at a 30-min retention delay

Following pretraining, testing on the DMP task was continued to examine if hippocampal microinfusions of the D1-class receptor antagonist SCH23390

(Experiment 1, $n = 16$ rats) or the partial agonist SKF38393 (Experiment 2, $n = 22$ rats) before encoding of novel place information (i.e., before trial 1) affects 1-trial place memory at a 30-min retention delay. The DMP task was run as described for the last 4 days of pretraining, with a 30-min retention delay between trial 1 and 2 and a 10–30 s ITI for the remaining trials. A new platform position, different from the pretraining locations, was used every day (Fig. 1C, middle and right panel). As during pretraining, half of the rats each were tested with one of two platform sequences, so that every day two different platform locations were used for testing.

Every second day, rats received one of three bilateral hippocampal infusions 15 min prior to the encoding trial (i.e., trial 1): saline only, or saline containing 1 μg or 5 μg of the D1-class receptor antagonist or agonist (1 μl per side). The order of the three infusions was counterbalanced, using a Latin square design. The series of three different infusions was repeated once more to obtain more accurate estimates of performance measures in each infusion condition from all rats (the resulting two values were averaged to yield one single value of each performance measure for each rat). Within each infusion series, start positions and platform locations were counterbalanced across the infusion conditions.

On infusion days, trial 2 was run as a probe to enable the measurement of search preference. Infusion days were always preceded by a day of standard DMP training without probe trial and without infusion to minimise carry-over effects of probe trials and of drug infusions.

2.9. Histology

At the end of the experiment, all rats were perfused transcardially with 0.9% saline followed by 4% formaldehyde solution. Brains were removed from the skull, post-fixated in 4% formaldehyde solution and cut in 30-μm sections on a cryostat. Every third section through the area of interest in the hippocampus was mounted on slides and stained using cresyl violet. Injection sites were determined using a light microscope and mapped onto coronal sections taken from a standard rat brain stereotaxic atlas (Paxinos and Watson, 1998).

2.10. Data analysis

Latencies (during pretraining), path lengths, path length savings, % time spent in the correct zone and swim speed were analysed. All numerical data are presented as mean ± SEM. The two values of any performance measure in each infusion condition that were obtained for each rat (because each rat received each infusion twice) were averaged to provide one value of each performance measure per infusion condition and rat. Data were analysed using ANOVA with infusion and trials as within-subject factors. Significant main effects were further analysed using Fisher's Least Significant Difference post-hoc procedure (which provides good power and controls the family-wise error rate, if preceded by ANOVA and if no more than three means are compared; Levin et al., 1994). Two-tailed one-sample t-tests were used to compare search preference to chance. The level of significance was set at $P < 0.05$ for all analyses.

3. Results

3.1. Pretraining and mock infusions

During pre-training, rats across Experiment 1 and 2 (overall $n = 38$) acquired asymptotic performance levels on the DMP task, similar to previous studies (Bast et al., 2009; Jackson et al., 2011; O'Carroll et al., 2006; Steele and Morris, 1999). Rats showed high latencies on T1, reflecting search for the novel platform location, and reduced latencies during subsequent trials (main effect of daily trials, $F(3,111) = 145.5$; $P < 0.0001$); there was an especially steep latency reduction from T1 (average across eight pre-training days, 58 ± 2.4 s) to T2 (25 ± 1.5 s) ($P < 0.0001$), demonstrating one-trial place learning (Fig. 2). In addition, overall latencies decreased across days (main effect of days, $F(7,259) = 17.6$; $P < 0.0001$) and the latency reduction between trials improved across days (interaction days × trials, $F(21,777) = 3.1$; $P < 0.0001$), indicating learning of the general task demands. On days 6 and 8, when trial 2 was run as a probe trial (at a 30-min retention delay), rats showed a strong search preference for the vicinity of the correct location (% time in correct zone, 23.6 ± 1.9% and 24.2 ± 1.4%, respectively; analysis of pre-training search preference data is based on $n = 29$ rats, as search preference data of 9 rats were lost due to problems with the software); on both days, this search preference was significantly higher than would have been expected based on chance (12.5%) ($t(28) > 5.6$, $P < 0.0001$).

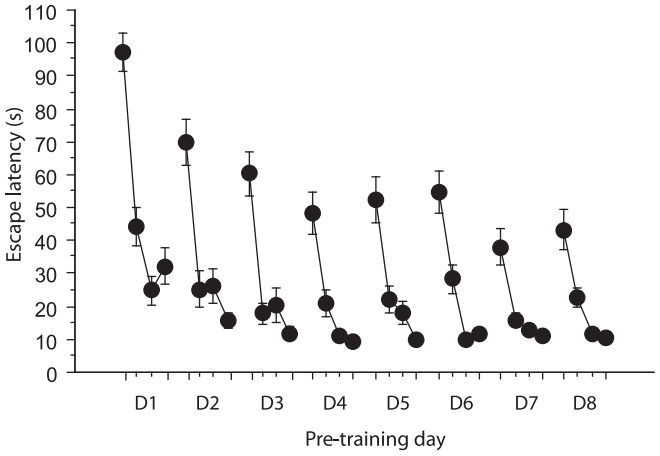

Fig. 2. Pretraining performance on the watermaze DMP task across experiment 1 and 2. Latencies (mean ± SEM) to reach the platform are plotted for trial 1–4 across the 8 pretraining days (D1-8) ($n = 38$). Note the steep latency reduction from trial 1 to 2, indicating 1-trial place learning. The retention delay between trial 1 and 2 was 10–30 s on days 1–4 and 30 min on days 5–8; the inter-trial intervals between trials 2–4 were always 10–30 s.

Mock infusions before trial 1 did not affect search preference on trial 2 (comparison of mock-infusion vs. no-mock-infusion condition: $F(1,28) = 1.6$, $P = 0.22$), nor did they affect latency reductions across trials (interaction mock condition X trials: $F(3,111) < 0.5$) (data not shown).

3.2. Experiment 1: hippocampal D1-class receptor blockade during encoding impairs 1-trial place memory at a 30-min retention delay

Hippocampal infusion of SCH23390 reduced swim speed on T1 at both doses ($F(2,30) = 3.42$; $P < 0.05$; saline *vs* 1 μg/side, $P < 0.03$; saline *vs* 5 μg/side, $P < 0.04$), without affecting swim speed on T2 ($F(2,30) < 1$) (Fig. 3A). This transient decrease in swim speeds on T1 is consistent with previous findings from our laboratory (O'Carroll et al., 2006).

Hippocampal infusion of SCH23390 before the encoding of the new platform location on trial 1 dose-dependently reduced search preference on trial 2 ($F(2,30) = 4.17$; $P < 0.03$), indicating impairment of 1-trial place memory (Fig. 3B). The highest dose significantly decreased search preference as compared to saline infusion (saline *vs* 5 μg/side, $P < 0.01$), whereas no significant difference was observed at the lower dose (saline *vs* 1 μg/side, $P = 0.27$). Search preference for the correct zone was significantly higher than chance in all infusion conditions (all $P < 0.01$), indicating significant 1-trial place memory.

Hippocampal infusion of 5 μg/side of SCH23390 also selectively increased search paths on trial 2 (Fig. 3C), further supporting impaired 1-trial place memory. An ANOVA of path length data yielded a significant interaction between drug treatments and trials ($F(6,90) = 4.23$, $P < 0.04$), indicating reduced path-length reduction from trial 1 to trial 2 when rats had received hippocampal infusion of 5 μg/side of SCH23390 before trial 1. Separate analysis of the four trials revealed that infusion of 5 μg/side of SCH23390, but not of the lower dose, selectively increased path lengths on T2 ($F(2,30) = 4.50$, $P < 0.02$; saline *vs* 1 μg/side, $P = 0.09$; saline *vs* 5 μg/side, $P < 0.006$), whereas path lengths on the other trials did not differ between infusion conditions (all $F < 0.12$). In contrast to the analysis of absolute path lengths, analysis of path length savings between T1 and T2 did not yield any significant difference between infusion conditions ($F(2,30) = 1.77$, $P = 0.19$) (Fig. 3D).

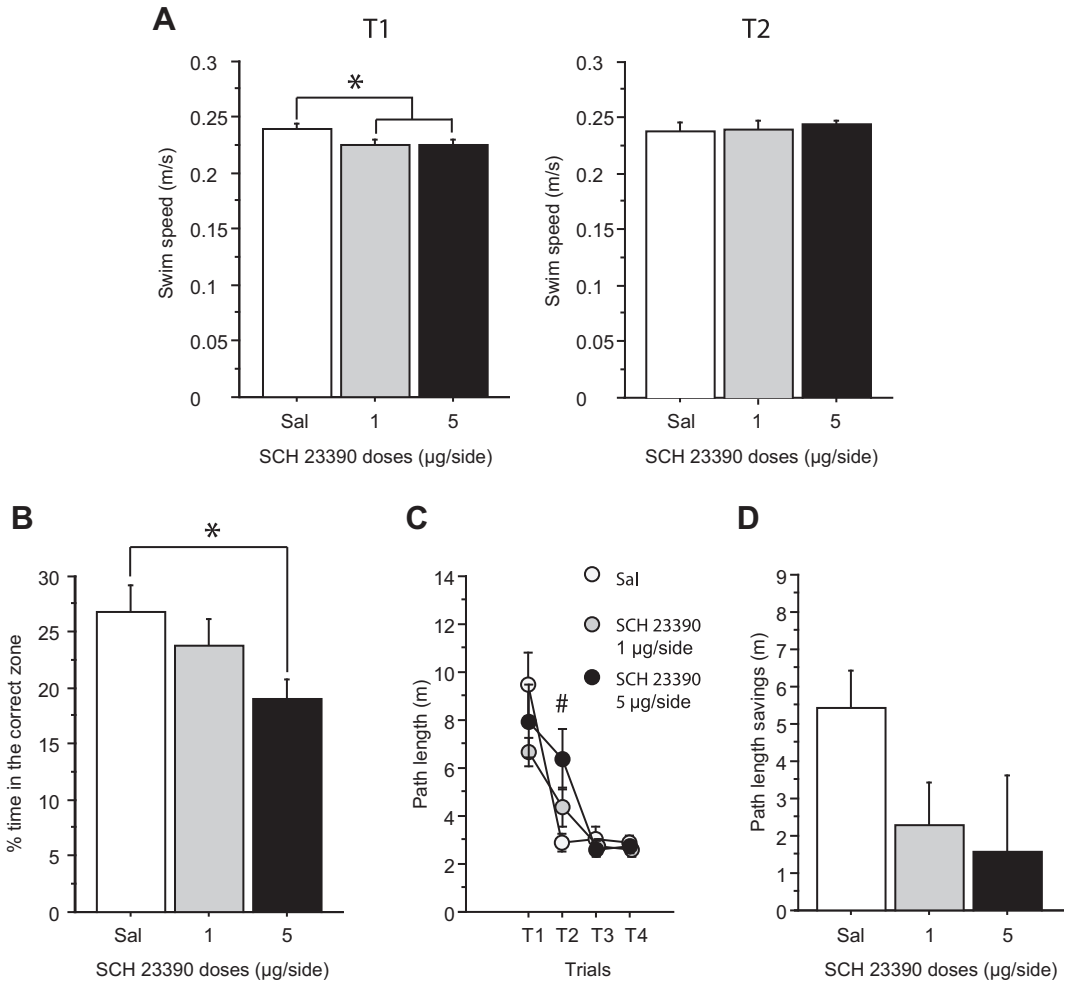

Fig. 3. Experiment 1: Effects of hippocampal D1-class receptor blockade (by local infusion of SCH23390) during learning (trial 1) on watermaze DMP task performance (within-subjects study, $n = 16$; data presented as mean ± SEM). A. Swim speed on trial 1 (T1) and 2 (T2). B. % of time spent in the correct zone during the probe trial (trial 2). C. Path length to reach the platform across the four daily trials (T1-4). D. Path length savings between trial 1 and 2. Outcomes of post-hoc comparisons using Fisher's Least Significant Difference test are indicated as follows: $^{*}P < 0.05$; $\#P < 0.006$, saline vs. 5 µg/side of SCH23390.

3.3. Experiment 2: hippocampal D1-class receptor stimulation during encoding does not affect place memory at a 30-min retention delay

Hippocampal SKF38393 infusions showed a very strong trend to reduce swim speeds dose-dependently on T1 ($F(2,42) = 2.86$; $P = 0.067$; saline *vs* 5 µg/side, $P < 0.04$; saline *vs* 1 µg/side, $P = 0.71$), without affecting swim speeds on T2 ($F(2,42) < 1$) (Fig. 4A).

Hippocampal SKF38393 infusions did not significantly affect any measure of 1-trial place memory. There was no effect of infusion on search preference for the correct location on T2 ($F(2,42) = 1.06$, $P = 0.36$) (Fig. 4B). Rats showed similarly strong and highly significant search preference for the correct location in all infusion conditions (all $P < 0.0001$). Furthermore, analysis of absolute path lengths did not indicate a significant interaction between infusions and trials ($F(6,126) = 1.41$, $P = 0.22$) (Fig. 4C) and path length savings did not differ between doses ($F(2,42) = 1.70$, $P = 0.20$) (Fig. 4D).

3.4. Histology

Injection sites were located within the posterior dorsal hippocampus, with the majority of sites located in the region corresponding to the hippocampal area between 3.60 and 4.16 mm posterior to bregma in the atlas of Paxinos and Watson (Paxinos and Watson, 1998) (Fig. 5). No gross damage was seen after drug infusion, and the morphological structure of the hippocampus was preserved.

4. Discussion

Hippocampal D1-class receptor blockade during learning, by SCH23390, impaired one-trial place memory on the watermaze DMP task at a short retention delay of 30 min. This points to a behavioural correlate of the D1-class receptor modulation of the induction of early LTP (Granado et al., 2008; Hamilton et al., 2010; Ito and Schuman, 2007; Kusuki et al., 1997; Lemon and Manahan-Vaughan, 2006; Li et al., 2003; Ortiz et al., 2010; Otmakhova and Lisman, 1996; Roggenhofer et al., 2010; Stramiello and Wagner, 2008; Zhang et al., 2009). Hippocampal D1-class receptor stimulation during learning, by SKF38393, did not affect measures of 1-trial place memory at the 30-min retention delay.

4.1. Hippocampal D1-class receptor blockade during learning impairs 1-trial place memory at a short retention delay

Hippocampal infusion of the D1-class receptor antagonist SCH23390 15 min before learning a novel platform location on trial

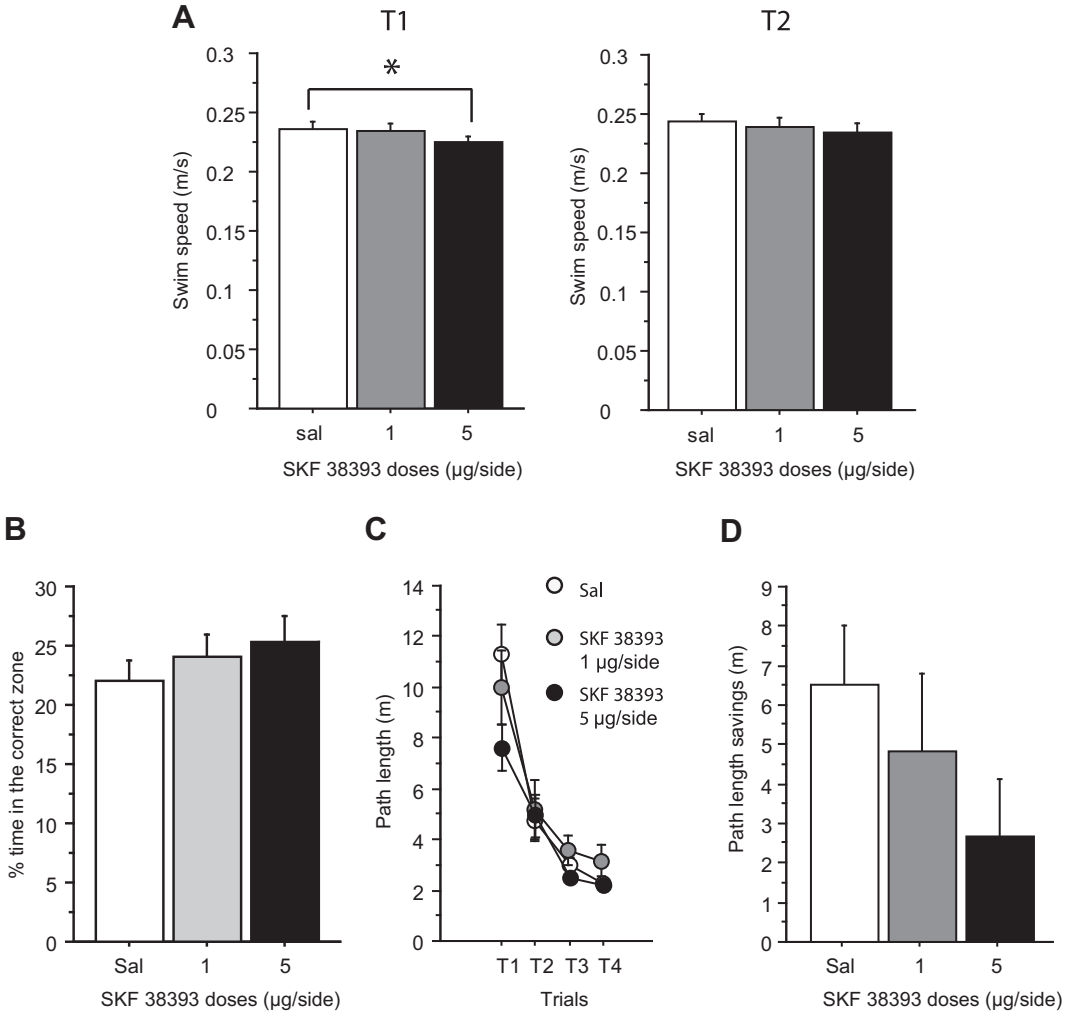

Fig. 4. Experiment 2: Effects of hippocampal D1-class receptor stimulation (by local infusion of SKF38393) during learning (trial 1) on watermaze DMP task performance (within-subjects study, $n = 22$; data presented as mean ± SEM). A. Swim speed on trial 1 (T1) and 2 (T2). B. % of time spent in the correct zone during the probe trial (trial 2). C. Path length to reach the platform across the four daily trials (T1-4). D. Path length savings between trial 1 and 2. *$P < 0.05$, post-hoc comparison using Fisher's Least Significant Difference test.

1 impaired 1-trial place memory on trial 2, as indicated by reduced search preference for the correct location and an increased path length to reach this location. This finding is most consistent with a contribution of hippocampal D1 receptors to memory encoding. Alternative explanations are less plausible. First, the drug could still have been active in the hippocampus during trial 2 and, thus, the impairment observed may reflect a performance or retrieval deficit. However, our finding of SCH23390-induced swim speed decreases on trial 1, but not on trial 2 (which was run 30 min after trial 1; also compare (O'Carroll et al., 2006)), suggests that the drug was mainly active during trial 1. Moreover, a previous watermaze DMTP study, testing the effects of hippocampal SCH23390 infusion after trial 1, 15 min before trial 2, found no evidence for impaired 1-trial place memory performance (O'Carroll et al., 2006). Second, the swim speed reduction during trial 1 may indicate a drug-induced sensorimotor or motivational impairment, and such non-specific impairments may have interfered with the rats learning the novel location. However, even though both doses of SCH23390 (1 and 5 µg/side) reduced swim speed during trial 1, only the higher dose led to an impairment of 1-trial place memory on trial 2, dissociating swim speed reduction from the memory impairment. Third, state dependency of memory, i.e. impaired retrieval due to different physiological states during encoding and retrieval, may be of concern. However, previous studies directly tested if hippocampal SCH23390 induces state dependency of hippocampus-dependent 1-trial memory, including 1-trial place memory on the water-maze DMTP test, and did not find evidence for this (Bethus et al., 2010; O'Carroll et al., 2006).

Thus, our findings suggest that hippocampal D1-class receptor-mediated mechanisms during encoding contribute to the strength of 1-trial place memory at a short retention interval. Hippocampal infusion of the D1 receptor antagonist SCH23390 before encoding, i.e. trial 1, significantly affected measures of 1-trial place memory on trial 2, after a 30-min retention delay: search preference for the correct location was reduced by about 25% and paths to reach the correct location were increased by about 100%; path length savings were not significantly affected. A previous watermaze DMP study from our laboratory, which did not include search preference measures, mainly highlighted that hippocampal SCH23390 infusions before encoding completely prevented 1-trial place memory at a 6-h retention delay; nevertheless, the study also found a trend ($0.1 > P > 0.05$) towards an approximately 50% increase in path lengths at a 20-min retention delay (O'Carroll et al., 2006). In support of our new finding, a moderate, but significant, impairment of 1-trial place memory at a 30-min retention delay was also found in mice, when a peptide interfering with D1-NMDA receptor

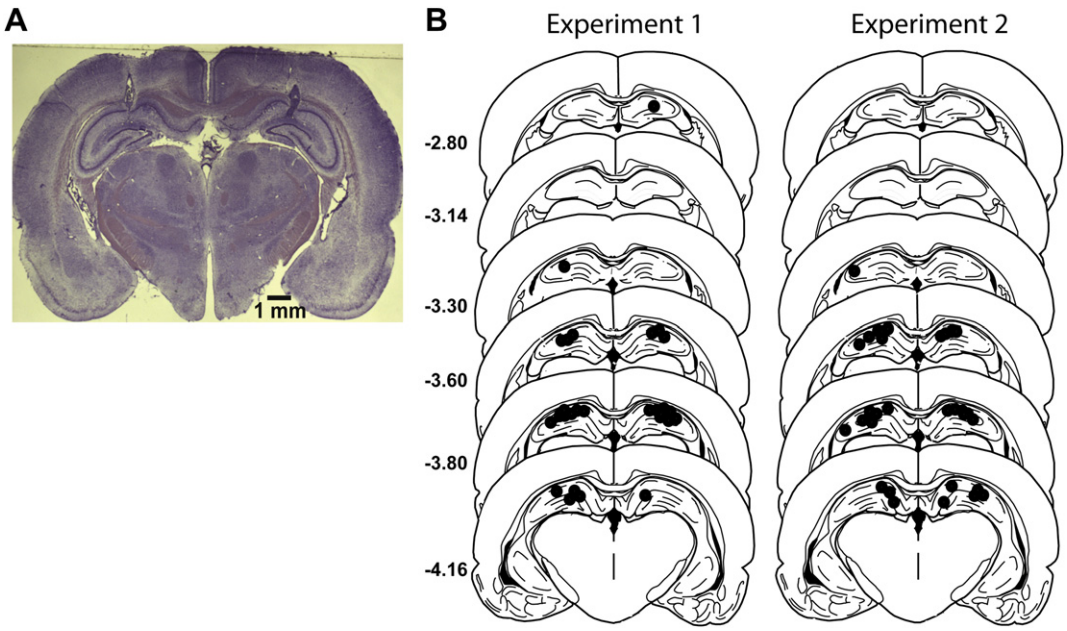

Fig. 5. Placement of injector tips in the hippocampus. A. Photomicrograph of a cresyl violet-stained coronal brain section showing representative bilateral hippocampal cannula placements. B. Reconstruction of injector placements on plates adapted from a standard rat atlas (with numbers indicating distance from bregma in mm) (Paxinos and Watson, 1998).

interactions was infused into the hippocampus before trial 1 of the watermaze DMTP task (Nai et al., 2010). In contrast to studies using the watermaze DMTP test, a recent study that examined the effects of hippocampal SCH23390 infusion on the encoding of hippocampus-dependent 1-trial flavour-place paired-associate memory in the event arena did not find evidence for a memory impairment at a short retention delay (30 min), even though a search preference measure was used and memory at a long retention delay (24 h) was completely abolished (Bethus et al., 2010). This may reflect the different neuropsychological mechanisms involved in the watermaze DMTP task and the event arena paired-associate task. For example, in the event arena task, rats are pre-trained to develop a 'schema' consisting of a series of over-trained paired associates; this schema strongly facilitates the subsequent encoding of new paired associates (Tse et al., 2007) and may render encoding of shorter-term memory less dependent on the facilitating effects of dopamine.

4.2. Relationship to the dopaminergic modulation of hippocampal LTP

Our finding that hippocampal D1-class receptor blockade during encoding impaired 1-trial place memory at a 30-min retention delay offers a behavioural correlate for the D1-class receptor modulation of early LTP (Granado et al., 2008; Hamilton et al., 2010; Ito and Schuman, 2007; Kusuki et al., 1997; Lemon and Manahan-Vaughan, 2006; Li et al., 2003; Ortiz et al., 2010; Otmakhova and Lisman, 1996; Roggenhofer et al., 2010; Stramiello and Wagner, 2008; Zhang et al., 2009). This impairment at the 30-min retention delay is moderate in comparison to the complete blockade of hippocampus-dependent 1-trial memory at longer retention delays (>6 h) that was found following hippocampal D1-class receptor blockade during encoding in previous studies (Bethus et al., 2010; O'Carroll et al., 2006). In contrast, hippocampal NMDA receptor blockade during encoding completely prevents hippocampus-dependent 1-trial place memory even at retention delays of 20 min (Bast et al., 2005; Steele and Morris, 1999). These behavioural-pharmacological effects are consistent with the emerging picture that the induction of early LTP (<1–3 h), while completely prevented by NMDA receptor blockade in most hippocampal subfields (Bast et al., 2005; Bliss and Collingridge, 1993; Martin et al., 2000; Nakazawa et al., 2004; Reymann and Frey, 2007; Steele and Morris, 1999), shows only moderate dopamine dependence in comparison to the induction of late LTP (>3 h) (reviewed in (Lisman et al., 2011)). Thus, there is a close correspondence between the dopaminergic modulation of the induction of hippocampal early vs. late LTP and the dopaminergic modulation of the formation of hippocampus-dependent short-term vs. long-term 1-trial memory. Even though our data do not speak to the specific D1-class receptor subtype (i.e., D1 or D5) involved in the modulation of hippocampal memory encoding, studies in transgenic mice with selective deletion of the D1 receptor gene indicate a critical role for the D1 receptor subtype (Granado et al., 2008; Ortiz et al., 2010; these papers also contain a discussion of possible underlying intra-cellular signalling mechanisms).

Apart from these effects of hippocampal D1-class receptor modulation during learning that correspond well with the dopaminergic modulation of LTP induction, hippocampus-dependent memory has also been reported to be affected by post-learning manipulations, suggesting additional contributions of D1-class receptors to the consolidation and maintenance of hippocampal memory. Thus, hippocampal D1-class receptor stimulation immediately after learning improved place memory on the delay-interposed (15-min delay) win-shift radial maze task (Packard and White, 1991). Another group reported effects of post-learning hippocampal D1-class receptor manipulations on the formation of watermaze reference place memory and on 1-trial inhibitory avoidance memory, with the critical post-learning time windows differing between the two memory types: hippocampal D1-class receptor stimulation or blockade immediately, but not 3 h, after daily place learning sessions (8 consecutive trials per day, for 5 days) improved or impaired, respectively, reference place memory 1 day after the last learning session (da Silva et al., 2012), whereas

hippocampal D1-class receptor stimulation or blockade many hours (between 3 and 12 h), but not immediately, after 1-trial inhibitory avoidance learning improved or impaired, respectively, avoidance memory days later (Bernabeu et al., 1997; Rossato et al., 2009).

4.3. Stimulation of D1-class receptors during encoding does not affect 1-trial place memory

Hippocampal infusion of the D1-class receptor partial agonist SKF38393 (1 and 5 μg/side) 15 min before learning a novel platform location on trial 1 did not affect 1-trial place memory on trial 2. It is possible that a higher dose or the use of a full agonist would have affected memory. Moreover, we dissolved SKF38393 in saline without addition of an antioxidant; even though this procedure is in line with previous studies that observed significant behavioural and electrophysiological drug effects (e.g., (Granon et al., 2000; Li et al., 2003; Packard and White, 1991; Pezze et al., 2007; Roggenhofer et al., 2010)), it is possible that the effective dose may have been reduced due to catecholamine oxidation in solution. However, it is important to note that there is clear evidence, at least for the higher dose that we used, to affect hippocampal function: hippocampal infusion of 5 μg/side of SKF38393 decreased swim speed in the present study and improved hippocampus-dependent memory when applied immediately after the learning trial of the delay-interposed (15-min delay) win-shift radial maze place memory task in a previous study (in which saline without antioxidant was used as vehicle) (Packard and White, 1991). Given that stimulation of hippocampal D1-class receptors during induction by application of D1-class agonists, including the partial agonist SKF38393, has been demonstrated to increase the magnitude of early LTP in vitro (30–40 min after induction) (Otmakhova and Lisman, 1996; Stramiello and Wagner, 2008), hippocampal SKF38393 during learning might have been expected to improve hippocampus-dependent 1-trial place memory at a 30-min retention delay. Even though the search preference for the correct location was numerically increased after hippocampal infusion of 1 and 5 μg/side of SKF38393, this difference was very far from statistical significance. Our findings may reflect that, under the conditions of the present study, D1-class receptor stimulation in the hippocampus is at an optimal level beyond which extra stimulation does not further improve hippocampal encoding mechanisms. Notably, whereas both too little and too much dopaminergic stimulation may impair some cognitive functions mediated by prefrontal cortex and ventral striatum (suggesting an inverted U-shaped relation between dopaminergic stimulation and the respective cognitive function) (e.g., (Cools and D'Esposito, 2011; Granon et al., 2000; Pezze et al., 2003, 2007; Robbins, 2000; Zahrt et al., 1997)), our data indicate that supra-normal hippocampal D1-class receptor stimulation does not impair hippocampus-dependent 1-trial place learning.

5. Conclusion

Our study suggests that hippocampal D1-class receptor activation during learning contributes to the strength of short-term (30-min) 1-trial place memory. This contribution is moderate as compared to the contribution of hippocampal D1-class receptors to the formation of long-term (>6 h) memory that was highlighted by previous studies (Bethus et al., 2010; O'Carroll et al., 2006; Rossato et al., 2009). Nevertheless, the present findings are theoretically important: They reveal a behavioural correlate of the modulation of hippocampal early LTP by D1-class receptors (Granado et al., 2008; Hamilton et al., 2010; Ito and Schuman, 2007; Kusuki et al., 1997; Lemon and Manahan-Vaughan, 2006; Li et al., 2003; Lisman et al., 2011; Ortiz et al., 2010; Otmakhova and Lisman, 1996; Roggenhofer et al., 2010; Stramiello and Wagner, 2008; Zhang et al., 2009), thereby supporting the idea that hippocampal LTP-like mechanisms underlie hippocampus-dependent learning (Bliss and Collingridge, 1993; Martin et al., 2000; Morris, 2006; Nakazawa et al., 2004).

Acknowledgements

Experiments reported in this paper were conducted in the Laboratory of Cognitive Neuroscience at the Centre for Cognitive and Neural Systems (CCNS) of the University of Edinburgh. We are grateful to Richard Morris for his support of our experiments and for helpful discussions. We were financially supported by a Medical-Research-Scotland Jean-Baxter Fellowship (2007–2009) to MP and a Caledonian-Research-Foundation Fellowship (2006–2008) to TB. Additional thanks are due to: Jane Tulloch for histology, Patrick Spooner for technical support, Ann Paterson for help with behavioural testing, and Richard Watson for animal care. MP is currently supported by a Leverhulme Trust Early Career Fellowship.

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