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ORIGINAL INVESTIGATION

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Distinct contributions of glutamate and dopamine receptors to temporal aspects of rodent working memory using a clinically relevant task

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Abstract *Rationale:* Understanding the mechanistic basis of working memory, the capacity to hold representation "on line," is important for delineating the processes involved in higher cognitive functions and the pathophysiology of thought disorders. *Objectives:* We compared the contribution of glutamate and dopamine receptor subtypes to temporal aspects of working memory using a modified rodent spatial working memory task that incorporates important elements of clinical working memory tasks. *Methods:* A discrete paired-trial variable-delay T-maze task was used. Initial characterization studies indicated that performance on this task is stable at seconds-long retention intervals, is sensitive to retention interval and proactive interference, and is dependent on the integrity of the medial prefrontal cortex. *Results:* Consistent with clinical findings, low dose amphetamine (0.25 mg/kg) produced a delay-dependent improvement in performance, while higher doses impaired performance at all retention intervals. D1 receptor blockade produced the predicted dose- and delay-dependent impairment. D2 receptor blockade had no effect. Activation of metabotropic glutamate 2/3 (mGluR2/3) receptors, which in the prefrontal cortex inhibits the slow asynchronous phase of glutamate release, also produced a delay-dependent impairment. Low doses of an AMPA/kainate antagonist had effects similar to the mGluR2/3 agonist. In contrast, NMDA receptor antagonist-induced impairment was memory load-insensitive, resulting in chance-level performance at all retention intervals. *Conclusions:* These findings suggest that activation of NMDA receptors is necessary for the formation of mnemonic encoding while modulatory components involving slow asynchronous release of glutamate and phasic release of dopamine contribute to the active maintenance of information during the delay period.

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Introduction

Working memory (WM) is a transient storage process, maintained by neuronal activity, that subserves other cognitive functions such as comprehension and reasoning (Baddeley 1981; Goldman-Rakic 1987). This mnemonic process has been the subject of intense research in recent years, in the context of both normal brain function (Goldman-Rakic 1996; Courtney et al. 1998; Smith and Jondies 1998) and psychiatric disorders, such as schizophrenia, that are associated with WM deficits (Fleming et al. 1997; Goldberg et al. 1998; Wexler et al. 1998).

Clinical and basic studies have implicated a critical role for glutamate (Pontecorvo et al. 1991; Krystal et al. 1994; Javitt et al. 1996; Verma and Moghaddam 1996; Adler et al. 1998; Aura and Riekkinen 1999; Romanides et al. 1999) and dopamine (Brozoski et al. 1979; Simon et al. 1979; Stam et al. 1989; Sawaguchi and Goldman-Rakic 1991; Williams and Goldman-Rakic 1995; Arnsten 1997; Muller et al. 1998; Suri and Schultz 1999) neurotransmission in maintaining WM. However, the relative contribution of these neuronal systems to the formation of mnemonic coding and active maintenance of WM is not clear. Furthermore, several important discrepancies exist between the two lines of literature; for example, amphetamine and other dopamine agonists generally improve human WM (Mattay et al. 1996; Elliott et al. 1997; Muller et al. 1998) but impair rodent WM (Kesner et al. 1981; Bushnell and Levin 1993; Baron et al. 1998).

The primary goal of this study was to assess the contribution of glutamate and dopamine receptors to the dynamic range (i.e., varying memory load) of rodent WM in a clinically relevant manner. However, as discussed below, because of the limitations associated with most commonly used rodent WM tasks, it was first necessary to modify and characterize a WM task that permits reli-

able assessment of load-dependent impairment *and* improvement in performance.

Human psychological tests of WM such as the "n-back" task measure temporary retention and on-line manipulation of mental representation (Gevins et al. 1990). In non-human primates, analogous tasks such as spatial delayed alternation have been successfully implemented to study WM (Goldman-Rakic 1987). Notwithstanding the scientific impact of primate studies, most behavioral investigations are performed in the rodent because of the greater feasibility of conducting pharmacological, developmental, and genetic manipulations in rodents versus primates. However, rodent WM test paradigms are confounded by several problems that limit extrapolation to human studies. For example, operant tasks such as delayed-matching, or non-matching, to sample (Kolb et al. 1974; Sokolowski and Salamone 1994; Herremans et al. 1996; Kesner et al. 1996) have been criticized because of the interference of mediating behaviors (Herremans and Hijzen 1997) suggesting that animals use their position rather than WM during the delay interval to discriminate between choice levers. Furthermore, manipulations that produce motor activation or incapacitation may affect performance without impairing mnemonic or cognitive processes per se.

Maze tasks are also used routinely to assess spatial WM in rodents. However, the validity of the commonly used radial arm maze as a parallel for human WM, where transient information is retained for seconds, has been questioned (Baddeley 1996) because long delay intervals of up to several hours are routinely used to maintain performance below 100% (Markowska et al. 1983). While tasks involving a Y- or T-maze (Brito and Thomas 1981) are thought to most closely model spatial delayed alternation tasks in primates, these tasks are also prone to overtraining, necessitating the use of long delay intervals of up to several minutes. Another confound of the maze tasks is that the performance of animals continuously improves with training. Therefore, it may be difficult to reliably obtain delay-dependent "baseline" performance that remains stable over repeated trials.

Considering these shortcomings, in the present study we used a modified T-maze task, the discrete paired-trial variable-delay alternation task. Prior to manipulation of glutamate and dopamine receptors, detailed characterization studies were carried out to establish that this task has important elements of human and monkey WM paradigms.

Materials and methods

General design of the WM task

We used a discrete paired-trial variable-delay T-maze task modified from tasks described by Freeman and Stanton (1991) and Granon et al. (1994). The most common delayed alternation task involves continuous alternation in the T-maze wherein the animal is presented with the choice of entering either arm of the maze and is rewarded (i.e., makes the correct choice) if it enters the opposite arm it had entered in the previous run. The distinguishing feature of the present task was that animals were presented with a sequence of discrete trial pairs in which a randomly chosen forced run was followed by a choice run. Specifically, each trial consisted of a forced run during which animals were given access to only one arm of the maze and rewarded after entering that arm. After an *intratrial delay* (or retention interval) they were presented with the choice run, during which they had access to both arms and were rewarded (i.e., made the "correct" choice) after entering the arm that they had not entered on the previous forced run. After this choice run and an *intertrial delay*, animals were exposed to the next forced run, etc. Animals were given one to three training blocks each day, where each block involved ten discrete forced run–choice run pairs. The same intratrial and intertrial delays were used within each block.

Animals

All animal use procedures were in accordance with the NIH *Guide for the Care and Use of Laboratory Animals* and were approved by the Yale University Animal Care and Use Committee. Male Harlan Sprague-Dawley rats (n=89, start weight 220–240 g) were used in this study. They were pair-housed in polycarbonate cages (44×22×21 cm) with free access to water. A restricted diet of 30 g Harlan Tekland food pellets was given to each cage daily (approximately 15 g/rat). In addition to the food pellets, animals received as food reward Kellogg's brand Applejacks cereal during the behavioral sessions. Weights were monitored and recorded weekly throughout the study. Animals gained weight at an average rate of 8.5 g/week. A 12-h light/dark cycle was used (light onset at 8:30 a.m.). Behavioral studies were conducted during the light period. Room temperature was maintained between 22 and 24°C.

Apparatus and test environment

The T-maze was constructed from gray Plexiglas (0.6 cm thick). The main alley, 65×14×28 cm, was connected to two side (goal) arms, 30×14×28 cm. Two sliding doors, 30 cm high and 16 cm wide, were manually operated to close off either goal arm. At the end of each goal arm, a 3-cm piece of Plexiglas blocked the reward (one-quarter of an Applejack morsel) from view. To avoid olfactory cues coming from the baited goal arm, small holes (1–2 mm in diameter) were drilled on the walls of both goal arms near the barrier and a handful of Applejack cereal was placed outside the maze adjacent to these holes. In addition, care was taken to not provide visual cues that could be used by the animal to guide their response: behavioral studies were conducted in a room without any visual landmarks (for example windows, etc.) and the maze was constructed with 28-cm walls which is 10–15 cm taller than a conventional T-maze.

During intertrial and intratrial periods, animals were placed in a plastic holding cage (50×35×28 cm) that was placed adjacent to the maze. To minimize mediating behaviors, the position of this cage was changed slightly between sessions. For the "1–2 s" delay, however, animals were placed back on the start alley immediately after they ate the reward.

Adaptation procedure

Animals were handled and exposed to the T-maze for a period of 3–5 days. Animals were handled in their home cage for 5 min and then placed in the T-maze in pairs (i.e., with their cage-mate) for an additional 5 min. Both goal arms of the maze were baited. Once the paired animals habituated to the maze, they were handled and placed in the maze alone for 5 min. This latter procedure continued until animals ran quickly to both goal arms and consumed the reward (typically 2–4 days).

Training procedure

Animals were first exposed to 3–4 days of ten forced-alternation runs. Specifically, they were placed in the T-maze with one goal

arm closed off and had up to 2 min to run and eat the reward in the open arm. After consuming the reward, they were removed from the maze, and after 10 s in a holding cage they were placed back in the maze with access only to the opposite arm they had visited previously. Next, the discrete paired-trial delayed alternation training began. Each discrete trial consisted of a forced run–choice run pair. For the forced run, animals were constrained to enter a randomly chosen arm. After they consumed the reward in that arm, and a 10-s retention interval in the holding cage, animals were placed back in the maze with access to both arms but with only the opposite arm entered in the previous forced run baited. Once an animal entered its choice arm, the door to that arm was closed off. After an intertrial period of 20 s, the animal was placed back in the maze for another forced run. A different, randomly chosen, pattern of forced runs (for example, R-R-L-R-L-L-R-L-R-L) was used every day. (However, on a given day the same pattern was used for all animals.) Animals were trained at a 10-s intratrial delay for 10 days, or until an animal successfully performed seven out of ten trials (70%) for 3 consecutive days. Animals that did not reach this criterion (approximately 10% in the present study) were rejected. Once an animal performed consistently at the 10-s intratrial delay, training at two additional delays (1 and 40 s) began. Animals were tested at all three delays until they reached criterion, i.e., their alternation score at each delay varied less than 10% in 3 consecutive days.

Drugs and intraperitoneal injections

MK801 and SCH23390 were purchased from Research Biochemical (Natick, Mass., USA). Haloperidol (in ampoule form, pH 7) was obtained from Solopak Laboratories, Elk Grove, Ill., USA. LY293558 and LY354740 were gifts from Lilly (Indianapolis, Ind., USA), and amphetamine was a gift from NIDA (Washington, D.C., USA). All drugs were dissolved (in the case of haloperidol, diluted) in water prior to injection. Therefore, water injections (1 ml/kg) were used as "vehicle" for the entire study. Animals randomly received vehicle or a drug for their first injection. All drugs were injected 45–55 min prior to testing with the exception of SCH23390 which was injected 20–30 min prior to testing due to its short duration of action. Postinjection test sessions, which involved all three delays, lasted approximately 30–40 min. A 7- to 10-day interval was allowed between each drug injection, during which time animals were tested at least 5 days a week. Each animal received a maximum of five injections. Animals were assigned randomly to drug and dose.

Ibotenic acid lesion of the prefrontal cortex

A group of animals that had reached criterion at all three delays was anesthetized with equithesian and placed on a stereotaxic apparatus with blunt earbars. Bilateral holes were drilled over the medial region of the prefrontal cortex [AP, ±3.5 mm; ML, ±0.6 mm, with respect to Bregma, according to Paxinos and Watson (1982)]. Two injections of ibotenic acid (5 g/0.5 l at 0.25 µl/min) were made at DV –5.0 mm and DV –3.0. For sham lesions, animals received an equal volume of vehicle (0.1 M PBS). Animals were allowed to recover for 10–12 days before they were tested at all three delays for 10 days. At the completion of the behavioral study, animals were deeply anaesthetized with chloral hydrate and perfused transcardially with 0.9% saline followed by 10% formalin. Brains were removed, sectioned, and stained with cresyl violet to determine the lesion boundary.

Data analysis

Data for the characterization studies, including the lesion study, were analyzed by parametric repeated measures ANOVA with delay interval or block (day) of trial as the within factor. Because of variations in baseline performance (for example, at the 10-s retention interval, performance of some animals would reach a steady state at 80–90% correct, whereas others would stabilize at 70–80% correct), comparison of vehicle and drug-treated groups was performed on data normalized for baseline performance. Specifically, "baseline performance" at each retention interval was defined as the average of % correct values for 3 consecutive days immediately before the day the animal received an injection (see Fig. 5A, B for examples of this design). For each animal, response to an injection (drug or vehicle) at all delays was first transformed to percentage of that animal's baseline performance. The transformed values for each drug dose and the vehicle group were then compared for all three delays with two-way Kruskal-Wallis ANOVA with delay as the within factor. "Delay dependency" of response for any treatment was determined by one-way Kruskal-Wallis ANOVA with the delay interval as the within factor. The significance was set at $P \leq 0.05$.

Results

General characterization studies

The criteria used to establish the validity of the present discrete paired-trial T-maze task as a clinically relevant WM task were as follows: (1) there was no predictive relationship between two consecutive trials, i.e., the correct choice in trial n was independent from the correct choice in trial n–1, (2) performance (choice accuracy) was affected by retention interval and proactive interference, (3) performance remained at submaximal levels across short (seconds-long) delays, (4) performance at each delay reached a steady state and was not sensitive to overtraining, and (5) performance depended on the integrity of the prefrontal cortex.

The discrete paired-trial design of the task satisfied the first criteria: because of the random selection of the forced run, the correct choices in consecutive trials were independent of each other. Figure 1 demonstrates data satisfying criteria 2 and 3. Performance decreased as the

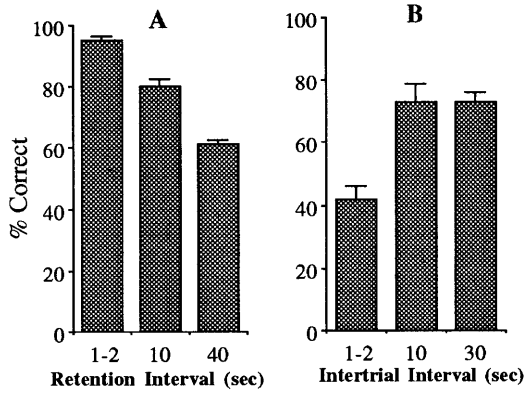

Fig. 1 Effects of varying (**A**) retention interval (the delay between forced and choice run) and (**B**) intertrial interval (the delay between the choice run and the subsequent forced run) on performance. During the trials where retention interval was changed, as well as all subsequent characterization and pharmacological studies, the intertrial interval was 20 s. For the studies presented on panel **B**, the retention interval was 10 s. There was a significant effect of retention interval (**A** $P<0.001$, $F=60.1$, $n=10$) and intertrial interval (**B** $P<0.001$, $F=30.3$, $n=6$) on performance

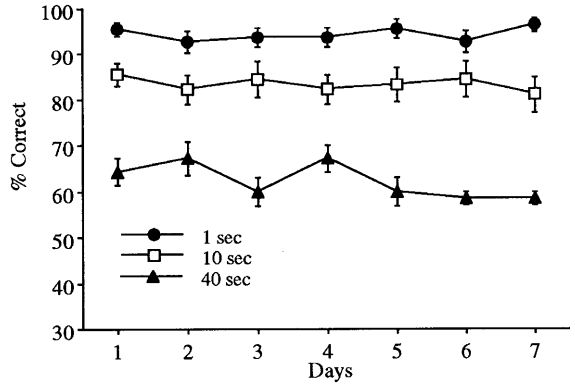

Fig. 2 Daily performance at three retention intervals. Animals (n=12) were tested every day at all three retention intervals. Performance remained stable; there was no significant interaction of performance × day at any delay. The performance throughout the 7 days was delay dependent: there was a significant effect of delay on performance (P<0.001, F=180)

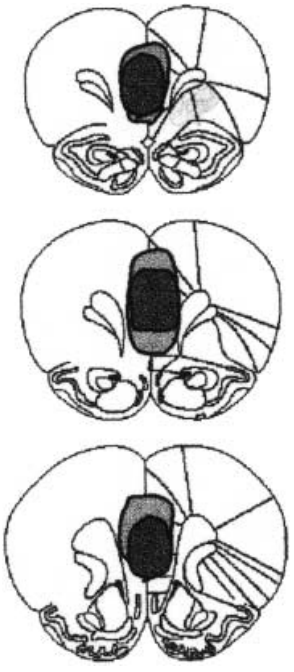

Fig. 3 Representative drawing of the prefrontal cortical lesions according to Paxinos and Watson (1982). The *shaded areas* show the boundaries of the smallest and largest lesions

intratrial delay increased indicating that accuracy in this task is inversely proportional to retention interval (Fig. 1A). This figure also demonstrates that performance at second-long delay remained at submaximal levels. Figure 1B demonstrates the dependency of performance on proactive interference, which was examined by changing the intertrial delay, i.e., imposing delays of various length between the choice run and the following forced run, while keeping the intratrial delay constant (10 s). This design is based on the theory that by spacing the trials more closely, the memory of the previous trial will interfere with processing of information presented for the current trial and thus reduce the response accuracy (Wickens et al. 1963; Grant 1975; Alber and Strupp 1996). Performance was significantly influenced by proactive interference; choice accuracy at a constant 10-s intratrial interval decreased as the intertrial delay was decreased from 10 s to 1–2 s. (For all the subsequent studies involving varying retention intervals, the intertrial interval was maintained at 20 s.)

In order to determine whether performance remains stable and does not continuously improve with daily training (criterion 4), several animals (n=12) were chosen from various stages of the study (i.e., some had just reached criterion and some that had reached criterion several weeks earlier and were used for proactive interference studies or pharmacological studies outlined below) and were tested at all three delays for 7 consecutive days (Fig. 2). As is evident, the daily performance was stable at each of the three delays and there was no trend toward improved performance at any retention interval.

Across species, the prefrontal cortex is considered an integral part of the WM network (Fuster and Alexander 1971; Kolb et al. 1974; McCarthy et al. 1994; Kesner et al. 1996; Cohen et al. 1997; Steckler et al. 1998a). In the rodent, the medioventral region of the frontal cortex is considered necessary for proper performance in WM tasks (Granon et al. 1994; Delatour and Gisquet-Verrier 1996). To examine the dependence of performance in the present task on the integrity of this cortical region, the effect of ibotenic acid and sham lesions of the ventromedial prefrontal cortex was examined in animals that had already reached criterion at all three delays. The extent of the lesion boundary is illustrated in Fig. 3. Animals were tested 10–12 days after the surgery. The testing was performed for 10 days (two periods of 5 consecutive days with a 2-day break in between). The experimenter was blind to the treatment during this period. Based on qualitative observations, all animals (sham and lesioned) appeared familiar with the maze at the onset of postsurgery testing; they started running when placed in the maze, found the food, and ate it rapidly. Figure 4 demonstrates the average performance for lesion and sham animals for 3 days prior to the surgery and the 10-day postsurgery test blocks. The performance of lesioned animals significantly deteriorated at all three retention intervals compared to the sham group. The mean daily performance during the 10-day postsurgery testing is shown in Fig. 4B in order to demonstrate that additional training was not necessary to improve the lesion group since there was no trend toward improved accuracy with repeated testing.

Pharmacological studies

The basic design of all pharmacological studies is illustrated in the example of the effect of 1.0 mg/kg scopolamine (Fig. 5). Although the emphasis of this study was on glutamate and dopamine receptors, for characterization purposes, the effect of the muscarinic antagonist scopolamine, as a prototypic drug with well-established detrimental effects on tests with WM component (see, for example, Beninger et al. 1986; Steckler et al. 1998b),

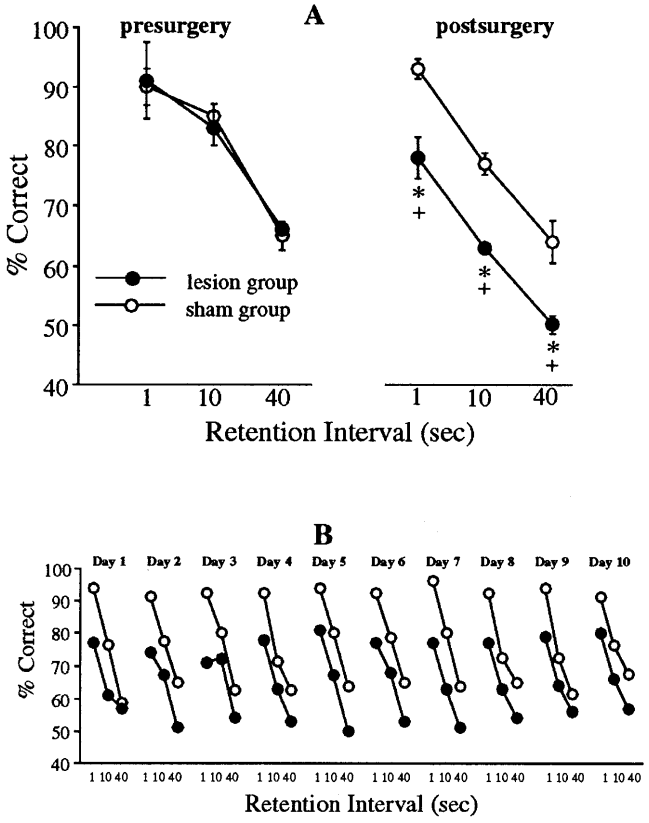

Fig. 4A,B Effect of ibotenic acid lesion of ventromedial prefrontal cortex on performance. The *top panels* show the average performance of sham (n=8) and lesion group (n=9) for a 3-day period before surgery and a 10-day period after surgery. The mean daily postsurgery performance is illustrated on the *bottom panel*. There was no presurgery difference in performance between the two groups. After the surgery, lesion animals were significantly impaired compared to the sham group at all retention intervals (at 1 s, P<0.001, F=24; at 10 s, P<0.005, F=13.2; at 40 s, P<0.005, F=0.009)

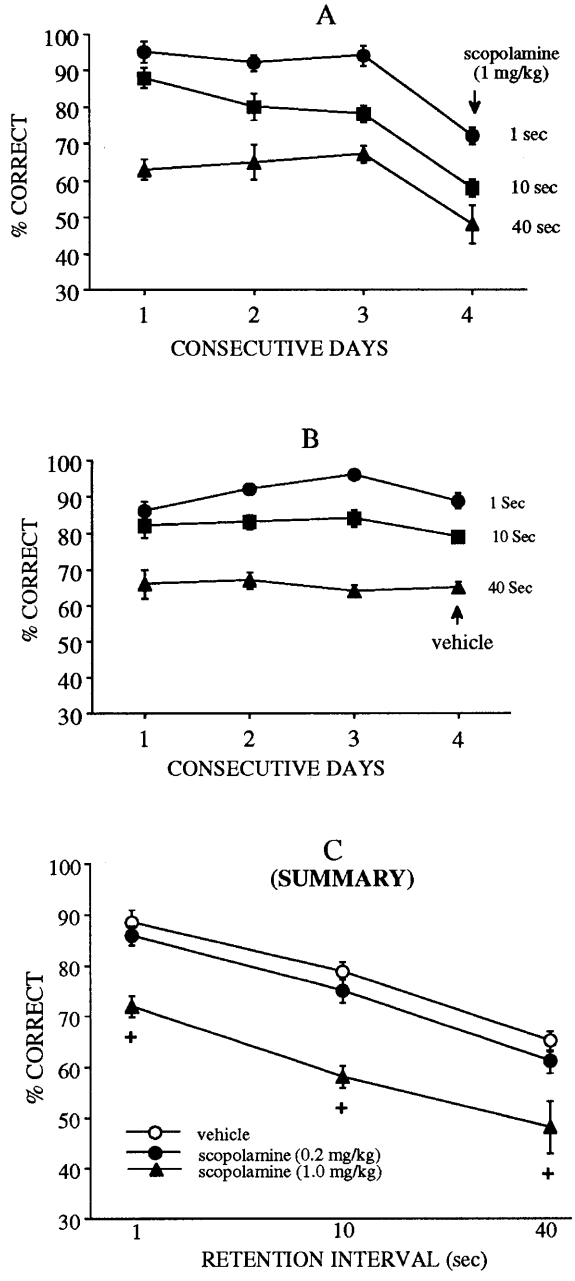

Fig. 5A–C An example of the general design of pharmacological experiments. Testing at each retention interval (delay) was performed for 4 consecutive days; 3 days to establish a "baseline" performance for each animal followed by drug injection prior to testing on the 4th day. The *top two panels* show the results from animals injected with 1.0 mg/kg scopolamine (**A** n=5–6) or vehicle (**B** n=10). The *bottom panel* shows the summary of the scopolamine study; only the data from day 4 (injection day) of each group are shown. The relative change in performance in response to both doses of scopolamine was compared to the corresponding vehicle value (+ P<0.005; see Table 1)

was examined first. For all pharmacological studies, performance at a given delay was assessed for three consecutive "baseline" days. On the 4th day, animals were injected with drug or vehicle before testing. The data points shown on the summary figures (Figs. 5C, 6, 7, 8), therefore, represent performance at each retention interval after 3 days of baseline measures were obtained for that interval. In addition to graphic representation of the effects of vehicle and drug treatment on performance (Figs. 6, 7, 8), the details of statistical analysis for all pharmacological data is presented in Table 1.

To examine the effect of activation of *endogenous* dopamine on WM, we used the dopamine releaser amphetamine (Fig. 6). This approach was used instead of applying exogenous dopamine receptor agonists because of the availability of human WM data utilizing amphetamine and related analogs and, more importantly, because under *in vivo* conditions, some postsynaptic effects of dopamine in the rodent prefrontal cortex are not replicated with exogenous agonists (Sesack and Bunney 1989; Shi et al. 1997). Amphetamine produced a biphasic dose-dependent response. At the low dose of 0.25 mg/kg, performance was improved in a delay-dependent manner, with a significant improvement observed at the 40-s delay. The higher doses of 1.0 and 2.5 mg/kg impaired performance at all delays tested.

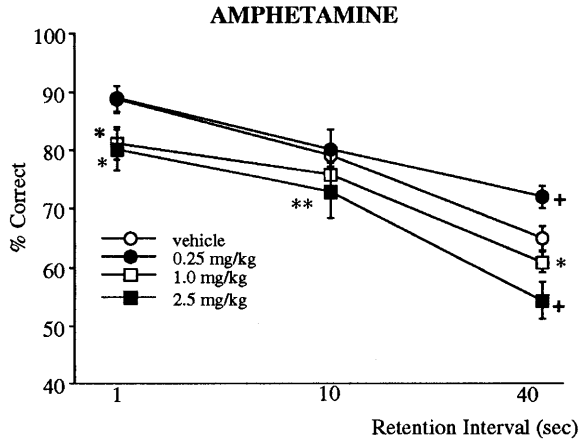

Fig. 6 Delay- and dose-dependent effects of amphetamine. At each delay, data were compared to the vehicle-injected group. The lower dose of amphetamine significantly improved performance at the 40-s delay, while the higher doses impaired performance at all delays (* $P \leq 0.05$, + $P < 0.005$; see Table 1)

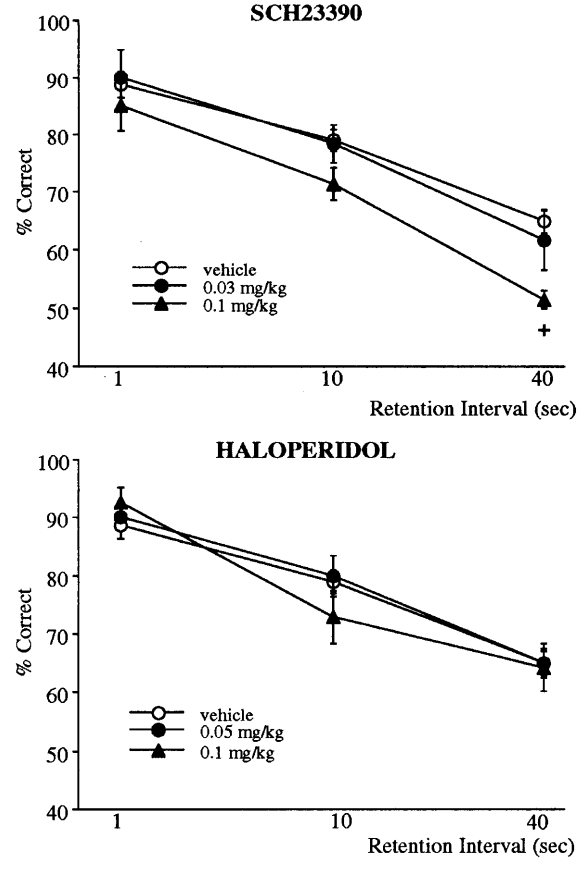

Fig. 7 Delay- and dose-dependent effects of the dopamine D1 antagonist SCH23390, and D2 antagonist, haloperidol. At each delay, data were compared to the vehicle-injected group. SCH23390 significantly impaired performance at the 40-s delay (+ $P < 0.005$; see Table 1)

The D1 antagonist SCH23390 impaired performance in a dose- and delay-dependent manner (Fig. 7); choice accuracy was reduced significantly at the longest retention interval in response to the higher dose of 0.1 mg/kg.

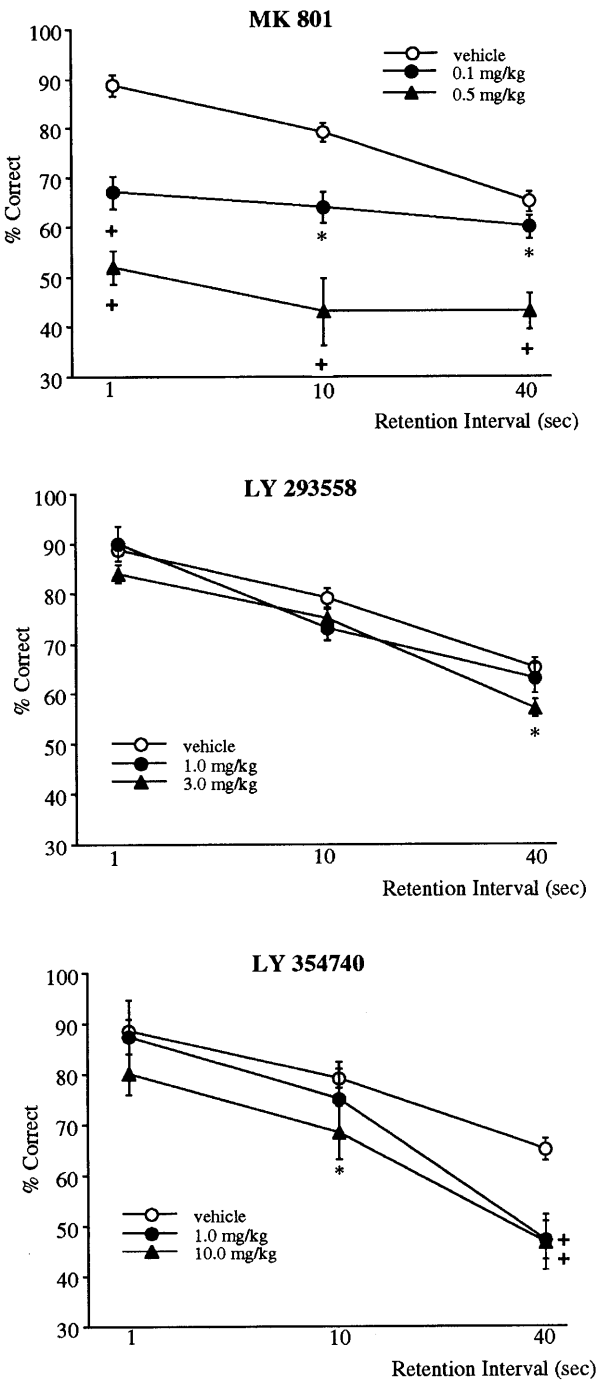

Fig. 8 Delay- and dose-dependent effects of the NMDA antagonist MK801, the AMPA/kainate antagonist LY293558, and the metabotropic glutamate 2/3 receptor agonist, LY354740. (* $P \leq 0.05$, + $P < 0.005$, as compared with the corresponding vehicle-injected group; see Table 1)

The D2 antagonist, haloperidol, even at a dose (0.1 mg/kg) that produced mild catalepsy, did not affect choice accuracy at any delay tested.

Figure 8 illustrates the effect of the systemically active NMDA antagonist MK801, AMPA/kainate antagonist LY293558, and metabotropic glutamate 2/3 (mGluR2/3) agonist LY354740. MK801 produced a

Table 1 The *P* and *F* values in each delay (retention interval) column indicate the significance level of differences between vehicle and drug groups, as determined with Kruskal Wallis analysis of variance. The *P* values stated below each dose of a drug indicate the significance level of the effect of delay interval on performance in response to that drug, thus determining if the effect of that dose was "delay-dependent." Only MK801 (see also Fig. 8) produced a delay-independent effect

	1-s delay			10-s delay			40-s delay		
Drug	*n*	*P*	*F*	*n*	*P*	*F*	*n*	*P*	*F*
Scopolamine, 0.2 mg/kg (*P*<0.005)	9	0.12	2.4	10	0.97	0.001	10	0.13	2.3
Scopolamine, 1.0 mg/kg (*P*<0.005)	5	*0.003	8.6	5	*0.002	9.5	6	*0.007	7.2
Amphetamine, 0.25 mg/kg (*P*<0.05)	5	0.22	1.5	5	0.09	3.0	6	*0.003	8.7
Amphetamine, 1.0 mg/kg (*P*<0.005)	9	*0.02	5.6	7	*0.05	3.7	10	*0.04	4.4
Amphetamine, 2.5 mg/kg (*P*<0.01)	8	*0.01	6.4	11	*0.025	3.9	7	*0.04	4.3
SCH23390, 0.03 mg/kg (*P*<0.001)	6	0.78	0.07	6	0.70	0.15	6	0.92	0.01
SCH23390, 0.1 mg/kg (*P*<0.001)	6	0.18	1.8	7	0.08	3.2	7	*0.004	8.1
Haloperidol, 0.05 mg/kg (*P*<0.001)	5	0.86	0.03	5	0.90	0.12	6	0.47	0.51
Haloperidol, 0.1 mg/kg (*P*<0.001)	8	0.65	0.21	7	0.23	1.4	7	0.79	0.06
MK801, 0.1 mg/kg (*P*=0.32)	6	*0.02	5.15	7	*0.03	4.6	6	*0.05	3.7
MK801, 0.5 mg/kg (*P*=0.33)	6	*0.001	12.1	6	*0.001	11	6	*0.005	7.6
LY293558, 1.0 mg/kg (*P*<0.001)	5	0.29	1.1	6	0.23	1.46	4	0.58	0.30
LY293558, 3.0 mg/kg (*P*<0.001)	8	0.88	0.02	8	0.59	0.29	9	*0.03	4.5
LY354740, 1.0 mg/kg (*P*<0.01)	4	0.29	1.1	6	0.23	1.4	7	*0.001	11
LY354740, 10 mg/kg (*P*<0.005)	6	0.27	1.2	6	*0.04	4.2	6	*0.004	8.2

*Significance was set at $P \leq 0.05$

dose-dependent, delay-independent, disruption of performance. (With the exception of MK801, performance after vehicle and all doses of other drugs tested in this study was delay dependent, i.e., there was a significant effect of delay on performance; see Table 1.) The AMPA/kainate antagonist was tested only at the low doses of 1 and 3 mg/kg, the latter of which produced a significant impairment at the 40-s retention interval. Higher doses of 5 and 10 mg/kg produce motor incapacitation and paralysis; no obvious motor effects were noted at 3 mg/kg. The mGluR2/3 agonist was chosen to complement the findings with ionotropic glutamate receptor antagonists because activation of mGluR2/3 receptors is thought to *inhibit* endogenous release of activated glutamate release, presumably by presynaptic mechanisms (Kilbride et al. 1998; Schoepp et al. 1999). Furthermore, recent studies demonstrate that this inhibition may be selective to the asynchronous phase of glutamate release (Marek and Aghajanian 1998; Aghajanian and Marek 1999), a slow component of glutamate release that evokes small excitatory postsynaptic currents (EPSC) with relatively long latencies of >500 ms (Barrett and Stevens 1972; Goda and Stevens 1994). Activation of mGluR2/3 receptors (Fig. 8) produced a delay-dependent impairment, with both doses significantly impairing performance at the 40-s retention interval.

Discussion

After establishing that a variable-delay discrete paired-trial T-maze task for the rodent duplicated important elements of human and monkey WM tasks, the contribution of dopamine and glutamate neurotransmission to performance of this task was investigated. Our findings suggest that stimulation of NMDA receptors is necessary for the formation of mnemonic encoding, while slow, modulatory components involving asynchronous release of glutamate and phasic release of dopamine contribute to maintenance of WM.

General characterization of the task

Most tests of rodent WM are associated with limitation such as continuously improving (and therefore unstable) baseline performance, and overtraining which necessitates minutes-long retention intervals to maintain perfor-

mance below 100%. Delays of up to several minutes or even hours suggests that mnemonic functions other than WM (defined as on-line retention of representation that is maintained by neuronal activity and not synaptic modification) also contribute to performance. A major advantage of the present task was that performance remained submaximal even at the 1-s retention interval, and deteriorated to near chance-level as the retention interval (memory load) increased to 40 s. Another advantage of this task was that animals' performance reached a steady state at all retention intervals tested. This is an important aspect of the task; considering that WM has a limited capacity, overtraining should not expand WM *per se*. The discrete-trial design of the present task also satisfied the trial-independency requirement that is a major component of human and monkey WM tasks and allowed us to demonstrate that performance is sensitive to proactive interference.

In agreement with previous findings suggesting that ventromedial prefrontal cortex is an integral part of the WM network in the rat (Granon et al. 1994; Aggleton et al. 1995; Delatour and Gisquet-Verrier 1996), animals displayed a disruption at all delays after lesions of this region. The stable delay-dependent performance of the lesion group suggests that these animals were able (and motivated) to perform the task but their WM capacity was reduced compared to the sham group.

Effects of glutamate and dopamine receptor manipulation

A significant observation of the present study was the distinct pattern of impairment in response to NMDA receptor blockade compared to other manipulations. Treatment with the NMDA antagonist, MK801, disrupted performance independent of memory load. Although a delay-independent impairment may be due to disruptions in non-mnemonic components of the task (Steckler et al. 1998b), such as lack of motivation or spatial distortion, our previous findings have shown that MK801, at the doses used here, does not affect the performance on a spatial discrimination task, a control task in the T-maze that involves all but the mnemonic component of the task (Verma and Moghaddam 1996). Thus, an alternative mechanism for the present results is that blockade of NMDA receptors may be preventing, or weakening in the case of low dose blockade, the formation of mnemonic coding. While the precise mechanism involved for this coding process remains to be elucidated, based on physiological data, the following chain of events has been suggested: sensory input to selected WM networks initially activates "cue" neurons that in turn activate "delay" neurons which remain active, i.e., hold information on line, during the retention interval (for a recent reviews see Steckler et al. 1998a, b; Goldman-Rakic 1999a, b). Thus, disrupting the activity of cue neurons, or other processes that are responsible for the initiation of neuronal activity that is maintained during the delay period, would be expected to affect performance independent of the memory load, a mechanism consistent with the MK801 results. On the other hand, manipulations that influence processes responsible for maintaining neuronal activity during the delay period should result in a delay-dependent influence on performance (see below).

Consistent with studies in the primate (Goldman-Rakic 1991; Sawaguchi and Goldman-Rakic 1991; Arnsten et al. 1994; Williams and Goldman-Rakic 1995) and rat (Didriksen 1995; Murphy et al. 1996; Seamans et al. 1998) describing a major role for D1 receptors in WM, the D1 receptor antagonist SCH23390 produced a delay- and dose-dependent impairment. This effect was "graded" in that accuracy was not affected at the 1-s retention interval but the level of impairment increased as the retention interval increased. A similar pattern of impairment was observed with the mGluR2 agonist, LY354740. Activation of this group of receptors, at least in the prefrontal cortex, is thought to block the slow asynchronous phase of glutamate release (Marek and Aghajanian 1998; Aghajanian and Marek 1999), presumably by presynaptic mechanisms (Kilbride et al. 1998). This component of glutamate release evokes small EPSCs with long latencies of >500 ms (Goda and Stevens 1994). Collectively, these findings suggest that while an initial activation of NMDA receptors is necessary for initiation of mnemonic coding, WM is maintained during the delay period by at least two slow components: the asynchronous release of glutamate resulting in sustained (i.e., seconds-long) activation of postsynaptic glutamate receptors, and phasic release of dopamine and subsequent activation of D1 receptors.

The finding that a low dose of amphetamine (0.25 mg/kg) improved performance in a delay-dependent manner is consistent with the above mechanism and suggests that enhanced dopamine release strengthens the modulatory processes that maintain activity during the delay period. Amphetamine at this dose increases dopamine release by about one- to two-fold (unpublished observations), a magnitude of increase that may be considered "physiological" because it is comparable with the increase in cortical dopamine release in response to physiological stimuli such as eating, tactile stimulation, and exposure to novelty (Feenstra et al. 1995; Taber and Fibiger 1997; Takahata and Moghaddam 1998). It should, however, be cautioned that a noradrenergic role (Arnsten 1997) for this effect of amphetamine cannot be ruled out; although, to our knowledge, there are no reports of the effect of low dose amphetamine on norepinephrine release. Nonetheless, it is noteworthy that our amphetamine data is consistent with human data showing amphetamine and its analogs at relatively low doses improve WM and attentional functions in humans (Mattay et al. 1996; Luciana and Collins 1997; Muller et al. 1998). In agreement with previous animal data (Kesner et al. 1981; Bushnell and Levin 1993) and the notion that "supranormal" release of dopamine impairs WM (Arnsten 1997; Zahrt et al. 1997), higher doses of amphetamine (1.0 and 2.5 mg/kg), which increase dopa-

mine release 10- to 40-fold (Zetterstrom et al. 1986; Kuczenski and Segal 1989), impaired performance.

Systemic administration of the low doses of AMPA/kainate antagonist LY293558 produced a significant effect at the 40-s retention interval. The doses of this drug used were low and most likely resulted in minor blockade of AMPA/kainate receptors. One plausible mechanism for the detrimental effects of this low dose AMPA/kainate antagonists may involve modulation of dopamine-mediated neurotransmission (Moghaddam et al. 1997).

Systemic administration of the D2 antagonist haloperidol even at the high dose of 0.1 mg/kg did not affect choice accuracy. This finding is generally consistent with human and animal studies (Sawaguchi and Goldman-Rakic 1991; Bushnell and Levin 1993; Goldberg and Weinberger 1996; Verma and Moghaddam 1996; Krystal et al. 1999), although some studies have reported at least a delay-independent impairment with haloperidol or other D2 antagonists (Didriksen 1995; Murphy et al. 1996; Arnsten and Goldman-Rakic 1998).

While discussing the cholinergic contribution to WM is beyond the scope of the present study, it is interesting to note that the pattern of impairment observed with scopolamine was quite distinct from the effects of dopamine and glutamate antagonists in that while performance was impaired as a function of retention interval, this impairment was not graded and followed the same slope as control animals, and was similar to the impairment observed with high doses of amphetamine and cortical lesions. This observation is consistent with the large body of evidence suggesting the involvement of cholinergic mechanisms in mnemonic (see Steckler et al. 1998b, for review) and attentional processes (see, for example, Everitt and Robbins 1997), disruption of which would impact on the performance of the present task at all retention intervals.

Finally, the mGluR2/3 agonist, which impaired WM at longer retention intervals, has been shown to improve the WM deficit produced by the psychotomimetic drug, phencyclidine (Moghaddam and Adams 1998), suggesting that this drug may have therapeutic efficacy for the adverse cognitive effects of phencyclidine intoxication and related disorders (Marek and Aghajanian 1998; Moghaddam and Adams 1998). The mechanism by which mGluR2/3 agonists affect behavior under normal conditions is likely to be distinct from its effect during phencyclidine intoxication which is associated with large increases in dopamine, glutamate, and serotonin release (Hondo et al. 1994; Adams and Moghaddam 1998; Martin et al. 1998). Thus, the detrimental effect of mGluR2/3 agonists on WM in a normal system should not detract from their potential clinical usefulness in normalizing a disrupted system.

Comparison of present results with previous rodent pharmacological studies

Although, to our knowledge, this is the first report of the effect of a mGluR2/3 agonist on WM, several other studies using maze or operant paradigms have examined the effect of representatives of classes of drugs used here. Previous studies with NMDA antagonists, including MK801, did not find an impairment on radial arm maze performance unless long delays (>5 min) were used (Shapiro and O'Connor 1992; Kesner et al. 1993; Li et al. 1997). Studies using a T-maze have found impairments (Hauber and Andersen 1993; Verma and Moghaddam 1996; Romanides et al. 1999); however, these studies only utilized one delay. Operant tasks have generally reported delay-independent deficits with systemic administration of NMDA antagonists (see, for example, Pontecorvo et al. 1991; Cole et al. 1993; Robinson and Crawley 1993; Stephens and Cole 1996).

Previous rodent studies with the D1 receptor antagonist SCH23390 are difficult to compare with the present results because they involve use of a single delay in radial arm maze or T-maze. Our previous study with a T-maze using a 10-s delay found no effect on performance (Verma and Moghaddam 1996). This study contrasts with the findings of Murphy et al. (1996) who used longer delays. Radial arm maze studies also found no significant effect on performance (Chrobak and Napier 1992; Bushnell and Levin 1993) following systemic injection of D1 receptor antagonists, although intracortical microinjections of SCH23390 produced an impairment (Seamans et al. 1998). The present findings that SCH23390 impairs WM in a delay-dependent fashion suggests that the discrepancies in previous studies may be attributed to the delay used. Previous studies with haloperidol (≤0.1 mg/kg) and other systemically active D2 receptor antagonists have also assessed only a single delay, although these studies have been more consistent in that no significant effect was observed (Chrobak and Napier 1992; Bushnell and Levin 1993; Murphy et al. 1996; Verma and Moghaddam 1996).

A striking difference between the present findings and previous reports is the effect of a low dose of amphetamine. Although clinical studies indicate that low doses of amphetamine improve performance of tasks with a WM component (Mattay et al. 1996; Luciana and Collins 1997; Muller et al. 1998), previous rodent studies have failed to observe an improvement with either maze or operant tasks (Kesner et al. 1981; Dunnett 1985; Sahgal 1987; Reading and Dunnett 1991; Bushnell and Levin 1993). Our finding that a low dose of amphetamine improves performance suggests that the present task is sensitive for assessing improvement in WM, and provides evidence for cross-species pharmacological homology in the effects of amphetamine, as well as NMDA antagonists, on WM.

Conclusions

The memory-load-dependent and -independent pattern of impairment with NMDA, AMPA, D1 receptor antagonists, or mGluR2/3 agonist, as well as the pattern of improvement by low dose amphetamine suggest the follow-

ing: (1) activation of NMDA receptors is necessary for the initiation of mnemonic encoding and (2) during the retention phase, WM is maintained by modulatory components that include the slow asynchronous phase of glutamate release, resulting in sustained postsynaptic activation of glutamate receptors, and phasic release of dopamine, resulting in activation of D1 receptors. These mechanisms are consistent with the proposed state-dependent modulatory role for cortical dopamine (Durstewitz et al. 1999; Goldman-Rakic 1999a; Yang et al. 1999) and with theoretical models (Lisman et al. 1998; Wang 1999) implicating a role for NMDA and slow glutamatergic neurotransmission in WM.

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