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Comparative effects of cholinergic drugs and lesions of nucleus basalis or fimbria-fornix on delayed matching in rats

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Abstract. To provide a more specific test of memory impairments following lesions to central cholinergic systems, rats were trained on an operant delayed matching task. Ibotenic acid lesions of the nucleus basalis produced a disruption of performance at all delay intervals (a parallel downward shift in the delay-performance curve). By contrast, fimbria-fornix transections had no effects at short delays, but produced a progressively greater impairment as the delays lengthened (an increased downward slope of the delay-performance curve). Scopolamine produced a dose-dependent disruption of performance, apparent at the shortest delays but greater at longer delays, that was similar to the two lesion deficits combined, whereas physostigmine induced a mild but significant enhancement of performance. The results support the hypothesis that disruption of hippocampal circuitries, including cholinergic afferents via the fimbria-fornix, produces short-term or working memory impairments, whereas disruption of the cortical cholinergic system implicates more stable long-term aspects of task performance. Peripherally administered cholinergic drugs produce both types of effect and thus may influence both systems.

Key words: Delayed matching – Short-term memory – Cholinergic systems – Nucleus basalis – Fimbria-fornix – Scopolamine – Physostigmine – Methamphetamine – Rat

Declining cognitive abilities, including impairments in memory, have been associated with aging in animals and man, and compared to the effects of impaired cholinergic transmission (Drachman and Sahakian 1980; Kubanis and Zornetzer 1981). This comparison has recently received renewed attention following the observation that patients with presenile and senile dementia of the Alzheimer type show a decline in cholinergic markers in the cortex and hippocampus which correlated with the degree of cognitive and memory impairment (Perry et al. 1978). This had led to the "cholinergic hypothesis" that the learning and memory impairments in aging are attributable specifically to a decline in central cholinergic function (Bartus et al. 1982; Coyle et al. 1983) as opposed to the other neuropathological changes associated with normal aging and Alzheimer's disease.

In support of this hypothesis, we have recently shown that cholinergic rich grafts placed into the neocortex or hippocampus of aged rats or rats with lesions that disrupt the cholinergic pathways innervating these targets are effective in ameliorating the rats' deficits in learning the Morris water maze (Gage et al. 1984), T-maze alternation (Dunnett et al. 1982), the 8-arm radial maze (Low et al. 1982) and retention of passive avoidance learning (Dunnett et al. 1985). However, none of these measures provides a pure test of memory performance, uncontaminated by deficits in learning capacity, spatial abilities, or more general motivational and arousal factors.

The present study uses a delayed matching to sample task, for the assessment of memory capacity in rodents to compare the effects of cholinergic drugs and of lesions that disrupt the two major forebrain cholinergic systems originating in the nucleus basalis and septum-diagonal band, and projecting to the neocortex and hippocampus, respectively. The advantage of a delayed matching task, as in other delayed response tasks, is that the interval between presentation of the sample stimulus and the response choice between alternative stimuli can be varied. The absence of a deficit following a particular treatment in the immediate response condition then suggests that an impairment at longer delays is indeed attributable to some form of memory deficit, rather than other factors that would be expected to impair performance under all conditions. Whereas visual stimuli have been used as descriminative cues in go-no go delayed matching tasks for rats (Cohen et al. 1984; Pontecorvo 1983), such cues are relatively ineffective in two-choice versions of delayed matching in this species (Wallace et al. 1980). By contrast, spatial sample and response cues (e.g. the response lever itself) have more frequently been used to assess delayed matching (Ksir 1974) or delayed alternation (Heise et al. 1976; Kesner et al. 1981; Ksir 1974; Rawlins and Tsaltas 1984; White 1974). The present study therefore employs a spatial sample and response in a delayed matching test, with the addition of a variable interval response that keeps the animals centralized during the delay and thus prevents the adoption of a side bias or mediating response to solve the memory task.

Materials and methods

Subjects

Twelve female rats of the Sprague-Dawley strain (OLAC, Bicester, UK) were used, aged approximately 10 weeks at the start of testing. They were housed two animals per cage, under a natural light-dark cycle, and with free access to water throughout. They were maintained on a food-depri-

vation schedule throughout, except during the 4 weeks following surgery, and fed daily at the end of the test session so as to maintain approximately 90% of normal body weight.

Apparatus

All testing was conducted in two operant chambers (Campden Instruments, London, UK) under the on-line control of a microprocessor (Control Universal System 10, Cambridge, UK). Each chamber was equipped with two retractable levers, situated 7.5 cm on either side of a central food tray which had a hinged perspex panel at which nose pokes could be registered. The chambers additionally had a house light in the centre of the ceiling, three stimulus lights located directly above the food tray and the two levers, and a light which back-illuminated the food tray. Reinforcement was provided by 45 mg food pellets (Abel Co., Charlbury, UK) dispensed individually to the food tray.

Training schedules

Pretraining. The rats wee initially habituated to the chambers with the two levers retracted, and trained over 4 days to collect pellets from the food well. The levers were then inserted into the chambers and the rats were trained for five daily 1 h sessions on continuous reinforcement, during which each press of either lever was reinforced by a single food pellet, provided only that the previous pellet had seen collected as determined by a nose poke response to the food tray panel. The rats were next trained on a simultaneous matching to sample task with visual stimuli which was, however, unsuccessful and did not provide a suitable behavioural baseline for assessing mnemonic performance. Since rats more readily utilize place cues than visual stimuli (e.g. Olton and Feustle 1981; Wallace et al. 1980), they were then switched to a delayed matching task in which the levers themselves provided the discriminative stimuli, and this provides the basis for all subsequent tests presented here.

Delayed matching to position. Rats were tested in daily sessions of 1 h unless otherwise specified. At the start of each trial one lever was automatically inserted into the chamber. A single response on the sample lever retracted it from the chamber and turned on the central panel light. A nose poke at the panel covering the central food tray extinguished the panel light and resulted in both levers being presented immediately ("0-delay" condition, although approximately 1 s was required for retraction and reinsertion of the levers). A correct response on the same lever which had been initially presented as the sample in that trial resulted in retraction of both levers, reward with a single food pellet and the commencement of the 5 s inter-trial interval. An incorrect response to the opposite lever also retracted both levers, but was followed by 5 s "time out", in which the house light was turned off. The next trial commenced with the onset of the house light and the start of the 5-s intertrial interval.

Once a rat had achieved >90% correct performance over 3 days in the 0-delay task, it was transferred to the delayed matching task. Following the response to the sample lever, a variable interval (VI) schedule was introduced for the nose poke response to the food tray panel, such that the first nose poke after the completion of the scheduled delay resulted in the presentation of both levers for the matching response. The VI panel response restricted the rat from adopting a position habit or response strategy, whereby it might simply wait in front of the sample lever until presentation of the two levers for matching. For each session, the numbers of trials and of correct matching responses were recorded and transformed to total percent correct for the session, as well as the percent correct responses for each delay of the variable interval.

Drug treatments

Scopolamine. Following achieving stable baseline performance on the delayed matching to position task, the rats were tested 20 min after injections of the muscarinic antagonist (−)-scopolamine hydrobromide (Sigma), or of (−)-scopolamine methyl bromide (Sigma) which does not cross the blood-brain barrier and so controls for the peripheral effects of scopolamine. Drugs were administered on alternate days, with the intervening days providing control data on baseline performance. Injections of scopolamine and methyl scopolamine were alternated, each drug being given twice at each dose, and at four doses (0.125, 0.25, 0.5 and 1.0 mg/kg, expressed as weight of the salt dissolved in 1 ml/kg isotonic saline) in ascending order, over 32 days. The daily sessions were of 1 h duration, using VI delays of 1, 2, 4, 8 or 16 s. On completion of the scopolamine tests, the rats were transferred to a schedule involving VI delays of 1, 4, 16, 32 and 64 s for 10 days prior to commencement of further drug tests.

Physostigmine. The anticholinesterase drug, physostigmine salicyclate (Addenbrookes Hospital, Cambridge) was administered IP 10 min before each drug session, twice at each of three doses: 0.0 (saline only), 0.05 and 0.1 mg/kg, in random order, with an injection-free day between each. The daily sessions were of 1 h duration, using the VI delays 1, 4, 16, 32 and 64 s.

Methamphetamine. The psychomotor stimulant and indirect catecholamine agonist methylamphetamine hydrochloride (Macarthy's, Romford, Essex) was administered in three doses in random order: 0.0 (saline, 0.25 and 1.0 mg/kg, 30 min prior to the test session, with at least 1 drug-free day between each test session. The daily test sessions were of 1.5 h duration, using the VI delays 1, 4, 16, 32 and 64 s.

Lesions

At the completion of drug testing, the animals were divided into three groups of four, matched according to their performance on the baseline days during the preceding sessions. All surgery was conducted under 0.3 ml/100 g Equithesin anaesthesia.

Nucleus basalis lesions. These were made by stereotaxic injection of 0.1 µl 0.06 M ibotenic acid (dissolved in 0.1 M phosphate buffer, pH = 7.5) into four sites in the region of the nucleus basalis bilaterally. Injections were each made through a 30 gauge cannula connected via polyethylene tubing to a 10 µl Hamilton syringe mounted in a microdrive pump, over 36 s with a further 90 s allowed for diffusion before commencing the next injection. Approximately 2 mm movement of a small air bubble in the tubing just above the cannula was used to ensure that the small injec-

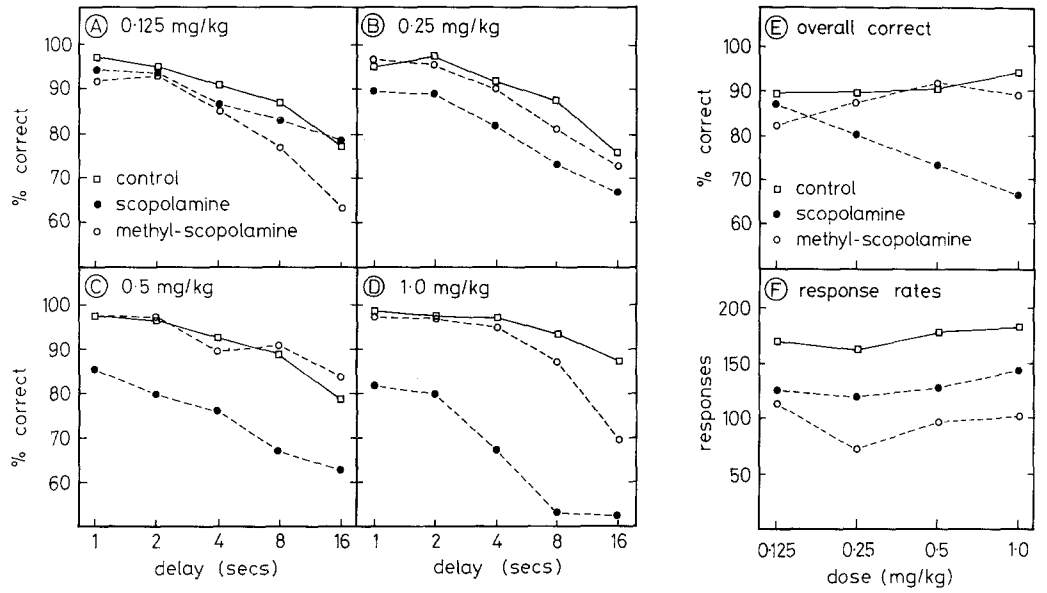

Fig. 1. Delayed matching to position performance of rats following injection of scopolamine or methyl scopolamine. **A–D** Percent correct performance at the five delay intervals (1–16 s) under the four doses of drug tested. **E** Dose-response curves in terms of the overall percent correct performance combined over delays. **F** Response rates in terms of total trials completed in the 1-h test sessions under different doses of drug

tion volumes were accurately delivered. The target stereotaxic coordinates used for the nucleus basalis were: A = −0.2, L = ±3.0, V = 6.0; A = −0.5, L = ±2.2, V = 6.5; A = −1.0, L = ±3.0, V = 6.8; and A = −1.8, L = ±4.0, V = 6.4, measured in mm anterior (A) to bregma, lateral (L) to the midline and vertical (V) below dura, with the incisor bar set at −2.3 below the interaural plane. All animals were aphagic and adipsic for 2–10 days following surgery, and two required intragastric tube feeding for several days in addition to providing bowls of palatable wet mash in their home cages.

Fimbria-fornix lesions. These were made by aspiration under visual guidance through an operating microscope. A 3 × 3 mm square bone flap was removed on each side, just posterior to bregma and lateral to the midline. The lesion removed the dorsal parietal cortex, and a small square of corpus callosum to expose the lateral ventricles at the level of the fornix. The fimbria-fornix bundle was then completely transected bilaterally by suction, so that the septal and hippocampal ends retracted. Care was taken to spare the sagittal sinus, but the midline cingulate cortex was removed, since cholinergic afferents to the hippocampus also course through this dorsal route (Gage et al. 1983).

In the light of the acute eating impairments in the nucleus basalis lesion group, 5 weeks were allowed for postoperative recovery before reinstatement of the food-deprivation schedule and retesting on the delayed matching to position schedule. The rats were tested for 18 days with 1, 2, 4, 8 and 16 s delays.

Histology

At the completion of behavioural testing, rats were transcardially perfused, under deep barbiturate anaesthesia, with isotonic saline followed by 10% formalin. The brains were removed, postfixed for 4 h in the fixative at 4° C, then transferred to 30% sucrose at 4° C until they sank. Brains were sectioned at 60 μ thickness, and every fifth section through the region of the nucleus basalis and hippocampus was mounted and stained for acetylcholinesterase by the thiocholine method, using 0.005% ethroproprazine as inhibitor of non-specific esterase, and 0.25% silver nitrate enhancement of the sulphide reaction product. Adjacent sections were collected for cresyl violet staining of cell bodies.

Results

All rats learned the 0-delay matching to position task to the 90% correct criterion in 7–22 sessions (median = 12). Upon reaching criterion, they were switched to training on the delayed matching condition for a minimum of 15 days before commencing drug tests. At the end of this period (see baseline control values in Fig. 1 A–D), all rats were performing close to 100% correct at the shortest delays (1 and 2 s), and choice accuracy declined monotonically to about 75–80% correct at the longest delay (16 s).

Observation of the rats during task performance indicated that the nose poke response was made at a rate of a little over 1/s, maintained over all delays, but this was not recorded systematically in the present animals. No obvious postural bias could be detected in the animals during the delay intervals, suggesting that the present procedure was effective in blocking various response strategies to solve the task.

Drug test

Scopolamine. The effect of scopolamine and methyl scopolamine on performance accuracy (in terms of % correct responses at each delay) in comparison with baseline performance are shown in Fig. 1. Three-factor repeated measures analysis of variance yielded significant main effects due to delay ($F = 98.70$, df 4,48, $P < 0.001$) and drug ($F = 58.00$,

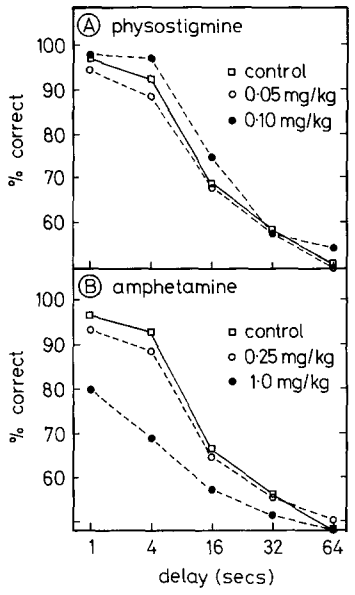

Fig. 2. Delayed matching to position performance of rats under two doses of physostigmine (**A**) or methamphetamine (**B**), each tested at five delay intervals (1–64 s)

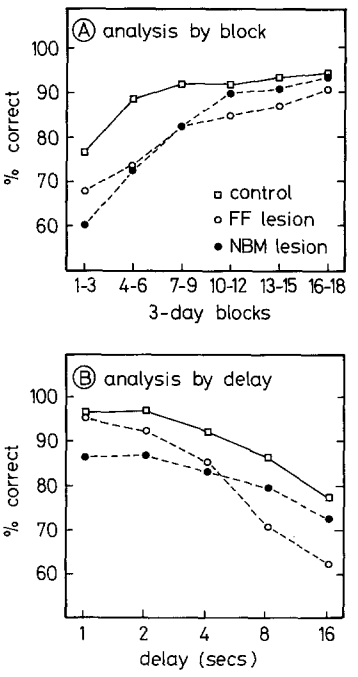

Fig. 3. Delayed matching to position performance of subgroups of rats following either fimbria-fornix (*FF*) or nucleus basalis (*NBM*) lesions or unoperated controls. In the absence of significant three-way interactions between lesion group, delay and test block, the data are separately presented for the three groups by session block (**A**) and by delay interval (**B**)

df 2,24, $P<0.001$) and significant interactions between drug × delay ($F=4.67$, *df* 8,96, $P<0.001$), drug × dose ($F=18.69$, *df* 6,65, $P<0.001$) and drug × delay × dose ($F=3.00$, *df* 24,259, $P<0.001$). In order to separate these effects, the levels of performance for each delay and drug are presented separately for the four doses of scopolamine and methyl scopolamine in Fig. 1A–D. The effects of dose and drug on the overall performance across delays are summarized in Fig. 1E. Scopolamine had minimal effects on performance at any delay when given at the lowest dose (0.125 mg/kg; see Fig. 1A), but at progressively higher doses (0.25–1.0 mg/kg; Fig. 1B–D) the drug produced an increasing disruption of performance. By contrast, injections of methyl scopolamine, which is largely restricted to a peripheral action, had no detectable effects on performance accuracy at the two middle doses. However, this drug appeared to produce a disruption of accuracy at the longest (16 s) delay at both the lowest and the highest dose (see Fig. 1A and D), and this was significant in the latter case (post hoc Scheffé tests: 0.125 mg/kg, $F=3.13$, *df* 1,259, ns; 1.0 mg/kg, $F=5.36$, *df* 1,259, $P<0.025$).

In contrast to the relatively specific effect of scopolamine on performance accuracy, both scopolamine and methyl scopolamine suppressed response rates (trials completed in the 1-h session), across all doses (see Fig. 1F). Analysis of variance yielded a large significant effect of drug ($F=54.74$, *df* 2,24, $P<0.001$), and a small, but still significant, effect of dose ($F=6.62$, *df* 3,35, $P<0.01$).

Physostigmine. The effects of physostigmine on performance over delays of 1, 4, 16, 32, 64 s are shown in Fig. 2A. Although the effect is small, there was a significant difference between doses ($F=4.89$, *df* 2,22, $P<0.025$), which was attributable to a higher overall level of accuracy at 0.1 mg/kg, but not at 0.05 mg/kg, than the saline control tests (means, 76.7%, 72.0% and 73.7%, respectively; Dunnett's test, *df* 22: 0.1 mg/kg, $t=3.10$, $P<0.01$; 0.05 mg/kg, $t=1.12$, ns). The interaction between dose and delay was not significant ($F=1.901$, *df* 6,64, $0.1>P>0.05$).

Methamphetamine. The effects of methamphetamine on performance over delays of 1, 4, 16, 32, 64 s are shown in Fig. 2B. The effects of dose, delay and the dose × delay interaction were all significant (dose: $F=12.99$, *df* 2,22, $P<0.001$; delay: $F=95.99$, *df* 4,44, $P<0.001$; dose × delay: $F=2.86$, *df* 8,88, $P<0.01$). From Fig. 2B, it can be seen that this is attributable to the lower dose (0.25 mg/kg) having only small effects on performance at all delays, whereas the higher dose (1.0 mg/kg) disrupted performance, in particular at the shorter delays. Any effect at the longest delay (64 s) was masked by the fact that the saline control rats were performing at chance levels.

Lesion effects

As reported previously (Flicker et al. 1982; Whishaw et al. 1985), even small bilateral lesions of the nucleus basalis produce temporary deficits in eating and drinking in rats. One of the present nucleus basalis animals died 1 week following surgery, and the behavioural tests were only conducted on the remaining 11 rats.

The performance of the three groups of lesioned and control rats on the six blocks of three daily sessions commencing 5 weeks after surgery are shown in Fig. 3. Although the overall difference between groups just failed to reach significance ($F=3.61$, *df* 2,8, $0.1>P>0.05$), significant interactions were found between group × session block (see Fig. 3A; $F=2.16$, *df* 10,40, $P<0.05$) and group × delay (see Fig. 3B; $F=8.83$, *df* 8,32, $P<0.001$). The group × block × delay interaction was not significant ($F=1.06$, *df* 40,160, $P>0.25$).

Inspection of Fig. 3 indicates that these interactions appear to be attributable to a cross over between the FF

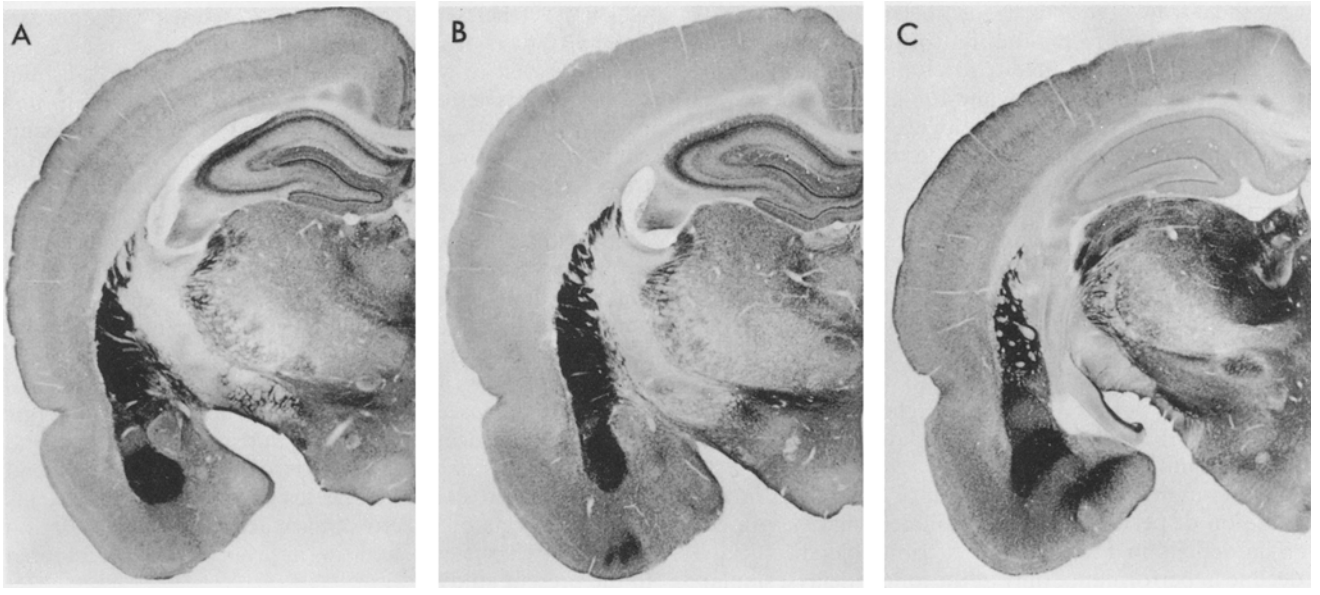

Fig. 4. Acetylcholinesterase-stained sections from the brains of an unoperated control (**A**), a rat with lesions in the nucleus basalis magnocellularis (**B**), and a rat with transection of the fimbria-fornix (**C**). Note the normal laminar pattern of AChE-positive fibres in both the neocortex and hippocampus of the control, and compare the loss of fibre staining in the dorsolateral quadrant of neocortex from the rhinal fissure to the cingulate cortex in the NBM-lesioned animal with the loss of hippocampal and cingulate cortical staining in the animal with fimbria-fornix transection

lesion and NBM lesion groups, both in the analysis of performance over blocks and over delays. Thus, whereas the NBM lesion rats were initially most disrupted by the lesion, they recovered to control levels of performance over approximately 10 days (see Fig. 3A). By contrast, the FF lesion rats were initially less impaired, but that impairment appeared to last throughout the 18 days of testing (see Fig. 3A). Newman-Keuls comparisons between the groups for each session block (critical values at $P=0.05$, $t=4.04$, *df* 3,8 and $t=3.26$, *df* 2,8) indicated that both FF and NBM rats were significantly impaired with respect to controls on the first two blocks (days 1–6), and additionally the NBM rats performed worse than the FF group on the first block (days 1–3). No differences were significant on the last four blocks of sessions, although on the third to fifth blocks (days 7–15) the difference between FF rats and controls approach significance ($t=3.90$, 3.31 and 3.42, respectively, all $0.1>P>0.05$), as did the difference between NBM rats and controls on block 3 only ($t=3.91$).

The analysis by delays showed a similar pattern across all test blocks (the three-way interaction was not significant), and the performance by delays over all sessions (Fig. 3B) is representative of performance at each stage. Whereas the NBM lesion rats showed deficits at all test delays (although only in the early blocks of sessions), they were still performing well above chance at the longest delay (16 s). By contrast, the FF-lesioned rats showed no difference from control performance at the shortest delays, but were more severely impaired than the NBM rats at the longest delays (see Fig. 3B). Newman-Keuls comparisons between the groups at each delay interval (critical values at $P=0.05$, $t=4.04$ *df* 3,8 and $t=3.26$ *df* 2,8) indicated that the FF rats were only significantly impaired with respect to controls at delays of 4 s or longer, whereas the NBM rats were significantly impaired at all delays except the longest (16 s, $t=3.22$ *df* 2,8), which just failed to achieve the critical level (value = 3.26). Moreover, FF rats performed significantly better than the NBM rats at the two shortest delays (1 s and 2 s), but significantly worse at the two longest (8 s and 16 s).

Histology

The AChE stain provides a sensitive index of cholinergic fibre innervation of both the neocortex and hippocampus. In the normal brain, this AChE-positive innervation manifests a laminar distribution in both target structures, and was clearly apparent in all intact rats of the present control group (see Fig. 4A).

Nucleus basalis lesions involved a loss of all cell types in the medial and ventral globus pallidus, and mild gliosis around the cannula tracks and at the injection sites. There was a corresponding loss of AChE-positive staining of magnocellular cells and the fibre plexus in the area of the lesions. AChE-positive fibres and terminals were extensively depleted in the dorsolateral neocortex throughout its rostro-caudal extent, while sparing the cingulate, perirhinal, piriform and entorhinal strips (see Fig. 4B).

Aspirative lesions through the cingulate cortex completely transected the fimbria-fornix in all animals. This resulted in a complete loss of AChE-positive fibres throughout the hippocampus, apart from its temporal pole, and of fibres in the cingulate and dorso-medial cortex posterior to the lesions (see Fig. 4C).

The lesions were similar in both procedure and histological appearance to those described in greater detail elsewhere [Dunnett et al. 1982; Whishaw et al. 1985].

Discussion

The present study has used a discrete trial, operant delayed matching to position task to provide a comparison not only

between the effects of lesions to the nucleus basalis magnocellularis (NBM) and to the fimbria-fornix (FF) (which respectively disrupt the two major forebrain cholinergic systems innervating the neocortex and the hippocampus), but also with the effects of pharmacological manipulation of central cholinergic systems, via systemically administered agents.

The pattern of post-operative performance suggests that lesions of the hippocampal and the neocortical cholinergic systems both disrupt performance on the delayed matching to position task, but for different reasons. Whereas both the NBM and the FF rats showed recovery over the 18 days of testing, the significant interaction between group and block indicated that the NBM rats showed a greater initial disruption, but recovered to a higher level of performance than the FF rats, although this latter difference did not achieve significance.

Of more interest is the observation of differences in the deterioration of performance across increasing delay intervals. The deficits in FF rats were attributable specifically to a decline in performance only at the longer delays, similar to the preiously reported effects of hippocampal lesions in operant alternation tasks (Rawlins and Tsaltas 1983; Walker et al. 1972). The intact performance of the FF rats at the shortest delays, and the increased slope of the decay function (Fig. 3B), is suggestive of a disruption of the animals' short-term memory capacity, whether formulated in terms of recognition memory (Gaffan 1974) or working memory (Olton et al. 1979).

By contrast, the NBM group was more impaired than either the control or the FF groups immediately post-surgery, but then (unlike the FF group) recovered to the same level as the control rats after 10 days of testing. Moreover, during the early sessions, the NBM rats were disrupted equally across all delay intervals, including the shortest, and their response rates were reduced. This pattern of deficits is incompatible with a specific short-term memory impairment, but may involve either an impairment in the detection and discrimination of relevant stimuli (as has been suggested in the case of anticholinergic drugs, see below), or a disruption of post-operative retention of task demands. Three other recent studies have shown that rats with NBM lesions are impaired in the acquisition and retention of learned behaviours, in a reinforced alternation paradigm using an elevated T maze (Salamone et al. 1984), in the Morris water maze spatial navigation task (Whishaw et al. 1985), and in a 16-arm version of the radial maze task first used by Olton and Pappas (1979) to separate working memory from reference memory components of spatial memory (Murray and Fibiger 1985). The latter study in particular is informative, since the rats with NBM lesions were disrupted in the reference memory component of the task, involving retention of those arms of the maze which were never baited, but they performed normally on the working memory component, involving retention of those arms of the baited set which had already been visited on the daily trial (Murray and Fibiger 1985). This suggests that the impairment induced by NBM lesions does not primarily involve a deficit in the rats' detection or discirmination of external stimuli relevant to accurate task performance, as this would be expected to influence both components of the task equally. Rather, the present deficits seen following NBM lesions can be interpreted in terms of a disruption of postoperative retention of task demands, which nevertheless the rats are able to relearn with approximately 10 days of further training.

The extent to which these effects of nucleus basalis and fimbria-fornix lesions can be attributed specifically to disruption of cortical and hippocampal cholinergic systems cannot be determined from the present results. The NBM lesions invade other neuronal systems in the vicinity of the ventral globus pallidus, and the FF transections cut subcortical efferents as well as afferents to the hippocampal formation as well as damaging midline cingulate cortex. Unfortunately, there exists no readily available cholinergic neurotoxin to make specific lesions in these forebrain cholinergic systems, and so only indirect approaches can be adopted to assess lesion specificity. One such approach is to study the consequences of reconstruction of cholinergic afferents to the deafferented target areas using intracerebral grafts, and this is currently under investigation. A second approach is to compare the lesion-induced impairments with the effects of selective pharmacological manipulation of cholinergic systems, and this approach has been adopted in the present study.

The present results confirm earlier reports that the competitive muscarinic antagonist drug scopolamine disrupts delayed response performance in a dose-dependent manner (Alpern and Marriott 1973; Bartus and Johnson 1982; Heise et al. 1975, 1976; Ksir 1974; Milar et al. 1978; White 1974). By contrast, methyl scopolamine, which does not cross the blood brain barrier but mimics all the peripheral effects of scopolamine, was without consistent effects on choice accuracy in the delayed matching to position task, only having a significant effect when administered at the highest dose and at the longest delay interval. This suggests that the disruption of response accuracy by scopolamine is attributable to its central, rather than its peripheral, action. By contrast, response rates were substanitally reduced by both scopolamine and methyl scopolamine, suggesting that this action of scopolamine is primarily due to its peripheral action and separable from the accuracy measure, as noted previously by Ksir (1975).

The disruption of response accuracy by scopolamine was apparent at all delays studied, including the shortest interval of 1 s programmed into the schedule, and such a downward shift in the decay curves (Fig. 1A–D) has generally been taken to exclude a memory interpretation in favour of an impairment in some aspect of the rat's initial discrimination of the discriminative stimuli or registration of that information (Heise et al. 1975, 1976; Ksir 1974; Milar et al. 1978; Warburton 1972). However, scopolamine will block muscarinic receptors at several central sites, including cholinergic terminal fields in both cortex and hippocampus, and thus its behavioural effects would be expected to involve a combination of those central actions. A comparison between Fig. 1C, D and Fig. 3B suggests that the disruptive effects of scopolamine on the delayed matching task – a short delay disruption similar to the NBM group and a decay slope similar to the FF group – may be attributable to a combination of the nucleus basalis and the hippocampal impairments. The observation that scopolamine produces a short-term memory deficit in delayed matching to sample in monkeys, with no impairment at the shortest delays (Bartus and Johnson 1976) may then be attributable to a different pattern of drug action in primates and rodents. It should be noted, however, that the comparison between the effect of drugs and lesions is indirect, and the

mnemonic disruption in the fimbria-fornix rats, although associated with cholinergic deafferentation of the hippocampus, may be fully attributable to non-cholinergic systems disrupted by the lesions.

In contrast to scopolamine, the anticholinesterase physostigmine, which increases the presynaptic availability of acetylcholine, significantly enhanced response accuracy, although this effect was small, and only apparent at 0.1 mg/kg.

The action of the dopaminergic stimulant methamphetamine was included for comparison with the cholinergic agents, since Kesner et al. (1981) have reported a short-term memory deficit following *d*-amphetamine treatment on a task similar to that used here. In the present study, methamphetamine disrupted response accuracy only at the higher dose used, but then in a manner incompatible with a memory interpretation. The present results may be attributable to nonspecific activation (Lyon and Robbins 1975), but a further comparison of the procedures used here with those employed by Kesner et al. (1981) is necessary to resolve the apparent descrepancy in results.

In conclusion, the present study has found a dissociation between the effect of lesions of the fimbria-fornix and the nucleus basalis, suggesting that damage in the two systems respectively disrupt short-term working memory and longer-term reference memory. The parallels between the pharmacological and lesion results in the same task support the notion that these lesions may indeed be having their effect via disruption of cortical and hippocampal cholinergic afferents, respectively.

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