Perseverative errors and reversal of a visual discrimination following basal forebrain lesions in the rat

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Abstract. Rats with electrolytic lesions of the nucleus basalis magnocellularis were compared to sham-lesioned rats in the retention of a continuously reinforced lever-pressing response and in the acquisition and reversal of a visual discrimination task. The muscarinic agonist pilocarpine, in conjunction with the peripheral muscarinic antagonist methyl-scopolamine, was administered in three doses to subsets of each group during acquisition. The lesion interfered with retention of the lever-pressing response. It did not affect the rate of acquisition of the visual discrimination, but facilitated reversal, and increased the number of perseverative errors made by the rats. Pilocarpine's only notable effect was to increase the latency to respond.

Key words: nucleus basalis, lesion, visual discrimination, reversal, perseveration, pilocarpine
Central cholinergic systems have been implicated in learning and memory (Hepler et al. 1985, Murphy and Boast 1985; see Olton and Wenk 1987 for a review), and damage to these systems is thought to be involved in the memory impairments that accompany Alzheimer’s disease (Davies and Maloney 1976, Whitehouse et al. 1981). One deficit apparent in the behaviour of Alzheimer’s patients is the inability to modify behaviour in the face of changes in contingencies, often described as perseveration because a behaviour that is no longer reinforced, or in fact is now punished, persists despite the change in the effect produced by that behaviour (Bigler et al. 1988, Kramer et al. 1989, Freedman 1990, Bandera et al. 1991, Sullivan 1991, Bondi et al. 1993).

We examined the effects of lesions of the nucleus basalis magnocellularis (nbm) on the retention of a continuously reinforced bar-pressing response, and on the ability of rats to acquire and to reverse a visual discrimination. In addition, we examined the effects of the muscarinic agonist pilocarpine in conjunction with the lesion on the acquisition of the visual discrimination, anticipating that the drug might overcome deficits induced by the lesion. A behavioural task was used that required the rats to select one of two levers based on the illumination of visual discriminative stimuli, and allowed repeated responses on the incorrect lever until the correct lever was chosen, providing the opportunity to measure perseverative errors.

A total of 57 female Sprague-Dawley rats, obtained from Harlan Sprague-Dawley (Indianapolis, USA) served as subjects. The rats were approximately 120 days old at the start of the experiment. After being shaped to bar-press (see below) rats received either sham surgery or bilateral electrolytic lesions directed at the nucleus basalis magnocellularis (Bregma -1.3 mm, ±2.3 mm from midline, 7.6 mm ventral to skull surface; Paxinos and Watson 1986). Surgeries were conducted under sodium pentobarbitol anaesthesia (45 mg/kg, i.p.). A total of 15 rats died either during surgery or as a result of reduced food intake after surgery.

Behavioural testing was conducted in an "automated T-maze" based on a design by Berger (1977). This is a chamber divided into a Start/Goal Box and two Arms (see Fig. 1). An automated dipper mechanism in the Start/Goal Box delivers a 0.03 ml drop of reinforcer consisting of 50 g nonfat powdered milk, 50 g sugar, and 300 ml water. A cue light (1.2 cm in diameter) is centred over the dipper 12.7 cm above the floor. At the end of each of the two Arms was a lever (3.2 x 2.5 x 1.0 cm, centred 4.5 cm above the floor) and a cue light (2.5 cm diameter, centred 17.8 cm above the floor). This apparatus was housed in a sound-attenuating, ventilated chamber, and was controlled by an IBM-PC compatible com-

![Fig. 1. Our implementation of Berger's (1977) behavioural apparatus, seen from above. Walls are white Plexiglas, and the box has a clear Plexiglas cover. All measurements in the figure are in cm. Walls are 23 cm high; dipper is 3 cm above the floor; dipper light is 1.2 cm in diameter and 9.5 cm above the dipper; levers are 3.2 x 2.5 cm; cue lights are 2.5 cm in diameter and 13 cm above the levers.](image-url)
puter through a locally developed interface and software.

Prior to surgery rats were shaped by the method of successive approximation to press either lever and then return to the Start/Goal Box for the reinforcer. Each lever-press resulted in the operation of the dipper, and a 5 s illumination of the light above the dipper. Once the dipper operated, the reinforcer remained available to the rat until the next operation of the dipper. On the day following shaping, rats were run on a continuous reinforcement (CRF) schedule for a session of 150 trials.

Rats next underwent either a bilateral nbM or sham lesion, followed by a 1 week recovery period. Following recovery, rats were again tested in a 150 trial CRF session. Only rats that had retained the response of lever-pressing after surgery continued in the experiment.

Visual discrimination training began on the next day. The cue light above one of the levers was illuminated during each trial, and rats were reinforced for selecting either the lighted or dark lever, in a counterbalanced fashion. A correct response resulted in the delivery of a milk reinforcer, after which the next trial began. A correction procedure was used such that following an incorrect response the trial continued until the rat pressed the correct lever. The position of the light varied randomly from trial to trial. Each session lasted 150 trials, or until the rat reached the criterion of 8 correct responses in a row.

In the next session, the rat’s visual discrimination was reversed; that is, rats that had been reinforced for selecting the lighted lever were now reinforced for pressing the dark one, and vice versa. This continued until the rat had reached the same criterion as in the original acquisition.

During each trial the following data were recorded: (1) latency to make the first response, (2) whether or not that response was correct, and (3) the number of times the incorrect lever was pressed following an initial error, thus constituting a repeat error. The number of repeat errors that occurred in the last 30 trials of either acquisition or reversal served as a measure of perseveration.

Each rat received the peripheral muscarinic antagonist methyl scopolamine (1.0 mg/kg i.p.) 20 min prior to each visual discrimination or reversal session. At 15 min prior to each visual discrimination session, rats were given one of three doses (0, 1.0, or 3.0 mg/kg, i.p.) of the muscarinic agonist pilocarpine. Control injections of saline were given 15 min prior to each reversal session.

At the conclusion of behavioural testing, rats were sacrificed with an overdose of sodium pentobarbitol (220 mg/kg, i.p.) and were perfused transcardially with isotonic saline followed by a 10% formalin solution. The brains were removed, and frozen sections were taken at 80 μm. Sections were photographed and examined visually to verify the site of the lesion.

The lesion missed the nbm in 5 rats, data from which were excluded from subsequent analysis. The maximum and minimum extent of the lesions in the remaining rats is presented in Fig. 2.

Following the surgery, 5 of the 20 nbm-lesioned rats failed to perform in the continuous reinforcement test. All 17 sham-lesioned rats performed in this post-lesion test in a manner comparable to their pre-lesion performance. This difference between
the groups in the retention of the task is significant ($P=0.04$, Fisher’s exact probability test).

The latency to make the first response was affected only by pilocarpine, which increased it in a dose-dependent manner (means ±SEM’s: 0 mg/kg: 14.64±2.16 s; 1.0 mg/kg: 24.44±5.48 s; 3.0 mg/kg: 76.29±34.74 s; $F(2,26)=3.181$, $P=0.06$). The lesion had no effect on latency ($F(1,26)=0.378$), and did not interact with the drug effect ($F(2,26)=0.808$). Pilocarpine’s effects on acquisition, reversal, and perseveration were not significant. Because pilocarpine had no effect on measures relating to learning, memory, or perseveration, data from rats receiving different doses of pilocarpine were combined in analyses of these measures.

Rats in both the nbm- and sham-lesion groups acquired the visual discrimination task equally well, requiring a mean (±SEM) number of trials to criterion of 117.53 (±16.69) for the control rats, and 121.53 (±17.92) for the nbm-lesioned rats ($t(30)=−1.16$, NS).

At the end of the initial visual discrimination training, in the last 30 trials before reaching criterion, nbm-lesioned rats made more perseverative errors than did the control rats (mean ±SEM, nbm: 28.32±8.65, sham: 11.71±2.14; $t(30)=−1.97$, $P<0.05$ one-tailed).

For each rat, a ratio of trials-to-criterion in reversal divided by trials-to-criterion in acquisition was calculated, yielding a measure that indicates how reversal learning compared to the original learning. As expected, more trials were necessary for the reversal than for the original learning. On average, the nbm-lesioned animals reversed more readily than the sham-lesioned controls (respective means ±SEM’s: 2.83±0.36, 4.95±1.13; $t(30)=9.546$, $P<0.001$).

In the last 30 trials of reversal training, lesioned animals continued to make more perseverative errors than did the controls (means ±SEM’s: 11.78±3.88 and 4.82±1.13, $t(30)=10.261$, $P<0.001$).

Lesions of the nbm disrupted performance of the previously acquired lever-press response, a finding consistent with the hypothesis that the cholinergic projection from nbm to cortex might play a role in reference memory (Olton and Wenk 1987). There was no apparent difference in the magnitude of the lesion in rats that continued to perform the lever-press task compared to those that did not. The relative ease with which the nbm-lesioned rats reversed is also suggestive of a disruption of reference memory. If memory of the original discrimination was stored in a more tenuous form in the lesioned rats than in the controls, then the lesioned animals would be expected to experience less proactive interference, thus allowing the reversal to proceed more quickly.

The nbm-lesioned rats, however, were more likely to make perseverative errors; they continued to press the incorrect lever more than once rather than switching to the correct one. The number of these perseverative errors remained higher than in control rats despite hundreds of trials. In addition to being reported in patients with Alzheimer’s disease, perseverative errors have been observed in psychiatric patients treated with anticholinergic drugs (Galdi 1993). Our finding that nbm-lesioned rats perseverate more so than do controls supports Galdi’s finding that disruption of cholinergic systems is linked to perseveration.

The combination of results that we observed is unexpected and counterintuitive. Increased perseveration should interfere with reversal of the discrimination, because perseveration involves a tendency to continue to make responses in the absence of reinforcement. Our results suggest that difficulty with reversing a previously acquired discrimination, which might be viewed as a sort of "meta-perseveration" or between-sessions perseveration, can be reduced even when within-trial perseveration is increased. Manipulations of the nbm differentially affect these two behavioural phenomena. An explanation of this differential effect awaits further research, perhaps involving lesions more neurotransmitter-specific than those produced electrolytically.

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