

UNILATERAL dopamine deficiency of the basal ganglia produced a profound impairment of visual search. Dopaminergic innervation of the monkey striatum was deprived unilaterally by infusing 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) into the caudate nucleus. The monkeys were shown a mirror in which they saw their own image and surroundings. Compared with the concentric and symmetrical distribution of visual search before MPTP infusion, the gaze after MPTP infusion was confined and sometimes frozen in peripheral regions in the hemisphere ipsilateral to the infusion; the contralateral side was largely neglected. An experiment using a choice saccade task indicated that the contralateral visual signal, which alone was processed normally, was suppressed by the ipsilateral signal.

Visual hemineglect induced by unilateral striatal dopamine deficiency in monkeys

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Introduction

The basal ganglia contribute to the initiation¹ and suppression² of saccadic eye movements with the GABAergic inhibitory connection from the substantia nigra pars reticulata to the superior colliculus.³ Dopamine is known to exert powerful modulatory effects on functions of the basal ganglia,^{4–6} but its relation to voluntary behaviour is still poorly understood. A series of studies from our laboratory^{7,8} showed that eye movements became deficient following local dopamine depletion in the unilateral caudate nucleus, suggesting that the effects of dopamine are mediated by the GABAergic system. In these studies, however, only one target was presented at a time on a blank screen to which the monkey reacted immediately or after a time delay. In visual search in a natural environment, however, the eyes are continually redirected by the interaction of attention and perception,⁹ the process which has been poorly studied.¹⁰ We found that in such natural visual search dopamine-deficient monkeys showed a profound spatial hemineglect.

Materials and Methods

Experimental animals: Three male Japanese monkeys (*Macaca fuscata*): monkey RO (8.1 kg), monkey IG (8.9 kg) and monkey PE (5.0 kg) were housed in individual primate cages in an air-conditioned room and brought to the experimental room at each experimental session. The monkeys had free access to food in the home cages, though water was restricted during periods of the experiment. Surgical procedures were

conducted in aseptic conditions under general anaesthesia, induced with ketamine (5 mg kg⁻¹) and xylazine (2 mg kg⁻¹) i.m. and maintained with i.v. pentobarbital sodium (initially 15 mg kg⁻¹ and then with 5 mg kg⁻¹ h⁻¹). Under such anaesthesia, an eye coil for measurement of eye movements and a head fixation device were implanted according to the method developed in our laboratory.⁷

MPTP infusion and tyrosine hydroxylase immunohistochemistry: MPTP-HCl (4 mg) was infused with an osmotic pump (Alzet® 2001 and 2002)^{7,11} placed between the temporal muscle and the temporal bone. Its outlet was connected to a stainless steel L-shaped cannula for infusion through polyethylene tubing. The site of infusion was aimed at the head-body junction of the caudate nucleus where saccade-related cells are clustered.¹ The length of the infusion cannula was pre-adjusted to the depth of the target which we determined based on MRIs (Hitachi Laboratory MRIS, 2.1 T). The infusion cannula was inserted into the caudate nucleus through a Teflon guide tube which had been implanted. MPTP was infused as a steady outflow (0.95 or 0.52 μ l h⁻¹) for 1 or 2 weeks. At the end of the experiments, the monkeys were deeply anaesthetized with pentobarbital and perfused with mixture of 4% formaldehyde, 0.5% glutaraldehyde, 0.2% picric acid in 0.2 M phosphate buffer pH 7.4. Brains were removed and placed into postfixative solution. After cryoprotection procedure, the tissue was cut into 50 μ m coronal sections on a freezing microtome and immunostained with tyrosine hydroxylase (TH) anti-serum (INCSTAR).

Visual search: The monkeys' eye movements were recorded with the search coil method. The monkey sat in a primate chair in a sound attenuated room with his head fixed. In front of him was a white tangent screen (57 cm away from his face). A mirror (height: 32.5 cm, width: 47.0 cm) was placed 23 cm away from the monkey's face so that he saw the mirror image of his own face at the distance of 46 cm (Fig. 1A). The visual angle subtended by the mirror was about 40° (vertical) \times 60° (horizontal). Initially the room was totally dark for 1.5 min and eye movement recording was started as the room light was turned on. The recording lasted 3 min in the light condition.

Simple and choice saccade tasks: In a simple saccade task, pressing of a lever by the monkey turned on a central spot of light which the monkey had to fixate; after 1.5–2.5 s another spot of light (target) came on as a fixation point went off, and the monkey had to make a saccade to and then fixate the target to detect its dimming. In a choice saccade task, two spots of light, a target and a distractor, came on simultaneously at the point-symmetrical positions, and the monkey had to make a saccade to the target to detect its dimming. The position of the target was cued 2–3 s before the fixation point went off. The target position was selected from 8 positions (eccentricity of 20° in eight directions).

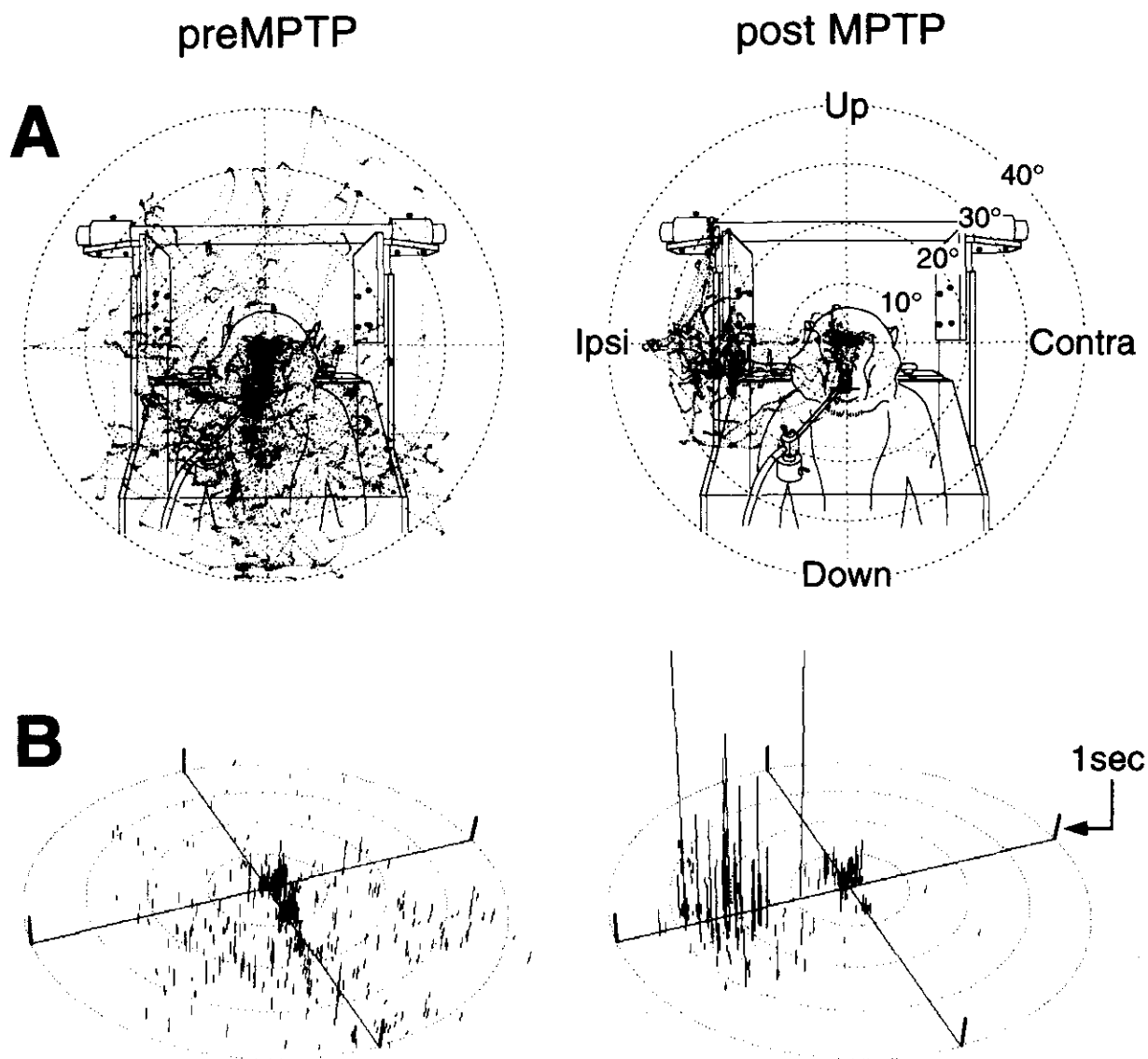


FIG. 1. Eye movements of the monkey while he was looking in a mirror before (*left*) and 31 days after (*right*) dopaminergic denervation of the left caudate nucleus by MPTP (see Fig. 2). (A) Trajectories of eye movements superimposed on the view seen in the mirror by the monkey, obtained before (*left*) and after (*right*) the MPTP infusion. (B) Duration of each fixation (indicated by the length of a vertical line) plotted on the position of the fixation. Data from monkey IG.

Results

The monkey could see in the mirror his own face straight ahead and other body parts encased in a translucent primate chair. Before dopamine depletion, the monkey looked in the mirror, most frequently at his own face (Fig. 1A, left). The gaze was frequently diverted to various points in the periphery, sometimes beyond 40° from the centre. The peripheral gaze was prevalent in the lower half where his own body and other points of interest were present. The duration of eye fixation was generally short, 88.9% and 94.6% of total fixations being less than 1 s for monkeys IG and PE respectively (Fig. 1B, left).

To locally deprive dopaminergic innervation, we infused MPTP at the caudate nucleus (A20 or 25) on one side.⁷ The later examination using tyrosine hydroxylase (TH) immunohistochemistry indicated that TH activity decreased profoundly around the infusion site in the caudate nucleus and dorsal part of the putamen (Fig. 2A). Within the substantia nigra a clear decrease in TH activity was found in its lateral part on the same side (Fig. 2B), suggesting the selective retrograde degeneration of dopaminergic neurones.

None of the three monkeys developed any obvious parkinsonian symptoms. However, the pattern of visual search changed: most eye fixations shifted to the side ipsilateral to the infusion. Monkey IG seldom fixated on the objects in the contralateral hemispace (Fig. 1A, right). The favourite point of fixation was the lat-

eral edge of the primate chair which was 20–30° off-centre to the ipsilateral side. These ipsilateral fixations were usually very long, sometimes lasting more than 10 s (Fig. 1B, right); only 64% of fixations in this region had short durations (< 1 s). Such 'frozen gaze' is very uncharacteristic of monkeys which usually make saccades more frequently than humans. In consequence, the average frequency of saccades during visual search decreased from 2.6 to 1.3 per second. The other two monkeys, in which dopaminergic denervation was more restricted to the body of the caudate, showed the same, but weaker, tendency.

Were the monkeys unable to see the objects in the contralateral hemifield, or were they able to see but unable to move their eyes to the contralateral direction? Both of these possibilities were unlikely, as suggested by the experiment utilizing saccade tasks (Fig. 3). In a saccade task, in which the target was presented alone (Fig. 3A), the monkeys had no difficulty in making saccades into the contralateral hemispace although the contralateral saccades were somewhat delayed. In a choice saccade task (Fig. 3B) two stimuli, the real target and a distractor, were presented simultaneously in opposite hemifields, and the monkey had to make a saccade to the target whose position had been indicated previously. The dopamine-deficient monkey made a saccade to the stimulus in the ipsilateral hemifield (whether or not it was the target), completely ignoring the contralateral stimulus.

Discussion

These results suggest that the hemineglect in unilaterally dopamine-deficient monkeys seems dependent on the presence of visual inputs from the ipsilateral hemifield. It appears that the objects in the intact side attracted gaze (and perhaps attention as well) so powerfully that any visual information from the contralateral (affected) side was neglected, the phenomenon reminiscent of 'extinction' which has been reported in patients with a lesion in the parietal association cortex.¹²

Our previous studies^{7,8} have shown that unilateral dopamine deficiency in the caudate leads to an impairment of saccades to the contralateral hemifield, suggesting that dopamine acts to reduce the final inhibitory output of the basal ganglia by facilitating GABAergic output neurones in the caudate nucleus. Crucial for the oculomotor control is the inhibitory connection from the substantia nigra pars reticulata to the superior colliculus.³

The present study further suggested that spatial attention is also controlled by the mechanism involving the caudate nucleus. This finding is consistent with previous studies showing that single cell activities in the caudate were often enhanced by attention¹³ or expectation^{14,15} and that the attention- or expectation-related neurones were intermingled with saccade-



FIG. 2. Frontal sections showing tyrosine hydroxylase (TH) immunoreactivity at the level of the anterior putamen and the caudate head (A) and the substantia nigra (B). MPTP had been infused into the left caudate nucleus 1 mm anterior to the anterior section (A).

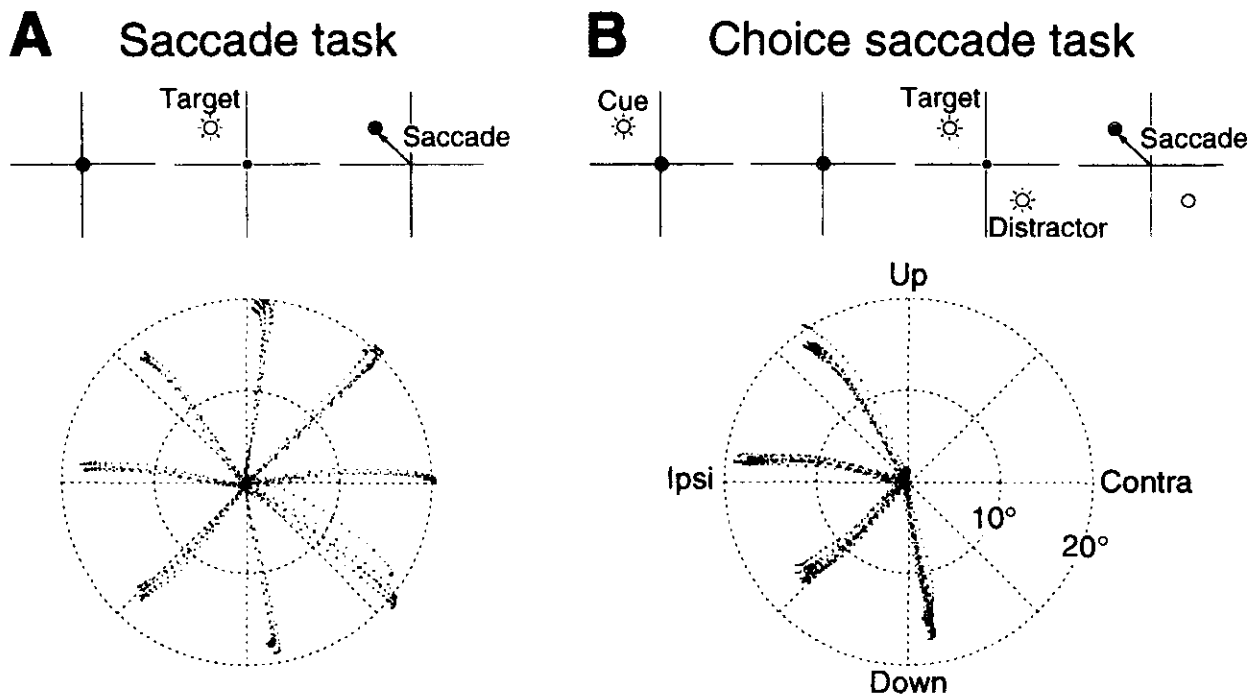


FIG. 3. Neglect of a contralateral target by an ipsilateral distractor. (A) Simple saccade task. (B) Choice saccade task. Trajectories of saccades that were made first after the target came on are superimposed (data from monkey IG after MPTP infusion). For each saccade trajectory, the eye positions were plotted with 2 ms intervals (500 Hz). In the single target condition (A) the saccades appeared normal, whereas in the double target condition (B) the monkey ignored the stimulus presented in the hemifield contralateral to the MPTP infusion, be it the target or distractor. When the targets were presented in the vertical direction, saccades were made always downward.

related neurones.¹³ The attention-related information may then be transmitted to the substantia nigra pars reticulata.¹⁶

Beyond the basal ganglia, however, it is unclear which neural substrates underlie the control of attention. Information from the prefrontal cortex, frontal eye field, and posterior parietal cortex¹⁷ may be integrated in the caudate, which then may be used for the control of attention. The result might be mediated by the nigro-collicular pathway, as in the case of saccadic eye movements. Alternatively, the attention-related information might be fed back to the frontal cortical areas through the thalamus¹⁸ to modulate or maintain the attention-related activities.^{19,20}

Conclusion

A unilateral dopamine deficiency of the monkey caudate nucleus produced a strong hemineglect for the contralateral visual hemifield. During visual search of his own face, the monkey's gaze was seldom directed to the contralateral hemifield, but tended to be frozen in the ipsilateral hemifield. This effect was enhanced when a distractor was present in the ipsilateral hemifield, as demonstrated by a choice saccade task. We conclude that the basal ganglia contribute to the control of attention to the contralateral visual space. Unilateral dopamine deficiency may enhance the

inhibitory outputs of the basal ganglia, leading to inattention to the contralateral space. Attention would then be attracted by whatever appears on the ipsilateral side.

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