

Dopaminergic stimulation in unilateral neglect

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Abstract

Objective—To explore the hypothesis that dopaminergic circuits play a part in the premotor components of the unilateral neglect syndrome, the effects of acute dopaminergic stimulation in patients with neglect were studied.

Methods—Two tasks were evaluated before and after subcutaneous administration of apomorphine and placebo: a circle crossing test and a test of target exploration (a modified version of the bell test), performed both in perceptual (counting) and in perceptual-motor (pointing) conditions.

Subjects—Four patients with left neglect. **Results**—After dopaminergic stimulation, a significant improvement was found compared with placebo administration and baseline evaluation, in the performance of the two tests. Three of the patients had a more marked improvement in the perceptual-motor condition (pointing) of the task than the perceptual condition (counting).

Conclusions—The findings suggest that dopaminergic neuronal networks may mediate, in different ways, both perceptive and premotor components of the unilateral neglect syndrome.

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The role of dopaminergic circuits in the exploration of personal space is not well understood. Some authors think that these circuits are purely motor¹ whereas others maintain that dopaminergic circuits also mediate perceptive aspects.^{2,3}

Experiments in animals touching on this problem have produced conflicting results. Thus unilateral lesions induced by 6-hydroxydopamine (6-OHDA) in dopaminergic systems of the rat mesencephalon give rise to sensory inattention,³ and a major behavioural effect of similar damage in marmosets is neglect of contralateral stimuli.⁴ Nevertheless, this behaviour in animals may be mainly attributable to premotor factors rather than to genuine contralateral inattention.¹

In experiments of dopaminergic stimulation with apomorphine, diminution of sensory inattention occurs in rats^{2,5}; King and Corwin⁶ used apomorphine to obtain a reduction in polysensory neglect in rats with unilateral dorsomedial frontal cortex lesions, whereas visual hemineglect, with an oculomotor deficiency component, can be induced by unilateral infusion of the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)

into the caudate nucleus in monkeys.⁷ Several studies have shown the existence of dopaminergic projections on to the frontal cortex from the ventral tegmental region of the mesencephalon.⁸

An effective method for achieving acute dopaminergic stimulation in humans is by means of the potent D1 and D2 dopamine agonist apomorphine. The technique was developed from clinical experience with Parkinson's disease.⁹ In parkinsonian patients with motor fluctuations subcutaneous apomorphine reverses the off state, with a latency of effect in about 15 minutes and duration of about 1 hour.⁹

In this study we have used apomorphine stimulation to investigate four patients with unilateral neglect—a condition characterised by an exploratory deficit towards the space contralateral to the side of a cerebral lesion. Both perceptual and premotor aspects are involved in human unilateral neglect^{10,11} and account for the heterogeneity of behaviour found in the condition.¹²

Our hypothesis was that dopaminergic circuits principally mediate the premotor components of spatial exploration behaviour, and our aim was therefore to determine whether acute dopaminergic stimulation had differing effects on the premotor and perceptual aspects of the neglect syndrome. Acute dopaminergic stimulation of brief latency and brief duration is useful for studying neglect, which is characterised, particularly in its acute phase, by greatly fluctuating day to day severity, and spontaneous recovery over a few days.

Methods

SUBJECTS

We studied four right handed patients with right hemispheric ischaemic lesions and unilateral neglect syndromes, evident clinically and by means of a crossing test (see below). Inclusion criteria were normal vigilance; absence of overt mental deterioration, assessed by means of the mini mental state examination (MMSE); and no evidence of heart, lung, or kidney disease. Both patients and relatives gave their informed consent to the experiment. In particular, we specified the aims of the study and explained that any amelioration in neglect would be transient. We also informed the patients of possible side effects (nausea, vomiting, and drowsiness) such as are sometimes found in parkinsonian patients given apomorphine.

Table 1 shows the clinical features of the patients and the lesion sites, assessed by CT. Three patients (1, 3, and 4) were examined in the acute phase of ischaemic stroke (18 to 28 days). One patient (2) had a chronic neglect

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Table 1 Features of patients

Patients	Age (y)	Sex	Duration (days)	MMSE	Motor score*	Sensory score*	Visual score*	CT†
1	81	F	18	27	3/3	3/3	3/3	cn,ic
2	61	M	450	29	3/2	3/3	3/2	P,T
3	62	F	25	28	3/2	3/3	3/0	post Th,ic
4	51	M	28	28	3/0	3/0	3/3	P,T

*Severity of neurological impairment ranged from 0 (no impairment) to 3 (plegia, anaesthesia, quadrantanopia); the first number refers to the left upper limb or quadrant and the second to left lower limb or quadrant.

†Sites of lesions in the right hemisphere.

MMSE=mini mental state examination (max=30); P=parietal lobe; T=temporal lobe; n=caudate nucleus; ic=internal capsule, postTh=posterior thalamus.

syndrome, still present 15 months after onset. None of the patients showed anosognosia or signs of personal neglect.

During the apomorphine effect, two patients (1 and 2) complained of slight nausea; three (1, 2, and 3) complained of drowsiness, severe in patient 1; one (patient 4) had moderate bradycardia. None of the patients developed marked hypotension.

A fifth patient was initially included in the study, but presented severe drowsiness, nausea, and continuous hiccups while under the effect of apomorphine, precluding further investigation. He was a 69 year old man with thalamomesencephalic haematoma, anosognosia, and showed signs of personal neglect; he was examined 19 days after the stroke.

For ethical and methodological reasons we decided not to test additional patients using the procedure described here. Marked effects on wakefulness and vigilance found in the excluded patient and in patient 1 were unexpected, on the basis of the experience with parkinsonian patients: we consider that there is a high probability that severe drowsiness could have made the neuropsychological assessment after acute apomorphine stimulation unreliable.

EXPERIMENTAL DESIGN

Patients were evaluated over two days: day 1, at baseline and after apomorphine (2 mg apomorphine 6-hydrochloride subcutaneously) and day 2, after placebo only (1 ml physiological solution).

To avoid the peripheral side effects of apomorphine (nausea and vomiting), for three days before the test patients received 60 mg/day domperidone, a dopaminergic antagonist not passing the blood-brain barrier. Clinical signs and blood pressure were monitored. Neuropsychological evaluation started as soon as the classic central side effects of the drug—mild sleepiness and yawning—were evident; this was usually about 15 minutes after drug administration.

NEUROPSYCHOLOGICAL EVALUATION

A preliminary neuropsychological evaluation of unilateral neglect was performed by means of an exploration task,¹⁵ with visual guidance and when blindfolded, following an ABBA design. In this task the patient had to pick up 13 plastic balls (2.5 cm diameter) that had been arranged in fixed non-symmetric positions on a 50 × 36 cm board. The board was placed in front of the patient; six balls were on

Table 2 Results of preliminary neuropsychological evaluation (number of stimuli explored on the left and right sides in the visually guided and blindfolded conditions of the task (sum of two trials for each condition; max 12))

Patient	Visual		Tactile	
	left	right	left	right
1	5	12	10	11
2	8	12	6	12
3	3	10	9	12
4	10	12	4	12

the patient's left side, six in the right side, and one in the centre.

The neuropsychological assessment at baseline after administration of apomorphine was as follows.

Circle crossing test

Thirteen circles (1 cm diameter) drawn on an A4 sheet of paper were presented, one in the centre and six arranged symmetrically on each side. The patient had to put a cross through all the circles. The number of crossed circles and side they were on was recorded.

Counting and pointing test

This is a modified version of the bell test.¹⁴ On A3 sheets were printed pictures of 15 objects (trees, apples, mushrooms, cars, saws, teapots, birds, fishes, horses, keys, bells, pistols, clouds, cottages, and guitars). On the first sheet all objects (targets and distractors) on the left side were blue and those on the right were red. On the other sheet the colour pattern was reversed. The target objects were 17 bells of one colour arranged on one side of the sheet. The centre of each sheet was placed in the mid-sagittal plane of the patient's trunk. There were counting and pointing parts to the test: firstly, the patient was asked to count the blue bells on the first sheet (on his left side) then the red ones (on his right side); secondly, the patient had to point to the red bells on the other sheet (on his left side) and then the blue ones (on the right side). Each component task was tested twice after an ABBA design (count, point, point, count) and after each test the sheet was changed. The number of counted and pointed bells on each side was recorded. Patients performed the motor tasks with their unaffected right hand.

Results

Table 2 shows the results at the preliminary exploration task in the visual and tactile condition. No significant dissociation between two conditions was evident in our patients.

Tables 3 and 4 show the number of stimuli explored by the patients in the circle crossing test and the counting and pointing test at basal evaluation, after dopaminergic stimulation using apomorphine, and after the placebo condition. Because patient 1 experienced adverse events (nausea and severe drowsiness), she refused the placebo treatment. For this reason we have only three patients in the placebo treatment; therefore, we compared baseline assessment with apomorphine treatment. No

Table 3 Results of circle crossing task (number of circles crossed on the left and right sides at baseline, and after apomorphine and placebo (max=6))

Patient	Baseline		Apomorphine		Placebo	
	left	right	left	right	left	right
1	0	3	0	6	—	—
2	0	6	2	6	0	6
3	0	5	4	6	0	4
4	1	6	5	6	2	6

Table 4 Results of counting or pointing task (number of stimuli explored on the left and right sides in the test at baseline, and after apomorphine and placebo (sum of two trials for each condition; max=34))

Patient	Condition	Baseline		Apomorphine		Placebo	
		left	right	left	right	left	right
1	Counting	3	12	5	9	—	—
1	Pointing	5	12	4	12	—	—
2	Counting	7	19	10	19	8	18
2	Pointing	7	19	10	22	10	20
3	Counting	0	7	5	11	0	11
3	Pointing	0	6	5	18	8	15
4	Counting	6	9	8	12	6	9
4	Pointing	5	10	13	26	4	15

significant differences were found between baseline and placebo performance in all patients assessed.

The difference between the mean scores at baseline and after dopaminergic stimulation was significant for the circle crossing test: the mean score of the four subjects varied from 5.25 (SD 1.71) at baseline to 8.75 (SD 2.22) after apomorphine (Student's paired *t* test 5.422, $p=0.012$); at placebo the mean score was 6.0 (SD 2.0): a difference was found versus dopaminergic stimulation (Student's paired *t* test 3.051, $p=0.093$) but not versus baseline.

For the counting and pointing test, the overall mean for the four subjects was 32.25 (SD 16.01), median 32 at baseline, 47.25 (SD 15.2), median 49 after dopaminergic stimulation, and 41.33 (SD 12.7), median 34 at placebo. No significant differences among the three conditions were found.

For the counting task, the mean score was 16.25 (SD 7.8), median 16 at baseline compared with 19.75 (SD 6.65), median 18 after dopaminergic stimulation, and 17.33 (SD 7.77), median 15 at placebo; for the pointing task the baseline score was 16.00 (SD 8.21), median 16 compared with 27.5 (SD 10.08), median 27.5 after stimulation, and to 24 (SD 5.57), median 23 at placebo. There were improvements in both counting and pointing scores after dopaminergic stimulation, although the differences among the three conditions were not significant due to the few observations. After dopaminergic stimulation the difference between counting and pointing condition was significant (Wilcoxon matched pairs test, $p=0.068$). A difference between pointing and counting condition was found only comparing baseline versus dopaminergic stimulation (Wilcoxon matched pairs test, $p=0.068$).

The improvements after dopaminergic stimulation occurred consistently in all patients for the circle crossing test and in three patients for the counting and pointing test; the other patient (1) showed a reduction in the stimuli pointed (from 17 to 16) and counted (from 17

to 14) after apomorphine. Patient 4 improved his pointing score much more than the others after apomorphine stimulation.

Discussion

A transitory reduction in unilateral neglect, as disclosed by the circle crossing, was obtained in three of our four patients after acute dopaminergic stimulation with apomorphine. It is noteworthy that patient 1, who did not improve in counting and pointing, became extremely drowsy during the execution of this tests after apomorphine, and her performance would have been adversely affected by this. This patient also had more severe neglect and was older than the other patients (table 1).

Our findings are in agreement with the results of Fleet *et al*¹⁵ in two patients after chronic treatment (3 and 4 weeks) with the D2 agonist bromocriptine, and with the fact that dopaminergic treatment in humans improves akinetic mutism¹⁶—a condition interpreted as a severe manifestation of bilateral neglect.¹⁷

It has been suggested that levodopa exerts a general arousal effect on cognitive performance.¹⁸ In our patients the selectiveness of the improvement seems to preclude this hypothesis for apomorphine. Moreover, one of the side effects of apomorphine, also evident in our patients, is somnolence, which would be expected to adversely affect performance in neuropsychological tests. In parkinsonian patients apomorphine induces improvement of motor disability, but cognitive performances measured by event related auditory evoked potentials and in the Benton visual retention test worsen.¹⁹ The reduction in unilateral neglect cannot therefore be ascribed to non-specific cortical arousal, but reflects specific involvement of the dopaminergic system in the neuronal circuits concerned with the exploration of space.

Neglect is a heterogeneous condition in which premotor and perceptual aspects often coexist.¹² However, patients with a predominantly premotor component have been described.^{11, 20} In none of our patients was baseline performance in the pointing (motor task) dissociated from performance in the counting test (perceptual task). It is therefore reasonable to suppose that our patients had neglect syndromes with both perceptual and premotor components.

An interesting finding of our study was the variation in improvement between the counting and pointing tasks. The improvement in the task in which the motor exploration component was prominent (pointing condition) was marked, whereas improvement was slight in the counting task which had only an oculomotor exploration component. It is noteworthy that dopaminergic stimulation failed to improve the representational deficit as demonstrated by the performance of patient 4 in a visual imagery task which had no motor exploration component (not even oculomotor). This test was used to assess the presence of representational deficit. The patient was asked to describe the Cathedral Square in Milan from two opposing view points. The

task was evaluated by counting the number of landmarks unequivocally belonging to the left and right sides of the square respectively identified by the subject in relation to his imagined point of view. A week after dopaminergic stimulation this patient was subjected to vestibular stimulation with ice water in his left ear. Interestingly, this caused a transitory amelioration in unilateral neglect, including performance, in this visual imagery task.²¹

The present study leads us to conclude that dopaminergic circuits are probably involved more in premotor components of the neglect syndrome than perceptual components, as also suggested by an animal model.³ Further study on a series of patients with unilateral neglect arising from cerebral lesions of differing aetiology, location, and duration is necessary to confirm this hypothesis. It may be, for example, that more pronounced dopaminergic stimulation effects will be obtained in patients with chronic subcortical lesions, because of the existence of postsynaptic dopaminergic hypersensitivity induced by denervation just as occurs in the striatum of parkinsonian patients. We consider that this theme can be further explored employing chronic stimulation with levodopa.

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- 1 Carli M, Evenden JL, Robbins TW. Depletion of unilateral striatal dopamine impairs initiation of contralateral actions and not sensory attention. *Nature* 1985;313:679–82.
- 2 Marshall JF, Gotthelf T. Sensory inattention in rats with 6-hydroxydopamine-induced degeneration of ascending dopaminergic neurons: apomorphine-induced reversal of deficits. *Exp Neurol* 1979;65:398–411.
- 3 Ljunberg T, Ungerstedt U. Sensory inattention produced by 6-hydroxydopamine-induced degeneration of ascending dopamine neurons in the brain. *Exp Neurol* 1976;53:585–600.
- 4 Annett LE, Rogers DC, Hernandez TD, *et al.* Behavioural analysis of unilateral monoamine depletion in the marmoset. *Brain* 1992;115:825–56.
- 5 Corwin JV, Kanter S, Watson RT, *et al.* Apomorphine has a therapeutic effect on neglect produced by unilateral dorso-medial prefrontal cortex lesions in rats. *Exp Neurol* 1986;94:683–98.
- 6 King V, Corwin JV. Neglect following unilateral ablation of the caudal but not the rostral portion of medial agranular cortex of the rat and the therapeutic effect of apomorphine. *Behav Brain Res* 1990;37:169–84.
- 7 Miyashita N, Hikosaka O, Kato M. Visual hemineglect induced by unilateral striatal dopamine deficiency in monkeys. *Neuroreport* 1995;6:1257–60.
- 8 Brown RM, Crane AM, Goldman PS. Regional distribution of monoamines in the cerebral cortex and subcortical structures of the rhesus monkey: concentrations and in vivo synthesis rates. *Brain Res* 1979;168:133–50.
- 9 Stibe CMH, Lees AJ, Kempster PA, *et al.* Subcutaneous apomorphine in parkinsonian on-off oscillations. *Lancet* 1988;i:403–6.
- 10 Coslett HB, Bowers D, Fitzpatrick E, *et al.* Directional hypokinesia and hemispatial inattention in neglect. *Brain* 1990;113:475–86.
- 11 Watson RT, Miller B, Heilman KM. Non-sensory neglect. *Ann Neurol* 1978;3:505–8.
- 12 Bisiaach E, Geminiani G, Berti A, *et al.* Perceptual and premotor factors of unilateral neglect. *Neurology* 1990;40:1278–81.
- 13 Vallar G, Rusconi ML, Geminiani G, *et al.* Visual and non-visual neglect after unilateral brain lesions: modulation by visual input. *Int J Neurosci* 1991;61:229–39.
- 14 Gauthier L, Dehaut F, Joannette Y. The bells test: a quantitative and qualitative test for visual neglect. *Int J Clin Neuropsychol* 1989;11:49–54.
- 15 Fleet WS, Valenstein E, Watson RT, *et al.* Dopamine agonist therapy for neglect in humans. *Neurology* 1987;37:1765–70.
- 16 Ross ED, Stewart RM. Akinetic mutism from hypothalamic damage: successful treatment with dopamine agonists. *Neurology* 1981;31:1435–9.
- 17 Watson RT, Heilman KM, Miller BD, *et al.* Neglect after mesencephalic reticular formation lesions. *Neurology* 1974;24:294–8.
- 18 Horvath TB, Meares RA. L-dopa and arousal. *J Neurol Neurosurg Psychiatry* 1974;37:416–21.
- 19 Ruzicka E, Roth J, Spackova N, *et al.* Apomorphine induced cognitive changes in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1994;57:998–1001.
- 20 Bottini G, Sterzi R, Vallar G. Directional hypokinesia in spatial hemineglect. A case study. *J Neurol Neurosurg Psychiatry* 1992;55:562–5.
- 21 Geminiani G, Bottini G. Mental representation and temporary recovery from unilateral neglect after vestibular stimulation. *J Neurol Neurosurg Psychiatry* 1992;55:332–3.