Paradoxical movement in Parkinson’s disease

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Patients with Parkinson’s disease, although impaired, can sometimes move effectively under visual guidance. The stimuli that often elicit such paradoxical movement are similar to those that relay visual information to the cerebellum. We suggest that many instances of paradoxical movement may be explained by the fact that the pathways relaying those visual stimuli can bypass the damaged basal ganglia and allow an intact cerebellar circuit to be used for visuomotor control.

Patients with Parkinson’s disease are rigid; they move with extreme difficulty, and typically they suffer tremor in several muscles when at rest. Nevertheless, despite these severe motor symptoms, patients with this disease can on occasion perform unexpectedly rapid, accurate, and even skilled movements. In some cases these actions appear to be provoked by intense emotion such as fear or anger. There are, however, other situations in which the patients can move effectively without any obvious cause of strong emotion. There is anecdotal evidence that under certain circumstances patients with Parkinson’s disease can walk up or down stairs, catch a ball, field a football, jog, or ride a bicycle almost normally.

The common feature of all these examples of paradoxical movement is that they seem to be under visual guidance. One of the best documented examples of such visual influences is the improvement in walking that was described by Purdon-Martin in his post-encephalitic patients with Parkinson’s disease. Walking was elicited by placing transversely oriented stripes along the path in front of the patients. Diagonal stripes were less effective, and stripes that were oriented parallel to the direction in which they were to walk were totally ineffective. Similar results using a different visual aid were reported by Forssberg et al. These authors recorded joint angles and leg position of the patients as they walked. They found that white papers placed on the floor in front of the patient were enough to cause their stride length to double, and this improvement in gait was independent of medication.

Two sorts of explanation have been put forward to account for such paradoxical sparing of motor function. One suggestion is that emotional arousal somehow concentrates the patients’ remaining motor capacities and thus briefly elicits normal movements. Favourite anecdotes among neurologists are of patients in which the intense fear generated by a runaway horse or a fire prompts an otherwise immobile subject to jump nimbly up from a wheelchair and flee. An alternative explanation is in terms of ‘goals’. Each successive transverse stripe might provide a ‘sub-goal’ that helps the patient to concentrate and thus overcome his difficulty in walking.

Intense emotion or clear goals may facilitate movement, but there is a simpler possibility that may account for many examples. The properties of the visual stimuli that are effective in helping the patients to control their movements are similar to those of the visual signals relayed to the cerebellum. An intact cerebellar pathway may allow parkinsonian patients to bypass their poorly functioning basal ganglia and enable them to use vision to guide their movements.

There are two totally different types of afferent fibres to the cerebellar cortex – mossy fibres and climbing fibres. Visually activated climbing fibres are relayed to a relatively small area of the cerebellar cortex by way of a subdivision of the inferior olivary nucleus. The anatomical circuits and the response properties of visual cells along this pathway have been well described. However, visual climbing fibres respond optimally to slowly moving targets; hence, they probably do not play a role in guiding rapid movement. The visual mossy fibres terminate more widely on the cerebellar cortex, and the receptive field properties of cells along this pathway seem particularly appropriate for visuomotor control.

In the case of transverse stripes on the floor, the salient property of the visual stimulus that helps patients to control their movement is, in effect, a horizontal grating placed in the lower visual field. When the patient walks, the stripes move downward in the visual field at a rate determined by his speed. A staircase also acts as a horizontal grating that moves downward in the visual field as the patient climbs the stairs. Similarly, the images of white papers on the floor in front of the patient as he walks are like that of an array of small targets moving downward in the visual field. A ball aimed towards the patient is a looming target, the edges of which move outward as its angular size grows larger with time. Each of these visual stimuli is an effective target for activating one or another of the classes of neurons that relay mossy fibre visual information via the pontine nuclei to the cerebellum in cats or monkeys. It seems likely that information about the motion of stripes, the stairs, the white papers, or the looming target of an approaching ball are relayed to the cerebellum as mossy fibres by way of the pontine nuclei.

Although an important role of the cerebellum in motor control has been recognized for over one hundred years, it is only recently that the role of sensory input in that control has become better understood. At first, the only sensory afferents to the cerebellar cortex that were recognized were those that are relayed to it by way of the spino-cerebellar tracts. The pontine nuclei were also known to provide an important input to the cerebellum, but it was assumed that this pathway only relayed inputs from collaterals of corticospinal axons or other pathways that originate in the motor cortex. The realization that there are other import-
ant sensory inputs projecting to the cerebellum began in 1944 when Snider and Stowell\(^{10}\) showed that clicks and light flashes could evoke potentials on the cerebellar cortex. These sensory responses were most prominent on lobule VII of the cerebellar vermis. Later experiments\(^{11}\) demonstrated that visually evoked potentials can in fact be recorded over a much wider area of the cerebellar cortex.

Far more is now known about the anatomical pathways and the visual response properties of cells that relay visual information via mossy fibres to the cerebellum. Anatomical studies in rats\(^{12}\), cats\(^{13-17}\), and monkeys\(^{18,19}\) have demonstrated that the cerebral cortex as well as the superior colliculus\(^{20-23}\), the pretectal areas\(^{24}\), and the ventral lateral geniculate body\(^{25,26}\) all project to the cerebellum by way of the pontine nuclei. Cells in the region of the pontine nuclei that receive input from the visual areas of the cortex\(^{6}\) or from the superior colliculus\(^{24}\) can be activated briskly by appropriate visual targets. The properties of the receptive fields of pontine visual cells are diverse, but they share the common characteristic of being relatively insensitive to the precise orientation or shape of visual targets; they are, however, strongly influenced by the direction and speed of the targets. Although they may respond weakly to a bright flash, pontine cells are relatively blind to stationary targets. These stimulus characteristics are similar to those that elicit paradoxical movement in parkinsonian patients.

The cortical areas that relay visual information via mossy fibres to the cerebellum are now known for several species of mammal. In monkeys, nearly all of the cortical visual output to the pons and cerebellum arises from a group of visual areas on the banks of the superior temporal and parieto-occipital fissures, and in adjacent areas of the posterior parietal cortex\(^{19}\). In rats\(^{12,27}\) and cats\(^{14-16}\), all of the known cortical visual areas project to the pons to some degree.

Cells in the cerebral cortex that project to the pontine nuclei are responsive to the direction and velocity of moving targets. In monkeys, it is the cortical areas especially sensitive to moving targets\(^{28-30}\) that provide the major visual input to the cerebellum. These cortical areas are probably involved in the perception of movement as well as in the visual guidance of movement. Although in cats, unlike monkeys, all of the known cortical visual areas project to the pontine nuclei, only a subset of cells — all of which are contained within lamina V — do so. Cortico-pontine cells in lamina V of area 18 in cats have receptive field properties that differ markedly from those of cells in the more superficial cortical laminae\(^{31}\). These cells, which have been identified by antidromic invasion following electrical stimulation of their axon terminals in the pontine nuclei, are not influenced by the precise shape or orientation of targets. They respond briskly to movements in a preferred direction at a preferred speed. The receptive field properties of these cortico-pontine neurons are thus similar to those of visual pontine cells. The only modification that would be necessary to account for the receptive field properties of pontine cells would be to concentrate the output from a number of cells from a broad region of cortex in area 18 onto a single pontine visual cell.

Cells in the pontine nuclei project to the cerebellar cortex, where they terminate as mossy fibres. The exact distribution of visual mossy fibre terminals is not yet completely mapped, but in rats\(^{12}\), cats\(^{32,33}\), and in monkeys\(^{34}\) there is an especially dense projection from pontine visual areas to the caudal regions of the cerebellar vermis and hemispheres, particularly the dorsal paraflocculus. These connections can be revealed both by anatomical tracing techniques or by antidromic activation of pontine cells following electrical stimulation of the cerebellar cortex.

Thus, there is a well-defined circuit that relays visual information about the rate and direction of moving objects from forebrain, diencephalic and midbrain visual areas to the cerebellum by way of the pontine nuclei. The axons of pontine visual cells terminate over a wide region of the cerebellar cortex as mossy fibres. The most salient quality of visual mossy fibres is that they are particularly responsive to rapidly moving targets. The evidence suggests\(^{35}\) that they are probably involved in the visual control of movement of the eyes, limbs and the body. In addition to its visual input there are also somatosen-sory and auditory projections to the cerebellum by way of the pontine nuclei. These other sensory inputs may also help parkinsonian patients to control their movements. The visual input, however, seems to be the most powerful. Insofar as the cerebellar pathways are unaffected by disease of the basal ganglia, this surviving pathway may account for paradoxical movements that are guided by vision.

Selected references

17. Glickstein, M., King, R. and Stein, J. (1972) Science 178,
Cholinergic controversies

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In his recent article in TINS¹, Fibiger argues that the evidence for the contribution of the degeneration of the cholinergic system to the symptomatology of Alzheimer's disease is weak. Obviously, there are differences between patients with Alzheimer's disease who have a chronic progressive disorder affecting many neural systems, and volunteers who are administered anticholinergic drugs. However, experiments have also been done in animals² and in humans³ that demonstrate clear effects of cholinergic blockade on the acquisition of new information, and, since patients with Alzheimer's disease do show a marked decline in cholinergic markers⁴, a similar impairment in acquisition consequent upon this cholinergic loss may be a component of their cognitive difficulties. It is unlikely, therefore, that drug therapy that does not acknowledge this cholinergic loss will be wholly effective in treating the cognitive symptoms of Alzheimer's disease.

Fibiger's problem in discerning the psychological function of ACh may be unfounded, since consideration of the anatomy of the cholinergic projections would suggest that it in fact does not have a psychological function. Rather, it has a mechanistic function, which is to facilitate and modulate activity in the target areas that then make their own contribution to psychological function. Where only part of the cholinergic projection is destroyed (e.g. by neurotoxic lesions), resulting impairments will be similar to those found following structural damage to the target areas. So, for example, lesions of the nucleus basalis magnocellularis (NBM) in primates⁵,⁶ produce decreases in cholinergic markers in neocortex [such as choline acetyltransferase (ChAT)], and result in impairments in the acquisition of visual discriminations comparable to those produced by ablations of frontal and temporal neocortex. On the other hand, lesions of the vertical limb of the diagonal band (VDB)⁷,⁸ produce decreases in ChAT in hippocampus and a specific impairment in the acquisition of tasks similar to that produced by surgical transection of the fornix⁹.

Lesions that include the NBM and VDB undoubtedly destroy non-cholinergic neurones as well. It is difficult to argue, however, that destruction of non-cholinergic interneurones in the vicinity of the VDB (e.g. in the adjacent nucleus accumbens) would produce the same specific impairment in visuospatial and conditional learning as is seen following fornix transection, since such non-cholinergic neurones are not known to have long projections through the fornix.

Fibiger then argues that cholinergic agonists might ameliorate the cognitive impairments resulting from such neurotoxic lesions by an unspecified but non-cholinergic mechanism. Though theoretically possible, this is an unnecessarily convoluted explanation. The effects of the lesion and the drug could only be said to 'summate', i.e. to have quantitatively opposite effects if each occurs via independent mechanisms. We have found, however, that a cholinergic agonist (arecoline) completely restored learning ability in animals with NBM lesions, but had no effect in unlesioned animals (including 'slow learners') on the same tasks or on other, more difficult tasks, which unlesioned animals found as hard to learn as the lesioned animals had found the easier tasks. Furthermore, animals with NBM lesions eventually regained apparently normal learning ability, but were then hypersensitive to the disruptive effects of very low doses of scopolamine.

In the neurotoxic lesion experiments the results cited by Fibiger, it is not clear whether performance on the tasks described would have been impaired following ablations of those cortical areas that showed greatest depletion of ChAT after quisqualate lesions of the NBM. Thus, while these results demonstrate that some of the effects of ibotenate NBM lesions are not related to cholinergic damage, they do not wholly assess the contribution of different parts of the cholinergic system to learning and memory. This requires the use of more appropriate tasks chosen on the basis of cortical and hippocampal localization studies, which are at present incomplete in the rodent.

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References