Saccade Responses to Dopamine in Human MPTP-Induced Parkinsonism

J. R. Hotson, MD, E. B. Langston, MD, PhD, and J. W. Langston, MD

Depletion of dopamine content in the substantia nigra resulting from 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) toxicity produces parkinsonism. Management of 3 patients with MPTP-induced parkinsonism required drug holidays during which there was a state of dopamine depletion followed by dopamine replacement. We used this opportunity to study the effect of the selective loss of pars compacta dopaminergic cells on vertical and horizontal saccade (fast) eye movements. During the drug holidays, visually guided saccades were hypometric and had long latencies but retained a normal saccade velocity-amplitude relationship. Dopamine agonists or precursors improved the accuracy and reaction times of saccades in all directions, but not their velocity. Two of the three patients also had intermittent blepharospasm during dopamine depletion. During the episodes of blepharospasm, saccade responses became slow eye movements. MPTP causes a dopaminergic-responsive disorder of saccade initiation that is similar to idiopathic parkinsonism. The inhibition of voluntary eyelid opening during MPTP-induced blepharospasm further increases this impairment of fast eye movements and altered saccade velocity, presumably via the pars reticulata of the substantia nigra.


The compound 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a newly recognized neurotoxin [29] that selectively kills dopaminergic cells in the pars compacta of the substantia nigra [4, 8, 30]. In humans, exposure to the street drug form of MPTP causes a Parkinson's disease symptom complex with bradykinesia, rigidity, tremor, and postural instability. In some patients there is also apraxia of eyelid opening and reflex blepharospasm [3, 29].

Patients with MPTP-induced parkinsonism have few of the additional problems accompanying the other forms of Parkinson's disease symptom complex such as multisystem involvement, aging, or dementia [13, 15, 17, 19, 33]. Therefore, interpretation of movement abnormalities in patients with MPTP-induced parkinsonism involves few additional confounding variables. Management of these patients, however, is complicated by the early appearance of dyskinesias and hallucinations after treatment with dopamine precursors and agonists. Drug holidays are required to reduce the dopamine-induced complications. This clinical requirement for drug holidays creates the unique situation of dopamine depletion followed by replacement in humans with presumed selective loss of pars compacta cells.

It has also recently been established that saccade-related cells in the superior colliculus are tonically inhibited by cells in the pars reticulata of the substantia nigra, an output of the basal ganglia [21, 22]. This inhibition appears to be mediated by \( \gamma \)-aminobutyric acid (GABA) [23, 24]. GABA agonists injected into the superior colliculus restrict saccadic eye movements, whereas GABA antagonists facilitate their initiation. GABA agonists injected into the pars reticulata of the substantia nigra also facilitate saccadic initiation, presumably by blocking its tonic inhibition of the superior colliculus. It is unknown, however, whether selective dopamine loss in the pars compacta also reversibly alters saccade initiation via this pathway.

For these reasons, we used the clinical opportunity offered by the drug holidays in MPTP-exposed patients to study the effects of selective dopamine depletion on visually guided saccades. During the study, we also found that MPTP-induced dopamine depletion caused severe blepharospasm accompanied by restriction of saccade responses in two patients. A brief report of these observations has been presented [26].

Methods

Clinical Aspects

The three patients studied were street drug abusers who developed a Parkinson's disease symptom complex after in-
travenous exposure to "synthetic heroin" containing MPTP. Detailed case reports have been published previously (see Patients 1, 3, and 5 in [3]). Patients were selected for drug holidays if they developed dyskinesia movement disorders and hallucinations to such a degree that they were unable to care for themselves. Informed consent was obtained from all patients. All recordings in this study were obtained while the patients were hospitalized and under close supervision, both during and after the drug holiday.

The clinical effect of the drug holiday was estimated using the Hoehn and Yahr 0–5 scale [25], a 0–15 point disability rating, and the time to briskly walk 6 m. The Hoehn and Yahr scale rates the functional severity of the disorder, but lacks sensitivity [11]. Our 0–15 point disability rating was adapted from other rating systems [1, 32] and was determined by clinical examination of five neurological signs: bradykinesia, tremor, rigidity, gait, and postural instability. Each subcategory of the disability rating was scored 0 (normal) to 3 (severe) based on clinical or functional definitions. These definitions are available upon request.

Oculomotor Recordings and Measurements

Analog saccade and pursuit eye movement recordings were obtained with a dual Purkinje Image Eyetracker and Gould rectilinear polygraph [7]. This system has a linear rectilinear horizontal and vertical 15- to 18-degree range of recording, a sensitivity of 1 minute, and a bandwidth of 0 to 75 Hz. Monocular recordings were obtained during binocular viewing with the head stabilized by chin and frontal-occipital head supports.

Saccadic responses were elicited by a Wavetech wide-screen oscilloscope dot positioned 57 cm in front of the patient. A waveform generator moved the dot in a vertical or horizontal square-wave pattern with a predictable amplitude but a pseudorandom interval between jumps. The target shifts subtended 3 to 15 degrees. Saccadic responses were amplified and electronically differentiated to provide both amplitude and velocity measurements. Saccades measured by this method have an overshoot that consists of both dynamic overshoot and a lens overshoot artifact. This overshoot is omitted in the measurements of saccade amplitude to exclude the artifact.

Peak velocity–amplitude plots were made for 30 to 50 saccades in each direction, as previously described [27]. In brief, glissades and overlapping saccades were excluded from the measurements by visual detection of the eye position and velocity traces. A power law (log velocity = a + b log amplitude) normally best fits the 3- to 15-degree portion of the saccade main sequence. Therefore, log values were used for determining linear regression curves for the patients' plots. The linear regression curves were used to estimate the peak velocity of 10-degree saccades. This estimate of saccade peak velocity has been shown to be as sensitive for detecting slowed saccades as for comparing the entire 3- to 15-degree plots to normal curves [27]. A Statistical Analyses System program was used for generating the plots and calculations.

Saccade latency and metric gain were measured for 15 to 30 responses to 12- to 15-degree target shifts in each direction. The latencies were measured for saccades that fell into a 100- to 800-msec interval following a target shift. Saccades occurring before 100 msec were considered anticipatory saccades, whereas saccades occurring after 800 msec may reflect inattention in spite of continuous verbal encouragement. Polygraph speed for latency measurements was 50 mm/sec. The same saccades used for latency measurements were also used for the measurement of saccade metric gain. Saccade metric gain equals the amplitude of the initial visually triggered saccade/amplitude of the total eye position change in response to the target. If a saccade reached the target with a single movement, the gain was 1. If an initial saccade was hypometric and undershot the target, the gain was less than 1. Hypometric saccades were followed, after an interval, by additional corrective saccades to reach the final eye position.

The saccade mean values of velocity, reaction time, and metric gain were determined for each vertical and horizontal direction for each patient during and after the dopamine drug holiday. The individual patient means were then combined to determine both a group mean in each direction and then a group mean for all directions.

Pursuit eye movements were elicited in one patient by a predictable triangular wave that subtended 10 degrees and moved at a velocity of 10 and 20 degrees. (Pursuit gain equals peak slow eye velocity/target velocity.) No attempt was made to remove saccades that were admixed but distinct from the slower pursuit velocity recording.

The stability of fixation in both the primary position of gaze and ± 7.5 degrees of arc horizontal and vertical gaze direction were recorded. The frequency of square-wave jerks greater than 30 minutes of arc was measured. Other saccadic intrusions and microsaccades were not measured. Measurements were performed by hand. Statistical comparisons used the Wilcoxon rank sum test with two-tailed p values.

Results

Clinical Observations

Three patients with MPTP-induced parkinsonism who developed severe dyskinesias and hallucinations in response to dopamine precursors and agonists were included in the study. Duration of treatment before the study ranged from 16 to 20 months. During drug holidays the patients became severely bradykinetic and rigid. They could not roll over in bed or feed themselves. They were unable to walk unassisted and required support while standing to prevent falling. Their speech was unintelligible. Tremor occurred intermittently but was not a consistent finding. A maximum Yahr score of 5 was assigned to all patients during the drug holiday (Table 1).

Examination of eye movements during the drug holiday revealed that voluntary upward vertical gaze was restricted to approximately 15 to 20 degrees in all three patients. The restriction of upward gaze was apparent with voluntary saccade and pursuit movements. This restriction could be overcome, however, by vertical oculocephalic movements consistent with a supranuclear vertical gaze paresis. All patients had hypometric, multistepped, visually guided saccades in both the horizontal and vertical directions. During the drug holiday, patients were also unable to track a target.

Horston et al: Saccades in MPTP Parkinsonism 457
Table 1. Mean Parkinson Disability Rating Scores

<table>
<thead>
<tr>
<th>Score</th>
<th>Dopamine Depletion</th>
<th>Dopamine Replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional disability</td>
<td>12.2</td>
<td>4.3</td>
</tr>
<tr>
<td>rating (0-15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yahr score (0-5)</td>
<td>5</td>
<td>3.3</td>
</tr>
<tr>
<td>Time to walk 6 m (sec)</td>
<td>. . a</td>
<td>23.6</td>
</tr>
<tr>
<td>Daily medication (mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbidopa/levodopa</td>
<td>0</td>
<td>50/500</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>0</td>
<td>40</td>
</tr>
</tbody>
</table>

*None of the patients could walk unassisted.

smoothly and used instead a series of saccades. One patient also had prominent saccadic intrusions in the form of square-wave jerks during fixation.

Two patients developed blepharospasm in addition to the Parkinson's disease symptom complex after exposure to MPTP. During the drug holidays, blepharospasm changed from a mild intermittent finding to severe, frequent bilateral contractions of the orbicularis oculi. This hypodopaminergic blepharospasm was intermittent and began with a slow tonic narrowing of the palpebral fissure that would fluctuate with various degrees of eyelid closure. It gradually evolved into complete eye closure caused by increasing active orbicularis oculi contraction.

The MPTP-induced blepharospasm frequently occurred spontaneously; however, a variety of external stimuli could also precipitate or speed the rate of eyelid closure, including visual threat, an ophthalmoscope light, touch of the eyelid, and a blink reflex. The active blepharospasm could last up to 3 to 5 minutes, during which persistent manual elevation assisted eyelid opening. The blepharospasm resolved slowly, again with fluctuations in eyelid closure. During the fluctuations of eyelid closing or opening there were periods when the eyelids could be manually but not voluntarily elevated with ease, similar to "apraxia" of eyelid opening [16].

During blepharospasm with eyelids manually elevated, the eyes appeared fixed in primary gaze. Attempts at saccadic refixation occurred with a prolonged initiation time followed by slow eye movement with a variable admixture of small saccades. Both effort and persistence by the patient were required to initiate these movements. Pursuit movements could still be elicited during blepharospasm and square-wave jerks were still apparent in one patient.

After the drug holiday and dopamine precursor and agonist replacement, both the mean functional disability rating and Yahr score decreased (Table 1). Patients became ambulatory without falling. Speech was dysarthric and self-care was regained, although family assistance was required in one case. Blepharospasm decreased in both severity and frequency. The upward vertical gaze paresis resolved.

Oculomotor Recordings

Saccadic responses to visual targets during the drug holiday and after dopamine precursor and agonist replacement were compared (Fig 1). Mean saccade reaction time, metric gain, and estimated peak velocity of 10-degree saccades were determined in both vertical and horizontal directions in both conditions (Table 2). Vertical and horizontal saccade reaction times were significantly \((p < 0.01)\) increased during dopamine depletion compared with during replacement. After dopamine agonist replacement, all reaction times fell within 2 SD of the laboratory's normal mean values (196 msec, SD 21, and 216 msec, SD 18, for horizontal and vertical saccade reaction times, respectively). Twelve- to 15-degree visually triggered saccade responses were also consistently hypometric. The metric gain of this response in all directions was significantly decreased \((p < 0.001)\) increased during dopamine depletion compared with during replacement. After dopamine agonist replacement, all reaction times fell within 2 SD of the laboratory's normal mean values (0.93, SD 0.05, and 0.97, SD 0.08, for horizontal and vertical saccades, respectively). Up-
Table 2. Saccade Responses

<table>
<thead>
<tr>
<th>Saccades</th>
<th>Dopamine Depletion</th>
<th>Dopamine Replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velocity (deg/sec)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up</td>
<td>387</td>
<td>450*</td>
</tr>
<tr>
<td>Down</td>
<td>385</td>
<td>361</td>
</tr>
<tr>
<td>Right</td>
<td>392</td>
<td>431</td>
</tr>
<tr>
<td>Left</td>
<td>465</td>
<td>424</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>414 (68)</td>
<td>417 (56)</td>
</tr>
<tr>
<td>Reaction time (msec)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up</td>
<td>318</td>
<td>245</td>
</tr>
<tr>
<td>Down</td>
<td>316</td>
<td>249</td>
</tr>
<tr>
<td>Right</td>
<td>316</td>
<td>221</td>
</tr>
<tr>
<td>Left</td>
<td>323</td>
<td>210</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>318 (112)</td>
<td>231 (40)*</td>
</tr>
<tr>
<td>Metric gain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up</td>
<td>0.40</td>
<td>0.76</td>
</tr>
<tr>
<td>Down</td>
<td>0.46</td>
<td>0.87*</td>
</tr>
<tr>
<td>Right</td>
<td>0.55</td>
<td>0.84</td>
</tr>
<tr>
<td>Left</td>
<td>0.52</td>
<td>0.87</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.49 (0.16)</td>
<td>0.84 (0.07)*</td>
</tr>
</tbody>
</table>

*Two-tailed p value = 0.02.

Two-tailed p value < 0.01.

ward saccades remained relatively hypometric even after treatment.

In contrast to saccade reaction times and metric gains, the saccade peak velocity–amplitude curves were the same during dopamine depletion and replacement (Fig 2). Similarly, there was no consistent change in estimated velocity for 10-degree saccades after dopamine replacement in the right, left, or downward directions (Table 2). Saccade peak velocity, however, did increase significantly ($p = 0.02$) in the upward direction in all three subjects after dopamine replacement. All 10-degree saccade velocities in all directions and conditions fell within 1 SD of the laboratory's normal mean values (437 degrees/sec, SD 98, and 405 degrees/sec, SD 82, for horizontal and vertical saccades, respectively).

Horizontal pursuit measurements were also taken in one patient during the drug holiday and after dopamine replacement (Fig 3). In this one person, the gain of the pursuit system (eye velocity/target velocity) was impaired at target velocities of both 10 and 20 degrees/sec. Normal subjects in an identical testing situation show a gain greater than 0.9 at these velocities, similar to that found in other laboratories [36]. Dopamine precursor and agonist replacement improved pursuit performance, particularly at the faster target velocity (Fig 3).

During fixation on a stationary target, prominent saccadic intrusions in the form of square-wave jerks occurred in one person. This subject had square-wave jerks larger than 0.5 degrees occurring at a frequency greater than 30/min independent of the state of treatment. No consistent change in the frequency of square-wave jerks was noted in this subject's response to dopamine replacement.

In 2 subjects, intermittent severe blepharospasm occurred frequently during the drug holiday and decreased after dopamine precursor and agonist replacement. The onset of blepharospasm was always heralded by failure of the Purkinje image eyetracker to track the eye. Eyelid narrowing interfered with the infrared Purkinje image reflections required for the eyetracker to work. Therefore, during blepharospasm manual elevation of the eyelids was required for eye movement recordings. In this situation, both vertical and horizontal ocular responses to 12- to 15-degree target shifts consisted of slow continuous eye movements with a variable admixture of small saccades (Fig 4). These slow eye movements had a peak velocity of 10 to 60 degrees/sec and a duration of 800 to 2,200 msec. These slow eye movements occurred only during active blepharospasm or when the patients could not voluntarily elevate their eyelids. The resolution of blepharospasm coincided with the return of multistep hypometric saccade responses.

When the restriction of saccades by blepharospasm was first observed, the possibility that it represented a Purkinje image recording artifact caused by manual elevation of the eyelids was considered. Attempts to confirm the observation with DC oculography were technically unsatisfactory because of interference produced by contraction of the orbicularis oculi. Direct clinical observation and videotape recordings, however, found slow ocular movements during blepharospasm. Also, during the Purkinje image recordings, small saccades as well as slow eye movements were
recorded, indicating that the eyetracker could follow both fast and slow eye movements. The slow eye movements during blepharospasm consistently followed the direction and position of target shifts and appeared similar to saccade responses recorded in patients with progressive supranuclear palsy using the same eyetracking system. Finally, control subjects were studied during voluntary tonic eye closure and manual eyelid elevation. Normal-velocity visually triggered saccades were accurately recorded during partial eyelid elevation with orbicularis oculi contraction. For these reasons, we concluded that the slow eye movements during blepharospasm were a pathophysiological event.

Discussion
The results demonstrate that pars compacta dopaminergic cells play a prominent role in the triggering and programming of visually triggered saccades but not in the generation of their peak velocity. Selective dopamine depletion prolonged saccade reaction time and produced hypometric saccades in all directions but did not consistently alter the peak velocity of 10-degree saccades. Both reaction times and saccade
Fig 4. Examples of horizontal eye movement responses to target steps during periods of blepharospasm. Attempts at saccadic refixation occurred with a prolonged initiation time followed by a slow eye movement with a variable admixture of small saccades. In A, a single small saccade (arrow) is followed by a slow eye movement. In B and C, a low-velocity eye movement is used to refixate the target. Upper trace is target position, middle trace is eye position, lower trace is eye velocity. Up is the direction of up or right eye movements.

A reversible supranuclear upward gaze paresis and a mild decrease in upward saccade velocity occurred in all three patients during their drug holidays. In addition, saccade metric gains showed the greatest attenuation in the upward direction during both dopamine depletion and replacement. A similar upward restriction of gaze and hypometric saccades also occurs frequently in other forms of Parkinson's symptom complex [6, 31]. These findings imply that upward saccades are selectively sensitive to disorders of the pars compacta of the substantia nigra.

We found two other studies of saccade response to dopamine precursors [6, 20]. The study of Highstein and associates [20] revealed that in one of two patients with idiopathic parkinsonism, horizontal saccade velocities increased in response to dopamine administration. In that study, eye movements were recorded with electrooculography and included hypometric glissades in the saccade measurements. (Glissades are dysmetric...
saccade responses that slowly glide the eye into final position.) Glissades occur in normal subjects [2, 14], may be increased by fatigue [2], and occur more frequently in patients with Parkinson’s disease [38]. They are a form of hypometric saccades, and would artificially change saccade velocity–amplitude plots if the appended glissadic component was not excluded. Therefore, the single observed increase in horizontal saccade velocity in response to dopamine may be caused by a decreased frequency of hypometric glissades rather than a change in the saccade velocity–amplitude relationship.

The report by Corin and colleagues [6] consists of a qualitative oculomotor study of 29 patients with Parkinson’s symptom complex of unknown cause [6]. Only six patients of this group had more than a mild generalized motor response to levodopa. Only two patients had a noticeable improvement in oculomotor function; however, saccade velocities, latencies, and gain were not measured. The overall poor therapeutic response in these patients suggests either inadequate dopamine levels in the striatum or a multisystem degeneration that might interfere with responses to dopamine. In our study, all three patients had a moderate to excellent response to dopamine replacement after a drug holiday and all three had consistent changes in saccade latency and gain. Also, evidence to date suggests that these patients have a pure dopaminergic deficiency of the striatonigral system.

A single result in the present study also suggests that pursuit tracking is responsive to dopamine. In one subject, the pursuit responses after a drug holiday and dopamine replacement improved more than fourfold. Since pursuit tracking of a predictable target is not only a measure of the pursuit system but also of anticipation and attention, the interpretation of the observation in a single subject requires caution. The finding does suggest, however, that the defective pursuit tracking observed in Parkinson’s disease symptom complex [38] does respond to dopamine replacement.

These results indicate that the previously observed saccade disorders seen in idiopathic Parkinson’s disease can be caused solely by loss of cells in the pars compacta. The results also add physiological evidence that MPTP produces an accurate model of Parkinson’s disease. Finally, the observations demonstrate that the oculomotor defects in parkinsonism are responsive to dopamine treatment.

MPTP-induced dopamine depletion not only altered human saccade and pursuit eye movements but also produced intermittent blepharospasm. The bilateral tonic eyelid contraction caused by MPTP is identical to the blepharospasm found in other diseases including idiopathic parkinsonism (see [28] for review). The blepharospasm was intermittent and could occur spon-

462 Annals of Neurology Vol 20 No 4 October 1986
a disorder mediated predominantly via the globus pal- lidus. The milder restriction of visually guided saccadic eye movements may be due to an increased tonic inhibi-
tion of the superior colliculus by the pars reticulata.
This proposed inhibition appears to be both reversible
by dopamine agonists and strikingly enhanced by
MPTP-induced blepharospasm, the latter resulting in
slowed saccade responses. If this postulate is true, then
some forms of neurogenic and essential blepharospasm
may also reflect a basal ganglia disorder mediated by
the pars reticulata.

11. Alba A, Trainor FS, et al: A clinical disability rating for Parkin-
12. Bahill AT, Stark L: Overlapping saccades and glissades are pro-
duced by fatigue in the saccadic eye movement system. Exp
Neurol 48:95–106, 1975
13. Ballard PA, Teetrud JW, Langston JW: Permanent human park-
ninsonism due to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
(MPTP): seven cases. Neurology (Cleveland) 35:940–955, 1985
parkinsonism: selective destruction of dopaminergic neurons in
the pars compacta of the substantia nigra by N-methyl-4-
phenyl-1,2,3,6-tetrahydropyridine. Proc Natl Acad Sci USA
80:4546–4550, 1983
with hem-Parkinson's disease. Invest Ophthalmol Vis Sci
(suppl) 26:258, 1985
16. Corin MS, Eitzen TS, Bender MB: Oculomotor function in pa-
17. Cornsweet TN, Crane HD: Accurate
tracker using first and fourth Purkinje images. J Opt Soc Am
65:921–928, 1975
18. Davis GC, Williams AC, Markey SP, et al: Chronic parkinson-
ism secondary to intravenous injection of meperidine analogues.
Psychiatry Res 1:249–254, 1979
19. Defjung JD, Jones GM: Akinesia, hypokinesia, and brady-
kinesia in the oculomotor system of patients with Parkinson's disease.
20. Delong JD, Georgopoulos AP: Motor functions of the basal
ganglia. In Brook VB (ed): Handbook of Physiology, Vol 2,
The Nervous System. Baltimore, Williams & Wilkins, 1981
21. Diamond SG, Markham CH: Evaluating the evaluations: or how
to weigh the scale of parkinsonian disability. Neurology (Clevel-
land) 33:1098–1099, 1983
22. Dieckmann G, Hasslet R: Opening and closing of eyes and signs
Acta Neuropathol 64:43–52, 1984
25. Hakim AM, Mathieson G: Dementia in Parkinson's disease: a
26. Hikosaka O, Wurtz RH: Visual and oculomotor functions of
monkey substantia nigra pars reticulata. I. Relation of visual and
auditory responses to saccades. J Neurophysiol 49:1230–1253,
1983
27. Hikosaka O, Wurtz RH: Visual and oculomotor functions of
monkey substantia nigra pars reticulata. IV. Relation of substan-
28. Hotson JR, Louis AA, Langston EB, Moreno JA: Vertical sac-
cades in Huntington's disease and non-degenerative choreo-
29. Jankovic J, Ford J: Blepharospasm and orofacial-cervical dys-
tonia: clinical and pharmacological findings in 100 patients. Ann
30. Langston JW, Ballard PA, Teetrud JW, Irwin I: Chronic parkin-
sonism in humans due to a product of meperidine-analog syn-
31. Langston JW, Forno LS, Rebert CS, Irwin I: Selective nigral
toxicity after systemic administration of 1-methyl-4-phenyl-
1,2,3,6-tetrahydropyridine (MPTP) in the squirrel monkey.
Brain Res 292:390–394, 1984
32. Leigh JR, Zee DS (eds): Diagnosis of central disorders of ocular
motility. In The Neurology of Eye Movements. Philadelphia,
Davis, 1983, pp 233–234
286, 1980
34. Oppenheimer DR: Diseases of the basal ganglia, cerebellum and
motor neurons. In Blackwood W, Corselles J (eds): Greenfield's
35. Petir M, Milbled G: Anomalies of conjugate ocular movement in
Huntington's chorea; applications to early detection. Adv
Neurol 1:287–294, 1973
36. Shibasaki H, Toku S, Kurokawa Y: Oculomotor abnormalities in
37. Sharpe JA, Sylvester TO: Effects of aging on horizontal smooth
38. Starr A: A disorder of rapid eye movements in Huntington's chorea.
Brain 90:545–564, 1967
motor deficits in Parkinson's disease: II. Control of the saccadic

Horson et al: Saccades in MPTP Parkinsonism 463

Supported by NEI Grant No EY03387 (Dr Horson) and the Pitney
Fund at Stanford University.
Dr Robert Wurtz provided a valuable review of the manuscript.

References
1. Alba A, Trainor FS, et al: A clinical disability rating for Parkin-
2. Bahill AT, Stark L: Overlapping saccades and glissades are pro-
duced by fatigue in the saccadic eye movement system. Exp
Neurol 48:95–106, 1975
3. Ballard PA, Teetrud JW, Langston JW: Permanent human park-
ninsonism due to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
(MPTP): seven cases. Neurology (Cleveland) 35:940–955, 1985
4. Burns RS, Chieue CC, Markey SP, et al: A prime model of
parkinsonism: selective destruction of dopaminergic neurons in
the pars compacta of the substantia nigra by N-methyl-4-
phenyl-1,2,3,6-tetrahydropyridine. Proc Natl Acad Sci USA
80:4546–4550, 1983
with hem-Parkinson's disease. Invest Ophthalmol Vis Sci
(suppl) 26:258, 1985
6. Corin MS, Eitzen TS, Bender MB: Oculomotor function in pa-
7. Cornsweet TN, Crane HD: Accurate
tracker using first and fourth Purkinje images. J Opt Soc Am
65:921–928, 1975
8. Davis GC, Williams AC, Markey SP, et al: Chronic parkinson-
ism secondary to intravenous injection of meperidine analogues.
Psychiatry Res 1:249–254, 1979
9. Defjung JD, Jones GM: Akinesia, hypokinesia, and brady-
kinesia in the oculomotor system of patients with Parkinson's disease.
10. Delong JD, Georgopoulos AP: Motor functions of the basal
ganglia. In Brook VB (ed): Handbook of Physiology, Vol 2,
The Nervous System. Baltimore, Williams & Wilkins, 1981
11. Diamond SG, Markham CH: Evaluating the evaluations: or how
to weigh the scale of parkinsonian disability. Neurology (Clevel-
land) 33:1098–1099, 1983
12. Dieckmann G, Hassler R: Opening and closing of eyes and signs
Acta Neuropathol 64:43–52, 1984
15. Greenfield JG, Bosanquet FD: The brainstem lesions in parkin-
sionism. J Neurol Neurosurg Psychiatry 16:213–226, 1953
16. Guiloff RJ, George RJ, Marsden CD: Reversible supranuclear
ophthalmoplegia associated with parkinsonism. J Neurol
Neurosurg Psychiatry 43:552–554, 1980
17. Hakim AM, Mathieson G: Dementia in Parkinson's disease: a
18. Hikosaka O, Wurtz RH: Visual and oculomotor functions of
monkey substantia nigra pars reticulata. I. Relation of visual and
auditory responses to saccades. J Neurophysiol 49:1230–1253,
1983