Saccadic eye movement deficits in the MPTP monkey model of Parkinson's disease

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Saccadic eye tracking was studied in a monkey given i.v. injections of N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). The Parkinson-like symptoms which appeared in the animal's general motor behavior (akinesia, bradykinesia, hypokinesia) were also observed in its eye tracking. Similar oculomotor deficits are seen in patients with idiopathic Parkinsonism. The MPTP model offers excellent possibilities for studying the mechanisms underlying the motor disabilities of Parkinson's disease.

Exposure to N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (NMPTP, or MPTP) in human drug addicts causes a syndrome strongly resembling idiopathic Parkinson's disease 4,14. Both humans and monkeys affected by MPTP exhibit rigidity, akinesia and bradykinesia, with variable tremor 2,6,15. Pathological changes produced by MPTP in monkey brains seem greatest in the dopaminergic cells of substantia nigra pars compacta; there appears to be little or no pathology in other brain areas, including potentially susceptible dopaminergic systems such as that originating in the ventral tegmental area 1,13. The selective action of MPTP and the similarity to human symptomatology have resulted in its increasingly popular use in monkey models of Parkinson's disease (P.D.) 2,15.

When asked to perform rapid, self-paced saccadic eye movements between two stationary visual targets or to follow unpredictable step changes in a visual target, P.D. patients reveal oculomotor deficits which parallel some of their general skeletal motor symptoms 3,5,17-20: latency to initiation of movement is often significantly longer than controls (akinesia); saccades frequently fall short of the target (undershoot or hypokinesia) and several small 'staircase' saccades occur to place the eye on target 18,20; the duration of saccades may be unusually long and their peak velocities decreased (bradykinesia) 5,18,20. In addition, the eye may have difficulty maintaining steady fixation of gaze during intersaccadic intervals (the P.D. patient may also have other oculomotor problems 3,18,20). We were able to document similar phenomena in monkey eye tracking, following injection of MPTP.

Data were obtained from a single adolescent (3 kg) rhesus monkey (M. mulatta) which furnished its own normal control measures prior to MPTP injection. The monkey was trained to track horizontal step changes in the position of a small red target as it moved across a dimly illuminated tangent screen. Accurate eye movements were directly rewarded by applesauce mixed with protein powder; the daily diet was consumed during training and testing sessions. The monkey was trained (1) to track periodic, horizontal step movements of the target spot of 5°, 10°, 20°, 30°, and 40° and (2) to track the spot when the timing, amplitude and horizontal direction of its movement were varied according to a pseudo-random program.

Eye movements were recorded by an electromagnetic technique (scleral search coil) developed by Fuchs and Robinson 7. Briefly, under general anesthesia a fine, teflon-coated, stranded stainless steel...
wire is passed under the 4 rectus muscles to form a
coil which rotates with the eye. The coil leads are led
under the skin to a Winchester plug, which is perma-
nently anchored to the skull with dental cement.
When the animal's head is fixed within horizontal and
vertical alternating magnetic fields, a voltage is in-
duced in the coil which is a function of the angle be-
tween the coil and the magnetic field. The frequency
response, DC to 1 kHz (-3 dB), is adequate to follow
the fastest saccade; the sensitivity is 15 min of arc.
The voltage output is linearly related to the angular
deviation of the eyeball within ±20° of visual angle
around the primary direction of gaze (eyes straight
ahead). All testing took place within an electrically
shielded room.

MPTP was purchased as the HCl salt from Chem-
Services (East Hanover, NJ). Its purity and stability
(dry) were assayed by HPLC, reversed phase, in
ODS columns with a 1:4 0.2 M ammonium acetate-
methanol solvent. The drug was freshly dissolved in
Ringer's solution and injected into the monkey's leg
vein at 0.4 mg/kg twice daily on two consecutive
days, with the intent to produce clear Parkinsonian
symptoms within 5–6 days after the first injection1,2.
Eye tracking movements were recorded on the day
before drug administration, on the two days of injec-
tion and on one day after the last injection, after
which the monkey refused to track until treated with
a mixture of 100 mg L-DOPA and 10 mg of a DOPA
decarboxylase inhibitor, carbidopa (Sinemet 100/10;
Merck, Sharp and Dohme). Parkinson symptoms in
gross behavior were semi-quantified with a modified
version of the Hoehn and Yahr human P.D. rating
scale6. The signs of akinesia, bradykinesia and hypo-
kinesia were quite marked by the 4th day after the
first injection. Acute effects immediately following
each injection and lasting less than 20 min included
skin flushing, pupillary dilation, piloerection, vocali-
ization, tremor and a dazed appearance, and were
similar to those noted by other authors1,2.

Fig. 1 gives an overview of eye tracking data be-
fore treatment with MPTP (Pre-drug, top panel), on
the two days during which the drug was administered
(Days 1 and 2), on the last day the animal was willing
to work (Day 3), and on day 6 when he was given Si-
memet. All tracking was recorded monocularly with
the implanted eye. As seen in the top panel, a target
step to the right (upward deflection) before MPTP
regularly elicited a single saccade whose amplitude,
duration, and average velocity were within the nor-
mal range6. In response to a leftward target step
(downward deflection) the eye frequently required a

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Fig. 1. Saccadic tracking of the target spot during horizontal
displacements of 10°, 20°, 30° or 40° in pseudo-random order of
timing and direction. Upper trace in each panel shows vertical
eye movement channel. Middle trace depicts target move-
ments; rightward movements are up and leftward are down.
The lowest trace showing horizontal eye movement record is
displaced downward to facilitate viewing. Each panel samples
approximately 36 s of tracking. Pre-drug: horizontal saccadic
tracking on the day before the first dose of MPTP. Leftward
movements in this animal frequently produced an undershoot
followed by a normal correction saccade. Day 1: records ob-
tained approximately 3 h following the first injection with
MPTP. Day 2: two h after the third injection with MPTP and 27
h after the first injection. Day 3: approximately 20 h after the
4th and final MPTP injection. On this day the animal ceased
working before the session was completed and did not resume
until treated with Sinemet. Sinemet: example of eye tracking
on Day 6 following tube ingestion of one tablet of 100/10 Sine-
met.
corrective saccade, but both saccades had normal
amplitude-duration relations. The Day 1 samples of
tracking, taken just after the animal had received the
second MPTP injection, are not appreciably differ-
ent from pre-drug conditions. The data of Day 2 how-
ever, taken immediately after the final MPTP injec-
tion, reveal some indications of saccadic abnormality
(increased hypometria, irregular trajectories). The
first, most noticeable deficit was a fixational instabil-
ity which appeared during intersaccadic intervals in
both the horizontal and vertical eye movement
records. On Day 2 the monkey also showed mild aki-
nesia and bradykinesia and was listless and inactive
in his home cage, although he ate normally and work-
ed during the entire test session. By Day 3 (20 h after
the final MPTP injection) instability during eye fixa-
tion was even more obvious, many saccadic move-
ments were bradykinetic and hypometric, and some-
times the animal failed altogether to respond to a tar-
get movement. Akinnesia and bradykinesia were also
marked in the animal’s other movements, and his ap-
petite was failing. By the 5th day following the first
injection of MPTP the animal displayed severe par-
kinsonian signs, required tube feeding, and was
largely immobile in the home cage. Spontaneous eye
movements occurred infrequently, with prolonged
periods of staring into space. He did not protest when
his limbs were extended (rigidity was apparent, al-
though we saw little cogwheeling), and tremor was
observed sporadically, especially on the few occa-
sions of self-initiated movement.

On the 6th day, one tablet of Sinemet was crushed,
mixed with water, and administered by stomach
tube, following which the animal was placed in his
primate testing chair. The change in his overall be-
behavior following Sinemet was dramatic; the monkey
became hyperactive within half an hour, twisting and
turning in his chair, pulling and pushing at its struc-
ture. Spontaneous saccadic eye movements were far
more frequent than before treatment with MPTP;
they often interfered with tracking behavior in the
post-Sinemet testing. When the animal finally settled
to eye tracking under good stimulus control, saccade
metrics were qualitatively normal as seen in the low-
est panel of Fig. 1. (They were also quantitatively
normal as shown in the Sinemet data of Fig. 3.) Post-
Sinemet records of Fig. 1 indicate that fixational sta-
Bility also returned to the pre-MPTP state, for both
horizontal and vertical eye movement. The animal
worked for the applesauce reinforcement for about
1.5–2 h. The effects of Sinemet were completely
gone approximately 7 h following its administration
and the animal once again was immobile in his home
cage.

Fig. 2 shows details of saccade waveforms made
before and after the injections of MPTP, on an ex-
panded time scale. Both rightward (top examples)
and leftward (bottom) target movements elicited
normal saccades before MPTP was administered. By
20 h after the last of the 4 MPTP injections, approxi-
mately 70% of all saccadic movements were hypome-
tric (post-MPTP examples). Although the latency of
the first of a hypometric (staircase or multi-step) se-
ries might be normal, the subsequent saccades, which
could number 2–4, were separated by intervals as
short as 20–30 ms or longer than 1 s. Such a multi-
step series almost always placed the eye ultimately on
target. Durations of saccades achieving target, and of
components of a multi-step series could be very long
(see right post-MPTP saccades). Although most
post-treatment saccades were altered in form and
timing, the monkey was capable of an occasional nor-
mal movement. Similar mixtures of normal and ab-
normal saccades are observed in parkinsonian pa-

tients18.
Fig. 3, upper panel, compares the duration of rightward saccades measured before and after MPTP treatment, and following oral ingestion of Sinemet. Duration was measured as the time from the onset of movement to the next zero velocity. Each pre-MPTP mean and S.D. is based on 20 or more saccades that achieved at least 90% or more of the target amplitude (saccades with oblique components were not included in the analysis; neither were leftward movements which frequently required a correction and had a long latency, probably because of a mild chronic irritation in the left outer canthus). The pre-MPTP data are within the normal range of monkey saccadic durations as described by Fuchs and Robinson. The durations of all the post-MPTP saccades that were measured on Day 3 of testing (20 h following the last injection) are plotted as triangles. The paucity of post-MPTP data is due to the fact that the monkey stopped tracking before the end of the session, and the large variety of durations and amplitudes reflect the inclusion of all saccades, including those in multi-step hypometric series. Approximately 65–70% of the post-MPTP durations significantly exceeded pre-MPTP durations; the large scatter in the data is also characteristic of the scatter of saccadic durations measured in Parkinson patients. The mean durations after treatment with Sinemet are based on 12 or more saccades; there were not enough target directed eye movements at the larger amplitudes to justify plotting mean values. The post-Sinemet data are well within the normal range for this monkey.

Despite meticulous nursing care and regular tube feeding, the animal expired from pneumonia 3 weeks after taking Sinemet, without being able to perform again in the eye tracking task. Histological reconstruction of the midbrain stained with Cresyl violet showed fewer than normal cells in the substantia nigra pars compacta.

These results indicate that monkeys rendered parkinsonian by MPTP have saccadic abnormalities very
similar to those observed in patients with Parkinson's disease. The abnormalities include hypometria (the breakdown of a single saccadic response into a staircase of smaller saccades), increase in saccade durations, and occasional long latency responses. It is likely that Parkinson-like deficits would also have been found in other classes of eye movements, including smooth pursuit and the vestibulo-ocular reflex, had there been adequate testing time. Perhaps the most sensitive early indicator of the MPTP syndrome in our pilot animal was the appearance of fixational instability during the intersaccadic intervals of tracking. A similar phenomenon has been documented in parkinsonian patients as 'gaze persistence' and gaze instability with frequent 'square wave jerks'. In the MPTP-treated monkey all of the symptoms were dramatically but transiently reversed by administration of Sinemet.

It has been suggested that some of the saccadic signs of parkinsonism may be due to defective supranuclear triggering of the saccadic event, possibly from the superior colliculus which is known to have a major role in the initiation of saccades and which is a major projection target of the substantia nigra pars reticulata. It is documented that MPTP causes dopaminergic insufficiency in the nigro-striatal projection. Damage to the dopaminergic leg of the nigro-striatal-nigral 'loop' has been associated with serial changes in GABAergic transmission to targets 'downstream' from the striatum, including the substantia nigra pars reticulata and its own GABAergic input to the superior colliculus. Dopamine deficiency may, therefore, be the first in a cascade of causally linked, neurotransmitter imbalances whose final motor expression is due, at least partly, to chemical malfunction at sites rather far from the striatum. Thus, the MPTP monkey model offers rich opportunities for the neurologic and pharmacologic investigation of the mechanisms underlying oculomotor and other motor deficits in Parkinson's disease.

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