

# The Vestibular Ocular Reflex In Parkinsonian Mice

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## Introduction

Parkinson's disease (PD) is a progressive neurological disorder characterized by poor balance, slow movement, rigidity, and uncontrollable tremors of the hands. These symptoms result from the degeneration of dopamine-producing nerve cells in the brain, specifically in the substantia nigra and the locus coeruleus. Dopamine is a neurotransmitter that is released by the brain and stimulates motor neurons. When dopamine production is depleted, the motor system is unable to control movement and coordination and PD symptoms occur.

The goal of this experiment was to gain a better understanding of the effects of PD on the vestibular system. More specifically, the effect of the destruction of the dopamine producing cells on the vestibular ocular reflex (VOR) was investigated. The VOR is a gaze-stabilization reflex which maintains eye fixation on an object during head rotation. As the head turns, the eyes compensate by slowly turning in the opposite direction. As the eyes reach the limit of their turning range, they quickly reset by returning to their starting position. Together, the VOR (slow phase) and the resetting (quick phase) make up the vestibular nystagmus. The VOR produced during horizontal and vertical rotations by untreated mice was compared with the VOR produced by those mice that were injected with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a drug known to destroy the dopamine producing neurons in humans, primates, and rodents. In addition, the relationship between peak eye velocity and amplitude of the quick phases was analyzed to see if the quick phase was altered in MPTP-treated mice.

## Methods

Prior to injection, eye movement recordings from two-month-old male mice were used to establish a VOR baseline. These mice were then injected with MPTP for a period of five days. Seven days after the start of the injection treatment, recordings were taken from the mice to determine the changes in the VOR and quick phase. Horizontal VOR was recorded at 20 and 40 deg/s rotations at frequencies from 0.1 Hz to 1.6 Hz. These velocities and frequencies were chosen because they are commonly used in the literature for VOR recordings. Vertical VOR was recorded at the same frequencies as the horizontal VOR, but only at 20 deg/s due to experimental constraints. Recordings for both the untreated and MPTP-treated mice were done in both light and dark conditions. The dark condition allowed for a more accurate measurement of the VOR to be taken because it eliminated visual cues that might have enhanced the VOR. An infrared pupil tracker video system was used to record the eye movements. Gain was then calculated from the eye movement data. Gain is eye velocity divided by head velocity. Under normal circumstances, the value for gain tends to be close to 1 due to the ability of the eye to closely compensate for head rotation by turning in the opposite direction. The mice were head-fixed to make the head velocity equal to the velocity of the turntable to which the mice were fixed. For analytical purposes, the gains of the MPTP-treated mice were normalized to the gains of the untreated mice. This was accomplished by setting the mean gains of the untreated mice to 1 for all frequencies and velocities. The MPTP gains were then altered by the corresponding amounts.

## Results and Discussion

The horizontal eye position/head position traces of untreated mice were compared to the traces of MPTP-treated mice. The amplitudes of the eye position signals were lower in the MPTP-treated mice, therefore, the VOR gains were lower in these mice (Fig. 1). When the MPTP-treated mouse data was normalized to the untreated mouse data, it was observed that in both light and dark conditions that the horizontal gains were significantly lower than 1 (Fig. 2 and 3). At the higher rotation velocity, the gains slightly increased but were still lower than 1. In light conditions, the largest reduction in VOR gain from normal values occurred at 0.4 Hz. These normalized gains were 0.42 and 0.53 at 20 and 40 deg/s rotations respectively (Fig. 2). In dark conditions, for frequencies less than 1 Hz, the gains were similar to those in light conditions. However, at 1.6 Hz, the gains were reduced more than they were at the same frequency in light. More specifically, at a velocity of 20 deg/s, the largest reduction in gain occurred at 0.4 Hz with a value of 0.47, while at a velocity of 40 deg/s it occurred at 1.6 Hz with a value of 0.48 (Fig. 3).

In contrast to the horizontal VOR results above, the normalized vertical VOR gains of MPTP-treated mice showed relatively little reduction. The vertical gains were greater than 0.6 across all frequencies tested for both light and dark conditions (Fig. 4 and 5). The lowest gain observed in light conditions was 0.68 at 0.8 Hz (Fig. 4). In dark conditions, it was seen that at the higher frequencies of rotation, the gains were slightly less than those in the light, with the lowest gain being 0.59 at 1.6 Hz (Fig. 5).

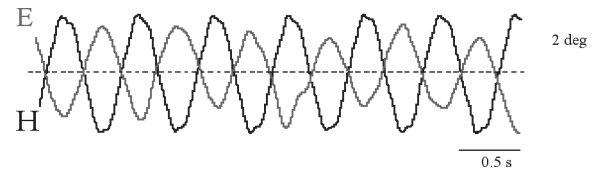
In addition, the relationship between the peak velocity of the quick phases and their associated amplitudes was not altered in MPTP-treated mice. The results were comparable to those found in the untreated mice. This finding is similar to those that have been found in human PD subjects (Hotson et al. 1986; Rottach et al. 1996).

These results show that MPTP-treated mice have subnormal VOR gains, with horizontal VOR being more affected than vertical VOR. This suggests a role for dopamine in the proper execution of the VOR. However, because the quick phases were not affected, it appears that dopamine depletion does not affect the brainstem neurons responsible for the quick phase. Hence MPTP only targets the VOR pathway and not the brainstem

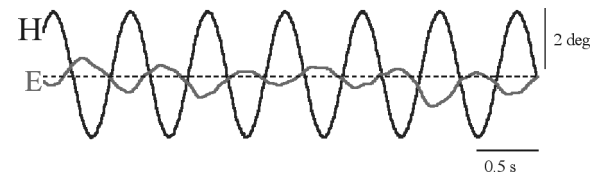
pathway that controls the quick phase. However, it remains to be determined where in the VOR pathway dopamine, and therefore MPTP, acts.

### Example of the Horizontal VOR in the Dark for an Untreated and a MPTP-treated Mouse

#### Untreated Mouse

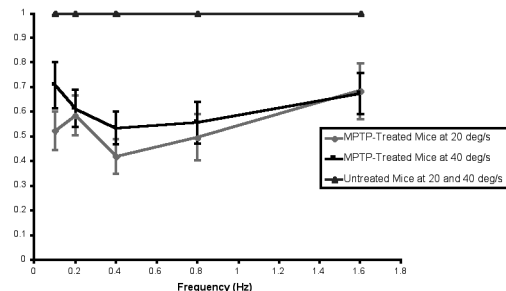


#### MPTP-treated Mouse



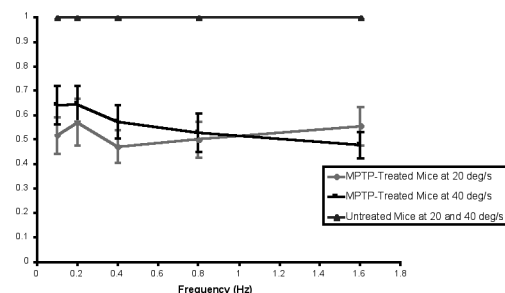
**Figure 1.** Untreated and MPTP-treated Horizontal VOR Traces: Horizontal VOR in the dark for untreated mouse 5E (left) and MPTP-treated mouse 6F (right) showing the head position (H) and the sinusoidal eye position (E). The mice were rotated at 20 deg/s velocity at 1.6 Hz. (Data presented is representative of all data)

**Normalized Horizontal VOR Gain Vs. Frequency at 20 deg/s and 40 deg/s Velocity for MPTP-Treated Mice**

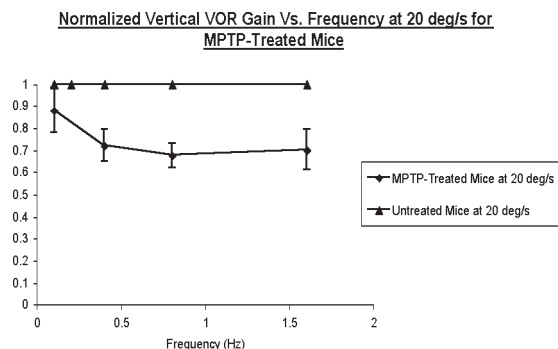


**Figure 2.** Normalized MPTP-treated Horizontal VOR in the Light Gains: Mean normalized gains from five MPTP-treated mice rotated horizontally at both 20 and 40 deg/s velocities. Untreated mice gains have been normalized by setting all gains to 1. Error bars represent SEM.

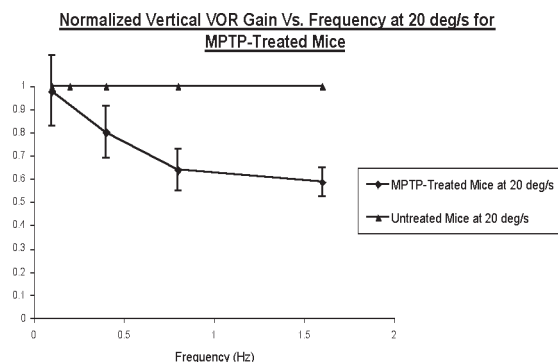
**Normalized Horizontal VOR Gain Vs. Frequency at 20 deg/s and 40 deg/s Velocity for MPTP-Treated Mice**



**Figure 3.** Normalized MPTP-treated Horizontal VOR in the Dark Gains: Mean normalized gains from five MPTP-treated mice rotated horizontally at both 20 and 40 deg/s velocities. Untreated mice gains have been normalized by setting all gains to 1. Error bars represent SEM.



**Figure 4.** Normalized MPTP-treated Vertical VOR in the Light Gains: Mean normalized gains from five MPTP-treated mice rotated vertically at 20 deg/s velocity. Untreated mice gains have been normalized by setting all gains to 1. Error bars represent SEM.



**Figure 5.** Normalized MPTP-treated Vertical VOR in the Dark Gains: Mean normalized gains from five MPTP-treated mice rotated vertically at 20 deg/s velocity. Untreated mice gains have been normalized by setting all gains to 1. Error bars represent SEM.

## Conclusion

Gaze stabilization reflexes in MPTP-treated mice can not compensate for the loss of dopamine producing neurons completely. This suggests that dopamine is needed for a proper VOR. This serves as supporting evidence for MPTP-treated mice as a PD model. Now that a link has been discovered between dopamine and the VOR, further studies are needed to determine where dopamine acts in the VOR pathway. Future experiments should look at both vestibular and visual pathways to see if they are affected by dopamine depletion. Hopefully, the knowledge gained from these mice models about PD will eventually lead to new treatments for this debilitating disease.

## References

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