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Experimental support that ocular tremor in Parkinson's disease does not originate from head movement

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ABSTRACT

Introduction: Our recent report of ocular tremor in Parkinson's disease (PD) has raised considerable controversy as to the origin of the tremor. Using an infrared based eye tracker and a magnetic head tracker, we reported that ocular tremor was recordable in PD subjects with no apparent head tremor. However, other investigators suggest that the ocular tremor may represent either transmitted appendicular tremor or subclinical head tremor inducing the vestibulo-ocular reflex (VOR). The present study aimed to further investigate the origin of ocular tremor in PD.
Methods: Eye movements were recorded in 8 PD subjects both head free, and with full head restraint by means of a head holding device and a dental impression bite plate. Head movements were recorded independently using both a high sensitivity tri-axial accelerometer and a magnetic tracking system, each synchronized to the eye tracker.
Results: Ocular tremor was observed in all 8 PD subjects and was not influenced by head free and head fixed conditions. Both magnetic tracking and accelerometer recordings supported that the ocular tremor was fully independent of head position.
Conclusion: The present study findings support our initial findings that ocular tremor is a fundamental feature of PD unrelated to head movements. Although the utility of ocular tremor for diagnostic purposes requires validation, current findings in large cohorts of PD subjects suggest its potential as a reliable clinical biomarker.

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1. Introduction

Duval and Beuter [1] originally noted ocular oscillations (binocular or monocular) among four subjects with PD with their heads moderately restrained. The authors found no correlation between the ocular and appendicular tremor and concluded that the ocular tremor represented primary eye oscillations [1]. Although also apparent in published figures in a number of other studies [2–4], all of which utilized some form of head restraint, ocular tremor had otherwise been a largely unrecognized feature of PD. Utilizing comparatively more modern and sensitive eye tracking equipment, we consistently observed binocular tremor in 112 subjects with PD and in 2 of 60 asymptomatic control subjects, both who converted to clinical PD within 3 years of their initial evaluations [5].

In response to our publication, Kaski et al. [6,7] and Leigh and Martinez–Conde [8] suggested that the perceived ocular oscillations might represent an oscillatory vestibulo-ocular reflex (VOR) induced by head tremor (either subclinical head tremor or transmitted arm tremor). Using a high resolution magnetic position tracking system in a subset of 62 subjects in our previous study, we however consistently failed to detect head tremor that would result in VOR activation [5]. Kaski et al. suggested that magnetic tracking systems lack sufficient resolution to detect subclinical head

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movements, though others have reported their high sensitivity and accuracy, specifically for tremor [9,10]. While scleral search coil systems represent the undisputed gold standard in eye tracking research, magnetic tracking systems utilize identical technology [11,12]. Specifically against the postulate that the ocular oscillations could originate from subclinical head tremor, we never observe similar ocular tremor in subjects with Essential Tremor, [13] a condition in which one could more readily anticipate subclinical head tremors. Negating the possibility that ocular oscillations reflect transmitted appendicular tremor, we, as well as Duval and Beuter [1], found no correlations between the ocular and appendicular tremors. Further, as would be expected, in our large cohort, many patients had no appreciable appendicular tremor [5]. Despite these many arguments in favor of a primary origin for ocular tremor [14], Kaski et al., in particular, maintain that ocular tremor could not originate from primary eye oscillations or it would be seen on fundoscopy and would cause oscillopsia [7]. In order to add objective scientific evidence to the ongoing discussion [7,8,14,15], we elected here to more rigorously investigate the origin of the ocular tremor in PD.

2. Methods

Eight patients (mean age 60.4 years, SD ± 10.1, range: 43–72 years) with medication confirmed PD completed oculomotor recordings and comprised the study population. Subjects were recruited from the Southeast Veterans Affairs Parkinson's Disease Research, Education, and Clinical Center (PADRECC) at the Hunter Holmes McGuire Veterans Affairs Medical Center in Richmond, VA. Patients with additional neurological disorders, deep brain stimulators, or ophthalmic conditions which either limited the subjects ability to complete the testing, or would introduce additional confounding abnormal features were excluded. Minor cataracts or mild visual acuity loss, for example, were not deemed exclusionary criteria. Also, because dental impressions were used to restrain subjects' heads, anyone with dentures was excluded. The study was approved by the Institutional Review Board at the Hunter Holmes McGuire VAMC and written informed consent was obtained from all subjects prior to testing.

Among the 8 study patients, the average duration of PD symptoms was 4.5 years (SD ± 4.4, range: 0.75–13 years), with an average Unified Parkinson's Disease Rating Scale (UPDRS) Part III motor score of 13.7 (±4.8, range: 8–24), while taking their usual prescribed medication (dopa-equivalent Average: 1020.3 S.D. ± 400.8). Two subjects were young onset PD (one with a strong family history of PD) and two were akinetic/rigid subtype without appreciable appendicular tremor. One subject was de novo untreated at the time of testing, but subsequently showed a marked beneficial response to levodopa. As per our previous study, horizontal and vertical binocular eye gaze positions were recorded at 500 Hz using a video based eye tracker (EyeLink II, SR Research Ltd). The system incorporates a built in head motion correction by means of tracking external optical landmarks mounted on the stimuli display.

Full depth rigid dental impressions of the upper and lower sets of teeth were made for each subject from hard dental wax molded around a 3 mm thick aluminum plate. These individualized bite plates were attached to a locking ball head mount, creating a head holding apparatus which also included a rigid chin cup (See Fig 1). The entire head holding apparatus was securely mounted to an aluminum optical bench (2.0 × 0.76 m, VERE, New Kensington, PA). The setup was designed to eliminate potential head movement and was well tolerated. Two measures were simultaneously used to assess head stability [16–18]: 1) magnetic tracking, used in our prior study and 2) acceleration, new to the present study. Head position was recorded at 125 Hz with a six degree of freedom magnetic tracking system (trakSTAR, Ascension Technology Corp, Burlington VT), while a tri-axial accelerometer (Freescale Semiconductor, Tempe, AZ, model MMA7260QT, 800 mV/g sensitivity) measured head acceleration, also at 125 Hz. The magnetic sensor was attached to the Eyelink II headband, which in turn, placed it just above the patient's left temple. The transmitter for the magnetic tracking system was mounted rigidly on a non-ferromagnetic platform and attached to the aluminum optical bench, for a total distance of ~20 cm from sensor to transmitter. The accelerometer was similarly mounted to the Eyelink II headband, on the opposite side, placing it just above the subject's right temple. Analog signals from the tri-axial accelerometer and synchronization pulse were sampled by a 14 bit analog to digital converter (USB 6009 Multifunction DAQ, National Instruments, Austin, TX). The sampling process and digital storage were controlled by the host computer through a custom written LabVIEW program (National Instruments, Austin, TX). Two separate magnetic sensors were employed on the head, one rigidly attached to the EyeLink II headband and one taped to the subject's temple to assess for any movement or slippage between the head and eye tracker headband. Finally, appendicular tremor was measured in two subjects, one with prominent tremor and one akinetic/rigid subject with no outwardly visible tremor, via a magnetic tracking sensor attached to the tip of the index finger on the more affected side. These appendicular tremor assessments were conducted during the eye tracking recordings, with the limb fully at rest on the subject's lap. The magnetic position sensors, accelerometer, and eye tracker were all synchronized by recording a timing pulse from the parallel output port of the EyeLink II computer at the beginning and end of each measurement trial.

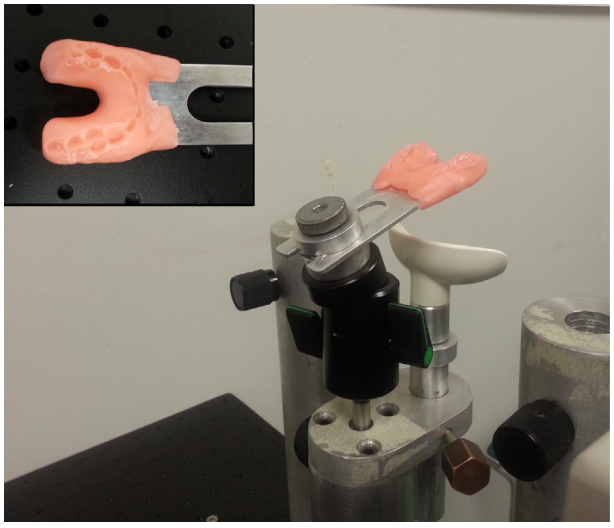

Fig. 1. Head holding apparatus with an example of the rigid dental bite plate used in this study. After sterilization, the wax was softened with a heat gun, and the patient bit down firmly to create impressions. Note the full depth impressions of the entire mandible from incisors to molars. The patient was then asked to bite onto the plate as installed in the apparatus, and once comfortable, the ball joint was tightened, and the chin cup raised to firmly lock the lower jaw in place and ensure a firm bite and fully immobilize the head.

The eye tracking setup and target stimuli presentation have been largely described previously [5,13]. Subjects were recorded twice, with and without head restraint. Also, using both direct and indirect fundoscopy, three different observers (one a trained ophthalmologist) examined the fundi and scleral blood vessels of each eye for outwardly visible tremor. Direct fundoscopy was done with a standard or PanOptic ophthalmoscope variably held by the examiner or held rigidly by a metal arm bolted to the optic table with the subject's head supported in a chin cup and forehead rest. Additionally, a prosthetic eye was used to approximate the threshold required to visualize simulated ocular tremor in a more idealized setting. To achieve this, the prosthetic eye was attached to the stalk of a mirror galvanometer motor and driven at various amplitudes and frequencies, while the imitation corneal vessels were examined using a restrained fundoscope with a corneal viewing magnification lens (see Fig 2).

To further address the sensitivity and accuracy of magnetic tracking devices, a separate methodological experiment was performed with the trakSTAR system. One

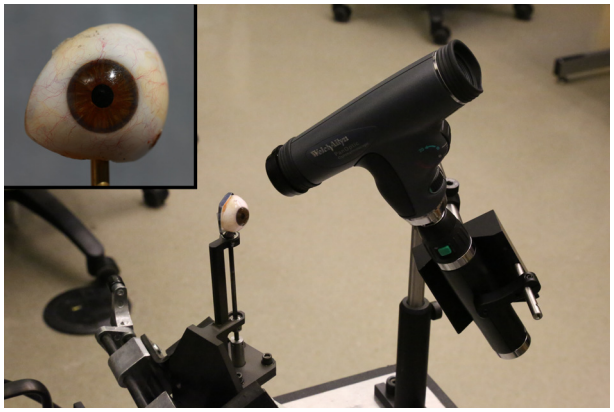

Fig. 2. Setup used to assess the threshold for observing simulated ocular tremor in an idealized setting. An artificial eye was attached to the stalk of a mirror galvanometer motor and driven at various amplitudes and frequencies similar to the observed behavior in PD patients. The ophthalmoscope with a corneal viewing magnification lens was positioned as closely as possible, set to maximum magnification, and was locked in place. The setup was designed to removal all movements except for that of the eye. Inset demonstrates the quality of the artificial eye and vessels.