PAPER

Abnormalities of optokinetic nystagmus in progressive supranuclear palsy

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Objectives: To measure vertical and horizontal responses to optokinetic (OK) stimulation and investigate directional abnormalities of quick phases in progressive supranuclear palsy (PSP).

Methods: Saccades and OK nystagmus were studied in six PSP patients, five with Parkinson's disease (PD), and 10 controls. The OK stimulus subtended 72° horizontally, 60° vertically, consisted of black and white stripes, and moved at 10–50°/s.

Results: All PSP patients showed slowed voluntary vertical saccades and nystagmus quick phases compared with PD or controls. Small, paired, horizontal saccadic intrusions (SWJ) were more frequent and larger in PSP during fixation. Vertical saccades were transiently faster at the time of SWJ and horizontal saccades in PSP. During vertical OK nystagmus, small quick phases were often combined with horizontal SWJ in all subjects; in PSP the vector was closer to horizontal. Vertical OK slow phase gain was reduced in PSP but, in most PD patients, was similar to normals. The average position of gaze shifted in the direction of vertical OK stimulus in PSP patients with preserved slow phase responses but impaired quick phases.

Conclusions: Vertical OK responses in PSP show impaired slow phase responses, and quick phases that are slowed and combined with SWJ to produce an oblique vector. SWJ facilitate vertical saccades and quick phases in PSP, but it is unclear whether this is an adaptive process or a result of the disease. A large OK stimulus is useful to induce responses that can be quantitatively analysed in patients with limited voluntary range of vertical gaze.

Examination of eye movements may provide useful diagnostic information in parkinsonian disorders, especially in differentiating progressive supranuclear palsy (PSP) from other conditions.¹ Most useful is the examination or measurement of voluntary saccades—the rapid eye movements by which we shift our line of sight between objects of interest.² During self rotation, which stimulates vestibular and optokinetic (OK) compensatory movements, quick phases of nystagmus move the eyes in the orbit in the same direction as that of head rotation to enable perusal of the oncoming visual scene.³ Quick phases are considered to be the evolutionary forerunners of voluntary saccades, and both types of rapid movement are generated by the same premotor circuitry, which comprises brainstem burst and omnipause neurones.¹ Horizontal saccades are generated by burst neurones in the paramedian pontine reticular formation (PPRF),⁴ and vertical saccades by burst neurones in the midbrain rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF).⁵ Activity in both populations of burst neurones is gated by omnipause neurones in the pontine nucleus raphe interpositus.⁶ The dynamic properties of saccades and quick phases show similarities that reflect this shared brainstem substrate, in addition to certain differences that reflect different inputs to brainstem burst and omnipause neurones.⁷

Most disorders that cause slow saccades, such as PSP, often eventually also cause difficulty in initiating saccades. Experience from studies of paediatric storage disorders, such as Gaucher's disease in children,⁸ suggest that a large field OK stimulus may evoke responses that can help diagnosis. The main goals of our present study were to determine whether measurement of OK nystagmus could be used to define abnormalities of rapid eye movements in PSP, and whether responses would provide insights into the nature of the underlying pathophysiology of this disorder. We were

also interested in determining whether the trajectory of vertical OK quick phases showed abnormalities similar to those of saccades that have been reported previously.⁹

METHODS

Subjects

We analysed saccades and OK nystagmus from six patients (two women) diagnosed as probable PSP according to NIH Society for PSP criteria¹⁰; their ages ranged from 64 to 76 years (median, 72.5), and the duration of illness ranged from two to five years. We similarly studied two groups of control subjects: (a) five patients (two women) diagnosed with idiopathic Parkinson's disease (PD), age range 56–80 years (median, 66), duration of illness 2–14 years, Hoehn-Yahr disability score stage 2¹¹; and (b) 10 healthy younger subjects (age range, 24–64 years; median, 35). We also referred to a data set of voluntary saccades from a group of seven healthy elderly subjects (age range, 62–75 years), which we have reported previously.⁹ Table 1 summarises the clinical features of the patients studied. After explanation of the protocol, which had been approved by our institutional review board, all patients and subjects gave written, informed consent in accordance with the Declaration of Helsinki.

Recording methods and visual stimuli

Horizontal and vertical gaze and head rotations were measured using the magnetic search coil technique with six foot field coils (CNC Engineering, Seattle, Washington, USA), as described previously.^{7–9} The system was 98.5% linear over

Abbreviations: A, amplitude; D, duration; FEM, fast eye movement; OK, optokinetic; OKN, optokinetic nystagmus; PD, Parkinson's disease; PSP, progressive supranuclear palsy; PPRF, paramedian pontine reticular formation; PV, peak velocity; riMLF, interstitial nucleus of the medial longitudinal fasciculus; SWJ, square wave jerks

Table 1 Summary of patients studied

Patient/Diagnosis	Age/Sex/Duration (years)	Speed and range of vertical saccades on examination	Medications
PSP1	74/F/3.5	Slow; moderate restriction	Amantidine, trazadone, paroxetine
PSP2	76/F/3	Slow; pronounced restriction	Benazepril
PSP3	64/M/4	Slow; pronounced restriction	Valsartan
PSP4	71/M/4	Slow; mild restriction	None
PSP5	75/M/5	Slow; pronounced restriction	Carbidopa/levodopa
PSP6	69/M/2	Slow; mild restriction	None
PD1	73/F/5	Normal; normal range	Carbidopa/levodopa
PD2	63/M/3	Normal; normal range	Pramipexole
PD3	80/M/2	Normal; mild upgaze restriction	Carbidopa/levodopa
PD4	66/F/6	Normal; normal range	Carbidopa/levodopa, pergolide
PD5	56/M/14	Normal; normal range	Carbidopa/levodopa

an operating range of $\pm 20^\circ$, the standard deviation of system noise was less than 0.02° , and crosstalk between vertical and horizontal channels was less than 2.5%. The OK stimulus was rear projected on to a semi-translucent tangent screen at a viewing distance of 1.2 m. The stimulus subtended 72° horizontally and 60° vertically. The OK stimuli were generated by a Cambridge Research Systems (Cambridge, UK) VSG2/5 visual stimulus generator and projected using an Epson Powerlite 9100i video projector. The stimulus consisted of alternating black and white stripes, with luminance of 0.7 and 13.7 cd/m^2 , respectively. The spatial frequency of the stimulus was 0.04 cycles/degree. The display was carefully aligned so that stimulus motion was either earth vertical or earth horizontal. The visual stimuli moved at 10, 20, 30, 40, and $50^\circ/\text{s}$ for 20 seconds, upwards, downwards, to the left, and to the right. The screen was blanked for 10 seconds between stimuli. During the period when the screen was blanked, subjects viewed either a stationary laser target, on half of the trials, or the featureless screen. The speed and direction of the OK nystagmus (OKN) stimulus were randomised.

We also studied visually guided saccades in response to the laser spot that jumped horizontally or vertically on the tangent screen. Target jumps of 5, 10, 15, 20, 25, 30, 35, and 40° horizontally and vertically were presented.

Subjects sat in a stationary vestibular chair, with their heads maintained in an erect position by a cushioned support throughout the test period. An investigator monitored head position during testing and, in some patients, we confirmed head immobilisation using a head fixed search coil. Alertness was maintained by frequent verbal encouragement. Subjects were randomly assigned as to whether OKN or saccades were tested first. Each subject was studied during one session that lasted for about 20 minutes.

Data analysis

To avoid aliasing, coil signals were passed through Krohn-Hite Butterworth filters (bandwidth of 150 Hz) before digitisation at 500 Hz with 16 bit resolution. These digitised coil signals were then passed through an 80 point Remez FIR filter (bandwidth 0–140 Hz), and differentiated to yield eye velocity. All measurements were checked interactively and eye movements associated with blinks were rejected. A saccade or OKN quick phase (fast eye movement; FEM) was detected when the velocity was continuously above $10^\circ/\text{s}$ for at least 5 points. The peak velocity of each FEM was then determined. FEM onset and offset were then defined as the last points either side of the peak velocity before which the velocity fell below $10^\circ/\text{s}$. These points were used to calculate the amplitude and duration of the FEMs. In a previous study, we showed that analysis of dynamic properties of saccades and quick phases made by patients with PSP poses problems

because these movements are often small, and fitting such data with exponential equations does not permit differentiation of normal and slow saccades.^{12, 13} If, however, a power function (rather than exponential) is used to fit the data, it is often possible to distinguish slow small saccades made by patients from small normal saccades made by control subjects.¹³ In practice, we constructed logarithmic (base 10) plots of peak velocity (PV) or duration (D) against amplitude (A) and performed linear regressions for saccades or quick phases for each data set from each eye to calculate the intercept and slope. Thus, the data of these log–log plots were fitted with an equation of the form:

- $\log PV = m \cdot \log A + c$ (1)
- $\log D = n \cdot \log A + d$ (2).

Where m and n are the slopes, and c and d are the intercepts. The equations used to fit the log–log data are equivalent to power functions:

- $PV = K \cdot A^m$ (3)
- $D = L \cdot A^n$ (4).

Where K and L are 10^c and 10^d (unlogged values), respectively. We then performed paired comparisons of the values of intercept and slope for each group of data sets, for saccades or quick phases, using a paired t test, or the Wilcoxon signed rank test if the distribution of data was not normal.

Data from 10 second epochs between OK stimulation, when subjects viewed either a laser spot or a featureless screen, were analysed for small, paired saccadic intrusions, “square wave jerks” (SWJ), which are common in PSP and occur in some normal subjects.^{14, 15} To identify SWJ, we used similar velocity criteria to those specified above for saccades, and selected horizontal movements that were (a) less than 5° in amplitude, and (b) followed by a return saccade within 100–600 ms. SWJ were also common during OKN and we compared corresponding SWJ and quick phase amplitudes for the $10^\circ/\text{s}$ stimulus (which produced the best OK response for patients with PSP). Similar criteria were used to identify SWJ during OK stimulation, based on results of previous studies.⁷ Synchronously generated vertical quick phases and SWJ caused eye movements with a diagonal trajectory; we calculated the angle of such movements from:

- Angle of quick phase = arctangent (quick phases amplitude/SWJ amplitude) (5).

Because horizontal SWJ and vertical quick phases are generated by separate populations of burst neurones in the pons and midbrain, respectively, we also compared separately the amplitudes of vertical quick phases and SWJ (Cartesian

Figure 1 Representative records of vertical saccades in a patient with progressive supranuclear palsy (PSP1). Upward deflections indicate upward and rightward eye rotations. Note that the horizontal channel has been offset to the left by 12° to aid clarity. At the onset of the first, slow upward saccade, the eye also moves to the right as the result of a small horizontal saccade (large double arrows). During this prolonged, hypometric vertical saccade, square wave jerks (SWJ) occur (small double arrows). During the following downward saccade (starting after two seconds), SWJ occur and are associated with transient increases in vertical eye velocity. A subsequent small leftward saccade (large double arrows) is also associated with an increase in vertical eye velocity.

coordinates). For this analysis of the interaction between SWJ and quick phases during vertical OK stimulation at 10°/s, we pooled data from the 10 normal subjects and then compared vertical and horizontal components with each patient with PSP or PD, using the Mann-Whitney rank sum test (the distribution of these data was not normal). Because multiple pairwise tests were performed, we performed a Bonferroni correction by a factor of six and used a cutoff value of $p = 0.008$ to determine significance.

We measured slow phase velocity interactively by placing cursor marks at the beginning and end of each movement; the program then calculated mean eye velocity for each slope based on all the points between the two cursor marks. At each stimulus speed, the OKN gains were calculated as the ratio of the mean slow phase velocity divided by stimulus velocity.

RESULTS

First, we will define the abnormality of saccades in our patients with PSP compared with patients with PD and control subjects. Second, we will describe the abnormalities of quick phases of nystagmus. Third, we will deal with the phenomenon of small saccadic intrusions (SWJ), which are common during attempted fixation in PSP, and influenced the OK response in our patients. Fourth, we will summarise the abnormalities of slow phases of OKN in our patients.

Comparison of vertical saccades in patients and normal subjects

All of our patients with PSP showed slow vertical saccades. Figure 1 shows a representative record from PSP1. Figure 2A shows examples of power function curve fits (equation 3) of peak velocity versus amplitude for all upward saccades of patients PSP1, PD3, and all normal subjects. Figure 2B summarises the values of parameters for this curve fit, for all patients with PSP and PD for all vertical saccades. The values for patients with PD lay within the 95% prediction intervals for normal subjects, but those for patients with PSP did not,

with the one exception of the power (m) value for PSP4. Figure 3A shows representative power function curve fits (equation 4) of duration versus amplitude for all upward saccades of patients PSP1 and PD3 and all normal subjects. Figure 3B summarises the values of parameters for this curve fit, for all patients with PSP and PD for all vertical saccades. The values for patients with PD for the slope and intercept generally lay within the 95% prediction intervals for normal subjects, but those for patients with PSP did not.

Comparison of vertical quick phases of nystagmus in patients and normal subjects

Figure 4 shows a representative record of vertical OK responses from PSP5, who experienced difficulty in initiating voluntary vertical saccades. Note the tonic deviation of the eyes that occurred in the direction of stripe motion, and the frequent horizontal SWJ. Figure 2B summarises the values of parameters for the peak velocity–amplitude curve fit (equation 3), for all patients with PSP and PD for all vertical quick phases. PSP2 made no downward quick phases and PSP3 made no upward quick phases. With the exception of PD2 upward, the values for patients with PD for the slope and intercept lay within the 95% prediction intervals for normal subjects, but those for the patients with PSP did not, with the exception of PSP4. Figure 3B shows the values of parameters for the duration–amplitude curve fit (equation 4), for all patients with PSP and PD for all vertical quick phases. All patients with PSP, except for PSP4, lay outside the 95% prediction intervals for control subjects. With the exception of PD2, all values for patients with PD for the slope and intercept lay within the 95% prediction intervals for the control subjects.

We also compared the frequency of vertical quick phases in patients and controls. Although patients with PSP tended to show lower frequencies of quick phases, there was substantial overlap between patients with PSP, those with PD, and controls.

Figure 2 (A) Examples of power function fits (equation 3) of peak velocity versus amplitude plots for the group of normal subjects, one patient with progressive supranuclear palsy (PSP1; crosses), and one with Parkinson's disease (PD3; squares). The parameter values of the fits for the patient with PD are similar to control subjects, but parameter values for the patient with PSP differ substantially. (B) Summary of parameter values for fits of vertical saccades and quick phases for all patients; the 5% and 95% prediction intervals for normal subjects are shown as horizontal bars. Parameter values for patients with PD lie within the prediction intervals for normals, whereas parameter values for most patients with PSP do not. SaccUp: saccades up; SaccDn: saccades down; QPU: quick phases up; QPDn: quick phases down. Closed circles, patients with PD; shaded triangles, patients with PSP.

Comparison of horizontal saccades and horizontal quick phases of nystagmus in patients and normal subjects

Patients with PSP and PD showed substantial overlap of parameter values of power function fits of both peak velocity–amplitude and duration–amplitude plots of horizontal saccades and quick phases. Furthermore, the parameter values for most patients with PSP and all those with PD showed overlap with normal subjects.

Disorders of the direction of OK responses and relation to SWJ

SWJ were common in our patients with PSP during fixation and table 2 summarises their characteristics. The frequency

and size of SWJ during fixation of a laser spot was significantly greater in the PSP group than in the controls during fixation, but not during viewing of the blank screen. The relation between the duration and amplitude of SWJ in patients with PSP was no different from that seen in PD or control subjects. SWJ or small horizontal saccades often occurred with voluntary vertical saccades in patients with PSP (fig 1), and appeared to affect the speed of the vertical movement. (We confirmed that these were not vergence movements using binocular eye coils.) We were not able to conduct a statistical comparison to determine whether vertical saccades were speeded up by horizontal saccades because horizontal saccades were an almost invariable accompaniment to vertical saccades in our patients with

Figure 3 (A) Examples of power function fits (equation 4) of duration versus amplitude plots for the group of normal subjects, one patient with progressive supranuclear palsy (PSP1; crosses), and one with Parkinson's disease (PD3; squares). The parameter values of the fits for the patient with PD are similar to control subjects, but parameter values for the patient with PSP differ substantially. (B) Summary of parameters for fits of vertical saccades and quick phases for all patients; the 5% and 95% prediction intervals for normal subjects are shown as bars. In general, the parameter values for patients with PD lie within the prediction intervals for normals, whereas those for most patients with PSP do not. SaccUp: saccades up; SaccDn: saccades down; QPU: quick phases up; QPDn: quick phases down. Closed circles, patients with PD; shaded triangles, patients with PSP.

PSP. We have dealt with other aspects of the relation between horizontal and vertical saccades in PSP previously.^{9,13} We were able to compare the dynamic properties of SWJ (relations between amplitude, peak velocity, and duration) during fixation or with vertical saccades, and found no differences in the patients with PSP.

In patients with PSP, SWJ were also a common accompaniment of quick phases of vertical OKN. For the range of OK stimulus frequencies, patients with PSP tended to have a higher ratio of SWJ to quick phases than did those with PD or control subjects, but there was overlap of data between the groups, except for downward quick phases induced by the 10/s stimulus (table 2).

To characterise the effects of SWJ on the OKN response more accurately, we analysed responses from normal subjects and both groups of patients in response to the 10/s stimulus, which produced the best OK response. Only responses in which a horizontal SWJ occurred synchronously with a vertical quick phase were analysed. Normals showed no differences between responses to upward or downward OK stimuli, and these data were pooled. Figure 5 summarises the results. Movements made by patients with PSP had smaller vertical quick phase components and larger horizontal SWJ components than did those made by patients with PD or controls. Consequently, the median angle of movements for patients with PSP was closer to the horizontal than was seen

Figure 4 Optokinetic responses of a patient with progressive supranuclear palsy (PSP5). Upward deflections indicate upward and rightward eye rotations. Note how the average gaze position is deviated in the direction of the stimulus motion. Horizontal square wave jerks (SWJ) occur throughout the record (see inset) and are made in synchrony with the vertical quick phases of nystagmus. Note how the amplitude of the SWJ may exceed the size of the vertical quick phases.

in all controls and most patients with PD. Using equation 5, we calculated that, for the group of normal subjects, the median angle was 65.4° (interquartile range, 45.7° to 77.3°). For all patients with PSP, the sizes of the angles were significantly different from controls ($p < 0.001$), with median values ranging from 8.8° to 41.2°. In general, the sizes of the angles for patients with PD were similar to controls, with the exception of PD2, who had the poorest OK responses (median angles, 21.5° upward stimulation and 37.7° downward stimulation), and PD5 for upward stimulation (median angle, 41.7°) ($p < 0.001$).

To determine why patients with PSP showed smaller angles than controls, as illustrated in fig 5, we compared separately the amplitudes of the vertical and horizontal components of the responses to vertical OK stimulation at 10°/s. All patients with PSP showed a decreased amplitude of the quick phases, and the differences from controls were

significant ($p < 0.001$) in eight of 10 cases. All patients with PSP, except for PSP3, showed increased amplitudes of SWJ components, and differences from controls were significant ($p < 0.001$) in seven of 10 cases. When patients with PD were compared with controls, PD2, who had the poorest OK responses (see next section), showed significant decreases of quick phase amplitudes in both directions and PD5 showed decreases for downward stimulation. PD5 was the only patient with PD to show a significant increase in SWJ size during upward OK stimulation.

OKN slow phase velocity

Figure 6 summarises the responses to each of the vertical OK stimuli in patients, together with the 95% prediction intervals for control subjects. As a group, patients with PSP had significantly smaller gain values ($p < 0.008$) compared with controls for all stimuli. However, PSP4 and PSP5 showed

Table 2 Summary of frequency of SWJ for different test conditions

Patient group	Frequency (SWJ/min)	Amplitude (deg)	Duration (ms)	SWJ/QP ratio (with 10°/s stimulus)
PSP				
Fixation	52.0 (8.8)**	1.40 (0.54)*	357 (141)	Up: 0.71 (0.33)
Ganzfeld	50.0 (17.2)	1.88 (0.85)	507 (201)	Down: 1.08 (0.48)**
PD				
Fixation	32.1 (17.8)	0.79 (0.45)	342 (83)	Up: 0.82 (0.16)
Ganzfeld	31.2 (15.7)	1.22 (0.43)	374 (116)	Down: 0.52 (0.20)
Normals				
Fixation	26.4 (16.0)	0.62 (0.47)	326 (118)	Up: 0.57 (0.19)
Ganzfeld	33.7 (15.3)	1.56 (0.72)	495 (103)	Down: 0.52 (0.23)

Values shown are mean (SD); comparisons were made using ANOVA.
*Significantly greater than normals ($p < 0.005$); **Significantly greater than normals and patients with PD ($p < 0.05$).
PD, Parkinson's disease; PSP, progressive supranuclear palsy; QP, quick phase; SWJ, square wave jerks.

Figure 5 Summary of the median size and direction of quick phases made synchronously with square wave jerks (SWJ) in individual patients with Parkinson's disease (PD) and progressive supranuclear palsy (PSP), and the group of normal subjects, during 10°/s vertical optokinetic (OK) stimulation. Movements made by patients with PSP had larger SWJ components and smaller quick phase components than those made by patients with PD or normals. Consequently, the angle of movements for patients with PSP was closer to the horizontal than that seen in all controls and patients with PD, except for PD2, who had poor OK responses. Positive values indicate upward quick phases.

some responses within the normal range; in these patients, a prominent deviation of gaze was seen in the direction of the OK stimulus motion (fig 4). Responses of patients with PD were not significantly different from those of normal subjects, with PD2 showing the lowest gains. The horizontal slow phase OK responses of the patients with PSP were not significantly different from those of normal subjects, although PSP2 and PSP3 showed reduced gain for all stimulus frequencies; patients with PD were not significantly different from controls.

DISCUSSION

The main general finding of our study is that a large OK stimulus is a useful way to study patients with PSP because it induces quick phases with abnormal dynamic features that can be subjected to quantitative analysis. A second finding concerns the interaction between horizontal SWJ and vertical quick phases of nystagmus, which may provide some insights into the nature of the ocular motor syndrome of PSP. In discussing our results, first, we will compare the dynamic features of vertical saccades and quick phases in patients versus controls; second, we will deal with the interactions of SWJ and vertical saccadic movements; third, we will summarise the changes of the slow phase component of OKN; and finally, we will indicate the potential implications of our study for clinical research.

We selected a group of patients with PSP based on clinical criteria.¹⁰ All had slow vertical saccades that, when fitted with power function equations (3 and 4), showed almost no overlap of data with normal subjects, or patients with PD (figs 2 and 3). In a previous study, we showed how fitting data with power functions has advantages over using exponential fits if the saccades are small (as is often the case in PSP).^{12,13} Vertical saccadic data from patients with PD

Figure 6 Summary of mean slow phase gain (eye velocity/stimulus velocity) for individual patients with Parkinson's disease (PD) and progressive supranuclear palsy (PSP) for each stimulus used. (A) Responses to upward stimuli; (B) responses to downward stimuli. The horizontal lines indicate the 95% prediction intervals for normal subjects. In general, the patients with PSP showed lower gain values than did the controls, whereas those with PD showed responses similar to controls (see text for statistical comparisons). Closed circles, patients with PD; shaded triangles, patients with PSP.

and younger control subjects fell within similar ranges, consistent with previous reports documenting no significant changes in the relations between amplitude and peak velocity or duration, either with age,¹⁶ or PD,⁹ except for advanced cases.¹⁷ Analysis of the quick phases of nystagmus, using similar methodology to that applied to saccade analysis, showed the same essential differences between the three groups (figs 2 and 3), with single patients with PSP and PD having some overlap of data. Although an exponential equation is more conventionally used to fit dynamic properties of saccades (because it incorporates a soft saturation of peak velocity), we have previously shown that a power equation approach, such as we used, gives more satisfactory results for smaller saccades than an exponential fit.¹³ Furthermore, 95% of quick phases made by controls to a range of OK stimuli were less than 10° in amplitude.⁷ Our study, based on the analysis of over 4000 quick phases, but a relatively small group of patients, suggests that OK stimuli are a useful means to generate and study the vertical saccade system of patients with PSP.

Figure 1 shows large vertical saccades made by PSP1. The record also displays the vertical velocity of eye movements, which can be seen to accelerate synchronously with the occurrence of small horizontal saccades, including SWJ (arrows). In the example shown in fig 1, the eye also moves horizontally at the onset of the vertical saccade; such a diagonal trajectory ("round the houses") has been noted previously.^{9, 18} During vertical OKN, SWJ were a common accompaniment of quick phases in patients with PSP, but also occurred in patients with PD and normal controls. Because quick phases tended to be smaller and SWJ larger than in controls or patients with PD, the resultant angle was closer to the horizontal in patients with PSP (fig 5). This finding has identified another feature of OK responses that might prove helpful in understanding PSP.

Before discussing the possible substrate for these findings, consideration should be given to the possibility that misalignment of the subjects' heads (such as a small lateral tilt) could account for some of the "crosstalk" between horizontal and vertical responses that we report. Although we attempted to keep the patients' heads erect, minor lateral tilt could account for the small horizontal deviation that occurs during upgaze in fig 1. In fig 4, a shift of horizontal gaze occurs during vertical OK stimulation; although this might be the result of a head tilt, a small diagonal response to vertical OK stimuli occurs in normal subjects, and is increased in patients with disorders of ocular alignment.¹⁹ Directional abnormalities of the slow phase OK responses in PSP were not the focus of our present paper, but deserve further study. However, we do not believe that artefacts caused by head tilt can account for the coupling between SWJ and the quick phases of nystagmus that we saw. Such artefacts will cause systematic errors (for example, upward movements will be coupled with rightward movements and downward movements will be coupled with leftward movements). However, as is evident in the inset in fig 4, subsequent horizontal saccades to the right and left were often paired with vertical saccades or quick phases in just one direction. Thus, we believe that the "crosscoupling" that we report between SWJ and vertical quick phases is biological in origin.

The finding of an interaction between SWJ and vertical saccadic movements raises issues about the pathophysiology of these findings. Vertical saccades and quick phases are generated by premotor burst neurones in the midbrain riMLF,⁵ whereas horizontal saccades are generated by premotor burst neurones in the PPRF.⁴ Both sets of premotor burst neurones receive inputs from so call long lead burst neurones, which provide an important component of the saccadic command.^{20, 21} Experimental and clinical evidence suggests that all types of burst neurones may eventually be affected in PSP.²²⁻²⁵

Anatomical and physiological studies indicate that both groups of premotor burst neurones are gated by omnipause neurones, which lie in the pontine nucleus raphe interpositus.^{6, 26} Although the omnipause neurones project to both sets of premotor burst neurones, it is unclear whether burst neurones in the PPRF project to the riMLF, or vice versa.²⁷ Thus, this raises the question: could a change in discharge of omnipause neurones occurring during a small horizontal saccade, such as shown in fig 1, transiently increase the speed of the vertical saccade? Although dysfunction of omnipause neurones had been suggested as the cause of slow saccades in PSP,²⁸ this seems unlikely to be the primary disorder because vertical saccades are slowed first in this disorder,²⁵ and experimental lesions of omnipause neurones slow both vertical and horizontal saccades.²⁹ If the population of omnipause neurones is incompletely inhibited during vertical saccades, but completely silenced during horizontal saccades, then a small horizontal saccade might speed up a large

vertical movement. Furthermore, the presence of SWJ might be adaptive, in the sense that their occurrence with each saccade or quick phase would have a speeding up effect. Our patients with PSP showed larger amplitude SWJ during fixation (table 2) or vertical OK stimulation (fig 5). Several structures project to the omnipause cell region, including the rostral pole ("fixation zone") of the superior colliculus,³⁰ and the central mesencephalic reticular formation,^{22, 23} regions of the brainstem that are known to be affected in PSP.²⁴ To account for our present finding, it would be necessary to postulate a graded effect of input to the omnipause neurones, so that a combined horizontal-vertical command could silence the omnipause neuronal population and increase saccade speed.

An alternative hypothesis to account for our findings is that slow saccades result from an impairment of the saccadic command from long lead and premotor burst neurones, whereas SWJ reflect a separate, diffuse involvement of the brainstem and cerebellar nuclei. Indeed, SWJ are encountered in a range of degenerative disorders affecting the basal ganglia, brainstem, cerebellum, and cerebral hemispheres.^{31, 32}

Patients with PSP often show impairment of smooth pursuit eye movements, in addition to saccades in the vertical plane.¹ It has been shown that using a larger visual target may improve vertical pursuit,³³ and a large field OK stimulus, such as we used, would seem to be optimal. However, OK slow phase responses were impaired in our patients with PSP (fig 6) compared with normals or patients with PD. These impaired responses may be the result of extensive involvement of the dorsolateral pontine nuclei, which are known to be an important relay in the pursuit pathway between visual cortical areas and the cerebellum.³⁴ In two patients with PSP, OK responses were similar to those seen in normal subjects, perhaps because involvement of the vertical quick phase mechanism was greater than that of the smooth pursuit pathways. In these two patients, the average gaze position was deviated in the direction of the OK stimulus (fig 4). This is the opposite of the case in normal individuals, for whom quick phases tend to hold the average gaze position opposite to the direction of stripe motion which, during self rotation (the natural OK stimulus), would point the eyes towards the oncoming visual scene.³ The mechanism underlying the trigger for quick phases is somewhat stochastic,³⁵ but it appears that a combination of hypometria and an increased threshold for triggering quick phases may lead to the observed gaze deviation.

Slow saccades are often apparent at the bedside in patients with PSP, if properly tested.^{1, 2} However, some patients are not able to cooperate or initiate voluntary vertical gaze shifts. In these patients, a vertical OK stimulus may induce quick phases that can be observed, along with a deviation of gaze in the direction of the stimulus motion. We found that in patients with PSP a large visual stimulus moving at a low speed (10°/s) was optimal to induce vertical OKN that could be quantified (fig 5). Such a stimulus is readily generated with modern video projectors, and does not need to fill the visual field or produce the illusion of self rotation to induce a useful response. Finally, we have shown that SWJ, which are a common clinical finding in patients with PSP (most evident during ophthalmoscopy) influence the direction and speed of vertical saccades and quick phases. SWJ are also encountered in a range of diseases affecting the cerebellum and cerebral hemispheres, and their effects on vertical eye movements in these disorders deserve further study.

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