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Influence of orbital eye position on vertical saccades in progressive supranuclear palsy

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Abstract

Disturbance of vertical saccades is a cardinal feature of progressive supranuclear palsy (PSP). We investigated whether the amplitude and peak velocity of saccades is affected by the orbital position from which movements start in PSP patients and age-matched control subjects. Subjects made vertical saccades in response to ± 5 degree vertical target jumps with their heads in one of three positions: head “center,” head pitched forward ~ 15 degrees, and head pitched back ~ 15 degrees. All patients showed some effect of starting eye position, whether beginning in the upward or downward field of gaze, on saccade amplitude, peak velocity (PV), and net range of movement. Generally, reduction of amplitude and PV were commensurate and bidirectional in the affected hemifield of gaze. Such findings are unlikely to be due to orbital factors and could be explained by varying degrees of involvement of rostral midbrain nuclei in the pathological process.

Keywords

saccades; midbrain; neural integrator; eyeball; parkinsonian disorders

Introduction

Vertical gaze palsy is a cardinal feature of progressive supranuclear palsy (PSP), a parkinsonian disorder also characterized by falls, swallowing difficulty, axial rigidity, and frontal lobe deficits.¹ We recently studied a group of 30 patients with PSP and found no overall preferential slowing of upward versus downward saccades.² However, limited range of upward saccades was twice as common as for downward saccades. Since a full range of vertical eye movements is possible in most PSP patients with vestibular eye movements (induced by pitch head rotation), the function of the motor unit (motoneurons and extraocular muscles) appears to be normal. However, orbital biomechanical factors may influence some aspects of saccades, even in normal subjects. For example, upward saccades made by healthy subjects are slower when made in the upper oculomotor range, whereas downward saccades are unaffected by starting eye position.³ Furthermore, progressive limitation of the vertical range of eye movements, especially upward, occurs in normal subjects after age 60 years.^{4,5} This limitation has been attributed to biomechanical changes in the orbital fascia.⁶

Aside from such orbital factors, abnormalities of vertical saccades in PSP can be attributed to prominent involvement of midbrain circuits in this disorder on the basis of studies in

monkeys. Inactivation of the rostral interstitial nucleus of the medial longitudinal fasciculus (RIMLF) causes vertical saccades to become slow and small,⁷ whereas inactivation of the interstitial nucleus of Cajal (INC) restricts the vertical range of saccades without affecting their speed.⁸

The goal of our study was to investigate the way in which the amplitude and peak velocity of vertical saccades is affected by starting orbital position in PSP patients and healthy control subjects. Since most PSP patients cannot reliably move their eyes to a new vertical orbital position, we employed head rotations to take their eyes to different starting positions for vertical saccades.

Methods

We studied seven patients with probable PSP diagnosed according to NINDS/SPSP criteria⁹ and one patient with PSP–Parkinson syndrome¹⁰ (four males); their age range was 61–84 years (median 73.5 years), and disease duration ranged 1.5–8 years (median 3 years). Their demographic details are summarized in Table 1. We also studied five healthy control subjects, age range 63–77 years (median 67 years). All subjects provided informed, written consent in accordance with our Institutional Review Board and the Declaration of Helsinki. Subjects made vertical saccades in response to ± 5 degree vertical jumps at 0.2 Hz of a visual target (laser spot) at a viewing distance of 1.2 m in an otherwise dark room. Each experimental run lasted 63 s. The total experimental duration was approximately 15 minutes. Horizontal and vertical movements of eyes and head movement were measured using the magnetic search coil technique, which is especially suited for reliable measurements in these patients.² The starting orbital position was varied by altering the pitch of the head, as PSP patients often have a limited range of voluntary vertical eye movements, but an intact vestibulo-ocular response, which allows the eye to be driven to the appropriate position in the orbit. An investigator stayed with subjects at all times, manually controlling head position (with the assistance of a head rest) and encouraging subjects during testing. Vertical saccades were tested with a subject's head in each of three positions, as measured by a head coil: head “center,” head pitched forward ~ 15 degrees, and head pitched back ~ 15 degrees. During control experiments in one patient and three control subjects, vertical target jumps were between zero position (straight ahead) and either up 10 degrees or down 10 degrees, as their head was in center position.

Saccade onset and end was determined by applying a velocity threshold of 10 deg/s. PSP patients typically showed a series (“staircase”) of hypometric saccades in response to each target jump. Thus, for each response to a target jump, we measured the amplitude and peak velocity of the first saccade and the “best” saccade, which we defined as the movement with the greatest velocity. In practice, we found that measurements of the best saccades were more consistent and representative of the capabilities of the patients, and we present these data here. We also measured the net displacement of gaze from the difference between starting position and final eye position at the end of the series of saccades to a target jump. To study the velocity of saccades, we created “main sequence” plots of peak velocity versus amplitude, as previously described.² To compare the effects of starting position in all subjects and patients studied, we normalized the amplitude, peak velocity, and net displacement for each subject, assigning a value of 1.0 for each of these measures with the head in center position. In this way, we were able to look for consistent patterns in the effects of different orbital starting positions on vertical saccades. In those cases in which data were normal in distribution, we used *t*-tests, and for those with non-normal distributions, we used the Mann–Whitney Rank Sum test.

Results

All patients showed some effect of starting eye position on saccade amplitude, peak velocity (PV), or net range of movement, which varied between individuals. Representative records are shown from a PSP patient in Figure 1 and from a control subject in Figure 2. Results from all PSP patients and control subjects are summarized in Figure 3, plotting corresponding values normalized to a value of 1.0 for the head center condition (see Methods).

For each PSP patient, similar trends in the amplitude and peak velocity of vertical saccades were noted, as would be expected given the dependence of saccadic peak velocity on amplitude, even in patients with this disorder.² PSP1 and 2 showed a decrease in the amplitude and peak velocity of both upward and downward saccades when the starting eye position was in the upper field of gaze (head pitched forward). PSP3 showed a reduction of the amplitude and peak velocity of upward saccades and difficulty initiating downward saccades (i.e., few downward saccades could be measured) in the upper field of gaze (head pitched forward). PSP4 showed a reduction of the amplitude and peak velocity of upward saccades in the upper field of gaze (head pitched forward); effects of head position on downward saccades were small. PSP 5 showed the opposite trend, such that downward saccades were decreased in amplitude and peak velocity starting in the lower field of gaze (head pitched back); upward saccades were unaffected by head position. PSP 6 showed upward saccades that were decreased in amplitude and peak velocity starting in the lower field of gaze (head pitched back); downward saccades were unaffected by head position. PSP 7 showed an increase of the amplitude and peak velocity of upward saccades when his head was pitched either forward or back; downward saccades were initiated with difficulty (i.e., few saccades could be measured) except in the lower field of gaze (head pitched back). PSP-PD8 showed a decrease in the amplitude and peak velocity of both upward and downward saccades in the upper field of gaze (head pitched forward) and difficulty initiating (i.e., few saccades could be measured) both upward and downward saccades with his eyes in the lower field of gaze (head pitched back). Gaze-evoked nystagmus was uncommon and not sustained in any patient or control subject.

When we compared medians of the group of patients with the group of controls, the amplitudes of downward saccades with the head pitched forward (eyes in the upper field of gaze) were significantly different ($P = 0.042$), the amplitude of PSP saccades being smaller. Although differences were observed between patients and control subjects for the amplitude of upward saccades in this head position and for the amplitude of both upward and downward saccades with head in center position and with head pitched backward (eyes in the lower field of gaze), the effect was not statistically significant ($P > 0.05$). The observed effect on velocity and net eye movement was not statistically significant ($P > 0.05$) for either upward or downward saccades in any of the three head positions. We also defined 95% prediction intervals for normal subjects, based on pooled saccades for each test condition and saccade direction; we found that patients' median values lay outside these prediction intervals for 6/8 for amplitude, 3/8 for velocity, and 5/8 for net displacement.

Comparison of the net displacement of gaze in response to the target jumps paralleled the effects of different starting positions on amplitude and peak velocity (Figure 3C); this might be expected, since net displacement comes from the sum of a series of saccades that were required to acquire the target. In PSP-PD 8, we compared the effects of starting position on saccade amplitude and peak velocity achieved by either vertical head rotation or a shift of the positions of the visual stimulus; effects were quantitatively similar, although the change in gaze induced by pitch head rotation was greater. In four control subjects, comparison of the effects of starting position by vertical head rotation versus shifting the visual stimulus

showed somewhat smaller saccades in the lower field of gaze with the head pitched back than with visual stimuli moving in the lower field.

In general, the control subjects showed smaller effects of starting eye position on the amplitude and peak velocity of vertical saccades than did the PSP patients. Similar to the report of Collewijn *et al.*,³ normal subjects showed mild decrease of peak velocity of upward saccades made in the upper field of gaze; effects on downward saccades were less consistent. Only control subject 4 showed a decrease in the amplitude and peak velocity of downward saccades, which occurred in his lower field of gaze (head pitched back).

In summary, PSP patients showed variable, often large effects of starting eye position on the amplitude and peak velocity of vertical saccades. Within the affected field of gaze, effects on amplitude and peak velocity were often bidirectional.

Discussion

Our main finding is that the speed and size of vertical saccades were influenced by the eye position at which the movement starts in all of our PSP patients. The pattern of this dependence of saccadic metrics on orbital position varied from patient to patient, but was generally different from the mild effect of upward gaze on upward saccades in healthy subjects noted in a prior study³ and confirmed in our control subjects (Fig.3). These findings raise questions about the pathogenesis and clinical significance of the dependency of vertical saccades on the starting eye position.

Current models for the brainstem generation of saccades are based on the electrophysiological properties of burst neurons.^{11,12} Excitatory burst neurons for vertical saccades lie in the RIMLF;¹³ their discharge properties correlate closely with the saccades that they generate. The rate of discharge (spikes per second) corresponds with eye speed, and the total number of spikes in the burst corresponds with the total change in eye position. Application of these electrophysiological studies, and of current models they engendered,¹⁴ indicate that the number of spikes generated by burst neurons dictates the size of saccades, rather than any specified eye position in the orbit. Our findings argue that such a model is incomplete and requires modification to incorporate the influence of either starting eye position in the orbit or vestibular inputs, or both.

Could the effects that we noted (Fig.3) be accounted for by orbital biomechanical factors? This certainly bears consideration in older individuals, such as our cohort, for whom orbital biomechanical properties show substantial changes, resulting in progressive limitation of the vertical range of eye movements, especially upward, after the age of 60 years.⁶ Several of our findings argue against this being the main determinant of orbital dependency of saccades in PSP. First, reduction of saccade amplitude and peak velocity was often bidirectional, whereas a unidirectional effect would be expected from mechanical factors, such as the reported progressive slowing of upward saccades as starting position moved into the upward field.³ Second, it is well known that even when vertical saccades can no longer be generated, PSP patients may still show a full range of vertical movements in response to pitch head rotations.

Thus, the evidence points strongly to a central cause for the orbital dependency of saccadic metrics in PSP. One candidate to account for this is the interstitial nucleus of Cajal, which is important for vertical gaze control and which is affected in this disorder.¹⁵ Inactivation of the INC limits the range of vertical saccades without substantially affecting their velocity;⁸ such a restriction of range might then be superimposed on the slowing and hypometria that follows RIMLF lesions.⁷ The INC receives inputs from the vestibular system, including the otoliths, which might determine the range and speed of vertical eye

movements.^{16,17} Changing the orbital starting position for testing is much more easily achieved in PSP by head rotation than by patients' attempts to direct their gaze at a visual target. Nonetheless, in PSP-PD 8 we were able to compare the effects of starting position achieved by either head rotation or a shift of the positions of the visual stimuli; effects on saccade amplitude and peak velocity were quantitatively similar. Taken together, these results challenge simple "displacement" models for the brainstem generation of saccades,¹⁴ and suggest that the discharge of burst neurons or components of the neural integrator are influenced by current eye position or head position, as well as the desired change in eye position.

For clinicians, these results have three important implications. First, testing of vertical saccades should be performed with the eyes in three starting positions, corresponding to the central, upper, and lower field of gaze; our study indicates that saccade behavior may change according to the field of gaze in which the movements are made. Second, there is a need to extend the present studies to other disorders that impair vertical gaze to determine whether affected patients also show an orbital dependency of their saccadic palsy. Finally, the effect of different starting eye positions on saccade amplitude and speed needs to be taken into account in any drug trial for PSP that uses eye movements as a therapeutic index.

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Figure 1.

Representative data from a PSP patient. (A) In response to strong visual and verbal stimuli, this patient could generate a maximum range of about 50 degrees for vertical saccades. (B) With his head erect, saccades are generally slower downward than upward to ± 5 degree target jumps. (C) With his head pitched up 22 degrees, the amplitude and peak velocity of saccades, both up and down, increases. (D) With his head pitched down 13 degrees, vertical saccades become smaller and slower. The effect is stronger for downward than for upward saccades. Note that scales differ.

Figure 2.

Representative data from a control subject. (A) In response to visual and verbal stimuli, this subject has a vertical saccadic range of almost 80 degrees and (B–D) shows no noticeable effect of head position on vertical saccade amplitude or peak velocity. Similar conventions as for Figure 1.

Figure 3.

Comparison of results from all eight PSP patients and five control subjects. In each panel, data were normalized assigning a value of 1.0 for each subject for measures with the head in center position. Thus, ratios < 1.0 indicate a decrease of that subject's measurement (amplitude, peak velocity, or net displacement) with the specified head position (shown in the cartoons below each panel). Note that PSP 7 and PSP-PD 8 failed to generate saccades that could be measured in some head orientations (see Results). Specified values are provided for data lying outside of the plots.

Table 1

Summary of Patient Demographics, Medications, and Saccadic Palsy Evaluations

Patient	Age *	Sex	Duration *	Drugs	Saccadic Palsy (Range/Main Sequence)**
PSP1	64	M	1.5 years	Levodopa/carbidopa	Symmetric/Symmetric
PSP2	62	F	3 years	Memantine, rivastigmine,	Worse up/Symmetric
PSP3	77	F	3 years	None	Symmetric/Symmetric
PSP4	74	F	5 years	Levodopa/carbidopa, rivastigmine, venlafaxine	Symmetric/Slower up
PSP5	78	M	2 years	Amlodipine, metoprolol	Worse up/Slower up
PSP6	73	F	2 years	None	Worse up/Slower up
PSP7	84	M	3 years	None	Worse up/Slower down
PSP-PD8	61	M	8 years	Levodopa/carbidopa, trihexyphenidyl	Worse down/Slower up

* Age and duration are in years

** Range is based on measured maximum excursion achieved by saccades. Medications listed are those with potential effects on the central nervous system