Saccadic function in spasmodic torticollis

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Abstract
Twelve patients with idiopathic spasmodic torticollis were compared with 19 normal controls on tests of saccadic eye movements thought to depend upon normal basal ganglia function. The patients were able to make random, predictive, remembered, and self-paced saccades equally as well as control subjects. This suggests that those parts of the basal ganglia which may be damaged in spasmodic torticollis, are separate from pathways responsible for the normal initiation and execution of saccades.

The cause and pathophysiology of idiopathic spasmodic torticollis, the most common form of focal dystonia, is unknown. It is assumed to be a disease of the basal ganglia by inference as occasionally it is produced by lesions in this region of the brain. To date there have been very few reports of abnormalities in ocular motor function in torticollis. These have dealt mainly with asymmetries in vestibular responses on caloric and rotational tests. Whilst no gross abnormalities of oculomotor function have been recognised, there have been no studies specifically focusing on the saccadic subsystems requiring the integrity of the basal ganglia for their production.

The saccadic ocular motor system utilises a number of pathways subserving specific functions, namely predictive and remembered saccades, as well as saccades to voluntary visual and novel visual targets. In sub-human primates, pathways traversing the basal ganglia are important for the generation of predictive and remembered saccades. In humans, the analysis of predictive and remembered saccades in diseases of the basal ganglia, such as Parkinson’s disease, has confirmed the presence of specific deficits in this saccadic subsystem.

We report the results of tests of saccadic function known to be sensitive to basal ganglia disease in a group of patients with idiopathic torticollis and compare them to a group of age-matched normal subjects.

Patients and methods
Twelve patients with isolated spasmodic torticollis producing pure horizontal rotation of the head were studied (table 1). Patients with isolated rotation were chosen because we were interested in right-left asymmetries of saccadic function; if such an asymmetry were present it would be most likely manifested in patients with a lateralised disorder of motor control. The direction of torticollis referred to the side to which the chin was displaced. There were 11 females and one male, with a mean age of 50·6 years (range 29–63). The mean disease duration was 9·6 years (range 1–25). Seven patients had rotation of the chin to the left and five to the right. Three patients were not taking medication at the time of the study, four were taking benzhexol (Artane), three were taking diazepam, one lorazepam and one mianserin. All had been on the stated medications for at least six months without any change in dosage. All patients had previously received at least one set of injections of botulinum toxin into the appropriate neck muscles, and some had been treated at regular intervals for up to two years. The patients were compared to a group of 19 normal controls; seven females and 12 males with a mean age of 43 years (range 30–65).

Eye movements were recorded with DC electroneystagmography (ENG) onto paper with an ink-jet polygraph (Mingograph) and recordings were then analysed by hand. Electrodes were placed near the inner and outer canthi of each eye and a reference ground electrode was placed onto the forehead. The subject’s head was supported by a head rest. In addition, a binaural head clamp was used in patients who could not keep their heads straight voluntarily. The recordings were made with the head directed to face the screen and with eyes in the primary gaze position.

Saccadic eye movements were made to a target projected onto a screen 1·3 metres from the patient by a video projector. The target, a 10 pixel diameter spot of light subtending an angle of 1·3', was generated using a graphics generator controlled by a micro-computer. The computer generated each of the target displacement sequences, each sequence being accessed by selection from an on screen menu. An analogue signal of target displacement was transformed to the paper recorder by a digital to analogue converter, so that latency measurements could be made directly from the recording.

The parameters of saccadic function examined were: random saccades, hidden predictive saccades, predictive saccades, remembered saccades, and self-paced saccades. The target moved in a square wave step fashion across the screen in the horizontal plane for each of the experimental conditions. Subjects and controls performed all of the following experiments in one session. Each experimental paradigm was separated by a rest period of approximately two minutes.
Random saccades The target moved randomly between five different positions on the screen (one central and two on either side) generating four possible target amplitudes (15°, 30°, 45°, 60°). The time interval between target displacements varied randomly between 0.5–2 s. The subject was instructed to look at the light as quickly as possible as the target would be moving in a random manner. The test duration was 78 s generating 36 steps.

Hidden predictive saccades In this paradigm the subject was given identical instructions as in the random sequence. The experiment began and ended with a series of random target displacements, in the midst of which a regular sequence of 20 target displacements of 30° (15° to either side of the midline with a time interval of 1 s), appeared without warning. The test duration was 46 s.

Predictive saccades This paradigm consisted of a regular sequence of 30 target displacements of 30° (15° to either side of the midline with a fixed time interval of one second). It was explained to the subjects that the target would now move regularly between two fixed points and that as previously they should look at the light as quickly as possible (without any instructions on whether they should try to predict or not). The test duration was 35 s.

Analysis of results of random, hidden predictive and predictive saccades Saccadic latencies and amplitudes (accuracy) were measured from the record. Saccadic velocities were measured from the random sequence, 10 saccades of 30° amplitude were used to calculate the mean saccadic velocity. The peak saccadic velocity was measured from the slope of the selected saccade directly from the record, with the paper speed at 100 mm/s and a calibration of 1° = 1 mm. In the predictive saccade sequence the mean saccadic latency was calculated once a relatively stable plateau of predictive responses had been achieved.

Remembered saccades In this paradigm a central fixation spot of light was presented to the subject for a period of two seconds. One second after its onset a second light was illuminated 20° to the right or left of the fixation spot, in a semi-randomised fashion, for a period of 200 ms. Eight hundred milliseconds after the eccentric light was extinguished the fixation spot was also extinguished. A final spot of light then appeared two seconds later at the same position as the previously flashed eccentric light and this remained on for five seconds. The subjects were instructed on the sequence of lights that would be presented and were asked to fixate upon the central target whilst it remained illuminated. They were then instructed to make a saccade to the position where they had seen the eccentric light, on extinction of the central fixation spot, though no instruction as to how quickly this should be performed was given. Subjects were asked to maintain fixation at this point until the final target was presented and then to shift fixation to that position. Subjects were instructed that the sequence constituted one individual trial but no instructions were given on the number of trials they would receive. One “sample” trial was then shown to the patient to establish whether the subject had understood the instructions.

Analysis of results The accuracy of the remembered saccades was analysed by measuring the amplitude of any corrective saccade made by subjects from the point they judged to be the position of the eccentric target (remembered saccade), to the true position of the eccentric target as represented by the final spot of light. Only the first four trials were analysed to minimise any learning effect. Unsuppressed saccades made to the eccentric target before the fixation light was extinguished, were also measured for their frequency, duration and relationship to the direction of torticollis.

Self-paced saccades In this experiment subjects were instructed to make saccadic reflexions as quickly as possible, between two fixed targets that were 15° to the right and left of the primary fixation point. The test duration was 30 s.

Analysis of results At least 20 gaze shifts were recorded in each direction. Saccadic accuracy was expressed as a percentage of the amplitude of the first saccade over total target displacement (30°). The other variables measured were: 1) the half cycle time, that is, the time taken from one target to arrival at the other; 2) the fixation time, the time of arrest on the target; 3) the transit time, the time taken from leaving one target to arrival at the other.

Statistical analysis of results Comparison was made between both patients and control groups as a whole, and within the control and patient groups for right and leftward saccades and ipsilateral and contralateral saccades, respectively. Ipsilateral saccades were those saccades made in the direction of chin displacement, and contralateral saccades were those made in a direction opposite to that of chin displacement.

Initial analysis showed that, apart from mean saccadic velocities, the data was not distributed normally, so non-parametric statistical methods were used. The non-parametric tests used were the Mann-Whitney U test and the Wilcoxon Rank Sum test. A Student’s t test was used to analyse the results of the mean saccadic velocity. In all the statistical analyses only values of p < 0.05 were considered significant.

Results Random saccades The mean latency of saccades for patients was 234 ms (SD 36), and for controls 208 ms (SD 29); this difference was not statistically significant (Z = 1.98). Nor
was there a significant difference when random saccades were related to the direction of torticollis; the latency of ipsilateral random saccades was 233 ms (SD 18) and of contralateral random saccades 241 ms (SD 34), (Z = 1.18), fig 1. The mean peak saccadic velocities for patients and controls were 452°/s (SD 86) and 434°/s (SD 68) respectively; this difference was not significant (t = 0.36, Student's t test).

Hidden predictive saccades Patients and controls were equally able to make predictive and anticipatory saccades. The rate at which the latency shortened appeared to be greater in the control group. However, this difference was not statistically significant using repeated measures analysis of variance (MANOVA, F = 0.55). When hidden predictive saccades were related to the direction of the torticollis (fig 1), there was no asymmetry in the patient's ability to progressively reduce their latencies, either ipsilateral or contralateral to the direction of torticollis.

Predictive saccades Both groups rapidly developed a predictive strategy and substantially reduced their latencies. There was no significant difference between the mean latency of predictive saccades for patients, -29.3 ms (SD 15.9) and controls, -32.3 ms (SD 16.4), (Z = 0.08). When predictive saccades in patients were related to the direction of their torticollis, the mean latency of ipsilateral saccades was -10.2 ms (SD 12.9) and of contralateral saccades was -23.3 ms (SD 17.0); this difference was not significant (Z = 1.18), (fig 1).

Remembered saccades Figure 2 shows the records of one patient and one control and demonstrates the ability of both to make accurate remembered saccades. In addition, the records show that both made occasional premature saccades to the eccentric target
before the central fixation point was extinguished. Such premature saccades were made no more frequently by patients (18% of trials) than controls (17%, of trials); nor was there a difference in the frequency with which they were made ipsilateral (51%, of) or contralateral (49%, of) to the direction of the torticollis \((Z = 1.09)\). The latency of remembered saccades was 437 ms (SD 161) in controls and 503 ms (SD 237) in patients; this difference was not significant \((t = 0.78)\). Remembered saccades which followed premature saccades tended to have much longer latencies than those not preceded by premature saccades. Occasionally latencies of up to two seconds were recorded as illustrated in Fig 2.

There was no significant difference between the mean inaccuracy of remembered saccades of patients 0.23° (SD 1.3) and controls 0.43° (SD 1.54), \((Z = 0.97)\). Nor was there a significant difference in the mean inaccuracy of remembered saccades made ipsilateral (0.31°, SD 1.12) and contralateral (0.16°, SD 1.40) to the direction of torticollis \((Z = 0.38)\).

**Self-paced saccades** Figure 3 shows the record of a patient and a control, demonstrating that both were equally able to make rapid and accurate self-paced saccades. Table 2 gives the collective data for all the parameters of self-paced saccades. There was no difference between mean half cycle times \((Z = 1.03)\), or fixation times \((Z = 1.04)\) of patients compared to controls. Both groups were able to make accurate saccades on rapid refixations. Within the patient group there was no difference between ipsilateral and contralateral saccades either for the fixation time \((Z = 1.11)\) or half cycle time \((Z = 0.40)\). There was no difference in the mean accuracy of the first saccade between patients and controls, the value being 98.3% (SD 1.7) for patients and 97.4% (SD 3.8) for controls.

**Discussion**

Patients with torticollis showed no deficit in the production of random, predictive, remembered or self-paced saccades. The ability to make predictive and remembered saccades may depend upon the integrity of projections from the frontal eye fields, via caudate nucleus, to the substantia nigra reticulata, and from there to cells within the intermediate and deep layers of the superior colliculus.10-13 It is via this pathway that the basal ganglia may exert their influence on saccadic eye movements. Hikosaka and Wurtz, using single cell recordings in primates, localised a population of nigral reticulata cells whose high baseline discharge rates consistently fell 200 ms before the production of saccades made to remembered targets in the contralateral visual field. These GABAergic cells were found to exert tonic inhibition upon cells within the superior colliculus. The nigra reticulata cells (SNr), in turn, receive inhibitory GABAergic input from the corpus striatum.10 Pathology affecting the basal ganglia might be expected to interfere with this striato-nigro-collicular pathway, and thus impair the ability to make remembered saccades. In addition, the ability to make predictive eye movements requires memory of the target both temporally and spatially, and therefore may also be expected to be impaired. Reduction of inhibitory striatal output would increase the tonic inhibition from nigra reticulata upon the cells of superior colliculus. These collicular cells are known to exhibit burst activity before saccades10-13 increased inhibition of superior collicular cells would therefore be expected to produce prolonged latencies and/or slowing of saccades. 

**Table 2** Parameters of self-paced saccades in torticollis patients and controls in ms, mean and (SD)

<table>
<thead>
<tr>
<th></th>
<th>Fixation time</th>
<th>Half cycle time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bilateral*</td>
<td>Ipsilateral</td>
</tr>
<tr>
<td>Patients</td>
<td>414 (106)</td>
<td>426 (99)</td>
</tr>
<tr>
<td>Controls</td>
<td>359 (99)</td>
<td></td>
</tr>
</tbody>
</table>

*Refers to ipsilateral/contralateral (right and left in controls), values combined.
mental support for this prediction was found, in that injection of the GABA agonist, muscimol into the superior colliculus produced slow, hypometric saccades with long latencies, especially to remembered saccades.\textsuperscript{14,17} Clinical evidence supporting the role of the basal ganglia in the production of predictive, remembered and self-paced saccades comes from several studies of eye movement in patients with Huntington's disease. With a history of the brain, and in particular in Parkinson's disease. De Jong and Melvill Jones\textsuperscript{16} found that whilst patients with Parkinson's disease had normal saccadic metrics to random target displacements, they took longer to make self-paced saccades between two stationary spots of light, and these were more inaccurate than those made by age matched controls. Bronstein and Kennard\textsuperscript{1} found that Parkinsonian patients had an impairment of predictive saccades and an inability to utilise verbal information on target displacement to improve their performance. In addition, these patients had a tendency to make saccades of longer latency than controls, regardless of the mode of presentation of the stimulus.\textsuperscript{1,17} These abnormalities were ascribed to reduction of excitatory dopaminergic input into the caudate nucleus, producing disinhibition of the SNr and subsequent inhibition of the superior colliculus.

In Huntington's disease (HD), in which there is a loss of caudate and SNr neurons\textsuperscript{16} with normal dopamine levels, a characteristic abnormality of saccadic function has been found. There is impairment in initiation of voluntary and remembered saccades, marked fixational instability, and an inability to suppress unwanted saccades to new visual stimuli.\textsuperscript{19-22} Loss of GABAergic inhibition of the superior colliculus by the SNr would reasonably explain the above abnormalities. Dysfunction of the superior colliculus has also been used to explain the more recent findings of saccadic slowing in younger patients with HD.\textsuperscript{22}

Though no pathological or neurochemical abnormality has been found in patients with torticollis, this condition may result from dysfunction of the basal ganglia.\textsuperscript{1} Clinical examination of eye movements in patients with idiopathic dystonia is usually normal, apart from minor abnormalities of smooth pursuit related to medication. Whilst there are reports demonstrating a directional preponderance of vestibular nystagmus\textsuperscript{23} and impaired oculocollateral counterrolling in torticollis,\textsuperscript{24} there have been no other detailed studies analysing eye movements in this condition. The absence of saccadic dysfunction in patients with torticollis shown by this investigation strongly suggests that, while other parts of the basal ganglia may be implicated pathophysiologically, it is unlikely that the striato(caudato)-nigro-collicular pathway is involved. It is now recognised that the basal ganglia are components of several parallel, "basal ganglia-thalamocortical" circuits, each receiving inputs from separate cortical areas, the above oculomotor pathway representing but one of these circuits. Each has functional specialisation and projects, in an anatomically segregated fashion, within the basal ganglia.\textsuperscript{24} The integrity of this "oculomotor circuit" therefore does not exclude the possibility of dysfunction in other regions of the basal ganglia in torticollis.

An alternative interpretation of the negative results in this study is that the basal ganglia may not be primarily involved in the pathogenesis of torticollis. There are very few reports of patients with torticollis due to an identified focal lesion in the basal ganglia. Focal lesions involving the caudate and putamen\textsuperscript{25} have produced torticollis, but so too have lesions of the mesencephalic tegmentum.\textsuperscript{26,27} spinal cord and posterior fossa.\textsuperscript{28,29} Unfortunately, many of the cases reported have had lesions at other sites making interpretation difficult. Experimental torticollis in primates has been reported with lesions of selected brainstem reticular nuclei, in particular the Interstitial Nucleus of Cajal which is known to have reciprocal connections with the vestibular nuclei.\textsuperscript{30,31} It is possible that the basal ganglia themselves are not primarily involved in the pathogenesis of spasmodic torticollis, which may be due instead to an abnormality of one or more brainstem structures, with which the basal ganglia are intimately connected.

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