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Control of volitional and reflexive saccades in Tourette's syndrome

Adrienne L. LeVasseur,[1] J. Randall Flanagan,[1,2] Richard J. Riopelle[3] and Douglas P. Munoz[1,2]

Departments of [1]Physiology, [2]Psychology and [3]Medicine, Queen's University, Kingston, Ontario, Canada

Correspondence to: Dr Doug Munoz, Department of Physiology, Queen's University, Kingston, Ontario, Canada K7L 3N6
E-mail: doug@eyeml.queensu.ca

Summary

Tourette's syndrome is characterized by involuntary tics and, although the underlying pathogenesis and pathophysiology of Tourette's syndrome remains unclear, it is suspected that basal ganglia structures are involved. The basal ganglia also play an important role in the control of saccadic eye movements and we therefore hypothesize that Tourette's syndrome patients have abnormal control of saccadic eye movements. In this study, 10 subjects with Tourette's syndrome and 10 age- and sex-matched controls performed four different oculomotor paradigms requiring the execution and/or suppression of reflexive and/or voluntary saccades. In the immediate saccade tasks, subjects were required to look either toward (pro-saccade task) or away from (anti-saccade task) a peripheral target as soon as it appeared. In the delayed saccade tasks, subjects were instructed to wait for a central fixation point to disappear before initiating eye movements. Among Tourette's syndrome subjects, saccadic reaction times were longer in all tasks. Saccadic amplitudes were smaller in Tourette's syndrome subjects, and they made more saccades to reach the eccentric target. The occurrence of direction errors (i.e. reflexive pro-saccades on anti-saccade trials) was normal in the immediate anti-saccade task, suggesting that the ability to inhibit reflexive saccades towards novel stimuli was not impaired in Tourette's syndrome. Timing errors (i.e. eye movements made prior to disappearance of the central fixation point in delayed saccade tasks) were significantly greater among Tourette's syndrome subjects. Moreover, these errors were predominantly made towards the first target of the remembered sequence in a delayed memory-guided sequential saccade task. These results indicate that the ability to inhibit or delay planned motor programmes is significantly impaired in Tourette's syndrome. We hypothesize that altered cortical–basal ganglia circuitry leads to reduced cortical inhibition making it harder for Tourette's syndrome subjects to withhold the execution of planned motor programmes.

Keywords: basal ganglia, cerebral cortex, eye movements

Abbreviations: ADHD = attention-deficit hyperactivity disorder; CIE = international chromaticity coordinate; FP = fixation point; LED = light emitting diode; OCD = obsessive–compulsive disorder; SRT = saccadic reaction time

Introduction

Tourette's syndrome is an inherited condition characterized by the presence of motor and phonic tics which can be worsened by anxiety or fatigue (Singer, 1997) and improved by concentration (Jankovic, 1997). Although the physiological basis for tics and Tourette's syndrome remains unknown, a substantial amount of evidence suggests a disorder of frontal–striatal circuits (Singer, 1997). Tourette's syndrome patients have demonstrated deficits in memory search, abstract reasoning and verbal fluency (Bornstein, 1991), which are processes that are believed to be regulated by frontal–striatal systems (Rauch and Savage, 1997). Volumetric abnormalities of the basal ganglia have been reported (Malison *et al*., 1995; Wolf *et al*., 1996), as well as increased dopamine binding within the caudate nucleus of the striatum (Peterson *et al*., 1993; Singer *et al*., 1993; Hyde *et al*., 1995; Malison *et al*., 1995; Wolf *et al*., 1996). Dopamine blockers have been most successful in treatment of the disorder (Kurlan, 1997), whereas dopaminergic drugs and CNS stimulants exacerbate tics (Hallett, 1993; Jankovic, 1997).

It has been suggested that Tourette's syndrome may result from overactivity of the direct pathway through the basal ganglia (Hallett, 1993). The direct pathway acts to enhance movement, while the indirect pathway acts to inhibit movement. Dopamine enhances transmission through the direct pathway and inhibits the indirect pathway, acting through D_1 and D_2 receptors, respectively. Because increased binding

capacity of D_2 receptors in the caudate nucleus correlates with symptom severity in monozygotic twins with Tourette's syndrome (Wolf *et al.*, 1996), the movement disorder may also be related to under-activity of the indirect pathway.

A powerful means to investigate the neural control of movement generation and impairment involving frontal–striatal and other pathways is to record saccadic eye movements under various well-studied experimental conditions. Saccades are rapid eye movements used to shift the line of sight from one point to another. Saccade studies can offer advantages over other limb movement studies because of the relative ease with which the movements can be measured and because of our understanding of the pre-motor circuitry controlling the behaviour (Wurtz and Goldberg, 1989; Leigh and Zee, 1999). Saccades are triggered via parallel descending pathways from the cerebral cortex to the superior colliculus and brainstem reticular formation. Reflexive saccades, to the locations of novel targets that appear suddenly in the visual field, depend primarily upon direct projections from the visual and parietal cortices to the superior colliculus, whereas volitional saccades, made in the context of learned or remembered behaviour, depend more upon the frontal cortex, which projects both directly and indirectly (via basal ganglia) to the superior colliculus and brainstem. Because the areas involved in the generation of volitional saccades include corticostriatal pathways, patients with frontostriatal disorders display characteristic dysfunctions in the execution of volitional saccades (Guitton *et al.*, 1985; Lasker *et al.*, 1987; Pierrot-Deseilligny *et al.*, 1991; Fukushima *et al.*, 1994; Kitagawa *et al.*, 1994; Briand *et al.*, 1999). Tourette's syndrome patients may therefore experience abnormal control of voluntary saccadic eye movements. The main aim of this study is to quantify saccade performance of Tourette's syndrome subjects in a variety of tasks to gain insight into the aetiology of the disorder.

Several saccade tasks are employed to specifically investigate the control of reflexive and voluntary saccades. A simple pro-saccade task (Fig. 1A), in which participants are instructed to look as quickly as possible from a central fixation point (FP) to a peripheral stimulus, can be used to evaluate the subject's ability to generate reflexive, visually triggered saccades. The anti-saccade task (Hallett, 1978) has been particularly useful in revealing underlying dysfunction of the frontal cortex and basal ganglia (Guitton *et al.*, 1985; for a review, see Everling and Fisher, 1998). In this task (Fig. 1B), presentation of the stimulus is identical to the pro-saccade task; however, subjects are instructed to look to the opposite side from the peripheral stimulus when it appears. To perform this task correctly, the subject must first suppress a reflexive saccade to the stimulus (pro-saccade) and then generate a voluntary anti-saccade away from the stimulus. The ability of subjects to delay saccades to eccentric stimuli is investigated by imposing a delay period between the identification of the saccadic goal and a GO signal (Fig. 1E). A memory-guided saccade task is also employed (Fig. 2), in which eccentric targets are flashed and the subjects must not only delay saccades until a later GO signal is provided, but must also remember target location.

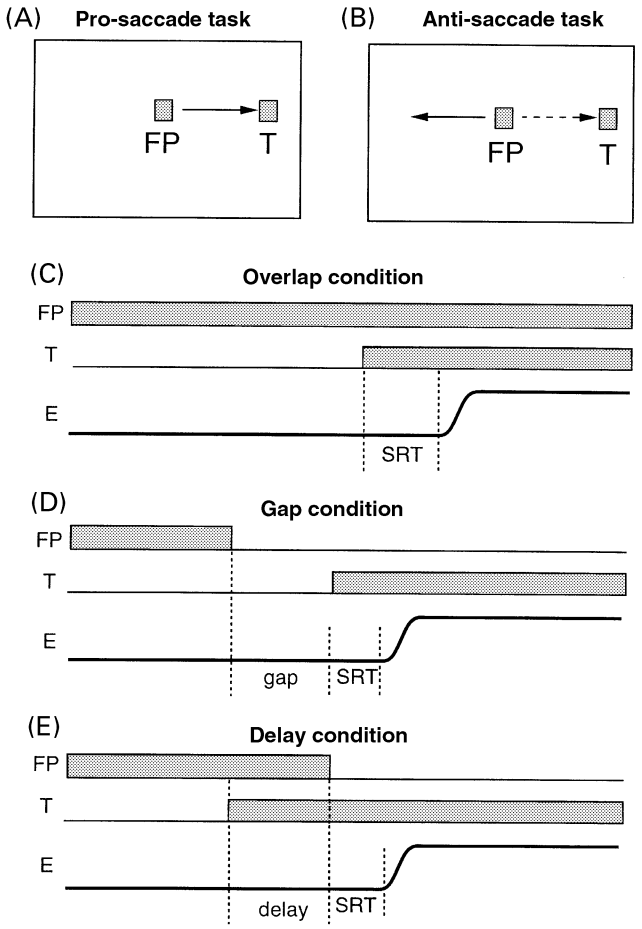

Fig. 1 Anti- and pro-saccade tasks. In the pro-saccade task (**A**) the subject was instructed to look from the central fixation point (FP) towards the eccentric target stimulus (T). In the anti-saccade task (**B**) the subject was instructed to look away from the eccentric target, towards its mirror position. In both tasks, the state of fixation prior to the saccade was manipulated. In the overlap condition (**C**), the FP remained on when the T appeared. In the gap condition (**D**), the FP disappeared 200 ms before the appearance of the target stimulus. In both conditions the SRT was measured from the time of target appearance to the onset of eye movement. In the delayed pro/anti-saccade task (**E**), the target appeared while the FP remained illuminated and the subject was instructed to refrain from initiating a saccade until the FP disappeared. The delay period between T appearance and FP disappearance varied from 200–1000 ms. In the delayed saccade task, SRT was measured from FP disappearance to the onset of the eye movement.

Previous studies examining saccades in Tourette's syndrome patients using some of the above tasks have reported conflicting results. Reflexive pro-saccade reaction times in Tourette's syndrome subjects have been reported as normal or only slightly elevated (Straube *et al.*, 1997; Farber *et al.*, 1999), but saccade durations may be reduced (Farber *et al.*, 1999). Anti-saccades have greater reaction times (Straube *et al.*, 1997; Farber *et al.*, 1999), and peak velocities may be reduced (Straube *et al.*, 1997). The frequency of

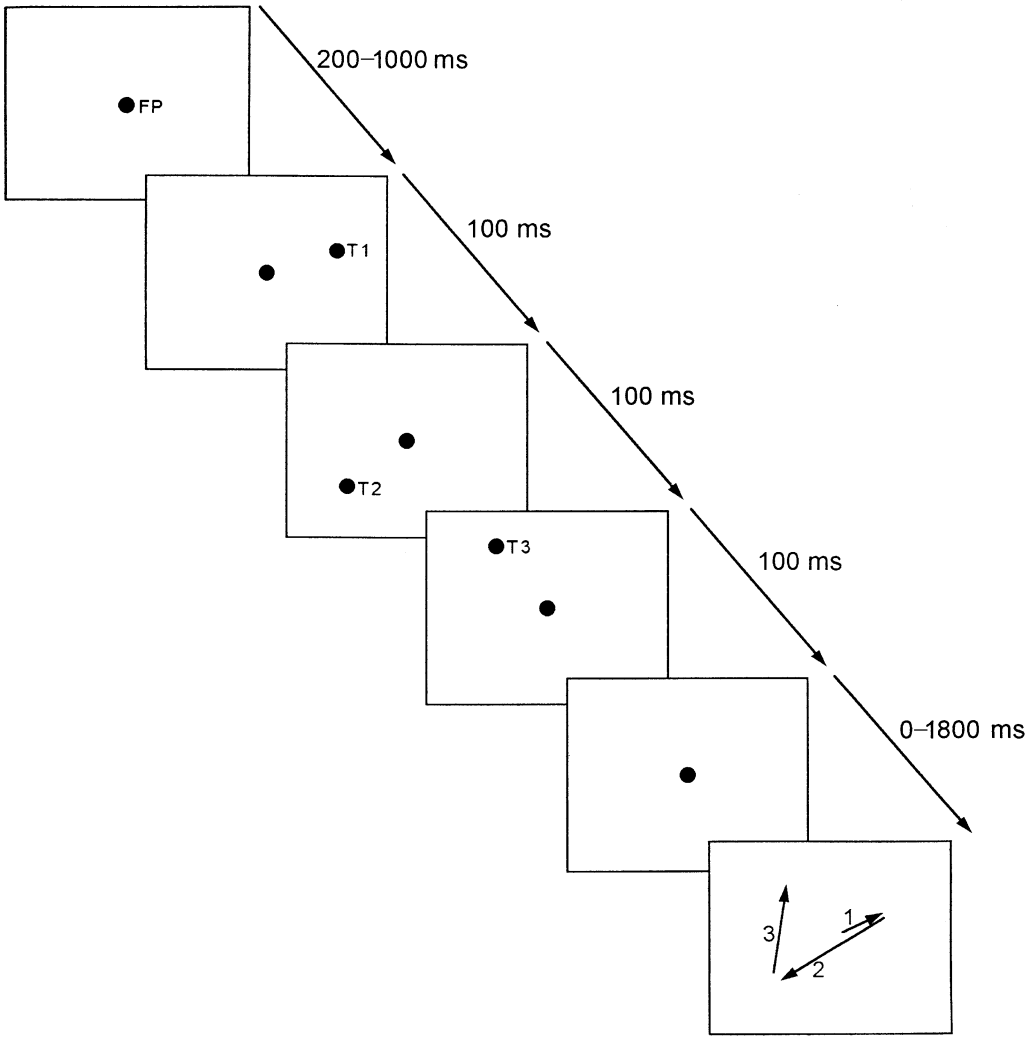

Fig. 2 Delayed memory-guided sequential saccade task. Subjects were instructed to fixate the central FP until it disappeared. On each trial, three target stimuli (T1, T2 and T3) were presented sequentially for 100 ms in three of the four quadrants of the visual field. Target location within each quadrant and sequence of the three targets varied randomly from trial to trial. The interval between disappearance of the final target of the sequence and disappearance of the FP was varied randomly (0, 600, 1200 and 1800 ms). Subjects were instructed to move their eyes after the FP disappeared to the remembered location of each of the targets in the correct order of their appearance.

direction errors among Tourette's syndrome subjects performing the anti-saccade task has been reported as normal (Straube *et al*., 1997) or abnormally high (Narita *et al*., 1997; Farber *et al*., 1999).

In the present study, we employ pro-, anti-, delayed- and memory-guided oculomotor tasks (Figs 1 and 2) to investigate the ability of Tourette's syndrome subjects to generate reflexive and voluntary saccades, suppress or delay saccades and generate remembered sequences of saccades.

Methods

Subjects

All experimental procedures were reviewed and approved by the Queen's University Human Research Ethics Board. Ten subjects with Tourette's syndrome, ranging between 11 and 55 years of age, were recruited along with 10 age- and sex-matched control subjects (Table 1). The Tourette's syndrome subjects met clinical criteria for diagnosis and were referred by a neurologist (R.J.R). Control subjects reported no history of neurological or psychiatric disorders. All subjects were informed of the nature of the study and consented to participate. Although some subjects were medicated and others were not (see Table 1), no performance differences were obvious between these groups. It was not possible to ask medicated subjects to cease their medication for experimental purposes given that it takes at least 1 week for clearance of such medications from the system. Such a request can be disruptive to the subject's everyday life, especially when employment is involved.

Table 1 *Subject information*

Subject	Age (years)	Age of control (years)	Sex	Medication	Co-morbid symptoms
1	55	53	M	Haloperidol (5 mg/day) Clonidine (0.1 mg qd)	–
2	38	41	M	Esperidone (4 mg/day)	–
3	11	12	M	Luvox (50 mg/day) Resperidone (4 mg/day)	ADHD
4	17	18	M	Prozac (20 mg/day) Pimozide (8 mg bd)	ADHD
5	43	45	F	Pimozide (6 mg/day) Luvox (50 mg/day)	Developmentally delayed
6	35	35	M	Pimozide (6 mg/day)	–
7	10	11	M	–	–
8	17	17	M	–	OCD
9	23	23	M	–	–
10	23	22	M	–	–

M = male; F = female.

Tourette's syndrome has a high rate of co-morbidity with other neurological disorders, such as attention-deficit hyperactivity disorder (ADHD) and obsessive–compulsive disorder (OCD) (Freeman, 1997; Singer, 1997). Several of the Tourette's syndrome subjects in this study had co-morbid conditions (see Table 1). Subjects 3 and 4 were also diagnosed with ADHD, subject 8 was diagnosed with OCD and Subject 5 was developmentally delayed. If and when the results of these subjects deviated from the other Tourette's syndrome subjects, analysis was carried out in order to ensure that these extreme values were not responsible for the overall trend observed in the Tourette's syndrome subjects.

Experimental paradigms

Subjects were required to participate in experiments on three separate days. Each recording session lasted no more than 60 min, and there were breaks between blocks of trials during which participants were provided with snacks and drinks to maintain alertness. On Day 1, subjects performed one block (120 trials) of immediate pro-saccades, followed by two blocks (120 trials each) of immediate anti-saccades. On Day 2, subjects performed three blocks (160 trials each) of randomly interleaved delayed pro- and anti- saccades. On Day 3, subjects performed two blocks (96 trials each) of delayed memory-guided saccade sequences to peripheral targets. Ten subjects performed the immediate and delayed anti-/pro-saccade tasks, but only seven subjects performed the delayed memory-guided sequential saccade experiment. Tourette's syndrome Subjects 3 and 10 dropped out of the study, and Subject 5 was unable to perform the more complex task.

Two separate laboratories were used for these experiments. On Days 1 and 2, subjects were seated upright in a dental chair equipped with a head rest, which could be adjusted for height, such that they faced the centre of a translucent visual screen 100 cm away (for details, see Munoz *et al*., 1998*a*). The experiments were performed in darkness and silence except for the controlled presentation of visual stimuli, which consisted of light emitting diodes [LEDs; international chromaticity coordinates (CIEs): red $CIE_x = 0.51$, $CIE_y = 0.04$, green $CIE_x = 0.37$, $CIE_y = 0.078$]. A red LED (2.0 cd/m^2) was back projected onto the centre of the translucent screen and served as a central FP. In the delayed saccade task, a central green LED (1.0 cd/m^2) alternated randomly with the central red FP. Eccentric red LEDs (5.0 cd/m^2) were mounted into small boxes on portable stands that were positioned 20° to the left and right of the central FP. Between trials, the screen was diffusely illuminated (1.0 cd/m^2) with background slides to reduce dark adaptation and boredom.

The delayed memory-guided sequential saccade task was performed on Day 3 in a separate laboratory (for details, see Cabel *et al*., 2000). Subjects were seated 60 cm in front of a black display monitor on which the white FP (0.2 cd/m^2; $CIE_x = 0.299$, $CIE_y = 0.300$) and green targets (0.2 cd/m^2; $CIE_x = 0.294$, $CIE_y = 0.533$) appeared. Stimuli were presented on a viewSonic 17PS monitor using an S3 VGA card. The visual display had a resolution of 640 × 480 pixels, with a frame rate of 60 Hz. Subjects wore a head-mounted infrared eye tracking device which recorded eye movements.

In the immediate pro-saccade task (Fig. 1A), subjects were instructed to look from the central FP to an eccentric target that appeared randomly either 20° to the left or right. Each trial began when the background illumination was turned off. After 250 ms of darkness, the FP appeared. After 1000 ms, one of two events occurred: in the overlap condition, the FP remained illuminated while the target appeared (Fig.1C); in the gap condition, the FP disappeared and, after a gap period of 200 ms, the target appeared (Fig. 1D). The target remained illuminated for 1000 ms, after which all LEDs were turned

off and the background illumination came on for 500 ms to signify the end of the trial. Gap trials yield shorter saccadic reaction times (SRTs) than overlap trials (Saslow, 1967) and increase the propensity of reflexive responses (Fischer and Rampsberger, 1984; Munoz and Corneil, 1995), probably due to disengagement of visual fixation prior to target appearance. Target location (20° right or left) and fixation condition (gap or overlap) were randomly interleaved within a block of trials.

In the immediate anti-saccade task (Fig. 1B), the presentation of stimuli was identical to the pro-saccade task. Subjects were instructed to look at the central FP, but then to look to the opposite side of the vertical meridian after the appearance of the target. Once again, target location (20° right or left) and fixation condition (gap or overlap) were randomly interleaved within a block of trials.

In the delayed pro/anti-saccade task (Fig. 1E), subjects were required to perform volitional saccades on every trial. Each trial began when the background illumination was turned off. After 250 ms of darkness, either the red or green FP appeared. After 1000 ms, the eccentric target appeared and remained illuminated. The FP then disappeared after a randomized delay of 200, 400, 600, 800 or 1000 ms. Subjects were instructed to remain fixated upon the visible FP until it disappeared and then look toward the target if the central FP was red and to look away from the target if the central FP was green. The target remained illuminated for 1000 ms, after which all LEDs were turned off and the background illumination came on for 500 ms to signify the end of the trial. Target location (20° right or left), colour of the fixation point (red or green) and delay interval (200, 400, 600, 800 and 1000 ms) were all randomly interleaved within a block of trials. Subjects were not given any practice prior to data collection. They were, however, asked to repeat the instructions to the experimenter prior to the initiation of data collection.

In the delayed memory-guided sequential saccade task (Fig. 2), performed on experimental day 3, subjects were instructed to fixate the central FP while eccentric targets were flashed sequentially in three of the four quadrants of the visual field. Within each quadrant, the target flashed at one of 25 preset locations, which were evenly spaced over a visual range of 9° eccentricity in the x and y direction at the centre of the quadrant. Each target appeared in isolation for 100 ms with no temporal gap between target presentations. Subjects were instructed to wait for disappearance of the FP, and then look to the remembered location of the targets in the sequence in which they appeared. The precise sequence of target appearance and location of the target within each quadrant varied randomly between trials, and there was equal probability of the target appearing in each quadrant. The interval between disappearance of the final target of the sequence and disappearance of the FP also varied randomly (0, 600, 1200 and 1800 ms). Each subject performed 20 practice trials before recording began.

Recording and analysis of eye movements

Immediate and delayed anti- and pro-saccade tasks

Horizontal eye movements were measured using direct current electrooculography. Ag–AgCl skin electrodes were placed bitemporally to record horizontal eye position. A ground electrode was placed just above the eyebrows in the centre of the forehead. The electro-oculography signal was amplified and low-pass filtered (50 Hz; Intronix) with a Grass P18 amplifier rated for human use. To minimize electro-oculography drift, subjects wore electrodes for ~10 min before the onset of calibration and recording. The experimental paradigms, visual displays and storage of eye-movement data were under the control of a 486 computer running a real-time data acquisition system (REX; Hays *et al*., 1982). Horizontal eye position was digitized at a rate of 500 Hz. Digitized data were stored on a hard disk, and subsequent off-line analysis was performed on a Sun Sparc 2 workstation.

Horizontal eye velocity was computed from the position traces by applying software differentiation (finite impulse response filter). The onset and termination of each saccade was determined when eye velocity increased or decreased, respectively, beyond 30°/s. Saccades were scored as correct if the first movement after target appearance was in the correct direction and if it occurred after disappearance of the FP in the delayed saccade paradigm. Saccades were classified as direction errors if the first saccade after target appearance was in the wrong direction, and as timing errors if they occurred before disappearance of the FP in the delayed saccade paradigm.

In the immediate pro- and anti-saccade tasks, SRT was measured from the time of target appearance to the onset of the first saccade. In the delayed saccade paradigm, SRT was measured from the time of FP disappearance to the onset of the first saccade. Movements in the immediate pro- and anti-saccade tasks were classified as anticipatory and were excluded from analysis if they were initiated $<$90 ms after target appearance. In the delayed pro-/anti-saccade task, saccades initiated before FP disappearance or within 90 ms after FP disappearance were excluded from analysis of SRT. Mean SRTs were computed from trials with SRTs between 90 ms and 1000 ms.

From the data of each subject, the following values were computed for gap, overlap, right and left trials: mean SRT for correct trials, coefficient of variation of SRTs for correct trials, percentage direction errors, percentage express saccades (saccades with latencies approaching the minimal conduction time in the oculomotor system: 90–140 ms) (for a review, see Fisher and Weber, 1993) in the anti- and pro-saccade tasks and percentage of timing errors (saccades executed prior to disappearance of FP) in the delayed saccade task. Saccade metrics and dynamics were analysed for correct trials of the immediate pro-saccade task. The average number of saccades required to reach the target was calculated, as well as the saccadic amplitude of the first saccade. Peak

velocity and duration were quantified for primary saccades that were between 18 and 21° in amplitude. Because values for right and left target positions were not significantly different, data were collapsed across direction for each task. Distribution of the data was reviewed. Normally distributed data were analysed with ANOVA tests and non-normally distributed data were analysed using non-parametric Mann–Whitney tests, comparing results from all Tourette's syndrome subjects with all age- and sex-matched controls.

Delayed memory guided saccade sequence task

Eye position data were collected using a video-based eyetracker (Eyelink; SR Research Ltd, Toronto, Canada) that was mounted on the subject's head with an adjustable headband. The eyetracker used infrared cameras to track the movements of the pupils, measuring vertical and horizontal eye position and pupil size with a sampling rate of 250 Hz. It also provided spatial information about head position for head motion compensation. The Eyelink system detected eye movements as saccades when peak velocities were >30°/s, acceleration was >9500°/s^2 and there was motion >0.15° from the position of fixation before saccade onset. The accuracy of subjects' movements to each target was measured by calculating the distance between each target location and the closest eye fixation. Eye movement sequences that were not executed in the same order as target sequences were classified as sequence errors. Eye movements occurring prior to disappearance of the FP were classified as timing errors. These movements were further analysed to determine the direction of the first saccade in which timing error movements were made. The percentage of timing and sequence errors was calculated for each subject. Distribution of the data was reviewed. Normally distributed data were analysed with ANOVA tests and abnormally distributed data were analysed using non-parametric Mann–Whitney tests, comparing results from all Tourette's syndrome subjects with all age- and sex-matched controls.

Results

Immediate pro-saccade task

The mean SRT in the immediate pro-saccade task was elevated among Tourette's syndrome subjects [$F(1,76) = 28.15$, $P < 0.001$; see Fig. 3]. Table 2 contains mean values for SRT and the gap effect, and median values for intra-subject variance in SRT expressed as the coefficient of variation of SRT, and the percentage of express saccades for Tourette's syndrome and control subjects in the immediate pro-saccade task. The table shows that the percentage of express saccades during gap trials was reduced among Tourette's syndrome subjects ($U = 122.00$, $P < 0.05$). Intra-subject variance was greater in Tourette's syndrome than control subjects [$F(1,76) = 6.22$, $P < 0.05$], and the difference in variability between the groups was consistent in both fixation conditions (gap versus overlap) [$F(1,76) = 0.08$, $P > 0.7$], indicating that the gap effect was not affected in Tourette's syndrome subjects.

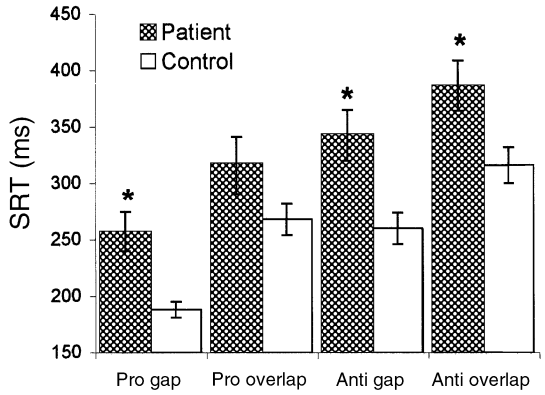

Fig. 3 Mean SRT (± standard error) for control and Tourette's syndrome subjects in the immediate pro- and anti-saccade tasks with gap and overlap conditions. *Statistically significant difference from control subjects (*t*-test, $P < 0.05$).

Table 2 *Results from the immediate pro-saccade task*

	SRT (ms)	Gap effect (ms)	CV	Express (%)
Patients	287 ± 12*	60 ± 22	30 ± 9*	3 ± 6*
Controls	225 ± 6	60 ± 7	25 ± 14	5 ± 11

Mean values (± standard error) for SRT (collapsed across direction and fixation state), gap effect (overlap SRT – gap SRT), coefficient of variation in SRT (CV) and percentage express saccades in Tourette's syndrome and control subjects. *Significant difference from controls.

Saccade metrics were analysed only for correct trials in the immediate pro-saccade task (Table 3). No significant difference in velocity [$F(1,78) = 3.38$, $P > 0.05$] or duration [$F(1,78) < 1$, $P > 0.4$] of the first saccade required to fixate the eccentric target was found between Tourette's syndrome and control subjects. However, the amplitude was smaller in Tourette's syndrome subjects ($U = 498.5$, $P < 0.005$), and they made more saccades to shift gaze to the targets located at 20° eccentricity ($U = 525.5$, $P < 0.01$).

Immediate anti-saccade task

Due to the nature of Tourette's syndrome, we hypothesized that Tourette's syndrome subjects would have difficulty suppressing reflexive saccades. Unexpectedly, the percentage of direction errors in the immediate anti-saccade task was not significantly greater in Tourette's syndrome subjects than control subjects ($U = 730$, $P > 0.4$; see Table 4). Tourette's syndrome subjects did have significantly greater mean SRT than control subjects [$F(1,76) = 32.9$, $P < 0.001$] in the immediate anti-saccade task (Fig. 3 and Table 4). Intra-subject variance of SRT was significantly greater for

Table 3 *Saccade metrics in the immediate pro-saccade task collapsed across fixation state (gap and overlap) and direction*

	Duration (ms)	Peak velocity (°/s)	Amplitude (°)	No. of saccades
Patients	70 ± 2	389 ± 6	19.4 ± 1*	1.17 ± 0.17*
Controls	72 ± 1	373 ± 6	19.7 ± 0.5	1.07 ± 0.19

Mean values (± standard error) for duration, peak velocity, amplitude and the number of saccades executed are included. *Significant difference between Tourette's syndrome and controls.

Table 4 *Results from the immediate anti-saccade task*

	SRT (ms)	Gap effect (ms)	CV	Direction errors (%)
Patients	365 ± 12*	42 ± 7	29 ± 14*	5 ± 16
Controls	286 ± 9	64 ± 12	20 ± 15	4 ± 17

Mean values (± standard error) for SRT (collapsed across direction and fixation state), gap effect (overlap SRT – gap SRT), coefficient of variation in SRT (CV) and percentage direction errors in Tourette's syndrome and control subjects. *Significant difference from controls.

Tourette's syndrome subjects ($U = 426.5$, $P < 0.001$). The gap effect (mean overlap SRT – mean gap SRT) was not significantly different between Tourette's syndrome and control subjects [$F(1,76) < 1$, $P > 0.4$].

Delayed pro-/anti-saccade task

When subjects were asked to delay saccades, Tourette's syndrome subjects made more timing errors than control subjects on both pro-saccade ($U = 19.00$, $P < 0.05$) and anti-saccade trials ($U = 22.00$, $P < 0.05$; Fig. 4). A timing error consisted of a saccade which was initiated before disappearance of the FP or within the first 90 ms after FP disappearance (i.e. anticipating FP disappearance). Although Tourette's syndrome subjects did not make more direction errors than controls in the immediate anti-saccade task, they did make significantly more direction errors on anti-saccade trials in the delayed saccade task ($U = 22.00$, $P < 0.05$; Fig. 4). Mean SRT of correct delayed saccades was significantly greater among Tourette's syndrome subjects [$F(1,54) = 21.1$, $P < 0.001$; Fig. 5].

To examine the influence of the delay interval (period from target appearance to FP disappearance), the percentage of each saccade type (correct, timing error, direction error, timing and direction error) was also computed independently for each delay interval employed (Fig. 6). As the duration of the delay interval increased, the percentage of correct trials decreased and the percentage of timing errors increased for Tourette's syndrome subjects, but remained relatively constant for controls. Among both Tourette's syndrome and control subjects, the number of direction errors diminished

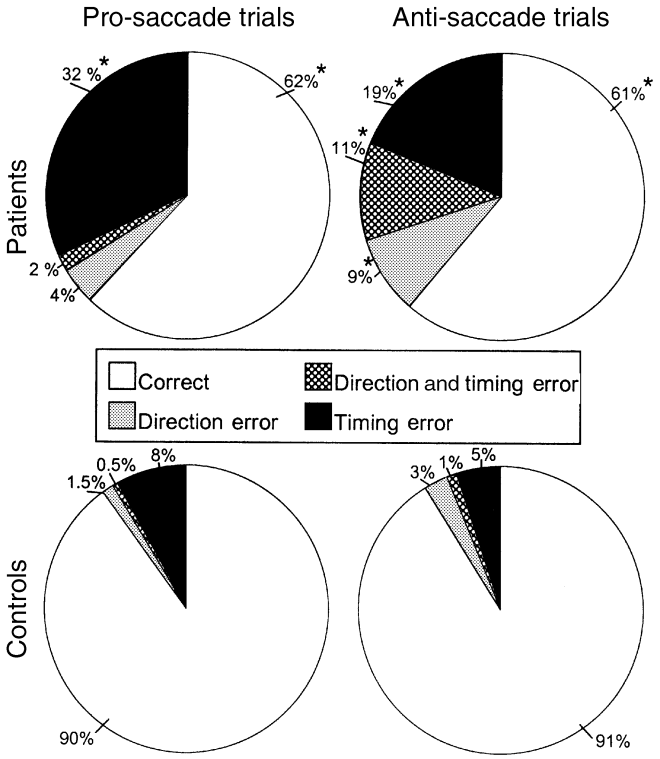

Fig. 4 Percentage of trial types obtained in the delayed pro-/anti-saccade task. *Significant difference between Tourette's syndrome and control subjects ($P < 0.05$).

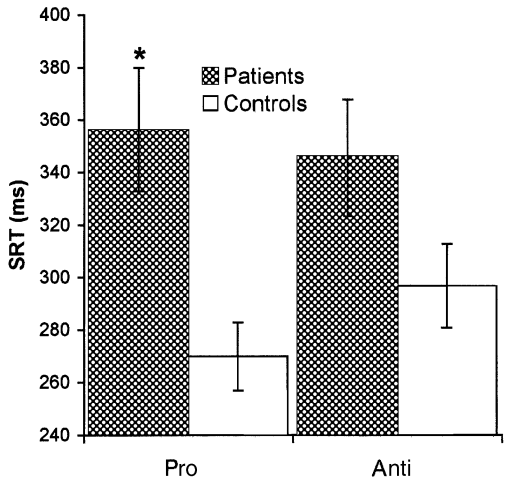

Fig. 5 Mean SRT (± standard error) in the delayed pro-/anti-saccade task. *Significant difference between Tourette's syndrome and control subjects ($P < 0.05$).

with increased delay intervals. These results indicate that Tourette's syndrome subjects experienced difficulty delaying the appropriate eye motor programme for prolonged periods of time, rather than difficulty inhibiting the eye motor programme altogether.

To further examine this apparent difficulty that Tourette's syndrome subjects had in delaying eye movements for

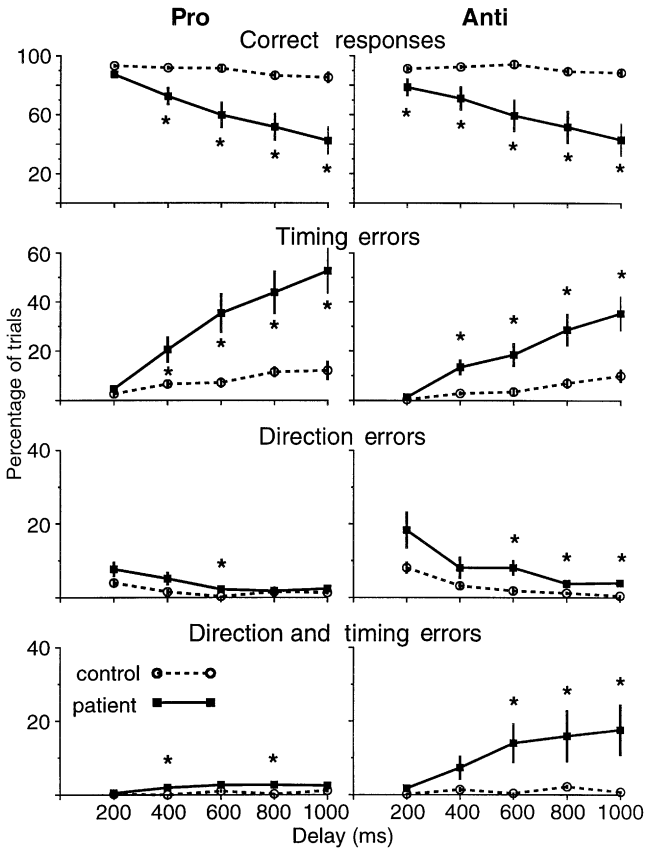

Fig. 6 Percentage (± standard error) of each trial type for each delay interval used in the delayed pro-/anti-saccade task. *Significant difference between Tourette's syndrome and control subjects ($P < 0.05$).

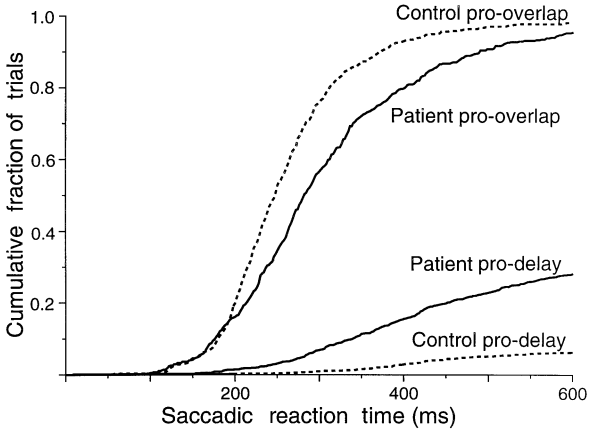

Fig. 7 Cumulative distribution of SRT after target appearance in immediate pro-overlap trials and delayed pro-saccade trials. Only delay trials with a delay of 600 ms or greater were plotted. The area between immediate and delayed saccade curves reflects subjects' ability to delay saccadic eye movements.

longer periods of time, cumulative distributions of SRT were constructed for pro-saccade trials from all Tourette's syndrome and control subjects using data from the immediate pro-saccade task. These were contrasted with the cumulative distribution of timing errors in the delayed pro-saccade task in which the delay interval (between target appearance and disappearance of the FP) was ⩾600 ms (Fig. 7). If no timing errors were made, the latter curves would be flat. If the subjects had absolutely no ability to delay their eye movements, curves for the delayed pro-saccade trials should be indistinguishable from those produced in the immediate pro-overlap task. Figure 7 reveals that, although Tourette's syndrome subjects had some ability to suppress eye movements until the appropriate GO signal (i.e. FP disappearance), they were impaired relative to controls. The area between the immediate and delayed saccade curves in Fig. 7 provides a measure of the ability to delay eye movements. This area is clearly smaller for Tourette's syndrome subjects.

Delayed memory guided sequential saccade task

The data in the immediate and delayed pro- and anti-saccade tasks suggest that Tourette's syndrome subjects are able to suppress reflexive saccades but often generate inappropriate early saccades when waiting for a delayed GO signal. To determine whether these early saccades result from an inability to suppress a movement to the most recently presented eccentric sensory stimulus, or an inability to suppress a planned movement, we devised a sequential memory-delayed task (Fig. 2) in which subjects had to remember the sequence of three successive target locations and delay the initiation of the sequence of saccades to the remembered locations of the targets until the FP disappeared. If Tourette's syndrome subjects were unable to suppress movements to the most recent stimuli during the delay interval, then timing errors should be directed to the last of the successive flashes. In contrast, if Tourette's syndrome subjects were unable to suppress the appropriate motor plan, then the first saccade of the timing error should be directed to the location of the first flash.

As expected, the percentage of timing errors in this task was significantly greater among Tourette's syndrome subjects, ($U = 11.00$, one-tailed $P < 0.05$; Fig. 8). *Post hoc* pair-wise comparisons for direction of timing errors showed that both Tourette's syndrome and control subjects [$F(1,12) = 2.00$, $P > 0.15$] most often looked to the first target, rather than the second or third target [$F(2,24) = 23.72$, $P < 0.001$; Fig. 9]. These findings indicate that for both Tourette's syndrome and control subjects, timing errors result from a failure to suppress a planned motor programme rather than a simple reflexive movement to the most previous sensory stimulus.

The percentage of appropriately delayed trials that had the correct sequence was also examined. On average, control subjects performed the correct sequence on 67% of delayed trials, while Tourette's syndrome subjects performed the correct sequence on 49% of delayed trials. This difference was not significant ($U = 15.5$, $P > 0.2$). The accuracy of subjects' eye movements to the three targets of the remembered sequence was also analysed for these trials

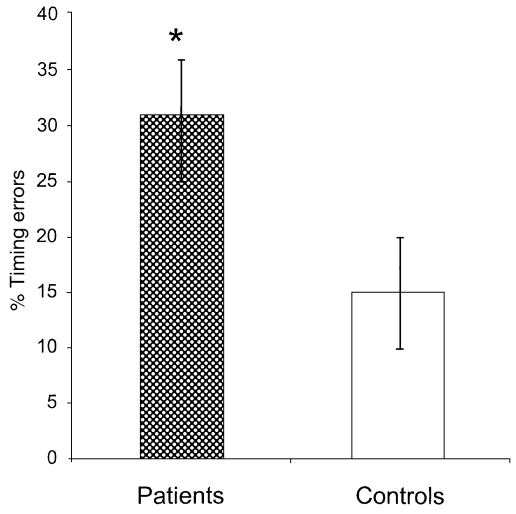

Fig. 8 Percentage of timing errors in the delayed memory-guided sequential saccade task. Tourette's syndrome subjects made significantly more timing errors ($P < 0.05$, indicated by *).

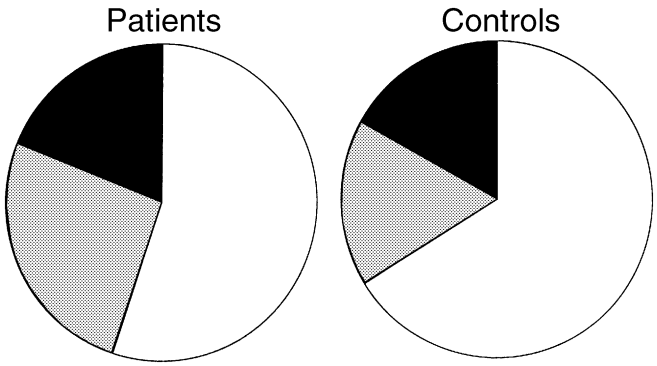

Fig. 9 Direction of timing errors in the delayed memory-guided sequential saccade task. Timing errors were made in the direction of the first target (white segment) more often than to the second (stippled segment) or third (black segment) target of the remembered sequence for both Tourette's syndrome and control subjects.

Table 5 *Mean (± standard error) eye position distance from targets t1, t2 and t3 for correct trials in the delayed memory-guided sequential saccade task in Tourette's syndrome and control subjects*

	Distance from t1 (°)	Distance from t2 (°)	Distance from t3 (°)
Patients	3.2 ± 3.5	3.4 ± 3.3	3.4 ± 3.0
Controls	1.9 ± 4.1	2.6 ± 1.5	2.6 ± 1.0

There were no significant differences between Tourette's syndrome and control subjects.

(Table 5). Accuracy of saccades to the remembered location of the first ($U = 13.0$, $P > 0.1$), second ($U = 13.0$, $P > 0.1$) and third ($U = 10.0$, $P = 0.07$) targets in the sequence was similar between Tourette's syndrome and control subjects. These results indicate that, although Tourette's syndrome subjects had difficulty with the timing of the sequence, they did not have significant difficulty with execution of the motor plan itself.

Medication and co-morbidities

Precautions were taken in order to ensure that neither treatments nor co-morbidities were responsible for the observed differences between Tourette's syndrome and controls rather than the disease itself. After analysing data of all subjects, statistical tests were carried out for the following subgroups of Tourette's syndrome patients and their age and sex matched control subjects: medicated Tourette's syndrome patients ($n = 6$), non-medicated Tourette's syndrome patients ($n = 4$), Tourette's syndrome patients without co-morbidities ($n = 6$), all Tourette's syndrome patients excluding the patient with a developmental problem ($n = 9$), all Tourette's syndrome patients excluding the patient with OCD ($n = 9$) and all Tourette's syndrome patients excluding patients with ADHD ($n = 8$).

Longer latencies, reduced saccade amplitude and an increase in the number of saccades to target were observed for Tourette's syndrome compared with control subjects during all tasks in all subgroups tested, with the exception of non-medicated subjects. However, in these cases, performance differences were consistent with significant findings; lack of significance ($P > 0.01$) was probably due to the small number of subjects in this subgroup ($n = 4$). It therefore does not appear that medication or co-morbidities were responsible for the longer latencies, smaller amplitudes or increased number of saccades observed in Tourette's syndrome subjects. Similarly, the lower percentage of express saccades in Tourette's syndrome subjects was consistent in non-medicated and non-co-morbid subgroups. In all subgroups analysed, the percentage of direction errors during the anti-saccade task remained similar in Tourette's syndrome and control subjects, and the percentage of timing errors in the delayed saccade task remained higher in Tourette's syndrome subjects. It can therefore be concluded that the Tourette's syndrome disorder itself was responsible for all of the above-mentioned findings.

In contrast, it is possible that medication and/or co-morbid conditions enhanced the increase in intra-subject variance observed in Tourette's syndrome subjects. Though intra-subject variance remained higher among Tourette's syndrome subjects in all subgroups, the difference was reduced below significance in both non-co-morbid (pro-task $P = 0.322$; anti-task $P = 0.170$) and non-medicated (pro-task $P = 0.196$; anti-task $P = 0.239$) subgroups. Lack of significance cannot be attributed to a small n value in this case, since the non-co-morbid group had $n = 6$. Three of the four subjects with co-morbid conditions were on medication, and it is therefore possible that increased intra-subject variance was enhanced by either or both of these two factors. This indicates that medication and co-morbidities are valid issues to be taken

into consideration, though they were not responsible for trends observed in SRT, amplitude, number of saccades, express saccades, direction errors or timing errors among Tourette's syndrome subjects.

Discussion

We have demonstrated that specific characteristics of saccade initiation are impaired in Tourette's syndrome subjects. Most importantly, Tourette's syndrome subjects demonstrated profound difficulties in delaying saccades in the delayed and memory-guided sequential saccade tasks. Moreover, timing errors in the memory-guided sequential saccade task were usually triggered in the direction of the first saccade of the remembered sequence. Therefore, we conclude that Tourette's syndrome subjects had difficulty delaying planned motor programmes. However, the percentage of direction errors in the immediate anti-saccade task was unaffected in Tourette's syndrome subjects and therefore these subjects did not have difficulty suppressing reflexive saccades. Saccadic reaction times were significantly greater in Tourette's syndrome subjects and saccadic amplitudes were significantly smaller. We first discuss these data in relation to previous findings and then provide a new theoretical framework to consider the dysfunction of Tourette's syndrome.

Saccadic abnormalities in Tourette's syndrome

Our SRT findings are consistent with those of Straube and colleagues, who reported a general elevation of SRTs in Tourette's syndrome subjects in several different oculomotor paradigms (Straube *et al*., 1997). Although Farber and colleagues reported significantly elevated SRTs in Tourette's syndrome subjects during anti-saccade overlap trials, they reported normal SRTs in Tourette's syndrome subjects during a pro-saccade task (Farber *et al*., 1999). This inconsistency between results may be related to task instruction: in the Farber study, subjects were instructed to perform saccades as rapidly as possible.

Previous studies have described either reduced duration of pro-saccades (Farber *et al*., 1999), or reduced peak velocity of anti-saccades (Straube *et al*., 1997) in Tourette's syndrome subjects. Because peak velocity and duration normally scale with saccadic amplitude (Leigh and Zee, 1999), the above findings are contradictory. In the present study, only the pro-saccades were analysed for metrics because our paradigm had no visual cue in the anti-saccade direction, and a high level of variability in metrics of anti-saccades was therefore present, even among control subjects. Although saccade dynamics were found to be normal among Tourette's syndrome subjects in the present study, the amplitude of the first saccade to the target was significantly reduced and number of saccades increased in Tourette's syndrome subjects. The higher number of saccades executed by Tourette's syndrome subjects to reach the target has also been observed in patients with Parkinson's disease (Lueck *et al*., 1992; Hodgson *et al*., 1999), and probably results from corrective feedback following hypometric saccades.

The results in the present study are also consistent with Straube and colleagues' finding that the ability to inhibit reflexive pro-saccades, indicated by the frequency of direction errors in the anti-saccade task, is not impaired in Tourette's syndrome subjects (Straube *et al*., 1997). Although Farber and colleagues reported an elevated number of direction errors in the anti-saccade task, they noted that this difference was caused by only 19% of the Tourette's syndrome subjects, and several of their subjects had co-morbid signs of attention deficit, hyperactivity or obsessive–compulsive symptoms (Farber *et al*., 1999). Narita and colleagues also reported in a case study that one Tourette's syndrome subject was unable to perform the anti-saccade task (Narita *et al*., 1997). However, this subject was referred to their department because he had the feeling that his eyes were crossing intermittently, a condition which may have complicated performance of eye movement tasks.

The increased frequency of direction errors in Tourette's syndrome subjects during delayed anti-saccade trials was likely to be caused by increased cognitive loading. Subjects were required not only to think about delaying eye movements, but also about whether to make a pro-saccade or anti-saccade on each trial. All types of errors (timing, direction, timing and direction) were significantly greater for Tourette's syndrome subjects during anti-saccade trials in the delay task.

We observed that Tourette's syndrome subjects experienced difficulty delaying purposeful saccades for extended periods of time in the delayed and memory tasks. The motor programmes themselves did not appear to be compromised, because timing errors were most often directed towards the first target of the sequence. Comparable results have been obtained in a study involving grasping movements in a single Tourette's syndrome subject (Flanagan *et al*., 1999). Although limb and eye movements appear to be subserved by distinct corticostriatothalamic circuits, these circuits have a similar architecture (for review, see Alexander *et al*., 1986; Rauch and Savage, 1997) and the basal ganglia may play a similar role in the control of eye and limb movements. It is therefore potentially instructive to compare deficits in Tourette's syndrome across these motor systems. The Tourette's syndrome subject in Flanagan and colleagues' study was instructed to wait for a GO signal before lifting an object up or down with a single arm movement (Flanagan *et al*., 1999). Several arm tics were recorded during the delay period before the GO signal, and these had the same direction and anticipatory grip force adjustments as the voluntary movements initiated after the GO signal. These results indicate that the tics represented an inability to suppress a planned and well-coordinated motor programme until the appropriate time.

Different disorders of the basal ganglia, such as ADHD (Munoz *et al*., 1998*b*, 1999), Huntington's disease (Lasker *et al*., 1987, 1997; Tian *et al*., 1991; Rubin *et al*., 1993),

Parkinson's disease (Crevits and DeRidder, 1997; O'Sullivan *et al*., 1997; Straube *et al*., 1998; Briand *et al*., 1999; Chen *et al*., 1999; Hodgson *et al*., 1999; Shaunak *et al*., 1999) and OCD (Sweeney *et al*., 1992; Tien *et al*., 1992; Rosenberg *et al*., 1997; Maruff *et al*., 1999), have overlapping yet distinct manifestations in terms of saccade abnormalities. A characteristic which has only been found in Tourette's syndrome subjects to date is the selective inability to delay eye motor programmes in delayed saccade tasks.

New theoretical framework

Recent models of saccade initiation (e.g. Carpenter and Williams, 1995; Trappenburg *et al*., 2001) suggest that there is a threshold level of pre-saccadic activity required to initiate a saccade. Saccadic reaction times are determined by the baseline and threshold levels of activity, as well as the rate of rise of activity toward the threshold. The increased SRTs and reduced occurrence of express saccades in Tourette's syndrome suggest that baseline levels of activity and/or the rate of rise may be abnormally low in Tourette's syndrome. Timing errors in delay tasks suggest that levels of delay activity, on the other hand, may be abnormally high in Tourette's syndrome, approaching the threshold level for saccade initiation.

Tics in Tourette's syndrome may result from excess activity in the brain areas responsible for storage of planned motor programmes. In a functional magnetic resonance imaging study, Biswal and co-workers showed that the average number of pixels activated in the sensorimotor cortices and supplementary motor area of Tourette's syndrome subjects during a finger-tapping task exceeded that in controls (Biswal *et al*., 1998). Using transcranial magnetic stimulation, Ziemann *et al*. (1997) revealed that intracortical inhibition, described as inhibitory action between areas of the motor cortex itself (Kujirai *et al*., 1993), was reduced in Tourette's syndrome subjects compared with controls. We hypothesize that this reduced inhibition in the cortex leads to overactivity, especially in a delay interval, resulting in the premature expression of motor programmes currently held in buffer.

Recent neurophysiological evidence from experiments involving non-human primates has revealed that successful suppression of reflexive saccades in the anti-saccade task is dependent on pre-stimulus reduction in excitability of saccade-related neurones in the superior colliculus (Everling *et al*., 1999) and the frontal eye fields (Everling and Munoz, 2000). Evidence from lesion studies also suggests that regions in the frontal eye fields and prefrontal cortex may be critical for suppression of reflexive pro-saccades in an anti-saccade task (Guitton *et al*., 1985; Heide and Kömpf, 1994; Pierrot-Deseilligny, 1995; Sommer and Tehovnik, 1997; Gaymard *et al*., 1998). Regardless of the identity of the cortical areas providing saccade suppression signals on anti-saccade trials, these pathways do not appear to be significantly impoverished in Tourette's syndrome subjects.

The basal ganglia may be responsible for the difficulty Tourette's syndrome subjects experience suppressing voluntary saccades by increasing cortical activity during delay periods. Parallel and overlapping circuits through the basal ganglia act as funnelling systems, integrating information from various areas of the cortex before projecting back to single cortical areas (Alexander *et al*., 1986). In doing so, the direct and indirect pathways through the basal ganglia normally cooperate competitively to ensure appropriate levels of signalling. If these pathways are not balanced properly, the intensity of resulting signals may be inappropriate, leading to altered levels of excitability in pathways involved in planning motor programmes. In a model of basal ganglia function, Hallet suggested that an overactive direct pathway gives rise to excessive voluntary movement, such as tics (Hallet, 1993). Although several hypotheses of neurotransmitter abnormalities in Tourette's syndrome have been proposed (for a review, see Singer, 1997), the theory of a dopamine abnormality is supported by most of the evidence. Singer (1997) suggested that dopamine hyperinnervation in the striatum of Tourette's syndrome patients may lead to increased activity of the direct pathway and decreased activity of the indirect pathway, via D_1 and D_2 receptors, respectively, which would cumulatively result in increased glutamatergic cortical excitation and inappropriate behaviour. Though reports of neuroanatomical pathology in Tourette's syndrome have varied (Demirkol *et al*., 1999; McAbee *et al*., 1999; Mostofsky 1999), reports of abnormalities of the striatum (Peterson *et al*., 1993; Singer *et al*., 1993; Hyde *et al*., 1995; Malison *et al*., 1995; Wolf *et al*., 1996) have been most consistent. It is therefore possible that an imbalance in the direct and indirect pathways through the basal ganglia result in abnormal corticostriatal circuits influencing areas which are involved in holding planned motor programmes in a buffer. Although the exact identity of these areas remains to be identified, the dorsolateral prefrontal cortex (Joseph *et al*., 1987; Fuster *et al*., 1997; Hasegawa *et al*., 1998), the supplementary motor area (Schall, 1991*a*) and the frontal eye fields (Schall, 1991*b*), are all areas which have delay activity in oculomotor tasks, and which also receive direct feedback integrated through the basal ganglia (Alexander *et al*., 1986).

Conclusions

Saccadic eye movements in Tourette's syndrome have characteristics which are significantly different from those in normal subjects and patients with other disorders with pathophysiology in the basal ganglia. Tourette's syndrome subjects do not have difficulty with the suppression of reflexive eye movements, but they do have difficulty with the prolonged suppression of planned motor programmes. This suggests that the disorder leads directly or indirectly to significant inefficiency or overactivity of pathways or areas that hold motor programmes in a buffer for later use, but does not significantly affect pathways or areas involved in the inhibition of simple motor reflexes.

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