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CHAPTER 31

Control of volitional and reflexive saccades in Tourette's syndrome

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Abstract: We hypothesized that Tourette's syndrome (TS) patients would display abnormal control of saccades because of overlap between brain areas suspected in TS pathophysiology and those involved saccade control. Subjects were required to look toward (pro-saccade) or away from (anti-saccade) a visual target. Saccadic reaction times were elevated among TS subjects in all tasks. The occurrence of reflexive pro-saccades in the immediate anti-saccade task was normal, suggesting that the ability to inhibit reflexive saccades was not impaired in TS. However, timing errors (eye movements made prior to GO signal in delayed saccade tasks) were increased in TS indicating that ability to inhibit or delay planned motor programs is significantly impaired in TS.

Introduction

Tourette's syndrome (TS) is an inherited condition characterized by the presence of motor and phonic tics that can be worsened by anxiety or fatigue (Singer, 1997) and improved by concentration (Jankovic, 1997). Although the physiological basis for tics and TS remains unknown, a substantial amount of evidence suggests a disorder of frontal–striatal circuits (Singer, 1997). TS 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 (Wolf et al., 1996), as well as increased dopamine binding within the caudate nucleus of the striatum (Singer et al., 1993; Hyde 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).

The saccadic system can be used effectively to investigate the neural control of movement. First, the movements can be measured relatively accurately and easily. Second, the premotor circuit controlling saccade generation is understood better than most other systems (Wurtz and Goldberg, 1989; Leigh and Zee, 1999; Munoz et al., 2000). Saccades are triggered via parallel descending pathways from the cerebral cortex to the superior colliculus and brainstem reticular formation. Saccades evoked by the sudden appearance of peripheral visual stimuli depend primarily upon direct projections from the visual and parietal cortices to the superior colliculus. Volitional saccades, made in the context of learned or remembered behavior, depend more upon the frontal cortex and its direct and indirect (via basal ganglia) projections to the superior colliculus and brainstem. In addition, regions of prefrontal cortex, the substantia nigra pars reticulata and superior colliculus may

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provide important fixation-related signals to suppress reflexive or unwanted saccades. Patients with pathophysiology in the frontal cortex and/or basal ganglia disorders display characteristic dysfunctions in saccade suppression and the execution of volitional saccades (Guitton et al., 1985; Lasker et al., 1987; Pierrot-Deseilligny et al., 1991; Fukushima et al., 1994; Kitawaga et al., 1994; Briand et al., 1999).

It has been suggested that TS may result from over activity of the direct pathway through the basal ganglia (Hallett, 1993). Activation of the direct pathway enhances saccade initiation, while activation of the indirect pathway inhibits saccade initiation (Hikosaka et al., 2000; Sato and Hikosaka, 2002). 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 TS (Wolf et al., 1996), the movement disorder may also be related to underactivity of the indirect pathway.

Because of the overlap in brain areas linked to saccade control and pathophysiology in TS, we hypothesized that TS patients will display abnormal control of voluntary saccadic eye movements (LeVasseur et al., 2001). The main aim of this paper is to describe some of the deficits in saccade control of TS subjects in a variety of tasks. We also contrast the TS results with results collected from other patient groups to gain insight into the etiology of the disorder.

Methods

Subjects

The details of the methodology have been described previously (Munoz et al., 1998a; LeVasseur et al., 2001). All experimental procedures were reviewed and approved by the Queen's University Human Research Ethics Board. Briefly, ten subjects with Tourette's syndrome (TS), ranging between 11 and 55 years of age, were recruited along with ten age- and sex-matched control subjects (Table 1). The TS subjects met clinical criteria for diagnosis and were referred by a neurologist. Control subjects reported no history of neurological or psychiatric disorders. No performance differences were obvious between groups of medicated and non-medicated TS subjects (see Table 1). 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 these medications from the system. Such a request can be disruptive to the subject's everyday life, especially when employment is involved.

TS has a high rate of comorbidity with other neurological disorders, such as attention-deficit hyper-

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 q.d.)	–
2	38	41	m	resperidone (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 b.d.)	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	–	–

activity disorder (ADHD) and obsessive–compulsive disorder (OCD) (Freeman, 1997; Singer, 1997). Several of the TS subjects in this study had comorbid 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 TS subjects, additional analysis was carried out in order to confirm that these extreme values were not responsible for the overall trend observed in the TS subjects.

Experimental paradigms

Subjects were required to participate in experiments on 3 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 (Fig. 1A, C, D), followed by two blocks (120 trials each) of immediate anti-saccades (Fig. 1B, C, D). On day 2, subjects performed three blocks (160 trials each) of randomly interleaved delayed pro- and anti-saccades (Fig. 1A,

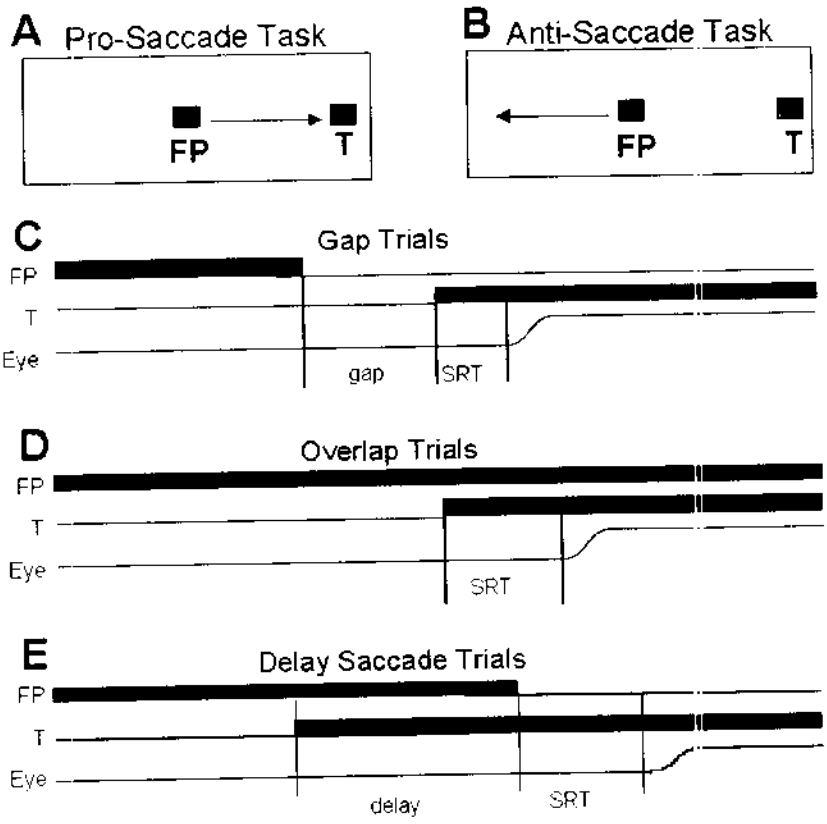

Fig. 1. Anti- and pro-saccade tasks. In the pro-saccade task (A) the subject was instructed to look from the central fixation point (FP) towards the eccentric target stimulus (T). In the anti-saccade task (B) the subject was instructed to look away from the eccentric target, towards its mirror position. 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 between 200 and 1000 ms. In the delayed saccade task, SRT was measured from FP disappearance to the onset of the eye movement.

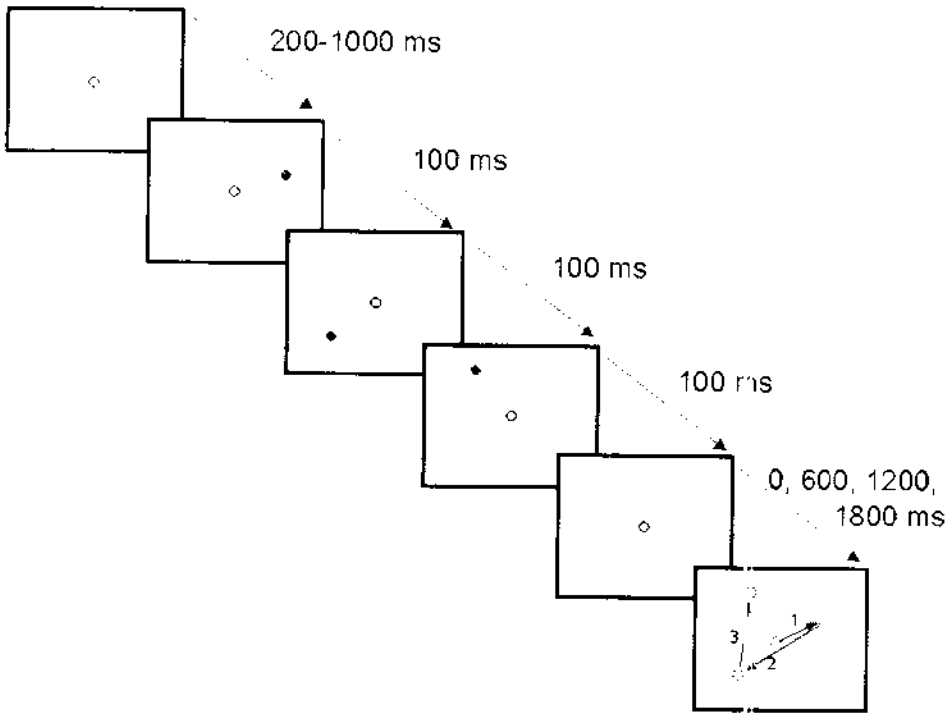

Fig. 2. Delayed memory-guided sequential saccade task. Subjects were instructed to fixate the central FP until it disappeared. On each trial, three target stimuli (1, 2, 3) were presented sequentially for 100 ms in three of the four quadrants of the visual field. Target location within each quadrant 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, 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.

B, E). On day 3, subjects performed two blocks (96 trials each) of delayed memory-guided saccade sequences to peripheral targets (Fig. 2). Ten subjects performed the immediate and delayed anti-/pro-saccade tasks but only seven subjects performed the delayed memory-guided sequential saccade experiment.

Two separate laboratories were used for these experiments. The immediate and delayed pro- and anti-saccade tasks were performed using electro-oculography to measure eye movements (Munoz et al., 1998a). Subjects were seated upright in a dental chair equipped with a head rest, that could be adjusted for height, such that they faced the center of a translucent visual screen 100 cm away. The experiments were performed in darkness and silence except for the controlled presentation of visual stimuli, which consisted of light emitting diodes (LEDs). A red LED (2.0 cd/m^2) was back projected onto the center of the translucent screen and served as a central fixation point (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 in a separate laboratory (see Cabel et al., 2000 for details). Subjects were seated 60 cm in front of a black display monitor on which the white FP (0.2 cd/m^2) 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 increases the propensity of reflexive responses (Fisher and Ramsperger, 1984; Munoz and Corneil, 1995), likely 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), color of the fixation point (red or green), and delay interval (200, 400, 600, 800, 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 center 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, 1800 ms). Each subject performed 20 practice trials before recording began.

Recording and analysis

Horizontal eye movements were measured using direct current electro-oculography in the immediate and delayed anti- and pro-saccade tasks. 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 for subsequent off-line analysis

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 sac-

cade 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 less than 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 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; see Fisher et al., 1993 for review) in the anti- and pro-saccade tasks, and percentage of timing errors (saccades executed prior to disappearance of FP) in the delayed saccade task. Normally distributed data was analyzed with ANOVA tests and non-normally distributed data analyzed using non-parametric, Mann–Whitney tests, comparing results from all TS subjects to all age- and sex-matched controls.

In the delayed memory guided saccade sequence task, eye position data were collected using a video-based eyetracker (Eyelink, SR Research Ltd.) that was mounted on the subject's head with an adjustable headband (see Cabel et al., 2000 for details). 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 analyzed to determine the direction of the first saccade in which timing error movements were made. The percentage of timing and sequence errors were calculated for each subject. Distribution of the data was reviewed. Normally distributed data was analyzed with ANOVA tests and non-normally distributed data analyzed using non-parametric, Mann–Whitney tests, comparing results from all TS subjects to all age- and sex-matched controls.

Results

Immediate pro-saccade task

Fig. 3 illustrates representative eye position traces recorded from a TS subject and an age- and sex-matched control subject in the immediate pro-saccade task. Note that both subjects were able to execute the tasks properly. In addition, the saccades of the TS subject tended to be initiated with reaction times greater than that of the control subject. The mean SRT in the immediate pro-saccade task was elevated among TS subjects ($F(1,76) = 28.15$, $P < 0.001$; see Fig. 4A). Table 2 contains mean values for SRT, the gap effect, intra-subject variance in SRT expressed as the coefficient of variation, and the percentage of express saccades for TS and control subjects in the immediate pro-saccade task. The percentage of express saccades during gap trials (Fig. 5A) was reduced among TS subjects ($U = 122.00$, $P < 0.05$). Intra-subject variance was greater in TS 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 vs. overlap) ($F(1,76) = 0.08$, $P > 0.7$), indicating that the gap effect was not altered in the TS subjects.

Immediate anti-saccade task

Due to the nature of TS, we hypothesized that TS subjects would have difficulty suppressing reflexive saccades. Fig. 3B illustrates eye position traces from a TS and control subject showing that the subject could perform the anti-saccade task correctly.

TABLE 2

Results from the immediate pro-saccade task

	SRT (ms)	Gap effect (ms)	CV	Express (%)
Patients	287 ± 12 [a]	60 ± 22	30 ± 9 [a]	3 ± 6 [a]
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 direction errors in TS and control subjects.

[a] Significant difference from controls.

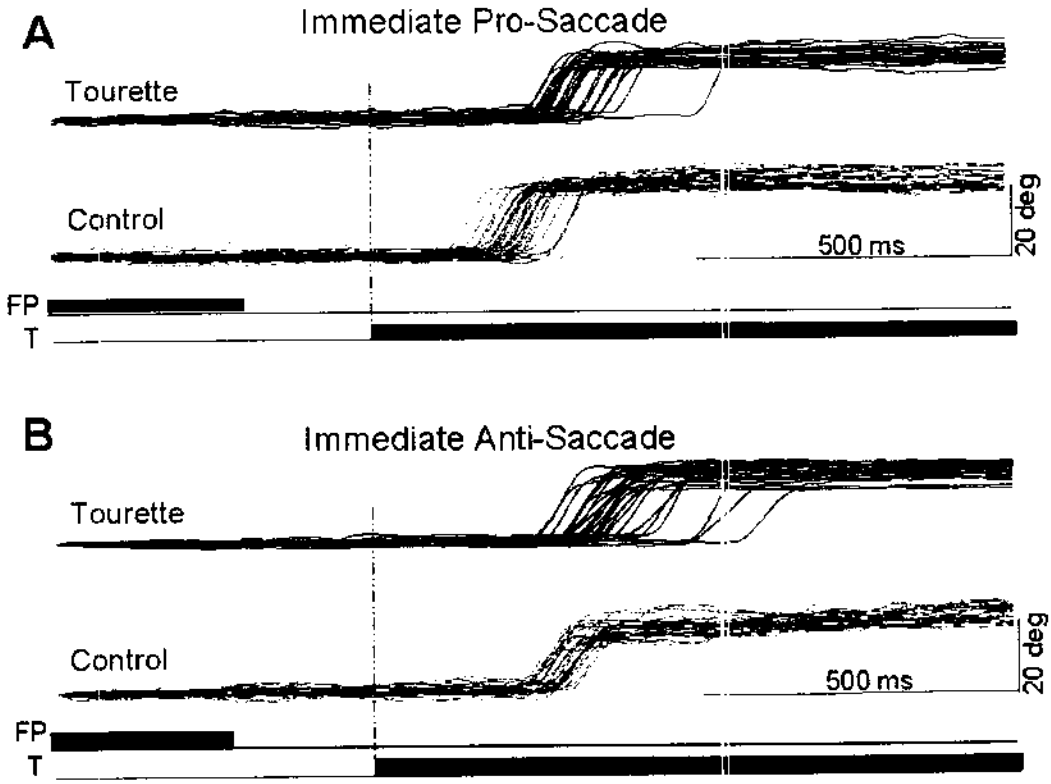

Fig. 3. Eye position traces recorded from a representative TS and control subject performing the immediate pro-saccade task (A) and immediate anti-saccade task (B).

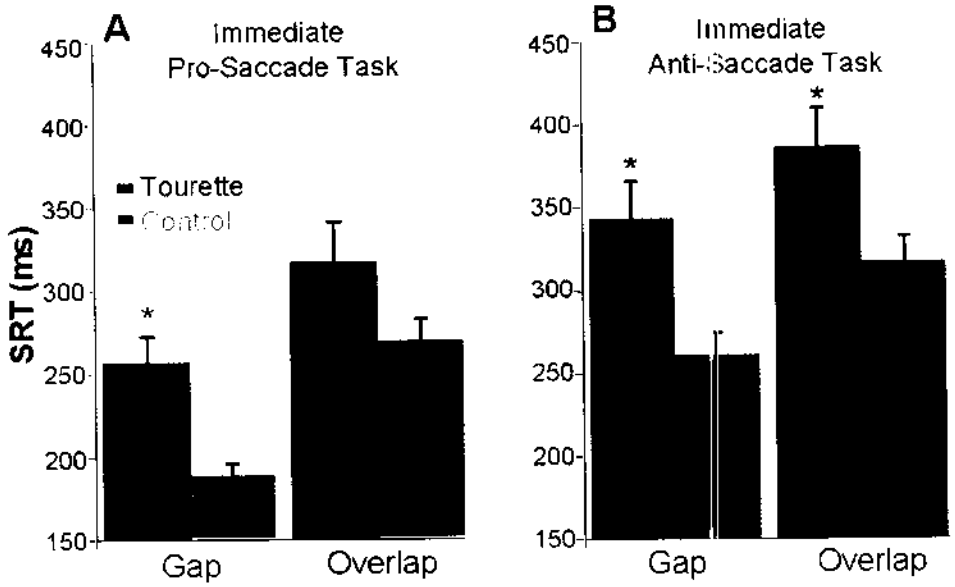

Fig. 4. Mean SRT (± standard error) for control and TS subjects in the immediate pro-saccade task (A) and anti-saccade task (B) with gap and overlap conditions. * Statistically significant difference from control subjects (*t*-test, $P < 0.05$).

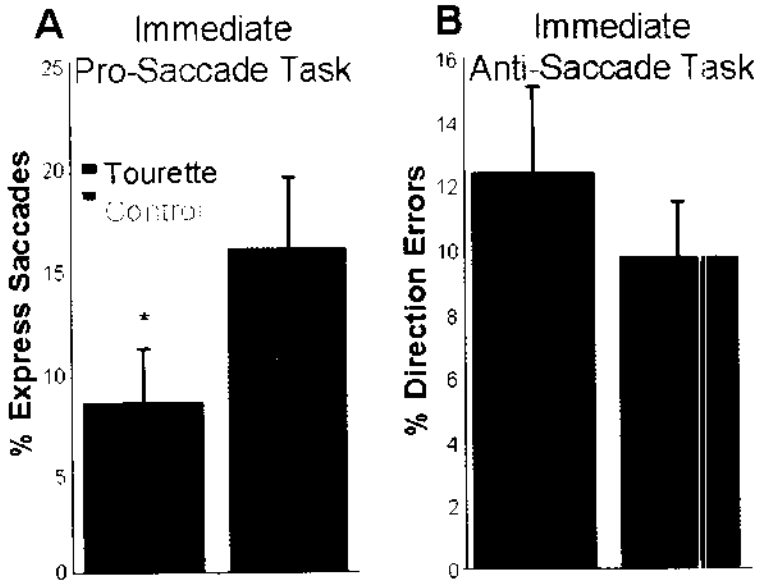

Fig. 5. (A) Percentage of express saccades elicited in the immediate pro-saccade task. (B) Percentage of direction errors made in the immediate anti-saccade task. * Significant difference between TS and control subjects ($P < 0.05$).

TABLE 3

Results from the immediate anti-saccade task

	SRT (ms)	Gap effect (ms)	CV	Direction errors (%)
Patients	365 ± 12 [a]	42 ± 7	29 ± 14 [a]	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 TS and control subjects.

[a] Significant difference from controls.

The percentage of direction errors in the immediate anti-saccade task was not significantly greater in TS subjects than control subjects ($U = 730$, $P > 0.4$; see Figs. 3B and 5B). TS subjects did have significantly greater mean SRT than control subjects ($F(1,76) = 32.9$, $P < 0.001$; see Fig. 4B, Table 3). Intra-subject variance of SRT was significantly greater for TS subjects ($U = 426.5$, $P < 0.001$). The gap effect (mean overlap SRT − mean gap SRT) was not significantly different between TS and control subjects ($F(1,76) < 1$, $P > 0.4$).

Delayed pro-/anti-saccade task

When subjects were asked to delay saccades, TS subjects made more timing errors than control subjects on both pro-saccade ($U = 19.00$, $P < 0.05$, Fig. 5A) and anti-saccade trials ($U = 22.00$, $P < 0.05$; Fig. 6B). A timing error consisted of a saccade that was initiated before disappearance of the FP or within the first 90 ms after FP disappearance (i.e. anticipating FP disappearance). Although TS subjects did not make more direction errors than controls in the immediate anti-saccade task (Fig. 5B), they did make significantly more direction errors on anti-saccade trials in the delayed saccade task ($U = 22.00$, $P < 0.05$). Mean SRT of correct delayed saccades were significantly greater among TS subjects ($F(1,54) = 21.1$, $P < 0.001$).

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. 7). As the duration of the delay interval increased, the percentage of correct trials decreased and the percentage of timing errors increased for TS subjects, but remained relatively constant for

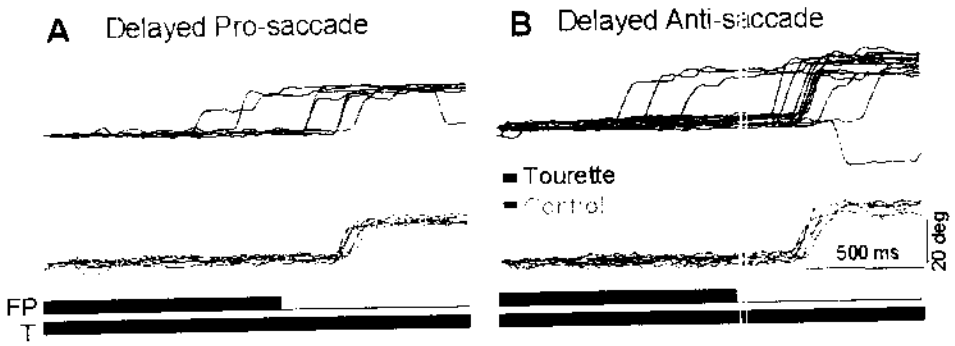

Fig. 6. Eye position traces recorded from a representative TS and control subject performing the delayed pro-saccade task (A) and delayed anti-saccade task (B).

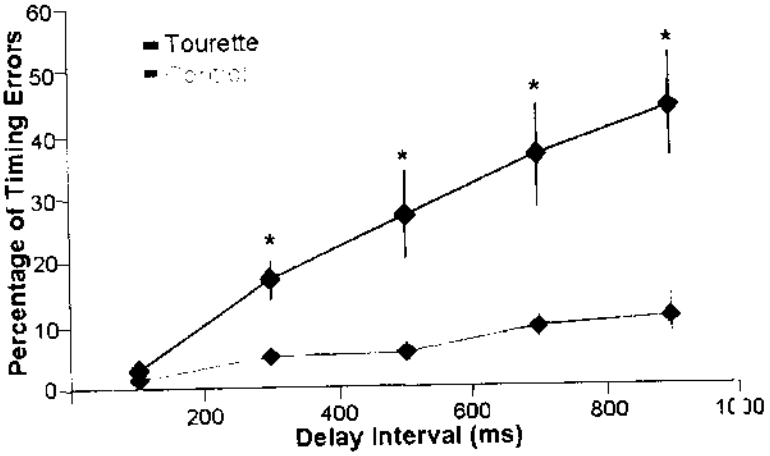

Fig. 7. Percentage (± standard error) of timing errors for each delay interval used in the delayed pro-/anti-saccade task. * Significant difference between TS and control subjects ($P < 0.05$).

controls. Among both TS and control subjects, the number of direction errors diminished with increased delay intervals (see LeVasseur et al., 2001). These results indicate that TS subjects experienced difficulty delaying the appropriate eye motor program for prolonged periods of time, rather than difficulty inhibiting the eye motor program altogether.

Delayed memory guided sequential saccade task

The data in the immediate and delayed pro- and anti-saccade tasks suggest that TS 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 TS 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 TS 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 TS sub-

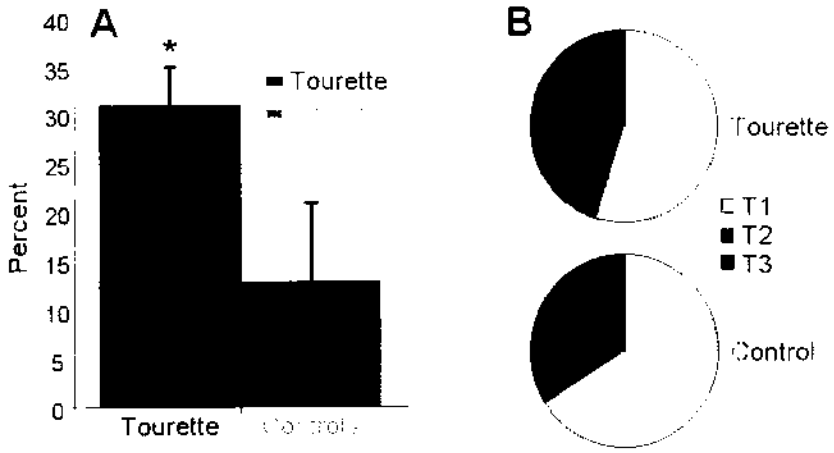

Fig. 8. (A) Percentage of timing errors in the delayed memory-guided sequential saccade task. * TS subjects made significantly more timing errors (*t*-test, $P < 0.05$). (B) Direction of timing errors. Timing errors were made in the direction of the first target (T1) more often than to the second (T2) or third (T3) target of the remembered sequence for both TS and control subjects.

jects, ($U = 11.00$, one-tailed $P < 0.05$; Fig. 8A). Post hoc pair-wise comparisons for direction of timing errors showed that both TS and control subjects ($F(1,12) = 2.00$, $P > 0.15$) most often looked to the first target, rather that the second or third target ($F(2,24) = 23.72$, $P < 0.001$; Fig. 8B). These findings indicate that for both TS and control subjects, timing errors result from a failure to suppress a planned motor program rather than a simple reflexive movement to the most previous sensory stimulus.

The percentage of appropriately delayed trials which had the correct sequence was also examined. On average control subjects performed the correct sequence on 67% of delayed trials, while TS 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 analyzed for these trials (Table 4). 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 TS and control subjects. These results indicate that, although TS subjects had difficulty with the timing of the sequence, they did not have significant difficulty with execution of the motor plan itself.

TABLE 4

Mean (± standard error) distance in eye position from targets T1, T2, and T3 for correct trials in the delayed memory-guided sequential saccade task in TS and control subjects

	Distance from T1 (degrees)	Distance from T2 (degrees)	Distance from T3 (degrees)
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 TS and control subjects.

Medication and comorbidities

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

Longer latencies were observed for TS compared to 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 likely due to the small number of subjects in this subgroup ($n = 4$). It therefore does not appear that medication or comorbidities were responsible for the longer latencies observed in TS subjects. Similarly, the lower percentage of express saccades in TS subjects was consistent in non-medicated and non-comorbid subgroups. In all subgroups analyzed, the percentage of direction errors during the anti-saccade task remained similar in TS and control subjects, and the percentage of timing errors in the delayed saccade task remained higher in TS subjects. It can therefore be concluded that the TS disorder itself was responsible for all of the above-mentioned findings.

In contrast, it is possible that medication and/or comorbid conditions enhanced the increase in intra-subject variance observed in TS subjects. Though intra-subject variance remained higher among TS subjects in all subgroups, the difference was reduced below significance in both non-comorbid (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-comorbid group had $n = 6$. Three of the four subjects with comorbid 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 comorbidities are valid issues to be taken into consideration, though they were not responsible for trends observed in SRT, express saccades, direction errors, or timing errors among TS subjects.

Discussion

We have demonstrated that specific characteristics of saccade initiation are impaired in TS subjects. We emphasize three main findings. First, TS subjects demonstrated profound difficulties in delaying saccades in the delayed and memory-guided sequential saccade tasks. Second, saccadic reaction times were significantly greater in TS subjects. Third, the percentage of direction errors in the immediate anti-saccade task was unaffected in TS subjects. From these findings we conclude that TS subjects had difficulty delaying planned motor programs but not reflexive responses. We first discuss these data in relation to previous findings and then provide a new theoretical framework to consider the dysfunction of TS.

Saccadic abnormalities in TS

We observed that TS subjects experienced difficulty delaying purposeful saccades for extended periods of time in the delayed and memory tasks. These timing errors were not the result of an inability to suppress reflexive saccades. In addition, the motor programs 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 TS 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 TS across these motor systems. The TS subject in the study of Flanagan et al. (1999) was instructed to wait for a GO signal before lifting an object up or down with a single arm movement. 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 program until the appropriate time.

Previous studies have observed elevated SRTs in TS subjects. Straube et al. (1997) reported a general elevation of SRTs in TS subjects in several different oculomotor paradigms. Although Farber et al. (1999) reported significantly elevated SRTs in TS subjects during anti-saccade overlap trials, they reported normal SRTs in TS subjects during a pro-saccade task. This inconsistency between results may be related to task instruction. In the study of Farber et al. (1999), subjects were instructed to perform saccades as rapidly as possible.

The results in the present study are also consistent with the finding of Straube et al. (1997) that the

ability to inhibit reflexive pro-saccades, indicated by the frequency of direction errors in the immediate anti-saccade task, is not impaired in TS subjects. Although Farber et al. (1999) reported an elevated number of direction errors in the anti-saccade task, they noted that this difference was caused by only 19% of the TS subjects, and several of their subjects had comorbid signs of ADHD or OCD. Narita et al. (1997) also reported in a case study that one TS subject was unable to perform the anti-saccade task. 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 TS subjects during delayed anti-saccade trials was likely 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 TS subjects during anti-saccade trials in the delay task.

Comparison with other neurological/psychiatric disorders

Different disorders of the basal ganglia, such as ADHD (Ross et al., 1994; Munoz et al., 1998b, 1999), Huntington's disease (Lasker et al., 1987; Tian et al., 1991; Rubin et al., 1993; Lasker and Zee, 1997), 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) present sometimes overlapping yet distinct manifestations in terms of saccade abnormalities. ADHD subjects have difficulties suppressing reflexive pro-saccades in an immediate anti-saccade task and they also trigger an excessive number of intrusive saccades during periods of instructed fixation (Munoz et al., 1998b, 1999). ADHD subjects also respond reflexively in a memory delayed saccade (Ross et al., 1994) tasks. We hypothesize that ADHD subjects lack a saccade suppression signal.

Recent models of saccade initiation (e.g. Carpenter and Williams, 1995; Trappenberg 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 (see Fig. 9). In normal individuals performing a delayed saccade task (solid lines in Fig. 9), the appearance of the peripheral target generates a phasic activation that will not reach saccade threshold. This information can then be held in a buffer until after the FP disappears and the correct saccade is triggered.

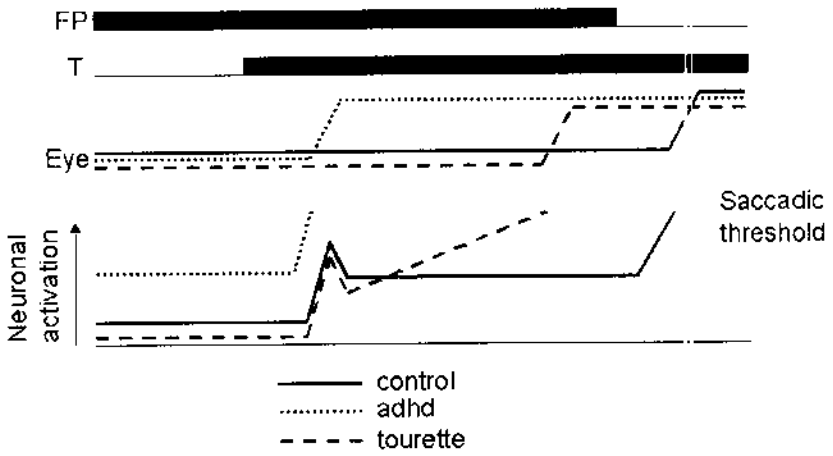

Fig. 9. Hypothetical saccade response and neural function accumulating to a threshold required for saccade initiation in control (solid line), ADHD (dotted line), and TS (dashed line) subjects. See text for additional details.

In ADHD subjects performing a delayed saccade task (dotted lines in Fig. 9), we believe that, because there is an impairment in saccade suppression, there is an elevated baseline so that it is easier to trigger a saccade immediately following the appearance of the peripheral target. The timing errors produced by TS subjects are very different; they are triggered long after target appearance (see Figs. 6 and 7). In addition, TS subjects have longer reaction times and fewer express saccades than age-matched control subjects. Therefore, we speculate that in TS subjects performing the delayed saccade task (dashed lines in Fig. 9), there is a reduced baseline so that it is harder to initiate a saccade. However, after the appearance of the saccade target, the information cannot remain in the buffer without drifting toward the saccade threshold such that a saccade can be triggered before the GO signal (FP disappearance) on long delay trials. Thus, the dysfunction in ADHD and TS is very different and suggests very different pathophysiology. The impaired saccade suppression ability in ADHD leads to an elevated baseline, while the inability to keep a motor program stored in buffer is impaired in TS.

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 prestimulus reduction in excitability of saccade-related neurons 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 et al., 1995; Sommer and Tehovnik, 1997; Gaymard et al., 1998). We hypothesize that in ADHD, these saccade suppression signals are weaker so that reflexive saccades are triggered too easily. These pathways appear to function normally in TS.

The basal ganglia may be responsible for the difficulty TS subjects experience suppressing voluntary saccades by increasing cortical activity during delay periods. Parallel and overlapping circuits through the basal ganglia act as funneling 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 signaling. 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 programs. In a model of basal ganglia function, Hallett (1993) suggested that an overactive direct pathway gives rise to excessive voluntary movement, such as tics. Although several hypotheses of neurotransmitter abnormalities in TS have been proposed (see Singer, 1997 for review), the theory of a dopamine abnormality is supported by most of the evidence. Singer (1997) suggested that dopamine hyperinnervation in the striatum of TS 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 behavior. Though reports of neuroanatomical pathology in TS have varied (Demirkol et al., 1999; McAbee et al., 1999; Mostofsky et al., 1999), reports of abnormalities of the striatum (Singer et al., 1993; Hyde 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 programs in a buffer. Although the exact identity of these areas remains to be identified, the dorsolateral prefrontal cortex (Joseph and Barone, 1987; Fuster, 1997; Hasegawa et al., 1998), the supplementary motor area (Schall, 1991a), and the frontal eye fields (Schall, 1991b), 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 TS have characteristics which are significantly different from those in normal subjects and patients with other disorders with pathophysiology in the basal ganglia. TS subjects do not have difficulty with the suppression of reflexive eye movements, but they do have difficulty with the prolonged suppression of planned motor programs.

This suggests that the disorder leads directly or indirectly to significant inefficiency or overactivity of pathways or areas that hold motor programs 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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