Saccadic performance characteristics and the behavioural neurology of Tourette’s syndrome

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Abstract

Objective—To better understand the neuropathological correlates of Tourette’s syndrome (TS), measures of saccadic eye movement performance were examined among patients with TS.

Methods—A case-control design was used. Twenty one patients with DSM-IV TS (mean age 40.6 years (SD 11.0); 38% female) mainly recruited from UCSD Psychiatry Services, and a community based sample of 21 normal subjects (mean age 34.6 years (SD 13.4); 43% women) participated in this study. Participants were administered ocular motor tasks assessing visual fixation, and the generation of prosaccades, predictive saccades, and antisaccades. Saccadic reaction time, amplitude, duration, and mean and peak velocity were computed. Intrusive saccades during visual fixation and the proportion of correct antisaccade responses were also evaluated.

Results—The groups had similar visual fixation performance. Whereas patients with TS generated prosaccades with normal reaction times and amplitudes, their saccade durations were shorter and their mean velocities were higher than in normal subjects. During a prosaccade gap task, patients with TS exhibited an increased proportion of anticipatory saccades (RTs<90). The proportion of “express” saccades (90<RTs<135) did not differ between groups. Patients with TS had fewer correct antisaccade responses than did normal subjects, an effect accounted for by 19% of the patients. Antisaccade reaction times among patients with TS were increased during an overlap version of the task.

Conclusion—These findings suggest that TS mildly affects the ocular motor control circuitry associated with saccade inhibition.

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Tourette’s syndrome (TS) is characterised by the presence of chronic motor and vocal tics which typically appear in late childhood or early adolescence.1 The symptomatology of TS is associated with dysfunction of basal ganglia-thalamocortical circuitry.2–6 Consistent with this hypothesis, neuroimaging data suggest that patients with TS have decreased metabolic activity in striatal and paralimbic regions (orbitofrontal and insular cortices, and parahippocampal gyrus).7–13 and perhaps increased metabolic activity in the premotor cortex.7 The reported abnormalities in these regions are theoretically consistent with difficulties inhibiting unwanted motor and vocal behaviours.14–16

Saccadic eye movement performance has been used to evaluate the functional integrity of corticosubcortical circuitry among several patient populations.17–25 For laboratory testing, saccades can be described on a continuum from more “simple” (for example, prosaccades generated to a novel peripheral stimulus) to more “cognitively complex” responses (for example, predictive, memory guided, and antisaccades).26 22 25 28 Performance on saccade tasks may be used to evaluate hypotheses about the location(s) of neuropathology.22 23 27–50 Administering both simple and cognitively complex saccade tasks to patients with TS, therefore, may be helpful for investigating the neurological correlates of this disorder.

Because TS is associated with behavioural disinhibition, saccade tasks assessing this phenomenon may be particularly useful for assessing the adequacy of ocular motor control among patients with this illness.17 27 50–53 Fixation tasks require subjects to maintain gaze at a specified location for a requisite time interval. Saccadic intrusions during fixation may be an index of failed inhibition.19 22 Excessive anticipatory responses during prosaccade and predictive saccade tasks may also be indices of failed inhibition.6 Antisaccade performance is also used to assess inhibitory abilities.23 31 Correct responses are generated to the mirror locations (same amplitude, opposite direction) of peripheral cues, and antisaccade errors (saccades to the peripheral cues) are typically interpreted as inhibitory failures.

Previous research on eye movement performance among patients with TS is both sparse and difficult to interpret. Lasker et al examined saccadic system functioning among patients with Huntington’s disease and patients with TS (n=8).19 20 For most analyses, the ocular motor data from patients with TS were pooled with those of normal subjects and subjects with developmental dyslexia. The graphically presented data for a response suppression task in the study of Lasker et al showed patients with TS falling between the normal and Huntington’s samples (see their fig 2, p 367).32

Bollen et al reported normal smooth pursuit and saccadic eye movements among 28 children with TS.34 This report did not include measures of central tendency or variability, lacked formal statistical analyses, and did not include data from a normal comparison
sample. In a case study by Narita et al, a 13 year old boy with TS exhibited hypometric saccades.39 Additionally, the patient had a marked inability to generate antisaccades compared with a healthy 9 year old subject. Straube et al reported that 10 adult patients with TS had normal prosaccade metrics, but had increased antisaccade latencies, reduced antisaccade peak velocities, and had difficulty generating correct sequences of memory guided saccades.30

Previous studies provided a useful background for planning the current investigation. To further evaluate ocular motor behaviour in TS, adult patients and normal subjects were administered tasks assessing visual fixation, and the generation of prosaccades, predictive saccades, and antisaccades. The behavioural symptoms and associated neuropathological theories of TS suggest that these patients may exhibit deficits of saccade inhibition indicative of prefrontal cortex or basal ganglia pathology.

Methods

SUBJECTS

Twenty one patients (mean age 40.6 (SD 11.0), range=18–58; 38% women) with DSM-IV TS1 and 21 normal comparison subjects (mean age 34.6 (SD 13.4), range=21–59; 43% women) participated in this study. Participants (mean age 34.6 (SD 13.4), range=21–59; 43% women) were recruited from UCSD Psychiatry Services and San Diego chapters of the Tourette Syndrome Association. They were evaluated with the Minnesota multiphasic personality inventory (MMPI),41 and were screened for a history of psychiatric disorders among their first degree biological relatives. Only subjects without a major affective disorder, a psychotic disorder, an elevation (T score>70) on MMPI scales L, F, 2, 6, 7, 8, the MacAndrews alcoholism and Wiggins psychoticism scales, a Goldberg index>60,42 or a family history of psychotic disorder, suicide, or admission to a psychiatric hospital were asked to participate.

APPARATUS

Ocular motor data were collected in a quiet, darkened (<0.1 cd/m²) room. Horizontal eye movements were recorded using an Eye Trak Model 210 eye movement monitor and infrared spectacles (4 ms time constant) mounted on eye glass frames (Applied Science Laboratories, Waltham, MA, USA). The subjects’ head position was stabilised using a bite bar. Stimuli were presented on a high resolution Zenith flat surface colour monitor (model ZCM-1792) positioned 43 cm from the subjects’ eyes. Eye movement recordings from both eyes were digitised at 256 Hz using a Data Translation (DT2821) A to D board connected to an IBM compatible computer. Recordings were displayed on a video screen so performance could be monitored continuously by the experimenter.

PROCEDURE

Subjects made an impression on dental wax affixed to the bite bar. They put on the infrared spectacles that were secured with an elastic band placed around the head. Subjects were then seated in front of the video monitor and positioned themselves on the bite bar. The background luminance (0.1 cd/m²), and size (1° of visual angle, within which was a small central spot subtending a few minutes of arc) and luminance (1.6 cd/m²) of the stimuli remained constant throughout testing. Before each task, subjects were presented with calibration targets at central fixation and ±5, 10, 15, and 17.5°. Order of task presentation was constant and identical to that described below (fig 1).

Fixation task

A trial began with a target presented at the central fixation. Subjects were told to maintain central fixation for the requisite time period (30 s). During fixation, ±4 or 8° distractor stimuli were presented for 100 ms at pseudorandom time intervals (every 2.5–4.5 s). Three blocks were presented with eight single distractors per block.

Prosaccade, midpoint task

The target jumped to different amplitudes (±5, 10, 15, 20, 25, 30, and 35°; centred on central fixation) with a 1.5–2.0 s intertrial interval. Subjects were told to find the target as quickly and accurately as possible. Four blocks of 28
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The target alternated constantly at 0.4 Hz between ±5, 10, or 15° positions. Subjects were told that the target would move in a regular fashion, and they were instructed to keep their eyes on the target as much as possible. Trials were presented for 22 cycles under the three amplitude conditions. Order of presentation for the three conditions was counterbalanced within groups.

Antisaccade task

A trial began with the target at central fixation. Following a 2.0–2.5 s intertrial interval, the target was extinguished and a cue was illuminated for 1000 ms at either ±8 or 16° from central fixation. Subjects were instructed to generate a saccade to the equal and opposite location of the cue. After 1 s, a 100 ms flash appeared at the cue’s mirror location to reinforce the accuracy component of the task. The stimulus then returned to central fixation. There were two different fixation conditions: gap and overlap. During gap trials, the illumination of the peripheral cue was preceded by a 200 ms gap; during overlap trials, the central fixation point remained illuminated for 200 ms after cue presentation. A practice block of eight trials was administered to each subject before the test blocks. Four test blocks of 20 trials were presented with a pseudorandom order of cue presentation (10 trials for each cue location, under each condition in each direction).

OCULAR MOTOR ANALYSES

Waveforms were displayed using ASYST (Version 4.0; Keithley Instruments, Inc). Digitised data were low pass filtered in the frequency domain at 60 Hz. Data from the eye with the cleanest recordings were used for all analyses. For each trial, the position, velocity, and acceleration arrays were presented simultaneously on a high resolution colour monitor. Only trials free of artifacts were scored. Averaging over all tasks, there was a modest difference in the number of usable trials between groups (mean TS 376.4 (SD 44.7); mean normal 417.9 (SD 49.7)). Nevertheless, all subjects had ample data available from which to estimate their “true” performance on all ocular motor tasks.

Our infrared recordings are linear through roughly ±16°; degrees of visual angle/number of digital units is typically a decelerating function for more extreme values (when predicting degrees of visual angle from digital units, the function is sigmoid in shape). To accurately change digital units into degrees of visual angle, we calculated first to fifth order polynomials, and visually inspected their fit to the fixation data. Digitised ocular motor data were then transformed to degrees of visual angle via application of the best fitting function. Each saccadic event was bracketed by the scorer, and reaction time, accuracy, duration, and mean and peak velocity were automatically computed. Saccadic reaction time was defined as the latency (ms) between target movement and eye velocity increase above 10%.

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in degrees of visual angle. Saccadic duration was defined as the time interval (in ms) between eye velocity increase above 10°/s and subsequent eye velocity decrease below 10°/s. Peak velocity was defined as the maximum velocity within the saccade duration window. Only saccades of at least 90 ms latency were considered stimulus triggered events. Spearman correlations were calculated, when appropriate, by taking the examine significant erctions and As with Huynh-Feldt adjusted degrees of repeated measures analyses of variance (ANO-

**Fixation task**

For each distractor stimulus, the interval from 250 ms before to 500 ms after stimulus presentation was bracketed by the scorer. Saccadic intrusions were identified based on their characteristic position, velocity, and acceleration profiles. To compare groups, the proportion of usable trials during which a saccadic intrusion occurred was calculated across distractor blocks (six blocks with four distractors each).

**Prosaccade tasks**

The interval from 250 ms before to 500 ms after the target jump was analysed. Prosaccades were defined as the first scorable saccadic event that occurred after fixation point offset.

**Predictive saccade task**

The predictive saccade tasks were divided into five successive blocks (four cycles in each block, excluding the first and last cycles). This approach allowed us to evaluate whether subjects learned to predict target relocation over successive trials. Because it is difficult to distinguish small intrusive and corrective saccades from hypometric refixation efforts, only saccades with amplitudes of at least 10° of the total target excursion were scored (for example, saccades >3° of visual angle for the ±15° condition). Scorable events were defined as those in the direction of target motion from 1000 ms before to 1000 ms after target relocation.

**Antisaccade task**

For the antisaccade task, the interval from 250 ms before to 1000 ms after cue presentation was analysed. The proportion of useable trials with a correct response (a saccade generated to the opposite screen location of the cue), and the metrics of both correct and error responses (saccades generated to the peripheral cue) were calculated.

**Results**

**DATA ANALYSES**

Data were analysed using mixed design repeated measures analyses of variance (ANO-VAs) with Huynh-Feldt adjusted degrees of freedom for the within subjects factors. Helmert contrasts and t tests were used to further examine significant effects. Effect sizes were calculated, when appropriate, by taking the difference between the patient and normal group means and dividing by the SD of the normal group. Spearman correlations were calculated to examine the relations between saccade and clinical symptom variables.

**PRELIMINARY ANALYSES**

The groups were similar in age and sex. There were no significant correlations between any of the ocular motor and clinical symptom variables. Patients’ medication status was also not correlated with any ocular motor measure. Finally, there were no significant differences on saccade variables between patients with TS with and those without a history of attention deficit hyperactivity symptoms.

**FIXATION TASK**

The proportion of saccadic intrusions was analysed using a group (TS, normal) by block (1–6) repeated measures ANOVA. The groups did not significantly differ on the proportion of saccadic intrusions across distractor blocks (mean TS 0.04 (SD 0.07), range=0.00–0.27; mean normal 0.02 (SD 0.04), range=0.00–0.14; effect size=0.50). Only a few subjects had intrusive saccades during fixation: 33% (seven of 21) of the patients with TS and 29% (six of 21) of the normal subjects. There were no other significant effects on variables from this task.

**PROSACCADE, MIDPOINT TASK**

Group by target amplitude (5, 10, 15, 20, 25, 30, 35) by direction (left, right) repeated measures ANOVAs were used to evaluate saccadic reaction times, amplitudes, durations, and mean and peak velocities. For saccade duration, there was a significant main effect of group (F(1,40)=4.59, p=0.04). Patients with TS generated saccades with shorter durations than did normal subjects (mean TS 95.9 (SD 21.9); mean normal 110.5 (SD 22.2); effect size=0.66). There were no other significant effects on variables from this task.

Main sequence functions were also generated for each group (collapsing over saccade direction) to further evaluate saccade metrics. Linear (y=a*x+b, where a is the slope and b is the y intercept) and exponential functions (y = a*[1-exp(-x/b)], where a is the estimated asymptotic value and b is the rate of approach) were fitted to each subjects’ data to examine the relations between saccade amplitude and target amplitude (linear); saccade duration and saccade amplitude (linear); and saccade mean and peak velocity and saccade amplitude (exponentials). Weighted least squares regressions were used to estimate parameters. Consistent with the ANOVA results, the only significant difference was on y intercept values for the saccade duration saccade amplitude relation (t(40)=2.32, p=0.03 (mean TS 46.8 (SD 14.1); mean normal 58.6 (SD=18.7); effect size=-0.63).

**PROSACCADE, GAP TASK**

Saccades were categorised by reaction time as anticipatory (<90 ms), express (90–135 ms), regular (135–250 ms), or long reaction time events (>250 ms) based on saccadic reaction time distributions from previous publications. Data were analysed using a group by type (anticipatory, express, regular, long reaction time) by direction (left, right) repeated measures ANOVA. There was a
significant group by saccade type interaction ($F(3,120)=4.04$, $p=0.02$). Patients with TS generated a greater proportion of anticipatory saccades, $t(40)=2.28$, $p=0.03$ (mean TS 0.16 (SD 0.10); mean normal 0.10 (SD 0.07); effect size=0.86) and a smaller proportion of regular reaction time saccades than did normal subjects, $t(40)=2.48$, $p=0.02$ (mean TS 0.59 (SD 0.15); mean normal 0.71 (SD 0.15); effect size=-0.80). The patients with TS also had more saccadic events during the catch trials than did normal subjects, $t(40)=2.85$, $p=0.007$ (mean TS 0.032, SD 0.018; mean normal 0.017, SD 0.016; effect size=0.94). There were no other significant effects on proportions of saccade types (fig 2).

Group by type by direction ANOVAs were also used to analyse saccade amplitudes, durations, and mean and peak velocities during gap trials. There was a significant main effect of group for saccade duration, $F(1,40)=7.93$, $p=0.008$. Similar to the midpoint results, patients with TS generated saccades with shorter durations than did normal subjects (mean TS 58.5 (SD 13.4); mean normal 71.9 (SD 17.2); effect size=-0.78). There were no other significant effects for the saccade metrics variables.

PREDICTIVE SACCADe TASK
Predictive saccade variables were analysed using group by block (1–5) by target amplitude (5, 10, 15) by direction repeated measures ANOVAs. For saccade reaction times, there was a significant main effect of block; $F(4,160)=5.95$, $p<0.001$. Subjects had slower reaction times during the first block than during the remaining blocks (fig 3). There were no other statistically significant effects for the predictive saccade variables.
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Discussion

The present results suggest that TS is associated with a modest difficulty with saccadic inhibition. On average, patients with TS had more anticipatory saccades during prosaccade gap trials and had fewer correct antisaccade responses than did normal subjects. Patients with TS also had shorter saccadic durations across the two prosaccade tasks. In addition, a linear combination of prosaccade durations, proportion of anticipatory saccades during a gap task, and proportion of correct antisaccade responses captured a larger amount of between group variation than any single saccadic variable. These results are consistent with the theory that TS is associated with behavioural disinhibition that is a consequence of dysfunction of basal ganglia thalamocortical circuitry.  

Saccadic responses are supported subcortically by superior colliculus and basal ganglia structures and cortically by posterior parietal and dorsolateral frontal cortex. 22 23 The superior colliculus participates in visual fixation and saccade generation. 51-54 On the one hand, patients with TS had normal proportions of saccadic intrusions during visual fixation and had prosaccades with normal reaction times and amplitudes, so it is unlikely that this disorder is associated with gross impairment of the superior colliculus. On the other hand, patients with TS had shorter duration saccades than did normal subjects. As expected based on the duration results, patients with TS also had higher mean saccade velocities than normal, although this effect was not significant (mean TS 176.3 (SD 32.0); mean normal=157.8 (SD 37.0); effect size=0.50). Shorter saccade durations and higher saccade mean velocities are found among non-human primates after pharmacological deactivation of collicular fixation cells. 55 The neurophysiological correlates of this behavioural effect among patients with TS are uncertain. Deactivation of fixation cells tends to disinhibit their collicular burst cell afferents, so perhaps the input to the former is aberrant in TS. Additional research carefully examining the duration characteristics of prosaccades among patients with TS will be necessary to better understand this phenomenon.  

Dorsolateral frontal cortex circuitry (including both prefrontal cortex and frontal eye fields) plays an important part in generating cognitively complex saccades (for example, predictive and antisaccades). 44 45 Performance during gap, predictive, and antisaccade tasks has been useful for examining the integrity of regions of the prefrontal cortex. 17 31 36 56-58 Dysfunction of frontal eye fields is associated with decreased proportions of express saccades, decreased proportions of anticipatory saccades, and an inability to reduce saccadic reaction times
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across predictive saccade trials.\textsuperscript{15} Patients with TS, however, generated a normal proportion of express saccades, had an increased proportion of anticipatory responses during gap provocation saccade trials, and were able to decrease their reaction times across predictive saccade trials. These findings are inconsistent with dysfunction of frontal eye fields in TS.

Dysfunction of dorsolateral prefrontal cortex circuitry results in fewer correct antisaccade responses\textsuperscript{15 19 26 35} and perhaps an increased frequency of express saccades during gap tasks.\textsuperscript{46} A small subgroup of patients with TS (19\%) had fewer correct antisaccade responses than did normal subjects and the groups did not differ on frequency of express saccades. These results would seem to be inconsistent, as a general rule, with prefrontal cortex dysfunction in TS.

There is evidence that TS is associated with mild dysfunction of ocular motor control. The pattern of findings, however, may be inconsistent with involvement of the cortical parts of this neural circuitry. Perhaps short duration saccades, an increased frequency of saccades generated prior to stimulus presentation (anticipatory events), and a modest decrease in proportion of correct antisaccade responses indicate a subcortical dysfunction of the prefrontal cortex circuitry. Additional neurophysiological and neurological studies reporting patterns of saccadic performance among subjects with subcortical dysfunction will be needed to more adequately address this possibility.

There are two additional details to consider when evaluating these data. Firstly, the ocular motor results among patients with TS were not related to medication status. Although few patients were receiving psychotropic medications at the time of testing (33\%), their saccadic performance during individual tasks was unremarkable within the TS group. Secondly, both attention deficit and obsessive-compulsive symptoms are found in TS. Recent studies suggest that the presence of comorbid conditions may adversely affect the performance of patients with TS during neurocognitive and neuromotor tasks.\textsuperscript{47} Whereas the assessment of comorbid attention deficit hyperactivity symptoms among our patients with TS was based on self report, the saccadic performance of these patients was not differentiable from that of patients with TS without a history of inattention or hyperactivity. Prospective studies assessing ocular motor performance among attention deficit hyperactivity disorder patients would be useful for evaluating the specific impact of these symptoms on saccadic response.

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43 Clementz BA. The ability to produce short reaction time saccades as a function of gap interval among schizophrenia patients. Psychophys 1996;111:121–30.