Enhanced saccadic control in young people with Tourette syndrome despite slowed pro-saccades

JeYoung Jung[1], Stephen R. Jackson[1,2], Kichun Nam[3], Chris Hollis[4]

and Georgina M. Jackson[3,4*]

[1]WCU Department of Brain and Cognitive Engineering, Korea University,

South Korea

[2]School of Psychology, University of Nottingham, UK

[3]Department of Psychology, Korea University, South Korea

[4]Division of Psychiatry, University of Nottingham, UK

Abstract

Tourette syndrome (TS) is a neurodevelopmental disorder characterised by motor and vocal tics. Tics are repetitive and uncontrolled behaviours that have been associated with basal ganglia dysfunction. We investigated saccadic eye movements in a group of young people with TS but without co-morbid ADHD. Participants performed two tasks. One required them to perform only pro-saccade responses (pure pro-saccade task). The other involved shifting, unpredictably, between executing pro- and anti-saccades (mixed saccade task). We show that in the mixing saccade task, the TS group make significantly *fewer* errors than an age-matched control group, while responding equally fast. By contrast, on the pure pro-saccade task the TS group were shown to be significantly slower to initiate and to complete the saccades (longer movement duration and decreased peak velocity) than controls, while movement amplitude and direction accuracy were not different. These findings demonstrate enhanced shifting ability despite slower reflexive responding in TS and are discussed with respect to a disorder-related adaptation for increased cognitive regulation of behaviour.

Keywords : Tourette syndrome; cognitive control; task-switching; saccades; eye movements; executive function.

Introduction

Tourette syndrome (TS) is a neurodevelopmental disorder characterised by motor and vocal tics. Tics are repetitive and uncontrolled behaviours and are categorised into simple and complex tics. Simple tics include behaviours such as eye blinking, mouth opening, and throat clearing, while complex tics involve consecutive co-ordinated sequences of movement such as head shaking, scratching and gestures, or complete utterances. Tics commence at around 5-7 years old, increase to maximum severity at 8-12 years old, and decline in their frequency and severity after that (Erenberg, Cruse, & Rothner, 1987; Leckman, 2002).

What causes TS is not clear, but it is generally agreed that abnormalities in the basal ganglia and frontostriatal circuits are involved (Albin & Mink, 2006; Singer, 2005, for reviews). Since these structures are important for the regulation of motor and cognitive responses, including eye movements, it has been suggested that TS may result in an impairment of cognitive function (Rankins, Bradshaw and Georgiou, 2006; Watkins et al, 2005; Georgiou, Bradshaw, Phillips and Chiu, 1996), or a more specific deficit in inhibitory control (e.g., Channon, Drury, Martino, Orth, Robertson and Crawford, 2009).

We have consistently found however that control of goal-directed behaviour is enhanced in children with 'pure' TS (i.e., without co-morbid ADHD) compared with age-matched controls. In our studies we used very demanding ocular switching tasks, in which participants are required to switch back and forth between executing pro-saccades and anti-saccades to visual targets to explore this. For clarification, a pro-saccade involves executing a saccadic eye movement from a central position toward an abrupt onset visual target, whereas in an anti-saccade the individual is instructed to execute a saccadic eye movement in the opposite direction to that specified by the location of the abrupt onset visual target. We showed that young people with TS make significantly fewer errors on task-switch trials (i.e., trial in which individuals change from executing a pro-saccade to executing an anti-saccade or vice versa) than age- and IQ-matched controls. Furthermore, the TS group do not differ from controls in terms of the number of errors made on the cognitively less demanding non-switch trials (e.g., where a pro-saccade trial immediately follows a pro-saccade trial), and their response latencies were as fast as those of controls in all conditions (Mueller, Jackson, Dhalla, Datsopoulos and Hollis, 2006; Jackson, Mueller, Hambleton and Hollis, 2007). These findings suggest that individuals with TS may make use of a more controlled mode of responding than the control group. This may be a compensatory consequence of having to suppress or otherwise control their tics for long periods (Mueller et al. 2006).

Consistent with this suggestion, it has been shown that adults with TS recruit a more comprehensive network of frontal and medial frontal brain areas than do controls when inhibiting responses during a Go-NoGo task and during tic suppression (Serrien et al. 2005). Practice in suppressing or delaying tics may result in a strengthening of general control networks and may enable the remission of tics by adulthood for most children with TS (Leckman 2002). As tics can be embarrassing socially, children with TS may attempt to inhibit or at least delay their tics when in public. As tics can occur several times a day and on most days, children with TS will get lots of opportunity to practice suppressing their tics. While a shift towards increased control in general may be advantageous for rule-based performance, it may result in the slowing of more reflexive behaviours. That is, we hypothesise that a shift toward increased control over motor output might alter the threshold for initiating a response, as proposed by LeVasseur et al. (2001), and produce longer response times on average. It is this issue that is the focus of the current study. Specifically, do we observe both increased cognitive control, in the form of fewer errors on switch trials, and slowed reflexive behaviour, in the form of increased saccade latencies on pure pro-saccade trials?

It has been suggested that pro-saccades can be driven to the location of visual targets quite reflexively, particularly in circumstances where only pro-saccade responses are required (LeVasseur, Flanagan, Riopelle, and Munoz, 2001). Thus, even though saccades are volitional, and too slow to be sub-cortically driven, saccade direction can be triggered by the location of the target and saccade initiation by target onset. In these circumstances directional errors are rare.

When pro-saccade and anti-saccade trials are mixed within the same block an instructional cue is required and the direction of pro-saccades, as well as anti-saccades, is therefore constrained by the current task rule. Under these circumstances directional errors occur for both saccade types and latencies for pro-saccades increase relative to a block of single task (pure) pro-saccade trials. Directional errors are typically corrected on-line however and while saccades are initiated in an incorrect direction, they are subsequently corrected, leading to accurate final eye position. Importantly, since direction errors are corrected it is not the case that participants are unaware of the task instruction, but rather that implementation of the rule is difficult.

Although the existing literature on pro-saccade performance in TS is inconsistent, a number of researchers have suggested that pro-saccade latencies are slowed in individuals

with TS compared to age matched controls (LeVasseur, et al. 2001). However, most of these studies have involved adults (Farber, Swerdlow, and Clementaz, 1999; Straube, Mennicken, Riedel, Eggert and Muller, 1997), mixed studies involving both children and adult (LeVasseur, et al. 2001), or have not excluded individuals with co-morbid disorders such as ADHD (e.g., LeVasseur et al. 2001).

In clinical samples ADHD co-occurs with TS in 50% of individuals with TS (Leckman, Peterson, Anderson, Arnsten, Pauls and Cohen, 1997). Co-morbid ADHD complicates the interpretation of the effects of TS on behaviour since ADHD by itself is known to result in response inhibition and in deficits in sustained attention (LeVasseur, et al. 2001). The most informative study of basic saccade performance in children with uncomplicated (or 'pure') TS is that of Mostofsky and colleagues (Mostofsky, Lasker, Singer, Denckla and Zee, 2001). In a group of fourteen boys with 'pure' TS they found a statistical trend towards increased latency for pro-saccade trials relative to an age-matched control group.

In the current study, we further examined this issue with a group of young individuals with 'pure' TS compared to a group of aged-matched, neurologically normal, individuals. We examined pro-saccade task performance in both mixed and pure blocks of trials. This allowed us within the same group of TS individuals to assess whether pro-saccadic latency could be increased while saccadic switching was enhanced. Directional accuracy, duration, amplitude and velocity were also assessed. Specifically we tested the following main hypotheses:

1. On mixed blocks of pro- and anti-saccade trials, all individuals should exhibit the predicted effects of longer latencies and more errors on anti-saccade trials compared to pro-saccade trials and on switch trials compared to repeat trials.
2. The TS group are predicted however to make fewer errors on task switch trials, relative to controls, with little if any difference in latencies.
3. During blocks of pure pro-saccade trials the TS group are expected to exercise increased control over their motor outputs. This is predicted to result in increased saccade latencies. Other measures, such as movement velocity (reduced), saccade amplitude (reduced), and saccade duration (increased), are also predicted to reflect increased control.

Methods

Participants

Nine participants who met the DSM-IV-TR criteria for TS (7 males, mean age 14.1 ± 1.8 years) participated in the study. Diagnosis was established by clinical examination and it was determined that none of the patients had co-morbid ADHD. The control group consisted of 30 age-matched students (16 males, mean age 14.1 ± 1.4 years). Ethical approval was granted by a local NHS Research Ethics Committee, and written consent was obtained from all the participants in advance of their participation.

						Motor tics		Vocal tics	
Participant ID	Gender	Age (years)	IQ	Medication	YGTTS	Simple	Complex	Simple	Complex
TS018	M	13.4	120	Clonidine	51	a,b,c,d, e,f,g	None current	None current	None current
TS030	M	11.3	103	Clonidine	52	b,f	+	k	None current
TS002	M	16.3	111	No meds	21	a,d,e,g,h	+	l	None current
TS008	M	16.3	104	No meds	12	a,e,g	None current	None current	None current
TS014	M	12.6	101	No meds	5	a,b,g	None current	None current	None current
TS004	F	14.7	95	Clonidine	0	None current	None current	None current	None current
TS013	M	12.6	135	Melatonin	5	a,g	None current	None current	None current
TS028	F	13.4	96	Clonidine	36	g,j	+	k	None current
TS006	M	16.1	76	Clonidine	18	a,d	None current	m	None current

Table 1. Characteristics of TS participants. Glossary of tics: a = eye blinking, b = eye movements, c = nose movements, d = mouth movements, e = facial grimacing, f = head jerking, g = shoulder movements, h = leg/foot movements, j = abdominal tensing, k = throat clearing, l = coughing, m = simple noises. '+' indicates complex tics are present.

The IQ of participants was assessed by the Wechsler Abbreviated Scale of Intelligence (WASI) vocabulary and matrix reasoning subscales (Hays et al 2002). Statistical analysis revealed that IQ did not differ between groups (means: controls = 114.9 ± SD 13.3, TS group = 104.6 ± SD 16.6). Current tic severity was assessed on the day of testing using the Yale Global Tics Severity Scale (Leckman et al. 1989). A description of the clinical sample is

summarised in Table 1.

Apparatus

Eye movements were recorded using an Ober saccadometer (Ober Consulting, Poznan). The saccadometer projects simple visual stimuli and records horizontal eye movements using infra-red oculography. It comes with a number of pre-programmed saccadic paradigms that include pure pro-saccade blocks of trials and also a randomly mixed pro-saccade and anti-saccade trial sequence. The saccadometer collects four measurements: saccade latency, saccade duration, saccade amplitude, and saccade velocity. Eye position is sampled at 1 kHz, providing 1ms temporal resolution.

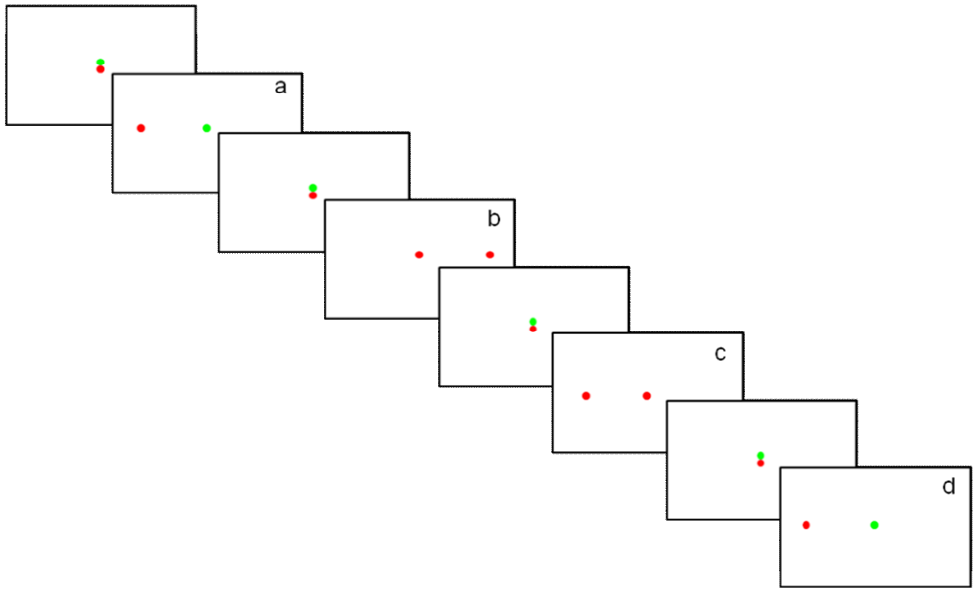

Figure 1 Mixed task block paradigm. ‘a’ is a pro-saccade trial, ‘b’ is an anti-saccade trial and represents a task switch trial, ‘c’ is a anti-saccade trial and represents a task repetition trial, ‘d’ is a pro-saccade trial and represents a task switch trial.

Design and Procedure

On mixed task trials, two dots were projected centrally with one green dot presented immediately above a second, red dot. These two stimuli disappeared briefly, to be replaced by only one of the two central dots (Green or Red) – the instructional cue – that was accompanied by a red peripheral target dot that could appear 10 degrees to the left or right of the central cue. If the cue was green, a pro-saccade was required. If the cue was red, an anti-saccade response was required. Two types of blocks were performed, pure pro-saccade blocks and mixed tasks (random switching between pro- and anti-saccade trials) blocks.

The initial display of two (Green and Red) dots lasted for a randomised duration that ranged between 1.5 and 2.5 seconds. After a 200 ms period, the cue and the target were presented. The inter-trial interval was 750ms. The task is illustrated in Figure 1. The single task blocks were composed of pro-saccade trials only. A single fixation dot was presented for 1-2 seconds.

Before conducting the experiment, participants were provided with verbal and written instructions. Twelve calibration trials were conducted prior to the experiment. All participants completed both pure and mixed blocks of trials. Each block consisted of two sessions, each containing 60 trials (thereby producing a total of 480 trials). The order of pure (A) and mixed (B) blocks was counterbalanced across subjects as follows (AABBAABB or BBAABBAA). After each session a short break was provided if subjects required it. Response latencies lower than 100 ms or greater than 1000 ms were excluded from the analysis.

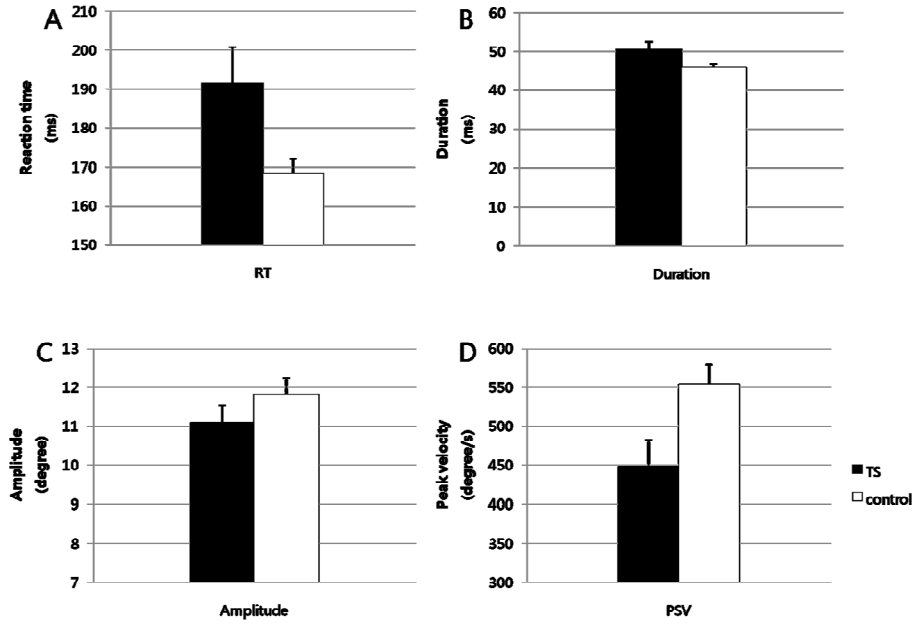

Figure 2 Results for pro-saccade pure block performance. **A.** Saccade latency for TS (black bar) and control group (white bar). **B.** Duration data (measured from movement onset to offset). **C.** Amplitude data (the targets were presented 10 degrees to the left and right of fixation). **D.** Peak saccade velocity data. Error bars represent standard error of the mean.

Results

Pure (pro-saccade) block performance

Both groups made very few errors (mean number of correct trials was 98.9% for the TS

group and 98.4% for the controls). The TS group were significantly slower to respond correctly than controls (mean difference increase 23.1ms; effect size (Cohen's d) = 0.97, t(40) = -2.9, $p < 0.05$). The TS group also had a significantly longer mean movement duration than the control group (t(40) = -2.6 , $p < 0.05$, effect size = 0.85) and exhibited a lower peak velocity than did the controls (t(40) = 2.2, $p < 0.05$, effect size = 0.89). But movement amplitude did not differ between the groups ($p > 0.1$). These effects are illustrated in Figure 2.

Task switching performance

To examine differences in switch costs between the groups, each dependent variable was analysed using a 3-way mixed ANOVA with the following factors: Trial type (pro-saccade vs. anti-saccade); Task type (switch task vs. repeat task); and Group (TS group vs. control group). Within subject factors were Task type and Trial type, and the between subject factor was Group.

Saccade error data

Both the TS group and control group made significantly more directional errors on anti-saccades compared to pro-saccades (main effect of Trial type: $F(1,40) = 36.9$, $p < 0.001$), and for switch trials compared with repetition trials (main effect of Task type: $F(1,40) = 39.4$, $p < 0.001$). Of more importance, there was a significant main effect of group ($F(1,40) = 5.6$, $p < 0.05$), with the TS group making significantly fewer errors than the control group. The interaction between Task type (pro-saccade vs. anti-saccade) and Trial type (repetition vs. switch trials) was also statistically significant ($F(1,40) = 6.0$, $p < 0.05$). An examination of Figure 3 shows that the difference between tasks (pro-saccade minus anti-saccade) was larger for switch trials (-28.4%) compared to repeat trials (-21.74%) and that switch costs (switch trials – repeat trials) were greater for anti-saccade trials (14.7%) than for pro-saccade trials (8.1%). No other interaction effects reached statistical significance (minimum $F < 0.3$, $p > 0.1$).

Saccade latency data

The latency (RT) data showed that the latencies for both groups were faster for pro-saccades than for anti-saccades (main effect of Trial type: $F(1, 40) = 18.2$, $p < 0.001$), and that latencies for task repetition trials were faster than for task switch trials (main effect of Task type: $F(1, 40) = 10.8$, $p < 0.01$). There was a significant interaction between Task type

and Trial type ($F(1, 40) = 7.0$, $p < 0.05$). Importantly, there was no main effect of Group ($F(1, 37) = 1.4$, $p > 0.5$) and no significant interaction involving Group. Therefore, the accuracy advantage for the TS group does not appear to be a consequence of any speed-accuracy trade off.

Saccade duration data

There was main effect of Task type for movement duration ($F(1, 40) = 47.5$, $p < 0.001$). Saccade durations were shorter for pro-saccade trials than for anti-saccade trials. There was also a marginally significant main effect of Trial type ($F(1, 40) = 3.6$, $p = 0.07$). See Figure 3.

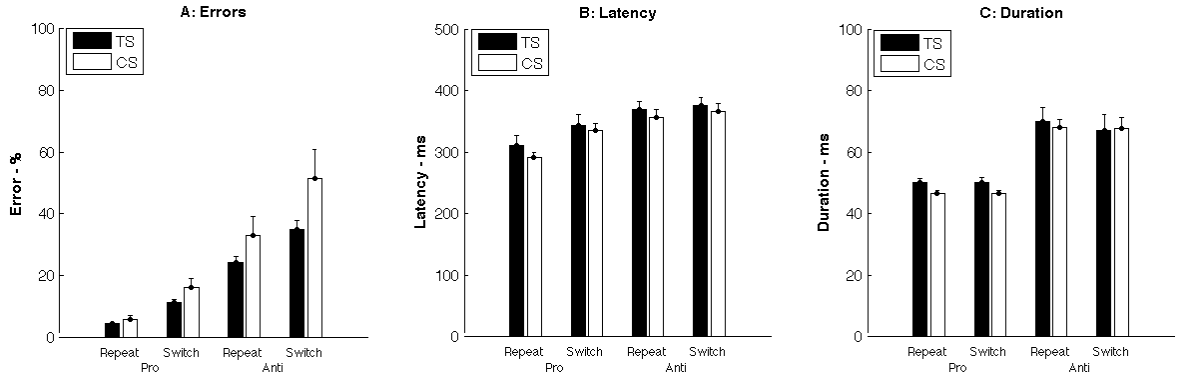

Figure 3. Mixed blocks. A. Error rate for TS (black bar) and control (white bar) groups split according to task and trial type. B. Latency (reaction time) data. C. Means for saccade duration (the time from the onset of eye movement to offset). Error bars denote standard errors.

Saccade amplitude data

Analysis of the saccade amplitude data revealed that both groups showed a significant difference between pro-saccades and anti-saccades, with anti-saccades exhibiting an increased amplitude ($F(1,40) = 22.1$, $p < 0.001$). All other effects failed to reach conventional levels of statistical significance.

Saccade velocity data

There were no significant effects for the peak velocity data. These results are illustrated in Figure 4.

Mixing costs

Mixing costs were calculated by subtracting measurements for pro-saccade trials in the pure blocks from those for repeat pro-saccade trials in the mixed task blocks. As error rates

were so low in the pure pro-saccade block, and some participants made no errors, a non-parametric statistical test was used to investigate any differences between means. There was no significant mixing cost for errors (Mann-Whitney U = 129.5, p > 0.9).

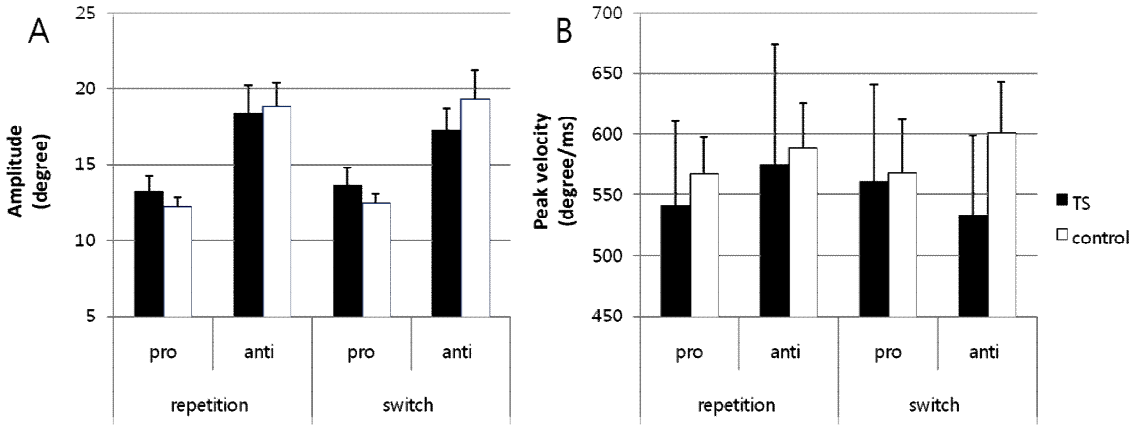

Figure 4. Means for amplitude and peak velocity. A. Saccade amplitude for TS (black bar) and control group (white bar). B. Saccade peak velosity data. Error bars denote standard errors.

A 2-way mixed ANOVA was carried out to analyse pro-saccade latency data with the following factors: Block type (pure block vs. mixed block) and Group (TS group vs. Control group). The ANOVA revealed that there was a significant main effect of Block ($F(1,40) = 110.3$, $p < 0.001$) and also a significant main effect of Group ($F(1,40) = 6.8$, $p < 0.05$). Additional analyses showed that both groups were significantly slower when executing pro-saccades in the mixed task block (repeat trials) compared to when pro-saccades were executed within the pure pro-saccade blocks, (Control group: mean mixing costs 98.2 ms, $t(31) = 11.4$, $p < 0.001$; TS: mean mixing costs 108.3 ms, $t(9) = 4.9$, $p = 0.001$). There were no statistically significant differences observed for the other dependent measurements, however the TS group did show a significant increase in amplitude in the mixed task blocks compared to the pure blocks (mean for pro-saccades within pure blocks = 11.1 degrees, mean for pro-saccade repeat trials in the mixed blocks = 13.2 degrees, $t(9) = 2.3$, $p < 0.05$).

Correlation of task performance with clinical scores

In order to examine the relationship between individual saccade task performance and tic severity, we correlated Yale Global Tic Severity Scale (YGTSS) scores with individual switch costs and saccade accuracy scores. These analyses revealed that there was a highly significant

correlation between global YGTSS score and pro-saccade switch costs (i.e., switch to pro-saccade – repeat pro-saccade) for errors (Pearson $r = 0.82$, $p < 0.01$). The correlation between Yale Tic Severity scores and the other switch costs (anti-saccade switch costs, and mixing costs) did not reach conventional levels of statistical significance (Maximum Pearson $r < 0.52$, $p > 0.2$) however the direction of the association was similar to that seen for pro-saccade switch costs. See Figure 5. These data indicate that *increased* switch costs are strongly associated with *increased* Yale score (which is an index of tic severity). At first glance this may appear a somewhat odd finding, however it is important to keep in mind the following points when interpreting these data. First, it is quite normal to make errors on switch trials. This is what healthy individuals do, and the somewhat paradoxical finding is in fact that individuals with TS actually exhibit significantly fewer errors, as a group, than do controls. Second, if adaptation to TS is associated with increased cognitive control of motor behaviour, as suggested above, then this might be expected to lead to *reduced* switch costs, i.e., the difference between controlled switch trials and reflexive repeat trials becomes smaller. In this way, reduced switch costs in individuals with TS would be associated with reduced tic (YGTSS) scores: and this is indeed the pattern that we observed.

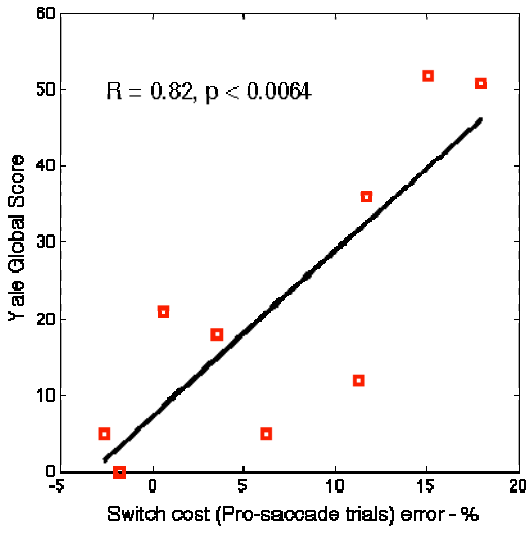

Figure 5. The graph shows the correlation between Yale Global Score and switch cost on pro-saccade trials in the mixed block for individual TS participants.

Discussion

In summary, the TS group were significantly slower to *initiate* and to *complete* a saccade (longer movement durations and decreased peak velocities) than the control group when

executing pro-saccades within pure blocks of only pro-saccades, although their movement amplitude and direction accuracy was not different than controls. By contrast, within the mixed task blocks, the TS group performed significantly more accurately than the age-matched control group, and their latencies were equally fast. Finally, and most importantly, when individual measures of task performance in the mixed block were calculated (i.e., switch-cost errors (switch to pro-saccade – repeat pro-saccade), it was found that these measures were strongly positively correlated with individuals' Yale scores indexing their current level of tics. These data suggest that individuals who show the greatest levels of cognitive control (i.e. smallest switch costs) also exhibit low levels of tics. These results are discussed further below.

The significant increase in pro-saccade latency in pure pro-saccade blocks observed in the TS group in the current study confirms the statistical trend reported by Mostofsky et al. (2001). The increase of 21 ms in their study tallies well with the increase of 20 ms found in the current study. The increase in response latency and movement duration, together with a decrease in peak velocity, is consistent with a shift away from a more automatic and reflexive mode of responding, toward a more controlled, less reflexive, mode of responding in the TS group.

Many individuals with TS gain control over their tics during adolescence and it has been suggested that this increased control arises as a result of the development of mechanisms that operate to alter the 'gain' of volitional movements by suppressing cortical-spinal excitability ahead of such movements. Evidence in support of this view come from TMS studies that demonstrate that individuals with TS exhibit significantly *reduced* cortical-spinal excitability in primary motor cortex, relative to matched controls, in the period immediately preceding the execution of volitional movements (Heise et al., 2010; Jackson et al., 2011). Furthermore, fMRI studies show that in individuals with TS there is reduced fMRI BOLD activation in primary motor cortex when motor performance is equivalent to that of controls (Jackson et al., 2011; Jung et al., 2012). Consistent with the above proposal, we find that in the current study the TS group were slower than controls to initiate and complete pro-saccades within pure blocks of only pro-saccades (i.e., longer RTs, longer movement durations and decreased peak velocities) than the control group when executing pro-saccades, although their movement amplitude and direction accuracy was not.

LeVasseur et al. (2001) has proposed that the threshold for generating a saccade may be increased in TS. In the current study latencies in all conditions were increased, but non-

significantly, in the TS group. However, this is difficult to interpret since error rates in all conditions were also lower in the TS group. However, previously we have found that the saccadic latencies of TS participants were significantly faster, as well as more accurate, than controls with a 200 ms pre-target instruction cue (Mueller et al 2006). In our 2007 study, with a 200ms or concurrent instructional pre-cue, the TS group were also slightly faster for all mixed task conditions apart from the pro-saccade repeat task.

Once again we found better task-switching performance in the TS group with an increase in accuracy but no significant increase in latency for mixed task blocks. We believe this enhanced task-switching performance reflects the operation of compensatory control mechanisms that may develop to compensate for a task selection deficit in the striatum that is associated with TS. This interpretation is supported by our finding of a statistically significant relationship between the magnitude of switch costs (pro-saccade errors) on the mixed task block and individual clinical measures of tic severity. Specifically, individuals with TS who perform more like the control group (i.e. have larger switch costs) also have more severe tics. In a recent functional imaging paper investigating task-switching in children with TS, Baym and colleagues demonstrated that tic severity was associated with increased activation in brain areas corresponding to midbrain dopaminergic nuclei (substantia nigra/ventral tegmental area), and in cortical, striatal and thalamic regions of the cortico-stiatal-thalamic-cortical brain circuits involved in the selection and control of action (Baym, Corbett, Wright, Bunge, 2008).

Although the prognosis is better for children without co-morbid ADHD, approximately 20% of children with TS have significant tics in adulthood (Leckman, 2002). Whether cognitive control measures such as those reported here can predict the likely remission of tics during adolescence is an extremely important question clinically that may require a longitudinal study to answer. Nevertheless, our finding that simple behavioural measures of oculomotor task-switching strongly predict clinical measures of tic severity suggest that such measurements may play a useful role in predicting the progression of the disorder at an individual level.

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