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Unique saccadic abilities associated with tourette syndrome: Pure and comorbid groups a controlled study

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ABSTRACT

Tourette Syndrome (TS) is a childhood onset disorder characterized by motor and vocal tics. TS often co-occurs with Attention Deficit Hyperactivity Disorder (ADHD) and Obsessive-Compulsive Disorder (OCD). Since neural networks associated with TS overlap with that of saccadic eye movements, saccadic performance may reflect psychopathology underlying TS+comorbidity. The aims of the present study were to determine whether heterogeneity in TS samples and use of various saccadic conditions are responsible for inconsistent findings. We examined: (1) saccadic behaviour in children groups: TS-only, TS+ADHD, TS+ADHD+OCD and healthy Controls; (2) the effect of different saccadic conditions. Participants (8–16 years) either looked towards (prosaccade) or in the opposite direction (antisaccade) of a peripheral visual stimulus in three conditions: fixation dot disappeared simultaneously (standard), 200 ms prior to (Gap200) and 800 ms following (Overlap800) stimulus onset. The findings demonstrated that sample heterogeneity and use of various saccadic conditions contribute to inconsistent findings. The TS+ADHD+OCD group displayed an enhanced saccadic ability substantiating the hypothesis of an enhanced adaptive cognitive control in certain groups of children with TS. The TS+ADHD group displayed significantly higher rates of antisaccade errors and unable to reduce their error rates. These findings lend further support to the nosological hypothesis.

1. Introduction

Tourette Syndrome (TS) is a childhood onset disorder characterized by the presence of multiple motor tics and one or more phonic tics. A tic is a sudden and recurrent motor movement or vocalization (Sandor 1993; DSM-IV-TR 2000). TS often occurs together with Attention Deficit Hyperactivity Disorder (ADHD) and Obsessive-Compulsive Disorder (OCD). TS and OCD appear to share certain clinical characteristics (Sheppared & Bradshaw, 1999). Both disorders involve repetitive acts/urges that are considered involuntary and increased tension is felt if such behaviour/urges are inhibited (Sheppared & Bradshaw, 1999). In fact OCD has been described as the "cognitive" counterpart to "TS" (Sheppard & Bradshaw, 1999). Genetic studies have confirmed that an early onset form of OCD shares common genetic factors with TS (O'Rourke, Scharf, Yu & Pauls, 2009).

Deficits within the basal ganglia and the areas of the frontal cortex to which the basal ganglia project to through the thalamocortical pathways are implicated in the pathophysiology of TS (Fredericksen et al., 2002; Segawa, 2003; Sweeney, Takarae, Macmillan, Luna & Minshew, 2004; Plessen, Royal & Peterson, 2007; Swain, Scahill, Lombroso, King & Leckman, 2007; Sowell et al., 2008; Makki, Govindan, Wilson, Behen & Chugani, 2009). These structures are also part of the neural circuitry involved in the generation of eye movements. Thus, oculomotor studies provide a simple and non-invasive method of examining the integrity of the neural circuitry underlying TS pathophysiology.

Saccade eye movements are high velocity eye movements used to scan the visual world (Leigh & Zee, 2006). The two tasks commonly used in oculomotor research are the prosaccade and the antisaccade tasks. In the prosaccade task, participants look toward a peripheral visual stimulus (a reflexive task), but in the antisaccade task they look in the opposite direction of the stimulus. The antisaccade task is sensitive to inhibitory control (Hallett, 1978; Munoz & Istvan, 1998; Fukushima, Hatta, & Fukushima, 2000) and working memory resources (Roberts, Hager,& Heron 1994; Malone & Iacono, 2002). Hence, data are Q2 commonly reported separately for each task.

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Research exploring saccade eye movements of children with TS is very sparse and findings are inconsistent. Earlier reports have indicated longer saccade latencies (Straube, Mennincken, Riedel, Eggert, & Muller, 1997; LeVasseur, Flanagan, Riopelle, & Munoz, 2001; Munoz, LeVasseur, & Flanagan, 2002) normal saccade latencies (Bollen et al. 1988) and faster saccade latencies (Jackson, Mueller, Hambleton & Hollis, 2007) in children with TS relative to those of healthy Controls. There have also been reports of children with TS committing significantly more error saccades (generating a saccade prior to the offset of the fixation dot) (Nomura, Fukuda, Terao, Hikosaka & Segawa, 2003) and significantly fewer errors in saccade generation relative to healthy children (Mueller, Jackson, Dhalla, Datsopoulos & Hollis, 2006; Jackson et al., 2007).

Two factors may be contributing to these inconsistent findings: (1) different oculomotor task/conditions have been used in studies; (2) the TS samples have been heterogeneous between studies, consisting of various composition of TS+comorbid disorders. Mostofsky et al. (2001) investigated eye movements of children with TS with and without the comorbid ADHD and reported increased number of antisaccade errors observed in TS+ADHD relative to those of TS-only group. Hence, comorbidity in TS may be an important factor to examine. The samples of children with TS in the above mentioned studies either consisted of participants with different combinations of TS+comoribid conditions, or were not assessed for the comorbid conditions with the exception of Muller et al. (2006) and Jackson et al. (2007) who excluded participants with the diagnosis of ADHD. Hence, the impact of comorbid conditions on oculomotor ability of TS participants requires further investigation.

The aims of the present study were to: (1) examine the effect of the comorbid conditions; and (2) the effect of oculomotor task/conditions on saccades of children with TS and to determine whether these factors contribute to inconsistent findings. Hence we hypothesized that the participants' performance would be moderated as a result of "Condition" and the presence of "comorbid" conditions. In terms of Group differences, based on the findings of the previous studies, we hypothesized that the TS+ADHD group would display greater antisaccade error rates than the TS-only group. We also hypothesized that the TS+ADHD+OCD group would display the greatest oculomotor problems because the behavioural data indicate greater behavioural and educational problems in this group (Debes, Hjalgrim & Skov, 2010).

2. Method

2.1. Subjects

Ten typically developed children 10–16 years of age ($M=12.8$, SD=2.3) and 22 children with Tourette syndrome 8–16 years of age ($M=12.1$, SD=2.3) participated in this study. Healthy children were recruited through e-mail advertisements posted on the list serve for all staff working at the Toronto Western Hospital and also on the advertisement boards present throughout the hospital. The children with TS were recruited from the Neurodevelopmental clinic at the Toronto Western Hospital. The parents of patients who were within the age-range of interest were contacted by one of the experimenters, the study was briefly explained to them over the phone and if they expressed interest in having their child participate in the study, a data collection appointment was booked for them on the same day as their clinic appointment at the hospital. The children with TS were divided into three subgroups: TS-only ($n=6$; $M=10.7$, SD=1.6), TS+ADHD ($n=9$; $M=11.8$, SD=2.5), and TS+ADHD+OCD ($n=7$; $M=13.9$, SD=1.6). For participants' demographic and medication information see Tajik-Parvinchi and Sandor (2011).

In order to substantiate the diagnoses of each group, an independent practitioner reviewed the patients' files and provided independent diagnoses of each patient participant. An inter-rater reliability analysis suing Kappa statistics was carried out in order to examine the consistency between the diagnoses concluded by the two physicians. The result of this analysis revealed the inter-rater reliability to be Kapp=0.861 ($p<0.001$)

The participants with TS were diagnosed according to DSM III R diagnostic criteria by an experienced neuropsychiatrist. Tic severity was assessed retrospectively, based on review of the clinical information by the same neuropsychiatrist. Life-time tic severity was rated on a 3-point scale (1-mild, 2-moderate and 3-severe) (Fig. 7). The participant's ADHD symptom severity was assessed retrospectively using the Clinical Global Impression of ADHD symptoms (CGI) both for life time and at the time of data collection (Fig. 7). The rater was not aware of the oculomotor performances of the participants when making the ratings. All control participants, by parental report, had no history of TS, OCD or ADHD, vestibular, ocular motor anomalies, or any type of surgery. Written informed assent was obtained from the participants and written informed consent was obtained from parents of the participants. This study was approved by the University Health Network Research Ethic Board and complied with the tenets of the Declaration of Helsinki.

2.2. Apparatus

Horizontal eye movements were recorded binocularly using a video-based cornea/pupil tracking system (El-Mar Series 2020 Eye Tracker, Toronto, Canada). This system is free from drifts and has a maximum resolution of 0.1 degree of visual angle. It has a linear range of ± 25 deg in the vertical meridian and greater than ± 30 deg in the horizontal meridian. Eye movements were sampled at 120 Hz. The head was stabilized by a chin-rest. Participants were seated in a chair, which was especially crafted to adjust to different heights to allow children's eyes to be aligned with the centre of the screen, which was located 200 cm in front of the participants. The stimuli were back projected onto this screen. The size of the stimuli extended about 0.25°. The room was dimly illuminated to encourage larger pupils for better data acquisition. Prior to data collection the eye tracker was calibrated binocularly for each participant by recording eye position at 7 locations horizontally and vertically with a range of $\pm 10°$. The data for the eye with the better calibration data was selected for further analyses.

2.3. Procedure

The prosaccade and antisaccade tasks were presented in separate blocks of trials in three conditions: Standard, Gap200 and Overlap800. Hence, each participant was assigned 6 blocks of trials. Each block consisted of 25 trials, making up 150 trials per participant. The order of presentation of blocks of trials was randomized. The fixation dot was presented in the centre of the screen and the peripheral stimuli were presented at ± 5, ± 10 and ± 15 relative to the fixation point in a random order.

In the Gap200 condition, the fixation dot disappeared 200 msec prior to stimulus presentation. In the Overlap800 condition, the fixation dot remained on for 800 msec following stimulus onset. The Standard condition consisted of the fixation dot disappearing simultaneously as the peripheral stimulus appeared. The duration of the stimulus presentation varied randomly from 1000 msec to 1500 msec.

Children were instructed prior to the presentation of each block of trials and the experiment continued when the child expressed understanding of the task instructions. In the prosaccade tasks, children were told to look towards the peripheral target as soon as it appeared. In the antisaccade tasks, they were instructed to look in the opposite direction of the peripheral target but mirror distance from the fixation dot. Data collection was incomplete for 6/32 children (1 in the Control, 2 in the TS-only, 1 in the TS+ADHD and 2 in the TS+ADHD+OCD groups). The reasons consisted of fatigue and technical difficulties.

3. Calculation

Eye movements with peak velocities greater than 50 deg/sec were marked as saccades by a custom-designed software program (AnYZll 3.3). The onset of a saccade was determined as the time at which its velocity surpassed 10°/sec. Eye blinks were filtered out by AnYZll 3.3, however, the experimenter viewed the marked saccades as well to ensure that these were not blink artifacts. The first saccade generated within 100–1000 msec of the target onset was selected for further analysis. The saccades outside of this time frame were considered anticipatory, secondary or not in response to the stimulus and therefore were excluded from further analyses. The digitized information of each saccade including time of onset and direction was imported into an excel sheet where the rest of the calculations were carried out. Saccade Latency was calculated by subtracting the time of target onset from that of the saccade onset. In the antisaccade task, a saccade was considered an antisaccade error, if it was generated in the same direction as the peripheral target. Hence, Error rates indicated the percentage of direction errors committed in a block of trial. Saccades, which were considered direction errors, were not included in the calculations of Latency.

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4. Results

A Repeated measures analysis of variance was carried out for each dependent variable (Antisaccade Latency, Prosaccade Latency and Antisaccade Error Rate); with Groups (Control, TS-only, TS+ADHD, TS+ADHD+OCD) as the between-subject factor and Condition (Standard, Gap200, Overlap800) as the repeated measure factor, hence a 4×3 mixed model was carried out. The variable Subject was nested within the between subjects factor and crossed with the repeated measures factor. All pair-wise comparisons were Bonferroni corrected.

4.1. Prosaccade Latency

4.1.1. Group differences, TS-subgroups

The ANOVA revealed a significant main effect for Condition $F(2,51)=78.914$, $p<0.001$. The follow up pairwise comparisons examining group differences revealed the following effects (Fig. 2A): In the Standard condition, the Control group displayed significantly shorter prosaccade latencies than the TS+ADHD group ($p=0.01$). In the Overlap800 condition, the TS+ADHD+OCD group exhibited significantly shorter prosaccade latencies than the Control group ($p=0.001$), the TS+ADHD group ($p<0.001$) and the TS-only group ($p=0.006$).

4.1.2. Group Differences, TS-entire group

Examining the prosaccade latency of the TS group as a whole (TS-entire) relative to those of the Control group revealed a main effect of Condition, $F(2,55)=83.905$, $p<0.001$. Pairwise comparisons revealed that in the Standard condition, the TS-entire group exhibited significantly longer prosaccade latencies relative to those of the Control group ($p=0.001$) (Fig. 1B).

4.1.3. Saccadic profiles across the Conditions

Results of the analyses for the saccadic profile of each group across the fixation offset conditions revealed similar saccadic performances. The Control group and all of the TS-subgroups demonstrated the 'Gap Effect'; i.e. significantly shorter saccade latencies in a Gap condition relative to an Overlap condition (Saslow, 1967; Lajonchere & Abrams, 2006; Rolfs & Vitu, 2007). For details please see Table 1.

4.2. Antisaccade Latency

4.2.1. Group differences, TS-subgroups

In antisaccade latency the repeated measure ANOVA revealed a main effect for Condition, $F(2,54)=29.657$, $p<0.001$. The pairwise comparisons exploring group differences revealed the following effects. In the Standard Condition, the Control group had significantly shorter antisaccade latencies than the TS+ADHD group ($p<0.04$) and the TS+ADHD+OCD group ($p=0.05$) (Fig. 3A). In the Overlap800 condition, the Control group had significantly shorter antisaccade latencies than those of the TS-only (0.01) and the TS+ADHD group ($p=0.04$). In the same condition, the TS+ADHD+OCD group also displayed significantly shorter antisaccade latencies relative to those of the TS-only ($p=0.008$) and to those of the TS+ADHD ($p=0.02$) groups, but not significantly different from the Control group ($p=1.0$).

4.2.2. Group Differences, TS-entire group

Results for the TS-entire group revealed a significant effect for Condition, $F(2, 58)=26.256$, $p<0.001$. Follow up pairwise comparisons revealed that in the Standard condition, the TS-entire group exhibited significantly longer antisaccade latencies than the Control group ($p=0.001$). Similarly, in the Overlap 800 condition, the TS-Entire group had significantly longer antisaccade latencies than the Control group ($p=0.01$) (Fig. 3B).

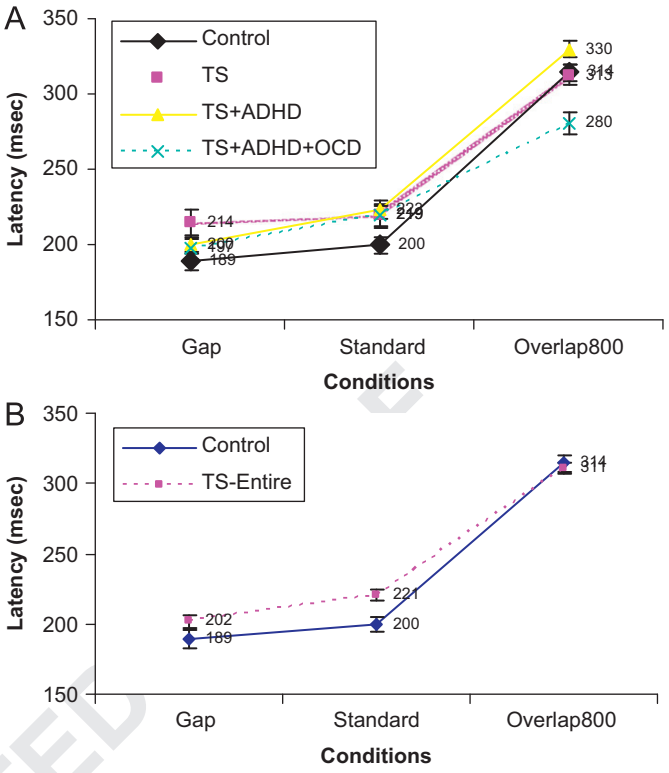

Fig. 1. The top graph 1(A) shows the average prosaccade latency of each TS-subgroup and those of the healthy Controls; graph 1(B) illustrates the average prosaccade latencies of the TS-Entire group and the those of the healthy Controls. Error bars are standard errors.

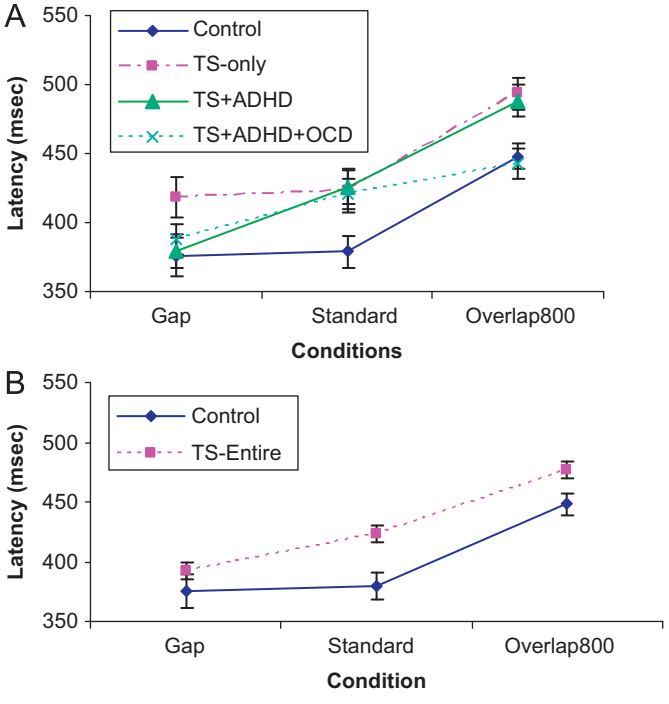

Fig. 2. Antisaccade latencies of the TS-subgroups and those of the healthy Control group across the three conditions (2A) and the antisaccade latency of the TS-Entire group relative to those of the healthy Controls (2B). Error bars are standard errors.

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Table 1
Average saccade latencies and error rates of each group across the three fixation offset conditions. Significant p-values for each pairwise comparison is provided.

	Gap200	p-value, Relative to X group	Standard	p-value, Relative to X group	Overlap800	p-value, Relative to X group
Statistical Profile of Each Group						
Prosaccade Latency (ms)						
Control (n=10)	188.981*	$p<0.001$ Overlap800	199.517*	$p<0.001$ Overlap800	314.172*	
TS-Only (n=6)	214.336*	$p<0.001$ Overlap800	219.047*	$p<0.001$ Overlap800	312.675*	
TS+ADHD (n=9)	199.722*	$P=0.01$ Standard; $p<0.001$ Overlap800	223.308*	$p<0.001$ Overlap800	329.732*	
TS+ADHD+OCD (n=7)	197.052*	$p<0.001$ Overlap800	219.034*	$p<0.001$ Overlap800	280.408*	
Antisaccade Latency (ms)						
Control (n=10)	375.268		379.0		448.132*	$p<0.001$ Gap200; $p<0.001$ Standard
TS-Only (n=6)	418.422		423.28		493.297*	$p<0.001$ Gap200; $P=0.001$ Standard
TS+ADHD (n=9)	378.979*	$P=0.023$ Standard	425.42*		488.327*	$p=0.001$ Gap200; $P=0.001$ Standard
TS+ADHD+OCD (n=7)	387.942		420.887		442.662*	$P=0.001$ Gap200
Antisaccade Error Rate (%)						
Control (n=10)	49.5		44		21.4*	$p<0.001$ Gap200; $p<0.001$ Standard
TS-Only (n=6)	41.7		46.4		22.8*	$P=0.001$ Gap200; $p<0.001$ Standard
TS+ADHD (n=9)	48.2		45.4		41	
TS+ADHD+OCD (n=7)	28.9		32.3		17.6*	$P=0.01$ Standard

4.2.3. Saccadic profiles across the Conditions

In antisaccade latency, in contrast to the prosaccade latency, each group displayed a different pattern of saccadic profile across the different conditions (Fig. 2A). However, there seemed to be an overall pattern of longer saccadic latency in the Overlap800 condition relative to those in the Gap200 condition (p-values ≤ 0.001) in all of the groups; and relative to those in the Standard condition (p-values ≤ 0.001) in all of the groups except for TS+ADHD+OCD group who generated similar antisaccade latencies in the two conditions ($p=0.49$). See Table 1 for details.

4.3. Antisaccade Error Rate

4.3.1. Group differences, TS-subgroups

The repeated measures ANOVA revealed a significant main effect for Condition, $F(2,54)=13.974$, $p<0.001$. The overall pattern of antisaccade error rate (Fig. 4A) was surprising and it is reviewed in detail in the next paragraph. The TS+ADHD+OCD group displayed a general pattern of lower antisaccade errors relative to those of the other groups which reached significant levels in several cases. However, the TS+ADHD group exhibited higher antisaccade latencies, which reached significant levels in the Overlap800 condition, relative to the other groups. Given that the comorbid ADHD is present in both of these groups; such a considerable difference in antisaccade error rate between these two groups is interesting.

In the Gap200 condition, the TS+ADHD+OCD made significantly lower antisaccade error rates relative to those of the TS+ADHD group ($p<0.001$) and the Controls ($p<0.001$). There was a trend for fewer errors in the TS+ADHD+OCD relative to the TS-only group ($p=0.058$). Similarly, in the Standard condition, the TS+ADHD+OCD group displayed significantly lower antisaccade errors relative to the Control ($p=0.048$), to TS-only ($p=0.026$) and to TS+ADHD ($p=0.022$) groups. In the Overlap800 condition, the TS+ADHD group exhibited significantly higher number of antisaccade errors relative to the Control group ($p<0.001$), to TS-only group ($p=0.001$), and to TS+ADHD+OCD group ($p<0.001$).

4.3.2. Group Differences, TS-entire group

Examining group differences between TS-Entire group and those of the Controls (Fig. 4B) revealed a main effect for Condition, $F(2,58)=13.993$, $p<0.001$. The pair wise comparisons revealed that in the Gap200 condition the TS-Entire group displayed significantly lower rates of antisaccade errors relative to those of the Control group ($p=0.008$). However, the reverse pattern was observed in the Overlap800; the Control group committed significantly lower rates of antisaccade errors relative to those of the TS-Entire group. These findings will be discussed below.

4.3.3. Saccadic profiles across the Conditions

The results of the pairwise comparisons across the fixation offset conditions for each group are listed in Table 1. Two important observations should be noted here. First, the condition Overlap800 generated the least number of antisaccade error rates; and second, the TS+ADHD group's antisaccade error rate

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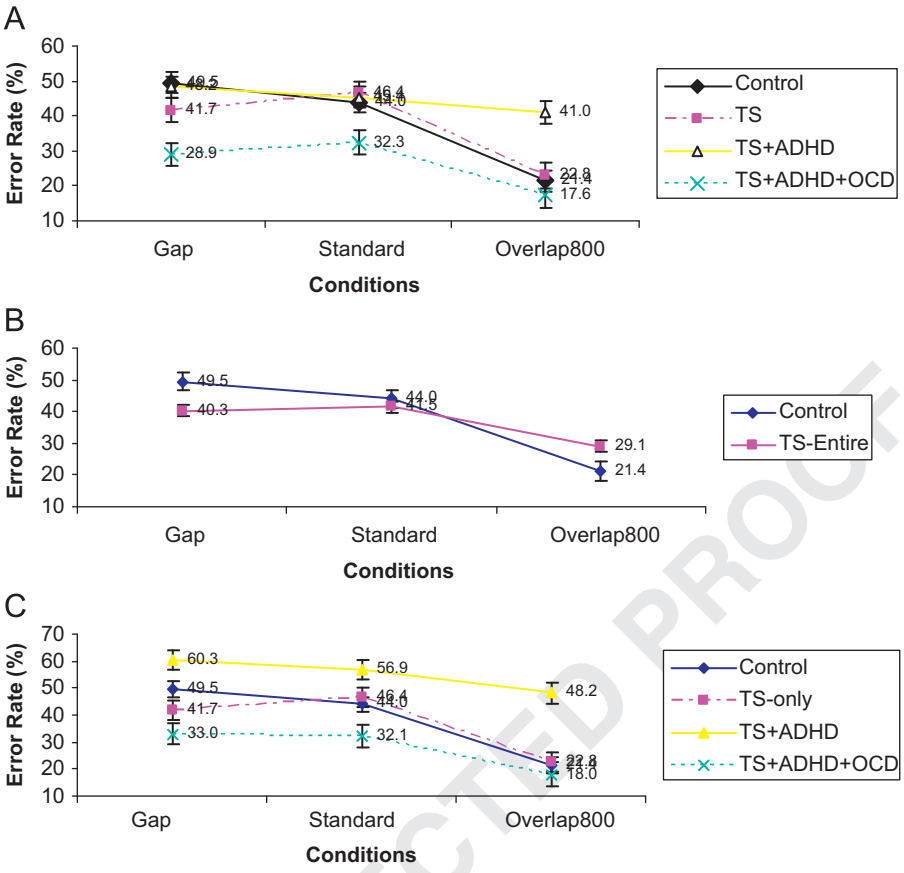

Fig. 3. The top graph (A) depicts the error rates of each TS-subgroup and the Control group. In graph (B) patient sub-groups have been combined into the TS-Entire group and their data is shown relative to those of the Control group. In Graph (C) the data of patients who were receiving Risperidone at the time of data collection were excluded and antisaccade error rates of each group is displayed without these patients. Error bars are standard errors.

was invariant across the three conditions. Their error rate did not alter significantly between the conditions. This was not observed in the TS-only, TS+ADHD+OCD and in the Control group, all of whom displayed significant variations in antisaccade error rates across the three conditions. See Table 1 for details.

4.4. Enhanced ability in TS+ADHD+OCD?

The results of the above analyses suggest an enhanced ability demonstrated by the TA+ADHD+OCD group. In order to explore this observation further, two analyses were carried out. First, since this group is on average older than the other groups, the effects of "Age" were explored. Second, in order to measure the TS+ADHD+OCD group's performance relative to the other groups, direct comparisons were made between this group and the other groups with both groups adjusted for age by excluding the data of the youngest(s) and/or the oldest(s) participant(s) to bring the ages of the two comparison groups close enough to explore performance differences with the contribution of "Age" kept at minimum.

In order to determine whether age was a contributing factor in the TS+ADHD+OCD group's enhanced saccadic performance, the main effects and interaction effects of "Age" were examined. First, the factor "Age" was entered as a between subjects factor along with "Comorbidity" and "Condition" and its main effects and interaction effects were examined for each dependent variable (Prosaccade Latency, Antisaccade Latency and Antisaccade Error Rate). The results of this series of analyses revealed no main effects of Age for any of the variables: Prosaccade latency, $F(7,11)=0.982$, $p=0.490$; Antisaccade Latency, $F(7,11)=0.510$, $p=0.809$; Antisaccade Error, $F(7,11)=1.688$, $p=0.210$. There were no interaction effects of Comorbidity*Age: Prosaccade latency, $F(10,11)=1.330$, $p=0.323$; Antisaccade Latency, $F(10,11)=1.176$, $p=0.395$; Antisaccade Error, $F(10,11)=0.430$, $p=0.903$. There were neither any interaction effects of Condition*Age: Prosaccade latency, $F(14,18)=1.443$, $p=0.23$; Antisaccade Latency, $F(14,22)=1.081$, $p=0.423$; Antisaccade Error, $F(14,22)=0.751$, $p=0.706$.

A second series of analyses were carried out to explore a possible enhanced saccadic ability in TS+ADHD+OCD group with the factor "Age" controlled. These analyses consisted of age-adjusted comparisons between the TS+ADHD+OCD group and another group repeated measure ANOVAs for each dependent variable: antisaccade error rate, antisaccade latency and prosaccade latency. In the ANOVA, the variable Condition was entered as the repeated factor and Groups was entered as the between subjects factor. In each comparison, the two groups were adjusted for age by excluding the data of the youngest(s) and/or the oldest(s) participant(s) to bring the average ages of the two groups closer. All pairwise comparisons were Bonferroni corrected for multiple comparisons. Although further effects emerged in these analyses, the overall pattern of findings still remained the same. The details of the analyses are reviewed below.

4.4.1. TS+ADHD vs TS+ADHD+OCD

In order to bring the average ages of the TS+ADHD and the TS+ADHD+OCD groups closer, the data of the 4 youngest participants in the TS+ADHD and the oldest participant in the TS+ADHD+OCD group were excluded (Adjusted-age of TS+ADHD: $M=164.6$ m, $SD=22.8$, $n=5$; Adjusted–age of TS+ADHD+OCD:

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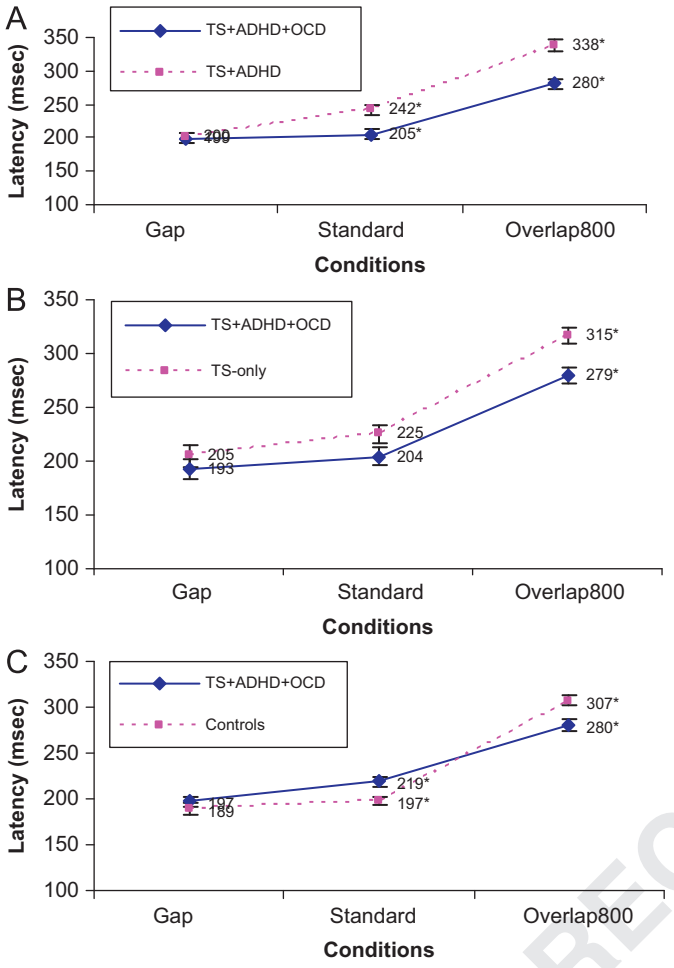

Fig. 4. Each graph illustrates the Age-adjusted prosaccade latency of the two groups being compared. Error bars are standard errors.

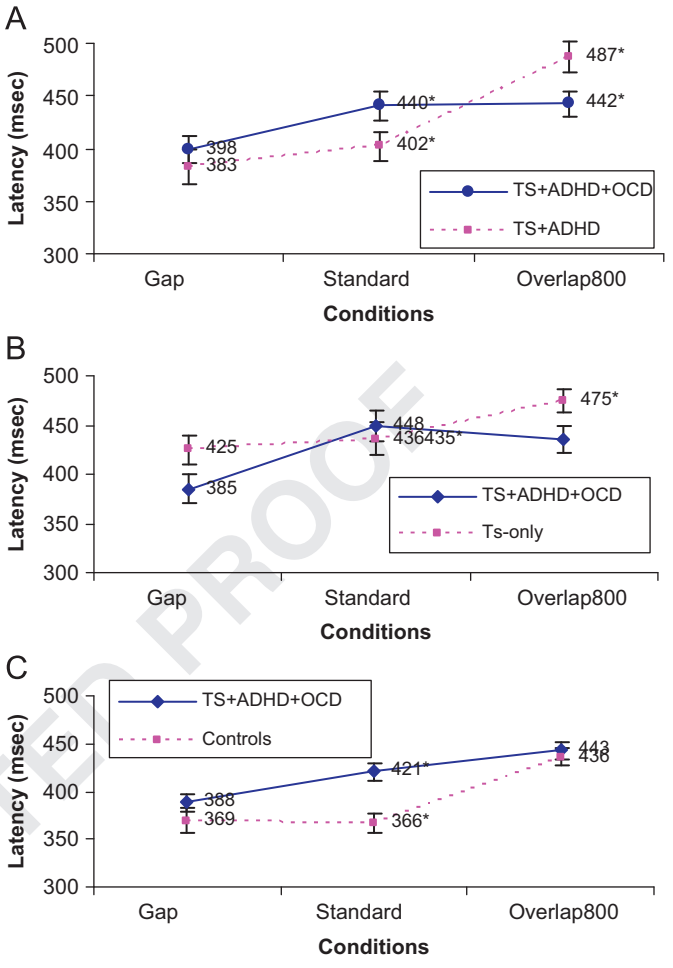

Fig. 5. Graphs illustrates the Age-adjusted antisaccade latencies of the two groups being compared following data exclusion. Error bars are standard errors.

$M=169.0$ m, SD$=18.9$, $n=6$). In the prosaccade latency, the ANOVA revealed a significant main effect of Condition, $F(2,17)=17.458$, $p<0.001$. The pairwise comparisons revealed that the TS+ADHD+OCD group displayed significantly shorter prosaccade latencies relative to those of the TS+ADHD group in the Standard Condition, $p<0.001$ and in the Overlap800 condition, $p<0.001$ (Fig. 4A).

The results from the antisaccade latency demonstrated a significant main effect of Condition $F(2,18)=12.2$, $p<0.001$ and a significant interaction effect of Groups*Condition, $F(2,18)=4.351$, $p=0.29$. The TS+ADHD+OCD group exhibited significantly shorter antisaccade latencies relative to those of the TS+ADHD group in the Overlap800 condition, $p=0.02$, but displayed significantly longer antisaccade latencies in the Standard condition, $p=0.046$ (Fig. 5A).

In the antisaccade error rate, the analysis revealed a significant interaction effect of Condition*Groups, $F(2,18)=3.672$, $p=0.046$. The pairwise comparisons revealed that the TS+ADHD+OCD group exhibited significantly lower rates of antisaccade errors relative to those of the TS+ADHD group in the Overlap800 condition, $p=0.001$ (Fig. 6A). Hence, all the significant effects that were present prior to the age-adjustments of the groups were still present following the age-adjustments. In order to determine whether the severity of the ADHD symptoms were significantly different between these two groups, an ANOVA was carried out to examine the differences between CGI-at-time and CGI-life-time between these two groups. The CGI-at-time of data collection $F(1,14)=0.847$, $p=0.373$ and the CGI-life-time $F(1,14)=0.011$, $p=0.918$ were not significantly different between the TS+ADHD and the TS+ADHD+OCD groups (Fig. 7). Hence, the difference in performance between these two group can not be attributed to Age or ADHD symptom severity.

4.4.2. TS-only vs TS+ADHD+OCD

In order to close the gap in average age in these the TS-only and TS+ADHD+OCD group, the data of the two youngest participants in the TS-only group (Age-adjusted $M=142$ m, SD$=14.7$, $n=4$) and the data of the three oldest participants in the TS+ADHD+OCD group (Age-adjusted $M=162$ m, SD$=19.8$, $n=4$) were excluded from this analysis. In the prosaccade latency, the ANOVA revealed a significant main effect of Condition, $F(2,11)=41.233$, $p<0.001$. The pairwise comparisons showed that the TS+ADHD+OCD group displayed shorter prosaccade latencies relative to those of the TS-only group which did not reach significance, $p=0.08$, in the Standard condition but was significant in the Overlap800 condition, $p=0.001$ (Fig. 4B).

In the antisaccade latency, there was a significant main effect of Condition, $F(2,14)=10.769$, $p=0.001$. The TS+ADHD+OCD group exhibited shorter antisaccade latencies relative to those of the TS-only which did reach significance in the Gap200 condition, $p=0.06$, but was significant in the Overlap800 condition, $p=0.038$ (Fig. 5B).

The results in the antisaccade error rate revealed a significant main effect of Condition, $F(2,14)=6.897$, $p=0.008$. However there were no significant differences between the groups (Fig. 6B). The findings here are consistent with those prior to age-adjustments of the groups and the significant effects between these two group in prosaccade and antisaccade latencies were still present.

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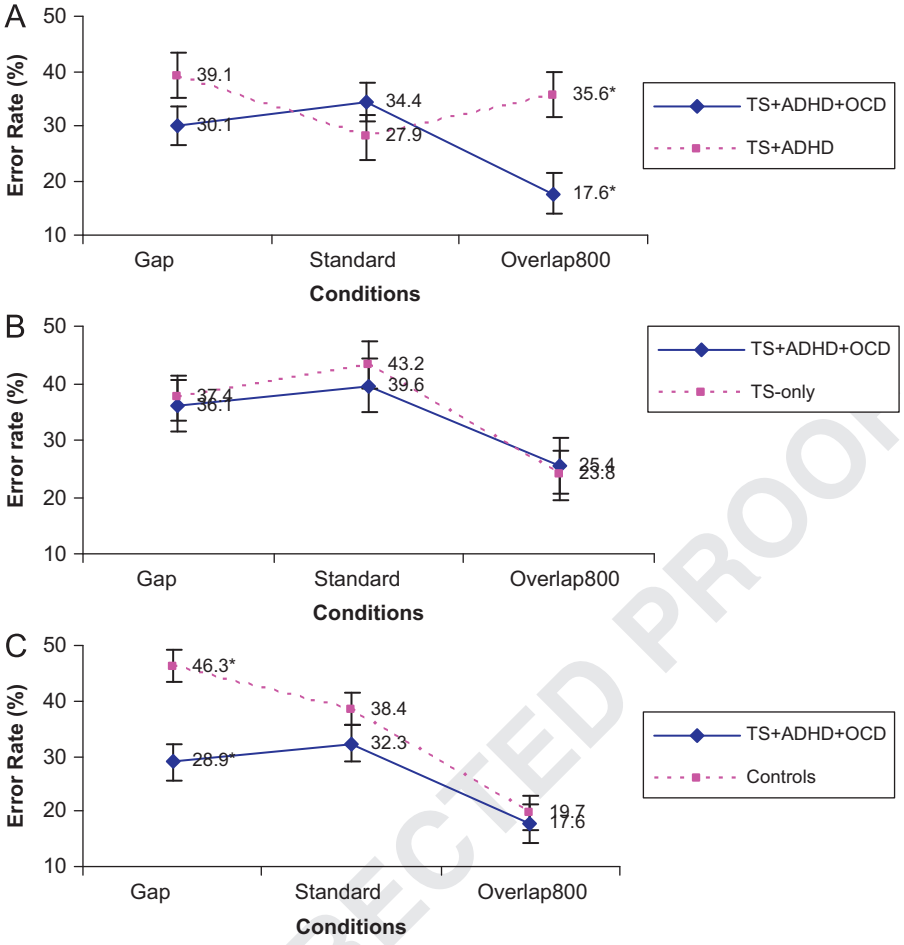

Fig. 6. Each graph illustrates the Age-adjusted antisaccade error rates of the two groups being compared. Error bars are standard errors.

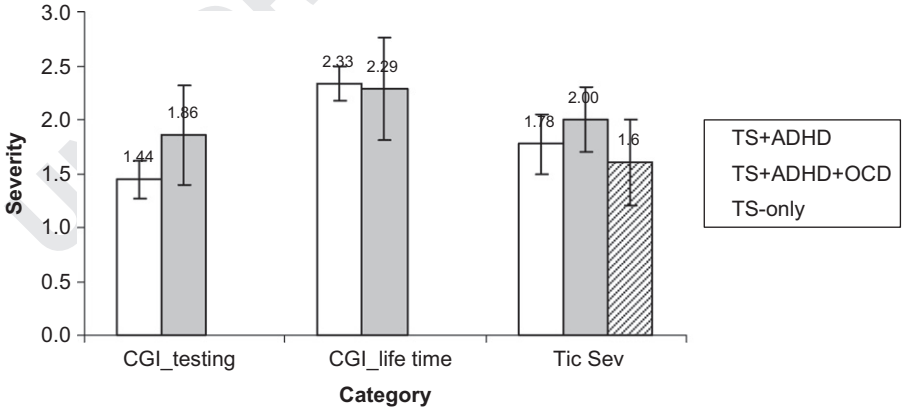

Fig. 7. The Clinical Global Impression of ADHD symptoms at the time of data collection (CGI_testing) and for life time (CGI-life time), in addition to the Tic severity are provided for the appropriate groups. Error bars are standard errors.

4.4.3. Controls vs TS+ADHD+OCD

In order to match the average ages of the Control and the TS+ADHD+OCD group, the data of the youngest participant in the Control group were excluded (Age-adjusted Control: $M=168$, SD=22.38, $n=8$; TS+ADHD+OCD: $M=173.1$, SD=20.5, $n=7$). In the prosaccade latency, the results indicated a main effect of Condition, $F(2,24)=45.570$, $p<0.001$. The TS+ADHD+OCD group displayed significantly shorter prosaccade latencies relative to those of the Control group in the Overlap800 condition, $p=<0.001$, but in the Standard condition the TS+ADHD+OCD group displayed significantly longer prosaccade latencies relative to those of the Control group, $p=0.003$ (Fig. 4C).

In the antisaccade latency, there was a significant main effect of Condition, $F(2,24)=15.136$, $p=<0.001$ and a significant interaction effect $F(2,24)=5.523$, $p=0.01$. The pairwise comparisons revealed that the TS+ADHD+OCD had significantly longer antisaccade latencies relative to those of the Control group in the Standard condition, $p<0.001$ (Fig. 5C). The longer saccadic latencies of the TS+ADHD+OCD group, along with the other TS-subgroups, relative to those of the Control group in the Standard condition is consistent with the findings prior to age-adjustment (Fig. 1A). Similarly, the

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TS+ADHD+OCD groups significantly shorter prosaccade latency relative to those of the Control group in the Overlap800 is consistent with our finding prior to age-adjustments of the groups.

The results in the antisaccade error rate demonstrated a main effect of Condition, $F(2,24)=6.517$, $p=0.005$. The pairwise comparisons revealed that the TS+ADHD+OCD group exhibited significantly lower rates of antisaccade error relative to those of the Control group in the Gap200 condition, $p<0.001$ (Fig. 6C). Taken all together, the same pattern of findings is revealed following the conservative method of age-adjustments of the groups. These findings confirm that the performance of the TS+ADHD+OCD group relative to the other groups is independent of the factor "Age".

4.5. Tic Severity and Saccade ability

In order to examine possible relationships between Tic Severity and oculomotor ability, Univariate analyses of variance were carried out for the dependent variables: Antisaccade Error Rate, Antisaccade Latency and Prosaccade Latency. The error terms were calculated with the variable Subject nested within tic severity. One patient participant did not have the tic severity ranking since the clinical information was not available and this subject was removed from this analysis. The Univariate ANOVAs revealed no significant effects in any of the dependent variables.

5. Discussion

5.1. Effect of Comorbidity and Fixation offset Manipulations

5.1.1. Latency

The results of the present study have demonstrated that both comorbidity and fixation offset conditions are important factors to control and both can contribute to inconsistent findings. Important observations may be missed or distorted when a heterogeneous sample of TS children is examined. Saccadic latency of TS participants have been found to be significantly longer (Straube et al.1997; LeVasseur et al. 2001; Munoz et al., 2002) normal (Bollen et al. 1988) and shorter (Jackson et al. 2007) relative to those of healthy controls. In the present study, when the TS participants were separated into TS-subgroups significant latency effects varied depending on the groups being compared and on the fixation-offset condition. For example, in the prosaccade Overlap800 condition, the TS+ADHD+OCD group displayed significantly shorter prosaccade latencies relative to those of the Control, the TS-only and the TS+ADHD groups (Fig. 1A). However, in the same condition, when the TS-entire group was examined (Fig. 1B), we found no significant difference in prosaccade latency between the Control and the TS-Entire groups. In this case, the significant differences between the TS+ADHD+OCD group and the other groups, including the Control group, were completely missed. Similarly, in the antisaccade Overlap800 condition, the TS+ADHD+OCD group exhibited antisaccade latencies comparable to those of the Control group. Whereas, the TS-only and the TS+ADHD groups displayed significantly longer antisaccade latencies relative to those of the Control group and the TS+ADHD+OCD group. When the TS-Entire group was examined, they displayed a significantly longer antisaccade latency relative to the Control group, obscuring the fact that children with TS+ADHD+OCD displayed similar antisaccade latencies to those of the Control group. Hence, varying the proportions of the participants with TS+ADHD+OCD, or TS+ADHD or TS-only within a single sample of children with TS can alter the overall group's average significantly in either direction, produce inconsistent findings and miss important observations.

5.1.2. Antisaccade Error Rate

Examination of this parameter also revealed that both comorbidity and Condition are confounding factors. For example, the TS+ADHD+OCD group exhibited significantly lower rates of antisaccade errors relative to the other groups in the Gap200 condition. However, TS-only and the TS+ADHD group displayed antisaccade errors at rates similar to those of the Control group in the same condition. When the TS-entire group was examined, they displayed significantly lower rates of antisaccade errors relative to those of the Control group. Hence, the TS+ADHD+OCD group's lower antisaccade errors rendered the TS-Entire group's average to a significantly low number relative to that of the Control group; although there were no significant differences between the Control group, the TS-only and TS+ADHD groups. The reverse pattern was revealed in a different condition. In Overlap800 condition, the TS+ADHD group made significantly higher rates of antisaccade errors relative to the other groups, who had similar antisaccade error rates relative to one another. However the TS-Entire group displayed significantly higher rates of antisaccade errors relative to the Control group, despite the facts that the TS-only and the TS+ADHD+OCD groups had similar antisaccade error rates to that of the Control group. These findings lend further support to the hypothesis that varying the composition of a sample of TS participants can alter the average antisaccade error rates for the entire TS-group to either direction in different conditions and contribute to inconsistent findings in the literature.

5.2. Saccadic profiles and Group Differences

5.2.1. The role of the co-morbid disorder

The TS+ADHD+OCD group, contrary to our original prediction, displayed an enhanced saccadic ability reflected by their overall lower antisaccade error rates and shorter antisaccade and prosaccade latencies which reached significant values relative to one or more groups under different fixation offset condition. This pattern of finding still remained following Age-adjusted comparisons between this group and the other groups. Thus, the TS+ADHD+OCD group's enhanced saccadic ability can not be attributed to the factor "Age".

Emerging evidences from series of studies have indicated enhanced motor abilities in children with TS. This ability does not appears to be a core symptom of TS, but an adaptive and compensatory mechanism developing due to frequently suppressing tic symptoms (Mueller et al., 2006; Jackson et al., 2007; Jackson, Parkinson, Jung, & Ryan, 2011). Mueller et al. (2006) observed that their TS group did not display a "cost" in performance when they switched between prosaccade and antisaccades in a block of trials. This finding was replicated and extended by Jackson et al. (2007) who confirmed the same pattern of observation and reported an enhanced cognitive ability in children with TS. Jackson et al. (2011) confirmed an enhanced motor control in children with pure-TS (children with comorbid ADHD and OCD were excluded from this sample, patients were receiving medication) in a manual switching task. They also used Diffusion-Weighted Imaging to investigate the myelination and density of axonal fibers in the prefrontal cortex in patients with TS. They revealed extensive alterations of white matter (WM) within the prefrontal cortex of the TS group reflected by reduced fractional anisotropy (FA) and increased mean diffusivity (MD) relative to those of the control group. These investigators proposed that children with TS gain control over their tic symptoms by developing an enhanced control over their motor output leading to changes in the microstructure of the white matter connecting the lateral and medial areas of the prefrontal cortex (forceps minor) and the neural networks connecting the prefrontal cortex with the primary and secondary motor areas creating a unique neurodevelopmental trajectory in these children. Data in our laboratory

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of the same group of children performing other oculomotor tasks have also revealed enhanced saccadic (in preparation) and smooth pursuit ability in the TS+ADHD+OCD group (Accepted, Aug 24 2011). The TS samples in the above studies (Mueller et al., 2006; Jackson et al., 2007; Jackson et al., 2011) excluded children with the comorbid ADHD and OCD. We propose that the hypothesis of enhanced motor control in children with TS should be expanded to include other populations of children with TS such as TS+comorbid groups ie TS+ADHD+OCD. Furthermore, this enhanced ability may result from not only suppressing tics, but from suppressing "unwanted behaviour" such as: tics, hyperactivity, compulsions and/or obsessions.

Further evidence supporting this hypothesis comes from imaging studies which have indicated larger prefrontal volumes in children with TS that has been interpreted as neural plasticity associated with frequently suppressing tics (Peterson et al., 2001; Plessen et al., 2004; Raz et al., 2009). Other studies have shown that patients with TS recruit a larger network of frontal and medial-frontal areas when successfully suppressing tics (Serrien, Orth, Evans, Lees & Brown, 2005). It is necessary to investigate this hypothesis further and expand our knowledge of this childhood onset disorder.

5.2.2. The role of the fixation/offset condition

The TS+ADHD group antisaccade error rate did not change across the different fixation offset conditions in contrast to those of the other groups. The antisaccade error rates of the TS-only, TS+ADHD+OCD groups and those of the healthy controls decreased significantly in the Overlap800 condition relative to their error rates in the Gap200 condition (Fig. 3A). Earlier reports have also observed significant reductions in antisaccade error rates in an Overlap condition relative to those in a Gap condition in healthy participants (Fischer and Weber, 1992; Fischer & Weber, 1997; Klein & Foerster, 2001). In the presents study, the TS+ADHD group was not able to reduce their antisaccade error rates in the Overlap800 condition and their error rates remained similar in all three conditions. This finding is consistent with that of Loe, Feldman, Yasui, and Luna (2009) who used oculomotor tasks, including the antisaccade task, to investigate cognitive control of children with ADHD. They observed that their healthy Control group improved their performance when interstimulus fixation (IS) periods were increased in the antisaccade task, but their ADHD group did not show the same improvement as a result of increased IS. They concluded that the children with ADHD were not able to use IS time to improve their performance. Similarly, our TS+ADHD group appears to be unable to improve their antisaccade error rates in the Overlap800 condition unlike the other groups.

In the present study, given that the comorbid ADHD was present in both TS+ADHD+OCD and the TS+ADHD groups, yet each group displayed unique saccadic profiles is interesting and supports the nosological hypothesis (Greimel, Herpertz-Dahlmann, Gunther, Vitt & Konrad, 2008). This hypothesis asserts that the combination of tic disorder and ADHD results in a unique behavioural profile not predictable from the knowledge of individual conditions. This hypothesis is mainly based on the observation of a unique ERP activity pattern in a comorbid group of Tic disorder+ADHD (Yordanova, Heinrich, Kolev & Rothenberger, 2006). Since, antisaccade behaviour has been shown to be associated with cognitive parameters such as inhibitory control (Hallett, 1978; Munoz & Istvan, 1998; Fukushima et al., 2000) and working memory (Roberts et al., 1994; Malone & Iacono, 2002), it is plausible that children with TS and different combination of comorbid conditions display unique cognitive behaviours as well. Further studies are required to examine inhibitory and working memory abilities in children with TS-only, TS+ADHD and TS+ADHD+OCD.

5.3. Limitations of the Present Study

Certain limitations in the present study must be addressed. Most of our patients were taking medication at the time of data collection and it was not ethical to ask these children to stop their medication for the purposes of data collection. However, antipsychotic medications do not appear to alter patterns of findings reported by many investigators (Crawford, Haeger, Kennard, Revelev & Henderson, 1995; Georgiou, Bradshaw, Phillops, Bradshaw & Chiu, 1995; Lynch, King, Green, Byth & Wilson-Davis, 1997; Straube et al., 1997; Green & King, 1998; LeVasseur et al., 2001).

In a recent paper, Reilly, Lencer, Bishop, Keedy and Sweeney (2008) reviewed the effects of various medications on oculomotor performances of healthy individuals and different patient populations. The most consistent finding in many studies examining the effect of various classes of medications such as benzodiazepines, first and second generation antipsychotics and antidepressants appears to be a decrease in the peak saccadic velocity in healthy participants. Since, saccadic peak velocity was not examined in the present study; alterations of this parameter as a result of medications are irrelevant in this context.

A study by Burk and Reveley (2002) indicated an improvement of antisaccade error rates of adult patients with Schizophrenia who were receiving Risperidone. In the present study, a number of our participants in the TS+ADHD group (three patients) and in our TS+ADHD+OCD group (two patients) were receiving Risperidone. In order to verify whether the significant effects of antisaccade error rate were the result of medication, the data of the patients who were receiving Risperidone at the time of data collection were excluded and the analysis on the antisaccade error rates was repeated. Following this data exclusion, the average antisaccade error rates of the TS+ADHD and the TS+ADHD+OCD groups increased and further significant differences emerged between the TS+ADHD group the other groups (Fig. 3C). However, the significant effects that were present prior to this data exclusion still remained and the pattern of enhanced antisaccade performance of the TS+ADHD+OCD group was still present. Hence, although Risperidone may improve antisaccade error rates, it did not change the patterns of an enhanced saccadic ability emerging from the TS+ADHD+OCD group relative to the other groups; and the higher rates of antisaccade errors displayed by the TS+ADHD group. In fact, removing the data of participants who were receiving Risperidone at time of data collection from the analyses strengthened the observation of higher antisaccade error rates in the TS+ADHD group leading to a greater difference between this group's antisaccade error rates and those of the other groups (Fig. 3C). Taken together, it appears that although medication is a valid factor to be considered and controlled as much as possible and our readers should exercise caution when interpreting the findings, a medication effect is not an adequate explanation for the difference in the pattern of findings in the present study. This view is especially strengthened in the light of similar findings reported by other researchers about an enhanced motor ability observed in children with TS (Jackson et al., 2007; Jackson et al., 2011; Mueller et al., 2006).

The other issue which needs to be addressed in this context is the differences in average ages of our groups. The aim of the present study was not to investigate the development of saccades and hence groups were not divided based on their ages. However, our attempt was to maintain the average ages of the groups similar between the groups in order to reduce any effects of "Age" on patterns of saccadic performances. One of the main findings of

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the present study has been the observation of an enhanced saccadic ability in the TS+ADHD+OCD. In order to determine whether the superior performance of this group could be explained by their older age, Age-adjusted comparisons by the way of data exclusions were carried out to close the gap between this group's average age and those of the other groups. In these series of analyses "Age" became well matched between the comparison groups. Despite the lost in power by utilizing a data exclusion method, the TS+ADHD+OCD group still displayed enhanced saccadic ability relative to the other TS subgroups. The reader, however, is cautioned when interpreting the findings between the TS-only and the TS+ADHD+OCD since the average ages of these groups were still different. Although the factor "Age" is a valid variable to investigate in children, this factor does not appear to be responsible for the pattern of an enhanced saccadic ability emerging from the TS+ADHD+OCD group.

The last issue, which deserves a comment, is our small sample sizes, which may have subjected our findings to type II errors (missing existing effects). Although we cannot exclude the possibility that with larger sample sizes additional smaller effects may surface, our sample sizes were adequate to detect statistically significant effects that we are reporting.

5.4. Conclusion

The present study has demonstrated that a heterogeneous sample of TS children composed of participants with different comorbid profiles requires a careful and detailed analysis. Ignoring the heterogeneity and analyzing them as one group will produce misleading results. We have established that each TS-subgroup exhibits a unique saccadic profile, supporting the nosological hypothesis (Greimel et al., 2008). The TS+ADHD group exhibited an inability to improve their antisaccade error rates and thus displayed significantly higher rates of antisaccade errors in the Overlap800 condition relative to the other groups. In contrast, the TS+ADHD+OCD group displayed an enhanced saccadic ability reflected by their significantly lower rates of antisaccade errors and shorter saccadic latencies. These findings lend further support to the hypothesis of an enhanced motor control present in certain groups of children with TS (Mueller et al., 2006; Jackson et al., 2007; Jackson et al., 2011). However, this enhanced ability may not be limited to Pure-TS groups but can also exist in other subgroups of children with TS such as TS+ADHD+OCD. It appears that certain children with TS gain control over their "unwanted behaviour" such as tics, hyperactivity, compulsive and obsessive urges by developing an enhanced self regulatory ability which may surface under certain experimental conditions. Since antisaccade behaviour has been shown to be associated with cognitive ability (Hallett, 1978; Roberts et al., 1994; Munoz et al. 1998; Fukushima et al. 2000; Malone & Iacono 2002), it is imperative that oculomotor and cognitive ability of children with multiple comorbid conditions such as TS+ADHD+OCD be investigated further. Research in this field is lacking and further understanding of the effect of comorbid conditions in TS is required.

Uncited references

(American Psychiatric Association (2000); Meeter, Van der and Theeuwes (2010))

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Appendix A. Supporting information

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