

Ocular motor indicators of executive dysfunction in fragile X and Turner syndromes [☆]

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Accepted 16 August 2006

Available online 14 November 2006

Abstract

Fragile X and Turner syndromes are two X-chromosome-related disorders associated with executive function and visual spatial deficits. In the present study, we used ocular motor paradigms to examine evidence that disruption to different neurological pathways underlies these deficits. We tested 17 females with fragile X, 19 females with Turner syndrome, and 40 females with neither disorder who comprised the comparison group. Group differences emerged for both the fragile X and Turner syndrome groups, each relative to the comparison group: Females with fragile X had deficits in generating memory-guided saccades, predictive saccades, and saccades made in the overlap condition of a gap/overlap task. Females with Turner syndrome showed deficits in generating memory-guided saccades, but not during either the predictive saccade or gap/overlap task. Females with Turner syndrome, but not females with fragile X, showed deficits in visually guided saccades and anti-saccades. These findings indicate that different brain regions are affected in the two disorders, and suggest that different pathways lead to the similar cognitive phenotypes described for fragile X and Turner syndromes.

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Keywords: Fragile X; Turner syndrome; Ocular motor; Executive function

1. Introduction

Fragile X and Turner syndromes are two X-chromosome-related disorders associated with neuropsychological deficits. Despite reports of deficits in memory, spatial, and executive function skills for persons with either disorder (as reviewed by Mazzocco & McCloskey, 2005), it remains unclear what primary neurobiological mechanisms underlie these corresponding cognitive phenotypes. The present study of ocular motor behavior was designed to investigate

possible mechanisms underlying the impairments associated with fragile X and Turner syndromes. Following a brief introduction to each disorder, we describe how ocular motor studies help to delineate neurological pathways that underlie cognitive deficits.

2. Fragile X and Turner syndromes

2.1. Fragile X syndrome

Fragile X syndrome is the most common known hereditary cause of mental retardation, occurring in approximately 1 per 4000 to 9000 individuals (Crawford, Acuna, & Sherman, 2001). In most individuals with fragile X, the disorder results from a mutation of a single gene on the X-chromosome (Verkerk et al., 1991). As an X-linked disorder, fragile X affects males more severely than it affects females. Nearly all males with fragile X (Bailey, Hatton, & Skinner, 1998), and approximately half of females with the

[☆] This work was supported by Grants NS 35356 awarded to Dr. M.B. Denckla and Grant RO1 HD 34061 awarded to Dr. Mazzocco. The authors thank the children who participated in this study and the children's parents; and acknowledge Research Assistants D. Lanham, J. Teisl, and G.F. Myers.

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disorder have mental retardation (Rousseau et al., 1994). The remaining females show varying degrees of impairment (Bennetto, Pennington, Porter, Taylor, & Hagerman, 2001; Mazzocco, 2001; Mazzocco, Pennington, & Hagerman, 1993), with significant lowering of Full-Scale I.Q. (FSIQ) scores relative to estimates based on familial intelligence (Reiss, Freund, Baumgardner, Abrams, & Denckla, 1995). However, the relatively “high functioning” females who do not have mental retardation nevertheless present with a cognitive phenotype (Abrams et al., 1994; Bennetto et al., 2001; Loesch et al., 2002; Mazzocco, Hagerman, Cronister-Silverman, & Pennington, 1992).

The reported fragile X cognitive phenotype includes deficits in executive function and working memory. When statistically accounting for the effects of low FSIQ, deficits in executive function are among the most robust and specific phenotypic features (e.g., Bennetto et al., 2001; Cornish, Munir, & Cross, 2001; Kirk, Mazzocco, & Kover, 2005; Mazzocco et al., 1992). This is in contrast to relatively spared basic language skills, including vocabulary and verbal memory, which are typically age appropriate in girls (Mazzocco, 2001) and women (Bennetto et al., 2001; Jäkälä et al., 1997; Mazzocco, Pennington, & Hagerman, 1994) with fragile X. In the present study, we assess whether deficits in ocular motor function support how a specific pathway may be associated with this manifestation of executive dysfunctions—broadly linked to frontal and prefrontal brain regions—in fragile X syndrome. We compare results from girls with fragile X to results from girls with Turner syndrome, another X-chromosome-related disorder with a characteristic cognitive phenotype.

2.2. Turner syndrome

Turner syndrome results from the total or partial loss of one of the two X-chromosomes typically present in girls. It occurs in 1: 2000 to 5000 live female births (Friás & Davenport, 2003). The global cognitive phenotype for Turner syndrome includes only slight lowering of IQ scores (Elliott, Watkins, Messa, Lippe, & Chugani, 1996; Mazzocco, 1998; Rovet, 1993; Temple & Carney, 1993), despite quite consistent group findings of specific difficulties on visual, visual memory, or executive function tasks. Verbal IQ scores typically exceed Performance IQ scores (Balottin et al., 1998; LaHood & Bacon, 1985; Pennington et al., 1985; Rovet & Ireland, 1994; Tamm, Menon, & Reiss, 2003).

Early studies of Turner syndrome led to the hypotheses of right hemisphere dysfunction (e.g., Alexander, Ehrhardt, & Money, 1966; Silbert, Wolff, & Lilienthal, 1977), although bilateral dysfunction was also proposed (Money, 1973; Pennington et al., 1985; Reiss et al., 1995). In general, findings regarding specific neuroanatomical correlates have been mixed, with inconclusive evidence of right versus bilateral, or frontal (Waber, 1979) versus parietal-occipital involvement (Brown et al., 2002; Murphy et al., 1993; Reiss, Mazzocco, Greenlaw, Freund, & Ross, 1995). Both verbal and visual short-term memory tasks appear difficult for

girls with Turner syndrome (Ross, Roeltgen, Feuillan, Kushner, & Cutler, 1998, 2000), whereas verbal skills are intact, and often above average (Bender, Linden, & Robinson, 1993; Elliott et al., 1996; LaHood & Bacon, 1985; Mazzocco, 2001; Rovet, 1993; Temple & Carney, 1995; Temple, Carney, & Mullarkey, 1996). The exception to generally strong verbal scores is slowed responding on rapid automatized naming (Mazzocco, 2001) and other oral fluency tasks (Temple, 2002) that suggest executive dysfunction.

Executive dysfunction in girls with Turner syndrome appears to be selective. Tamm and colleagues (2003) reported that girls with Turner syndrome have difficulty inhibiting a prepotent response set. On a computerized “Go/NoGo” task, girls with or without Turner syndrome showed an expected activation in frontal regions, but girls with Turner syndrome also showed more bilateral activation than comparison participants, specifically in the dorsal and superior frontal regions (Tamm et al., 2003). Considered together, these and other findings (e.g., Kirk et al., 2005; Temple et al., 1996) suggest difficulty inhibiting strongly prepotent responses and a lack of organization in rapid retrieval of information, but intact skills in planning ahead to execute a strategy, and intact ability to shift response set.

In addition to findings of executive dysfunction, there is a limited but growing literature on spatial deficits in Turner syndrome, indicating difficulties in visual perception (Alexander et al., 1966; Temple & Carney, 1995), visuo-constructional tasks (Alexander et al., 1966; Temple & Carney, 1995; Waber, 1979), and visual memory (Mazzocco et al., 2005). Indeed, some researchers report that visual working memory—versus visual, spatial, or visual memory skills per se—may be a hallmark deficit in girls with Turner syndrome (Buchanan, Pavlovic, & Rovet, 1998; LaHood & Bacon, 1985).

3. Contribution of ocular motor assessment to neuropsychological theory

Eye movement studies can be a useful complement to other diagnostic and exploratory methods, because ocular motor assessments afford a degree of quantification about signal processing and timing (i.e., latencies) that is not found in methods such as MRI and neuropsychological testing alone. Consequently, with judicious use of specific ocular motor paradigms, it is possible to assess involvement of areas known to be associated with ocular motor control. For example, in a study of the cognitive phenotype of Neurofibromatosis 1 (NF1), ocular motor findings implicated partial involvement of different components of a widely distributed cerebral network controlling saccade behavior, including areas in the basal ganglia pathways that modulate superior colliculus activity (Lasker, Denckla, & Zee, 2003). In a study of ADHD, ocular motor findings suggested that deficits in prefrontal functions, both motor and response inhibition, contributed to ADHD behaviors in children, and that stimulant medication appeared to ameliorate the motor

for the fragile X and Turner syndrome phenotypes. For instance, the parietal eye fields (PEF) are primarily involved in the generation of visually guided saccades (VGS). Lesions to this area usually result in an increase in saccade latency. The frontal eye fields (FEF) are involved in the generation of voluntary saccades (i.e., intentional saccades made to a predetermined location), whereas the dorsolateral prefrontal cortex (dlPFC) plays a role in inhibiting unwanted saccades to inappropriately presented stimuli, such as those that occur in an anti-saccade task (Leigh & Kennard, 2004; Gaymard, Francois, Ploner, Condy, & Rivaud-Pechoux, 2003; Gaymard, Ploner, Rivaud-Pechoux, & Pierrot-Deseilligny, 1999). Visual spatial memory involves the dorsolateral prefrontal cortex, which connects to a loop that includes the frontal eye fields, caudate nucleus (CN), substantia nigra pars reticulata (SNpr), and thalamus (Thal; Gaymard, Ploner, Rivaud, Vermersch, & Pierrot-Deseilligny, 1998). The dorsolateral prefrontal cortex is also involved in the control of memory-guided saccades (MGS), and—when damaged—it leads to an increase in errors in both MGS and in the anti-saccade task (AS) (Pierrot-Deseilligny, Israel, Berthoz, Rivaud, & Gaymard, 1993; Pierrot-Deseilligny, Rivaud, Gaymard, Müri, & Vermersch, 1995; Ploner, Rivaud-Pechoux, Gaymard, Agid, & Pierrot-Deseilligny, 1999). (See Table 1 for a detailed summary.)

4. The present study

In the present study, we used five eye movement testing paradigms based on the model of the ocular motor system described above, in order to measure neuropsychological performance implicated by ocular motor behavior. These paradigms were used to test the ability to generate reflexive

saccades (visually guided saccade paradigm), disengage fixation (gap/overlap paradigm), inhibit reflexive saccades and generate a volitional saccades (anti-saccade paradigm), inhibit and initiate volitional saccades (memory-guided saccade paradigm), and generate appropriately timed anticipatory saccades (predictive saccade paradigm). We hypothesized that group differences in ocular motor behavior would emerge for both the fragile X and Turner syndrome groups, relative to performance of girls in a comparison group. Specifically, we hypothesized that girls with Turner syndrome would have difficulty in generating visually guided saccades, based on evidence of compromised parietal areas in this population (Brown et al., 2002; Murphy et al., 1993; Reiss & Mazzocco et al., 1995). In view of the working memory deficits associated with both disorders, we hypothesized that girls with fragile X and girls with Turner syndrome would show increased latencies of memory-guided saccade. We also expected both groups to show increased difficulty in disengaging fixation, because this may reflect difficulty in shifting attention. In contrast, we hypothesized that girls with fragile X would not produce anticipatory errors in the memory-guided saccade task nor produce directional errors in the anti-saccade task, whereas girls with Turner syndrome would make these errors based on evidence for a lack of response inhibition in this group.

5. Methods

Informed consent for this study was obtained according to procedures approved by an institutional review board, prior to carrying out any of the procedures. Participants 18 years of age or older signed consent forms, whereas children below 18 years of age signed an assent form in the presence of the examiner. Parents of children under 18

Table 1
The effect of lesions on various cortical areas subserving saccade behavior

Oculomotor variable	Primary area of involvement	Effect of lesions ^a
Visually guided saccades	Parietal eye fields	↑ latency & ↓ accuracy
	Posterior internal capsule	↑ latency
Gap/overlap	Parietal eye fields	↑ latency gap & overlap
	Frontal eye fields	↑ latency overlap
	Anterior cingulate cortex	↑ latency overlap
Anti-saccades	Frontal eye fields	↑ latency
	Anterior cingulate cortex	% Errors in AS ↑
	Dorsolateral prefrontal cortex	% Errors in AS ↑ & % Errors in MGS ↑
Memory guided saccades	Parietal eye fields	↑ latency & ↓ accuracy
	Frontal eye fields	↑ latency & ↓ accuracy
	Prefrontal cortex	↓ accuracy
	Anterior cingulate cortex	↓ gain
	Anterior internal capsule	↑ latency & ↓ accuracy
	Caudate	↑ latency & ↓ accuracy as cue delay ↑
Predictive saccades	Frontal eye fields	% Predictive saccades ↓
	Prefrontal cortex	% Predictive saccades ↓

Note. Based on Funahashi et al. (1993); Israel et al. (1995); Pierrot-Deseilligny et al. (1995); Gaymard et al. (1998); Gaymard and Rivaud et al. (1998); Ploner et al. (1999); Vermersch et al. (1999); Milea et al. (2003) and Condy et al. (2004).

^a ↑ = increased, ↓ = decreased, ↔ = no change.

years of age signed consent forms. All consent and assent forms indicated that participation was voluntary.

5.1. Participants

Participants included 17 girls with fragile X syndrome, ages 7.5 to 22.1 years (mean age 14.6, $SD = 4.4$) and 19 girls with Turner syndrome, ages 7.6 to 20.8 years (mean age = 13.4, $SD = 3.9$), all with normal vision and hearing. The diagnosis was confirmed with DNA or karyotype testing, respectively. The participants were participating in a larger study on genetic aspects of learning disabilities. For that study, girls with fragile X or Turner syndrome were recruited through genetics and pediatric clinics, support groups, and through our institution's registry of families who inquired about research opportunities.

The comparison group included 40 girls, ages 7.7 to 20.9 years (mean age = 13.4, $SD = 3.7$), with neither fragile X nor Turner syndrome. These girls were recruited using notices distributed through local newspapers, and through clinics serving children with learning disabilities.

In order to focus on primary deficits rather than deficits secondary to mental retardation, recruitment for our study was limited to participants with an FSIQ > 80. IQ score was not, however, considered to be a variable for analysis, because of the lack of evidence that IQ is associated with eye movement latencies (e.g., Eden, Stein, Wood, & Wood, 1994; Goldberg et al., 2002). IQ scores available for children in the fragile X and Turner syndrome groups were obtained from one of a variety of methods, including administering a Wechsler test during the testing protocol, or accepting a Wechsler or alternative IQ test score as reported from an independent or school-based assessment from up to one year prior to enrollment. All participants from the comparison group attended school in a regular classroom setting with no accommodations or special education services.

5.2. Procedures

5.2.1. Preparation

Testing for this study occurred either as the first morning visit to our research center, or immediately following a lunch break. Upon entering the laboratory, the participant and one or both of her parents were shown the equipment and acquainted with the procedures. It was explained that either the participant or a parent could stop the testing at any time. Informed consent was then requested. Except when specifically requested by the participant, parents remained outside the room, but were able to see their child via a closed circuit video monitor.

5.2.2. Paradigm types

Five testing paradigms were used (see Appendix A). Two paradigms were designed to elicit reflexive saccades. The *Visually Guided Saccade Paradigm* (VGS) is used to establish a baseline for comparisons with other tasks, whereas

the *Gap/Overlap Paradigm* (ONG) is used to determine if participants have difficulty in releasing fixation. The *Anti-saccade Paradigm* (AS) is designed to test the suppression of reflexive saccades and the generation of volitional saccades to the opposite hemifield; the *Memory Guided Saccade Paradigm* (MGS) involves the role of visual spatial working memory. The *Prediction Paradigm* (PRED) is used to test the ability of the participants to anticipate (predict) the onset of a regularly repeated stimulus. Each paradigm is described in detail below.

5.2.3. Placement and apparatus

For all five paradigms, the participant sat in front of a tangent screen, on which an array of red light emitting diodes (LEDs) (3 milli-candela) were located at 0°, and at both right and left 10°, 20°, and 30°. Head movements were restricted with the use of a bite bar, except for the few children who were unable to tolerate it and with whom we used a chin rest. The bite bar resembled a pencil held between the teeth and consisted of a 1/4 in. non-porous plastic rod surrounded by a layer of dental wax (Allcezon Dental Wax, Missy, Inc.). The participants were instructed to bite down on the dental wax, in order to obtain an impression of their teeth. The bar was then placed into an adjustable holder. The participants were then asked to place their teeth back on the bar into the impression previously obtained, but not to bite down hard. Forward and backward adjustment of the holder was then made in order to obtain the most comfortable position for the participant.

Once a participant could maintain this position without discomfort, the assembly was locked into place to maintain a fixed distance between the participant and the target screen. This allowed participants to come off the bite bar if needed and to quickly relocate back onto the bar when ready to resume testing. The bar was tolerated quite well by even the youngest participants. Head stability was monitored throughout testing via a closed circuit video system. If a participant moved her head, the testing could be stopped until she was ready to resume.

5.2.4. Recordings

Target presentation was under computer control. Eye movements were recorded using bitemporal direct-current electrooculography (EOG) with an accuracy within 1° to 2°. The position signals were low pass filtered (90 Hz bandwidth) and digitized at a sample rate of 500 Hz. The data were stored on disk for off-line analysis.

5.3. Paradigm details

Prior to each test, the participant was told what task would follow. After hearing the task description, the participant was asked to repeat the instructions in her own words. This procedure was followed to increase the likelihood that the participant understood what was expected of her. In addition, because the AS task was the most difficult task to explain and to perform, each participant was given

specific practice trials in order to verify comprehension. Breaks were permitted during the testing, when appropriate.

5.3.1. Visually guided saccade paradigm (VGS)

This paradigm was used to test the ability of the participant to initiate saccades to a suddenly appearing visual stimulus. Each trial began with the illumination of the center LED. At a random time (1400 to 2400 ms), direction (right or left), and amplitude (10°, 20°, or 30°) one of the six peripheral LEDs illuminated, and the center LED turned off. Participants were instructed to “quickly move your eyes to the target.” One hundred trials were presented.

5.3.2. Gap/overlap paradigm (ONG)

This paradigm tested the effects of early or late removal of a central fixation target upon saccade latency. The three conditions used included a Gap Stimulus, a Neutral Stimulus, or an Overlap Stimulus. Each trial began with the illumination of the center LED. At a random time (1400 to 2400 ms), direction (right or left), and amplitude (20°), one of the two peripheral LEDs was illuminated. The center light went out at either 250 or 50 ms prior to LED illumination; and either simultaneously with LED illumination, or at 50 or 250 ms after illumination of the target LED. The instructions were the same as those presented for the VGS task. Two hundred trials were presented.

5.3.3. Anti-saccade paradigm (AS)

This paradigm was designed to test the ability of the participant to suppress reflexive saccades to a suddenly appearing visual stimulus, and to initiate a volitional saccade (i.e., the anti-saccade) into the dark mirror hemifield. Each trial began with illumination of a 0° LED. At a random time (1400 to 2400 ms), direction (left or right), and amplitude (10°, 20°, or 30°s), one of the peripheral LEDs was illuminated while the center LED was simultaneously extinguished. The participant was instructed to make a saccade to the mirror position, opposite to that of the illuminated LED; that is, the participant was asked to, “quickly move your eyes the *same distance* but in the opposite direction of the target light when it comes on.” For each trial, 750 ms after initial illumination of a LED, that LED was extinguished, and an LED located in the mirror position (e.g., in the location at which the participant should have looked) was illuminated. The participant was then required to look at the light. Using this method, it was possible to determine the discrepancy between where the participant actually looked and where the participant was instructed to look. The percentage of errors indicated the degree to which the individual was unable to suppress reflexive saccades to the illuminated LED. Sixty trials were presented.

5.3.4. Memory-guided saccade paradigm (MGS)

This paradigm was designed to test the ability of the participant to make a volitional saccade to a remembered target location. Each trial began with the illumination of the

center fixation LED, on which the participant was to focus. After a variable interval of 1 to 1.5 s, a 100 ms flash appeared at one of the target locations (right or left 10°, 20°, or 30°). After a variable interval of 3.5 to 4 s, the fixation light was extinguished, and at this point the participant was to look to the position where she believed the earlier 100 ms flash had occurred. After a variable interval of 1 to 1.5 s, the exact location of the earlier flash (i.e., the location to which the participant should have been looking) re-illuminated, and the participant was instructed to look at it. The participant was told, “as long as the center light is on, look only at the center light. *Do not* look at the flash when it occurs. When the center light goes out, then immediately look to the place where you saw the flash, keep looking there, and the light will come on where you should be looking. Look at that light when it comes on.” Sixty trials were presented.

5.3.5. Prediction paradigm (PRED)

The predictive paradigm called for the participant to look back and forth between two alternately illuminated LEDs located at left and right 10°. Three different frequencies were used (1.0, 0.5, and 0.25 Hz.). Each frequency was run as a single block with 30 trials in each block. The participants were asked to, “move your eyes in time with the lights.” This paradigm tested the ability of the participant to predict the timing between the illumination of each LED. Thirty trials were presented.

5.4. Data analysis

5.4.1. Variables

Saccade latencies, amplitudes and peak velocities were determined for each trial using an interactive program that allowed for verification of the accuracy of the eye movement trace. With the exception of the predictive paradigm, trials with negative latencies (e.g., saccades made before the presentation of the cue to move the eyes) were eliminated. Each trial was individually calibrated using the final eye position of the participant, to eliminate inaccuracies due to fluctuations in the amplitude of the corneoretinal potential of the electrooculography (EOG). To verify that the participants were looking at the target, they were required to maintain gaze at the final eye position for at least 500 ms. Latencies were computed from the time the cue appeared to when the saccade began, with the onset of the saccade defined when eye velocity reached 25°/s. Accuracy of saccades (gain) was expressed as a ratio of the amplitude of the initial eye movement to the amplitude of the final eye position (i.e., target position). Peak velocities were obtained with digital differentiation with a 0 to 40 Hz bandwidth. Means and standard deviations were computed for all latencies, peak velocities, and gains for saccades to each target position.

In the VGS, MGS, and AS paradigms, saccades that were initiated after the signal to move the eyes, but prior to 115 ms were defined as anticipatory; these were eliminated

from the analysis. We based this criterion on the finding that saccades with latencies less than 115 ms had a 50/50 chance of moving in the correct direction. For all paradigms, saccade trials with latencies greater than two standard deviations from the mean were eliminated to control for excessively long latencies, presumably as a result of inattention. In any given paradigm, fewer than 5% of the trials in each group needed to be eliminated for the above reasons.

5.4.2. Analyses

Statistical analyses were carried out with SYSTAT version 9, (SPSS Inc, Chicago, IL). Saccade latencies are age dependent (Munoz, Broughton, Goldring, & Armstrong, 1998; Ross, Radant, Young, & Hommer, 1994), so three-group MANCOVAs were computed with age as the covariant for analyses of normally distributed continuous variables. For data that were not normally distributed, the Kruskal–Wallis test was used with all three groups included.

Of greatest interest in this study were the planned pairwise comparisons, because our primary aim was to assess whether fragile X and Turner syndrome profiles differed, each relative to a comparison group. In view of our hypotheses, two separate sets of planned post hoc analyses were carried out with the comparison group and either the fragile X or Turner syndrome group. In third and final set of pairwise comparisons, the fragile X and Turner syndrome groups were compared each other. All pairwise comparisons were based on either parametric (ANCOVA or *t*-tests) or Mann–Whitney *U* statistics, for normally or non-normally distributed results, respectively.

For the VGS and MGS paradigms, the between-participants factor was Group (fragile X, Turner syndrome, comparison group), whereas the within-participants measures were latency, velocity and gain. Target position (10°, 20°, and 30°) was the repeated measure. For the AS paradigm, the between-participants factor was Group and the within-participants measures were latency, velocity, and gain of the anti-saccade. Target position (10°, 20°, and 30°) was the repeated measure. For the Gap/Overlap paradigm, the between-participants factor was Group and the within-participants factor was timing asynchrony (250 ms gap, 50 ms gap, 0 ms, 50 ms overlap and 250 ms overlap). For the MGS paradigm we also evaluated the percentage of premature saccades. Premature saccades, also called response suppression errors, were defined as eye movements made after the onset of the target flash but before the ‘go signal’ (when the straight ahead fixation light went out) to look at the flashed location. We also measured the percentage of errors made by each group in the AS paradigm. For the PRED paradigm, the between-participants factor was participant Group, whereas the within-participants measures were latency, velocity, or gain of the predictive saccade. Saccades with latencies between –200 and +100 ms were defined as predictive. We chose 100 ms as the maximum predictive range in view of the lack of any evidence that visually

guided saccades can be made at latencies less than 100 ms unless there is a gap between the disappearance of a fixation target and the appearance of another target in a new location (Smit & Van Gisbergen, 1989). We defined –200 ms as the lower limit of the predictive range in order to take into account the saccade duration, which is approximately 100 ms over the range of 20°; and the average variance of predictive latencies, which is about 100 ms (Isotolo, Lasker, & Zee, 2005).

6. Results

6.1. Preliminary analyses

There was no group difference in age at testing across the three participant groups, $p = 0.498$. As expected, there was an inverse correlation between age and the other variables measured. Therefore, age was included as a covariate in the subsequent parametric analyses.

6.2. Primary analyses using three group comparisons

The results of the three-group MANCOVA were significant for the majority of dependent variables. These are summarized in Table 2. Results of the subsequent planned pairwise comparisons are summarized in Tables 3 and 4, and are discussed below.

6.3. Fragile X and comparison groups

6.3.1. Visually guided saccades

In the visually guided saccade paradigm there were no main effects of participant group for saccade latency, velocity, or gain, nor for left or right-going saccades.

6.3.2. Gap/overlap

Group differences emerged in the ONG paradigm, but only for the 250 ms overlap condition, $F(1, 53) = 4.63$, $p = .04$. All other conditions produced latencies that were statistically indistinguishable between the two groups. When the latency for the 250 ms gap was subtracted from the latency for the 250 ms overlap condition, a significant group difference emerged, due primarily to the increased latency for the 250 ms overlap condition among girls with fragile X, $F(1, 53) = 9.29$, $p = .004$. There were no group differences in gain or velocity.

6.3.3. Anti-saccades

There were no group differences in the latency, velocity, or accuracy of saccades nor in the number of directional errors (saccades made incorrectly toward the visual target), during the anti-saccade task.

6.3.4. Memory-guided saccades

Several group differences emerged for the memory-guided saccades (MGS) task. In general, the latency of a saccade to a previously seen target is greater than the latency to a visible target. Both groups showed this

Table 2
Group least square means \pm SEM from three group comparisons

Oculomotor variable	Turner	Fragile X	Comparison	Test statistic
<i>Visually guided saccades</i>				
Latency, target right	235.0 \pm 8.5	217.8 \pm 9.0	214.9 \pm 5.8	$F_{2,72} = 1.96$
Latency, target left	42.2 \pm 7.6	208.4 \pm 8.0	212.3 \pm 5.2	$F_{2,72} = 6.40^{**}$
Latency, combined	38.6 \pm 8.0	213.1 \pm 8.2	213.6 \pm 5.3	$F_{2,72} = 4.02^*$
<i>Gap/overlap</i>				
Overlap minus Gap	165.9 \pm 9.6	173.2 \pm 9.7	138.0 \pm 6.4	$F_{2,69} = 5.82^{**}$
<i>Anti-saccades</i>				
Directional errors, %	49.9 \pm 3.8	40.6 \pm 4.1	34.3 \pm 2.5	K–W = 6.1*
<i>Memory-guided saccades</i>				
Latency	415.8 \pm 16.7	386.0 \pm 17.3	332.8 \pm 11.4	$F_{2,70} = 9.40^{***}$
Latency (Coeff of Var.)	31.2 \pm 1.9	36.4 \pm 2.0	30.2 \pm 1.3	$F_{2,70} = 3.43^*$
Gain, 30° target	0.82 \pm 0.03	0.79 \pm 0.03	0.88 \pm 0.02	$F_{2,70} = 3.91^*$
Gain (Coeff. of Var.)	36.0 \pm 2.1	32.1 \pm 2.2	25.9 \pm 1.5	$F_{2,70} = 8.20^{***}$
Response Suppression errors, %	30.4 \pm 2.9	21.8 \pm 3.0	16.8 \pm 2.0	K–W = 12.5**
MGS minus VGS	181.4 \pm 14.6	173.9 \pm 15.1	119.8 \pm 10.0	$F_{2,70} = 8.07^{***}$
<i>Predictive latency</i>				
1.0 Hz	45.1 \pm 21.1	71.9 \pm 21.9	33.5 \pm 14.2	$F_{2,71} = 1.08$
0.5 Hz	–88.1 \pm 27.5	–7.2 \pm 28.5	–91.4 \pm 18.5	$F_{2,71} = 2.79$
0.25 Hz	–61.5 \pm 54.3	28.6 \pm 56.2	–55.8 \pm 36.5	$F_{2,71} = 0.91$
<i>% Predictive saccades</i>				
1.0 Hz	50.8 \pm 5.0	51.0 \pm 5.3	64.9 \pm 3.4	K–W = 4.8
0.5 Hz	44.5 \pm 3.9	43.5 \pm 4.2	54.0 \pm 2.7	K–W = 2.9
0.25 Hz	13.8 \pm 2.6	8.4 \pm 2.5	18.3 \pm 1.6	K–W = 11.9**

Note. Results are from a three way MANCOVA or Kruskal–Wallis test statistic.

Coeff of Var (Coefficient of Variation = SD/mean).

* $p < .05$.

** $p < .01$.

*** $p < .001$.

expected increased latency for MGS for all target eccentricities. However, as seen in Fig. 2A, girls with fragile X took much longer to make saccades to a remembered target than girls in the comparison group. When we subtracted the latency of VGS from MGS latency, we observed that this difference was significantly larger for girls with fragile X than for girls in the comparison group, $F(1, 53) = 8.74$, $p = .005$, (Fig. 3A). There was a significant difference in the accuracy of saccades to the 30° target, $F(1, 53) = 7.25$, $p < .01$, but not to the 10° or 20° targets, $ps > .5$. There were no group differences in saccade velocity, nor in the percentage of premature saccades (response suppression errors). Girls with fragile X did exhibit a slight increase in response variability for latency and gain, $F(1, 53) = 6.08$, $p = .017$; $F(1, 53) = 5.86$, $p = .019$, respectively.

6.3.5. Predictive saccades

In the predictive task, girls with fragile X had longer latencies than girls in the comparison group. Although this was true for all of the frequencies tested (Fig. 5), differences were statistically significant at only the middle frequency (0.5 Hz, or one-half cycle per second), $F(1, 55) = 6.77$, $p = .012$; remaining $ps > .14$. There was also a significant difference between the two groups in the number of predictive saccades made for the lowest frequency (0.25 Hz) tested, $U = 544$, $p = .0008$.

In summary, relative to girls in the comparison group, girls with fragile X syndrome were less accurate at making memory guided saccades to the 30° targets; and had more difficulty generating memory-guided saccades, predictive saccades or saccades on one of the gap/overlap tasks. Girls with fragile X did not differ from the comparison group on either the visually guided saccade or anti-saccade tasks.

6.4. Turner syndrome and comparison groups

6.4.1. Visually guided saccades

Latencies of VGS for girls with Turner syndrome were longer for all of the target positions, relative to girls in the comparison group (Fig. 4). The saccade latencies for eye movements made to the left targets were the primary source of differences between these two groups, $F(1, 56) = 9.69$, $p = .003$. There was no group difference in velocity or gain, but girls with Turner syndrome exhibited a greater response variability of saccade gain, $F(1, 56) = 5.36$, $p = .024$.

6.4.2. Gap/overlap

Girls with Turner syndrome showed a consistent increase in saccade latencies for all conditions except the 250 ms gap. Although none of the individual conditions

Table 3
Group least square means \pm SEM for females with or without fragile X

Oculomotor variable	Fragile X	Comparison	Statistics
<i>Visually guided saccades</i>			
Latency, Combined	213.0 \pm 5.0	213.0 \pm 7.7	$F_{1,54} = 0.00$
<i>Gap/overlap</i>			
Overlap minus Gap	173.9 \pm 9.8	138.1 \pm 6.4	$F_{1,53} = 9.29^{**}$
<i>Anti-saccades</i>			
Directional errors, % ^a	40.6 \pm 4.1	34.5 \pm 2.5	M–W $U = 255$
<i>Memory-guided saccades</i>			
Latency	385.5 \pm 15.9	332.6 \pm 10.5	$F_{1,53} = 7.64^{**}$
Latency (Coeff of Var.)	36.5 \pm 2.2	30.1 \pm 1.4	$F_{1,53} = 6.08^*$
Gain, 30° target	0.79 \pm 0.03	0.88 \pm 0.02	$F_{1,53} = 7.25^{**}$
Gain (Coeff. of Var.)	32.1 \pm 2.1	25.8 \pm 1.4	$F_{1,53} = 5.86^*$
Response suppression errors, % ^a	21.3 \pm 2.4	16.9 \pm 1.6	M–W $U = 275$
MGS minus VGS	172.9 \pm 14.9	120.0 \pm 9.8	$F_{1,53} = 8.74^{**}$
<i>Predictive latency</i>			
1.0 Hz	73.2 \pm 20.8	37.1 \pm 13.3	$F_{1,55} = 2.12$
0.5 Hz	–6.7 \pm 23.8	–80.7 \pm 15.2	$F_{1,55} = 6.78^*$
0.25 Hz	23.9 \pm 57.2	–63.3 \pm 36.6	$F_{1,55} = 1.63$
% Predictive saccades ^a			
1.0 Hz	50.5 \pm 5.0	63.8 \pm 3.2	M–W $U = 444$
0.5 Hz	43.5 \pm 4.1	53.6 \pm 2.6	M–W $U = 428$
0.25 Hz	8.2 \pm 2.2	18.2 \pm 1.4	M–W $U = 545^{***}$

Note. Results are from a two way ANCOVA. Coeff of Var (Coefficient of Variation = SD/mean).

^a Mann–Whitney U .

* $p < .05$.

** $p < .01$.

*** $p < .001$.

reached statistical significance, subtracting the latencies for the 250 ms gap condition from latencies for the 250 ms overlap condition, produced a significant group difference relative to the comparison group. This was due to the increased latency shown by girls with Turner syndrome in the 250 ms overlap condition, $F(1, 53) = 7.45$, $p = .008$.

6.4.3. Anti-saccades

The Turner syndrome group made more directional errors during the AS tasks than did the comparison group, $U = 176$, $p = .01$. Nevertheless, for the anti-saccades (correct responses) there were no statistical group differences in latencies, velocities, or gains.

6.4.4. Memory-guided saccades

Girls in both the Turner syndrome and comparison groups showed an increased latency for MGS for all target eccentricities. However, girls with Turner syndrome produced significantly longer latencies relative to girls in the comparison group, $F(1, 54) = 17.6$, $p < .001$ (Fig. 2B). Subtracting the VGS latencies from the MGS latencies resulted in a substantial group difference, $F(1, 54) = 13.81$, $p < .001$ (Fig. 3B). There was a difference in the accuracy of saccades to the 30° target, $F(1, 54) = 4.50$, $p = .04$, but not to the 10° or 20° targets. There was no group difference in saccade velocity. Girls with Turner syndrome did exhibit more response variability than did girls in the comparison group in response gain, $F(1, 54) = 16.91$,

$p < .001$; and also made more premature saccades (response suppression errors) than did girls in the comparison group, $30.8 \pm 2.9\%$ vs. $17.2 \pm 2.0\%$, respectively, $U = 192$, $p = .006$.

6.4.5. Predictive saccades

There were no group differences in latencies in the predictive paradigm for all of the frequencies tested (Fig. 5). There was also no group difference in the number of premature saccades made at any frequency, $ps > .074$.

In summary, relative to the comparison group, girls with Turner syndrome showed deficits in generating visually guided saccades, memory-guided saccades, and anti-saccades. However, latencies in the predictive paradigm were comparable across groups. In the gap/overlap task, only the overlap-gap group difference was statistically significant.

6.5. Fragile X and Turner syndrome groups

6.5.1. Visually guided saccades

As anticipated, there was a significant difference between the fragile X and Turner syndrome groups in VGS latencies combined, $F(1, 33) = 4.98$, $p = .033$ (Table 1). No other statistically significant differences emerged between these two groups for any of the other ocular motor tasks. Although direct comparisons of these two

Table 4
Group least square means \pm SEM for females with or without Turner syndrome

Oculomotor variable	Turner	Comparison	Statistics
<i>Visually guided saccades</i>			
Latency, target right	236.5 \pm 8.9	216.4 \pm 6.0	$F_{1,56} = 3.61$
Latency, target left	243.4 \pm 7.9	213.5 \pm 5.4	$F_{1,56} = 9.69^{**}$
Latency, targets combined	240.0 \pm 8.0	215.0 \pm 5.5	$F_{1,56} = 6.71^*$
<i>Gap/overlap</i>			
Overlap minus Gap	167.8 \pm 8.6	139.4 \pm 5.7	$F_{1,53} = 7.45^{**}$
<i>Anti-saccades</i>			
Directional errors, % ^a	50.6 \pm 3.8	34.7 \pm 2.5	M–W $U = 176^*$
<i>Memory-guided saccades</i>			
Latency, ms	418.1 \pm 16.5	334.6 \pm 11.2	$F_{1,54} = 17.60^{***}$
Latency (Coeff of Var.)	31.2 \pm 1.9	30.2 \pm 1.3	$F_{1,54} = 0.22$
Gain, 30° target	0.79 \pm 0.03	0.88 \pm 0.02	$F_{1,54} = 4.50^*$
Gain (Coeff. of Var.)	36.3 \pm 2.1	26.1 \pm 1.4	$F_{1,54} = 11.54^{***}$
Response suppression errors, % ^a	30.8 \pm 2.9	17.2 \pm 2.0	M–W $U = 192^{**}$
MGS minus VGS	182.5 \pm 13.8	120.4 \pm 9.4	$F_{1,54} = 13.81^{***}$
<i>Predictive latency</i>			
1.0 Hz	47.4 \pm 21.1	34.9 \pm 14.1	$F_{1,55} = 0.24$
0.5 Hz	–87.0 \pm 28.0	–79.3 \pm 18.8	$F_{1,55} = 0.05$
0.25 Hz	–65.0 \pm 58.3	–57.4 \pm 39.2	$F_{1,55} = 0.01$
<i>% Predictive saccades^a</i>			
1.0 Hz	50.8 \pm 5.0	64.5 \pm 3.3	M–W $U = 462$
0.5 Hz	44.5 \pm 3.9	53.3 \pm 2.6	M–W $U = 440$
0.25 Hz	13.8 \pm 2.6	18.1 \pm 1.8	M–W $U = 466$

Note. Results are from a two way ANCOVA. Coeff of Var (Coefficient of Variation = SD/mean).

^a Mann–Whitney U .

* $p < .05$.

** $p < .01$.

*** $p < .001$.

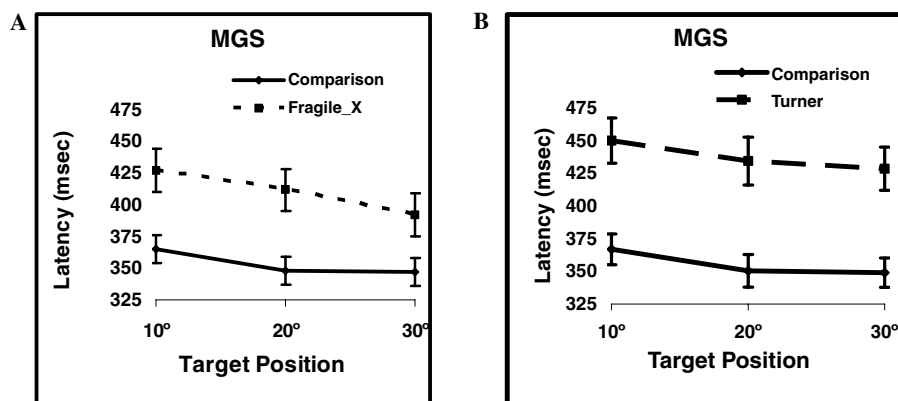


Fig. 2. For MGS, females with (A) fragile X and (B) Turner syndrome produced latencies that were significantly longer than those for the comparison participants.

groups revealed only this one area of difference, the profile patterns relative to comparison groups suggests additional group differences in neuropsychological pathways, which we review in the discussion that follows.

7. Discussion

The aim of the present study was to use eye movement paradigms to infer differences in the underlying neurobiological mechanisms in children with fragile X or Turner

syndrome, two developmental disorders with globally similar cognitive phenotypes. Based upon previous neuropsychological and neuroimaging studies, we hypothesized that girls with Turner syndrome would have difficulty in generating visually guided saccades, but that girls with either syndrome would show deficits in latencies during memory-guided saccades. We also expected girls with fragile X would not produce anticipatory errors in the memory-guided saccade task nor produce directional errors in the anti-saccade task, whereas girls with Turner

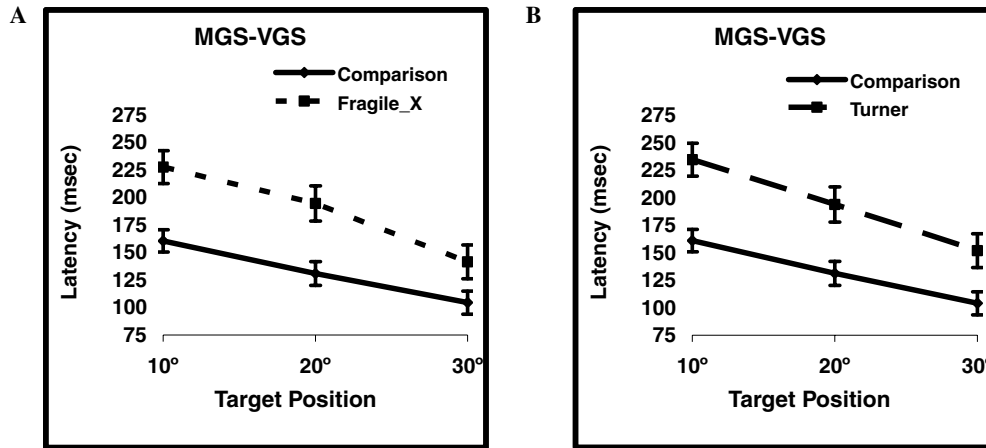


Fig. 3. Subtracting VGS latencies from MGS latencies for each target position reveals a significant disparity between females in the (A) fragile X and (B) Turner syndrome groups compared with the comparison group, indicating that memory is affected.

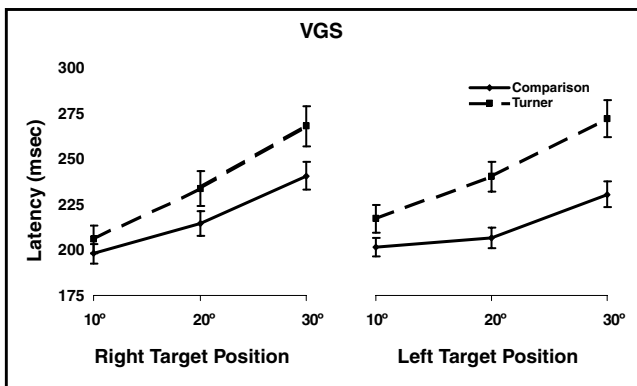


Fig. 4. Females with Turner syndrome took a longer time to generate visually guided saccades for both right and left target positions than did females in the comparison group.

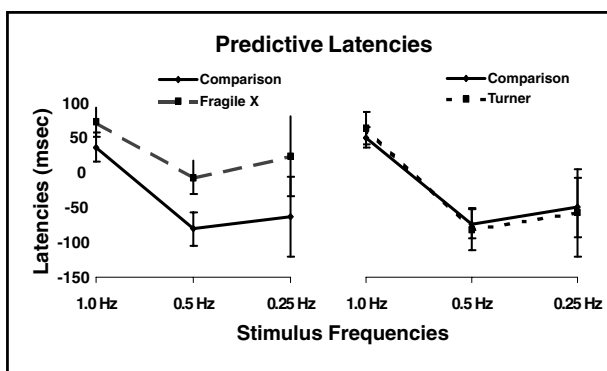


Fig. 5. Mean predictive latencies for females with fragile X or Turner syndrome. Females with fragile X are less successful at lowering their predictive latencies compared to females in the Turner syndrome or comparison groups.

syndrome would make these errors. Our results support these hypotheses. The neurobiological mechanisms that underlie these apparent impairments are of particular interest to neuropsychologists, both as an explanation for the reported phenotypes and as models of neurobiological pathways leading to executive dysfunction.

7.1. Fragile X and Turner syndrome phenotypes: Differences in ocular motor performance

7.1.1. Differences in visually guided saccades

The primary difference between the fragile X and Turner syndrome groups was observed in the VGS task. Specifically, girls with fragile X showed no difference in VGS latency, velocity or accuracy, relative to girls in the comparison group, implying that basic visual motor control is not compromised in fragile X. In contrast, girls with Turner syndrome took longer to make VGS compared with girls in either the fragile X or comparison groups; however, saccade accuracy and speed were within normal limits. Although saccade latency typically increases as a function of target eccentricity, there was a greater effect of eccentricity on the latencies for left-going saccades, for girls with Turner syndrome. Increases in VGS latency are observed with structural (Pierrot-Deseilligny, Rivaud, Gaymard, & Agid, 1991) or functional (using transcranial magnetic stimulation) (Elkington, Kerr, & Stein, 1992) lesions of the posterior parietal cortex (PPC). In addition, the right PPC appears to have a larger effect on VGS latency than does the left PPC (Law, Svarer, Holm, & Paulson, 1997; Pierrot-Deseilligny et al., 1991). Additional evidence comes from a study by Mort and colleagues (2003), who contrasted reflexive and voluntary saccade generation using event-related fMRI, and found increased activation of the right angular gyrus of the inferior parietal lobule for VGS compared with voluntary saccades. This collection of findings is consistent with the notion that Turner syndrome is associated with dysfunction of the right parietal lobe (McGlone, 1985; Money, 1973) or the right cerebral hemisphere (Silbert et al., 1977). This contention, however, is only partially supported by MRI findings that suggest a wider range of neuroanatomical abnormalities including reduced right prefrontal volume (Reiss et al., 1993) and bilateral decreases in both white and gray matter surrounding larger than normal lateral ventricles (Ross, Reiss, Freund, Roeltgen, & Cutler, 1993).

7.2. Phenotypic differences in profiles relative to a comparison group

Although no further differences emerged from pairwise comparisons between the fragile X and Turner syndrome groups, there were additional differences in the profile that each of these groups displayed relative to the comparison group. As evident in Table 2, girls with fragile X often had an intermediate level response relative to the two remaining groups; thus differences were often larger between the Turner syndrome and the comparison groups than between the fragile X and the comparison groups, as discussed below. This observation suggests that it would be useful to compare effect sizes between the respective syndrome group and the comparison group, which we do below using Cohen's d , comparing differences in group means relative to the groups' standard deviation.

7.2.1. Gap/overlap

Relative to girls in the comparison group, girls in both the fragile X and Turner syndrome groups took longer to make a saccade in the overlap condition than in the gap condition. Girls from the two syndrome groups did not differ from each other, and differences were comparable for each syndrome group relative to the comparison group, $d=0.53$ and 0.55 , respectively. This suggests an inability to disengage fixation, compared to the gap condition in which fixation is released by turning off the fixation light prior to target light onset. The longer the fixation light remained on after the target light had illuminated, the longer it took for the girls with fragile X or Turner syndrome to make the required eye movement. This finding implies a functional deficit in the frontal cortex, which has been implicated in controlling attentional fixation (Pierrot-Deseilligny, Milea, & Müri, 2004; Rivaud, Müri, Gaymard, Vermersch, & Pierrot-Deseilligny, 1994).

The frontal eye fields (FEF) also work in conjunction with the dorsomedial prefrontal cortex (dmPFC) to control active fixation in addition to generating volitional eye movements (Bon & Lucchetti, 1992). In a study of the dmPFC in the macaque monkey, Bon and Lucchetti (1992) found that cells discharged during active fixation but not when the eye was simply looking at a position; they concluded that these neurons are involved in attentional fixation. In addition, other saccade-related neurons discharged when the monkey made self-generated eye movements, implying that the dmPFC may share—along with the FEF—intentional motor behaviors. This is consistent with attentional difficulties reported for girls with fragile X or Turner syndrome.

7.2.2. Anti-saccades

On the AS task, participants with fragile X had performance levels comparable to girls in the comparison group, whereas girls with Turner syndrome made significantly more errors than did girls in the comparison group. In

practical terms, this reflects not being able to suppress the saccade to the illuminated LED. The ability to cancel a reflexive saccade requires an intact dorsolateral prefrontal cortex (Milea, Lobel, Lehericy, Pierrot-Deseilligny, & Berthoz, 2005; Müri et al., 1998; Pierrot-Deseilligny et al., 2003; Pierrot-Deseilligny et al., 1991); thus our findings imply more significant dysfunction of the dorsolateral prefrontal cortex in girls with Turner syndrome, relative to girls with fragile X syndrome. Although this was not apparent when comparing the two groups to each other, effect sizes relative to the comparison group differed, Cohen's $d=0.74$ and 0.34 , respectively.

7.2.3. Memory-guided saccades

In contrast to the visually guided saccades (VGS task), for which only girls with Turner syndrome were impaired, girls with either fragile X or Turner syndrome took much longer to generate memory-guided saccades (MGS) than did girls in the comparison group. The saccade latencies in the MGS task were similar between the two groups, as was saccade accuracy. Effect sizes for latency, relative to the comparison group, however, were large for the Turner syndrome group, $d=0.99$; but only moderate for the fragile X group, $d=0.64$. Processes guiding the generation of memory-guided saccades and visually guided saccades share a number of pathways. When we subtracted the latencies of visually guided saccades from the latencies of memory-guided saccades, girls in both the fragile X and Turner syndrome groups continued to show a larger increase in latency, relative to the comparison group, with comparable effect sizes of 0.81 and 0.96 , respectively. Both the fragile X and Turner syndrome groups showed a moderate decrease in gain for saccades made to the 30° target, d 's = 0.61 and 0.47 , respectively, but not for the 10° or 20° targets. There was an overall increase in the coefficient of variation for the gain. Both of these findings imply a deficit in spatial accuracy. Lesions in the frontal eye fields impair memory guided saccades, as do lesions in the dorsolateral prefrontal cortex (Pierrot-Deseilligny, Ploner, Müri, Gaymard, & Rivaud-Pechoux, 2002; Ploner et al., 1999), striatum (Vermersch, Gaymard, Rivaud-Pechoux, Ploner, & Agid, 1999), thalamus (Pierrot-Deseilligny et al., 1995), and anterior cingulate cortex (Gaymard & Rivaud et al., 1998). Variability of MGS gain has also been linked to the dlPFC even when MGS gain appears to be normal (Pierrot-Deseilligny et al., 2003). Thus, although the two groups showed the same type of deficits, the differences in effect size suggest that the deficits differed by degree. Therefore, it may be that the same brain area (i.e., the dlPFC) is affected, but to different extents, in the two syndrome groups; or that more than one neuroanatomical area contributes to saccade accuracy in the MGS task, with comparable outcomes resulting from different functions across the fragile X and Turner syndrome groups.

The hypothetical circuitry (Fig. 1) involved in memory-guided behaviors consists of the parietal eye fields (PEF), dorsal lateral prefrontal cortex (dlPFC), frontal eye fields

(FEF; Pierrot-Deseilligny et al., 2002; Ploner et al., 1999); caudate nucleus (CN), substantia nigra pars reticulata (SNpr; Vermersch et al., 1999); and thalamus (Pierrot-Deseilligny et al., 1995). Lesions of either the dIPFC or FEF have been shown to disrupt the generation of memory-guided saccades (Ploner et al., 1999; Rivaud et al., 1994), possibly through a feedback loop involving the FEF, CN, SNpr, thalamus, and back to the FEF (Gaymard et al., 1998). Simply put, this loop appears to provide a short-term store for information that can be accessed for up to about 20 seconds (see Pierrot-Deseilligny et al., 2004). Lesions to the caudate nucleus have also been shown to impair memory-guided saccades (Gaymard et al., 1998; Vermersch et al., 1999) possibly as part of the above-mentioned feedback loop. Working together, the CN along with the thalamus, SNpr, FEF, dIPFC, and PEF could store visual information that is used to direct the eyes to the previously attended location. Consequently, for a short period (up to about 20 s; Pierrot-Deseilligny et al., 2002) the location of the target is thought to be maintained within this circuit until the signal to move the eyes to the remembered target occurs (Gaymard et al., 1998). For longer memory periods, other areas—such as the parahippocampus and hippocampal formation—are believed to play an important role. Girls with fragile X and with Turner syndrome took about 60 ms longer than girls in the comparison group to generate saccades in the memory-guided paradigm. This could reflect a delay in passing the command signal from the FEF to the ocular motor generating circuits, either as a result of delays in the FEF or in the basal ganglia pathways (CN and SNpr) that connect to the superior colliculus (SC). As previously stated, the girls with Turner syndrome showed a larger effect size for memory-guided saccades than did girls with fragile X. Unlike girls with fragile X, girls with Turner syndrome showed impairment of visually guided saccades relative to the comparison group, which implies involvement of the parietal cortex.

The parietal cortex has been shown to be involved in shifts of attention. In a study by Cutrell and Marrocco (2002), sub-threshold electrical PPC stimulation by micro-electrodes in monkeys induced shifts of attention, without evoking saccadic eye movements. The intention to make an eye movement to a stimulus rather than to simply attend to its presentation also appears to involve the parietal cortex (see Snyder, Batista, & Andersen, 2000, for a review). The parietal cortex and frontal cortex are reciprocally connected and certainly interact with each other during generation of saccades of all types. Recently, Hart et al. (2006), using fMRI to study the neural circuitry of working memory, found reduced frontoparietal activity in a group of girls with Turner Syndrome relative to a comparison group. Thus, communication between the frontal and parietal eye fields appears to be important in directing attention to specific locations. It follows that reduced communications between the two areas affects the intentional control of eye movements and could delay the abil-

ity to generate a saccade to the appropriate target. Finally, the anterior cingulate cortex (ACC) may also play a role in memory-guided saccades, as it appears to be involved with the preparation of intentional eye movements (Gaymard & Rivaud et al., 1998; Pierrot-Deseilligny et al., 2004).

In the memory-guided saccade paradigm (as in the AS paradigm), girls with Turner syndrome also showed suppression errors, by making premature responses during the memory-guided saccade task. Together, the different deficits in the memory-guided saccade task support the contention that the areas most affected in Turner syndrome are the FEF and dIPFC, as lesions in these areas have been shown to increase memory-guided saccade latency (Rivaud et al., 1994), decrease the ability to inhibit the generation of inappropriate saccades, and increase variability in the amplitude of memory-guided saccades (Pierrot-Deseilligny et al., 2003; Ploner et al., 1999).

Girls with fragile X did *not* make more suppression errors in the memory-guided saccade task, nor did they make more errors in the AS task, relative to girls in the comparison group. Nevertheless, relative to the comparison group, girls with fragile X did have more variability in the amplitude of their memory-guided saccades. It is possible, then, that the dIPFC may still be affected in girls with fragile X, but to a lesser extent; or that areas within the basal ganglia (i.e., the CN or SNpr) are those that are affected in fragile X.

7.2.4. Predictive saccades

Prediction is defined as the ability of a participant to anticipate the onset of an LED when it is presented as a regularly timed stimuli. Deficits of predictive saccades are associated with dysfunction in the frontal eye fields (Rivaud et al., 1994) and basal ganglia (Bronstein & Kennard, 1985; Tian, Zee, Lasker, & Folstein, 1991). Relative to the comparison group, girls with Turner syndrome did not show deficits in prediction, suggesting an intact frontal eye field, basal ganglia, and associated pathways. On the other hand, girls with fragile X did show deficits in prediction even at what is usually the optimal frequency for predictive tracking. It has been suggested that deficits in prediction also result from generalized basal ganglia dysfunction, based on studies of persons with Parkinson (Bronstein & Kennard, 1985; Ventre, Zee, Papageorgiou, & Reich, 1992) or Huntington's disease (Tian et al., 1991). Persons with Parkinson disease have dopamine depletion due to decreased dopamine from the substantia nigra pars compacta (SNpc), whereas those with Huntington disease have reduced levels of dopamine in both the putamen and caudate nucleus (Sedvall et al., 1994; Spektor et al., 2002; Weeks, Piccini, Harding, & Brooks, 1996). It therefore appears that, for typical predictive behavior, the frontal eye field and basal ganglia work together. Consequently, one may speculate that females with fragile X have involvement

of the basal ganglia in addition to the frontal eye field, possibly due to reduced dopamine.

7.3. Full-scale IQ as a possible covariate

The lack of systematic IQ testing, and the absence of individual scores for the control group, prevented including IQ as a meaningful covariate in any of the analyses. It is likely that FSIQ scores for the group with fragile X were lower than for the Turner syndrome and comparison groups, because this would be representative of the populations from which the participants were drawn. However, the participants with fragile X represented relatively high functioning individuals within their population, because only girls without mental retardation were included in the study. Still, it is unlikely that IQ differences between the fragile X and Turner syndrome groups accounted for their group differences in ocular motor behavior, because the most significant difference to emerge (on visually guided saccades) was in the direction of more impaired performance by the Turner syndrome group, which is likely to have had a higher mean IQ score. Our decision to omit IQ as a variable was based in part on the lack of valid IQ scores available for the comparison group and the lack of consistent IQ testing for the syndrome groups, but primarily on the evidence that IQ is not correlated with eye movement behaviors, whether it involves reading (Eden et al., 1994), VGS, MGS, or AS tasks (Goldberg

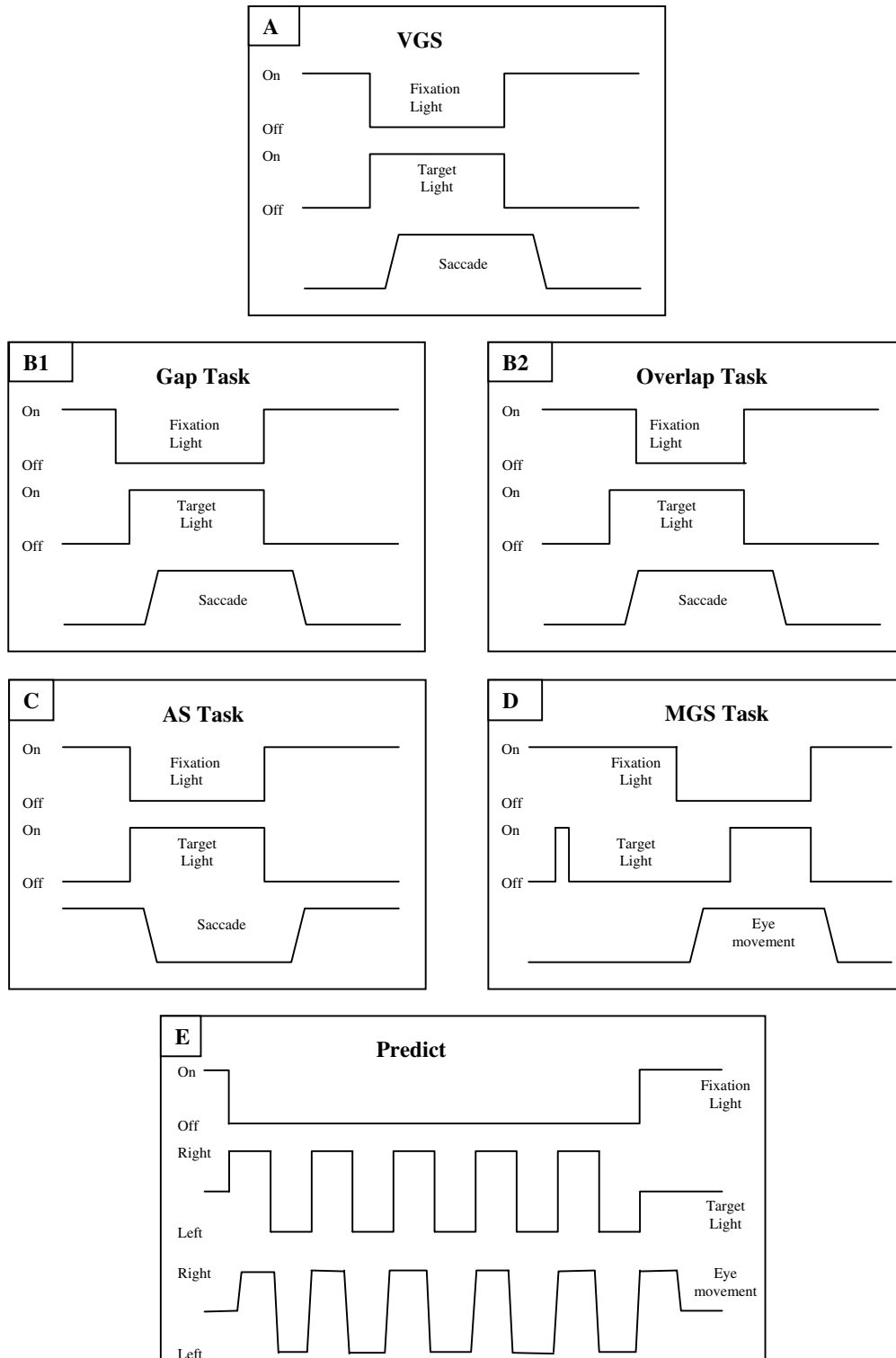
et al., 2002), or vestibular ocular reflex (VOR) time constants (Goldberg, Landa, Lasker, Cooper, & Zee, 2000).

7.4. Conclusion

The ocular motor findings from the present study demonstrate important distinctions between two different developmental disorders associated with globally similar cognitive phenotypes. The findings support the contention that the use of ocular motor paradigms may contribute to our understanding of the complexities that underlie constructs such as “executive function” and “visual spatial” difficulty. Our findings, of course, are limited to the areas implicated by the ocular motor circuitry illustrated in the Fig. 1, but these areas are relevant to the cognitive deficiencies reported for fragile X or Turner syndromes (see Appendix B). Our findings suggest that deficits in girls with Turner syndrome are associated with multiple brain regions including the parietal eye fields, frontal eye fields, dorsolateral prefrontal cortex, and basal ganglia. The regions implicated in girls with fragile X also appear to include the frontal eye fields, possibly basal ganglia, and the dorsolateral prefrontal cortex but to a lesser degree. Although these results do not preclude brain regions that we did not assess, the findings suggest that different neurological pathways underlie the cognitive deficits reported for girls with fragile X versus Turner syndrome, and that there is greater specificity in fragile X and more widespread effects in Turner syndrome.

Appendix A

(A) The *visually guided saccade paradigm* (VGS), tests the ability to generate reflexive saccades towards a novel target and establishes a baseline for comparisons with other tasks. (B1 Gap & B2 Overlap) The *gap/overlap paradigm* (ONG) tests the ability to generate reflexive saccades and fixation release. (C) The *anti-saccade paradigm* (AS) tests the suppression of reflexive saccades, and the generation of volitional saccades to the opposite hemifield. (D) The *memory guided saccade paradigm* (MGS) tests visual spatial working memory. (E) The *prediction paradigm* (PRED) tests the participant’s ability to anticipate (predict) the onset of a regularly repetitive stimulus.



Appendix B

Oculomotor response due to proposed lesions affecting a specific brain region, relevant to findings from the two groups of interest

Ocular motor deficits	References	Fragile X findings	Turner syndrome findings
<i>Lesions of the FEF</i>			
1. Latency of overlap task ↑	Funahashi, Bruce, and Goldman-Rakic (1993)	1. Latency ↑	1. Latency ↔
2. Latency of MGS ↑	Israel, Rivaud, Gaymard, Berthoz, and Pierrot-Deseilligny (1995)	2. Latency ↑	2. Latency ↑
3. Latency of AS ↑	Gaymard et al. (1998)	3. Latency ↔	3. Latency ↔
4. VGS and MGS hypometric	Ploner et al. (1999)	4. VGS and MGS ↔	4. VGS and MGS ↔
5. % Predictive saccades ↓		5. % Predictive saccades ↓	5. % Predictive saccades ↔
<i>Lesions of the FEF and PFCdl</i>			
1. Gain of MGS ↓	Ploner et al. (1999)	1. Gain of MGS ↔	1. Gain of MGS ↔
2. Variability of MGS ↑	Vermersch et al. (1999)	2. Variability of MGS ↑	2. Variability of MGS ↑
<i>Lesions of the PFC</i>			
1. MGS accuracy impaired	Pierrot-Deseilligny et al. (1995)	1. MGS accuracy ↓ only 30°	1. MGS accuracy ↔
2. % Errors in MGS ↑	Ploner et al. (1999)	2. % Errors in MGS ↔	2. % Errors in MGS ↑
3. % Predictive saccades ↓	Condy, Rivaud-Pechoux, Ostendorf, Ploner, and Gaymard (2004)	3. % Predictive saccades ↓	3. % Predictive saccades ↔
4. % Errors in AS ↑		4. % Errors in AS ↔	4. % Errors in AS ↑
<i>Lesions of PEF</i>			
1. Latency for gap/overlap ↑	Gaymard et al. (1998)	1. Latency for overlap only ↑	1. Latency ↔
2. Latency for VGS ↑	Pierrot-Deseilligny et al. (2002)	2. Latency for VGS ↔	2. Latency for VGS ↑
3. Accuracy of VGS and MGS impaired		3. Accuracy ↔	3. Accuracy ↔
<i>Lesions of the caudate</i>			
1. MGS accuracy ↓ as cue delay ↑	Vermersch et al. (1999)	1. MGS accuracy ↓ only 30°	1. MGS accuracy ↔
2. Latency ↑		2. MGS latency ↔	2. MGS latency ↑
<i>Lesions of the anterior cingulate cortex</i>			
1. Latency of overlap task ↑	Gaymard and Rivaud et al. (1998)	1. Latency ↑	1. Latency ↔
2. Gain of MGS ↓	Milea et al. (2003)	2. Gain of MGS ↓ only 30°	2. Gain of MGS ↔
3. % Errors in AS ↑		3. % Errors in AS ↔	3. % Errors in AS ↑
<i>Lesions of anterior internal capsule</i>			
1. MGS accuracy ↓	Gaymard et al. (1998)	1. MGS accuracy ↓ only 30°	1. MGS accuracy ↔
2. MGS latency ↑		2. MGS latency ↑	2. MGS latency ↑
<i>Lesions of posterior internal capsule</i>			
VGS latency ↑	Gaymard et al. (1998)	VGS latency ↔	VGS latency ↑

↑ = increased.

↓ = decreased.

↔ = no change.

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