

Prosaccade and Antisaccade Behavior in Fragile X-Associated Tremor/Ataxia Syndrome Progression

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ABSTRACT: Background: Quantitative measurement of eye movements can reveal subtle progression in neurodegenerative diseases.

Objective: To determine if quantitative measurements of eye movements may reveal subtle progression of fragile X-associated tremor and ataxia (FXTAS).

Methods: Prosaccade (PS) and antisaccade (AS) behavior was analyzed in 25 controls, 57 non-FXTAS carriers, and 46 carriers with FXTAS.

Results: Symptomatic individuals with FXTAS had longer AS latencies, increased rates of AS errors, and increased AS dysmetria relative to non-FXTAS carriers and controls. These deficits, along with PS latency and velocity, were greater in advanced FXTAS stages.

Conclusion: AS deficits differentiated FXTAS from non-FXTAS premutation carriers implicating top-down control and frontostriatal deterioration. However, the absence of group differences between non-FXTAS carriers and controls in AS and PS markers suggests saccade performance may not be a sensitive enough measure for detecting conversion to FXTAS, but instead more helpful as translational biomarkers of FXTAS progression.

Quantitative measures of oculomotor control represent promising approaches for characterizing sensorimotor changes based on their high levels of precision in both spatial and temporal domains. These protocols are highly translational, reliable over multiple time points, and can be more sensitive to neurodegeneration in diseases of aging than clinical examination.¹

Saccadic eye movements, defined as rapid, ballistic shifts in eye gaze, are key targets for disease tracking because multiple dimensions of sensorimotor control can be probed using experimental manipulations to assess both sensory-driven motor behaviors as well as top-down control of sensorimotor output. Reactive saccades often are studied using prosaccade (PS) tasks in which subjects are instructed to look toward a suddenly appearing peripheral stimulus, whereas volitional saccades typically are studied using

paradigms in which participants are instructed to look toward targets that remain present on a screen, or away from suddenly appearing targets, such as in antisaccade (AS) tasks.² Neuroimaging studies have found reactive saccades made during PS tasks involve discrete cortical circuits including frontal and parietal eye fields as well as the cerebellum, whereas top-down inhibition of PS during AS tests involves dorsolateral prefrontal cortex and striatum.^{3,4} PS and AS paradigms have proven useful for parsing discrete dysfunctions of separate cortical, striatal, and cerebellar circuits in multiple clinical populations including schizophrenia and other neurodegenerative diseases.^{5,6}

Here, we use PS and AS paradigms to better understand sensorimotor features underlying fragile X premutation carriers (fXPCs) with and without fragile X-associated tremor/ataxia syndrome

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(FXTAS). FXTAS is a neurodegenerative disorder frequently seen in individuals over the age of 50 who have a premutation expansion (55–200 CGG repeats) in the promoter region of the fragile X mental retardation 1 (*FMR1*) gene,⁷ characterized by an intention tremor, cerebellar ataxia, and cognitive decline.⁸ Our previous study documented inhibitory dysfunction in a group of young (30.1 years \pm 6.4) asymptomatic fXPCs suggesting *FMR1* premutations may be associated with frontostriatal alterations.⁹ In the current study, we expected FXTAS to show PS and AS deficits relative to asymptomatic fXPCs and controls suggesting disease-specific impairments in both top-down volitional control of sensorimotor behaviors (AS) and sensorimotor control (PS). We predicted, because dysfunction in inhibitory control processes is reported in FXTAS, we would observe more deficits of inhibitory control (increased errors, increased AS latency) in FXTAS carriers relative to fXPCs without FXTAS and these deficits would be associated with higher stages of FXTAS. This would suggest these variables could serve as a phenotypic marker of disease severity. We also hypothesized dysfunction in saccadic eye movements for the AS task would correlate negatively with cognitive scores in an executive function battery.

Methods

This study was approved by the local institutional review board (IRB nos. 254134 and 473010). Consented participants came from two different National Institutes of Health (NIH) funded studies for the investigation of the *FMR1* premutation carriers.

Because one of these studies only enrolls males, data were available from 108 males and only 20 females. Twenty-five controls, 46 fXPCs with FXTAS, and 57 fXPCs without FXTAS completed the two eye-tracking tasks: PS and AS. The cohort of fXPCs with FXTAS was significantly different in age from both the control group ($P < 0.0001$) and fXPCs without FXTAS ($P = 0.0003$). Because of this significant difference, age was included as a covariate in the analyses (Table 1). Demographic information including race, ethnicity, and education is included in the Appendix S1 (Table S1).

Fragile X genetic testing (Table 1) was carried out to determine the CGG repeat length and the *FMR1* premutation carrier status of each participant, as previously described in Tassone et al¹⁰ and Filipovic-Sadic et al.¹¹ The diagnosis of FXTAS was determined according to the diagnostic criteria described in Jacquemont et al.⁷

Cognitive testing included the Mini-Mental Status Exam (MMSE), Behavioral Dyscontrol Scales 2 (BDS-2), and the subscales of the Wechsler Adult Intelligence Scales (WAIS-IV) including the verbal IQ domains (verbal comprehension and working memory) and performance IQ domains (perceptual organization and processing speed) (Table 1).

FXTAS Diagnostic Criteria

We selected only individuals who met the criteria for probable or definite FXTAS to be assigned to the FXTAS group (Table S5).⁸ In addition, participants with FXTAS had to meet Bacalman et al¹² criteria for at least FXTAS stage 2. Those who

TABLE 1 Mean (standard deviation) and statistical tests for molecular results and neuropsychological data

	Ctrls	fXPC–	fXPC+	Overall significant test	Post hoc tests		
					Ctrls vs. fXPC–	Ctrls vs. fXPC+	fXPC– vs. fXPC+
No.	25	57	46				
Age, y	57.9 \pm 10.4	61.1 \pm 9.0	68.2 \pm 7.6	<0.0001	0.289	<0.0001	0.000
CGG repeat	29.6 \pm 4.3	83.2 \pm 21.4	93.2 \pm 15.5	<0.0001	<0.0001	<0.0001	0.013
mRNA level	0.5 \pm 0.2	1.2 \pm 0.7	2.3 \pm 0.6	<0.0001	0.001	<0.0001	<0.0001
BDS2	22.8 \pm 2.4	21.8 \pm 2.7	18.1 \pm 5.4	<0.0001	0.550	<0.0001	<0.0001
MMSE	30 \pm 0 ($n=2$)	28.3 \pm 2.2 ($n=16$)	27.5 \pm 3.1	0.356	0.690	0.444	0.635
VCI	125.9 \pm 14.2	122.5 \pm 13.6	108.0 \pm 16.0	<0.0001	0.604	<0.0001	<0.0001
PRI	121.0 \pm 13.1	119.1 \pm 15.4	99.98 \pm 13.78	<0.0001	0.852	<0.0001	<0.0001
WMI	116.4 \pm 22.6	109.1 \pm 22.2	101.4 \pm 19.5	0.024	0.343	0.020	0.200
PSI	115.2 \pm 23.3	103.2 \pm 22.6	90.9 \pm 17.9	<0.0001	0.061	<0.0001	0.020
FSIQ	127.1 \pm 15.8	122.5 \pm 15.7	102.0 \pm 15.5	<0.0001	0.449	<0.0001	<0.0001

The MMSE was not originally given to control subjects because they were recruited through a separate protocol from those with FXTAS. Controls were evaluated by a different screening battery that included several executive measures (not mentioned in this manuscript) and did not show any difficulties that would indicate their cognitive abilities were impaired.

Abbreviations: Ctrls, controls; fXPC–, fragile X premutation carriers without FXTAS; fXPC+, fragile premutation carrier with FXTAS; BDS-2, behavioral dyscontrol scale; MMSE, mini-mental status exam; Wechsler Adult Intelligence Scale subtests; VCI, verbal comprehension index; PRI, perceptual reasoning index; WMI, working memory index; PSI, processing speed index; FSIQ, full scale intelligence quotient. Numbers in bold indicate significant difference between pairwise comparisons.

did not have a tremor or had only equivocal signs without WMH and did not meet probable or definite FXTAS were placed in the non-FXTAS category. Participants in the non-FXTAS group may not have been entirely asymptomatic; they may have presented with inconclusive symptoms, but they did not meet formal diagnostic or staging criteria.

Oculomotor Assessments

The PS and AS tasks were presented using EPrime software on a Tobii T120 monitor (Tobii Technology, Stockholm, Sweden). Participants were instructed to look at the central fixation cross and then look to the stimulus (PS task) that appeared above, below, to the right, or the left of fixation or the opposite location of the stimulus (AS task) as soon as it appeared. Stimulus onset varied randomly between 200, 400, or 600 ms. Dependent variables were kept consistent with our previous study and included latency (ms), velocity ($^{\circ}/s$), percentage of trials with directional errors, magnitude ($^{\circ}VA$), pupil dilation (mm), and the variability of each variable from trial to trial. The AS also included inhibitory cost (ms), a function of the intra-participant difference between the AS latency and the PS latency.¹³ To examine reaction times in both tasks, latency was measured as the time between the appearance of the stimulus to the beginning of the saccade (eye movement with velocity $>100^{\circ}/s$) for at least 16 ms duration. Pupil dilation was calculated as an average of the intra-participant difference between pupil size when presented with the fixation cross and pupil size when presented with the stimulus. A more detailed description of the assessments and variables may be found in Wong et al.⁹

Statistical Analysis

Data analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC). Results were expressed as mean \pm standard deviation (SD) for continuous variables or frequencies (%) for categorical variables as appropriate. Data for each continuous variable were examined for normality using the Shapiro–Wilk test and Kolmogorovo–Smirnov test before statistical inferential analyses. Normally distributed continuous variables were analyzed using analysis of variance (ANOVA) for group comparisons followed by Tukey's honest significance tests for post hoc pairwise group comparisons. Fisher's exact test was applied to categorical variables. The assumption of normality of distribution was determined to be violated for almost all eye-tracking variables, and therefore, group comparisons were carried out using nonparametric rank-based analysis of covariance (ANCOVA) with age as a covariate, followed by Tukey's tests for pairwise group comparisons. Type I error was controlled using Benjamini–Hochberg false discovery rate (FDR) procedure for multiple testing for a number of variables. When any significant difference was detected by the overall *F* test from ANOVA at FDR <0.05 , Tukey's honest significance tests were carried out to determine, which specific groups significantly differed. Correlations between two variables were assessed with Spearman's correlation, and group comparisons in correlations were carried out using Fisher's *Z* test. Two-tailed *P* values <0.05 were considered statistically significant unless stated otherwise.

Results

Significant group differences were detected for four eye movement variables at FDR <0.05 , including AS latency, AS

TABLE 2 Group comparisons of prosaccade and antisaccade tasks

	Ctrls	fXPC–	fXPC+	Raw <i>P</i> -value	FDR*	Post hoc tests		
						Ctrls vs. fXPC–	Ctrls vs. fXPC+	fXPC– vs. fXPC+
AS pupil diameter (mm)	2.6 \pm 0.3	2.8 \pm 0.5	2.7 \pm 0.5	0.024	0.068	0.064	0.021	0.798
AS latency (ms)	370.2 \pm 50.2	401.1 \pm 72.6	495.0 \pm 146.2	0.004	0.017	0.438	0.005	0.034
AS velocity ($^{\circ}/s$)	1830.5 \pm 198.5	1852.6 \pm 214.3	1847.5 \pm 203.2	0.308	0.436	0.700	0.287	0.625
AS direction errors	25% \pm 16%	30% \pm 23%	55% \pm 27%	0.001	0.004	0.849	0.004	0.002
AS magnitude ($^{\circ}VA$)	3.9 \pm 1.3	4.6 \pm 1.6	5.2 \pm 1.3	0.001	0.004	0.123	0.0004	0.034
PS pupil diameter (mm)	2.6 \pm 1.3	2.7 \pm 0.5	2.7 \pm 0.5	0.148	0.296	0.253	0.135	0.876
PS latency (ms)	232.3 \pm 26.8	251.9 \pm 40.1	266.2 \pm 52.2	0.059	0.138	0.168	0.048	0.709
PS velocity ($^{\circ}/s$)	1900.9 \pm 145.1	1873.6 \pm 190.3	1815.1 \pm 185.6	0.455	0.579	0.703	0.421	0.817
PS direction errors	5% \pm 5%	9% \pm 15%	11% \pm 15%	0.768	0.768	1.000	0.849	0.780
PS magnitude ($^{\circ}VA$)	3.6 \pm 0.5	3.5 \pm 0.7	3.5 \pm 0.6	0.722	0.768	0.882	0.986	0.714
Inhibitory cost (ms)	138.0 \pm 52.2	149.2 \pm 52.2	227.7 \pm 118.1	0.008	0.028	0.985	0.040	0.013
Pupillary difference (mm)	0 \pm 0.2	0.1 \pm 0.2	0.1 \pm 0.2	0.312	0.436	0.472	0.285	0.877

Abbreviations: Ctrls, controls; fXPC–, fragile X premutation carriers without FXTAS; fXPC+, fragile X premutation carrier with FXTAS; *FDR, false discovery rate while controlling for multiple testing; $^{\circ}VA$, visual angle. Numbers in bold indicate significant difference between pairwise comparisons.

direction errors, AS magnitude, and inhibitory cost (Table 2). We conducted Tukey's post hoc tests for those variables to determine, which groups statistically differed as described below.

Controls versus fXPCs without FXTAS

There were no significant differences found in any of the eye-tracking movement-dependent variables on either task between these groups. Group means and SDs are reported.

Controls versus fXPCs with FXTAS

There were no significant differences found between controls and fXPCs with FXTAS in the PS task. In the AS task, individuals with FXTAS showed increases in saccade latency, saccade magnitude, number of errors, and inhibitory cost.

fXPCs with FXTAS versus without FXTAS

fXPCs with and without FXTAS showed no differences in the PS task. During the AS task, fXPCs with FXTAS showed increased saccade latencies, saccade magnitude, number of errors, and inhibitory cost compared to fXPCs without FXTAS.

Variability between eye-tracking measures was compared between the three groups as well. fXPCs with FXTAS showed increased variability of AS magnitude and PS latency relative to controls (Table S2).

Neuropsychological Functions

There were no significant group differences in cognitive (BDS and WAIS-IV) scores between controls and fXPCs without FXTAS (Table 1). However, the fXPCs with FXTAS had significantly lower cognitive scores in verbal comprehension, perceptual reasoning, processing speed, and full scale intelligence quotient (FSIQ) compared to controls and fXPCs without FXTAS (Table 1). Additionally, there was a significant difference in working memory between controls and fXPCs with FXTAS, but not between the two fXPCs groups. In correlation analyses, we found the BDS-2 was negatively correlated ($\rho = -0.45$; $P = <0.0001$) with disease severity (FXTAS stage) among all fXPCs. The MMSE was positively correlated with disease severity in fXPCs without FXTAS ($\rho = 0.52$; $P = 0.0390$), whereas the correlation was negative for fXPCs with FXTAS ($\rho = -0.041$; $P = 0.0079$).

Oculomotor Measures and Executive Function

Lower BDS-2 scores were significantly correlated with longer AS and PS latencies, and greater inhibitory cost for fXPCs with FXTAS. Lower MMSE scores were associated with longer AS latencies and greater inhibitory cost in the FXTAS group. BDS-2 was also negatively associated with AS number

of errors and inhibitory cost in the non-FXTAS group (Table S3).

Discussion

Our findings that aberrant anti-saccadic eye movements are associated with FXTAS suggest deterioration of top-down cortical-striatal systems. In contrast, basic sensorimotor systems involving cortical-cerebellar systems associated with pro-saccadic eye movements appear less affected during the early stages of FXTAS.

One explanation for PS behaviors being relatively spared in early stages of FXTAS is parietal or frontal eye field circuits may compensate for striatal and cerebellar degeneration common in FXTAS. Several functional magnetic resonance imaging (MRI) studies reported atypical functional connectivity of sensorimotor networks in FXTAS, despite intact clinically rated motor behavior.¹⁴⁻¹⁶

Many cerebellar lesion studies have indicated intact cerebellar processes are necessary to maintain eye movement precision during saccades. In one primate study, lesions in dorsal cerebellar vermis resulted in increased saccade latencies and an increase in trial-to-trial variability of saccade amplitude. Although the primates eventually recovered saccade amplitude accuracy, elevations in the variability of saccade amplitudes persisted.¹⁷ This suggests alterations affecting the dorsal cerebellar vermis acutely disrupt the precision of saccadic eye movements and cause long-term impairments in the ability to consistently modulate saccadic amplitude. This may help explain the relative preservation of saccade amplitudes despite increases in saccade amplitude variability in FXTAS individuals, and further implicate cerebellar dysfunctions in the course of FXTAS.

In a group comparison, we also saw increased variability in PS latencies for those with FXTAS compared to controls (Table S2). Variability of saccade latencies can be an index of attentional fluctuation.^{18,19} The present findings of increased latency variability in FXTAS suggest attentional modulation during basic sensorimotor tasks is disrupted. Differences in AS latency variabilities between individuals with FXTAS and controls were specific to PS and not evident during AS testing suggesting the increased attentional demands of the AS task may serve to limit deficits in attention evident during basic sensorimotor processes.

Inhibitory Control Systems in FXTAS

In the FXTAS cohort, increased inhibitory cost also correlated with lower BDS-2 and MMSE scores (Table S3), as well as increased FXTAS severity (Table S4). Voluntary saccadic eye movements often deteriorate with age in older adults as top-down regulation circuits lose efficiency because of the degeneration of prefrontal cortical circuits. In a functional MRI study

involving healthy older adults, increased right frontal eye field activation, along with decreased connectivity with the right dorsolateral prefrontal cortex, correlated with poorer performance on the AS task.²⁰ More directional errors have been reported in individuals with Alzheimer's disease (AD) compared to their peers.²¹

Unlike our previously reported findings,⁹ there were no differences between inhibitory costs in non-FXTAS fXPCs relative to controls. One explanation for this discrepancy may be the screening process used for the current cohort of non-FXTAS fXPCs. Specifically, the study design, emphasizing enrollment of carriers without neurological symptoms at baseline, may be biased toward individuals who have some neuroprotective factors because they are older, but have not developed FXTAS. Our non-FXTAS fXPCs and controls did not differ in latencies or directional errors in either the PS or AS tasks. This suggests these oculomotor tasks may not be as sensitive to the prodromal phases of FXTAS.

Limitations

SDs for most of the eye-tracking variables were the highest among the FXTAS group highlighting broad heterogeneity within this group. There is often dual neurological pathology in FXTAS; several of the individuals in the FXTAS group had observable parkinsonian signs and three were suspected of AD.^{22,23} None of the controls or non-FXTAS fXPCs had another major neurological diagnosis. Finally, we did not disqualify any individual's eye-tracking data based on their medication regimen.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

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D.R.H.: 1C, 3A, 3B

S.M.R.: 1A, 1C, 3B

T.J.S.: 1A, 3B

F.T.: 1C, 3B

R.J.H.: 1B, 1C, 3A, 3B

Disclosures

Ethical Compliance Statement: This study was approved by the university's Institutional Review Board (IRB Number: 254134) and all 128 participants provided signed informed consent. In addition, the authors have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

Supporting information may be found in the online version of this article.

Appendix S1 Supplementary Tables