Integrative cortical dysfunction and pervasive motion perception deficit in fragile X syndrome

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Abstract—*Background:* Fragile X syndrome (FXS) is associated with neurologic deficits recently attributed to the magnocellular pathway of the lateral geniculate nucleus. *Objective:* To test the hypotheses that FXS individuals 1) have a pervasive visual motion perception impairment affecting neocortical circuits in the parietal lobe and 2) have deficits in integrative neocortical mechanisms necessary for perception of complex stimuli. *Methods:* Psychophysical tests of visual motion and form perception defined by either first-order (luminance) or second-order (texture) attributes were used to probe early and later occipito-temporal and occipito-parietal functioning. *Results:* When compared to developmental- and age-matched controls, FXS individuals displayed severe impairments in first- and second-order motion perception. This deficit was accompanied by near normal perception for first-order form stimuli but not second-order form stimuli. *Conclusions:* Impaired visual motion processing for first- and second-order stimuli suggests that both early- and later-level neurologic function of the parietal lobe are affected in Fragile X syndrome (FXS). Furthermore, this deficit likely stems from abnormal input from the magnocellular compartment of the lateral geniculate nucleus. Impaired visual form and motion processing for complex visual stimuli with normal processing for simple (i.e., first-order) form stimuli suggests that FXS individuals have normal early form processing accompanied by a generalized impairment in neurologic mechanisms necessary for integrating all early visual input.

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Fragile X syndrome (FXS) is the most common cause of heritable mental retardation (MR) and results from the silencing of a single gene, Fragile-X Mental Retardation 1 (*FMR1*),[1,2] due to expansion of a trinucleotide repeat region in the promoter. Repeat expansion appears to accumulate across generations, reaching a so-called full mutation beyond a critical threshold (>200 repeats).[3] Due to X chromosome hemizygosity, men possessing the full mutation lack or have decreased *FMR1* protein product (FMRP). A constellation of strengths and weaknesses serves to distinguish FXS from other forms of MR.[4-6] A striking aspect of FXS is the deficit in visual motor skills,[7-9] possibly reflecting an underlying impairment in processing visual information critical for guiding adaptive motor behavior.

In support of this idea, neurobiological and behavioral experiments have demonstrated that FXS is associated with impairment in the magnocellular (M) portion of the thalamus,[10] whereas the parvocellular (P) portion remains unaffected. These findings suggest that an M channel deficit may also affect processing at higher cortical centers in the parietal lobe, which receive dominant M input.[11-14] The parietal stream is crucial for processing dynamic aspects of the visual scene for the visual control of action. The temporal stream, which receives a dominant P input, is involved in object identification and visual awareness,[11,13,14] functions that appear to be relatively spared.

We examined whether the visual motor deficits in FXS are due solely to impairments in low-level processing or are also caused by deficits in higher cortical mechanisms. It may be that visual encoding is only compromised at the early stages of processing or alternatively that the low-level impact is compounded by further deficits of an integrative nature at higher levels. We distinguished between these alternatives by using first- and second-order visual stimuli that probe either low- or higher-level cortical function.[15-19]

Methods. *Participants.* Eleven men or adolescent boys with FXS (mean chronological age [CA] = 17.61 ± 3.47 years; mean verbal mental age [MA] = 7.43 ± 1.28 years) were recruited in the United Kingdom through the UK Fragile X Society and in Canada through the Department of Pediatrics and Human Genetics at the Montreal Children's Hospital. All patients had a DNA confirmed diagnosis of a FXS full mutation. Eleven age-matched control participant men or adolescent boys (CA = 17.28 ± 3.17 years) and

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11 developmental-matched control participant boys (MA = 7.18 ± 2.39 years) were recruited through newspaper advertisements. The MA controls were matched according to their verbal mental age and therefore were chronologically younger than the patients with FXS. The CA and MA groups were selected to control for the separate influences of chronological age on visual perception (i.e., the CA controls) and cognitive ability on performance of the psychophysical tasks (i.e., the MA controls). Participants or their caregivers gave their or their ward's/children's written consent to take part in this study and were paid for their participation. The ethics committees of the Department of Psychology, McGill University, the Montreal Neurologic Hospital and Institute, and the Montreal Children's Hospital approved the study.

Cognitive assessment. Participants in the MA-matched comparison group were selected according to their achievement of overall similar performance as the FXS participants on a test of verbal mental ability. Patients with FXS and the MA-matched control participants were assessed using the Peabody Picture Vocabulary Test[20] (PPVT-R, Form L) for English-speaking participants or its French translation, the Échelle de Vocabulaire en Images Peabody[21] (EVIP, Forme A), for French-speaking participants. The PPVT and EVIP are individually administered tests that consist of 175 vocabulary items of increasing difficulty used to assess breadth of receptive language.

Apparatus. For data collected at the Visual Psychophysics and Perception Laboratory of the Université de Montréal (Canada), stimulus presentation and data collection were controlled by a Power Macintosh G3 computer and presented on a 16-inch AppleVision 1710 monitor (frame refresh rate of 75 Hz), which was gamma-corrected using a color look-up table. The screen resolution was 832 × 624 pixels. Stimuli were generated and animated by the VPixx graphics program (www.vpixx.com). The mean luminance of the display was 32.1 cd/m^2 (u' = 0.1888, v' = 0.4349 in CIE [Commission Internationale de l'Eclairage] u' v' color space) where L_{min} was 0.206 and L_{max} was 64.4 cd/m^2. Color calibration and luminance readings were taken using a Minolta Chromameter. For data collected at the Queen's Medical Centre in Nottingham (United Kingdom), stimulus presentation and data collection were controlled by a Power Macintosh G3 laptop computer and presented on a 15-inch Hansol 710A monitor (frame refresh rate of 75 Hz), which was gamma-corrected using a color look-up table. In order to ensure physical equivalencies between the stimuli presented in Canada and those in the United Kingdom, a Minolta Chromameter was used to match the mean luminance, L_{max} and L_{min}, as well as the color of the gray values used (i.e., u' and v' values) to define the stimuli. Stimuli were generated and animated as described above for the data collected in Canada.

Visual stimuli—motion condition. The stimuli used for the motion direction-identification task are shown in figure 1. They consisted of first- and second-order translating patterns, constructed by either adding or multiplying static grayscale noise to a modulating vertically oriented sinewave.[22,23] The stimuli were presented within a hard-edged circular region at the center of the display subtending a visual angle of 10 deg in diameter when viewed from a distance of 57 cm. The noise consisted of dots (1 pixel × 1 pixel, measuring approximately 2.235 minutes arc) whose individual luminances were randomly assigned as a function of sin (x), where (x) ranged from 0 to 2 π. The average contrast of the noise was set at half its maximal value. All motion stimuli had a spatial frequency of 1 cycle per degree (cpd) and a drift frequency of 2 cycles per second (Hz). Direction-identification thresholds for the first-order patterns were found by varying the contrast (luminance modulation or luminance modulation depth), defined as the amplitude of the modulating sinewave, which ranged between 0.0 and 0.5:

$$\text{Luminance modulation depth} = (L_{max} - L_{min})/(L_{max} + L_{min})$$

where L_{max} and L_{min} refer to the average highest and lowest local luminances in the pattern. The first-order patterns were presented at five levels of luminance modulation (0.04, 0.02, 0.01, 0.005, and 0.0025).

Second-order patterns were produced by multiplying the same modulating sinewaves with grayscale noise. Direction-identification thresholds for the second-order patterns were found by varying the contrast modulation (contrast modulation depth) of the motion patterns, defined as the amplitude of the modulating sinewave, which ranged between 0.0 and 1.0:

$$\text{Contrast modulation depth} = (C_{max} - C_{min})/C_{max} + C_{min})$$

where C_{max} and C_{min} are the maximum and minimum local contrasts in the pattern. The second-order patterns were also presented at five levels of contrast modulation (1.0, 0.333, 0.143, 0.111, and 0.059).

Visual stimuli—form condition. The physical properties and parameters of the static stimuli used for the orientation-

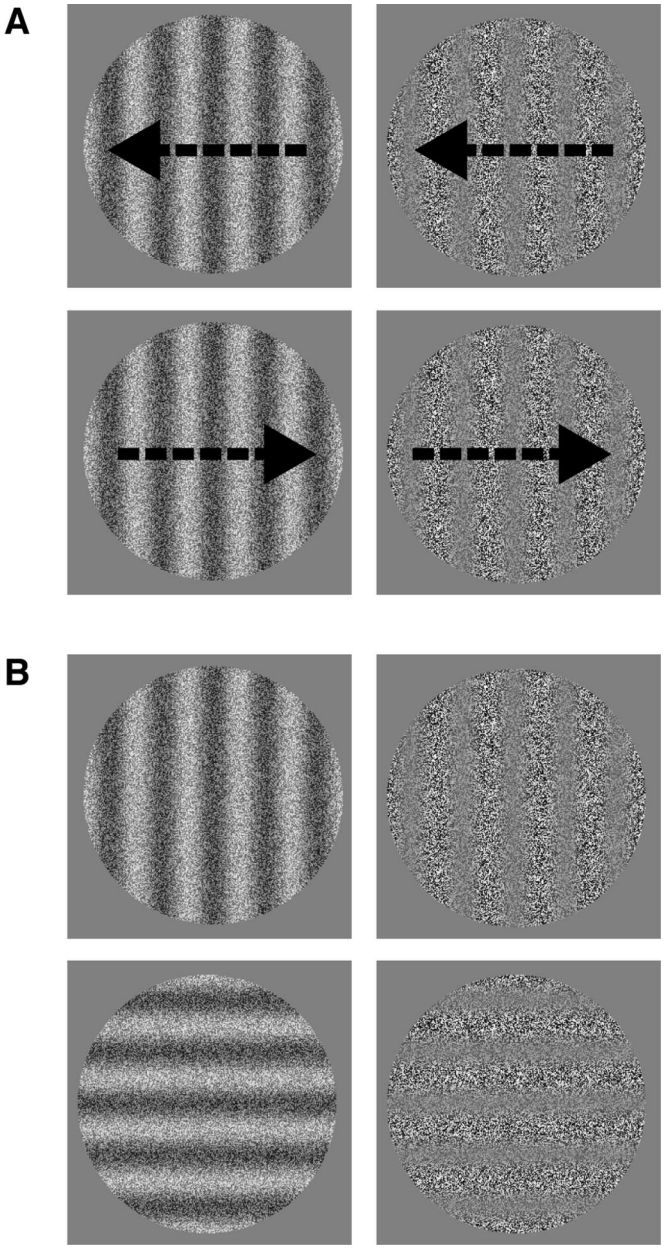

Figure 1. Examples of the first-order (FO) and second-order (SO) motion and form stimuli employed to obtain motion- and orientation-identification thresholds. First-order stimuli are shown on the left while the second-order stimuli are shown on the right. (A) Motion stimuli. Vertically oriented gratings drifted either to the right or to the left, as indicated by the arrows. (B) Form stimuli. Stationary gratings were oriented either vertically or horizontally. Luminance (first-order) and contrast (second-order) properties of the form and motion stimuli were identical.

Table *Number of participants successfully completing the tasks*

Task type	Complexity	Fragile X (n = 11)	Age-matched (n = 11)	Developmental-matched (n = 11)
Dynamic	First-order	5	11	11
	Second-order	3	11	11
Static	First-order	8	11	11
	Second-order	11	11	11

identification task were identical to the motion patterns used in the dynamic condition except that they were stationary (i.e., drift frequency of 0 Hz). They were constructed by either adding or multiplying static grayscale noise to either a vertically or horizontally oriented stationary sinewave grating (see figure 1). Therefore, the stimuli used in both the dynamic and static conditions were physically identical except for their defining attribute; motion (i.e., left-right) in one case and orientation (i.e., vertical-horizontal) in the other.

Psychophysical testing. Participants were tested individually in a dimly lit laboratory room and viewed the display binocularly from a distance of 57 cm for each of two separate testing sessions (i.e., dynamic and static testing sessions). Procedural instructions were given verbally prior to each session, followed by a series of practice trials to familiarize participants with the procedure and to assure the experimenters that the participants understood the task at hand by being able to respond correctly to the stimuli before actual testing began. To ensure full comprehension of the task, participants had to obtain a criterion level of 10 consecutive correct responses during each of the practice sessions before continuing on to the thresholds estimation phase of the experiment. The experimenter was present throughout the testing and initiated successive trials only when he was sure that he participant's gaze was oriented toward the point of fixation.

Within a dynamic testing session, each participant was presented with trials consisting of first- and second-order stimuli moving in either of two possible directions (i.e., left vs right). The motion stimuli were presented for 1 second, after which each participant responded verbally or by using a hand gesture (i.e., pointing in a certain direction), depending on what was less demanding, in the two alternative forced choice (2AFC) task. The experimenter entered the responses after each trial. For the static testing session, each participant was presented with trials consisting of stationary first- and second-order stimuli oriented either vertically or horizontally for 1 second. Similarly, the participants responded to the orientation of the stimuli either verbally or with hand gestures in the 2AFC task.

The method of constant stimuli was used to measure direction- and orientation-identification thresholds for each experimental condition and included five levels of luminance modulation for the first-order stimuli and five levels of contrast modulation for the second-order stimuli. Testing order of static and dynamic conditions was counterbalanced across participants. Moreover, within each testing condition first- and second-order stimuli were presented in random order. Stimuli were presented 10 times in either direction/orientation at each level of modulation (for a total of 20 trials at each level of modulation for each of the experimental conditions). Where possible, Weibull[24] functions were fitted to the responses for each condition in order to derive direction- and orientation-identification thresholds at a 75% correct level of performance.

Results. *Motion condition.* All of the FXS participants tested were capable of discriminating the direction of motion during practice sessions where luminance and contrast modulation depth for first- and second-order stimuli were set at their respective maximal values. However, we were able to obtain direction-of-motion thresholds for only a fraction of these individuals (table), which cannot be attributed to nonspecific effects (e.g., lack of attention) because all of the FXS participants were able to complete at least one of the testing conditions. Although thresholds were not calculable for many of the patients with FXS, group performance at the highest levels of luminance modulation for the first-order task and contrast modulation for the second-order task were determined, using one-sample *t*-tests, to be greater than chance (first-order motion: $t = 7.069$, $p < 0.05$; second-order motion: $t = 2.906$, $p < 0.05$). This indicates that the FXS participants understood the task instructions. In contrast, we were able to obtain direction-of-motion thresholds for all control participants using both types of dynamic stimuli. The severity of the visual motion processing deficit in FXS participants precluded the use of standard parametric statistical analyses. Therefore, we conducted two non-parametric Kruskal-Wallis one-way analysis of variance (ANOVA) tests, one for each of the motion conditions (first- and second-order), to compare group medians, with Group (FXS, Age-matched, Developmental-matched) as the independent measures variable (figure 2). Separate analyses were necessary because the attributes defining the first- and second-order motion stimuli (i.e., luminance vs contrast) are qualitatively different, making a direct comparison of threshold values across stimuli type uninformative. A comparison of the median threshold values for the first-order static stimuli revealed a main effect of Group ($\chi^2 = 19.458$, $p = 0.005$). Post hoc pairwise comparisons using Mann-Whitney *U* test with Bonferroni correction ($\alpha = 0.05/3 = 0.017$) confirmed that the FXS group had elevated luminance thresholds when compared to both the age-matched comparison group ($p = 0.002$) and the developmental-matched comparison group ($p = 0.002$).

A similar pattern of results was found for the second-order motion stimuli with a main effect of Group ($\chi^2 = 7.858$, $p = 0.02$). Post hoc pairwise comparisons using Mann-Whitney *U* test with Bonferroni correction ($\alpha = 0.05/3 = 0.017$) confirmed that the FXS group had significantly elevated contrast thresholds when compared to both the age-matched comparison group ($p = 0.010$) and the developmental-matched comparison group ($p = 0.010$). Thus, there are significant differences between the median threshold values for both first- and second-order dynamic stimuli between the FXS group and the two comparison groups. Furthermore, comparing the success rates on the dynamic tasks (see the table), a majority of FXS individuals had difficulty perceiving simple motion stimuli and an even greater number had difficulty perceiving complex motion.

Form condition. Static luminance and contrast modulation depth thresholds were obtained for all participants with the exception of three of the FXS participants when tested with the first-order static stimuli (see the table). We conducted two one-way ANOVA tests, one for each of the static conditions (first- and second-order), with Group (FXS, Age-matched, Developmental-matched) as the independent measures variable (figure 3). Separate ANOVAs were necessary for the same reason that separate analyses were conducted on the data obtained for the first- and second-order motion stimuli; that is, because the attributes defining the first- and second-order static stimuli (i.e., luminance vs contrast) are qualitatively different.

A comparison of the mean threshold values for the first-order static stimuli revealed a main effect of Group ($F_{2,33} = 10.76$, $p < 0.01$). Post hoc pairwise comparisons

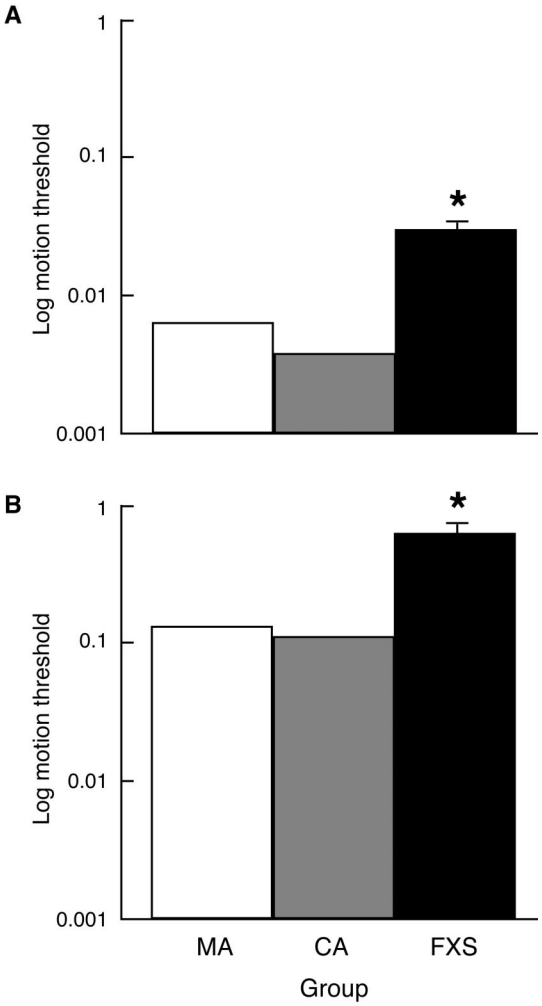

Figure 2. Visual motion thresholds (ordinate) for first- and second-order stimuli and for three participant groups. (A) First-order motion. Only a fraction of the fragile X (FXS) affected participants (5 of 11) were able to perceive the direction of motion of the first-order stimuli while developmental-matched (MA) and age-matched (CA) controls maintained similar thresholds. Patients with FXS for whom thresholds were calculable had significantly elevated luminance thresholds when compared to the MA and CA control groups. (B) Second-order motion. Similarly, only a fraction of the FXS affected participants (3 of 11) were able to perceive the direction of motion of the second-order stimuli while MA and CA controls maintained similar thresholds. Patients with FXS for whom thresholds were calculable had significantly elevated contrast thresholds when compared to the MA and CA control groups. An asterisk indicates significance at the 0.017 level.

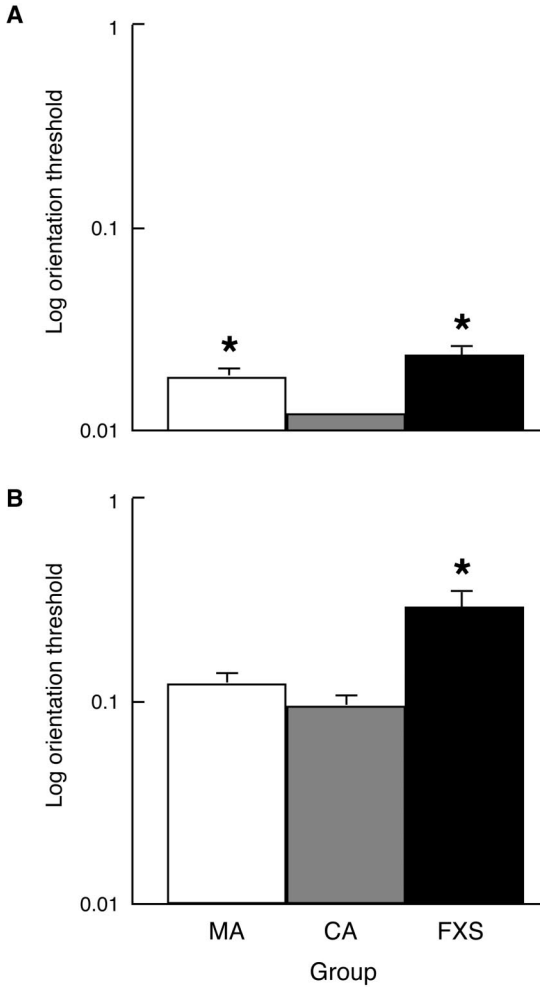

Figure 3. Visual form thresholds (ordinate) for first- and second-order stimuli and for the three participant groups. (A) First-order form. A majority of FXS affected participants were able to complete the first-order form task and had similar thresholds when compared to the developmental-matched controls (MA) but not the age-matched controls (CA). (B) Second-order form. All FXS affected participants were able to complete the second-order task. However, when compared to the MA and CA controls, the FXS group had a significantly elevated mean threshold. An asterisk indicates significance at the 0.05 level.

using Tukey's honestly significant difference (HSD) confirmed that both the FXS group ($p < 0.05$) and the developmental-matched comparison group ($p < 0.05$) had elevated luminance thresholds when compared to the age-matched comparison group. That differences could not be found in performance between the FXS and developmental-matched participants for first-order stimuli indicates a mental age-dependent difference in the ability to perform the method of constant stimuli threshold task and highlights the need for the developmental-matched comparison group. Thus, compared to the dynamic conditions, the FXS participants' perception of the first-order static stimuli appears to be intact.

A similar pattern of results was found for the second-order static stimuli with a main effect of Group ($F_{2,35} = 8.67$, $p < 0.05$). However, unlike the first-order findings, post hoc pairwise comparisons using Tukey's HSD revealed that the FXS group had significantly elevated contrast thresholds when compared to both the age-matched comparison group ($p < 0.05$) and the developmental-matched comparison group ($p < 0.05$). This result suggests that the FXS group had difficulty integrating local elements in the more complex second-order form task in order to identify the orientation of the stimuli.

Discussion. In this study, we evaluated the integrity of the parietal and temporal streams in patients

with FXS by comparing motion and form perception using physically identical stimuli that differed only in terms of their defining attribute (static or dynamic) and the degree of stimulus complexity (first- or second-order). Our results can be briefly summarized as follows: 1) the majority of FXS participants performed poorly on dynamic tasks and were unable to discriminate the direction of motion for first- and second-order stimuli, 2) FXS individuals who were able to complete both first- and second-order tasks had significantly elevated thresholds for direction of motion when compared to age- and developmental-matched control participants, 3) a majority of FXS participants were able to discriminate the orientation of static first- and second-order stimuli, 4) FXS individuals who were able to complete the first-order task had thresholds that were similar to those of the developmental-matched control participants, and 5) static second-order thresholds were significantly elevated in FXS individuals relative to both comparison groups.

These results support the hypothesis that the M pathway deficit previously reported in patients with FXS[10] also yields a parietal stream deficit regardless of whether the occipital-parietal axis is probed at early (first-order stimuli) or later levels (second-order stimuli). This reflects a clear pervasive impairment of motion perception in FXS. Furthermore, the deficit seen only with second-order form processing reveals a later-level temporal processing impairment without a concomitant early-level deficit. We take this finding as evidence of a generalized cortical dysfunction in integrative mechanisms of early visual input regardless of its source.

Our use of first- and second-order motion and form stimuli ensured an equitable comparison of functional integrity of the two cortical visual streams at both early and later levels. It is generally believed that first- and second-order stimuli are processed at different levels within the cortical hierarchy.[25,26] An important consideration in the design of perceptual experiments is to ensure that high-level cognitive factors have little differential impact on the dependent measure. We therefore used an identical instruction set for the motion and form tasks, whether defined by first- or second-order attributes, so as to minimize differences in the cognitive load needed to comprehend the task objective.

Our finding that patients with FXS have elevated thresholds for first- and second-order motion stimuli but normal thresholds for first-order static stimuli can be understood in the context of current knowledge of hierarchical cortical processing. A functional imaging study showed that first-order motion activation appears initially in area V1 whereas second-order motion shows that activation first arises in later areas, such as areas V3 and VP. Both types of motion are further processed in area V5 (also known as area MT).[26] The preferential input that these areas receive from the M pathway leads to the conjecture that the previously observed impairment of that pathway affects later parietal stream areas in FXS.[10] Indeed, the results of this study strongly support the hypothesis that a pervasive parietal stream deficit is present at both early and later levels within the occipito-parietal axis. Our finding that form perception is affected only at later stages of temporal visual stream processing highlights both the specificity of the parietal impairment as a dysfunction of afferent input (i.e., M pathway impairment) and points to an additional deficit in FXS in cortical integrative processing of all early visual input.

We found an effect of complexity for both parietal and temporal streams. The impairment in motion perception was more pronounced for second- than for first-order stimuli (i.e., fewer patients with FXS were able to complete the second-order task). Similarly, the impairment in form perception was evident only with second-order stimuli. Contemporary models and empirical findings differentiate first- and second-order stimuli by the level at which they are processed along the cortical visual pathways. First-order information is processed by neural circuits in area V1 where local luminance variations are used to detect motion and orientation. For this reason, first-order stimuli are considered to be simpler. However, additional nonlinear processing is required with second-order signals in order to resolve the direction or orientation of this class of visual information, something that is presumed to occur in later visual areas.[18,27] Second-order visual information is therefore considered to be of a more complex nature because it requires recruitment of more extensive neural circuitry as well as additional processing prior to perception.

The perception of complex second-order stimuli may be more susceptible to neurologic abnormalities because there is a greater computational requirement for integration and coordination of low-level inputs. In fact, complexity has been used as a measure of neural integrity and should be considered independently of the functional specialization of the parietal and temporal streams. First- and second-order stimuli have been used to investigate the effects of aging on visual perception.[28] Findings were of a larger decrease in sensitivity with aging for both static and dynamic second-order stimuli but not for their first-order counterparts. These results suggest that the perceptual deficits in older adults are due to diffuse and non-specific cell death in the aging brain.[29,30] Similarly, we take the deficit in FXS for second-order stimuli that probe both parietal and temporal lobes to suggest that a generalized later- vs early-level deficit occurs in this syndrome. However, for the parietal visual stream we propose an additional mechanism whereby the selective deficit in the M pathway is compounded or amplified in later parietal areas that are reliant upon a dominant M input. Such a pervasive deficit in motion perception may account for some of the observable relative performance deficits for neuropsychological tasks with a visual motor component.[7-9]

A study investigating putative motion perception deficits in autism revealed normal first-order detec-

tion of motion thresholds alongside elevated second-order ones.[23] The authors proposed a deficit in integrative mechanisms acting at higher levels within the cortex rather than a motion perception deficit per se. Similarly, we suggest that the elevated thresholds for the more complex second-order form stimulus reflect a neurologic deficit in integrative mechanisms in FXS rather than a specific form perception impairment.

Pervasive parietal stream impairment may not be exclusive to FXS. In fact, several studies have demonstrated deficits in global motion processing in individuals with a wide array of etiologically diverse conditions including autism,[31] Williams syndrome,[32] dyslexia,[33] and hemiplegia,[34] raising the interesting possibility that this stream is more vulnerable during development as compared to its temporal counterpart.[35] Given the importance of including complexity as an independent variable, its absence in prior studies opens up the possibility that integrative deficits may also play a role in other neurologic conditions.[23]

Patients with FXS show pervasive and selective parietal visual stream impairment at both early and later levels of processing. These impairments are accompanied by a sparing of early level but interestingly, a deficit in later-level form processing. The selectivity of this impairment suggests that early-level form processing is spared but that later integrative mechanisms are compromised in the form-processing pathway as well. We propose that the observed deficits in motion perception in FXS arise as a result of abnormalities acting at two levels. First, pathologic features at the neuroanatomic level have been previously reported. Specifically, autopsy material from one FXS patient showed that the LGN was alaminar and that M-LGN neurons displayed significantly reduced size in this condition.[10] Second, at the functional level, patients with FXS have selectively elevated thresholds for high-temporal frequency stimuli, information normally relayed by the M portion of the retino-thalamo-cortical pathway.

Our results show the importance of task selection for tests of visuo-perceptual function, especially with regard to parietal vs temporal pathway integrity. The use of first- and second-order visual stimuli may be especially important in identifying the level at which disruption in neurologic processing is presumed to occur.

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