

To Look or Not to Look? Typical and Atypical Development of Oculomotor Control

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Abstract

■ The ability to inhibit saccades toward suddenly appearing peripheral stimuli (prosaccades) and direct them to contralateral locations instead (antisaccades) is a crucial marker of eye movement control. Typically developing infants as young as 4-month-olds can learn to inhibit reflexive saccades to peripheral stimuli, but they do not produce antisaccades, whose development later in infancy and its underlying neural computations remain unexplored. Here we tested oculomotor control in typically developing toddlers and toddlers with fragile X syndrome (FXS), a disorder of known genetic origin that allows the investigation of the neuro-computational properties contributing to the development of saccadic control. Typically developing toddlers decreased looking toward peripheral cues that predicted contralateral

rewards, whose appearance they anticipated. Furthermore, this correlated with age, indicating a gradual development of saccadic control. In contrast with the typical case, toddlers with FXS did not decrease their looks to peripheral onsets that predicted contralateral events. Importantly, the atypical pattern of performance was also evident in the elimination of the correlation with mental or chronological age found in controls. Taken together, the findings suggest that control of saccades and its developmental trajectory is atypical in toddlers with FXS, consistent with inhibitory deficits previously shown at later ages in this condition. Potential implications for the neural mechanisms underlying the typical and atypical development of oculomotor control are discussed. ■

INTRODUCTION

The ability to visually orient toward stimuli relevant to current goals is a crucial aspect of visual selection. Indeed, during the first year of life, eye movements are the major means for infants to inspect their surroundings, constraining their ability to select and perceive stimuli in their visual world. In adults, voluntary influences on saccade generation, and their overriding of stimulus-driven influences, have traditionally been measured in the antisaccade task (Hallett, 1978), in which participants are asked to suppress the usual prosaccade toward a suddenly appearing peripheral stimulus and to direct their eyes toward a contralateral location instead (antisaccades). Data from patients with localized brain damage, adult neuroimaging studies, and monkey electrophysiology implicate a large network of cortical and subcortical areas in the voluntary control of saccades (e.g., Everling & Munoz, 2000; O'Driscoll et al., 1995; Guitton, Buchtel, & Douglas, 1985). How does this functional network develop?

Studies of eye movements in infants have investigated the control of saccades by manipulating the relationship between central and peripheral stimuli and the location at which rewarding stimuli appear. Infants as young as 3.5-month-olds anticipate the appearance of visual stimuli at predictable locations (Haith, Hazan, & Goodman, 1988). However, less is known about infants' ability to inhibit saccades toward peripheral stimuli. Johnson (1995) presented 4-month-olds with a brief peripheral stimulus that always predicted the appearance of a rewarding dynamic stimulus at a contralateral location. Interestingly, infants reduced prosaccades toward the cue, but they did not produce looks that anticipated the appearance of targets at the contralateral location. These findings suggest that infants can develop "expectancies" (i.e., exhibit some contingency-dependent looking) based on predictive events and inhibit prosaccades accordingly. However, their concurrent inhibition of prosaccades and production of antisaccades have not been demonstrated to date. In contrast to the findings with young infants, these have both been measured in older children. Ten-year-old children are better able than 8-year-olds to inhibit reflexive saccades to sudden peripheral onsets (Paus, Babenko, & Radil, 1990). Furthermore, participants between 5 and 79 years display age-related reductions in

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the proportion of errors in the antisaccade task, with the most striking changes occurring between 5 and 15 years old (Munoz, Broughton, Goldring, & Armstrong, 1998; see also Fischer, Biscaldi, & Gezeck, 1997). Indeed, age accounts for up to 51% of the variance in the decrease of erroneous looks toward peripheral stimuli in antisaccades from 6 to 28 years (Klein, 2001). However, to date, the concurrent inhibition of prosaccades and production of antisaccades have not been tested in toddlers younger than 5 years and this will be the focus of our first experiment.

What are the neural bases underlying changes in oculomotor control? Dramatic improvements in saccadic control have been attributed to the delayed maturation of prefrontal cortex (Munoz et al., 1998; Paus et al., 1990). More recently, Luna et al. (2001) found gradual age-related increases in distributed parietal, striatal, and thalamic as well as frontal activation in tasks requiring antisaccades from 8 to 30 years old, suggesting that developmental changes in oculomotor control depend on a large network including, but not exclusively constituted by, prefrontal cortex. Alongside imaging studies of typical development, neurodevelopmental disorders represent unique tools for investigating the neural basis of oculomotor control. For example, Munoz, Armstrong, Hampton, and Moore (2003) revealed an increased number of errors and a reduced decrease in antisaccade latencies compared with prosaccade latencies with increasing age in attention deficit/hyperactivity disorder (ADHD), pointing to how the known dysfunctional development of fronto-striatal circuits characteristic of the syndrome can impact the development of oculomotor control. Although there is growing interest in saccadic control in developmental disorders that may have relatively mixed etiology, there are fewer studies investigating parallel issues in developmental disorders of known genetic origin, despite their potential for linking performance and neural processes to gene expression. One such condition is fragile X syndrome (FXS), the most common cause of genetically inherited mental retardation (de Vries et al., 1997), that is associated with the silencing of a single gene (Verkerk et al., 1991). FXS is characterized by striking inhibitory difficulties in adulthood (Cornish, Munir, & Cross, 2001) and later childhood (Munir, Cornish, & Wilding, 2000), and these may relate to the dysfunction of fronto-striatal circuits recently measured in able women with FXS (Menon, Leroux, White, & Reiss, 2004). Very recently, deficits in the inhibition of manual responses have also been demonstrated in toddlers with FXS (Scerif, Cornish, Wilding, Driver, & Karmiloff-Smith, 2004). However, to date, there are no published studies investigating oculomotor control in FXS, at any age. Our second experiment, therefore, examined the development of oculomotor control in toddlers with FXS compared with individually matched typically developing controls.

EXPERIMENT 1: THE DEVELOPMENT OF OCULOMOTOR CONTROL IN TYPICALLY DEVELOPING TODDLERS

Studies of antisaccades in human adults require participants not to orient toward a peripheral onset (equivalent to the cues used here) and to direct a saccade instead to the opposite direction in the absence of a stimulus appearing there. These verbal instructions must be adapted for use with nonhuman primates, human infants, and toddlers with little language, and one of the original studies of antisaccades in humans provided a potential solution. Guitton et al. (1985) asked patients to orient away from a suddenly appearing peripheral cue and toward a contralateral location at which a target stimulus occurred (Figure 1A). Adults with lesions in dorsolateral and mesial frontal cortex had difficulties in suppressing glances to the cue and saccades in the contralateral direction were nearly always triggered by the appearance of the target stimulus, rather than preceding it. Using a similar design, Johnson (1995) trained 4-month-old infants to orient away from a peripheral cue by associating it with the subsequent appearance of a dynamic stimulus at the opposite location. Infants decreased saccades toward peripheral cues when these predicted the appearance of a target at the contralateral location, but not when cues were not predictive, suggesting that they could control these looks to some extent. However, they did not produce saccades toward the opposite location before the appearance of the target stimulus, the antisaccade, as traditionally measured in human adults. Johnson's adaptation was groundbreaking. It allowed, in preverbal infants, the investigation of both the production of reflexive saccades toward the peripheral cue and in principle also any ability to look toward the contralateral location before the appearance of the target. However, there remains a considerable gap in knowledge, as published studies to date have investigated the inhibition of prosaccades either in 4-month-olds (Johnson, 1995) or in children older than 5 years old (e.g., Munoz et al., 1998), but not the intervening age group.

Therefore, Experiment 1 had 2 main aims. First, it sampled from an understudied age range: toddlers between 8 and 38 months old. Secondly, it investigated the developmental trajectory of performance across that age range, rather than focusing on limited age groups, because studies with older children indicate gradual changes in prosaccade and antisaccade parameters over development (e.g., Munoz et al., 1998). Figure 1B illustrates the sequence of trial events, designed following Johnson (1995). Initial calibration trials ensured that toddlers could see and orient toward the cue and preceded experimental trials. These were then divided into a first and a second half. We measured the percentage and latency of saccades toward the cue (prosaccades) and of saccades directed toward the target

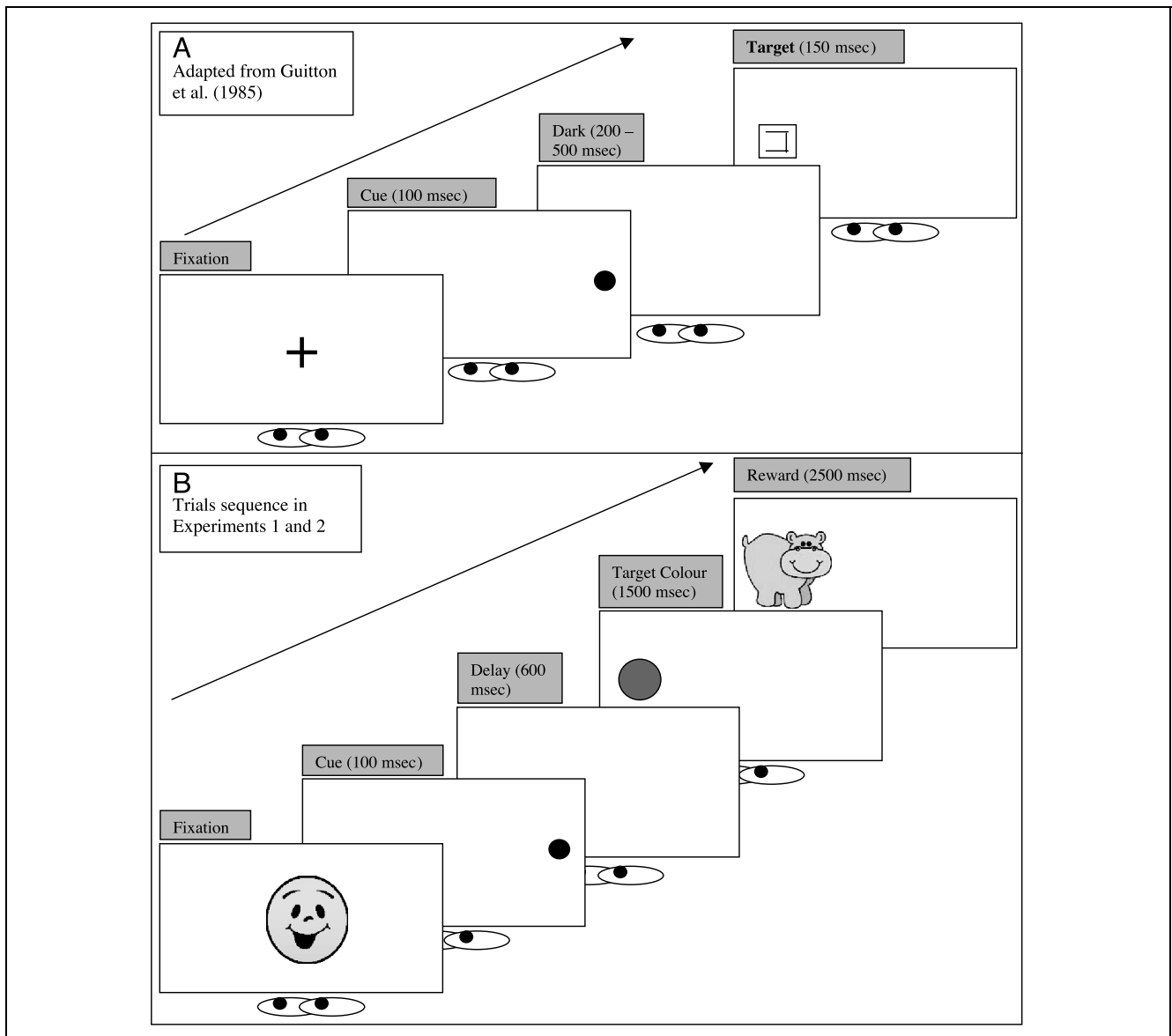


Figure 1. Stimulus sequence used by (A) Guitton et al. (1985), (B) stimulus sequence for experimental trials in Experiments 1 and 2 (stimuli not drawn to scale—see text for accurate relative sizes of the stimuli). Experimental trials were preceded by 4 calibration trials presenting the peripheral cue alone to ensure that toddlers could both detect it and orient toward it. During experimental trials, a cue-to-target stimulus onset asynchrony of 700 msec was chosen to maximize the possibility of anticipatory saccades to the target location, without incurring in toddlers’ fussiness. Experimental trials were subdivided into a first and a second half.

location before target onset in the absence of a prosaccade (antisaccades) during these halves. Furthermore, to test that potential age-related differences in antisaccades did not depend on simple improvements in producing predictive saccades, we also calculated the percentage of “corrective” (i.e., anticipatory saccades toward the target preceded by looks toward the cue) and “reactive” saccades (i.e., stimulus-driven saccades that followed the appearance of the target) during the first and second half of trials. We predicted that typically developing toddlers would decrease looking toward predictive but uninteresting peripheral onsets, as 4-month-olds do according to Johnson. This pattern

should be more marked in older than in younger toddlers, indicating a developmental improvement in the ability to control reflexive saccades. Finally, although 4-month-olds in the study by Johnson did not produce antisaccades, we predicted that this ability should emerge and gradually improve through toddlerhood, independently of the ability to produce predictive saccades.

Results

Overall, typically developing toddlers decreased looking toward the peripheral cue from the first to the second

half of trials. They produced antisaccades, and, as in older children and adults, these eye movements were significantly slower than reactive looks toward the cue locations. During the second half of trials, looks toward the cue and number of antisaccades were correlated with age, with older toddlers producing fewer cue looks and more antisaccades than younger toddlers. These results were statistically supported as follows. First, a preliminary analysis comparing trials in which the cue had been presented to the left or right of fixation did not reveal differences, so these trials were collapsed.

Saccades toward the Cue and Antisaccades toward the Target Location

Table 1 reports the number of trials (total and unscorable) and the percentage of looks toward the cue and toward the target location for the group. Toddlers looked at the cue on 68.9% of trials during the first half

Table 1. Experiment 1: Number of Trials (Total and Unscorable) for Typically Developing Children Overall and During the First and Second Half, as Well as the Percentage of These Trials That Were Characterized by Different Saccade Types.

	<i>Overall</i>	<i>First Half</i>	<i>Second Half</i>
<i>Mean (Range)</i>			
<i>Trials</i>			
Total	22.7 (12–32)	11.3 (6–16)	11.3 (6–16)
Unscorable	5.1 (0–17)	2.1 (0–7)	2.9 (0–10)
<i>Percent Mean (Range)</i>			
Cue looks	62.8 (36.4–100)	68.9 (42.9–100)*	56.6 (11.1–100)*+
<i>Target looks</i>			
Antisaccades	14.0 (0–33.3)	13.5 (0–50)	14.5 (0–44.4) ⁺
Corrective	35.2 (0–69.7)	38.4 (0–72.7)	31.8 (0–66.7)
Reactive	50.8 (16.7–78.9)	48.6 (0–77.8)	52.4 (0–100)

(a) Cue looks: These represent the percentage of trials in which toddlers looked toward the cue location. Toddlers were included in the final analysis only if they produced at least 40% cue looks in the first half of trials (following Johnson, 1995), to ensure that they could detect the cue. (b) Target looks: Looks toward the target location were classified as antisaccades only if they anticipated the appearance of the target (up to 100 msec posttarget onset, following Guitton et al., 1985) in the absence of prosaccades toward the cue. This criterion distinguishes them from anticipatory saccades that are not accompanied by inhibition of cue looks (labeled *corrective saccades* in the adult antisaccade literature). It also from distinguishes them from reactive saccades toward the target location, which are stimulus-driven, rather than anticipatory, because they initiate 100 msec after target onset, whether or not they are preceded by a cue look.

*Significant difference between the first and second half of trials, $p < .05$.

⁺Significant correlation with age, $p < .05$.

($SE = 4.9$) and 56.6% of trials during the second half of the experiment ($SE = 5.8$), showing a statistically significant decrease in looks to the cue from the first to the second half, $t(17) = 2.392, p = .029$. With regard to looks toward the target, the percentage of antisaccades did not differ statistically during the first ($13.5 \pm 3.2\%$) compared with the second half of trials ($14.5 \pm 3.2\%$), $t(17) = -.235, p = .817, ns$. Similarly, the percentage of corrective and reactive saccades did not differ from the first to the second half of trials, $t(17) = 1.527$ and $-.534, p = .145$ and $.600$, respectively. The average latency of cue saccades (323.2 ± 36.9 msec) was faster than that of antisaccades (675.2 ± 37.4 msec), $t(14) = 6.920, p < .001$. Cue saccades were also faster than corrective saccades (on average, 713.7 ± 15.7 msec), $t(16) = 15.745, p < .001$, and reactive saccades (on average, 943.2 ± 17.0 msec), $t(17) = 22.880, p < .001$.

Age-related Changes in Performance

Firstly, younger and older toddlers did not differ statistically in the number of scorable trials, $r(18) = .410, p = .091$. Age did not correlate with the percentage of prosaccades to the cue during the first half, $r(18) = -.263, p = .292$, but it did correlate negatively with cue looks in the second half of trials, $r(18) = -.524, p = .026$. In other words, older toddlers produced fewer reflexive looks toward the cue during the test trials. This is illustrated in Figure 2.

Age did not correlate with the production of antisaccades in the first half of trials, $r(18) = .218, p = .385, ns$, but it correlated with the number of antisaccades produced on the second half of trials, $r(18) = .854, p < .001$, suggesting that older toddlers produced more antisaccades than younger toddlers after training, as illustrated

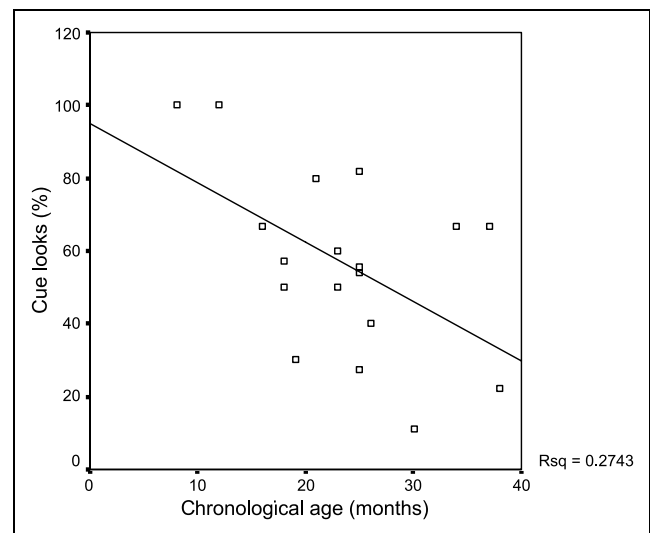


Figure 2. Experiment 1. Percentage of trials in which toddlers looked toward the cue during the second half of the experiment plotted as a function of their age.

in Figure 3. Age also correlated with the overall number of antisaccades, $r(18) = .698, p = .001$, and tended to do so with the percentage increase in antisaccades from the first to the second half of trials, $r(18) = .449, p = .061$. The 4-month-old infants tested by Johnson (1995) did not produce antisaccades toward the target locations. In contrast, only 4 here did not and they were all younger than 18 months.

Did these age-related changes in the number of antisaccade simply index increases in the ability of older toddlers to produce anticipatory saccades preceding the appearance of the target? We tested this possibility by studying the correlation between age and saccades anticipating the appearance of the target, preceded by a look toward the cue (corrective saccades). Counter to what would have been predicted by simple improvements in anticipations, these saccades did not correlate with age, either during the first, nor the second half of trials, $r(18) = -.380$ and $-.231, p = .119$ and $.355$, respectively.

Age did not correlate either with prosaccade latency, $r(18) = -.260, p = .338$, with antisaccade latency, $r(18) = -.233, p = .424$, with corrective saccade latency, $r(18) = -.321, p = .209$, or with reactive saccade latency, $r(18) = -.167, p = .508$.

Discussion

Experiment 1 sought to investigate whether typically developing toddlers tested with a variant of Johnson's (1995) infant antisaccade paradigm would decrease looks toward a peripheral stimulus and how this ability

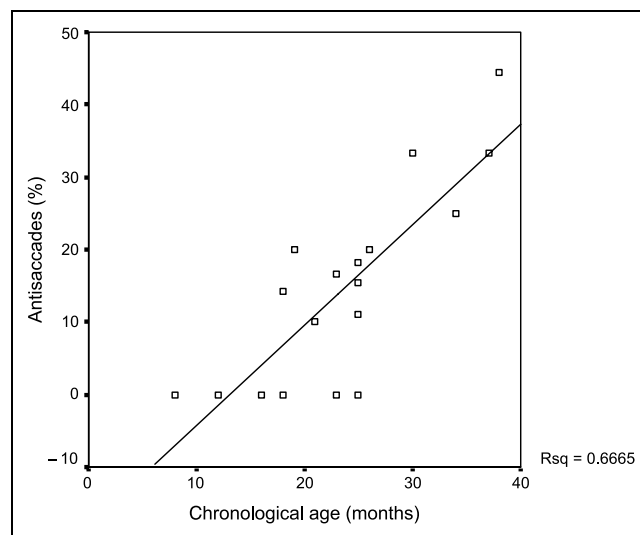


Figure 3. Experiment 1. Percentage of trials in which toddlers produced antisaccades during the second half of the experiment as a function of their age. Antisaccades are defined here as saccades anticipating the appearance of the target (up to 100 msec posttarget onset, following Guitton et al., 1985) in the absence of prosaccades toward the cue.

might change with age. It is the first study addressing this question in children between the ages of 4 months (Johnson, 1995) and 5 years old (the youngest age group tested by Munoz et al., 1998). The percentage of looks toward the cue decreased during test trials, replicating the findings obtained at 4 months, but the larger age range tested here critically allowed us to also uncover age-related changes in cue looks for the first time in toddlers. Furthermore, infants tested by Johnson did not produce antisaccades. The older toddlers tested here did produce them, and these were characterized by longer onset latency than prosaccades, as is typically found in older children and adults (Munoz et al., 1998). Most importantly, the number of antisaccades increased greatly during the toddler years, independently of other types of predictive looks toward the target location.

These findings raise a number of questions. Firstly, could low-level habituation to the cue itself explain for the decrease in looks toward the cue? Johnson (1995) tested a different group of infants presenting them with peripheral cues with no predictive value and found that they did not decrease looking toward the cue, a result that would have been expected if the infants in Experiment 1 had simply habituated to the cue. An additional argument is that habituation to the cue cannot explain the true antisaccades found for the first time here. We thank an anonymous reviewer for the suggestion that changes in the ability to inhibit prosaccades could be further corroborated by using a go-nogo paradigm with infants. Secondly, are the antisaccades measured here equivalent to those of the standard adult task? With some exceptions (e.g., Guitton et al., 1985), in the most commonly used antisaccade task, human adults are asked to orient away from peripheral cues to an empty location in space. This paradigm must be adapted for use with subjects with little or no language, including human infants and nonhuman primates. For example, macaque monkeys are extensively trained to associate different fixation stimuli and the requirement to make either prosaccades or antisaccades when presented with a peripheral stimulus. In the case of antisaccades, a stimulus is presented at the contralateral location to the initial peripheral stimulus to provide the monkey with posttrial information about accuracy (e.g., Everling & Munoz, 2000). Given this necessary training component and use of reward, parallels between these antisaccades and those measured with human adults and older children should be treated with caution. It would, therefore, be extremely useful to validate the current results by building a full developmental trajectory of performance for older toddlers and children, as has been done for other tasks (Karmiloff-Smith et al., 2004). This would allow a direct comparison of the developmental changes measured by Johnson's task used here and by the standard antisaccade task.

Finally, what are the neurodevelopmental changes underlying these age-related differences in performance?

Childhood difficulties in oculomotor control were originally attributed to the delayed maturation of prefrontal cortex (Munoz et al., 1998; Paus et al., 1990); more recently, increases in activation in a larger network including prefrontal, parietal, striatal, and thalamic areas have been implicated in age-related changes in the control of saccades (Luna et al., 2001). Although such accounts exist at the systems level, less is known about the neurocomputational and cellular properties underlying these changes. Neurodevelopmental disorders of known genetic origin offer unique tools to investigate them. Experiment 2, therefore, examined performance on the same task in toddlers with FXS.

EXPERIMENT 2: OCULOMOTOR CONTROL IN INFANTS AND TODDLERS WITH FRAGILE X SYNDROME

FXS is the most common form of inherited mental retardation and is associated with the silencing of a single gene, the Fragile X mental retardation gene (*FMRI*, Verkerk et al., 1991). Greenough et al. (2001) have demonstrated the involvement of its protein product, FMRP, in the postsynaptic refinement of dendritic spine morphology mediated by second messenger cascades that are initiated by the excitation of metabotropic glutamatergic receptors of Type I. Loss of FMRP in FXS is associated with immature dendritic spine morphology, as shown in *FMRI* knockout mice (Comery et al., 1997) and human postmortem samples in FXS (e.g., Hinton, Brown, Wisniewski, & Rudelli, 1995). These morphological changes seem to be ubiquitous to neocortical neurons, but they may be particularly disruptive for executive control functions, on which antisaccade performance (and action control in general) appears so reliant (Scerif, 2003). These are supported by cortical circuits that rely more extensively than others on the integration of inputs, such as prefrontal projections and the large network to which they belong (e.g., fronto-striatal connections).

Do individuals with FXS, indeed, exhibit deficits in the control of action over and above what is expected given their overall developmental delay? Consistent with this suggestion, adult women with FXS have shown white-matter tract alterations of fronto-striatal pathways (Barnea-Goraly et al., 2003), dysfunctional activation of prefrontal and parietal areas during Stroop interference (Tamm, Menon, Johnston, Hessel, & Reiss, 2002), and in prefrontal and striatal areas when required to inhibit go responses (Menon et al., 2004). Serious problems of inattention and hyperactivity are particularly striking through development in boys with the condition. Adult men (Cornish et al., 2001) and older boys with FXS (Wilding, Cornish, & Munir, 2002; Munir et al., 2000) differ from typically developing and other atypically developing control groups in their ability to inhibit

task-irrelevant repetitive responses in executive and selective attention tasks. More recently, Scerif et al. (2004) tested toddlers on a search task that required them to find multiple targets among distractors. Toddlers with FXS, as young as 30 months old, produced more repetitive errors on previously successful responses than younger typically developing toddlers matched on mental age suggesting very early difficulties in response inhibition.

It remains unknown whether inhibitory difficulties in the control of manual responses extend to the control of eye movements. Thus far, no studies on FXS have focused on eye movements as measures of the control of action, in any age group. Here, boys with FXS, aged between 14 and 55 months, were individually matched to typically developing toddlers (henceforth referred to as "MA controls") based on their developmental level and were tested using the paradigm validated in Experiment 1. If toddlers with FXS already exhibit these difficulties over and above what is expected given their overall developmental delay, they should show reduced decrease of looks to the cue compared with controls. If this is also accompanied by difficulties in planning saccades, we may observe reduced antisaccades. Given the developmental changes in antisaccade parameters in children with ADHD (Munoz et al., 2003), it will be crucial to investigate whether performance of toddlers with FXS changes in line with either their chronological or mental age or whether it follows an atypical pattern regardless of their developmental level.

Results

Overall, and in contrast to typically developing toddlers, toddlers with FXS did not decrease looks toward the peripheral cue during test trials, compared with training trials. Importantly, they produced just as many correct antisaccades toward the target location as their individually matched controls, showing that their oculomotor system could anticipate the target there, but could not suppress prosaccades toward the cue as did control subjects. Although general developmental level in controls predicted the percentage of looks toward the cue and of antisaccades during test trials, it did not do so for toddlers with FXS. All these findings were supported statistically as follows.

Calibration and Experimental Trials (First and Second Half)

Table 2 reports the number of trials (total and unscorable), as well as the percentage of looks toward the cue and the target location for FXS toddlers and MA controls. Firstly, toddlers with FXS and typically developing toddlers did not differ in either the accuracy (71.8% and 75%, respectively) or the speed (220.7 vs. 225.41 msec) of saccades toward the cue during the calibration trials

Table 2. Experiment 2: Number of Trials (Total and Unscorable), as Well as the Percentage of These Trials That Were Characterized by Different Saccade Types for MA Controls and FXS Toddlers (see Table 1 for criteria)

	<i>Overall</i>	<i>First Half</i>	<i>Second Half</i>
<i>MA Controls</i>			
<i>Mean (Range)</i>			
<i>Trials</i>			
Total	22.4 (12–32)	11.1 (6–16)	11.1 (6–16)
Unscorable	4.5 (0–9)	2.2 (0–5)	2.3 (0–5)
<i>Percent Mean (Range)</i>			
Cue looks	62.3 (36.4–100)	71.7 (42.8–100)*	52.8 (11.11–100)* ⁺
<i>Target looks</i>			
Antisaccades	12 (0–33.33)	13.2 (0–50)	10.8 (0–33.3) ⁺
Corrective	38.5 (9.1–83.3)	42.3 (9.1–100)	34.8 (0–66.7)
Reactive	51.2 (16.7–77.3)	49.3 (0–81.8)	53.1 (33.3–83.3)
<i>FXS Toddlers</i>			
<i>Mean (Range)</i>			
<i>Trials</i>			
Total	24.4 (12–32)	12 (6–16)	12 (6–16)
Unscorable	8.1 (0–17)	3.3 (1–9)	4.8 (2–9)
<i>Percent Mean (Range)</i>			
Cue Looks	74.2 (55.1–100)	74.4 (53.8–100)	73.9 (55.5–100)
<i>Target Looks</i>			
Antisaccades	12.7 (0–26.5)	11.8 (0–27.3)	13.5 (0–23.1)
Corrective	40.4 (15.3–58.7)	36.1 (12.7–67.3)	44.6 (16.6–73.2)
Reactive	46.1 (27.6–77.8)	52.4 (38.5–100)	32.9 (14.3–55.5)

*Significant difference between the first and second half, $p < .05$.

⁺Significant correlation with age.

($p = .80$ and $.83$). They also did not differ in the number of valid trials, on average 17 and 19.6 for MA controls and FXS toddlers, respectively, $t(18) = -1.209$, $p = .242$, *ns*.

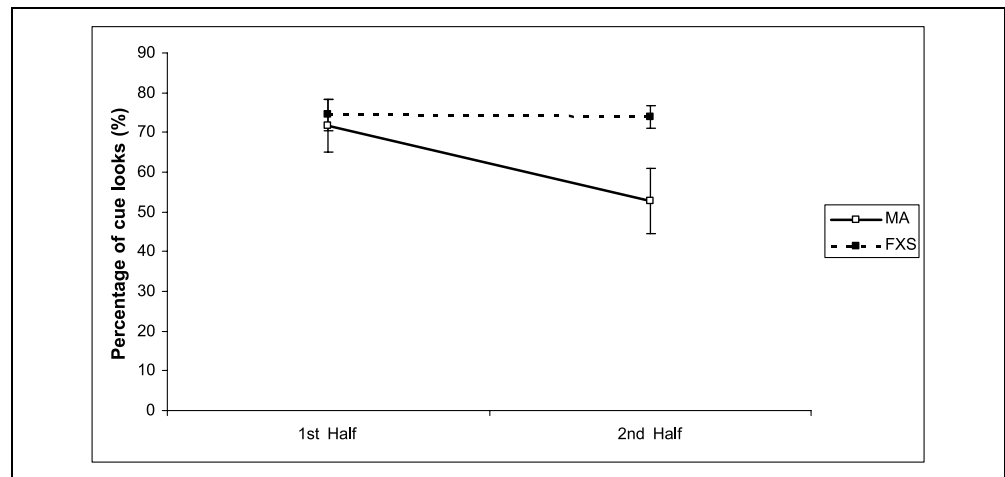
Saccades toward the Cues and Antisaccades

Figure 4 illustrates the percentage of trials during which toddlers looked at the cue, during the first and second half. Empty squares represent MA controls; filled squares, toddlers with FXS. There was a statistically significant interaction between group and trial type, $F(1,18) = 5.636$, $p = .029$. Paired t tests confirmed that the MA controls decreased looks toward the cue during the second ($52.8 \pm 8.3\%$) in comparison to first half of trials ($71.7 \pm 6.7\%$), $t(9) = 2.782$, $p = .021$, whereas toddlers with FXS did not, $t(9) = .130$, $p = .900$. Furthermore, the MA controls produced significantly fewer

looks toward the cue than toddlers with FXS during the second half of trials, $t(18) = 2.394$, $p = .028$. However, the 2 groups produced equal looks toward the cue during the first half of trials, $t(18) = .325$, $p = .749$, *ns*.

The total number of correct antisaccades toward the target location before the appearance of the target object during the first and second half did not differ for the toddlers with FXS (first: 11.8 ± 4.0 , *SE*; second: $13.5 \pm 5.5\%$) and individually matched MA controls (first: $13.2 \pm 4.5\%$, *SE*; second: $10.8 \pm 7.7\%$, $p = .873$ and $.577$ for group and the interaction of group and trial type). There was a main effect of saccade type, $F(3,42) = 90.441$, $p < .001$. The onset of saccades toward the cue (on average, 330.7 msec) was statistically faster than that of antisaccades (680.35 msec), of corrective saccades (716.6 msec), and of reactive saccades (on average, 1027 msec), $p < .001$ for all pairwise comparisons

Figure 4. Experiment 2. Percentage of trials during which typical and atypical toddlers looked toward the cue during the first and second half of trials. Full squares represent toddlers with FXS, empty squares represent individually matched controls. Bars represent standard errors.



(Bonferroni corrected). Furthermore, reactive saccades were slower than all other saccades, $p < .001$ (Bonferroni corrected), whereas antisaccades and corrective saccades did not differ $p = 1.0$ (Bonferroni corrected). Importantly, the effect of saccade type did not differ for FXS infants and toddlers compared with MA controls, $F(3,42) = 1.678$, $p = .186$, *ns*, for the interaction between group and saccade type. Furthermore, the 2 groups did not differ in the onset of saccades of any types, $F(1,14) = .443$, $p = .517$, *ns*, for the main effect of group.

Differential Age-Related Changes in Performance

Figure 5 illustrates the percentage of looks toward the cue during the second half of trials, for toddlers with

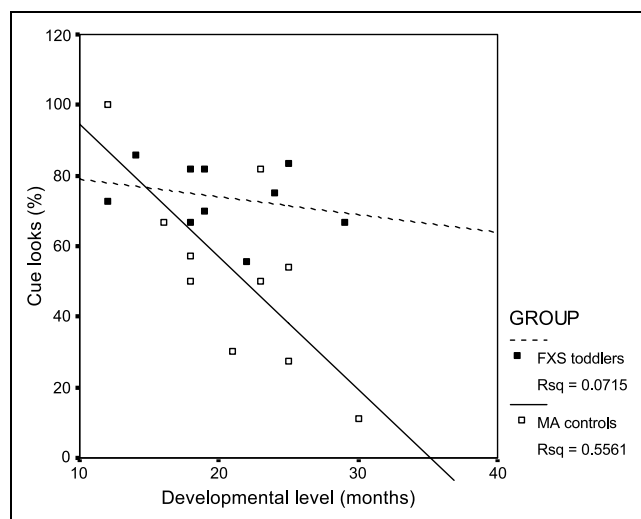


Figure 5. Experiment 2. Percentage of trials in which toddlers with FXS (full squares) and MA controls (empty squares) oriented toward the cue during the second half of the experiment as a function of their mental age.

FXS (filled squares) and MA controls (empty squares). Older MA controls produced less looks toward the cue than younger controls during the second half of trials, $r(10) = -.746$, $p = .013$. In contrast, for toddlers with FXS, mental age did not correlate with the percentage of looks toward the cue during either the first, $r(10) = .070$, $p = .848$, *ns*, or the second half of trials, $r(10) = -.267$, $p = .455$, *ns*. Their chronological age also did not correlate with either measure, $r(10) = .128$ and $= -.489$, $p = .724$ and $.152$, *ns*.

For MA controls, mental age correlated positively with the percentage of correct antisaccades during test trials, $r = .799$, $p = .006$, suggesting that older toddlers produced more antisaccades than younger ones. In contrast, for toddlers with FXS the percentage of correct antisaccades did not correlate with either mental age ($r = .056$, $p = .877$) or chronological age ($r = -.114$, $p = .753$). Figure 6 illustrates the relationship between mental age and antisaccades to the cue during the second half of trials. Chronological age did not correlate with either prosaccade or antisaccade latency for both MA controls, $r(10) = .010$ and $.282$, $p = .979$ and $p = .431$, respectively, and toddlers with FXS, $r(10) = -.376$ and $.124$, $p = .285$ and $p = .733$, respectively.

Discussion

Experiment 2 is the first study to investigate oculomotor control in a sample of individuals with the FXS. It aimed to compare saccades in typically developing toddlers and toddlers with the condition. Toddlers with FXS did not decrease looking toward “unrewarding” but predictive peripheral cues, in contrast to the behavior displayed by typically developing controls matched for their developmental level. Furthermore, although they produced an equivalent number of correct antisaccades to the controls (showing that they could learn the contingency between the cue and the target location), this did not correlate with either mental or chronological age in

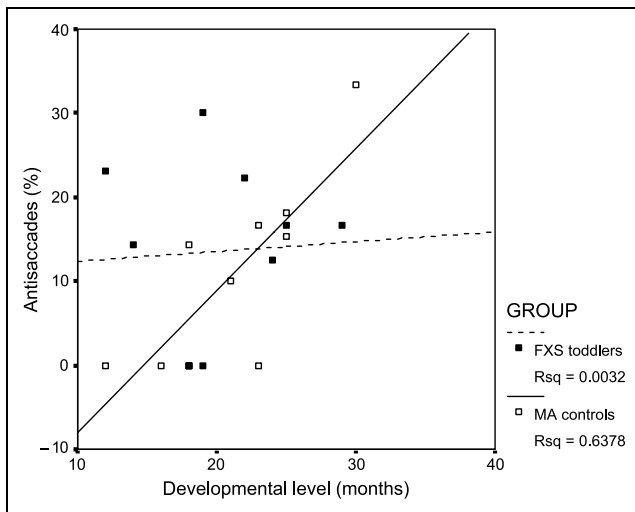


Figure 6. Experiment 2. Percentage of trials in which toddlers with FXS (full squares) and MA controls (empty squares) produced antisaccades during the second half of the experiment as a function of their mental age.

the FXS group. Similarly, and in contrast with matched controls, the number of looks toward the cue did not correlate with either age or mental age within the clinical sample, suggesting a highly atypical developmental trajectory.

A number of explanations could account for the lack of a decrease in looks toward the cue in FXS toddlers. Could it be that they simply did not learn about the association between the location of the cue and the target? This is unlikely, because as a group, they produced as many antisaccades toward the target location as controls. It is more likely that, having learned the contingency between cue and target location, toddlers with FXS were not able to use it fully to modify their behaviour adaptively in the same way as typically developing controls and as would be expected given their overall developmental level by inhibiting cue looks. This is the interpretation that we find the most consistent with our results. We thank an anonymous referee for the suggestion that the antisaccades produced by toddlers with FXS, in contrast with matched controls, may also depend on subcortical mechanisms such as those underlying inhibition of return, as opposed to the gradually improving functioning of fronto-striatal circuits that may account for both typical performance and its developmental trajectory. This additional possibility would also support our suggestion of atypical oculomotor control in FXS. Indeed, multiple aspects of performance by toddlers with FXS appear atypical, from the inability to decrease prosaccades toward the cue, to the elimination of age-related changes in both cue looks and antisaccades. Taken together, these results indicate atypical saccadic control in infants with FXS as young as 14 months old (the youngest child in the group). This is consistent with the inhibitory deficits displayed by

toddlers, older children and adults with the syndrome (Scerif et al., 2004; Wilding et al., 2002; Cornish et al., 2001; Munir et al., 2000).

Why would individuals with FXS display difficulties in the control of actions, including eye movements? The general focus in studies of the genetic bases of neurodevelopmental conditions with atypical action control has been on genes involved in the modulation of prefrontal circuits by extrinsic neurotransmitters like dopamine. Indeed, studies of disorders like schizophrenia have targeted candidate genes regulating dopaminergic function, as the catechol-*o*-methyl transferase gene (e.g., Egan et al., 2001). In this context, FXS presents an intriguing case, as the sole cause of the disorder is the silencing of a gene involved in activity-dependent changes at glutamatergic synapses across neocortex, rather than specifically involving frontal striatal circuits.

We propose 3 intertwined mechanisms for these effects. First, prefrontal networks are characterized by large and complex dendritic fields and these seem to relate to the higher degree of convergent processing required of higher association areas (Elston, 2003; Elston & Rosa, 1998). Dendritic spine morphology is abnormal through all neocortical areas examined thus far in FXS, but this abnormality may have larger effects on functions that rely more heavily on integration, as is the case for networks supporting endogenous control of actions, including eye movements (Scerif, 2003). An analogous argument has been proposed to account for larger effects of FXS on functions supported by M neurons (that normally have a large dendritic field) in the lateral geniculate nucleus of the thalamus, in contrast with weaker effects on the functions of P neurons, that have smaller dendritic fields and lower reliance on their integrative role (Kogan et al., 2004). Secondly, in prefrontal cortex in particular, recurrent connections may provide analogous functions to horizontal connections in sensory cortices such as V1, but do so through excitatory, glutamatergic inputs rather than through GABA-ergic lateral inhibition. Therefore, the recurrent activity proposed to be crucial for goal maintenance and attentional control (Miller & Cohen, 2001) relies on networks that, in turn, may depend on complex dendritic field structure. These functions should be differentially more affected by the abnormal dendritic spine morphology in FXS. Thirdly, extrinsic modulators interact with intrinsic excitatory signals at the level of asymmetric synapses (Nimchinsky, Sabatini, & Svoboda, 2002). Modulation of excitatory inputs by extrinsic neurotransmitters depends of the fine structure of the dendritic spines on which these inputs converge (Gao & Goldman-Rakic, 2003), making them potentially more vulnerable to the abnormalities characteristic of FXS. This, in turn, suggests that atypical development of oculomotor control may depend on structural and functional disturbances influencing both extrinsic and intrinsic neurotransmitter systems.

Importantly, our suggestion does not imply that FXS is characterized by localized selective abnormalities in prefrontal cortex, in isolation, as would be the case in cases of adult brain damage. Indeed, recent structural and functional imaging data on able women with FXS suggests atypical connectivity and function of distributed frontal, parietal and striatal circuits in individuals with FXS (Menon et al., 2004; Barnea-Goraly et al., 2003; Tamm et al., 2002). We propose instead that although the effects on dendritic spine morphology associated with FXS are ubiquitous, these changes may be most relevant to the neurocomputational properties that are critical for the development of functions supported by prefrontal cortex and its related cortical and subcortical partners. This is the essence of a more dynamic view of neurocognitive development in developmental disorders (Karmiloff-Smith, 1998).

GENERAL DISCUSSION

Taken together, results from these experiments suggest that the inhibition of prosaccades and the generation of antisaccades can be successfully measured in both typically and atypically developing toddlers. In Experiment 1, we showed that typically developing toddlers decrease looks toward an informative but “unrewarding” cue and produce antisaccades in the opposite direction. Both of these measures change within the age range tested, with older toddlers producing fewer reactive saccades toward the cue and more antisaccades. These changes in the control of reactive saccades and antisaccades converge with those obtained in standard versions of the antisaccade task, used with older children and adults. Indeed, errors (measured here as the percentage of looks toward the cues) have been found to reflect the largest age effects in all studies investigating developmental changes in antisaccade performance (e.g., Klein, 2001; Munoz et al., 1998) and associated neural changes (Luna et al., 2001). Higher percentages of errors also best characterize atypically developing individuals with attentional difficulties (Munoz et al., 2003). Indeed, Experiment 2 showed that in contrast to typically developing toddlers, toddlers with FXS do not decrease looks toward the cue, with their performance neither correlating with mental nor chronological age. Furthermore, although they produced antisaccades, these did not correlate with either developmental level or chronological age in the FXS group. This suggests that oculomotor control follows an atypical developmental trajectory for toddlers with FXS, which is consistent with their later striking difficulties in tasks requiring manual responses (Scerif et al., 2004; Wilding et al., 2002; Cornish et al., 2001; Munir et al., 2000) and with the atypical functional neuroanatomy of fronto-striatal circuits in adult women with FXS (e.g., Menon et al., 2004).

Important issues for future investigation emerge from the data presented here. We proposed a mechanistic

account for oculomotor control abnormalities in FXS, a disorder known to affect morphological and functional changes at glutamatergic synapses. The integrative functions of areas with high dendritic field size and complexity may be differentially more affected by the abnormal dendritic spine morphology associated with FXS. This is certainly crucial for executive functions supported by prefrontal neurons and by the large circuits in which prefrontal neurons take part. Furthermore, recurrent excitatory connections may implement maintenance of activity relevant to action control and the normal functioning of extrinsic modulatory neurotransmitters depends at least in part on the structure of dendritic spines, abnormal in FXS. In turn, atypical saccadic control in FXS suggests a role for both intrinsic and extrinsic neurotransmitter systems in the development of normal oculomotor control. These hypotheses will need to be tested with direct measures of gene expression, cortical structure and function, by integrating neuroanatomical, functional, and behavioral information.

In conclusion, for the first time the current experiments investigated both the production of prosaccades and of antisaccades through the toddler years, in typical development as well as in FXS, a population known to have later striking difficulties in the executive control of action. From a neuroscientific perspective, FXS represents an intriguing case in which to study cascading developmental effects of a single gene silencing leading to dysfunctions that have been more traditionally linked to extrinsic neurotransmitter modulation. More generally, the findings stress the role of genetic disorders in an integrated framework to study developmental cognitive neuroscience. This remains a daunting research enterprise, but one that is increasingly within reach, as studies of genomics and proteomics uncover the molecular and cellular processes involved in systems cognitive neuroscience, and as cognitive processes can be studied behaviorally at earlier and earlier ages, and thus, throughout the course of development.

METHODS

Participants

Participant for Experiment 1 were 18 infants and toddlers (6 girls), whose age ranged from 8 to 38 months (mean = 23.5 months, median = 24 months), recruited through local maternity wards, nurseries, and word of mouth. For Experiment 2, toddlers with FXS were recruited through the Fragile X Society, UK, and local genetic services, as part of a larger longitudinal study of early attentional control in FXS. As FXS is an X-linked disorder, girls tend to be less severely affected than boys, be diagnosed later, and exhibit larger individual variability (due to variable rates of inactivation of the fragile X chromosome). Our study, therefore, focused

solely on boys. Ten boys satisfied the criteria for inclusion set below (chronological age range = 14–55 months, mean = 35.9 months, $SD = 12.7$ months). Their developmental level assessed using the Bayley Scales of Infant Development—Revised, Mental subscale (Bayley, 1993) was equivalent to 20.0 months on average (range = 12–30, $SD = 5.1$). These boys were individually matched by mental age equivalent within 1 month with 10 typically developing boys (mental age equivalent: mean = 21.1, $SD = 5.2$, range = 12–30), all of whom had contributed to Experiment 1 (“MA controls”). Toddlers with FXS and MA controls did not differ in developmental level, $p = .639$, *ns*.

Procedure

The experimental protocol was approved by the Local Ethics Committee, Great Ormond Street Hospital, and Institute of Child Health. Informed parental consent was obtained before testing. At their preference, toddlers sat either alone (9 toddlers in Experiments 1, 6 were older than 24 months; 10 toddlers in Experiment 2, 8 were older than 24 months) or on their caregivers’ lap, 70 cm from the center of a large color monitor, controlled by a Pentium III computer. Parents were requested to refrain from encouraging their toddler to look in either direction during trials, whether they sat with him or her or not, and reminded throughout if necessary. Indeed, there were no statistically significant differences in saccade parameters between toddlers who preferred sitting on their own and those who sat on their own (lowest $p = .236$), except for more antisaccades produced during the second half by toddlers who sat on their own in Experiment 1 ($p = .046$). The experimenter could monitor the toddler and parent by means of a video camera mounted above the display screen. Each trial began with the presentation of an attractive fixation display subtending 20° of visual angle from the viewing distance above, that served to ensure that the toddler was looking at the center of the screen at the start of each trial, as confirmed by off-line video coding.

Calibration Trials

For each participant, the first 4 trials aimed at determining whether they could detect the cue, also providing a baseline measure of accuracy and speed of orienting. The amplitude of saccades during these trials was also used to calibrate the relative positions of left versus right appearing stimuli for each child. Each trial started with a bleeping sound and the animation of the fixation stimulus, which zoomed in and outward in steps of 500 msec for a total of 2 sec. One hundred milliseconds after fixation offset, the cue stimulus for experimental trials, a black circle (subtending 5.5°) was presented to the right

or left of fixation (18° to the right or left) until the child oriented toward it. The experimenter waited for the child to refixate to the center to initiate a new trial.

Training and Test Trials

The sequence of events in each experimental trial is depicted in Figure 1B. As the fixation stimulus disappeared at the center of the screen, the cue stimulus was presented for 100 msec to the right or left of fixation (18° to the right or left). In contrast to the stimulus sequence used by Johnson (1995), in which the fixation stimulus remained on while the cue was presented, we chose to present the cue after the offset of fixation, as this increases the probability of initial cue looks during the training phase (Fischer et al., 1997). A blank screen was presented for 600 msec before appearance of a target stimulus (an expanding and contracting colored circle, subtending between 9.2° and 6°) at the opposite location. The cue-to-target-onset asynchrony (CTOA) of 700 msec was chosen between that used with 4-month-olds (550 msec, Johnson, 1995) and that found to elicit the largest number of anticipatory saccades without incurring in infants’ fussiness while staring at a blank screen (800 msec, Csibra, Tucker, & Johnson, 2001). Five hundred fifty milliseconds may have been too brief to allow for antisaccades at 4 months (Johnson, 1995), but a CTOA longer than 700 may cause fussiness in 8- to 55-month-olds. The color of the target circle was random and the association between black cue and target did not depend on particular color pairs (to avoid the undue influence of potential color vision deficits across groups), but specifically on their relative location. After 1.5 sec of successive expansions and contractions, the colored circle was replaced by a cartoon animal or object (20°), randomly drawn from a set of 24, which animated on screen for 2.5 sec. The experimenter waited for the child to refixate to the middle before starting the following trial. The side of presentation of the cue stimulus was determined by a pseudorandom sequence, which lasted a minimum of 12 and a maximum of 32 experimental trials or until the toddler fussed or was no longer attending to the stimulus displays. After video coding, trials were divided into halves (for odd trial numbers, the last trial was dropped from analysis).

Video-coding Protocol and Interrater Reliability

Videotapes of eye movements during the task were coded off-line. All trials were coded with the observer being blind to the precise onset of the cue and target stimuli. She recorded the onset of the initial auditory signal indicating the beginning of a trial, the direction (center, left, and right) and onset of saccades, as well as eye blinks and frames spent looking elsewhere. Saccade direction was coded relative to positions on the video

screen established during the initial calibration trials. Saccade onset was recorded by selecting the first frame in which an eye movement to a discrete center/left/right location was detected. Trials were most commonly rejected in the following cases: toddler was not looking at the fixation stimulus at cue onset, toddler randomly oriented toward the cued side before the appearance of the cue, or toddler looked elsewhere throughout the duration of the trial. Following the criterion employed by Johnson (1995), data from each toddler were included in the final analyses only if they completed at least 12 scorable trials and if they produced looks to the cue on at least 40% of training trials. This criterion ensured that only toddlers who had detected the cue (and, therefore, had experienced the relationship between cue and target location) were tested for changes in their behavior during test trials. Data from 14 additional typically developing toddlers and 4 FXS toddlers were discarded because they did not meet the former criterion, whereas data from 1 typically developing toddler and 1 with FXS did not meet the second. This rate of participant attrition is not uncommon in infants' studies and is in line with that of the study by Johnson. Reliability between the experimenter and a trained coder blind to children's identity, age, or group membership (on 20% of videotapes) was .8 (Cohen's *K*) for whether trials should be rejected, and 1.0 for direction of saccades.

We considered a true antisaccade an anticipatory look toward the upcoming target location. Whereas saccades prior to the appearance of the target can be clearly labeled as anticipatory, several previous studies have classified saccades occurring shortly after the target's appearance as also anticipatory, rather than reactive. Could this imply that the antisaccades here were stimulus-driven rather than internally generated? We believe not. Although we do not claim that they here would be generated in the absence of any form of stimulation, antisaccades are directed away from the cue stimulus and arrive at the other side too soon for them to have been caused by the onset of the subsequent stimulus on that other side. The arbitrary cutoff of 100-msec post-target onset was chosen for considering saccades as anticipatory saccades toward the target location, as in studies of antisaccades in adults (Guitton et al., 1985). Confirming the validity of this criterion, plots of the frequency of saccade latencies revealed a bimodal distribution with 2 peaks around the cutoff. We measured antisaccades onset latency from cue onset as is standard procedure in studies of older populations. As suggested by an anonymous referee, to test whether age-related changes in the ability to produce antisaccades could simply be accounted for by age-related increases in predictive saccades, we calculated the percentage of saccades that anticipated the appearance of the target, but were preceded by a cue look (*corrective saccades* in the antisaccade literature). This critically differentiated them from antisaccades as the latter require concurrent

inhibition of prosaccades, as well as the production of contralateral saccades.

Statistical Analyses

The percentage of trials during which a saccade was made to the peripheral cue and the percentage of antisaccades were calculated for each toddler. To provide a measure of saccadic latency, the mean onset of saccades toward the cue stimulus and of antisaccades to the target location (i.e., in the absence of looks toward the cue and measured from cue onset) were calculated for each toddler. All variables were tested for normality (Kolmogorov–Smirnov test, lowest $p = .166$). Given that the children in this sample spanned a relatively large age range, we investigated age effects by testing correlations between performance and age. For children with FXS, the correlation between developmental level and performance was also explored, as the mental and chronological age of the clinical group obviously differed significantly. There are inevitable practical constraints when seeking to recruit toddlers with FXS to complete experimental tasks. We conducted compromise power analyses (Faul & Erdfelder, 1992) to establish whether the smallest sample sizes were too small to yield statistically significant results. For a medium effect size, with the smallest group size ($n = 10$, Experiment 2), the power to detect a significant within-subject effect with ANOVA would be .91 and .63 for an interaction or between-group effect, which can be considered satisfactory. Furthermore, this sample size provided satisfactory statistical power (.68) to detect significant correlations, as was necessary to investigate age-related changes in saccadic parameters.

UNCITED REFERENCES

- Bell, Everling, & Munoz, 2000
- Everling, Dorris, Klein, & Munoz, 1999
- Paterson, Brown, Gsödl, Johnson, & Karmiloff-Smith, 1999

Acknowledgments

The present research was supported by a Graduate Research Studentship and Research Project Fund from University College London to G.S. and by Medical Research Programme Grant G9715642 and The Health Foundation Grant 1748/961 to A.K.S. The authors thank all the families and children who took part in the project. The authors also thank Dr. Angela Barnicoat, Barbara Carmichael, and the Fragile X Society, UK, for continuous support with participant recruitment, Bryony Whiting for assistance with video coding, Prof. Mark Johnson for advice during the early stages of design, and Dr. John Wilding for helpful comments on an earlier draft.

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REFERENCES

- Barnea-Goraly, N., Eliez, S., Hedeus, M., Menon, V., White, C. D., Moseley, M., & Reiss, A. L. (2003). White matter tract alterations in fragile X syndrome: Preliminary evidence from diffusion tensor imaging. *American Journal of Medical Genetics*, *118*, 81–88.
- Bayley, N. (1993). *Bayley Scales of Infant Development* (2nd ed.). San Antonio, TX: Psychological Corporation.
- Bell, A. H., Everling, S., & Munoz, D. P. (2000). Influence of stimulus eccentricity and direction on characteristics of pro- and antisaccades in non-human primates. *Journal of Neurophysiology*, *84*, 2595–2604.
- Comery, T., Harris, J., Willems, P., Oostra, B., Irwin, S., Weiler, I., & Greenough, W. (1997). Abnormal dendritic spines in fragile X knockout mice: Maturation and pruning deficits. *Proceedings of the National Academy of Sciences, U.S.A.*, *94*, 5401–5404.
- Cornish, K. M., Munir, F., & Cross, G. (2001). Differential impact of the FMR-1 full mutation on memory and attention functioning: A neuropsychological perspective. *Journal of Cognitive Neuroscience*, *13*, 144–151.
- Csibra, G., Tucker, L., & Johnson, M. H. (2001). Differential frontal cortex activation before anticipatory and reactive saccades in infants. *Infancy*, *2*, 159–174.
- de Vries, B. B., van den Ouweland, A. M., Mohkamsing, S., Duivenvoorden, H. J., Mol, E., Gelsema, K., van Rijn, M., Halley, D. J., Sandkuijl, L. A., Oostra, B. A., Tibben, A., & Niermeijer, M. F. (1997). Screening and diagnosis for the fragile X syndrome among the mentally retarded: An epidemiological and psychological survey. Collaborative Fragile X Study Group. *American Journal of Human Genetics*, *61*, 660–667.
- Egan, M. F., Goldberg, T. E., Kolachana, B. S., Callicot, J. H., Mazzanti, C. M., Straub, R. E., Goldman, D., & Weinberger, D. R. (2001). Effect of COMT Val108/158Met genotype on frontal lobe function and risk for schizophrenia. *Proceedings of the National Academy of Sciences, U.S.A.*, *98*, 6917–6922.
- Elston, G. N. (2003). Cortex, cognition and the cell: New insights into the pyramidal neuron and prefrontal function. *Cerebral Cortex*, *13*, 1124–1138.
- Elston, G. N., & Rosa, M. G. (1998). Complex dendritic fields of pyramidal cells in the frontal eye field of the macaque monkey: Comparison with parietal areas 7a and LIP. *NeuroReport*, *9*, 127–131.
- Everling, S., Dorris, M. C., Klein, R. M., & Munoz, D. P. (1999). Role of primate superior colliculus in preparation and execution of anti-saccades and pro-saccades. *Journal of Neuroscience*, *19*, 2740–2754.
- Everling, S., & Munoz, D. P. (2000). Neuronal correlates for preparatory set associated with pro-saccades and anti-saccades in the primate frontal eye field. *Journal of Neuroscience*, *20*, 387–400.
- Faul, F., & Erdfelder, E. (1992). *G-Power: A priori, post-hoc, and compromise power analyses for MS-DOS*. Bonn: University of Bonn.
- Fischer, B., Biscaldi, M., & Gezeck, S. (1997). On the development of voluntary and reflexive components in human saccade generation. *Brain Research*, *754*, 285–297.
- Gao, W. J., & Goldman-Rakic, P. S. (2003). Selective modulation of excitatory and inhibitory microcircuits by dopamine. *Proceedings of the National Academy of Sciences, U.S.A.*, *100*, 2836–2841.
- Greenough, W. T., Klintsova, A. Y., Irwin, S. A., Galvez, R., Bates, K. E., & Weiler, I. J. (2001). Synaptic regulation of protein synthesis and the fragile X protein. *Proceedings of the National Academy of Sciences, U.S.A.*, *98*, 7101–7106.
- Guitton, D., Bachtel, H. A., & Douglas, R. M. (1985). Frontal lobe lesions in man cause difficulties in suppressing reflexive glances and in generating goal-directed saccades. *Experimental Brain Research*, *58*, 455–472.
- Haith, M. M., Hazan, C., & Goodman, G. S. (1988). Expectation and anticipation of dynamic visual events by 3.5-month-old babies. *Child Development*, *59*, 467–479.
- Hallett, P. E. (1978). Primary and secondary saccades to goals defined by instructions. *Vision Research*, *18*, 1279–1296.
- Hinton, V. J., Brown, W. T., Wisniewski, D., & Rudelli, R. D. (1995). Analysis of neocortex in three males with the fragile X syndrome. *American Journal of Medical Genetics*, *41*, 239–294.
- Johnson, M. H. (1995). The inhibition of automatic saccades in early infancy. *Developmental Psychobiology*, *28*, 281–291.
- Karmiloff-Smith, A., Thomas, M., Annaz, D., Humphreys, K., Ewing, S., Brace, N., Duuren, M., Pike, G., Grice, S., & Campbell, R. (2004). Exploring the Williams syndrome face-processing debate: the importance of building developmental trajectories. *Journal of Child Psychology and Psychiatry*, *45*, 1258–1274.
- Karmiloff-Smith, A. (1998). Development itself is the key to understanding developmental disorders. *Trends in Cognitive Sciences*, *2*, 389–398.
- Klein, C. (2001). Developmental functions for saccadic eye movement parameters derived from pro- and antisaccade tasks. *Experimental Brain Research*, *139*, 1–17.
- Kogan, C. S., Boutet, I., Cornish, K., Zangenehpour, S., Mullen, K. T., Holden, J. J., Der Kaloustian, V. M., Andermann, E., & Chaudhuri, A. (2004). Differential impacts of the FMR1 gene on visual processing in fragile X syndrome. *Brain*.
- Luna, B., Thulborn, K. R., Munoz, D. P., Merriam, E. P., Garver, K. E., Minshew, N. J., Keshavan, M. S., Genovese, C. R., Eddy, W. F., & Sweeney, J. A. (2001). Maturation of widely distributed brain function subserves cognitive development. *NeuroImage*, *13*, 786–793.
- Menon, V., Leroux, J., White, C. D., & Reiss, A. L. (2004). Frontostriatal deficits in fragile X syndrome: Relation to FMR1 gene expression. *Proceedings of the National Academy of Sciences, U.S.A.*, *101*, 3615–3620.
- Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience*, *24*, 167–202.
- Munir, F., Cornish, K., & Wilding, J. (2000). A neuropsychological profile of attention deficits in young males with fragile X syndrome. *Neuropsychologia*, *38*, 1261–1270.
- Munoz, D. P., Armstrong, I. T., Hampton, K. A., & Moore, K. D. (2003). Altered control of visual fixation and saccadic eye movements in attention-deficit hyperactivity disorder. *Journal of Neurophysiology*, *90*, 503–514.
- Munoz, D. P., Broughton, J. R., Goldring, J. E., & Armstrong, I. T. (1998). Age-related performance of human subjects on saccadic eye movement tasks. *Experimental Brain Research*, *121*, 391–400.
- Nimchinsky, E. A., Sabatini, B. L., & Svoboda, K. (2002). Structure and function of dendritic spines. *Annual Review of Physiology*, *64*, 313–353.
- O'Driscoll, G. A., Alpert, N. M., Matthyse, S. W., Levy, D. L., Rauch, S. L., & Holzman, P. S. (1995). Functional neuroanatomy of antisaccade eye movements investigated with positron emission tomography. *Proceedings of the National Academy Sciences, U.S.A.*, *92*, 925–929.
- Paterson, S. J., Brown, J. H., Gsödl, M. K., Johnson, M. H., & Karmiloff-Smith, A. (1999). Cognitive modularity and genetic disorders. *Science*, *286*, 2355–2358.

- Paus, T., Babenko, V., & Radil, T. (1990). Development of an ability to maintain verbally instructed central gaze fixation studied in 8- to 10-year-old children. *International Journal of Psychophysiology*, *10*, 53–61.
- Scerif, G. (2003). *Infant and toddler precursors of attentional difficulties in fragile X syndrome: A neurodevelopmental perspective*. Unpublished doctoral dissertation, University College London.
- Scerif, G., Cornish, K., Wilding, J., Driver, J., & Karmiloff-Smith, A. (2004). Visual search in typically developing toddlers and toddlers with fragile X or Williams syndrome. *Developmental Science*, *7*, 118–130.
- Tamm, L., Menon, V., Johnston, C. K., Hessel, D. R., & Reiss, A. L. (2002). fMRI study of cognitive interference processing in females with fragile X syndrome. *Journal of Cognitive Neuroscience*, *14*, 160–171.
- Verkerk, A. M., Pieretti, M., Sutcliffe, J. S., Fu, Y.-H., Kuhl, D. P., Pizzuti, A., Reiner, O., Richards, S., Victoria, M. F., Zhang, F., Eussen, B. E., van Ommen, G. B., Blonden, L. A. J., Riggins, G. J., Chastain, J. L., Kunst, C. B., Galjaard, H., Caskey, C. T., Nelson, D. L., Oostra, B. A., & Warren, S. T. (1991). Identification of a gene (FMR-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. *Cell*, *65*, 905–914.
- Wilding, J., Cornish, K., & Munir, F. (2002). Further delineation of the executive deficit in males with fragile-X syndrome. *Neuropsychologia*, *40*, 1343–1349.

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