

# Neurobehavioral Abnormalities in First-Degree Relatives of Individuals With Autism

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**Context:** Studying sensorimotor and neurocognitive impairments in unaffected family members of individuals with autism may help identify familial pathophysiological mechanisms associated with the disorder.

**Objective:** To determine whether atypical sensorimotor or neurocognitive characteristics associated with autism are present in first-degree relatives of individuals with autism.

**Design:** Case-control comparison of neurobehavioral functions.

**Setting:** University medical center.

**Participants:** Fifty-seven first-degree relatives of individuals with autism and 40 age-, sex-, and IQ-matched healthy control participants (aged 8-54 years).

**Main Outcome Measures:** Oculomotor tests of sensorimotor responses (saccades and smooth pursuit); procedural learning and response inhibition; neuropsychological tests of motor, memory, and executive functions; and psychological measures of social behavior, communication skills, and obsessive-compulsive behaviors.

**Results:** On eye movement testing, family members demonstrated saccadic hypometria, reduced steady-state pur-

suit gain, and a higher rate of voluntary response inhibition errors relative to controls. They also showed lateralized deficits in procedural learning and open-loop pursuit gain (initial 100 milliseconds of pursuit) and increased variability in the accuracy of large-amplitude saccades that were confined to rightward movements. In neuropsychological studies, only executive functions were impaired relative to those of controls. Family members reported more communication abnormalities and obsessive-compulsive behaviors than controls. Deficits across oculomotor, neuropsychological, and psychological domains were relatively independent from one another.

**Conclusions:** Family members of individuals with autism demonstrate oculomotor abnormalities implicating pontocerebellar and frontostriatal circuits and left-lateralized alterations of frontotemporal circuitry and striatum. The left-lateralized alterations have not been identified in other neuropsychiatric disorders and are of interest given atypical brain lateralization and language development associated with the disorder. Similar oculomotor deficits have been reported in individuals with autism, suggesting that they may be familial and useful for studies of neurophysiological and genetic mechanisms in autism.

*Arch Gen Psychiatry.* 2010;67(8):830-840

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**A**UTISM IS A HIGHLY HERITABLE neurodevelopmental disorder with considerable genetic and phenotypic heterogeneity.<sup>1,2</sup> Its core behavioral features include social and communication impairments, behavioral inflexibility, and executive dysfunction. Disturbances in these domains also have been identified in unaffected family members,<sup>3-10</sup> suggesting that they are familial traits. Neurophysiological and cognitive phenotypes are difficult to study in individuals with severe cognitive impairment, but family studies can include individuals without regard to proband disability and therefore provide potentially more gener-

alizable findings about autism and familial mechanisms. Studying variation in neurobehavioral phenotypes may help resolve pathophysiological mechanisms in autism and provide quantitative traits for family genetic research.

Studies of unaffected family members of individuals with autism have reported multiple informative findings, including increased rates of macrocephaly,<sup>11,12</sup> decreased cortical serotonin receptor density,<sup>13</sup> elevated whole-blood serotonin levels,<sup>14</sup> neurophysiological<sup>15,16</sup> and neuroanatomic abnormalities<sup>15</sup> associated with face processing deficits,<sup>17</sup> and minor physical anomalies.<sup>18</sup> Sensorimotor functions, which have been shown to be ab-

**Table 1. Demographic Characteristics of Family Members of Individuals With Autism and of Healthy Control Subjects<sup>a</sup>**

	Parents (n=42)	Siblings (n=15)	Parent Controls (n=26)	Sibling Controls (n=14)
Age, y	42.4 (6.6)	12.4 (5.3)	43.1 (5.6)	12.6 (3.1)
Male sex, No. (%)	18 (43)	7 (47)	11 (42)	7 (50)
FSIQ	110.8 (9.4)	113.6 (10.8)	112.7 (9.7)	108.4 (14.5)
VIQ	108.8 (7.8)	112.4 (11.1)	110.2 (9.7)	108.3 (16.0)
PIQ	110.5 (12.3)	111.9 (11.3)	111.9 (9.1)	106.7 (15.9)
Standardized head circumference, z score	0.37 (1.09)	-0.43 (1.28)	0.06 (1.29)	-0.37 (1.08)

Abbreviations: FSIQ, full-scale IQ; PIQ, performance IQ; VIQ, visual IQ.

<sup>a</sup>Unless otherwise indicated, data are expressed as mean (SD).

normal in individuals with autism, have not been extensively examined in familial studies.

Saccadic and smooth-pursuit eye movement impairments in autism represent potential intermediate phenotypes owing to their well-defined neurophysiological features, quantitative nature, heritability,<sup>19</sup> and stability over time.<sup>20-23</sup> Saccades are rapid eye movements that shift gaze between objects in the visual field. Saccade dysmetria (reduced saccade accuracy) and increased variability of saccade accuracy implicating variability-reducing functions of the cerebellum have been reported in some<sup>24-26</sup> but not all studies of autism,<sup>27,28</sup> suggesting pontocerebellar deficits. Saccade abnormalities are of interest in the context of abnormal Purkinje cell size and number,<sup>29-33</sup> reductions in levels of the signaling molecule reelin in the cerebellum,<sup>34</sup> and association or altered expression of genes related to cerebellar development in autism.<sup>35,36</sup>

Smooth-pursuit eye movements stabilize gaze on slowly moving objects. Deficits in sustained and open-loop (approximately the first 100 milliseconds) pursuit have been documented in autism.<sup>37,38</sup> Sustained pursuit impairments have been associated with dysfunction within the cerebellar and frontoparietal sensorimotor systems.<sup>28,38</sup> Although sustained pursuit deficits in autism are not lateralized, individuals with autism show slower rightward open-loop pursuit than healthy control subjects.<sup>37</sup> Because there is no lateralized alteration in motion perception during psychophysical testing<sup>38</sup> or in V5 activation during sustained pursuit tracking,<sup>28</sup> the absence of a rightward open-loop advantage in individuals with autism suggests an alteration in the transfer of motion information from the left extrastriate cortex to sensorimotor systems.

Procedural learning of motor sequences with interresponse intervals on the order of 1 second depends on striatal learning and response timing systems.<sup>39,40</sup> Reduced temporal precision of responses during an oculomotor serial reaction time task has been described in autism.<sup>41</sup> This abnormality was greater for rightward predictive saccades,<sup>42</sup> which, like the lateralized open-loop pursuit deficits, indicates a left hemisphere dysfunction. Deficits in the executive control of saccades assessed with antisaccade and memory-guided saccade tasks have been reported in autism,<sup>24,27,41,43</sup> implicating bilateral alterations in prefrontal systems.<sup>44</sup> Koczat et al<sup>45</sup> reported reduced accuracy of memory-guided saccades in 11 unaffected parents of patients with autism.

Oculomotor studies in individuals with autism thus document distinct deficits that implicate pontocerebellar circuitry, left frontotemporal circuitry, left striatum, and prefrontal systems. In the present study, we sought to determine whether oculomotor deficits evident in individuals with autism are present in unaffected family members and whether they are related to other putative familial traits, including neuropsychological, psychological, and head circumference measures.

## METHODS

### SAMPLE

Study participants consisted of 42 parents and 15 siblings of individuals diagnosed as having autistic disorder and 40 healthy matched controls (**Table 1**). To recruit a relatively representative sample of family members, first-degree relatives of consecutive individuals with autistic disorder seen in our clinics were identified regardless of the age or illness severity of the affected proband. Thirty probands with autistic disorder were recruited through clinics at the University of Illinois at Chicago. Proband diagnoses were confirmed by the Autism Diagnostic Interview-Revised<sup>46</sup> and the Autism Diagnostic Observation Schedule-Generic<sup>47</sup> using *DSM-IV* criteria. Family members of probands who met criteria for Asperger disorder or pervasive developmental disorder not otherwise specified were not included. Individuals with a known genetic or metabolic disorder associated with autism were excluded. All but 9 probands were too young (<8 years of age) or too cognitively/behaviorally impaired to complete eye movement and neuropsychological testing; thus, proband testing data are not reported. Proband clinical characteristics are included in the supplementary materials available on the authors' Web site ([http://ccm.psych.uic.edu/PublishedSupplementaryData/Mosconi\\_et\\_al.\\_Autism\\_family\\_study\\_Supplementary\\_tables.html](http://ccm.psych.uic.edu/PublishedSupplementaryData/Mosconi_et_al._Autism_family_study_Supplementary_tables.html)).

Only family members who did not meet cutoffs on the Social Communication Questionnaire<sup>48</sup> for autism were included in the analyses. History of psychiatric disorders was assessed using the Autism Family History Interview Revised-Modified.<sup>49</sup> Seven family members had psychiatric diagnoses, including attention-deficit/hyperactivity disorder, depression, and anxiety; none met current symptom criteria. Four of these individuals reported a history of taking antidepressants, psychostimulants, or benzodiazepines. At the time of testing, one was taking clonazepam (Klonopin) (16 hours before testing) and another had received sertraline hydrochloride (Zoloft) for more than 1 month.

Controls were recruited through local newsletters and had no history of mood or psychotic disorder, neurological disorder, family history of autism in first- or second-degree rela-

tives, or first-degree relatives with a major mental illness or developmental disorder. Family members and controls had no history of head injury, birth injury, drug dependence or recent abuse, or seizure disorder and had a full-scale IQ of more than 80. Groups were matched by IQ, age, and sex. Family member and control groups were matched in the proportion of individuals (49 of 57 [86%] for the family member group and 35 of 40 [88%] for the control group) who had reached the age (14 years) at which performance on cognitive tasks of interest approaches adult levels.<sup>50</sup> Far visual acuity was normal or corrected to at least 20/40. Informed consent was obtained from all adult participants; minors provided assent, and their parents provided consent. Study procedures were approved by the institutional review board of the University of Illinois at Chicago.

## EYE MOVEMENT STUDIES

Participants were tested in a darkened black room, positioned in a chin rest 140 cm from a display screen. Visual stimuli subtending 0.5° to 1° of visual angle were presented in the horizontal plane at eye level on a 183 × 244-cm seamless rear-projection screen (TechPlex 150; Stewart Filmscreen Corporation, Torrance, California) with the use of a high-resolution projector (Marquee 8500 Ultra projector; Christie Digital Systems, Cypress, California) with 2500 × 2000 resolution and a 120-Hz refresh rate. Direct current electrooculography was used to record eye movements during saccade tasks to assess large-amplitude saccades (Grass Neurodata 12 Acquisition System; Astro-Med, Inc, West Warwick, Rhode Island). Smooth pursuit was monitored using infrared sensors (Model 310; Applied Science Laboratories, Inc, Bedford, Massachusetts) that detected catch-up saccades with amplitudes on the order of 0.20° to 0.25°. Fixation of static targets across the horizontal plane was used to calibrate eye movement recordings. Blinks were monitored using electrodes placed above and below the left eye linked to an AC-coupled bioamplifier. Eye movement data were digitized at 500 Hz with a 12-bit A/D converter (DI-720; DATAQ Instruments, Akron, Ohio). Digital finite impulse-response filters with nonlinear transition bands were applied. Data from each trial were visually inspected and scored without knowledge of subject characteristics. For pursuit tasks, saccades and blinks were excluded before calculating pursuit gain.

## VISUALLY GUIDED SACCADE TASK

The visually guided saccade task was used to evaluate saccade latencies (time from the appearance of the peripheral target to the response initiation), saccade error (distance in degrees of the angle between eye location at the end of the saccade and the target location), and variability of saccade error (standard deviation of saccade error for all of the trials). Participants fixated a central target for 1500 to 2500 milliseconds before a peripheral target appeared unpredictably with equal probability at 10°, 20°, or 30° to the left or right of center. In the gap condition, the central fixation target was extinguished 200 milliseconds before the peripheral target appeared. In the overlap condition, the central fixation remained illuminated for 200 milliseconds after the appearance of the peripheral target. The overlap condition assesses the inhibitory modulation of saccade initiation by the visual fixation system, whereas the gap condition assesses response latencies without the delaying influence of ongoing central fixation.<sup>51</sup> Thirty-six trials of each condition were interleaved and presented in a fixed pseudorandom order.

## FOVEOFUGAL RAMP TASK

To assess pursuit latency and pursuit gain (ratio of average pursuit speed to target speed), targets were presented at center fixation for 2 to 4 seconds and then swept 15° to the left or right at a constant speed of 4°/s, 8°/s, 16°/s, 24°/s, or 32°/s. The onset, speed, and direction of target movement were pseudorandomly assigned for 40 trials (4 trials × 5 velocities × 2 directions). The latency to initiate pursuit was computed only when pursuit initiation preceded the first catch-up saccade.

## FOVEOFUGAL STEP-RAMP TASK

To assess open- and closed-loop gains separately, a step-ramp task was used in which targets stepped 3° to the left or right and immediately continued moving in the same direction at a constant speed of 4°/s, 8°/s, 16°/s, or 24°/s until reaching 15° of visual angle. In this paradigm, participants typically make a catch-up saccade approximately 200 milliseconds after the onset of target motion followed immediately by smooth pursuit. The first 100 milliseconds of pursuit is referred to as *open-loop pursuit* because it is driven by sensory motion information, and it occurs too early for visual feedback to affect performance.<sup>52</sup> The subsequent sustained pursuit is referred to as *closed-loop pursuit* because performance feedback can be used to reduce tracking error. The latency and gain of initial catch-up saccades and pursuit gain for open- and closed-loop phases were examined. Thirty-two trials were presented (4 trials × 4 velocities × 2 directions).

## PREDICTIVE SACCADE TASK

This serial reaction time task assesses procedural learning of a motor response. Individuals shifted gaze between targets alternating at 6° to the left and right of center every 750 milliseconds (1.33 Hz) 40 times. Participants quickly learn to anticipate the timing and location of target appearance, leading to a marked reduction in saccade latencies because saccades are based on internally generated predictions rather than on a response to target appearance. The latency and gain (response amplitude over the target distance) of primary saccades were measured, as was the proportion of trials with anticipatory saccades (latency < 90 milliseconds).<sup>40,42,53</sup>

## ANTISACCADE TASK

This task assesses the ability to inhibit saccades toward peripheral targets and instead to look immediately to the target's mirror location in the opposite hemifield. Stimulus parameters were identical to those used in the visually guided saccade task. Participants were reminded of task instructions if consecutive errors were made. Performance on 10 practice trials verified task comprehension. The percentage of trials in which participants looked toward rather than away from targets and the latency of those responses were measured.

## NEUROPSYCHOLOGICAL AND PSYCHOLOGICAL EVALUATION

Tests of motor, memory, and executive functions were selected on the basis of findings from previous studies of individuals with autism and their family members and an interest in covering a broad range of cognitive abilities to characterize areas of relative strength and deficit. The Yale-Brown Obsessive Compulsive Scale<sup>54</sup> and the Children's Yale-Brown Obsessive Compulsive Scale<sup>55</sup> were administered to individuals 15 years or older and to those younger than 15 years, respectively. The Autism-Spectrum Quotient was administered to individuals 16 years or older to assess commu-

**Table 2. Performance on Neuropsychological Domains and Individual Neuropsychological Tests for Family Members of Individuals With Autism and for Healthy Control Subjects<sup>a</sup>**

Measure (Test)	Mean (SD)		F Value	Uncorrected P Value
	Family Members (n=57)	Controls (n=40)		
Motor domain score	0.05 (0.63)	-0.09 (0.62)	1.08	.28
Annett handedness	8.52 (6.47)	9.06 (4.39)	0.44	.66
Grooved pegboard, s				
Dominant hand	67.42 (12.64)	72.06 (10.85)	1.70	.10
Nondominant hand	75.38 (13.33)	77.64 (13.91)	0.79	.43
Finger tapping, s				
Dominant hand	46.36 (9.58)	45.76 (7.51)	0.18	.86
Nondominant hand	41.76 (7.88)	42.09 (7.72)	-0.29	.77
Trail Making Test A, s	22.96 (8.09)	20.43 (6.86)	1.53	.13
Memory domain score	0.09 (0.59)	-0.11 (0.74)	1.47	.14
Faces, immediate <sup>b,c</sup>	37.04 (4.64)	36.34 (5.45)	0.81	.42
Faces, delayed <sup>b,c</sup>	37.76 (3.95)	36.89 (4.25)	1.07	.29
Word list, delayed recall <sup>b,c</sup>	8.13 (2.26)	7.73 (2.05)	0.75	.46
Word list, recognition <sup>b,c</sup>	26.64 (1.94)	27.46 (1.51)	0.49	.62
Executive functioning domain score	-0.12 (0.60)	0.22 (0.68)	2.34	.02
Spatial span <sup>b,d</sup>	14.77 (3.20)	17.09 (3.31)	3.22	.002
Digit span <sup>b,e</sup>	18.54 (4.77)	19.91 (4.30)	1.42	.16
Letter number sequence <sup>b,e</sup>	12.68 (3.29)	13.74 (3.16)	1.21	.23
Trail Making Test B, s	56.72 (28.16)	48.65 (27.74)	1.34	.18
Social-emotional domain score	-0.05 (0.25)	0.06 (0.33)	1.83	.07
Emotion differentiation <sup>f</sup>	26.33 (4.74)	25.65 (4.98)	1.02	.31
Emotion differentiation (RT) <sup>f</sup>	5.39 (1.91)	4.46 (1.35)	3.22	.002
Social skills (AQ) <sup>g</sup>	2.02 (2.15)	1.08 (1.53)	2.18	.03
Communication domain score	-0.22 (0.75)	0.29 (0.59)	3.21	.002
PPVT-III	104.83 (11.41)	108.35 (13.41)	1.49	.14
Communication (AQ) <sup>g</sup>	1.57 (1.63)	0.64 (0.78)	2.88	.005
Obsessive-compulsive behaviors	-0.12 (0.71)	0.17 (0.60)	3.97	.05
Attention to detail (AQ) <sup>g</sup>	3.64 (2.20)	4.53 (2.67)	1.58	.12
Attention switching (AQ) <sup>g</sup>	3.67 (2.02)	2.17 (1.37)	3.20	.002
CY-BOCS, total <sup>h</sup>	2.11 (3.30)	0.42 (1.17)	1.66	.11
CY-BOCS obsessions <sup>h</sup>	1.44 (3.01)	0.42 (1.17)	1.09	.29
CY-BOCS compulsions <sup>h</sup>	0.67 (2.00)	0.00 (0.00)	1.17	.26
Y-BOCS, total <sup>i</sup>	3.52 (5.41)	0.04 (0.20)	4.54	<.001
Y-BOCS obsessions <sup>i</sup>	1.88 (3.14)	0.04 (0.20)	4.13	<.001
Y-BOCS compulsions <sup>i</sup>	1.64 (3.04)	0.00 (0.00)	3.82	<.001

Abbreviations: AQ, Autism-Spectrum Quotient; CY-BOCS, Children's Yale-Brown Obsessive Compulsive Scale; PPVT-III, Peabody Picture Vocabulary Test III; RT, reaction time; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

<sup>a</sup>All test scores are reported as raw scores. The z scores for individual tests were computed relative to age-appropriate test norms, and then domain scores were computed by averaging the z scores from relevant subtests. Performance on the imagination subscale of the AQ is not reported because this subscale was not included in domain comparisons. Family members had higher mean (SD) scores than controls (2.57 [1.72] vs 1.53 [1.33]), reflecting reduced imagination skills ( $t_{96}=2.99$ ;  $P=.004$ ). The italicized rows are domain scores that consist of the subtests listed in the rows below them.

<sup>b</sup>Subtest of the Wechsler Memory Scale—Third Edition.

<sup>c</sup>Subtest of the Children's Memory Scale.

<sup>d</sup>Subjects were instructed to repeat a sequence of tapping with their finger an array of blocks that is modeled by the examiner. Sequences increase in length and complexity as the task progresses and are completed in both forward and reverse orders.

<sup>e</sup>Subtest of the Wechsler Intelligence Scale for Children—Fourth Edition.

<sup>f</sup>Penn Emotion Discrimination Task.

<sup>g</sup>Administered only to participants 16 years or older.

<sup>h</sup>Administered to participants younger than 15 years (8 family members and 5 controls).

<sup>i</sup>Administered to participants 15 years or older.

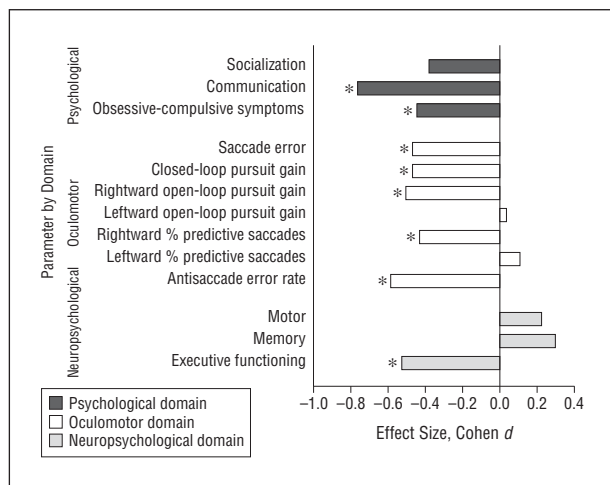
nication, socialization, attention switching, attention to detail, and imagination.<sup>56</sup> The Penn Emotion Discrimination Task<sup>57</sup> was administered to examine participants' ability to recognize facial affect (**Table 2**).

### HEAD CIRCUMFERENCE MEASUREMENT

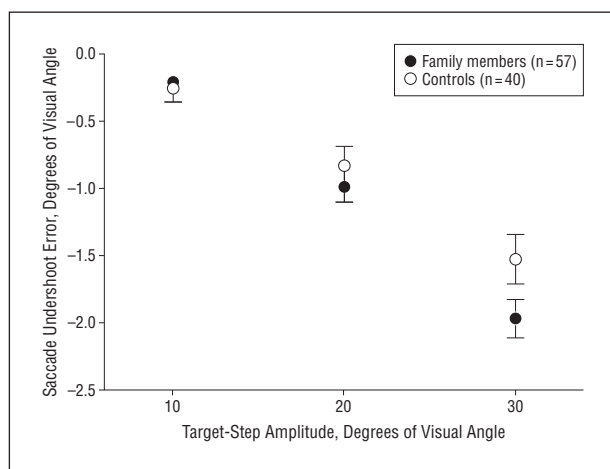
Head circumference was measured by placing a tape around the head covering the glabella and opisthocranium. Two measurements were recorded and averaged.

### DATA ANALYSIS

Repeated-measures analyses of variance were used to compare groups on visually guided saccade, antisaccade, and pursuit tasks. Some subjects' data were not included for some tasks owing to excessive blink artifacts or failures to complete tasks. For predictive saccades, latency and gain data were each modeled over the logarithm of trial number (to linearize exponential learning curves). Then, mixed-effects regression was used to model differential learning effects. No significant interactions were ob-



**Figure 1.** Effect sizes for psychological, oculomotor, and neuropsychological domain parameters. Negative values indicate that family members performed worse compared with the control participants. \*Effects were statistically significant ( $P < .05$ ).



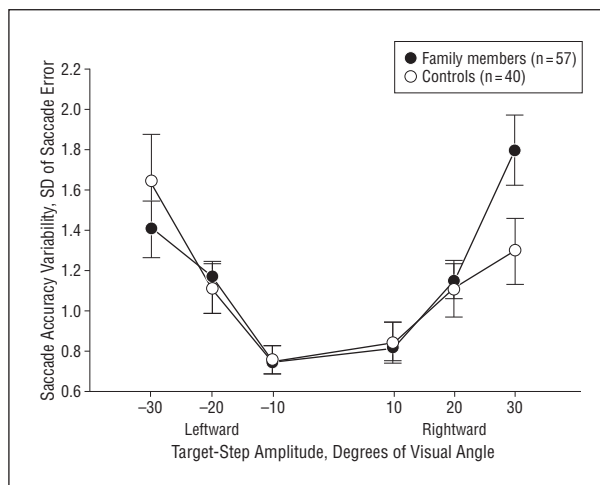
**Figure 2.** Accuracy of saccades in family members and control participants. Data are expressed as mean (SE) saccade error (degrees of visual angle from target) during a visually guided saccade task with unpredictable targets presented at 10°, 20°, and 30° from central fixation.

served for diagnostic group with sex or age for any task. No obvious bimodality was present for any measure.

Neuropsychological test scores were converted to z scores using age-normed standard scores and then combined on an a priori basis into motor, memory, and executive function domains. Psychological symptom ratings were converted to z scores relative to the healthy control group and averaged to assess social-emotional, communication, and obsessive-compulsive domains. Multivariate analyses of variance were performed to assess group differences on neuropsychological and psychological symptom domains. For these analyses, age and sex were entered as random factors, and subject group was entered as the fixed factor. No interactions of age or sex with group effects were observed. Tables with means and standard deviations of all parameters for each eye movement task are available in the supplementary material.

## RESULTS

Performance on eye movement tasks generally did not vary as a function of age ( $P > .30$ ). The exception was



**Figure 3.** Variability of saccade accuracy in family members and control participants. Data are expressed as mean (SE) trial-wise variability in saccade task error (standard deviation of saccade error) during a visually guided saccade task with unpredictable targets presented at 10°, 20°, and 30° from central fixation.

antisaccade performance, in which younger subjects made more inhibitory errors ( $r_{97} = -0.39$ ;  $P < .001$ ); however, this effect did not differ across groups ( $F_{2,94} = 0.79$ ;  $P = .66$ ). Thus, all relatives were combined without regard to age except for exploratory correlational analyses in which age effects were statistically controlled.

## VISUALLY GUIDED SACCADDES

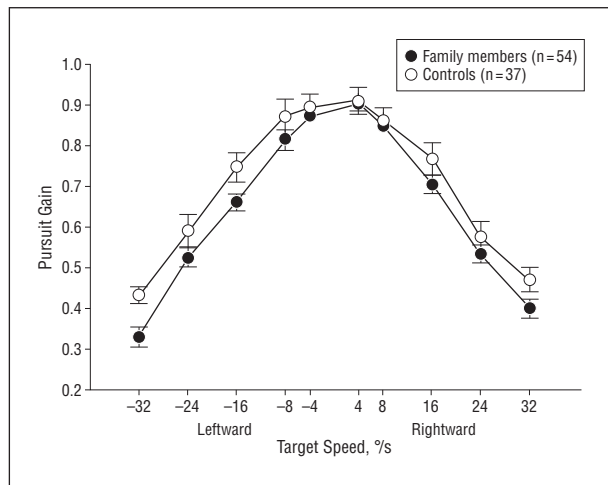
Saccade error was greater for family members than controls ( $F_{1,95} = 7.06$ ;  $P = .009$ ) (**Figure 1** and **Figure 2**), especially for targets further from center ( $F_{2,94} = 7.13$ ;  $P = .001$ ). For variability in saccade error, the group  $\times$  hemifield ( $F_{1,95} = 4.14$ ;  $P = .04$ ) and group  $\times$  hemifield  $\times$  target-step amplitude interactions ( $F_{2,94} = 5.86$ ;  $P = .004$ ) were significant (**Figure 3**). Variability in saccade accuracy was greater for family members relative to controls for rightward saccades, primarily for larger saccades. For saccade latency and velocity, the main effect of group and the interactions with group were not significant ( $P > .10$ ).

## FOVEOFUGAL RAMP TASK

Family members had lower pursuit gain than controls ( $F_{1,89} = 10.50$ ;  $P = .002$ ), especially when tracking faster target speeds ( $F_{4,86} = 4.90$ ;  $P = .001$ ) (**Figure 4**). Group  $\times$  direction effects were not significant, and no group differences were observed for pursuit or saccade latency ( $P > .10$ ). However, the proportion of trials in which pursuit initiation preceded the first catch-up saccade was higher in family members (53%) than controls (43%) for leftward but not rightward (42% vs 49%) trials ( $F_{1,88} = 12.82$ ;  $P = .001$ ).

## FOVEOFUGAL STEP-RAMP TASK

For open-loop pursuit gain, the main effect of group and the group  $\times$  target speed interaction was not significant ( $P > .10$ ), but the group  $\times$  direction interaction was significant ( $F_{1,87} = 5.72$ ;  $P = .02$ ) (**Figure 5**). Mean (SD) rightward and leftward open-loop gains of 0.71 (0.04) and 0.76



**Figure 4.** Mean (SE) pursuit gain across target speeds during the closed-loop stage of the foveofugal ramp task in family members and control participants. Three family members and 3 controls were not included in analyses because they either failed to complete the ramp task ( $n=1$ ) or had excessive blink artifacts ( $n=5$ ).

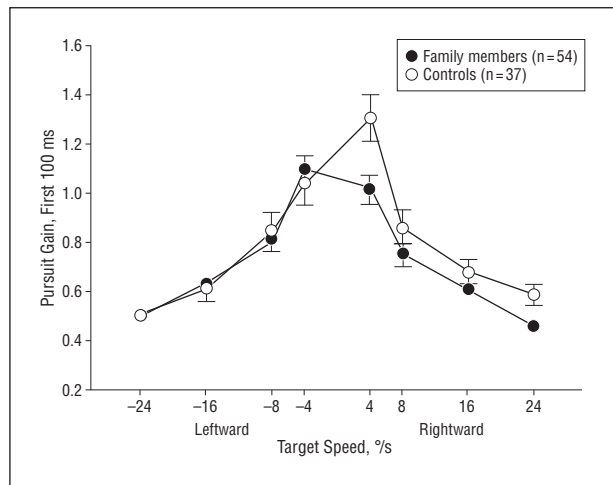
(0.04), respectively, seen in family members, did not show the rightward advantage ( $t_{53}=1.61$ ;  $P=.11$ ) that was seen in healthy controls ( $t_{36}=2.05$ ;  $P=.05$ ), who had mean (SD) rightward and leftward gains of 0.86 (0.05) and 0.75 (0.06), respectively. For closed-loop pursuit gain, group differences were significant ( $F_{1,87}=4.17$ ;  $P=.04$ ). The group  $\times$  target speed interaction was significant ( $F_{3,85}=3.96$ ;  $P=.001$ ), with family members showing lower closed-loop gain than controls for faster target speeds. No group differences in the accuracy or latency of initial catch-up saccades were observed ( $P>.10$ ).

#### PREDICTIVE SACCADDE TASK

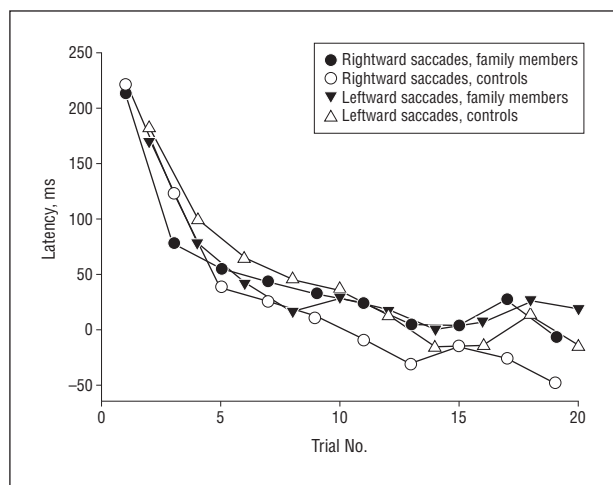
The group  $\times$  trial interaction was significant, indicating that reductions in saccade latencies across trials were less robust in family members than controls ( $\beta=-45.56$ ;  $SE=16.24$ ;  $P=.005$ ). Also, a group  $\times$  direction effect was observed, with family members showing similar response latencies for leftward and rightward responses, not the increasingly faster rightward relative to leftward responses across trials seen in controls ( $\beta=19.88$ ;  $SE=8.28$ ;  $P=.02$ ) (**Figure 6**). Consistent with these observations, family members showed a lower percentage of anticipatory saccades than controls for rightward (55% vs 63%) but not leftward responses (57% vs 54%; group  $\times$  direction,  $F_{1,88}=4.72$ ;  $P=.03$ ). Saccade gain did not differ between groups for rightward or leftward responses ( $P>.10$ ).

#### ANTISACCADDE TASK

Family members failed to voluntarily suppress saccades to peripheral targets more often than controls ( $F_{1,95}=4.26$ ;  $P=.04$ ) (**Figure 7**). This effect was greater for gap than overlap trials ( $F_{1,95}=7.25$ ;  $P=.008$ ) and when targets were presented closer to center fixation ( $F_{2,94}=6.10$ ;  $P=.02$ ). There were no group differences in relation to target direction or in response latencies for correctly performed trials ( $P>.10$ ).



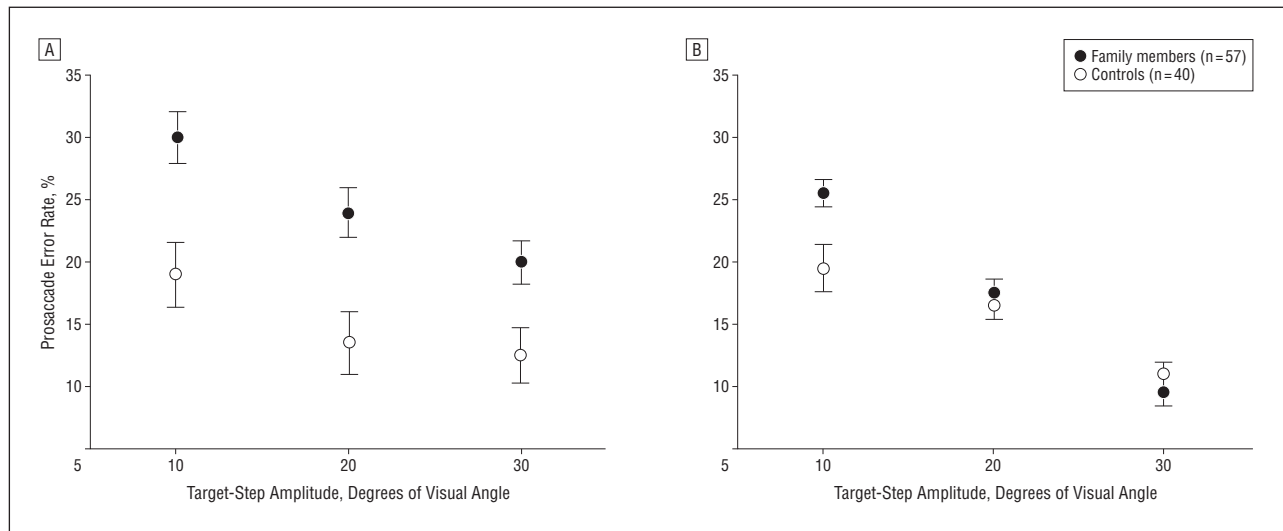
**Figure 5.** Mean (SE) pursuit gain across target speeds during the open-loop stage of the foveofugal step-ramp task in family members and control participants. Three family members and 3 controls were not included in analyses because they either failed to complete the step-ramp task ( $n=1$ ) or had excessive blink artifacts ( $n=5$ ).



**Figure 6.** Average latency of onset for rightward and leftward saccades in family members and control participants during the predictive saccade task. Data points reflect the average values of consecutive pairs of same-direction trials (eg, trials 1 and 3 and trials 2 and 4).

#### NEUROPSYCHOLOGICAL AND PSYCHOLOGICAL MEASURES

The multivariate test for overall group differences across neuropsychological domains was significant ( $F_{3,94}=3.62$ ;  $P=.02$ ). Univariate comparisons indicated that family members showed poorer executive function performance but no impairments in motor or memory abilities (Figure 1). The greatest group differences in executive functions were in visual-spatial working memory. Groups also differed on psychological symptom ratings ( $F_{3,74}=4.49$ ;  $P=.006$ ). Family members reported deficits in pragmatic and nonverbal communication but not reduced vocabulary knowledge. Obsessive-compulsive behaviors were more common in family members (Table 2).



**Figure 7.** Percentage of prosaccade errors during the gap and overlap conditions of an antisaccade task. Data are expressed as mean (SE) rate of prosaccade errors across various target-step amplitudes from center fixation in degrees of visual angle during the gap (A) and overlap (B) conditions.

### HEAD CIRCUMFERENCE

Normative data considering differences related to age and sex<sup>58</sup> were used to calculate *z* scores for each subject's head circumference.<sup>12</sup> Head circumference did not differ between groups, nor did proportions of macrocephalic ( $\geq 97$ th percentile; 5 of 57 [9%] for family members; 3 of 40 [8%] for controls) or microcephalic ( $\leq 3$ rd percentile; 1 of 57 [2%] for family members; 1 of 40 [2%] for controls) subjects ( $P > .20$ ; Table 1).

### CORRELATIONAL ANALYSES

In analyses controlling for effects of age, we examined relationships among performance parameters and compared the strength of these correlations between groups using the Fisher *z* conversion. In the eye movement data, sensorimotor disturbances were more strongly related to alterations in executive abilities in family members than controls. For family members, visually guided saccade error was associated with error rate on the antisaccade task ( $R^2_{.4} = 0.08$ ;  $P = .02$ ). This relationship was not significant for controls ( $P = .18$ ), and it was stronger for family members than controls ( $z = 2.51$ ;  $P = .01$ ). Decreased pursuit gain during the ramp task ( $R^2_{.5} = 0.08$ ;  $P = .02$ ) and decreased open-loop pursuit gain for rightward targets during the step-ramp task ( $R^2_{.5} = 0.10$ ;  $P = .01$ ) were associated with antisaccade error rate for family members but not controls ( $P = .29$  and  $.21$ , respectively). These relationships were significantly stronger for family members than controls (pursuit gain and antisaccade error rate:  $z = 2.52$ ,  $P = .006$ ; rightward open-loop pursuit gain and antisaccade error rate:  $z = 2.61$ ,  $P = .01$ ). Manual motor performance was positively correlated with executive function in neuropsychological testing for family members ( $R^2_{.4} = 0.12$ ;  $P = .006$ ) but not controls ( $P = .23$ ); however, the strength of this relationship did not differ between groups.

Response latencies on different tasks were more highly intercorrelated in controls than family members. Visually guided saccade latencies were associated with cor-

rect antisaccade latencies in controls ( $R^2_{.7} = 0.14$ ;  $P = .03$ ) but not family members ( $P = .50$ ). This relationship was stronger in controls than in family members ( $z = 2.15$ ;  $P = .03$ ). Saccade accuracy (saccade error [ $R^2_{.7} = 0.29$ ;  $P < .001$ ] and variability in saccade error [ $R^2_{.7} = .34$ ;  $P < .001$ ]) was associated with visuospatial search (time to complete Trail Making Test A) for controls but not family members ( $P = .34$  and  $.40$ , respectively). Both relationships were stronger for controls than family members (saccade error and visuospatial search:  $z = 2.99$ ,  $P = .02$ ; variability in saccade error and visuospatial search:  $z = 3.18$ ,  $P = .01$ ). No other associates of eye movement performance, neuropsychological performance, psychological measures, or head circumference were significant in family members or controls ( $P > .20$ ).

### COMMENT

Autism is a heritable disorder with behavioral, neurobiological, and genetic heterogeneity. Identifying functional alterations in specific neural pathways is a crucial step in understanding pathophysiological mechanisms in this disorder. The present findings document that first-degree relatives of individuals with autism demonstrate a unique pattern of oculomotor impairments similar to that previously reported in independent samples of individuals with autism, suggesting that these alterations within sensorimotor and cognitive brain circuitry may be familial traits. Family members also demonstrated executive dysfunction on neuropsychological tests, communication abnormalities, and increased rates of obsessive and compulsive behaviors, but these were independent from one another and from oculomotor impairments.

The different oculomotor abnormalities demonstrated by family members implicate distinct neural circuits. Saccadic dysmetria and variable saccade accuracy implicate pontocerebellar circuitry. Given available functional magnetic resonance imaging data in individuals with autism,<sup>28</sup> decreased closed-loop pursuit gain may in part

also result from alteration in this circuitry. Open-loop pursuit and predictive saccades of family members lacked the rightward advantage evident in controls, suggesting reduced left hemispheric specialization in frontotemporal and striatal systems, respectively. Increased rates of antisaccade errors suggest that prefrontal systems are affected bilaterally. These different alterations were moderately intercorrelated ( $R^2$  range, 0.08-0.12) in family members, suggesting a general profile of deficit but also significant variability in the extent to which the different alterations are expressed in different family members. These discrete laboratory measures thus may provide useful tools for studying specific neural circuit-level dysfunctions across the autism spectrum and for parsing more homogeneous phenotypes in family genetic research.

### OCULOMOTOR IMPAIRMENTS IN FAMILY MEMBERS OF INDIVIDUALS WITH AUTISM

Saccadic dysmetria and increased variability of saccade accuracy observed in family members parallel findings we reported previously in some<sup>24-26</sup> but not all<sup>27,28</sup> independent samples of individuals with autism. Alterations in saccade accuracy indicate that the modulatory role of the cerebellum on pontine output is attenuated in some individuals with autism. Cells in the vermis and fastigial nuclei of the cerebellum encode motor error signals during saccades and use this information to alter saccade dynamics to reduce systematic inaccuracy and the variability in responses over time.<sup>59-62</sup> Altered saccade metrics in family members is consistent with multiple reports of cerebellar histopathological features<sup>29-33</sup> and functional and anatomic abnormalities in some<sup>63-65</sup> but not all<sup>66,67</sup> magnetic resonance imaging studies of autism. The functional integrity of the cerebellum has not been studied systematically in unaffected family members. Thus, our findings provide novel evidence that altered cerebellar function evident in individuals with autism also is evident in unaffected family members.

Decreased accuracy of sustained smooth pursuit in family members may also be a manifestation of cerebellar dysfunction. Projections from the cerebellum to frontal eye fields modulate the velocity and trajectory of sustained pursuit based on sensory feedback regarding position and velocity errors.<sup>68</sup> Reduced activation in the cerebellum and frontal eye fields during pursuit in individuals with autism has been reported in functional magnetic resonance imaging studies.<sup>28</sup> Preliminary evidence exists for the familiarity of saccade and smooth-pursuit function,<sup>19</sup> consistent with the possibility that these deficits may reflect familial neural system alterations in autism.<sup>28</sup>

On the foveofugal step-ramp task, family members exhibited lower open-loop pursuit gain toward rightward moving targets relative to controls. This observation parallels our previous findings in an independent sample of individuals with autism.<sup>37</sup> Alterations of closed-loop pursuit have also been described in patients with schizophrenia<sup>21,69,70</sup> and their unaffected family members,<sup>71,72</sup> as well as in other disorders.<sup>73,74</sup> Therefore, this abnormality lacks diagnostic specificity. In contrast, the atypical lateralized open-loop pursuit deficit in individuals with

autism, which we now show in unaffected relatives, has not been reported in any neuropsychiatric illness. Initial cortical processing of visual motion signals is performed by contralateral extrastriate area V5, which sends motion-related signals to sensorimotor systems in ipsilateral frontal eye fields and cerebellum to regulate open-loop pursuit.<sup>75,76</sup> Available psychophysical evidence suggests no lateralized deficit in motion processing in autism.<sup>38</sup> Therefore, the lateralized deficit in pursuit is not likely to involve sensorimotor systems but rather circuitry supporting the feed-forward input of motion information to sensorimotor systems.

Atypical procedural learning for rightward saccades also was observed in family members. This alteration in procedural learning implicates left frontostriatal systems, especially the basal ganglia, where chronometric mechanisms regulate the precise timing of learned response intervals.<sup>77</sup> Similar to the lateralized alteration in open-loop pursuit, lateralized procedural learning effects have not been identified in other neuropsychiatric disorders. In both cases, the lateralized effects appeared to reflect a lack of typical hemispheric advantage for rightward movements because controls showed a rightward advantage, whereas leftward and rightward responses were similar in autism. This might result from an alteration in the maturation of hemispheric specialization or from an abnormality that differentially affects the left hemisphere.

Alterations in the specialization of left hemisphere functions in autism suggested by the present findings align with evidence of atypical language development,<sup>78,79</sup> reduced left hemisphere motor dominance,<sup>80-82</sup> and left lateralized white matter abnormalities in some<sup>83,84</sup> but not all<sup>85</sup> previous studies. Our observations also are consistent with reports of greater impairments in verbal than in nonverbal cognitive abilities in many individuals with autism.<sup>86-88</sup> Thus, the left lateralized neurophysiological alterations in our unaffected family members indicate that this atypical lateralization associated with autism may extend to unaffected family members in ways that can be detected with sensitive neurophysiological measurements.

Family members made more inhibitory errors on the antisaccade task and scored lower on neuropsychological measures of executive function than did controls. Deficits on the antisaccade task were more pronounced on gap trials, suggesting diminished inhibitory control of saccade generation by fixation neurons in rostral superior colliculus that receive significant modulatory input from the prefrontal cortex. These findings parallel previous neuropsychological studies of family members,<sup>6,8,10,89</sup> demonstrations of antisaccade deficits in individuals with autism,<sup>24,27,41,43,90</sup> and functional magnetic resonance imaging findings of prefrontal and anterior cingulate alterations during tasks requiring response monitoring and planning in individuals with autism.<sup>90-92</sup>

Family members' reduced executive functioning performance was most evident for spatial working memory. This effect is consistent with previous reports of spatial working memory impairments in individuals with autism<sup>93-95</sup> and their unaffected family members<sup>45,89</sup> and with prefrontal cortical abnormalities during an oculomotor working memory task.<sup>96</sup> Thus, our findings indicate that alterations in prefrontal systems important for



planning volitional behaviors and voluntarily suppressing context-inappropriate behavior occur in unaffected family members.

### PSYCHOLOGICAL CHARACTERISTICS OF FAMILY MEMBERS OF INDIVIDUALS WITH AUTISM

Consistent with previous work, we found evidence of atypical social communication and increased rates of obsessive-compulsive behaviors in family members, but these were not related to deficits on oculomotor tasks.<sup>4,5,7-10,97,98</sup> Family members did not show impairments on a standardized test of receptive vocabulary, suggesting deficits in pragmatic aspects of communication rather than in vocabulary knowledge per se. Although eye movement abnormalities were observed on several paradigms, family members did not show manual motor impairments on neuropsychological testing. This apparent disparity between oculomotor and manual motor measures suggests that standard neuropsychological tests of manual skill do not provide equivalent sensitivity to deficits in manual motor control or that sensorimotor impairment within family members is relatively confined to oculomotor systems. Further studies are needed to resolve this inconsistency.

### CLUES TO THE PATHOPHYSIOLOGICAL MECHANISMS OF AUTISM

The findings of the present study show that alterations in cerebellar, frontotemporal, striatal, and prefrontal circuitry can be detected with laboratory tests in unaffected family members of individuals with autism. These results represent a significant contribution to the ongoing development of etiopathophysiological models of autism. The demonstration of cerebellar dysfunction is relevant given findings of cerebellar histopathology in autism, which our results suggest may be familial. The deficit in left frontotemporal circuitry is important because the relevant long-fiber tracts directly overlay pathways crucial for language skills. Impairments in striatal learning systems may affect procedural learning and the development of coordinated motor control. The deficits in executive functions observed in oculomotor and neuropsychological testing are likely a manifestation of alterations in prefrontal systems that are associated with autism. Further work is needed by way of replication of our findings, quantitative evaluation of the familiarity of these traits in family trios, and efforts to demonstrate association of oculomotor and other phenotypes with genetic mechanisms.

The distinct pattern of oculomotor abnormalities observed in autism and the specific paradigms evaluating the functional integrity of different neural circuits may provide promising intermediate phenotypes for family research. Furthermore, because the neurophysiological measures were unrelated to atypical social, communication, and cognitive flexibility and head circumference measurements, they may provide independent phenotyping information beyond that yielded by psychological and morphometric evaluations. By providing a direct and

quantitative evaluation of the integrity of functional brain systems, oculomotor measures may provide useful tools for localizing neural circuitry alterations in individuals with autism and their unaffected family members.

**Submitted for Publication:** August 21, 2009; final revision received January 20, 2010; accepted February 8, 2010.

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**Author Contributions:** All statistical analyses were performed by Drs Mosconi and Sweeney.

**Financial Disclosure:** Dr Sweeney reported receiving funding support through a Janssen Pharmaceutica research grant and as a consultant to Pfizer Inc.

**Funding/Support:** This study was supported by grant HD35469 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Program of Excellence in Autism, grant P50HD055751 from the National Institute of Mental Health Autism Center of Excellence, the National Alliance for Autism Research, and Autism Speaks fellowship 4853.

**Role of the Sponsors:** The funding agencies had no role in the design, analysis, or reporting of results.

**Previous Presentation:** Portions of this study were presented at the 2009 Neural Control of Movement conference; May 1, 2009; Kona, Hawaii, and the International Meeting for Autism Research; May 8, 2009; Chicago, Illinois.

**Online-Only Material:** Supplementary material available at [http://ccm.psych.uic.edu/PublishedSupplementaryData/Mosconi\\_et\\_al.\\_Autism\\_family\\_study\\_Supplementary\\_tables.html](http://ccm.psych.uic.edu/PublishedSupplementaryData/Mosconi_et_al._Autism_family_study_Supplementary_tables.html).

**Additional Contributions:** We gratefully acknowledge the participation of the individual subjects and their families in these studies.

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#### Correction

**Error in Text.** In the Original Article titled "Neurobehavioral Abnormalities in First-Degree Relatives of Individuals With Autism" by Mosconi et al, published in the August issue of the *Archives* (2010;67[8]:830-840), an error occurred in the text. On page 835, in the first sentence of the "Predictive Saccade Task" subsection of the "Results" section, the  $\beta$  coefficient for the test of the group  $\times$  trial interaction on saccade latencies during the predictive saccade task should have been  $-45.56$  rather than  $-5.56$ . This article was corrected online.