

SHORT REPORT

Oculomotor abnormalities parallel cerebellar histopathology in autism

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Objective: To investigate cerebellar function in autism by measuring visually guided saccades.

Methods: A visually guided saccade task was performed by 46 high-functioning individuals with autism with and without delayed language acquisition, and 104 age and IQ matched healthy individuals.

Results: Individuals with autism had increased variability in saccade accuracy, and only those without delayed language development showed a mild saccadic hypometria. Neither autistic group showed a disturbance in peak saccade velocity or latency.

Conclusions: The observed saccadic abnormalities suggest a functional disturbance in the cerebellar vermis or its output through the fastigial nuclei, consistent with reported cerebellar histopathology in autism. The pattern of mild hypometria and variable saccade accuracy is consistent with chronic rather than acute effects of cerebellar vermis lesions reported in clinical and non-human primate studies, as might be expected in a neurodevelopmental disorder. The different patterns of oculomotor deficits in individuals with autism with and without delayed language development suggest that pathophysiology at the level of the cerebellum may differ depending on an individual's history of language development.

Neuropathological abnormalities of the cerebellum have been a consistent histopathological finding in autism. Reduced Purkinje cell counts are most prominent in the posterolateral cerebellar hemispheres and adjacent archicerebellar cortex.¹ Abnormalities in the inferior olive and fastigial nuclei have been reported, which are input and output structures of the oculomotor vermis (lobules VI and VII).^{1–3} Some magnetic resonance imaging (MRI) studies have reported altered volumes of vermal lobules VI and VII.^{4–5}

The cerebellum is crucial for eye movement control.^{6–7} Purkinje cells in the hemispheres and vermis optimise saccade accuracy by influencing the onset and offset of saccades.^{8–10} Markedly hypometric and hypermetric saccades are seen immediately after cerebellar lesions.^{11–12} While overall saccade accuracy typically improves gradually after cerebellar lesions, increased variability in saccade accuracy often persists after posterior vermis lesions.^{12–13} Thus, increased variability of saccade accuracy may provide a useful index for neurodevelopmental abnormalities of the cerebellum associated with autism.

The current study examined saccade dynamics and accuracy in high-functioning individuals with autism who did not have mental retardation. Recent genetic studies suggest that language delay may be an endophenotypic marker for a subgroup of individuals with pervasive developmental disorders (PDD).^{14–15} For this reason, and because

Asperger's disorder, which is differentiated from autism primarily by the absence of delayed language development, has traditionally been described as having more prominent motor abnormalities,¹⁶ we examined oculomotor parameters in relation to each individual's history of delayed language development.

METHODS

Participants

A total of 46 individuals meeting DSM-IV¹⁷ criteria for autism based on the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule^{18–20} participated in the study. DSM-IV allows diagnoses of autistic disorder with or without a history of early language delay. Of these individuals with autism, 28 had a history of delayed language acquisition and 18 did not. Language delay was defined as the absence of single word utterances by 24 months and/or spoken phrases by 3 years of age. Individuals with autism were excluded if they had an associated infectious, genetic, or metabolic disorder such as fragile X syndrome or tuberous sclerosis.

All participants had Verbal and Full Scale IQ scores of 70 or higher based on the age appropriate Wechsler Intelligence Scale (table 1), and thus no participant met the DSM-IV criteria for mental retardation. All participants were at least 8 years old (by which time the ability to make visually guided saccades typically reaches adult levels).²¹

A total of 104 healthy individuals—who had no current or past history of psychiatric or neurological disorder, birth or developmental abnormalities, or family history of psychiatric and neurological disorders thought to have a genetic component—were recruited from the community through newspaper advertisement.

None of the participants was taking medications known to affect cognitive or oculomotor abilities at the time of testing, and none had a history of head injury, birth injury, or seizure disorder. Far acuity was normal or corrected to at least 20/40. All participants and their guardians provided informed consent.

Eye movement tasks

Procedure

Participants were tested alone in a dark room, and instructions were provided via an intercom. Stationary visual targets were presented in the horizontal plane on a circular arc (1 m radius) at eye level with red light emitting diodes, each subtending 0.2° of visual angle. Participants were seated at the centre of the arc with a chin rest. Eye movements were measured using infrared reflection sensors mounted on spectacle frames (Model 210; Applied Science Laboratories, Bedford, MA). Blinks were identified using electrodes placed immediately above and below the left eye.

Visually guided saccade task

Each trial started with a half second tone and a central target with variable duration of 1.5–2.5 seconds. At the offset of the

Table 1 Demographic characteristics of the participants and eye movement measurements

	Healthy group	Autism with language delay	Autism without language delay	
No. of participants	104	28	18	
Age (mean (SD))	19.76 (11.48)	20.50 (11.73)	14.00 (7.86)	NS
Verbal IQ (mean (SD))	108.04 (12.40)	104.57 (13.52)	113.56 (14.90)	NS
Performance IQ (mean (SD))	105.79 (12.34)	101.79 (15.18)	105.33 (16.55)	NS
Full Scale IQ (mean (SD))	107.53 (12.96)	103.57 (14.61)	110.44 (15.69)	NS
% male	83.7%	85.7%	100.0%	NS
Handedness (% right)	90.7%	92.0%	88.9%	NS
Peak velocity in deg/sec (mean (SD))	314.8 (43.5)	296.9 (43.0)	289.2* (41.5)	NS when corrected for saccade amplitude
Latency in msec (mean (SD))	224 (37)	226 (39)	228 (27)	NS
Peak acceleration in deg/sec ² (mean (SD))	19247 (3492)	18372 (3155)	17813 (3239)	NS when corrected for saccade amplitude
Peak deceleration in deg/sec ² (mean (SD))	17035 (3995)	15711 (3552)	14927 (3010)	NS when corrected for saccade amplitude
Gain	0.947 (0.047)	0.927 (0.056)	0.917* (0.072)	$F_{2,147} = 3.53, p < 0.05$
Standard deviation of individual subjects' saccade gain	0.090 (0.031)	0.118* (0.031)	0.108* (0.034)	$F_{2,147} = 10.13, p < 0.001$

*Significant difference from the healthy group at $p < 0.05$.
NS, not significant.

central target, a peripheral target appeared 10° to the left or right (15 trials at each location, pseudorandomly assigned). Peak velocity, peak acceleration and deceleration, gain (ratio of saccade amplitude over target distance), and latency were measured for each primary saccade.

Eye movement measurement procedure

Eye movement recordings were digitised at 500 Hz with a 14 bit A/D converter (DI-210; Dataq Instruments, Akron, OH) and smoothed using a custom finite impulse response filter after differentiating the position trace to calculate velocity and acceleration. The filter had a gradual transition band (from pass to no pass) between 20 Hz and 65 Hz for velocity and position data, and 30 Hz and 65 Hz for acceleration data. Trials were excluded from the analysis if blinks occurred between 100 msec before and 70 msec after the onset of a peripheral target. Saccades were identified when eye acceleration exceeded 1000°/sec² until 25% of peak deceleration.

RESULTS

Saccade accuracy

There was a significant group difference in saccade gain, $F_{2,147} = 3.53, p < 0.05$. Individuals with autism without language delay had significantly lower saccade gain than healthy participants, $t_{120} = 2.25, p < 0.05$. The autistic group with language delay did not differ from the other groups. Analysis of absolute saccade error yielded similar results.

Peak saccade velocity

Because the hypometric saccades of some individuals with autism would likely have lower peak velocities, we computed the ratio of peak velocity over amplitude for each saccade before testing for differences in peak saccade velocities across groups. No group differences were detected.

Saccade latency

There was no overall group difference in saccade latencies, indicating that the individuals with autism shifted attention and initiated eye movements toward peripheral targets as rapidly as healthy individuals.

Acceleration and deceleration of saccades

When peak saccade acceleration and deceleration were adjusted for saccade amplitude, there were no significant group differences in either of these measures.

Consistency of saccade accuracy

To evaluate variability in saccade accuracy, we computed the standard deviation of saccade gain over all trials separately for each individual subject. There were significant group differences in this measurement, $F_{2,147} = 10.13, p < 0.001$. Both, the group without language delay, $t_{120} = 2.28, p < 0.05$, and the group with language delay, $t_{130} = 4.22, p < 0.001$, had more variable saccade accuracies than healthy individuals. The two autistic groups were not significantly different from each other (fig 1).

DISCUSSION

We examined visually guided saccades in high functioning individuals with autism and observed a subtle motor deficit attributable to cerebellar dysfunction. The observation of reduced saccade accuracy in the context of normal saccade

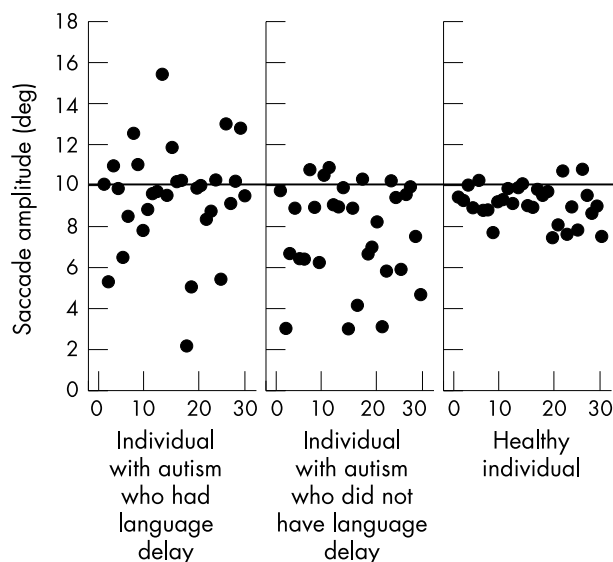


Figure 1 Variability in saccade landing positions. Illustrative examples of the increased "within-individual" variability in saccade landing positions seen in an individual with autism who had language delay, an individual without early language delay and a healthy individual. Each point in the figure represents the landing position of one saccade. The X axis in the graph is organized from first (leftmost) to last (rightmost) eccentric saccade for each of the three subjects. The solid line indicates the 10° target step amplitude.

latencies suggests a deficit in motor function rather than in visual attention.

Reduction in saccade accuracy has been reported in autism,²² but the sample in that study was small and included individuals with mental retardation. Further, this deficit was not examined in relation to clinical characteristics such as early language development. In the present study, individuals without language delay demonstrated mildly hypometric (undershooting) saccades and reduced consistency of saccade accuracy over trials. In contrast, individuals with early language delay did not show a reduction in average saccade accuracy, consistent with our previous report.²³ However, this group had increased variability in saccade accuracy caused by a mixture of hypometric and hypermetric saccades. Normal peak saccade velocity or acceleration suggests that the abnormalities in saccade accuracy do not arise at the level of pontine burst neurones. However, characterisation of saccade dynamics across larger saccade amplitudes and using higher resolution measurements is needed to rule out deficits we could not detect. Further, the absence of prolonged saccade latencies suggests that basal ganglia dysfunction is not the cause of the saccade abnormalities we observed. Rather, the observed increase in saccade variability implicates the cerebellum, which plays a primary role in determining the accuracy of saccades.^{8,9} This interpretation is consistent with histopathological and neuroimaging evidence of cerebellar abnormalities in autism.¹⁻⁴

Dysmetria of saccades is commonly seen after cerebellar lesions. Acute lesions and inactivation of the cerebellar vermis and caudal fastigial nuclei result in gross hypometria and hypermetria, respectively.^{11,12,24} However, because cerebellar pathology in autism is neurodevelopmental rather than the result of an acute event, the expected pattern of oculomotor deficits is likely to parallel chronic effects of cerebellar lesions. Adult monkeys with experimental cerebellar vermis lesions show recovery over a period of months in the ability to make accurate saccades but increased variability in saccade accuracy remains an enduring deficit.^{12,13} This is understood to result from the absence of the dynamic adaptive modulation of saccades by the cerebellar vermis, which leaves the subject unable to adapt saccade commands to compensate for ongoing subtle biomechanical variability within the oculomotor system resulting from factors such as muscle fatigue.^{7,25}

The relatively subtle hypometria and increased variability in saccade accuracy are modest relative to abnormalities observed immediately after lesions. However, they are clinically important in documenting abnormal cerebellar functioning in autism because the compensatory capacity of cerebellar sensorimotor systems is typically very robust. Though subtle, patterns of performance were different between the two autism groups. While those with and without language delay showed increased variability in saccade accuracy, only those without language delay showed a pattern of hypometric saccades. This raises the possibility that oculomotor control in these two groups of individuals with autism may be fundamentally different at the level of the cerebellum, which warrants further investigation.

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