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Oculomotor evidence for neocortical systems but not cerebellar dysfunction in autism

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Abstract

Objective—To investigate the functional integrity of cerebellar and frontal system in autism using oculomotor paradigms.

Background—Cerebellar and neocortical systems models of autism have been proposed. Courchesne and colleagues have argued that cognitive deficits such as shifting attention disturbances result from dysfunction of vermal lobules VI and VII. Such a vermal deficit should be associated with dysmetric saccadic eye movements because of the major role these areas play in guiding the motor precision of saccades. In contrast, neocortical models of autism predict intact saccade metrics, but impairments on tasks requiring the higher cognitive control of saccades.

Methods—A total of 26 rigorously diagnosed nonmentally retarded autistic subjects and 26 matched healthy control subjects were assessed with a visually guided saccade task and two volitional saccade tasks, the oculomotor delayed-response task and the antisaccade task.

Results—Metrics and dynamic of the visually guided saccades were normal in autistic subjects, documenting the absence of disturbances in cerebellar vermal lobules VI and VII and in automatic shifts of visual attention. Deficits were demonstrated on both volitional saccade tasks, indicating dysfunction in the circuitry of prefrontal cortex and its connections with the parietal cortex, and associated cognitive impairments in spatial working memory and in the ability to voluntarily suppress context-inappropriate responses.

Conclusions—These findings demonstrate intrinsic neocortical, not cerebellar, dysfunction in autism, and parallel deficits in higher order cognitive mechanisms and not in elementary attentional and sensorimotor systems in autism.

Autism is a behavioral syndrome defined by specific qualitative deficits of developmental origin in social skills and behavior, verbal and nonverbal language and its use for communication, and reasoning abilities and related complex behavior.^{1,2} This syndrome is now widely viewed as being of developmental neurobiological origin.^{3,4} Studies of brain structure in autism have provided evidence of abnormalities in the cerebral cortex, limbic structures, and the cerebellum, indicative of disturbances in the elaboration of dendritic and axonal ramifications, the selective elimination of neuronal processes, and programmed cell death during brain development.^{3,5–9} The functional significance of these developmental abnormalities is not known and has become the focus of controversy that is reflected in current neurobehavioral models for autism.

One question that has been alternately raised and refuted during the last 40 years is the role played by disturbances in the cerebellum in the pathophysiology of this behavioral syndrome.¹⁰ The current cerebellar model for autism hypothesizes that a structural

abnormality of cerebellar vermal lobules VI and VII is expressed functionally as a deficit in the capacity for shifting attention and is a primary cause of the behavioral abnormalities that define this syndrome.¹¹ In contrast, frontal systems models originating during the last 10 years have proposed deficits in executive function and working memory as major elements of the cognitive and neural basis of autism.^{12,13}

The purpose of the current study was to test the cerebellar and neocortical systems models of autism using oculomotor paradigms administered to high-functioning autistic subjects comparable in age, intelligence quotient (IQ), and gender to the subjects studied in the investigations that led to these models. Autistic subjects and matched healthy control subjects performed three saccadic eye movement tasks with differential sensitivity to disturbances in the cerebellum and frontal cortex. A visually guided saccade task was included because disturbances in cerebellar vermal lobules VI and VII are associated with reduced accuracy of visually guided saccades.^{14,15} Antisaccade and oculomotor delayed-response tasks were included to assess prefrontal and associated neocortical circuitry. The antisaccadic task assesses the capacity of frontal circuitry for suppressing context-inappropriate responses.¹⁶ The oculomotor delayed-response task is the prototypic test of spatial working memory.^{17,18}

Methods

Subjects

The subjects for this study consisted of 26 nonmentally retarded autistic adolescents and young adults, and a matched group of 26 medically healthy, neuropsychiatrically normal control subjects drawn from community volunteers. Each autistic subject was matched to a healthy control subject by gender and age (± 2 years). All subjects were required to have Full Scale and Verbal IQ scores of 80 or higher. IQ was assessed with the Ammons vocabulary test,¹⁹ a brief test that is highly correlated with Full Scale IQ scores. Autistic subjects were also administered the Wechsler Intelligence Scale-III or the Wechsler Adult Intelligence Scale-Revised to define full-scale (94.0 ± 14.1), Verbal (98.5 ± 16.9), and Performance (90.1 ± 12.7) IQ scores important in characterizing autistic subject samples. Paired *t*-tests revealed no significant differences between groups in age (autistic group, 20.2 ± 8.5 years; control group, 20.0 ± 8.7 years), Ammons IQ score (autistic group, 104.6 ± 13.4 ; control group, 100.5 ± 18.3), gender (one female subject in each group), or socioeconomic status of family of origin. All subjects were white with the exception of one Asian-Indian individual in the control group. All subjects were free of medications known to affect eye movements, had no history of seizure disorder, and provided informed consent prior to participating in the study.

The diagnosis of autism was documented with expert clinical evaluation, two structured research instruments (Autism Diagnostic Interview-Revised²⁰ and Autism Diagnostic Observation Schedule²¹), and review and rescore of tapes of the structured instruments from all autistic subjects by Dr. Catherine Lord, one of the developers of these instruments. Historical evidence of delayed and disordered language development was required for a diagnosis of autism, thus excluding individuals with Asperger's disorder. Potential subjects were also excluded if they were found to have an associated disorder such as tuberous sclerosis, fragile-X syndrome, or fetal cytomegalovirus infection. Control subjects were required to have no current history, past history, or clinical evidence of a psychiatric or neurologic disorder, a medical disorder with implications for the CNS or requiring regular medication, or a family history of autism, developmental cognitive disorder, mood disorder, anxiety disorder, or other neuropsychiatric disorder thought to have a genetic component.

Apparatus

Stationary visual targets were presented in the horizontal plane on a circular arc (1-m radius) at eye level with densely packed, individually addressable red light-emitting diodes subtending 0.2 deg of visual angle and illuminated under computer control. Direct current electro-oculographic recordings of each eye were obtained (Grass Neurodata 12 Acquisition System; West Warwick, RI) to assess eye movement activity. Data from the right eye were scored unless there were problems with this recording (i.e., signal clipping or high noise artifact). Blinks were monitored using electrodes placed above and below the left eye. Forehead and occipital restraints and a head strap were used to minimize head movement. Subjects were able to wear corrective lenses during testing, and far acuity for the testing condition (corrected or uncorrected) was determined to be at least 20/40 for all subjects.

Procedure

Subjects were seated in front of the stimulus array in a darkened black room. Instructions were given to subjects by a technician via intercom from an adjacent room. The technician monitored eye movement activity during testing to identify head movement and the need for recalibration, and to determine whether subjects needed to be realerted to task instructions. At the beginning of each trial, a brief tone sounded behind the central fixation target concurrently with the reappearance of the central fixation light to realert the subjects to central fixation after the preceding trial. Except for the brief presentation of to-be-remembered targets on the oculomotor delayed-response task, the central fixation light was turned off concurrently with the presentation of peripheral targets. The visually guided saccade task was presented first. It was followed by the antisaccade task and then the oculomotor delayed-response task.

Visually guided saccade task—This task required subjects to fixate the central stimulus for 1.5 to 2.5 seconds, and then to look immediately at a peripheral light appearing at any of three angular displacements—10, 20, or 30 deg of visual angle—to the left or right of central fixation. Peripheral targets were presented for 1.5 seconds. The timing of presentation and location of the peripheral targets was unpredictable. The latency, accuracy (error in degrees of visual angle), duration, and peak velocity of the primary saccade to peripheral targets were recorded. A total of 54 trials were presented.

Antisaccade response suppression task—In this task, subjects were required to fixate a central stimulus for 3 to 5 seconds, after which a peripheral stimulus appeared for 1.5 seconds at one of three locations—8, 16, or 24 deg—to the left or right of center fixation. Subjects were not to look at the light, but were to move their eyes immediately in the opposite direction to a point equal in distance from center fixation. One and one-half seconds after the peripheral stimulus was presented it was extinguished, and feedback was provided by a light appearing at the location where subjects should have been fixating. If a subject made two consecutive errors during testing (i.e., looked at the peripheral target instead of to the opposite side), the tester realerted the subject to the task instructions to ensure that poor performance was not a result of subjects having forgotten task instructions. A total of 36 trials were presented. The percent of trials in which the subject looked toward the peripheral targets (response suppression errors), and the latency, velocity, and accuracy of saccades toward the correct location, were recorded. Antisaccades that followed response suppression errors (i.e., trials in which subjects looked to the correct location after having looked at the peripheral cue) were not included in analyses of response latency, velocity, and accuracy.

Oculomotor delayed-response task—This task began with subjects fixating a central cue. After 1.5 to 3.5 seconds, a target was presented briefly (100 msec) at a point 9, 18, or

27 deg to the left or right of center fixation. Subjects were not to look at the peripheral target when it appeared, but to remember its location while holding central fixation. After a varying delay period of 1, 2, 4, or 8 seconds, the central light was extinguished, and this was the subject's cue to look at the place where the peripheral target had been presented. After 2 seconds, a target appeared at the to-be-remembered location and subjects were to fixate that target when it appeared. This cue provided feedback about performance on each trial. A total of 24 trials were administered. Measurements obtained included the number of failures to suppress saccades to peripheral targets (response suppression failures), saccade latency, the accuracy of primary saccades, and the accuracy of fixation after subjects made as many saccades as required to fixate the remembered location.

Before each task, careful standardized instructions were provided until subjects demonstrated an understanding of the procedure. In the case of the antisaccade and delayed-response tasks, subjects were trained using eight slow presentations of the task, during which the tester pointed manually to desired locations at the time the subjects were to look there, and explained verbally why this was the correct location to look at that time. Subjects were then asked to explain the task to the tester. These procedures, together with the fact that all subjects made a substantial number of correct responses on all tasks, ensured that lack of comprehensive of task instructions was not the basis for performance failure.

Data processing and analysis

Eye movement recordings were analyzed off-line using customized software developed in our laboratory. Before any processing of the eye movement data took place, the data were smoothed with a finite impulse response filter. The filter was designed to pass through a signal between 16 and 70 Hz to reduce high-frequency noise with a minimum of signal distortion. The passband frequencies were chosen empirically with custom filter design software. Eye position recordings were converted from raw voltage recordings to eye position in degrees of visual angle for each trial independently. This was done using data acquired while subjects fixated the central fixation cue and the peripheral location toward which subjects were to move their eyes. Saccades were identified using velocity information, and the duration of saccades was computed as the time between the rise and fall of eye velocity beyond a 30 deg/sec criterion. Performance on each trial was reviewed to identify blink artifacts and occasional failures of the software to identify primary saccades. Quantitative assessment of oculomotor function was performed without knowledge of subject characteristics.

Data within condition were averaged for each subject before statistical analyses were performed. Repeated-measures analysis of variance (ANOVA) was used to compare autistic and control subjects. For all tasks, the main effects examined in these analyses were subject group, target location, and visual hemifield. During the oculomotor delayed-response task, a main effect for delay period duration, instead of target location, was used in analyses of saccadic accuracy and the accuracy of final resting eye position.

Results

Visually guided saccade task

Repeated-measures ANOVA indicated that there were no significant differences between the autistic and control groups for peak velocity, duration, latency, or accuracy of saccades during the visually guided saccade task (table). There were also no significant interactions between subject group and any of the task parameters (e.g., target displacement).

Table Peak velocity, duration, latency, and absolute error of visually guided saccades made to spatially and temporally unpredictable targets presented at 10, 20, and 30 deg of visual angle from central fixation

Antisaccade task

Repeated-measures ANOVA indicated no significant group differences for saccade velocity or latency in the antisaccade task. However, as depicted in figure 1, autistic subjects made significantly more response suppression errors (i.e., looking at peripheral cues despite being instructed not to do so) than healthy subjects ($F[1,25] = 5.80, p < 0.05$).

Oculomotor delayed-response task

Repeated measures ANOVA indicated no significant group differences for peak saccade velocity or latency in the oculomotor delayed-response task. As in the antisaccadic task, autistic subjects had increased rates of response suppression errors ($F[1,24] = 5.69, p < 0.05$), failing to inhibit saccades even to the briefly presented peripheral target cue used in this task. In addition, the autistic subjects had greater absolute error in their initial saccades ($F[1,24] = 7.44, p < 0.05$; figure 2) and in the final resting position of their eyes after making as many saccades as necessary to fixate the remembered target locations ($F[1,24] = 11.26, p < 0.01$). These effects did not vary as a function of the duration of delay periods. The fact that the memory-guided saccades of the autistic subjects approximated the correct target location documents their understanding of the procedure and their effortful compliance with task demands.

Discussion

This study of reflexive and volitional saccades was undertaken to investigate the conflicting hypotheses of the cerebellar and neocortical systems models regarding the neural origin and cognitive basis of behavioral abnormalities in autism. The findings of the current study provide rigorous laboratory evidence of intrinsic dysfunction in the neural circuitry of the prefrontal cortex and possibly also its neural connections with the parietal cortex, and of related cognitive deficits in spatial working memory and the executive control over reflexive behavior. No evidence was found of dysfunction of cerebellar vermal lobules VI and VII. Furthermore, no deficits were detected in the automatic processes of disengaging, shifting, and reengaging visual attention in the task that had no competing response demands and was not dependent on voluntary/endogenous regulation of attentional processes.

These findings have significant negative implications for the cerebellar model of autism.¹¹ This study demonstrated intact saccade metrics and dynamics in the autistic subjects (i.e., normal latency, duration, and peak velocity of saccades on all tasks and accuracy of visually guided saccades). These data, in particular the normal accuracy of visually guided saccades, do not support the model that proposes a significant functional disturbance in cerebellar vermal lobules VI and VII in autism. The argument underlying the cerebellar model that focal vermal pathology in lobules VI and VII causes a disturbance in the complex regulation of attention is itself questionable, because such processes are widely accepted as being subserved by cortical systems.²² The data provided by the current study, which explicitly demonstrate a deficit in the executive and not in the reflexive or automatic regulation of visual attention, both support the cortical systems model of autism and fail to identify any attentional deficit that could be attributed reasonably to vermal pathology.

On both the antisaccade and oculomotor delayed-response tasks, the autistic subjects exhibited an increase in response suppression errors, reflecting an impaired capacity of the prefrontal cortex for volitionally suppressing context-inappropriate reflexive responses. In

the oculomotor delayed-response task, the autistic subject also demonstrated reduced accuracy of saccades to remembered locations. This abnormality indicates a reduced capacity of the prefrontal cortex, and perhaps also its functional connectivity with the parietal cortex, to sustain location information in spatial working memory over brief periods of time to guide behavior.²³ The role of the prefrontal cortex and its neural connections in subserving the capacity to volitionally suppress behavioral responses to compelling stimuli when the responses are not context appropriate, and for holding spatial information on-line over time to subserve anticipated behaviors, has been well documented with a variety of methods, including unit-recording and lesion studies with nonhuman primates,^{23,24} human functional neuroimaging,¹⁷ and clinical studies of behavioral deficits after stroke.²⁵

The intact, visually guided saccades of the autistic subjects indicate that impaired performance on the volitional saccade tasks is reflective of intrinsic dysfunction of neocortical circuitry and is not secondary to impairments in the pons, cerebellum, or superior colliculus that subserve basic saccade mechanisms. The nature of the autistic subjects' abnormalities in volitional saccades is also not consistent with the profile of increased saccade latencies and intact performance on antisaccade tasks seen in the earlier stages of Parkinson's disease—one example of subcortical pathology.^{26,27} It could be argued that deficits demonstrated in the autistic subjects with the volitional saccade tasks reflect greater task difficulty, and that the autistic subjects merely put forth less effort or failed to understand these tasks. However, such an explanation is not supported by the performance curves of the autistic subjects on these tasks. On the antisaccade task, the autistic subjects demonstrated the same declining relationship between response suppression failures and increasing target distance from central fixation as the control subjects, as well as the capacity for successfully suppressing a reflexive response on a substantial percentage of the trials. Similarly, on the oculomotor delayed-response task, the performance curve for saccade error as a function of delay interval in the autistic group was parallel to that of the control group, demonstrating less precision in identifying the target location but responses that were in the general proximity of correct locations. It also could be argued that the autistic and control groups exhibited intact performance on the visually guided saccade task because of a floor effect related to the low difficulty of this task. However, visually guided saccades subserved by the cerebellum and the brainstem are reflexive saccades, and thus are inherently less difficult than voluntary saccade tasks. It is the increase in difficulty of the volitional saccade tasks associated with demands on endogenous attentional processes that brings neocortical systems into play for assessment. Furthermore, visually guided saccades are readily perturbed by a range of disorders, drowsiness, and inattentiveness, and thus are not insensitive to subtle pathology.¹⁴

The pattern of abnormal volitional saccades with preserved reflexive saccades is consistent with the generally accepted neurophysiologic characterization of autism.^{4,28} Event-related potential studies of autism in the past decade have documented a profile characterized by abnormalities in endogenous cognitive potentials and by the integrity of early and middle latency sensorially elicited event-related potentials.⁴ The consistency of the electrophysiologic profile with the saccadic eye movement profile provides evidence of the same pattern of supratentorial dysfunction from studies of two separate systems: the motor system subserving saccadic eye movements and the sensory systems assessed with electrophysiologic methods.

The findings of the current study are also consistent with recent neuropsychological studies in autism. Three studies comparing executive function and attention-shifting abilities in the same autistic subjects have found no evidence of impairment in the capacity for reflexive shifting of attention in autism, but have shown consistent evidence of deficits in the higher order voluntary regulation of attentional focus.^{29–31} These neuropsychologic studies have

provided consistent evidence with different experimental methods that the abnormality in regulating attentional focus in autism has a conceptual rather than a perceptual basis. Reexamination of the neuropsychologic paradigm used to document the shifting attention deficit in autism^{11,32} in the study leading to the current cerebellar model of autism reveals substantial executive function and working memory demands in the paradigm used to cue subjects to the need to shift attention from one focus to another. These demands were not examined separately from the effects of the exogenous demand for an attention shift, nor were they considered in the interpretation of the cognitive basis of the impaired capacity for shifting attention. Several studies of autism³³ have since demonstrated that it is the information processing demands of the cue to shift attention that determine whether an abnormal voluntary or normal reflexive response is elicited, and thus whether deficits are observed.

The findings of the current eye movement study provide evidence of intrinsic dysfunction of neocortical systems in autism and deficits in executive and working memory abilities as important elements of the cognitive and neural basis of autism. The findings do not support the hypotheses of the cerebellar model that vermal lobules VI and VII are dysfunctional or responsible for functional deficits in the regulation of attention.

The current study was confined primarily to a consideration of disturbances in the neocortical circuitry of frontal systems in autism. However, recent evidence^{7,9,30,34,35} suggests that the involvement of neocortical systems and the higher order cognitive abilities they subserve will likely be more widespread. Structural imaging studies in autism have reported evidence of delayed maturation of the frontal lobes⁹ and increased gray and white matter volumes of the temporal, parietal, and occipital cortex,³⁴ which have been consistent with reports of increased head circumference and brain weight in autism.^{7,35} Similarly, a recent neuropsychological study³⁰ examining the profile of cognitive function in autism has reported deficits in higher order cognitive abilities besides executive function, including motor praxis, complex memory, complex language, and concept formation abilities with preservation of simpler abilities in these domains and in sensory perception and attention. This cognitive profile suggests selective involvement of higher order cognitive abilities across domains and the likelihood of neocortical systems involvement beyond frontal systems.

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Figure 1.

Percent of trials on an antisaccade task during which autistic subjects and healthy control subjects failed to suppress reflexive responses to look toward visual targets presented at 8, 16, or 24 deg of visual angle from center fixation in the horizontal plane collapsed across left and right visual fields.

Figure 2.

Absolute error of the first saccade (in degrees of visual angle) made after a delay period of 1, 2, 4, or 8 seconds to remembered target locations in an oculomotor delayed-response task by autistic subjects and healthy matched control subjects.

Table

Parameter	Target step, deg	Autistic group, mean (SD)	Control group, mean (SD)
Peak saccade velocity, deg/see	10	317 (35)	314 (35)
	20	444 (70)	435 (52)
	30	480 (101)	475 (62)
Saccade duration, msec	10	51 (4)	51 (6)
	20	73 (8)	71 (8)
	30	105 (18)	101 (12)
Saccade latency, msec	10	207 (32)	211 (35)
	20	222 (31)	223 (36)
	30	232 (29)	241 (37)
Saccade error, deg	10	0.95 (0.27)	0.96 (0.34)
	20	1.73 (0.61)	1.86 (0.61)
	30	2.72 (1.06)	2.20 (0.98)

No group differences were significant.