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Oculomotor studies of cerebellar function in autism

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Abstract

Histopathological, neuroimaging and genetic findings indicate cerebellar abnormalities in autism, but the extent of neurophysiological dysfunction associated with those findings has not been systematically examined. Suppression of intrusive saccades (square wave jerks) and the ability to sustain eccentric gaze, two phenomena requiring intact cerebellar function, were examined in 52 high-functioning individuals with autism and 52 age- and IQ-matched healthy subjects during visual fixation of static central and peripheral targets. Rates of intrusive saccades were not increased in autism during visual fixation, and foveopetal ocular drift was also not increased when subjects held an eccentric gaze. The absence of gross disturbances of visual fixation associated with cerebellar disease in individuals with autism, such as increased square wave jerk rates and foveopetal drift when holding eccentric gaze, indicates that the functional integrity of cerebellar–brainstem networks devoted to oculomotor control is preserved in autism despite reported anatomic variations. However, increased amplitude of intrusive saccades and reduced latency of target refixation after intrusive saccades were observed in individuals with autism, especially when subjects maintained fixation of remembered target locations without sensory guidance. The atypical metrics of intrusive saccades that were observed may be attributable to faulty functional connectivity in cortico-cerebellar networks.

Keywords: Developmental disabilities; Cerebellum; Eye movements; Motor control; Saccades

1. Introduction

Autism is a complex, polygenetic neurodevelopmental disorder characterized by deficits in social relatedness and verbal and nonverbal communication, as well as restricted and repetitive behaviors. The developmental neurobiology of this disorder, particularly with regard to the brain regions most commonly and severely affected, is not yet well understood. Widespread

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abnormalities observed in neocortex suggest atypical patterns of cortical connectivity leading to reduced integration within functional brain systems and, consequently, deficits in complex information processing (Minshew et al., 1997; Schultz et al., 2000; Just et al., 2004). While studies have acknowledged the contribution of underconnectivity in corticocortical tracks to the pathophysiology of autism, potentially important connections involving the cerebellum have not been thoroughly explored. This is potentially important given histopathological findings in the cerebellum (Ritvo et al., 1986; Bauman, 1991; Kemper and Bauman, 1993).

Eye movement testing is a widely used clinical approach for evaluating cerebellar function. Most previous quantitative studies of eye movements in autistic individuals have not reported significant disturbances in the latency, accuracy or peak velocity of visually guided saccades; however, we recently reported mild saccadic dysmetria in a large patient sample (Rosenhall et al., 1988; Minshew et al., 1999; Goldberg et al., 2002; Minshew et al., 2002; Takarae et al., 2004b). Examining the stability of visual fixation is another way of investigating the functional integrity of cerebellar and brainstem systems. Although gaze behavior in autism has been studied to characterize how individuals with autism explore visual scenes, the basic neurophysiological functioning of the visual fixation system has not been systematically examined (Klin et al., 2002).

In this study, we examined intrusive square wave jerks (SWJs) during visual fixation of static central and eccentric targets. An increased rate of SWJs, resulting from reduced inhibitory control of pretectal oculomotor structures, is a known consequence of cerebellar pathology (Zee et al., 1976; Dell'Osso et al., 1977). The metrics of SWJs were analyzed to explore potential alterations in saccade inhibition. We also evaluated foveopetal ocular drift during fixation of eccentric targets, which can be increased with impaired flocculus and paraflocculus function (Zee et al., 1980).

2. Methods

2.1. Subjects

Fifty-two individuals with autism and 52 healthy individuals (48 males, 4 females in each group) participated in this study. Diagnosis of autism was established by the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule, confirmed by expert clinical opinion using DSM-IV criteria. Participants with autism were excluded if they had an associated infectious, genetic or metabolic disorder known to cause features of autism, e.g., fragile X syndrome or tuberous sclerosis.

Healthy participants were recruited from the community through newspaper advertisement. Exclusion criteria for healthy subjects were as follows: current or past history of psychiatric or neurological disorder, family history of autism in first-, second- or third-degree relatives, and history in first-degree family members of developmental cognitive disorder, mood disorder, or other potentially genetic neuropsychiatric disorder.

Potential healthy participants and/or their parents completed a screening questionnaire, which includes prenatal, birth and developmental history, general medical history, treatment/medication history, and personal and family history of psychiatric and neurological disorders. Exclusion criteria were further evaluated using telephone review of the completed questionnaire, personal interview, and observation during screening testing by skilled staff. The screening tests were used to rule out learning disabilities as evidenced by significant disparities in Verbal and Performance IQ scores or achievement scores significantly below IQ expectations. Subjects were also observed during testing for speech articulation, attention, and social and behavior problems.

Individuals were excluded if they were taking medications known to affect oculomotor abilities at the time of testing, e.g., benzodiazepines and anticonvulsants. Treatment with methylphenidate was prohibited within 24 h of testing. Subjects had corrected or uncorrected far acuity of at least 20/40. No participant had a history of head injury, birth injury or seizure disorder. All participants and their parents/guardians, as appropriate, provided informed consent for participation. This study was approved by the Institutional Review Board of the University of Pittsburgh.

The two subject groups were matched in age and IQ, which was determined using the age-appropriate Wechsler Intelligence Scale. Mean age was 17 ± 9 years (range 8–46) for subjects with autism and 18 ± 9 years (range 8–45) for healthy subjects ($F_{1,102} = 0.03$,

NS). Subjects in the autism group had a mean IQ of 106 ± 13 (range 82–135), and subjects in the healthy group had a mean IQ of 109 ± 12 (range 80–133; $F_{1,102} = 0.82$, NS). In addition, to help ensure group matching and for certain analyses as described below, healthy individuals were individually matched to particular individuals with autism on the basis of age (± 1 year for subjects <12 years old; ± 4 years for subjects ≥ 12 years old), gender and Full Scale IQ (± 15 points).

2.2. Eye movement tasks and procedures

Visual targets were presented in the horizontal plane on an acrylic hemi-arc with a 1-m radius placed at eye level using light emitting diodes. Subjects were seated 1 m from the arc in a darkened room painted optical flat black. Their heads were secured in a chin rest with occipital support and a head strap to minimize head movement.

The visual fixation task included three conditions: (1) fixation of a central target, (2) fixation of the remembered central target location after the central target had been extinguished, and (3) fixation of targets 15° of visual angle to the left and right of the central location. Fixation of each target location continued for 15 s.

2.3. Eye movement measurements

Eye movements were measured using infrared reflection sensors mounted on spectacle frames (Applied Science Laboratories, Inc., Model 210; Bedford, MA, USA). Blinks were identified using electrodes placed immediately above and below the left eye. An experimenter monitored eye movement activity during task performance to verify that subjects were alert and performing according to instruction. Fixation data were collected to calibrate eye movement recordings by presenting targets for 5 s at central fixation and at $\pm 3°$, 6°, 9°, 12° and 15° of visual angle.

Eye movement recordings were digitized at 500 Hz with a 14-bit A/D converter (Dataq Instruments, DI-210; Akron, OH, USA) and smoothed using a custom finite impulse response filter after differentiating the eye position trace to calculate eye velocity and acceleration. The filter had a gradual transition band (from pass to no pass) between 20 and 65 Hz for velocity and position data, and 30 and 65 Hz for acceleration data. Data were reviewed off-line, without knowledge of subject characteristics, to detect and eliminate artifacts (e.g., blinks, periods of inattention/discontinued task performance). Saccades were identified when eye acceleration reached 1000°/s/s. An SWJ was defined as a small ($\leq 5°$) initial intrusive saccade away from the target followed by a second "corrective" saccade in the opposite direction that refoveated the target. The second saccade of comparable amplitude had to occur no more than 400 ms from the onset of the first saccade. Minimum saccade amplitude detectable was approximately 0.20°; thus, both saccades in the pair of eye movements constituting the SWJ had to be at least of this order of magnitude. The number of SWJs per second of task performance was computed, excluding periods with blinks. The amplitude of the first intrusive saccade in each SWJ and the intersaccade interval (time from the end of the first saccade in a SWJ to the initiation of the second saccade) during fixation were also measured. Eye velocity was measured during all fixation tasks, with particular interest in detecting foveopetal drift during fixation of static peripheral targets.

3. Results

3.1. Number of SWJs

Table 1 presents the rate of SWJs for each task condition. Due to skewness in SWJ rate data distributions, nonparametric Mann–Whitney tests were used for group comparisons. No significant group differences in rates of SWJs were found between groups during fixation of static central and peripheral targets, or during fixation in the dark of a remembered target location. However, significant correlations were found between the age of autistic subjects and the rate of SWJs in the remembered target fixation condition ($\rho = 0.45$, $P = 0.001$), and when fixating static targets in the right ($\rho = 0.28$, $P < 0.05$) and left ($\rho = 0.37$, $P < 0.01$) eccentric locations. No such age associations were observed in the healthy individuals.

3.2. Amplitude and intersaccade interval of SWJs

Mean amplitude of the first saccade in the SWJ pair and the mean intersaccade interval between the

Table 1
SWJ rates (per second) during visual fixation

	Healthy group			Autism group			Mann–Whitney U	Effect size Cohen's d
	Mean	Median	S.D.	Mean	Median	S.D.		
Fixation of central target	0.31	0.18	0.32	0.33	0.30	0.28	$U=1121$, $P=0.13$	0.067
Fixation of remembered central target	0.23	0.07	0.40	0.30	0.17	0.42	$U=1109$, $P=0.11$	0.17
Fixation 15° right of center	0.41	0.32	0.36	0.35	0.27	0.29	$U=1264$, $P=0.57$	0.18
Fixation 15° left of center	0.38	0.29	0.31	0.36	0.31	0.27	$U=1348$, $P=0.98$	0.069

two saccades constituting the SWJ were calculated and examined in two repeated measures analyses of variance (ANOVAs): Group × Condition (Center vs. Remembered) and Group × Location (Center, Left and Right). For these analyses, we included only autism/healthy subject pairs in which both pair members had at least one SWJ in all conditions in the analysis, so that group and task differences in quantitative measures of saccade amplitude and intersaccade interval could be meaningfully evaluated. This resulted in 23 matched autism/healthy pairs in the center vs. remembered target analysis, and 34 pairs in the center vs. peripheral targets analysis.

In analyses comparing SWJs during static fixation, the autism group had larger intrusive saccade amplitudes than the healthy group in the remembered relative to the central visual target condition ($F_{1,44}=4.99$, $P<0.05$; Fig. 1). The analysis of SWJ amplitudes during central and peripheral fixation indicated that the autism group had larger intrusive saccades during fixation of peripheral targets ($F_{2,65}=4.09$, $P<0.05$), an effect that was similar during leftward and rightward fixation. In the analysis of intersaccade intervals within SWJs, the intersaccade interval was significantly briefer in the autism group overall ($F_{1,44}=4.68$, $P<0.05$), but follow-up analyses revealed that group differences were only significant for the remembered target condition ($t_{1,44}=2.57$, $P<0.05$; Fig. 1). No group differences in the duration of intersaccade intervals in SWJs were observed in the comparison of central and peripheral target fixation conditions.

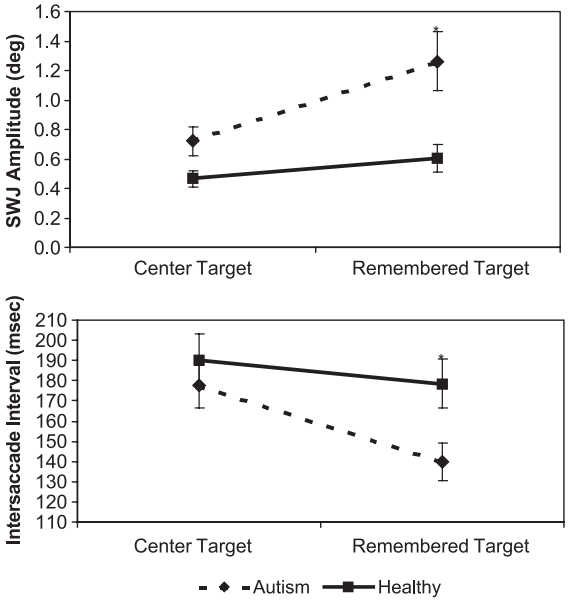

Fig. 1. Amplitude and intersaccade interval of SWJs during fixation of the center and the remembered targets. Mean and standard error of the mean are illustrated. Significant differences ($P<0.05$) are indicated by *.

There were no significant correlations between age and amplitude of SWJs among subjects in either group in any condition. A correlation was found between age and intersaccade interval in the remembered target condition in the autism group ($r=0.43$, $P<0.05$), but not in other conditions or in healthy individuals.

3.3. Drift velocity during fixation

Foveopetal ocular drift was not significantly increased during peripheral fixation ($F_{1,102}=0.33$, $P=0.57$). In both subject groups, mean drift velocity did not exceed 0.05°/s for any fixation condition.

4. Discussion

Although histopathological findings in the cerebellum have been reported in autism, the physiological or functional integrity of the posterior fossa is not yet well characterized. In this study of a large sample of

cooperative high-functioning individuals with autism, we measured characteristics of SWJs and foveopetal ocular drift, which are attributed to the cerebellum and its brainstem projections. No differences were observed in the frequency of SWJ intrusions or in the degree of foveopetal drift during fixation, suggesting that the functional integrity of cerebellar–brainstem networks is preserved in autism despite evidence for anatomical variations in these regions.

4.1. SWJs during visual fixation

While normal adults exhibit some SWJs during fixation, high rates of SWJs most commonly result from cerebellar pathology (Baloh et al., 1975; Herishanu and Sharpe, 1981; Hotson, 1982; Shallo-Hoffmann et al., 1989, 1990). SWJ rates are increased in several disorders of the cerebellum, including cerebellar ataxia, Friedrich's ataxia, and adult-onset Alexander disease (Zee et al., 1976; Spieker et al., 1995; Rabiah et al., 1997; Martidis et al., 1999). SWJs have also been observed in other neurological disorders affecting pretectal and striatal systems, including progressive supranuclear palsy, Parkinson's disease, and Huntington's chorea (Troost and Daroff, 1977; Sharpe et al., 1982; White et al., 1983; Bollen et al., 1986; Rascol et al., 1991; Averbuch-Heller et al., 1999). Some evidence suggests that SWJ rates increase with age, though this effect is usually observed in individuals older than those recruited for the present study (Herishanu and Sharpe, 1981).

Fig. 2 illustrates the neural systems involved in supporting normal visual fixation. During normal fixation, burst neurons in the paramedian pontine reticular formation (PPRF) are suppressed by omnipause neurons (OPNs) in the raphe interpositus nucleus. The relative balance in activity of brainstem saccade generators (burst neurons) and inhibitory OPNs determines the rate of SWJs. It is noteworthy that OPN cell bodies are in the dorsal raphe nucleus and are modulated by serotonergic input (Ashikawa et al., 1991; Kaneko and Fuchs, 1991). This is potentially important in autism because of genetic and functional disturbances of serotonergic systems linked with the disorder (Anderson et al., 1987, 1990; Cook et al., 1997; Kim et al., 2002).

OPNs receive direct projections from the fastigial nucleus of the cerebellum, which in turn receives projections from the dorsal vermis (May et al., 1990). The vermis is believed to be important in utilizing proprioceptive information about extraocular muscles and eye position during fixation to stabilize gaze in the absence of a visual stimulus, making it especially important for maintaining fixation of remembered targets in darkness (Ohtsuka et al., 1986).

In this study, increased rates of SWJs in individuals with autism were not observed in any fixation condition. However, the size of the first intrusive saccade in SWJs was increased, and the time interval for a second saccade to correct for the intrusive saccade was reduced. These observations may provide evidence for a subtle imbalance between excitatory and inhibitory modulation of eye movement control systems in the brainstem. This abnormality is not sufficient to cause the more severe disinhibition of saccade control that has been associated with several cerebellar and brainstem disorders, but it may be sufficient to alter the metrics of SWJs that do occur. One possible basis for our observation is that reduced inhibition of saccade generators could both increase the intensity of burst cell firing to cause larger spontaneous intrusive saccades and also reduce the post-saccadic inhibition of burst cells that normally limits the time before a second corrective saccade can be initiated to correct for fixation error. Furthermore, the increase in amplitude was more pronounced when subjects fixated remembered targets in darkness, which, being particularly dependent upon vermal input, may suggest a possible alteration in visuomotor integration and ultimately the vermal modulation of brainstem systems in autism.

Although we acknowledge the possibility for cerebellar dysfunction in autism, our findings are more consistent with grossly intact cerebellar control of motor function as evidenced by similar rates of SWJs in the autism and healthy groups. This parallels our group's observations from studies of postural control in autism (Minshew et al., 2004), which indicated intact basic motor control but impaired motor function when somatosensory input was required for postural stabilization. In addition, an altered developmental trajectory of sensorimotor systems in autism is suggested by findings from the present study. This was also observed in both our postural data (Minshew et al., 2004) and our study of pursuit eye movements in autism (Takarae et al., 2004a).

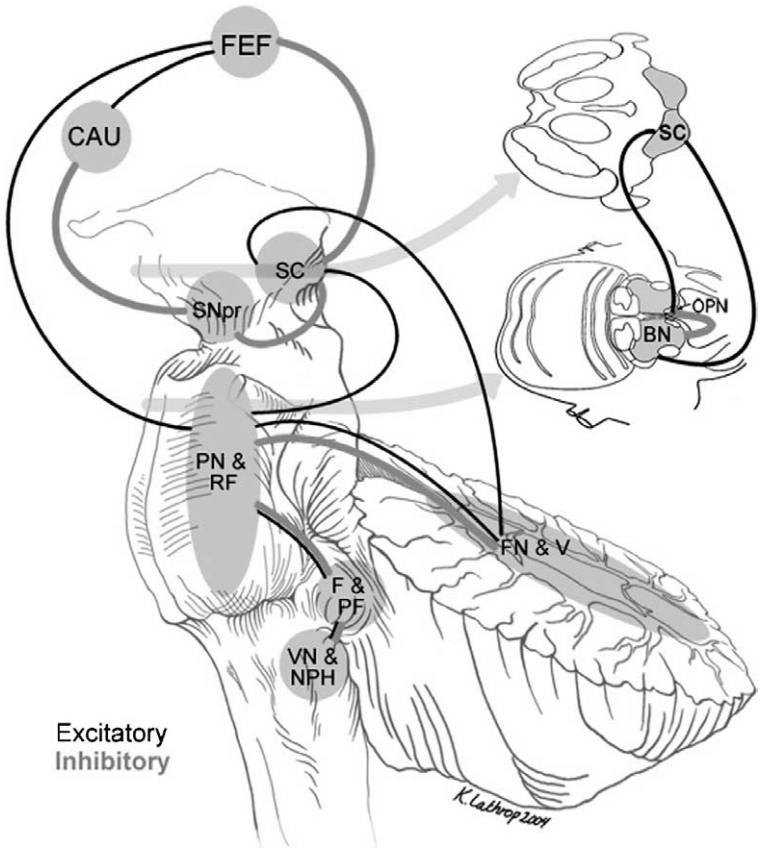

Fig. 2. Neural systems involved in supporting normal visual fixation. A 3D cross-sectional view of the cerebellum and its connections to brainstem oculomotor systems is illustrated. Horizontal sections through the brainstem at the points indicated by the light gray arrows are inserted in the upper right of the figure. Excitatory pathways are indicated by solid black lines; inhibitory pathways by dark gray lines. BN=burst neurons; CAU=caudate nucleus; F & PF=flocculus and paraflocculus; FEF=frontal eye fields; FN & V=fastigial nucleus and cerebellar vermis; OPN=omnipause neurons; PN=pontine nuclei; RF=paramedian pontine reticular formation; SC=superior colliculus; SNpr=substantia nigra pars reticulata; VN & NPH=vestibular nucleus and nucleus prepositus hypoglossi.

4.2. Foveopetal drift when holding eccentric gaze

When saccades are initiated to fixate peripheral targets, a brief "pulse" command moves the eyes to the peripheral location, and a sustained "step" command holds the eyes at that location to prevent drift back to the central orientation. Projections from pontine nuclei to the paraflocculus and flocculus, which subsequently send projections to the vestibular nuclei and nucleus prepositus hypoglossi in the brainstem, are involved in maintaining the step command to prevent drift back toward a central focus of gaze after an eccentric saccade (Zee et al., 1981). The lack of increased foveopetal drift when holding eccentric gaze in the present study provides further evidence for normal cerebellar function in autism, particularly in the relevant systems in flocculus and paraflocculus.

4.3. Implications for autism

Multiple lines of research have revealed abnormal brain maturation in autism. Morphometric and histopathological studies have found abnormal growth trajectories for cerebral cortex, closely packed undersized neurons in limbic areas, alterations in cortical volume, and delayed neuronal maturation in multiple regions of neocortex (Kemper and Bauman, 1993; Bailey et al., 1998; Casanova et al., 2002; Aylward et al., 2002; Herbert et al., 2004). These

disturbances have garnered much interest because of their implications for potential neocortical involvement in the behavioral neurology of the disorder.

However, other findings indicate that the cerebellum and perhaps brainstem may also be compromised in autism. Histopathological studies have reported decreased number and density and abnormal size of Purkinje cells in cerebellar cortex, as well as abnormal cell size in the inferior olive (Ritvo et al., 1986; Bauman, 1991; Kemper and Bauman, 1993). Additionally, post-mortem molecular studies have shown maturational abnormalities in cerebellar nuclei, such that young autistic individuals demonstrate an abnormally large size and increased number of neurons, while adults with autism have small, pale neurons that are reduced in number (Bauman, 1991). Consistent with autopsy data, MRI has shown smaller vermian lobules VI–VII likely due to cellular hypoplasia (Hashimoto et al., 1995; Bauman and Kemper, 1996; Courchesne et al., 2001; Kaufmann et al., 2003). Recent genetic findings linking mutations of the homeobox transcription factor Engrailed2 to autism offer evidence suggestive of a dysmaturational process in the cerebellum of individuals with autism (Gharani et al., 2004). How these histopathological, neuroimaging, and genetic abnormalities may account for functional disturbances in autism remains unclear. Furthermore, potentially interesting connections between cerebellum and brainstem in autism have not been systematically investigated.

With the growing recognition of the important role of the cerebellum in human cognition, and with problems of motor control and praxis not uncommon in autism, delineating potential cerebellar pathology is important for developing a full understanding of the associated neurodevelopmental disturbances that reduce adaptive function in the disorder (Middleton and Strick, 2001). Because the roles of the cerebellum in motor control are currently better understood than those supporting higher-order cognition, studies of visuomotor function provide an important initial strategy for evaluating the integrity of cerebellar systems in autism (Hardan et al., 2003). Our findings of intact cerebellar–brainstem inhibition of intrusive saccades and intact flocculus/parafloccular circuitry governing the ability to maintain eccentric gaze signify that these neural pathways are not compromised in autism. However, in the context of our recent report of saccadic dysmetria in autism, our observation of altered SWJ metrics provides convergent support to the view that there may be a subtle abnormality of cerebellar vermis function in autism (Takarae et al., 2004b), possibly involving reduced inhibitory input from the cerebellum to the brainstem. There are other possible contributing factors to the observed alterations in SWJ metrics, such as altered serotonergic modulation of OPN neurons. However, the more prominent disturbances when fixating target locations in darkness are more consistent with a reduced capacity for integration in sensorimotor systems that alters vermal modulation of brainstem function. Our data also indicate that dysfunction in this circuitry may increase with age at an accelerated rate in autism, suggesting lifelong dysmaturational processes in the ongoing refinement and elaboration of cerebellar neural circuitry in this disorder.

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