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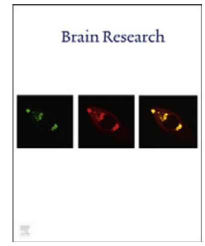

Research Report

Contribution of olivofloccular circuitry developmental defects to atypical gaze in autism

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ABSTRACT

Individuals with autism demonstrate atypical gaze, impairments in smooth pursuit, altered movement perception and deficits in facial perception. The olivofloccular neuronal circuit is a major contributor to eye movement control. This study of the cerebellum in 12 autistic and 10 control subjects revealed dysplastic changes in the flocculus of eight autistic (67%) and two control (20%) subjects. Defects of the oculomotor system, including avoidance of eye contact and poor or no eye contact, were reported in 88% of autistic subjects with postmortem-detected floccular dysplasia. Focal disorganization of the flocculus cytoarchitecture with deficit, altered morphology, and spatial disorientation of Purkinje cells (PCs); deficit and abnormalities of granule, basket, stellate and unipolar brush cells; and structural defects and abnormal orientation of Bergmann glia are indicators of profound disruption of flocculus circuitry in a dysplastic area. The average volume of PCs was 26% less in the dysplastic region than in the unaffected region of the flocculus ($p<0.01$) in autistic subjects. Moreover, the average volume of PCs in the entire cerebellum was 25% less in the autistic subjects than in the control subjects ($p<0.001$). Findings from this study and a parallel study of the inferior olive (IO) suggest that focal floccular dysplasia combined with IO neurons and PC developmental defects may contribute to oculomotor system dysfunction and atypical gaze in autistic subjects.

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1. Introduction

Autism is a neurodevelopmental disorder characterized by deficits in social interactions and verbal and non-verbal communication, and restricted, repetitive behaviors (American Psychiatric Association, 2000). Among the most striking features of the social impairments in autism are deficits in coordinating visual attention with others. Making eye contact is one of the most fundamental aspects of human social behavior (Dawson et al., 2002). Face-to-face interactions and mutual gaze establish the first social relations and may be the driving force behind infants' interest in human faces long before the acquirement of vocal language (Gliga and Csibra, 2007; Hoehl et al., 2009). In triadic person-object-person interactions, eye gaze indicates another person's focus of attention and guides learning in the first months after birth (Striano and Reid, 2006). Numerous studies reveal abnormalities in processing information from the eyes (Johnson et al., 2005), with numerous implications for autistic subjects' social development (review by Hoehl et al., 2009). However, active avoidance of eye contact, poor eye contact or lack of eye contact reported very early in infancy appears to be the primary abnormality that is most likely caused by developmental defects within infant olivofloccular neuronal networks.

1.1. *Atypical gaze in autism*

Eye gaze-processing impairments appear early in the development of children with autism (Dawson et al., 1998; Mundy et al., 1986). Even high-functioning individuals with autism exhibit deficits in performing tasks involving mental interferences from viewing expression in the eyes (Baron-Cohen et al., 2001). Gaze-processing deficits result from impairment in using gaze to understand the intentions and mental states of other people (Baron-Cohen, 1995, 1999, 2001; Leekam et al., 1998, 2000). Children with autism demonstrate "atypical" gaze and frequently have stereotypies including eye-pressing and light-gazing. Several studies have revealed impairments in smooth visual pursuit in autism (Rosenhall et al., 1988; Scharre and Creedon, 1992; Takarae et al., 2004). Abnormalities of the oculomotor system, including atypical optokinetic nystagmus, gaze avoidance and stereotypic behaviors related to eyes, were reported in 91% of 34 children diagnosed with autism (Scharre and Creedon, 1992). A study of 60 high-functioning individuals with autism revealed pursuit eye movement deficits (Takarae et al., 2004). The subjects had a reduced closed-loop pursuit gain when tracking both oscillating and ramp targets. More apparent deficits after mid-adolescence suggest reduced maturational development of the pursuit system in autism. Bilateral disturbances in the ability to use internally generated extraretinal signals for closed-loop pursuit suggest defects in the frontostriatal or cerebellar circuitry. An fMRI study using saccadic and pursuit eye movement paradigms revealed reduced activation in cortical eye fields and cerebellar hemispheres in autistic subjects (Takarae et al., 2007).

1.2. *The role of flocculus in eye movement control*

Experimental studies indicate that the cerebellar flocculus is the part of the oculomotor system involved in both the olivo-cerebellar circuit and the vestibulooccular reflex arc. The flocculus exerts a specific inhibitory modulation of both excitatory and inhibitory branches of the vestibulo-ocular reflex pathways to the extraocular muscles. This modulation is mediated through inhibitory projections of floccular Purkinje cells (PCs) to the vestibular nuclei neurons, described as flocculus target neurons (reviewed by Du Lac et al., 1995; Sato and Kawasaki, 1991). The flocculus is also a region of vestibular afferent signal convergence, through the input of mossy fibers from the vestibular nuclei, and of visual signals received via the climbing fibers of the inferior olive (IO) (Sato and Kawasaki, 1991).

A substantial number of PCs in the flocculus of the monkey receive converging visual inputs from functionally distinct portions of the retina and are involved in oculomotor control during slow eye movements. The flocculus provides the oculomotor system with eye position information during fixation and with velocity information during smooth pursuit and participates in the control of oculomotor functions (Noda and Suzuki, 1979; Zee et al., 1981). Velocity plays a stronger role (64%) than position (36%) in determining firing rate modulation during circular pursuit (Leung et al., 2000). The majority of visual PCs (85%) are identified as horizontal gaze-velocity neurons. The presence of position and velocity signals in the flocculus and paraflocculus suggests that these two cerebellar regions generate the position and velocity signal that are used to control eye motion (Leung et al., 2000). Moreover, PCs in the flocculus help to coordinate eye and head movements during active gaze shifts by modulating the vestibulo-ocular reflex (Belton and McCrea, 1999).

1.3. *Olivo-cerebellar system*

From a movement perspective, the olivo-cerebellar system has been considered to be involved in motor learning (Hesslow and Yeo, 2002; Highstein et al., 2005; Ito, 2001) and in the timing of motor execution (Lang et al., 1999). The olivo-cerebellar system is involved in both somatomotor and oculomotor cerebellar control. Electrophysiological studies have revealed that neurons in the dorsal cap of Kooy and the adjacent ventrolateral outgrowth of the IO control eye movements via their climbing fiber projections to the cerebellar flocculus, whereas neurons in the principle olive are involved in control of limb and digit movements via their climbing fiber projections to the lateral part of the cerebellar hemisphere (reviewed by Ito, 1984 and Voogd and Bigaré, 1980).

Neuropathological studies indicate that the oculomotor circuit is often developmentally affected in individuals with autism. Our study of serial sections of the brain revealed multiregional dysregulation of cerebellum development in nine of 13 (69%) subjects with autism. The presence of cerebellar floculonodular dysplasia in six autistic subjects (46%), focal dysplasia in the vermis of one subject, heterotopia in one case and focal cerebellar hypoplasia in one subject reflected a high susceptibility of the cerebellum to developmental defects (Wegiel et al., 2010). The presence of olivary dysplasia in three of five subjects with autism and of ectopic neurons related to the olivary complex in two cases reported by Bailey et al. (1998) suggests that both components

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