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Title: Familiality of Oculomotor Control Abnormalities in Autism Spectrum Disorder

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Introduction: Individuals with autism spectrum disorder (ASD) and their first-degree relatives exhibit abnormalities across multiple tests of eye movements, suggesting that oculomotor impairments in ASD may be heritable (1,2). While previous studies of oculomotor control in family members have examined parents separately from their children with ASD, we studied the degree to which these impairments inter-correlate amongst family members by examining oculomotor control in family trios (child and biological mother and father). As the discrete neurophysiological processes that support eye movements have been well defined through single cell recording studies in monkeys and neuroimaging in humans (3), examination of the familiality of these traits allows the potential to identify neurological intermediate phenotypes involved in ASD.

Method: Forty-four individuals with ASD (aged 5-22 years), 105 unaffected biological parents, and 73 age-, sex-, and nonverbal IQ-matched typically developing controls (27 matched to ASD participants, 46 matched to parents) completed three tests of oculomotor control. Our sample included 32 complete family trios plus additional duos (child with ASD and one parent) and individual parents whose children with ASD did not complete testing. During the visually guided saccade task, participants were instructed to look toward peripheral stimuli (i.e., white circles appearing pseudorandomly at $\pm$ 12 or 24 degrees) as quickly as possible. Accuracy, latency, duration, and peak velocity of rapid eye movements (i.e., saccades) were examined. Procedural learning of oculomotor responses was examined during a predictive saccade task in which a stimulus shifted between two target locations ($\pm$ 6 degrees) at regular intervals (1500 ms). The rate at which latency decreased across trials was measured. During a smooth pursuit task, participants tracked moving targets that swept from center to $\pm$ 15 degrees. Pursuit gain was examined by calculating pursuit velocity relative to target velocity. We also analyzed the degree to which performance across all variables of interest were familial within complete family trios.

Results: Compared to controls, individuals with ASD and their parents exhibited less accurate visually guided saccades to 24-degree targets as well as saccades with shorter durations and higher peak velocities (controlling for saccade amplitude). Latencies of visually guided saccades did not differ between ASD and control groups, but ASD parents showed reduced latencies relative to controls in response to 12-degree targets. Saccade latency, duration, and peak velocity were familial within family trios, but saccade accuracy was not. No group differences were found in the rate at which latency decreased across trials during the predictive saccade task, but the familiality of this rate of procedural learning was significant. Probands showed reduced pursuit gain compared to controls, but parents and controls did not differ on pursuit gain, and pursuit gain was not inter-correlated across family members.

Discussion: Our findings indicate that atypical saccade dynamics identified in individuals with ASD are familial. These results suggest that alterations in cerebellar-brainstem circuits involved in control of rapid, reactive sensorimotor behaviors may represent pathophysiological mechanisms associated with familial risk for ASD. Individuals with ASD and their unaffected parents also demonstrate saccade dysmetria implicating alterations in cerebellar mechanisms involved in feedforward movement control. The inter-correlation of procedural learning of oculomotor responses within family trios suggest that chronometric systems involving striatal circuits may be affected within some families of individuals with ASD. Individuals with ASD also showed reduced smooth pursuit gain, though pursuit eye movements were spared in parents and not familial, suggesting that alterations in fronto-temporal pathways, including frontal eye field, middle temporal, and medial superior temporal cortices, may represent trait markers specifically associated with the presence of ASD. Overall, our findings implicate dysfunction in cerebellar-brainstem systems in the pathophysiology of ASD and suggest that impairments in oculomotor control may serve as candidate intermediate phenotypes useful for studies identifying heritable mechanisms of ASD.

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