**Sex-Dependent Behavioral Changes in a Mouse Model of Autism Spectrum Disorder**

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Abstract: According to the CDC, the incidence of Autism Spectrum Disorders (ASD) in the US has been consistently increasing. Animal models for neurodevelopmental disorders such as ASD indicate that several factors contribute to disease severity including genetics, prenatal infections, and sex. However, most studies using animal models have focused only on males, assuming females are simply attenuated males. Therefore, we investigated the impact of sex on behaviors associated with ASD. We induced systemic inflammation by injecting recombinant interleukin-6 (IL-6) twice daily from postnatal days 3-6, at a dose of 75 ng per injection, which we previously showed doubled plasma levels of IL-6 and produced social behavior deficits in male mice.

Transiently increasing IL-6 soon after birth elicited a small but significant increase in body temperature that persisted for the first 2 months of life and was more notable in males. The IL-6 injected males also had decreased daily food intake at 9 weeks of age; however, this did not cause any growth delay. To determine the phenotypic effects of briefly increased systemic IL-6, we analyzed behaviors classically associated with ASD. At 10 weeks of age, both male and female mice were slower to find the goal box in the Barnes Maze of spatial memory, but this was due to increased freezing. Indeed, in female mice their memory of the task was significantly improved over PBS injected litter-mates. At 11 weeks, the IL-6 injected mice showed a trend, though nonsignificant, towards increased anxiety in the elevated plus maze and open field task, which was more prominent in females. At 17 weeks, both IL-6 injected sexes engaged in more self-grooming. Overall, our data support the conclusion that female mice respond differently to perinatal systemic inflammation and that their neuropsychiatric behavioral deficits are not simply an attenuated version of those seen in males.