

**Differences in White Matter Fiber Tract Development  
Present from 6 to 24 Months in Infants with Autism**

*American Journal of Psychiatry, In Press*

Jason J. Wolff, Ph.D.<sup>1</sup>, Hongbin Gu, Ph.D.<sup>1,2</sup>, Guido Gerig Ph.D.<sup>1,3</sup>, Jed T. Elison, Ph.D.<sup>1,4</sup>,  
Martin Styner, Ph.D.<sup>1,2</sup>, Sylvain Gouttard, M.S.<sup>3</sup>, Kelly N. Botteron, M.D.<sup>5,6</sup>, Stephen R. Dager,  
M.D.<sup>7</sup>, Geraldine Dawson, Ph.D.<sup>2,8</sup>, Annette M. Estes, Ph.D.<sup>9</sup>, Alan Evans, Ph.D.<sup>10</sup>, Heather C.  
Hazlett, Ph.D.<sup>1,2</sup>, Penelope Kostopoulos, Ph.D.<sup>10</sup>, Robert C. McKinstry, M.D., Ph.D.<sup>6</sup>, Sarah J.  
Paterson, Ph.D.<sup>11</sup>, Robert T. Schultz, Ph.D.<sup>11</sup>, Lonnie Zwaigenbaum, M.D.<sup>12</sup>, & Joe Piven,  
M.D.<sup>1,2</sup> for the IBIS Network\*

<sup>1</sup>Carolina Institute for Developmental Disabilities, University of North Carolina, Chapel Hill, NC

<sup>2</sup>Department of Psychiatry, University of North Carolina, Chapel Hill, NC

<sup>3</sup>Scientific Computing and Imaging Institute, University of Utah, Salt Lake City, UT

<sup>4</sup>Division of Humanities and Social Sciences, California Institute of Technology, Pasadena, CA

<sup>5</sup>Department of Psychiatry, Washington University, St. Louis, MO

<sup>6</sup>Department of Radiology, Mallinckrodt Institute of Radiology, Washington University School  
of Medicine, St. Louis, MO

<sup>7</sup>Department of Radiology, University of Washington, Seattle, WA

<sup>8</sup>Autism Speaks, New York, NY

<sup>9</sup>Department of Speech and Hearing Sciences, University of Washington, Seattle, WA

<sup>10</sup>Montreal Neurological Institute, McGill University, Montreal, QC

<sup>11</sup>Center for Autism Research, Children's Hospital of Philadelphia, and University of  
Pennsylvania PA

<sup>12</sup>Department of Pediatrics, University of Alberta, Edmonton, AB

## Author Note

Corresponding author: Jason Wolff, Ph.D., Carolina Institute for Developmental Disabilities, UNC – Chapel Hill, CB# 3366, Chapel Hill, NC 27599, [jason.wolff@cidd.unc.edu](mailto:jason.wolff@cidd.unc.edu)

Competing interests: All study authors report no financial relationships with commercial interests.

\* The IBIS Network. Clinical Sites: University of North Carolina: J. Piven (IBIS Network PI), H.C. Hazlett, C. Chappell; University of Washington: S. Dager, A. Estes, D. Shaw; Washington University: K. Botteron, R. McKinstry, J. Constantino, J. Pruett; Children’s Hospital of Philadelphia: R. Schultz, S. Paterson; University of Alberta: L. Zwaigenbaum; Data Coordinating Center: Montreal Neurological Institute: A.C. Evans, D.L. Collins, G.B. Pike, P. Kostopoulos; Samir Das; Image Processing Core: University of Utah: G. Gerig; University of North Carolina: M. Styner; Statistical Analysis Core: University of North Carolina: H. Gu; Genetics Analysis Core: University of North Carolina: P. Sullivan, F. Wright.

This work was supported by grants from the National Institutes of Child Health and Development, R01 HD055741, HD055741-S1, P30 HD031110, and T32 HD40127; Autism Speaks, and the Simons Foundation. Further support was provided by the National Alliance for Medical Image Computing (NA-MIC), funded by the NIH through grant U54 EB005149.

We wish to thank our IBIS children and families for their ongoing participation in this longitudinal study. Thanks also to Varun Puvanesarajah and Eric Maltbie for assisting with tractography, and Rachel G. Smith, Cheryl Dietrich, and Mahshid Farzinfar for the DWI/DTI correction and QC efforts.

## **Abstract**

**OBJECTIVE:** Evidence from prospective high-risk infant studies suggests that early symptoms of autism usually emerge late in the first- or early in the second-year of life after a period of relatively typical development. The purpose of this study was to prospectively examine white matter fiber tract organization from 6 to 24 months in high-risk infants who develop autism spectrum disorders (ASDs) by 24 months.

**METHOD:** Participants included 92 high-risk infant siblings from an ongoing imaging study of autism. All participants had diffusion tensor imaging at 6 months and behavioral assessments at 24 months, with a majority contributing additional imaging data at either or both 12 and 24 months. At 24 months, 28 infants met criteria for ASDs; 64 infants did not. Microstructural properties of white-matter fiber tracts reported to be associated with ASDs or related behaviors were characterized by fractional anisotropy (FA) and radial and axial diffusivity.

**RESULTS:** FA trajectories differed significantly between infants who did versus did not develop ASDs for 12 of 15 fiber tracts. Development for most fiber tracts in infants with ASDs was characterized by elevated FA at 6 months followed by slower change over-time relative to infants without ASDs. Thus, by 24 months of age, lower FA values were evident for those with ASDs.

**CONCLUSION:** These results suggest that the aberrant development of white matter pathways may precede the manifestation of autistic symptoms in the first year of life. Longitudinal data are critical to characterizing the dynamic age-related brain and behavior changes underlying this neurodevelopmental disorder.