Archival Report

Biological Psychiatry

The Emergence of Network Inefficiencies in Infants With Autism Spectrum Disorder

John D. Lewis, Alan C. Evans, John R. Pruett Jr., Kelly N. Botteron, Robert C. McKinstry, Lonnie Zwaigenbaum, Annette M. Estes, D. Louis Collins, Penelope Kostopoulos, Guido Gerig, Stephen R. Dager, Sarah Paterson, Robert T. Schultz, Martin A. Styner, Heather C. Hazlett, and Joseph Piven, for the Infant Brain Imaging Study Network

ABSTRACT

BACKGROUND: Autism spectrum disorder (ASD) is a developmental disorder defined by behavioral features that emerge during the first years of life. Research indicates that abnormalities in brain connectivity are associated with these behavioral features. However, the inclusion of individuals past the age of onset of the defining behaviors complicates interpretation of the observed abnormalities: they may be cascade effects of earlier neuropathology and behavioral abnormalities. Our recent study of network efficiency in a cohort of 24-month-olds at high and low familial risk for ASD reduced this confound; we reported reduced network efficiencies in toddlers classified with ASD. The current study maps the emergence of these inefficiencies in the first year of life.

METHODS: This study uses data from 260 infants at 6 and 12 months of age, including 116 infants with longitudinal data. As in our earlier study, we use diffusion data to obtain measures of the length and strength of connections between brain regions to compute network efficiency. We assess group differences in efficiency within linear mixed-effects models determined by the Akaike information criterion.

RESULTS: Inefficiencies in high-risk infants later classified with ASD were detected from 6 months onward in regions involved in low-level sensory processing. In addition, within the high-risk infants, these inefficiencies predicted 24-month symptom severity.

CONCLUSIONS: These results suggest that infants with ASD, even before 6 months of age, have deficits in connectivity related to low-level processing, which contribute to a developmental cascade affecting brain organization and eventually higher-level cognitive processes and social behavior.

Keywords: Autism, Connectivity, Development, Efficiency, Infant siblings, Network analysis

http://dx.doi.org/10.1016/j.biopsych.2017.03.006

Autism spectrum disorder (ASD) is a developmental disorder defined by impairments in social communication and social interaction and a restricted repertoire of activities and interests (1). A great deal of research has focused on relating these behavioral symptoms to brain-based measures to understand how neurological abnormalities give rise to the symptoms of ASD. The majority of this research, however, has been based on adults, adolescents, and older children, but the behavioral manifestations of ASD first appear during the first or second year of life (2–5). Differences in the brains of individuals with ASD who are far past this age may be the result of a complex cascade of effects compounding some early neuropathology with the progressive impact of this neuropathology and its associated behaviors on brain development. These results therefore tell us little about the emergence of the neuropathology that is associated with the earliest behavioral signs of ASD. To elucidate this, we study brain development during infancy.

In a recent study (6), we sought to determine what, if any, differences in structural networks were present around the age at which the characteristic symptoms of autism consolidate (2–5). Motivated by recent research relating abnormalities in brain connectivity in ASD to a number of the behavioral features (7–25), we assessed white matter connectivity differences in 24-month-old siblings of older children diagnosed with ASD, who are known to be at high familial risk for ASD, as well as 24-month-olds at low familial risk for ASD (i.e., with no first-degree relative with ASD or intellectual disability). We assessed regional abnormalities in network efficiency in ASD (i.e., the capacity to exchange information across a network) and the relation between these regional differences and symptom severity. Our results showed significantly decreased efficiency in regions of the temporal, parietal, and occipital lobes, and in Broca's area in high-risk infants classified as having ASD. This was among the earliest evidence of atypical connectivity in ASD, reported at an age when diagnosis first becomes feasible and stable (26–28).

The current study aims to map the emergence of these network inefficiencies earlier in development, before symptom

SEE COMMENTARY ON PAGE 152

consolidation (28,29). We use magnetic resonance imaging data together with clinical diagnosis and measures of symptom severity (28). As in our earlier study, we obtain tractography-based measures of the length and strength of connections between anatomical brain regions and assess the efficiency of information transfer for each brain region to all other brain regions and within local subnetworks (30–33). These measures simultaneously capture differences in the strengths of the connections between brain regions and differences in the spatial organization of the brain. We assess differences in these measures of efficiency for every region of the brain in infants with ASD versus non-ASD infants, as well as the relation between efficiency and symptom severity. To ascertain the developmental progression, we measure these effects over time.

METHODS AND MATERIALS

Here we present an abbreviated version of the methods; a detailed version can be found in the Supplement.

Participants

Participants were drawn from the Infant Brain Imaging Study, an ongoing multisite longitudinal study funded by the National Institutes of Health Autism Centers of Excellence program. The Infant Brain Imaging Study documents brain and behavioral development in infants at high familial risk for ASD by virtue of having an older sibling with ASD, as well as in infants deemed to be at low familial risk for ASD by virtue of having no first-degree relative with ASD or intellectual disability and an older sibling.

Neuroimaging and behavioral data were collected from high and low familial risk infants at 6, 12, and 24 months of age. The data acquired included T1- and T2-weighted images and diffusion data. Usable data were acquired from 260 infants: 116 infants with longitudinal data, 33 infants for whom all imaging data were available at 6 months of age and structural but not diffusion data were available at 12 months, and 111 infants for whom all imaging data were available at 12 months of age but not at 6 months. These data were stratified by risk status and according to whether or not they received a diagnosis of ASD at 24 months of age. Table 1 provides the sample characteristics for high-risk infants diagnosed with ASD (HR^{POS}), high-risk infants diagnosed as not having ASD (HR^{NEG}), and low-risk infants diagnosed as not having ASD (LR^{NEG}). Note that much of the data are from LR^{NEG} and HR^{NEG} infants, limiting the power of the analysis of group differences. The analysis of the relation between efficiency and symptom severity does not suffer this limitation because it uses both the HR^{POS} and HR^{NEG} infants.

Behavioral Assessment

A clinical best-estimate diagnosis was made by two clinicians based on all available information to determine whether a participant met the DSM-IV-TR criteria for autistic disorder, pervasive developmental disorder not otherwise specified, or neither. ASD symptom severity was derived from the Autism Diagnostic Observation Schedule (34) according to Gotham *et al.* (35). The means and standard deviations of the symptom severity scores for each group are reported in Table 1.

Imaging and Image Processing

Magnetic resonance imaging scans were performed while infants were naturally sleeping. Data were collected at each site on Siemens 3T TIM Trio scanners (Siemens Medical Solutions, Malvern, PA) with 12-channel head coils. T1-, T2-, and diffusion-weighted images were collected.

T1- and T2-weighted images were subjected to a visual quality control during postprocessing. The diffusion-weighted

Table 1. Sample Characteristics of the Study Groups

	HR^{POS}		HR^{NEG}		LR^{NEG}	
	n	Age, Months (Mean ± SD)	*n*	Age, Months (Mean ± SD)	*n*	Age, Months (Mean ± SD)
V06						
Male	15	6.7 ± 0.8	47	6.6 ± 0.7	40	6.8 ± 0.7
Female	2	6.7 ± 0.4	33	6.7 ± 0.8	12	6.5 ± 0.5
V12						
Male	27	12.8 ± 0.8	77	12.6 ± 0.5	37	12.7 ± 0.6
Female	2	12.9 ± 0.6	62	12.7 ± 0.7	22	12.9 ± 0.9
V06 + V12						
Male	13	—	39	—	27	—
Female	2	—	27	—	8	—
		ADOS Severity (Mean ± SD)		ADOS Severity (Mean ± SD)		ADOS Severity (Mean ± SD)
V06, V12, V06 + V12						
Male	—	5.3 ± 2.3	—	1.4 ± 0.8	—	1.4 ± 1.0
Female	—	7.0 ± 1.2	—	1.5 ± 1.1	—	1.2 ± 0.6

V06 rows provide the sample sizes and ages (in months) at the 6-month visit for individuals for whom there are only 6-month efficiency measures and individuals for whom there are longitudinal measures. Likewise, the V12 rows provide the sample sizes and ages at the 12-month visit for individuals for whom there are only 12-month efficiency measures and individuals for whom there are longitudinal measures. V06 + V12 rows provide the sample size for the longitudinal portion of the sample.

ADOS, Autism Diagnostic Observation Schedule; HR^{NEG}, high-risk infants diagnosed as not having autism spectrum disorder; HR^{POS}, high-risk infants diagnosed with autism spectrum disorder; LR^{NEG}, low-risk infants diagnosed as not having autism spectrum disorder.