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Archival Report

The Emergence of Network Inefficiencies in Infants With Autism Spectrum Disorder

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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

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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

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.

images were cleaned of motion and other artifacts using DTI-Prep (36), which corrects artifacts where possible, and excludes directions from the data when correction is not possible. Further visual quality control potentially eliminated additional artifacts. If this process excluded >20% of the directions for any size subset of the largest b-values, the dataset was deemed unacceptable. Only datasets with acceptable T1-, T2-, and diffusion-weighted images were included in the analysis.

The T1 and T2 volumes were corrected for geometric distortion (37) and then processed with CIVET, a fully automated structural image analysis pipeline developed at the Montreal Neurological Institute. The contrast in the 6-month data is insufficient for CIVET to extract accurate surfaces, so 6-month data were included in the analysis only if the 12-month T1 and T2 volumes were acceptable.

The CIVET results were used to construct the seed, stop, and target masks for use with FSL's *probtrackx* (38). Seed masks were the entire white matter. Stop masks were the voxels on the boundary of the white matter. Target masks consisted of the cortical labels of the DKT40 surface parcellation (39), as well as subcortical labels defined on a template derived from pediatric data (40).

After artifact rejection and motion correction with DTIPrep (36), the diffusion-weighted images were unwarped to the distortion-corrected T2 volume. Two copies of these data were then preprocessed for probabilistic tractography with FSL's *bedpostx* (38): one in native space, and one scaled to the 12-month template. Connection lengths were estimated using the native space data; connection strengths were estimated using the scaled data. The unwarped diffusion volumes were affine registered to the T1 volumes in stereotaxic space. Probabilistic tractography using FSL's *probtrackx* was then seeded from each voxel of the seed masks, with and without distance bias correction (38,41), both in native and in 12-month standard space. These results were then compiled for each region of the cortical parcellation, generating undirected matrices of the total number of connections between each pair of regions from the results in standard space and the mean physical length of those connections from the results in native space. The total number of connections between each pair of regions of the parcellation divided by the average surface area of the two regions in stereotaxic space is referred to as connection "strength."

Analysis

We performed a longitudinal analysis of network efficiency using the methods developed in our previously reported analysis of the 24-month data (6). Based on Rubinov and Sporns (42), we define the weighted distance between nodes i and j as

$$d_{ij}^w = \sum_{\forall uv \in S_{ij}} \frac{d_{uv}}{w_{uv}}$$

where S_{ij} is the shortest path, in terms of tractography-based measures of physical distances, between nodes i and j; d_{uv} is the length of the edge between u and v along that path, and w_{uv} is the connection strength between nodes u and v. The

shortest paths, in terms of weighted distances, have "transmission times" that decrease with the strengths of the connections involved and increase with the tractography-based measures of the physical distances involved. Our weighted formulations of nodal global efficiency and nodal local efficiency, also based on Rubinov and Sporns (42), are

$$E_{nodal\ global}^{weighted}(G,i) = \frac{1}{(N-1)} \sum_{j \in G, i \neq j} \left(d_{ij}^w\right)^{-1}$$

where N is the number of nodes in the network graph G; and d_{ij}^w is the shortest path, in terms of weighted distance, between nodes i and j; and

$$E_{nodal\ local}^{weighted}(G,i) = \frac{1}{N_{G_i}(N_{G_i}-1)} \sum_{j \neq k \in G_i} \left(\left(d_{jk}^w\right)^{-1} w_{ij} w_{ik}\right)^{1/3}$$

where N_{G_i} is the number of nodes in the subgraph G_i consisting of all of the neighbors of i; d_{jk}^w is the shortest path, in terms of weighted distance, between nodes j and k; and w_{ij} and w_{ik} are the connection strengths between nodes i and j and i and k, respectively. According to Latora and Marchiori (30), these measures are normalized by considering the fully connected network.

Differences in nodal local efficiency and nodal global efficiency between infants with ASD and non-ASD infants were assessed via mixed-effects linear models. The group of non-ASD infants was based on clinical best-estimate diagnosis, ignoring familial risk (i.e., combines the LR[NEG] and HR[NEG] infants). At each node, the best-fit model was determined by the Akaike information criterion with the data centered at 9 months of age (43,44). In addition to subject-specific random effects, the models could control for any of the following: age, age^2, sex, site, age × sex, age^2 × sex, age × group, and age^2 × group. All possible models were evaluated, and group differences were assessed within the model with the lowest Akaike information criterion value. Group differences were assessed across time to evaluate how the models differed by group over development. Group differences were assessed with the data centered at 6, 9, and 12 months of age.

Finally, to determine the extent to which network structure might explain individual behavioral differences—both across individuals with ASD and across the broader autism phenotype (45–48)—we assessed the relation between the measures of network efficiency and the Autism Diagnostic Observation Schedule–calibrated severity scores (35) across all high-risk infants. This was also assessed at each node within the model with the lowest Akaike information criterion value; in this case, with models that could control for site and any of severity, age, age^2, and sex, and interactions of these terms with each other and with severity.

In all analyses, we use a false discovery rate (FDR) correction for multiple comparisons (49).

RESULTS

Relative to the non-ASD infants, HR[POS] infants showed reductions in nodal local efficiency from 6 months of age onward (Figure 1; Supplemental Table S1). The HR[POS] infants showed FDR-corrected significant reductions in nodal local
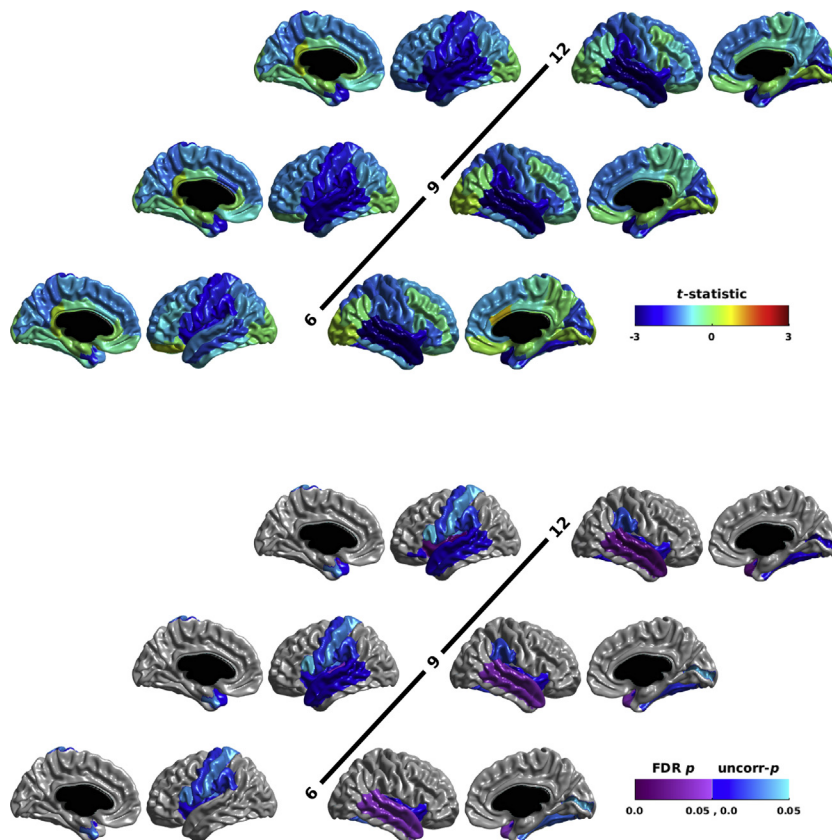
Figure 1. The group differences in nodal local efficiency for high-risk infants diagnosed with autism spectrum disorder vs. high-risk infants diagnosed as not having autism spectrum disorder and low-risk infants diagnosed as not having autism spectrum disorder assessed at 6, 9, and 12 months of age. The *t* statistic is shown in the top half of the figure; the *p* statistic is shown in the bottom half. Reduced efficiency in high-risk infants diagnosed with autism spectrum disorder yields a negative *t* statistic (blue); increased efficiency yields a positive *t* statistic (red). The *p* statistic maps show both the *p* values that survive a false discovery rate (FDR) correction for multiple comparisons (purple), as well as those that are significant uncorrected, but do not survive multiple comparison correction (blue). Each row shows the results for the left hemisphere on the left and the right hemisphere on the right. The medial views for the left hemisphere are furthest to the left; the medial views for the right hemisphere are furthest to the right. Age is indicated in the center of each row. Note that false discovery rate–significant reductions in nodal local efficiency in high-risk infants diagnosed with autism spectrum disorder are seen at 6 months of age in the right primary auditory cortex and superior and middle temporal gyri; reductions in the left primary auditory cortex become significant by 9 months of age, followed by reductions in the left insula by 12 months of age.

efficiency over the right primary auditory cortex and the superior and middle temporal gyri from 6 months of age onwards. With the data centered at 9 months of age, the HR^{POS} infants showed FDR-corrected significant reductions in the left primary auditory cortex as well, and also in the left insula with the data centered at 12 months of age. This development of group differences was reflected in the models for these regions; both included an age^2 × group interaction term. Note that all group differences at all time points were reductions in nodal local efficiency in HR^{POS} infants.

Relative to the non-ASD infants, the HR^{POS} infants also showed reductions in nodal global efficiency (Figure 2; Supplemental Table S2). HR^{POS} infants showed an FDR-corrected significant reduction in nodal global efficiency only in Broca's area at 12 months of age. The emergence of this group difference was reflected in the age^2 × group interaction term in this region. As with nodal local efficiency, all group differences at all time points were reductions in nodal global efficiency in HR^{POS} infants.

Across the high-risk infants, the measures of network efficiency and the symptom severity scores were inversely related (i.e., symptom severity increased with decreasing efficiency). There were FDR significant inverse relations of symptom severity to nodal local efficiency from 6 months of age onward, and no significant positive correlations at any time point (Figure 3; Supplemental Table S3). At 6 months of age, the inverse relations between severity and nodal local efficiency reached FDR-corrected significance in the left primary auditory

cortex and the right superior temporal gyrus. By 9 months of age, the inverse relation in the left primary visual cortex reached FDR significance, as well as the left insula and supramarginal and superior temporal gyri, and the middle temporal gyri bilaterally. By 12 months of age, the inverse relation in bilateral medial visual cortex reached FDR significance, as well as the left somatosensory cortex and angular gyrus, the right insula, and superior parietal lobule. Though the left primary auditory cortex showed a significant relation between nodal local efficiency and severity from 6 months onward, the relationship strengthened with age, as reflected by the *t* statistic; this developmental change in the relationship was reflected in an age^2 × severity interaction term in the model for this region. The strengthening relationships between nodal local efficiency and severity seen in the bilateral insula, the right cuneus and superior parietal lobule, and the left somatosensory cortex and angular gyrus were also reflected in age^2 × severity interaction terms in the models for those regions.

The emerging relations between symptom severity and nodal global efficiency were also exclusively inverse relations (Figure 4; Supplemental Table S4). The inverse relations first reached FDR significance at 9 months of age in the right somatosensory cortex and angular gyrus and the supramarginal gyrus bilaterally. The emergence of these relationships in each of these regions was reflected in an age × sex × severity^2 interaction term in the models, and for the right angular gyrus, also an age × sex × severity interaction term.
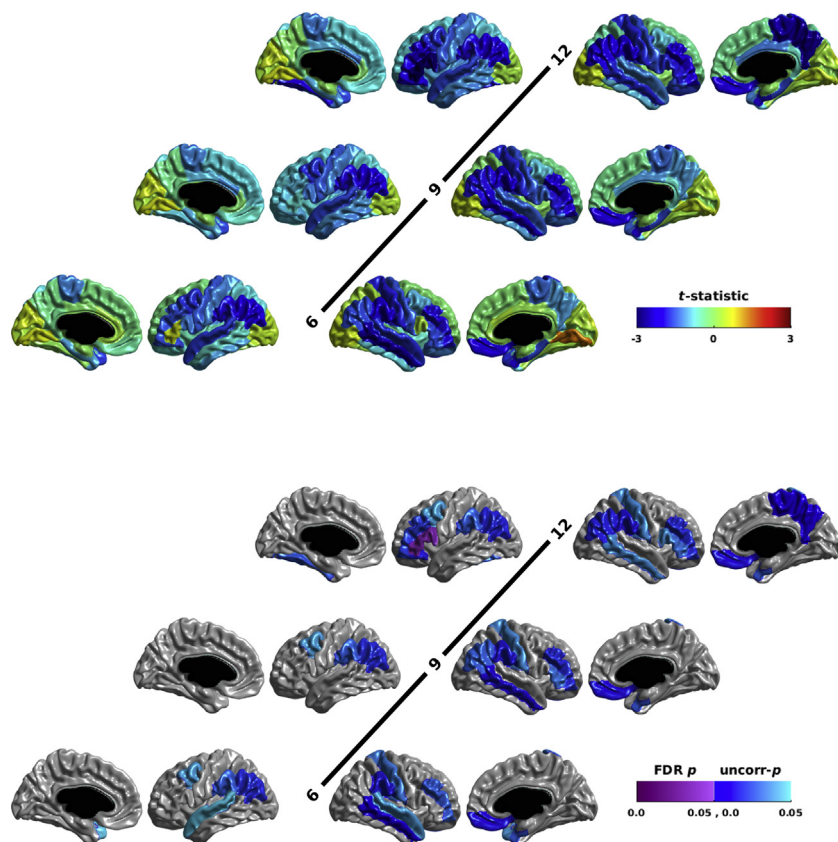
Figure 2. The group differences in nodal global efficiency for high-risk infants diagnosed with autism spectrum disorder vs. high-risk infants diagnosed as not having autism spectrum disorder and low-risk infants diagnosed as not having autism spectrum disorder assessed at 6, 9, and 12 months of age. The *t* statistic is shown in the top half of the figure; the *p* statistic is shown in the bottom half. Reduced efficiency in high-risk infants diagnosed with autism spectrum disorder yields a negative *t* statistic (blue); increased efficiency yields a positive *t* statistic (red). The *p* statistic maps show both the *p* values that survive a false discovery rate (FDR) correction for multiple comparisons (purple), as well as those that are significant uncorrected, but do not survive multiple comparison correction (blue). Each row shows the results for the left hemisphere on the left and the right hemisphere on the right. The medial views for the left hemisphere are furthest to the left; the medial views for the right hemisphere are furthest to the right. Age is indicated in the center of each row. Note that false discovery rate–significant reductions in nodal global efficiency in high-risk infants diagnosed with autism spectrum disorder are seen in Broca's area at 12 months of age.

By 12 months of age, there were FDR significant inverse relations in bilateral somatosensory cortex, the left motor cortex, and supplementary motor cortex, as well as Broca's area and its right hemisphere homologue, the bilateral supramarginal and angular gyri, and the right precuneus, medial orbitofrontal cortex, and middle frontal gyrus. The emergence of the additional relations seen at 12 months of age in Broca's area and its right hemisphere homologue, as well as the left motor cortex and right precuneus and medial orbitofrontal cortex, are again reflected in an age × sex × severity^2 interaction term in the models for these regions.

Notably, both for the analyses of the group differences in efficiency and for the relation of efficiency to symptom severity, the best-fit model for the majority of nodes included age as a covariate, and in all cases, age was significantly positively related to efficiency.

DISCUSSION

Our previous analysis of network efficiency in 24-month-olds showed reductions in efficiency in ASD and an inverse relation between efficiency and symptom severity within the high-risk group. Our goal in the current analysis was to map the emergence of these network inefficiencies during the first year of life in infants who go on to develop ASD, in order to identify more precisely where and when these inefficiencies first appear. Our results show inefficiencies already present at 6 months of age in regions associated with auditory processing, and by 12 months

of age in additional regions known to be involved in low-level processing and integration, as well as Broca's area, a region involved in more abstract aspects of language processing. In addition, across high-risk infants, lower network efficiency at 6 months of age in regions encompassing primary and secondary auditory areas was associated with greater 24-month symptom severity; and over the next 6 months, visual, somatosensory, and motor areas, as well as areas involved in sensory integration and higher-level processing (e.g., Broca's and Wernicke's areas), also became associated with 24-month symptom severity. Children and adults with ASD, and in the broader autism phenotype, commonly have abnormalities in motor behaviors, responses to tactile, auditory, and visual stimuli, and in their processing of language and nonlinguistic social stimuli (e.g., faces) as well as in higher-level cognitive processes [e.g., executive function (45–48,50–60)]. Both this pattern of emergence of reductions in efficiency in infants who go on to develop ASD and the pattern of emergence of inverse relations between efficiency and 24-month symptom severity are consistent with the conjecture that some of the most developmentally proximal deficits in ASD, and in the broader autism phenotype, are in low-level sensory processing (61) rather than higher-level cognitive processes (14,62,63), and that abnormalities in higher-level processes (e.g., language) stem from these low-level inefficiencies. It should be noted, however, that inclusion of the cerebellum and subcortical regions in the analysis may alter the results, particularly given their importance in sensory and motor processing (64–66).
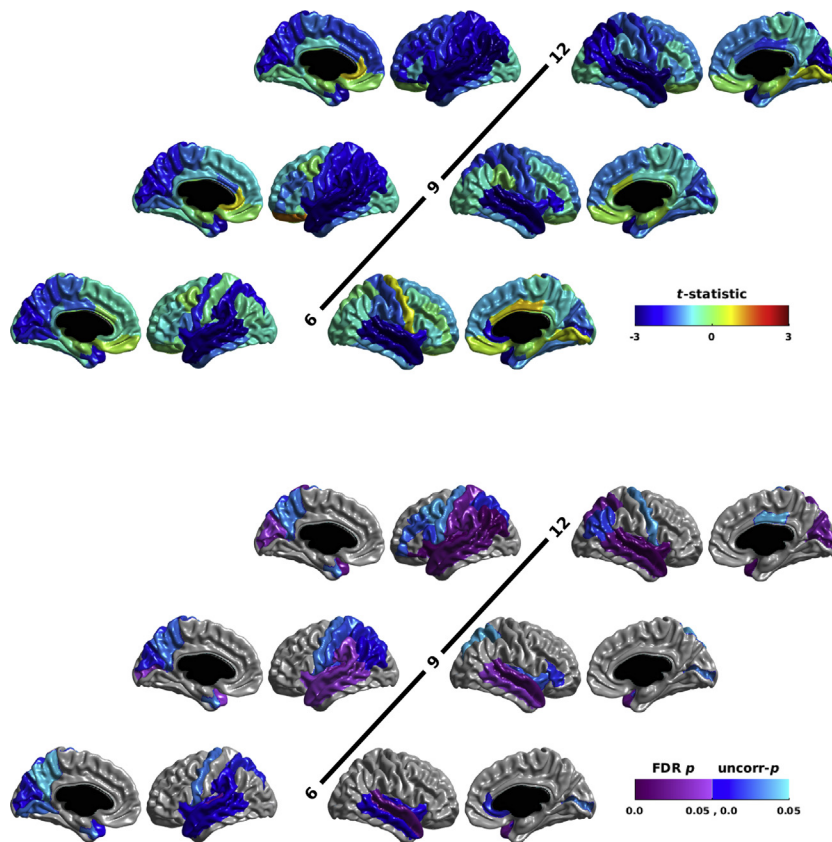
Figure 3. The relation of autism severity scores to nodal local efficiency in the high-risk infants, assessed within linear mixed effects models at 6, 9, and 12 months of age. The *t* statistic is shown in the top half of the figure; the *p* statistic is shown in the bottom half. A positive correlation between efficiency and severity yields a positive *t* statistic (red); an inverse relation between efficiency and severity yields a negative *t* statistic (blue). The *p* statistic maps show both the *p* values that survive a false discovery rate (FDR) correction for multiple comparisons (purple), as well as those that are significant uncorrected but do not survive multiple comparison correction (blue). Each row shows the results for the left hemisphere on the left and the right hemisphere on the right. The medial views for the left hemisphere are furthest to the left; the medial views for the right hemisphere are furthest to the right. Age is indicated in the center of each row. Note that there are false discovery rate–significant inverse relations between autism severity and nodal local efficiency at 6 months of age in primary auditory cortex, and that by 12 months of age there are also inverse relations in visual and somatosensory regions, as well as the insula.

We have suggested that findings reported for cohorts that included older children, adolescents, or adults would, at least in part, reflect cascade effects of earlier abnormalities in neural circuitry and behavioral abnormalities, rather than representing the primary neural underpinnings of the disorder. Our previous analysis of network efficiency in 24-month-olds reduced the possibility that the observed abnormalities were contaminated by cascade effects from earlier neuropathology or behavioral abnormalities, but did not eliminate that possibility (6). The current analysis further reduces that possible confound. The fact that significant reductions in efficiency are seen in infants with ASD by 6 months of age indicates that neural abnormalities are present before the onset of the defining behavioral features of autism. To date, infant studies have not been able to identify behavioral markers of the defining features of ASD before 12 months of age (67–70). In addition, within the Infant Brain Imaging Study sample, the HR infants with ASD show no abnormalities in the social communication or repetitive behaviors domains at 6 months of age (28); however, those with high 24-month severity scores do show abnormalities in sensorimotor behaviors (28). This appears to be reflected in the pattern of reductions in efficiency at 6 months of age. Though there are reductions in efficiency already at 6 months of age in HR infants with ASD, those reductions are only associated with primary auditory cortex and the superior and middle temporal gyri; likewise, efficiency at 6 months of age is associated with 24-month symptom severity only for the primary auditory cortex and the superior temporal gyrus. These results suggest

that reductions in efficiency in frontal regions (71) typically associated with higher-level cognitive processes (e.g., executive function) may be cascade effects from these earlier deficits in regions supporting lower-level processing of sensory inputs (61). Such cascade effects might underlie findings of parametric relationships between social communicative symptoms of autism and brain responses in nonsocial perceptual decision tasks (72). Inefficiencies in regions associated with higher-level cognitive functions might, of course, arise independently, potentially because of the same neuropathology effecting regions involved in low-level sensory processing (61); but neural abnormalities that yield basic level deficits early in development are likely to have cascade effects over developmental time through interactions within the brain, altered interactions with the environment, and altered gene expression (73).

It is important to note, however, that regional differences in efficiency indicate differences not in the nodes themselves but in the networks associated with those nodes. Therefore, reduced efficiency in early sensory processing regions does not mean that those regions, in isolation, are deficient; but rather that the structure of the network is less optimal for those regions. In addition, nodal local and nodal global efficiency are not simply indices of connectivity, implying abnormalities in short- and long-range connectivity, respectively. The reductions in both nodal local and nodal global efficiency in HR^POS infants more likely reflect a more random configuration than seen in the non-ASD infants, having less of the modular structure seen in the typical mature brain. Reductions in nodal
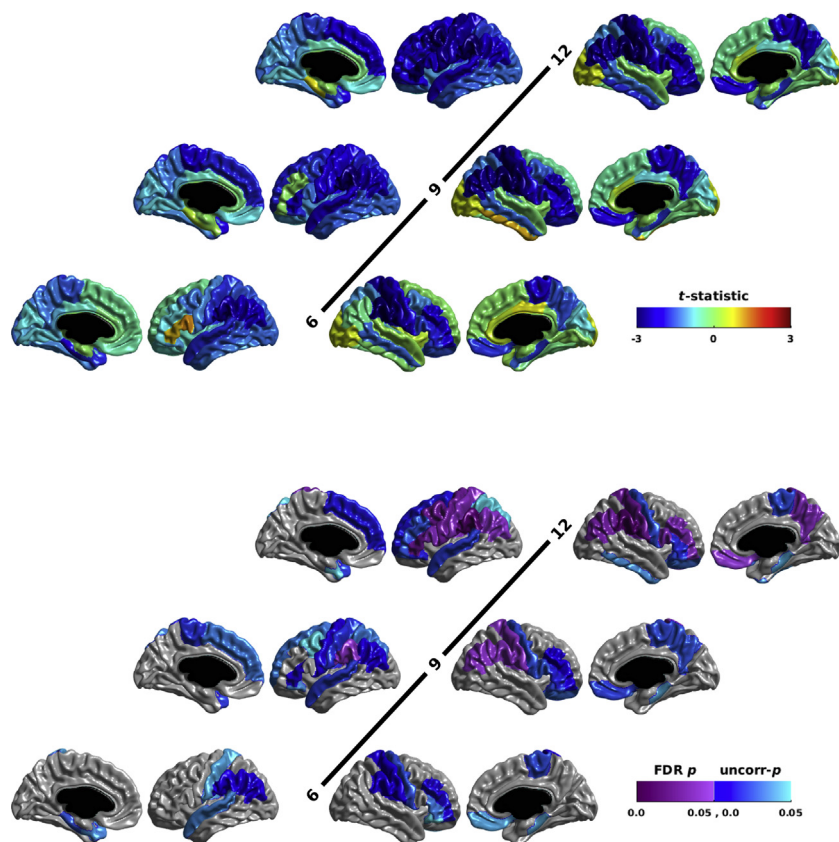
Figure 4. The relation of autism severity scores to nodal global efficiency in the high-risk infants, assessed within linear mixed-effects models at 6, 9, and 12 months of age. The t statistic is shown in the top half of the figure; the p statistic is shown in the bottom half. A positive correlation between efficiency and severity yields a positive t statistic (red); an inverse relation between efficiency and severity yields a negative t statistic (blue). The p statistic maps show both the p values that survive a false discovery rate (FDR) correction for multiple comparisons (purple), as well as those that are significant uncorrected but do not survive multiple comparison correction (blue). Each row shows the results for the left hemisphere on the left and the right hemisphere on the right. The medial views for the left hemisphere are furthest to the left; the medial views for the right hemisphere are furthest to the right. Age is indicated in the center of each row. Note that there are false discovery rate–significant inverse relations between autism severity and nodal global efficiency by 9 months of age in areas involved in somatosensory processing and language processing, and that by 12 months of age there are inverse relations in a more extensive set of language areas, including Broca's area and its right hemisphere homologue, as well as areas involved in motor processing and more abstract aspects of cognition.

local efficiency suggest that corticocortical organization is deficient with respect to the spatial clustering required for rapid processing, whereas reductions in nodal global efficiency suggest that corticocortical organization is deficient with respect to the long-range connectivity that provides for integration of information between different brain regions. The results here indicate that the first deficits in corticocortical organization in infants with ASD are in terms of forming spatially local clusters of regions with strong interconnectivity—specifically clusters including regions involved in auditory processing. We speculate that these deficits in spatial clustering may then lead to reductions in integration with more spatially distant regions (e.g., between temporal or occipital lobe areas involved in low-level processing and frontal lobe areas involved in higher-level processing).

This is not to suggest, however, that there is a single etiology of these initial local deficits. The multitude of genetic mutations associated with autism (74), as well as the behavioral heterogeneity of the disorder, argue otherwise. Nor is it to suggest that the underlying processes are themselves necessarily spatially local; in fact, that reduced nodal local efficiency at 12 months is associated with increased symptom severity at 24 months in regions associated with auditory, visual, and somatosensory processing suggests a general deficit. Multiple mechanisms might alter development timing to yield such an outcome. Children with ASD show reduced developmental synaptic pruning (75,76). Such a decrease in synaptic pruning will hamper the axonal remodeling that refines the massively

exuberant connectivity produced prenatally, resulting in inefficient overconnectivity. Alterations in neurotrophic factors might also yield such an outcome (77). Abnormalities in attention or social reward might also impact neural processing, and in turn, structure (78). The fact that these associations appear first in regions involved in low-level processing may reflect only that development proceeds from primary to secondary to tertiary areas (79,80), or that there is less variability in the way these regions are connected with other regions. Once such deficits in low-level processing exist, however, they will propel an altered developmental cascade, with consequences to downstream neural development. Therefore, without early longitudinal data, it will be difficult to determine whether later seen abnormalities are consequences of such a developmental cascade or instead arise independently.

Perhaps even more important than where in the brain these deficits first arise is when they arise. These results indicate that the neuropathology of ASD must originate before 6 months of age. By 6 months of age, HR infants who go on to develop ASD already show deficiencies in corticocortical organization. This is important for several reasons. First, it suggests that neural biomarkers of ASD could be present before 6 months of age, which might allow for identification presymptomatically. Abnormalities within a developing system give rise to further abnormalities; therefore, intervention later in development is operating on a vastly altered neural landscape, and likely therefore meets with limited success (81–84). Intervention should likely begin

as soon as the first signs of abnormality appear and should be theoretically directed to stem the cascade of abnormalities. Preliminary evidence from animal research suggests that intensive auditory behavioral training may be able to limit or eliminate the abnormalities seen here in auditory cortex (85). Second, such early biomarkers, with little contamination from cascade effects, would provide a way to characterize heterogeneity in the neuropathology associated with ASD, and an improved possibility of linking neuropathology to genetic alterations. Third, the presence of abnormalities at 6 months of age narrows the set of possible environmental triggers, improving our chances of identifying such triggers.

However, it bears repeating that the group differences reported here are based on 31 HR[POS] infants, of which only two are female, and 15 provide longitudinal data. The results for the analysis of the relation between efficiency and symptom severity provide supporting evidence, and are based on a larger number of infants (i.e., 184 infants, of which 70 are female, and 81 provide longitudinal data). Nonetheless, larger amounts of longitudinal data from even younger infants will be required to determine more precisely, and with greater certainty, when and where the reductions in efficiency first appear in infants who go on to develop ASD.

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