The Emergence of Network Inefficiencies in Infants With Autism Spectrum Disorder

Supplementary Information

Supplemental Methods and Materials

Participants

Participants were drawn from the Infant Brain Imaging Study (IBIS), an ongoing multisite longitudinal study funded by the National Institutes of Health Autism Centers of Excellence program. IBIS is a study of brain and behavioral development in infants at high familial risk for ASD by virtue of having an older sibling with ASD, as well as a comparison group of infants deemed at low familial risk for ASD by virtue of having no 1st degree relative with ASD or intellectual disability, and an older sibling. IBIS participants were recruited and assessed at four clinical sites (University of North Carolina at Chapel Hill, University of Washington, Children's Hospital of Philadelphia, Washington University in St. Louis); quality control and pre-processing were done at the University of Utah, the University of North Carolina at Chapel Hill, and the Montreal Neurological Institute (McGill University), the Data Coordinating Center. The study was approved by the institutional review boards at all sites. A parent or legal guardian gave informed consent. Exclusionary criteria were: 1) diagnosis or physical signs of specific genetic conditions/syndromes (e.g., fragile X syndrome), 2) significant medical or neurological conditions affecting growth, development or cognition (e.g., CNS infection, seizure disorder, congenital heart disease), 3) sensory impairments such as vision or hearing loss, 4) low birth weight (<2000) or prematurity (<36 weeks gestation), 5) evidence of significant perinatal brain injury or exposure to in-utero neurotoxins (e.g., alcohol, selected prescription medications), 6) non-English speaking families, 7) contraindication for magnetic resonance imaging (e.g., metal implants), 8) adopted children, and 9) family history of first degree relative with intellectual disability (not associated with ASD), psychosis, schizophrenia, or bipolar disorder.

Neuroimaging and behavioral data were collected from high and low familial risk infants at 6, 12, and 24 months of age. The current study utilized all possible 6- and 12-month data for infants, stratified at 24

months based on the presence or absence of an ASD diagnosis. The data acquired included T_1- and T_2-weighted images, and diffusion data. The success-rate for acquisition of each modality was high, but the analysis required all three modalities, and the success rate for obtaining usable data for all three modalities was between 50 and 60 percent at each time-point. Additionally, the low contrast in the 6-month data prohibited successful processing without the support of the 12-month T_1- and T_2-volumes. Thus the usable 6 month data were limited to those subjects for which all modalities were successfully acquired at 6 months, and at least the T_1- and T_2-weighted images were successfully acquired at 12 months; approximately 15 percent of subjects were scanned for the first time at the 12-month time-point. Usable data were acquired from 260 infants: 116 infants with longitudinal data; 33 infants for whom all imaging data was available at 6 months of age and structural but not diffusion data was available at 12-months of age; and 111 infants for whom all imaging data was 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. Descriptive data for the participants are shown in Table 1 in the manuscript. Note that Table 1 includes 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}). One low-risk infant received an ASD diagnosis and was excluded from the current analysis. Note also that the majority of the data are from LR^{NEG} and HR^{NEG} infants, particularly for the females. The 31 HR^{POS} infants, of which only 2 are female, and 15 provide longitudinal data, limit the power of the analysis of group differences. The analysis of the relation between efficiency and symptom severity does not suffer this limitation since it utilizes both the HR^{POS} and HR^{NEG} infants; it involves 184 infants, of which 70 are female, and 81 provide longitudinal data.

Behavioral Assessment

The behavioral test battery included measures of cognitive development, adaptive functioning, and behaviors associated with autism. Developmental level and adaptive functioning were assessed at each time-point using the Mullen Scales of Early Learning (1) and Vineland Scales of Adaptive Behavior-II (2). Participants were also assessed using the Communication and Symbolic Behavior Scales of

Development Profile (CSBS-DP) (3) at 12 and 24 months, and the Autism Diagnostic Observation Schedule (ADOS) (4) at 24 months. A clinical best estimate diagnosis was made by two clinicians based on all available information (e.g., ADOS, Mullen, Vineland) 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 ADOS, as per Gotham et al. (5). Severity ranged from 2 to 9 for the HR^{POS} infants, from 1 to 7 for the HR^{NEG} infants, and from 1 to 5 for the LR^{NEG} infants. Note the overlap in the symptom severity ranges for infants diagnosed with ASD, and those diagnosed as not having ASD, particularly for those with siblings with ASD. 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 (MRI) scans were performed while infants were naturally sleeping. Data were collected at each site on Siemens 3T TIM Trio scanners with 12-channel head coils. Intra- and inter-site reliability was verified (6). T_1-, T_2-, and diffusion-weighted images were collected. T_1-weighted images were acquired using a 3D MPRAGE sequence (resolution = 1.0 x 1.0 x 1.0 mm; TE = 3.16 ms; TR = 2400 ms; matrix = 224 x 256); T_2-weighted images were acquired using a 3D FSE sequence (resolution = 1.0 x 1.0 x 1.0 mm; TE = 499 ms; TR = 3200 ms; matrix = 256 x 256); and diffusion-weighted images were acquired using a 2D echo planar sequence (resolution=2.0 x 2.0 x 2.0; TE=102ms; TR=12800ms; directions=25; b-values: unique values distributed between 0 and 1000s/mm^2). Data were visually quality controlled at the MRI console; if motion artifacts were noted, the scan sequence was repeated to attempt to acquire artifact free data.

The T_1- and T_2-weighted images were subjected to an additional visual quality control during post-processing. The diffusion-weighted images (DWI) were cleaned of motion and other artifacts using DTIPrep (7), which corrects artifacts where possible, and excludes directions from the data when correction is not possible. Rotation less than 0.5 degrees and translation less than 1.98mm was corrected; greater motion was eliminated. Further visual quality control potentially eliminated additional artifacts. If this process excluded more than 20% of the directions for any size subset of the largest b-values, the

dataset was deemed unacceptable. This resulted in the elimination of 24.6% of the 6-month datasets, and 28.4% of the 12-month datasets; there were no between-group differences in this rejection rate. The surviving datasets retained on average 24 of their 25 directions, with no between group differences at either time-point in either data exclusion or quantitative measures of motion. Only datasets with acceptable T_1-, T_2-, and diffusion-weighted images were included in the analysis. In cases with multiple acceptable T_1-, T_2-, or diffusion-weighted images, the best sets of images were manually selected for inclusion in the analysis.

The selected T_1- and T_2-volumes were corrected for geometric distortion (8) and then processed with CIVET, a fully automated structural image analysis pipeline developed at the Montreal Neurological Institute. CIVET corrects intensity non-uniformities using N3 (9); aligns the input volumes to the Talairach-like ICBM-152-nl template (10); classifies the image into white matter, gray matter, cerebrospinal fluid, and background (11, 12); extracts the white-matter and pial surfaces of the cerebrum (13); and warps these to a common surface template (14). The resolution of neither the T_1, T_2, nor diffusion data are sufficient to allow for accurate tractography within the cerebellum, so the analysis was restricted to the cerebrum. 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 T_1- and T_2-volumes could be successfully processed by CIVET; the 12-month T_1-volumes were registered to the 6-month T_1-volumes, and the linear and non-linear transformations were used to warp the CIVET results from the 12-month data to the 6-month data.

The CIVET results were used to construct the seed, stop, and target masks for use with FSL's *probtrackx* (15). Seed masks specify the voxels from which tracts propagate; seed masks were the entire white-matter. Stop masks specify where tract propagation is halted; stop masks were the voxels on the boundary of the white-matter. Target masks determine the interpretation of tracts; target masks consisted of the cortical labels of the DKT40 surface parcellation (16), as well as subcortical labels defined on a template derived from pediatric data (17).

Following artifact rejection and motion correction with DTIPrep (7), the DWI were unwarped to the distortion-corrected T_2-volume via non-linear registration. Two copies of these data were then

preprocessed for probabilistic tractography with FSL's *bedpostx* (15): 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, so as to mitigate the effects of the distance bias inherent in probabilistic tractography. A multiexponential model was used in bedpostx (18), with a maximum of 2 fibers per voxel, and a multiplicative factor of 0 on the prior for the second fiber; default settings were used for all other parameters. The unwarped diffusion volumes were affine registered to the T_1-volumes in stereotaxic space using FSL's *flirt* (19) to provide the mapping from the seed, stop, and target masks to either diffusion space. Probabilistic tractography, utilizing FSL's *probtrackx* was then seeded from each voxel of the seed masks, with and without distance-bias correction (15, 20), both in native and in 12-month standard space. Streamline propagation is bi-directional, stopping when the tract enters the stop mask. This so-called 'brute-force' seeding approach has been shown to increase the validity of probabilistic tractography results (21). To further ensure the validity of the probabilistic estimates, samples were generated from 20000 random positions within each voxel. Further, the 'loopcheck' option was used to eliminate tracts that pass through the same point twice. The defaults were used for all other settings. The 'omatrix3' option was used, and so a connection between the voxels at either end of each tract generated is recorded, if those voxels are both within the target mask. This approach produces a list of voxel-to-voxel connectivity within the target mask, which includes all cortical regions. 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'. Note that, at least for the atlas used here, there were no group differences in regional stereotaxic-space surface area, nor were these measures related to symptom severity.

Analysis

We performed a longitudinal analysis of network efficiency utilizing the methods developed in our previously reported analysis of the 24-month data (22). Our definition of network efficiency is based on that of Latora and Marchiori (23). They defined the efficiency ε_{ij} in the communication between nodes *i* and *j* to be inversely proportional to the shortest path length d_{ij} between nodes *i* and *j*. The shortest path length d_{ij} was defined as the smallest sum of the physical distances from node to node along the path, evaluated over all of the possible paths from *i* to *j* in the network. The efficiency of a network, *G*, was defined as the average of the efficiency of communication between all pairs of nodes in G, or more precisely

$$E(G) = \frac{\sum_{i \neq j \in G} \varepsilon_{ij}}{N(N-1)} = \frac{1}{N(N-1)} \sum_{i \neq j \in G} \frac{1}{d_{ij}}$$

where ε_{ij} is the efficiency of the connection between nodes *i* and *j* ; *N* is the number of nodes in the network graph *G* ; and d_{ij} is the length of the shortest path, in terms of physical distances, between nodes *i* and *j*. This measure is normalized by $E(G_{IDEAL})$, the efficiency of the fully connected network. This formulation of efficiency takes into account the physical distances involved in information transfer, and so presumably relates more closely to the neurobiological substrates than does the pure graph theoretic version, which assesses only the topological properties of networks (24-26).

Latora and Marchiori (23) applied this formulation to both the entire network and to the subnetworks of the immediate neighbors of each node. They defined *global efficiency* as *E*(*G*), where *G* is the entire network; they defined *local efficiency* as the mean of $E(G_i)$, for all nodes *i*, where G_i is the subgraph of all the neighbors of node *i*. These definitions give a single measure of *local efficiency* and of *global efficiency* for the entire network, which may conceal interesting regional or nodal differences. Moreover, these definitions treat connections in a binarized fashion, whereas the strengths of the connections in the brain are critical to an accurate assessment of its efficiency (27). We therefore created a version of these measures that dissects the averages to provide *nodal global efficiency* and *nodal local efficiency*, and

incorporates connection strengths. Based on Rubinov and Sporns (25), 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,* thus 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 (25), 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. As per Latora and Marchiori (23), these measures are normalized by considering the fully connected network.

Note that *nodal local efficiency* is defined in terms of the neighbors of a given node in the graph-theoretic sense of 'neighbor', *i.e.* non-spatially. The neighbors of a node *i*, in Latora and Marchiori (23) original formulation, were those nodes to which *i* was directly connected. The weighted formulation used here counts nodes as neighbors according to the strength of the connection between them. Connection strength has a tendency to decline with distance, so graph-theoretic 'local' tends toward spatially local, but the two meanings should not be conflated.

Differences in *nodal local efficiency* and *nodal global efficiency* between infants with ASD versus 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. Mixed-effects models utilize the longitudinal aspect of the data, accommodate missing data, and handle uneven spacing of repeated measurements (28). Since different regions of the brain mature at different rates, and differently by sex, model selection was region specific (29, 30). At each node, the best model was determined by the Akaike information criterion (AIC) with the data centered at 9 months of age (31, 32). 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 AIC value amongst those for which the residuals were normally distributed. Group differences were assessed across time in order to evaluate how the models differed by group over development. This was done by evaluating the group differences with the data centered at successive ages, a technique introduced by Shaw et al. (33). Note that this is a longitudinal analysis, with the trajectories of efficiency established via mixed effects models. 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 (34-37), we assessed the relation between the measures of network efficiency and the ADOS calibrated severity scores (5) across all high-risk infants. This was also assessed at each node within the model with the lowest AIC value amongst those for which the residuals were normally distributed; 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 utilize a false discovery rate (FDR) correction for multiple comparisons (38).

Supplemental Results

The following tables provide the *t*- and *p*-statistics corresponding to the results shown in Figures 1 through 4 in the manuscript.

Table S1. Regional statistics for group differences in nodal local efficiency. The regions of the atlas are listed in the left column. The *t*- and *p*- statistics for each region are shown to the right at each of 6, 9, and 12 months. Results that are significant without correction for multiple comparisons are shown in blue. Results that are significant with correction for multiple comparisons are shown in bold purple.

	6 months		9 months		12 months	
	t	***p***	***t***	***p***	***t***	***p***
Left Caudal Middle Frontal Gyrus	-1.16	0.123	-1.16	0.123	-1.06	0.145
Left Entorhinal Cortex	-1.88	0.030	-1.82	0.034	-1.82	0.034
Left Postcentral Gyrus	-1.84	0.034	-1.84	0.034	-1.77	0.038
Left Lateral Frontal Triangularis	-1.03	0.152	-1.03	0.152	-1.03	0.152
Left Supramarginal Gyrus	-2.11	0.018	-2.11	0.018	-2.07	0.020
Left Insula	-2.32	0.010	-2.32	0.010	**-3.27**	**0.001**
Left Lateral Orbitofrontal Gyrus	0.52	0.302	-0.23	0.411	-1.47	0.071
Left Lateral Frontal Orbitalis	-0.09	0.466	-1.33	0.092	-2.60	0.005
Left Middle Temporal Gyrus	-1.63	0.052	-2.36	0.009	-2.31	0.011
Left Pericalcarine	-1.25	0.105	-1.25	0.105	-1.25	0.105
Left Parahippocampal Gyrus	-0.05	0.479	-0.25	0.401	-0.19	0.423
Left Paracentral Gyrus	-1.06	0.146	-1.06	0.146	-1.02	0.154
Left Medial Orbitofrontal Gyrus	-0.34	0.368	-0.67	0.252	-0.62	0.267
Left Cuneus	-1.11	0.134	-1.11	0.134	-1.06	0.146
Left Inferior Temporal	-0.83	0.205	-1.19	0.118	-1.27	0.103
Left Rostral Middle Frontal Gyrus	-0.84	0.200	-1.19	0.118	-1.19	0.118
Left Rostral Anterior Cingulate	-0.03	0.487	-0.03	0.487	-0.03	0.487
Left Isthmus Cingulate Gyrus	0.38	0.351	0.38	0.351	0.50	0.307
Left Inferior Occipital Cortex	-0.09	0.465	-0.09	0.465	-0.09	0.465
Left Lingual Gyrus	-0.44	0.332	-0.41	0.342	-0.35	0.362
Left Superior Parietal Lobule	-1.23	0.110	-1.23	0.110	-1.18	0.120
Left Lateral Frontal Opercularis	-1.81	0.035	-1.71	0.044	-1.71	0.044
Left Fusiform Gyrus	-0.44	0.332	-0.44	0.332	-0.44	0.332
Left Caudal Anterior Cingulate Gyrus	-0.79	0.214	-1.59	0.056	-1.00	0.159
Left Superior Frontal Gyrus	-1.22	0.112	-1.22	0.112	-1.19	0.118
Left Precuneus	-1.37	0.085	-1.37	0.085	-1.34	0.091
Left Transverse Temporal Gyrus	-1.57	0.058	**-2.84**	**0.002**	**-3.74**	**0.000**
Left Precentral Gyrus	-2.14	0.017	-2.14	0.017	-2.09	0.019
Left Inferior Parietal Lobule	-1.04	0.149	-1.04	0.149	-1.02	0.154
Left Posterior Cingulate Gyrus	-0.36	0.361	-0.36	0.361	-0.36	0.361
Left Superior Temporal Gyrus	-1.19	0.118	-2.47	0.007	-2.44	0.007
Right Caudal Middle Frontal Gyrus	-0.26	0.399	-0.26	0.399	-0.20	0.420
Right Entorhinal Cortex	-1.57	0.058	-1.57	0.058	-1.57	0.058
Right Postcentral Gyrus	-1.42	0.079	-1.42	0.079	-1.36	0.087
Right Lateral Frontal Triangularis	-1.45	0.074	-1.51	0.066	-1.29	0.099
Right Supramarginal Gyrus	-1.37	0.086	-2.03	0.022	-1.99	0.024
Right Insula	-2.47	0.007	-2.37	0.009	-2.33	0.010
Right Lateral Orbitofrontal Gyrus	-0.48	0.316	-0.48	0.316	-0.39	0.347
Right Lateral Frontal Orbitalis	-1.46	0.073	-1.20	0.115	-0.96	0.168
Right Middle Temporal Gyrus	**-2.91**	**0.002**	**-2.91**	**0.002**	**-2.91**	**0.002**
Right Pericalcarine	-1.73	0.042	-1.73	0.042	-2.52	0.006
Right Parahippocampal Gyrus	-0.24	0.404	-0.24	0.404	-0.24	0.404
Right Paracentral Gyrus	-0.48	0.317	-0.48	0.317	-0.43	0.335
Right Medial Orbitofrontal Gyrus	0.20	0.419	-0.15	0.439	-0.15	0.439
Right Cuneus	-1.56	0.060	-1.56	0.060	-1.53	0.064
Right Inferior Temporal Gyrus	-1.01	0.157	-1.06	0.145	-1.14	0.127
Right Rostral Middle Frontal Gyrus	-0.25	0.403	-0.53	0.300	-0.70	0.242
Right Rostral Anterior Cingulate Gyrus	-1.03	0.153	-1.28	0.101	-1.28	0.101
Right Isthmus Cingulate Gyrus	-0.20	0.423	-0.20	0.423	-0.95	0.171
Right Inferior Occipital Cortex	0.32	0.376	0.32	0.376	-0.12	0.453
Right Lingual Gyrus	0.19	0.423	0.19	0.423	0.19	0.423
Right Superior Parietal Gyrus	-1.51	0.066	-1.51	0.066	-1.46	0.072
Right Lateral Frontal Opercularis	-0.56	0.289	-1.48	0.070	-0.24	0.406
Right Fusiform Gyrus	-1.93	0.027	-2.14	0.016	-2.39	0.009
Right Caudal Anterior Cingulate Gyrus	0.99	0.161	-1.15	0.126	-0.30	0.382
Right Superior Frontal Gyrus	-1.07	0.143	-1.30	0.097	-1.27	0.103
Right Precuneus	-0.11	0.457	-0.50	0.308	-0.86	0.196
Right Transverse Temporal Gyrus	**-2.88**	**0.002**	**-2.88**	**0.002**	**-2.88**	**0.002**
Right Precentral Gyrus	-1.35	0.089	-1.17	0.122	-1.12	0.132
Right Inferior Parietal Lobule	-0.12	0.451	-0.12	0.451	-0.52	0.303
Right Posterior Cingulate Gyrus	-0.58	0.282	-0.81	0.210	-0.49	0.313
Right Superior Temporal Gyrus	**-3.14**	**0.001**	**-3.14**	**0.001**	**-3.14**	**0.001**

Table S2. Regional statistics for group differences in nodal global efficiency. The regions of the atlas are listed in the left column. The *t*- and *p*- statistics for each region are shown to the right at each of 6, 9, and 12 months. Results that are significant without correction for multiple comparisons are shown in blue. Results that are significant with correction for multiple comparisons are shown in bold purple.

	6 months		9 months		12 months	
	t	*p*	*t*	*p*	*t*	*p*
Left Caudal Middle Frontal Gyrus	-1.77	0.039	-1.77	0.039	-1.77	0.039
Left Entorhinal Cortex	-1.03	0.151	-1.03	0.151	-1.11	0.134
Left Postcentral Gyrus	-1.23	0.110	-1.23	0.110	-1.23	0.110
Left Lateral Frontal Triangularis	0.63	0.264	-0.69	0.245	**-3.24**	**0.001**
Left Supramarginal Gyrus	-1.96	0.025	-1.96	0.025	-1.96	0.025
Left Insula	-0.50	0.307	-0.76	0.225	-1.04	0.150
Left Lateral Orbitofrontal Gyrus	-0.69	0.247	-0.92	0.180	-1.10	0.135
Left Lateral Frontal Orbitalis	-1.62	0.053	-1.04	0.149	-2.22	0.014
Left Middle Temporal Gyrus	-0.67	0.251	-1.11	0.134	-1.14	0.129
Left Pericalcarine	0.28	0.391	0.28	0.391	0.28	0.391
Left Parahippocampal Gyrus	-1.07	0.144	-1.04	0.150	-1.04	0.150
Left Paracentral Gyrus	-1.24	0.108	-1.24	0.108	-1.27	0.102
Left Medial Orbitofrontal Gyrus	-0.38	0.352	-0.59	0.279	-0.72	0.235
Left Cuneus	0.54	0.294	0.54	0.294	0.52	0.302
Left Inferior Temporal	-1.08	0.140	-1.28	0.100	-1.28	0.100
Left Rostral Middle Frontal Gyrus	-1.58	0.058	-0.94	0.173	-2.07	0.019
Left Rostral Anterior Cingulate	0.22	0.415	-0.10	0.460	-0.10	0.460
Left Isthmus Cingulate Gyrus	-0.31	0.379	-0.31	0.379	-0.31	0.379
Left Inferior Occipital Cortex	0.41	0.342	0.35	0.363	0.22	0.413
Left Lingual Gyrus	0.64	0.260	0.64	0.260	0.64	0.260
Left Superior Parietal Lobule	-0.79	0.216	-0.79	0.216	-0.82	0.206
Left Lateral Frontal Opercularis	-1.27	0.103	-1.27	0.103	**-3.08**	**0.001**
Left Fusiform Gyrus	0.06	0.476	-0.85	0.197	-1.97	0.025
Left Caudal Anterior Cingulate Gyrus	0.21	0.417	-1.23	0.109	-1.29	0.099
Left Superior Frontal Gyrus	-0.21	0.415	-0.80	0.211	-0.80	0.213
Left Precuneus	-0.27	0.392	-0.27	0.392	-0.06	0.475
Left Transverse Temporal Gyrus	-0.56	0.288	-1.24	0.108	-1.24	0.108
Left Precentral Gyrus	-1.51	0.066	-1.51	0.066	-1.51	0.066
Left Inferior Parietal Lobule	-2.14	0.016	-2.14	0.016	-2.18	0.015
Left Posterior Cingulate Gyrus	-0.07	0.470	-0.95	0.171	-1.00	0.159
Left Superior Temporal Gyrus	-1.71	0.044	-1.62	0.053	-1.62	0.053
Right Caudal Middle Frontal Gyrus	-1.00	0.160	-0.87	0.191	-0.87	0.191
Right Entorhinal Cortex	-1.97	0.025	-1.97	0.025	-1.97	0.025
Right Postcentral Gyrus	-1.87	0.031	-1.81	0.035	-1.81	0.035
Right Lateral Frontal Triangularis	-1.62	0.053	-1.89	0.030	-1.89	0.030
Right Supramarginal Gyrus	-2.24	0.013	-2.24	0.013	-2.28	0.012
Right Insula	-0.59	0.277	-0.01	0.497	-0.04	0.486
Right Lateral Orbitofrontal Gyrus	-1.23	0.109	-1.35	0.089	-1.63	0.053
Right Lateral Frontal Orbitalis	-1.53	0.064	-1.37	0.085	-1.56	0.059
Right Middle Temporal Gyrus	-2.60	0.005	-2.29	0.011	-1.81	0.036
Right Pericalcarine	0.03	0.488	-0.04	0.484	0.03	0.489
Right Parahippocampal Gyrus	-1.62	0.053	-1.62	0.053	-1.62	0.053
Right Paracentral Gyrus	-1.36	0.087	-1.36	0.087	-2.54	0.006
Right Medial Orbitofrontal Gyrus	-2.30	0.011	-2.30	0.011	-2.30	0.011
Right Cuneus	0.28	0.389	0.28	0.389	0.24	0.404
Right Inferior Temporal Gyrus	-0.81	0.208	-1.08	0.141	-0.94	0.173
Right Rostral Middle Frontal Gyrus	-1.95	0.026	-2.15	0.016	-2.15	0.016
Right Rostral Anterior Cingulate Gyrus	0.11	0.457	-0.16	0.436	-0.16	0.436
Right Isthmus Cingulate Gyrus	-0.01	0.498	-0.62	0.269	-0.62	0.269
Right Inferior Occipital Cortex	0.53	0.297	0.53	0.297	0.53	0.297
Right Lingual Gyrus	1.45	0.074	0.47	0.320	0.47	0.320
Right Superior Parietal Gyrus	0.28	0.392	-0.12	0.453	-0.44	0.328
Right Lateral Frontal Opercularis	0.30	0.382	-1.40	0.082	-1.80	0.036
Right Fusiform Gyrus	0.20	0.421	0.20	0.421	0.20	0.421
Right Caudal Anterior Cingulate Gyrus	0.33	0.372	-1.04	0.149	-1.25	0.107
Right Superior Frontal Gyrus	-0.11	0.455	-0.29	0.386	-0.33	0.372
Right Precuneus	-1.10	0.136	-1.10	0.136	-2.77	0.003
Right Transverse Temporal Gyrus	-0.21	0.415	-1.36	0.087	-1.36	0.087
Right Precentral Gyrus	-1.53	0.063	-1.53	0.063	-1.56	0.059
Right Inferior Parietal Lobule	-1.60	0.056	-1.94	0.026	-2.21	0.014
Right Posterior Cingulate Gyrus	0.11	0.455	-1.15	0.126	-1.31	0.096
Right Superior Temporal Gyrus	-1.78	0.038	-1.45	0.075	-1.22	0.112

Table S3. Regional statistics for severity and nodal local efficiency. The regions of the atlas are listed in the left column. The *t*- and *p*- statistics for each region are shown to the right at each of 6, 9, and 12 months. Results that are significant without correction for multiple comparisons are shown in blue. Results that are significant with correction for multiple comparisons are shown in bold purple.

	6 months		9 months		12 months	
	t	***p***	***t***	***p***	***t***	***p***
Left Caudal Middle Frontal Gyrus	0.62	0.269	-0.04	0.482	-1.78	0.038
Left Entorhinal Cortex	-1.87	0.032	-1.85	0.033	-1.85	0.033
Left Postcentral Gyrus	-0.29	0.387	-2.00	0.023	**-2.54**	**0.006**
Left Lateral Frontal Triangularis	-0.82	0.206	-0.82	0.206	-0.82	0.206
Left Supramarginal Gyrus	-2.54	0.006	**-2.54**	**0.006**	**-2.47**	**0.007**
Left Insula	-2.41	0.008	**-2.63**	**0.005**	**-3.36**	**0.000**
Left Lateral Orbitofrontal Gyrus	-0.08	0.470	1.39	0.082	0.00	0.499
Left Lateral Frontal Orbitalis	-0.26	0.399	-0.33	0.370	**-3.11**	**0.001**
Left Middle Temporal Gyrus	-2.77	0.003	**-2.77**	**0.003**	**-2.77**	**0.003**
Left Pericalcarine	-2.49	0.007	**-2.49**	**0.007**	**-2.49**	**0.007**
Left Parahippocampal Gyrus	-0.37	0.357	-0.37	0.357	-0.36	0.359
Left Paracentral Gyrus	-1.37	0.085	-1.37	0.085	-1.35	0.089
Left Medial Orbitofrontal Gyrus	0.26	0.397	0.01	0.495	0.01	0.495
Left Cuneus	-2.26	0.012	-2.26	0.012	-2.24	0.013
Left Inferior Temporal	-1.37	0.086	-1.37	0.086	-1.37	0.086
Left Rostral Middle Frontal Gyrus	-0.69	0.244	-1.37	0.086	-1.96	0.026
Left Rostral Anterior Cingulate	-0.46	0.325	0.81	0.210	0.90	0.185
Left Isthmus Cingulate Gyrus	-0.83	0.205	-0.83	0.205	-0.75	0.228
Left Inferior Occipital Cortex	-0.57	0.283	-0.57	0.283	-0.57	0.283
Left Lingual Gyrus	-1.87	0.031	-1.33	0.093	-0.38	0.353
Left Superior Parietal Lobule	-2.21	0.014	-2.21	0.014	-2.18	0.015
Left Lateral Frontal Opercularis	-1.26	0.104	-1.45	0.075	-2.08	0.019
Left Fusiform Gyrus	-0.52	0.301	-0.52	0.301	-0.49	0.314
Left Caudal Anterior Cingulate Gyrus	0.05	0.481	-1.55	0.061	-1.61	0.054
Left Superior Frontal Gyrus	-0.52	0.301	-0.78	0.219	-1.63	0.052
Left Precuneus	-1.72	0.044	-1.91	0.029	-1.91	0.029
Left Transverse Temporal Gyrus	**-3.36**	**0.000**	**-3.49**	**0.000**	**-3.99**	**0.000**
Left Precentral Gyrus	-1.88	0.031	-1.88	0.031	-1.82	0.035
Left Inferior Parietal Lobule	-0.42	0.337	-2.41	0.008	**-3.25**	**0.001**
Left Posterior Cingulate Gyrus	-0.43	0.333	-0.43	0.333	-0.40	0.346
Left Superior Temporal Gyrus	-2.62	0.005	**-2.83**	**0.003**	**-2.83**	**0.003**
Right Caudal Middle Frontal Gyrus	-0.47	0.320	-0.68	0.248	-1.42	0.078
Right Entorhinal Cortex	-1.53	0.064	-1.53	0.064	-1.53	0.064
Right Postcentral Gyrus	-1.53	0.063	-1.53	0.063	-1.45	0.074
Right Lateral Frontal Triangularis	-0.73	0.234	-0.90	0.184	-1.40	0.082
Right Supramarginal Gyrus	-1.34	0.091	-0.06	0.478	-2.00	0.023
Right Insula	-2.38	0.009	-1.97	0.025	**-3.20**	**0.001**
Right Lateral Orbitofrontal Gyrus	-0.08	0.469	-0.08	0.469	0.05	0.479
Right Lateral Frontal Orbitalis	-0.86	0.196	-0.55	0.290	-0.55	0.290
Right Middle Temporal Gyrus	-2.68	0.004	**-2.68**	**0.004**	**-2.68**	**0.004**
Right Pericalcarine	-1.86	0.032	-1.86	0.032	**-2.81**	**0.003**
Right Parahippocampal Gyrus	0.28	0.390	0.28	0.390	0.28	0.390
Right Paracentral Gyrus	-0.61	0.270	-0.61	0.270	-0.53	0.297
Right Medial Orbitofrontal Gyrus	0.38	0.354	0.15	0.440	0.01	0.497
Right Cuneus	-1.38	0.084	-1.55	0.061	**-2.43**	**0.008**
Right Inferior Temporal Gyrus	-1.02	0.155	-1.02	0.155	-1.02	0.155
Right Rostral Middle Frontal Gyrus	-0.15	0.441	-0.41	0.341	-0.56	0.288
Right Rostral Anterior Cingulate Gyrus	-2.17	0.015	-0.13	0.447	-0.44	0.330
Right Isthmus Cingulate Gyrus	-0.36	0.359	-0.36	0.359	-1.14	0.128
Right Inferior Occipital Cortex	-0.47	0.320	-0.47	0.320	-0.47	0.320
Right Lingual Gyrus	0.60	0.273	-0.80	0.214	0.60	0.273
Right Superior Parietal Gyrus	-0.18	0.430	-1.74	0.041	**-2.62**	**0.005**
Right Lateral Frontal Opercularis	-0.53	0.297	-0.75	0.228	-0.75	0.228
Right Fusiform Gyrus	-1.18	0.119	-1.37	0.085	-1.30	0.097
Right Caudal Anterior Cingulate Gyrus	0.76	0.225	0.51	0.305	-1.40	0.082
Right Superior Frontal Gyrus	-0.99	0.161	-1.26	0.105	-1.20	0.115
Right Precuneus	-0.76	0.223	-0.76	0.223	-0.70	0.242
Right Transverse Temporal Gyrus	-2.51	0.006	**-2.51**	**0.006**	**-2.51**	**0.006**
Right Precentral Gyrus	0.72	0.237	-1.58	0.057	-1.79	0.037
Right Inferior Parietal Lobule	-0.58	0.280	-0.58	0.280	-2.08	0.019
Right Posterior Cingulate Gyrus	1.03	0.153	-0.63	0.264	-1.75	0.041
Right Superior Temporal Gyrus	**-3.25**	**0.001**	**-3.25**	**0.001**	**-3.25**	**0.001**

Table S4. Regional statistics for severity and nodal global efficiency. The regions of the atlas are listed in the left column. The *t*- and *p*- statistics for each region are shown to the right at each of 6, 9, and 12 months. Results that are significant without correction for multiple comparisons are shown in blue. Results that are significant with correction for multiple comparisons are shown in bold purple.

	6 months		9 months		12 months	
	t	***p***	***t***	***p***	***t***	***p***
Left Caudal Middle Frontal Gyrus	-1.36	0.088	-1.67	0.048	**-2.93**	**0.002**
Left Entorhinal Cortex	-1.80	0.036	0.16	0.436	-1.68	0.047
Left Postcentral Gyrus	-1.76	0.040	-2.12	0.017	**-2.56**	**0.006**
Left Lateral Frontal Triangularis	1.04	0.149	-2.31	0.011	**-2.91**	**0.002**
Left Supramarginal Gyrus	-2.73	0.003	**-2.91**	**0.002**	**-3.40**	**0.000**
Left Insula	-0.62	0.269	-1.12	0.132	-1.12	0.132
Left Lateral Orbitofrontal Gyrus	-0.68	0.249	-1.08	0.140	-1.35	0.090
Left Lateral Frontal Orbitalis	-1.13	0.130	-1.81	0.036	-2.20	0.015
Left Middle Temporal Gyrus	-1.52	0.065	-1.52	0.065	-1.52	0.065
Left Pericalcarine	-1.02	0.154	-1.16	0.125	-1.36	0.088
Left Parahippocampal Gyrus	-1.97	0.025	0.37	0.355	0.82	0.208
Left Paracentral Gyrus	-1.53	0.063	-2.12	0.018	-1.65	0.050
Left Medial Orbitofrontal Gyrus	-0.43	0.334	-0.79	0.217	-0.70	0.241
Left Cuneus	-0.75	0.226	-0.89	0.187	-1.04	0.149
Left Inferior Temporal	-1.31	0.096	-1.48	0.070	-1.50	0.068
Left Rostral Middle Frontal Gyrus	-0.82	0.208	0.00	0.500	-1.99	0.024
Left Rostral Anterior Cingulate	-0.21	0.416	-0.21	0.416	-0.21	0.416
Left Isthmus Cingulate Gyrus	-1.00	0.158	-1.00	0.158	-1.00	0.158
Left Inferior Occipital Cortex	-1.40	0.082	-1.40	0.082	-1.40	0.082
Left Lingual Gyrus	-0.83	0.204	-0.83	0.204	-0.83	0.204
Left Superior Parietal Lobule	-1.55	0.062	-1.85	0.033	-1.68	0.047
Left Lateral Frontal Opercularis	1.31	0.096	-1.36	0.088	**-2.46**	**0.007**
Left Fusiform Gyrus	-1.20	0.116	-1.20	0.116	-1.20	0.116
Left Caudal Anterior Cingulate Gyrus	-0.12	0.451	-0.12	0.451	-0.12	0.451
Left Superior Frontal Gyrus	-0.33	0.369	-1.87	0.032	-2.26	0.012
Left Precuneus	-1.34	0.092	-1.34	0.092	-1.29	0.100
Left Transverse Temporal Gyrus	-1.12	0.133	-1.43	0.078	-1.35	0.089
Left Precentral Gyrus	-1.23	0.110	-2.36	0.010	**-2.80**	**0.003**
Left Inferior Parietal Lobule	-2.45	0.008	-2.45	0.008	**-2.38**	**0.009**
Left Posterior Cingulate Gyrus	-0.61	0.272	-0.61	0.272	-0.54	0.296
Left Superior Temporal Gyrus	-1.83	0.035	-2.07	0.020	-2.07	0.020
Right Caudal Middle Frontal Gyrus	-1.21	0.114	-1.45	0.074	-1.45	0.074
Right Entorhinal Cortex	-1.44	0.075	-1.44	0.075	-1.44	0.075
Right Postcentral Gyrus	-2.74	0.003	**-2.90**	**0.002**	**-2.94**	**0.002**
Right Lateral Frontal Triangularis	-1.87	0.032	-2.19	0.015	-2.15	0.016
Right Supramarginal Gyrus	-3.06	0.001	**-3.21**	**0.001**	**-3.55**	**0.000**
Right Insula	0.38	0.353	-0.02	0.492	-0.02	0.492
Right Lateral Orbitofrontal Gyrus	-1.53	0.064	-1.89	0.030	-1.89	0.030
Right Lateral Frontal Orbitalis	-1.67	0.048	-2.01	0.023	-2.01	0.023
Right Middle Temporal Gyrus	-1.43	0.078	-1.42	0.078	-1.34	0.091
Right Pericalcarine	-0.51	0.306	-0.72	0.237	-1.22	0.112
Right Parahippocampal Gyrus	-1.74	0.041	-1.74	0.041	-1.74	0.041
Right Paracentral Gyrus	-2.00	0.023	-2.00	0.023	-2.00	0.023
Right Medial Orbitofrontal Gyrus	-1.76	0.040	-2.05	0.021	**-2.32**	**0.011**
Right Cuneus	-0.80	0.213	-0.79	0.215	-0.70	0.244
Right Inferior Temporal Gyrus	-0.07	0.471	1.12	0.131	-1.80	0.036
Right Rostral Middle Frontal Gyrus	-2.32	0.010	-2.55	0.006	**-2.55**	**0.006**
Right Rostral Anterior Cingulate Gyrus	0.47	0.319	0.19	0.427	0.19	0.427
Right Isthmus Cingulate Gyrus	-0.07	0.473	-0.32	0.375	-0.25	0.400
Right Inferior Occipital Cortex	0.59	0.277	0.59	0.277	0.59	0.277
Right Lingual Gyrus	0.01	0.498	-0.19	0.425	-0.13	0.450
Right Superior Parietal Gyrus	-1.14	0.127	-1.30	0.098	-1.19	0.118
Right Lateral Frontal Opercularis	-1.65	0.050	-1.97	0.025	**-2.47**	**0.007**
Right Fusiform Gyrus	-0.24	0.406	-0.24	0.406	-0.24	0.406
Right Caudal Anterior Cingulate Gyrus	0.45	0.327	0.45	0.327	0.45	0.327
Right Superior Frontal Gyrus	-0.03	0.488	-0.39	0.350	-0.31	0.377
Right Precuneus	-1.55	0.061	-1.98	0.024	**-2.47**	**0.007**
Right Transverse Temporal Gyrus	-0.90	0.186	-1.23	0.110	-1.20	0.116
Right Precentral Gyrus	-2.00	0.023	-2.00	0.023	-2.00	0.023
Right Inferior Parietal Lobule	-0.28	0.391	**-2.80**	**0.003**	**-2.73**	**0.003**
Right Posterior Cingulate Gyrus	0.75	0.227	-0.81	0.209	-0.69	0.244
Right Superior Temporal Gyrus	0.10	0.461	-0.12	0.453	-0.06	0.477

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