Supplementary Materials

Fibromyalgia is Characterized by Altered Frontal and Cerebellar Structural Covariance Brain Networks

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Supplementary Methods

Small-worldness

Small-worldness scalar δ was defined by the following equation (Watts and Strogatz, 1998).

$\delta = \gamma / \lambda,$

where $\gamma = C / C_{random}$,

$\lambda = L / L_{random}$,

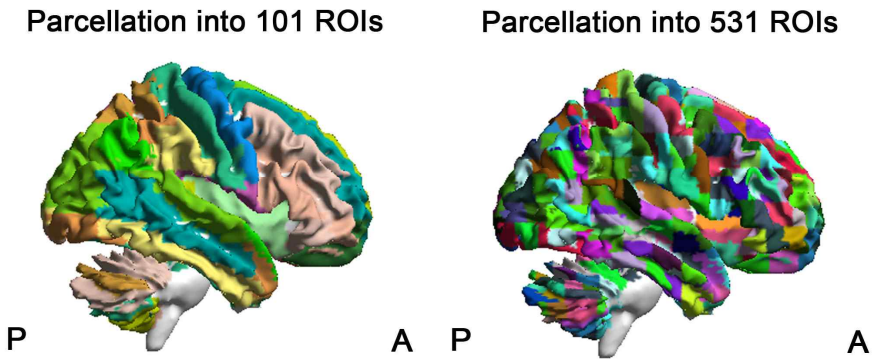
C is the mean clustering coefficient over all nodes in the graph G,

L is the mean characteristic path length over all nodes in the Graph G,

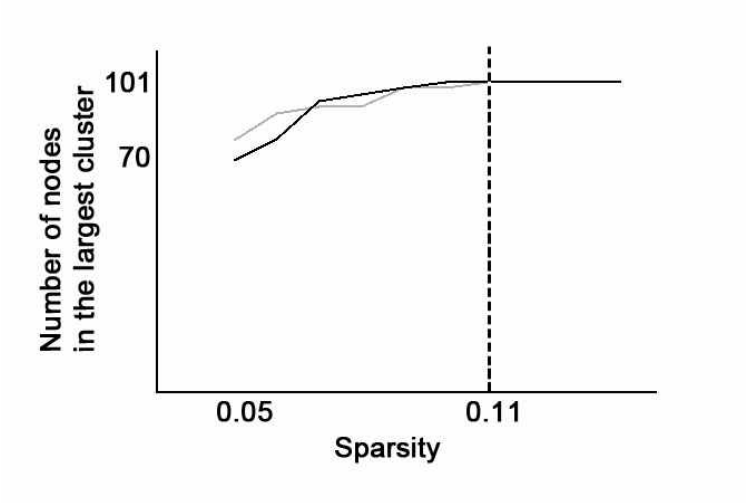
C_{random} and L_{random} are calculated from 1000 random graphs with the same numbers of nodes and edges as the graph G,

The clustering coefficient C_i is defined as the number of existing connections between the node's neighbors divided by all their possible connections at node i,

The characteristic path length L_i is the smallest number of connections required to connect one node to another, averaged over all pairs of nodes at node i. In this calculation, we used harmonic mean distance between pairs proposed by Newman (2003).

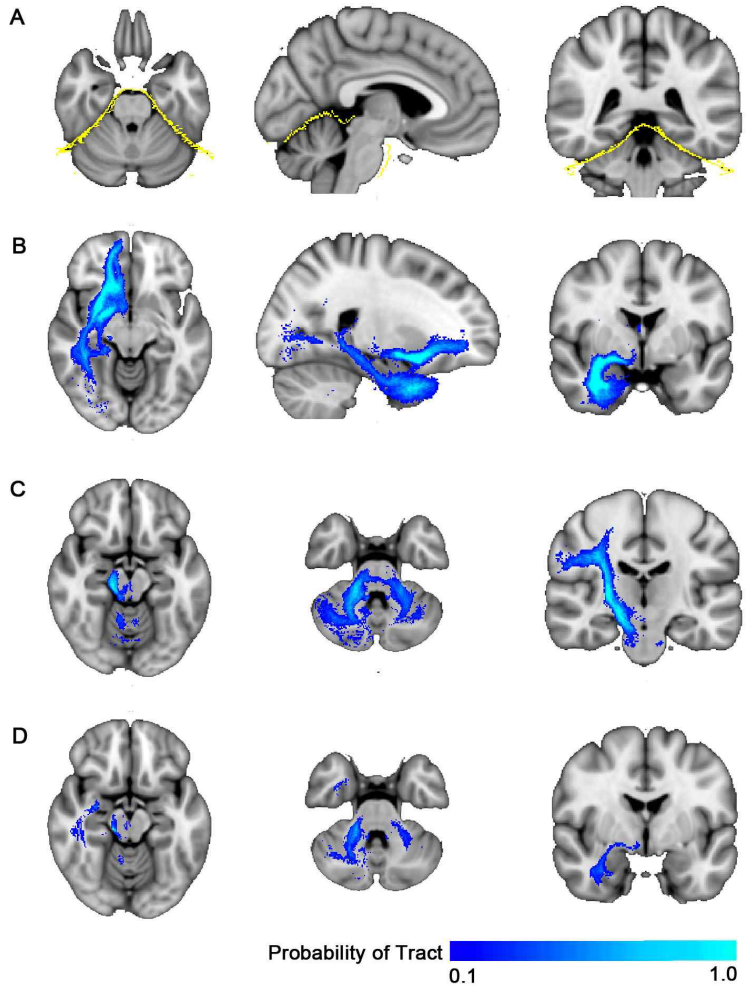


Supplementary Fig. 1. Brain parcellation map
Based on automated anatomical labeling (AAL) atlas, cerebral cortices and cerebellar regions are divided into 101 ROIs. As the number and volume of ROIs may influence structural connectivity networks, we further divided brain areas into 531 equal-volume ROIs (The volume of each ROI is approximately 2.5 cc.), and repeated the analyses, which gave similar results as those with 101 ROIs.



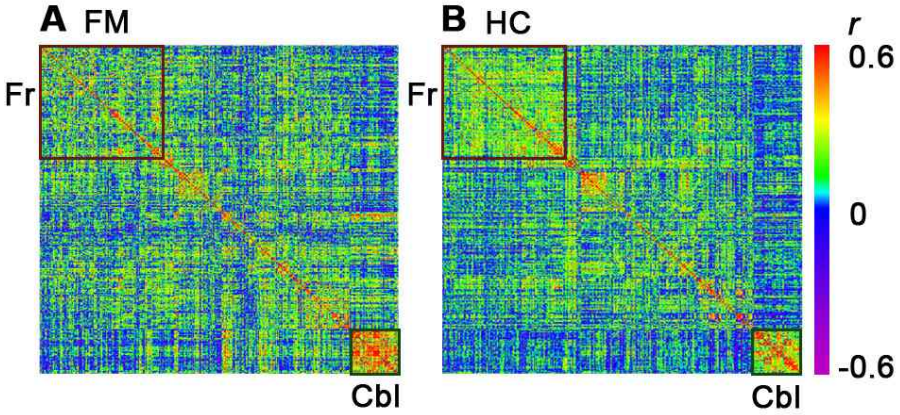
Supplementary Fig. 2. Network sparsity estimation was used to define threshold for the structural covariance network

The numbers of nodes (ROIs) in the largest cluster as a function of the sparsity threshold are shown for fibromyalgia patients (gray) and healthy controls (black). At a sparsity of 0.11, the largest cluster in the network for both fibromyalgia patients and healthy controls covers all 101 ROIs, assuring that all nodes are fully connected (i.e. no islands). This sparsity value corresponds to a minimum correlation coefficients of 0.409 (controls) or 0.437 (patients), respectively.



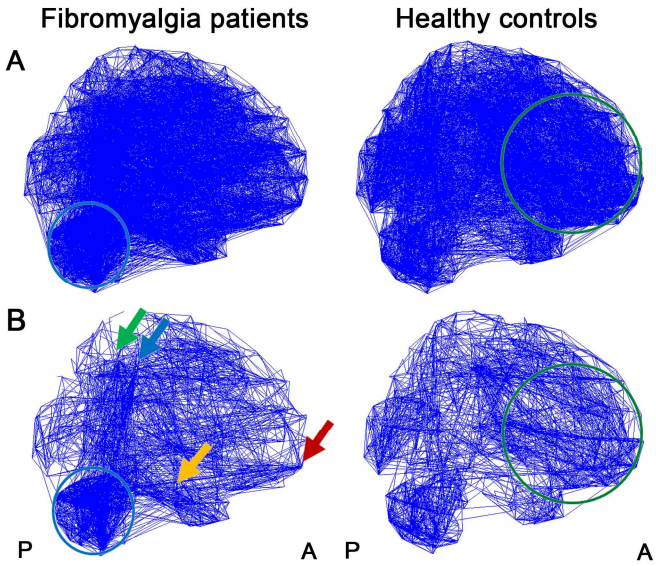
Supplementary Fig. 3. Exclusion mask used for tracts connecting the clusters of Submodule 1

In corticopontocerebellar tractography, we used an exclusion mask around the cerebellar tentorium to limit false connections (**A**). After enacting this exclusion mask, the mean probability tracts between right medial orbitofrontal gyri and medial temporal lobe (**B**), between right inferior parietal lobule and cerebellum (**C**), and between right medial temporal lobe and cerebellum (**D**) are displayed in blue. Note that the corticopontocerebellar tract from the inferior parietal lobule is passing through the lateral portion of the cerebral peduncle (**C**), consistent with a previous DTI study (Ramnani et al., 2006).



Supplementary Fig. 4. Brain structural covariance matrices for fibromyalgia patients and healthy controls with 531 ROIs

We repeated the structural covariance analyses using a greater number (531) of smaller sized ROIs. Inter-regional correlation coefficients were re-calculated for fibromyalgia patients [A] and healthy controls [B]. These partial correlations were conducted after controlling for age, sex, and intracranial volume. FM patients demonstrated greater correlation in the cerebellum (asymptotic χ^2-test, $P = 0.0005$), while healthy controls demonstrated greater correlation in the frontal lobe ($P < 0.0001$). Abbreviations: Cbl, cerebellum; Fr, frontal lobe.



Supplementary Fig. 5. Structural covariance network visualization for 531 ROIs The brain structural covariance networks for 531 ROIs are visualized for both fibromyalgia patients and healthy controls. Inter-regional correlation coefficients greater than the sparsity-based threshold value are shown connected by a blue line. In Panel A, threshold was determined at 0.046, where all nodes were fully connected. In Panel B, at 0.02, where 95% of nodes were connected. In fibromyalgia patients, dense connections were noted within the cerebellum (blue circle). In healthy controls, prefrontal cortical regions showed dense connectivity (green circle). In panel B, FM network demonstrated dense connections between cerebellum and inferior parietal lobe (green/blue arrow), medial temporal lobe (orange arrow), and orbitofrontal areas (red arrow), which was the similar pattern as those of 101 ROIs. which represented a similar as for 101 ROIs.

Supplementary References

Newman ME. (2006): Modularity and community structure in networks. Proc Natl Acad Sci U S A 103(23):8577-82.

Ramnani N, Behrens TE, Johansen-Berg H, Richter MC, Pinsk MA, Andersson JL, Rudebeck P, Ciccarelli O, Richter W, Thompson AJ and others. (2006): The evolution of prefrontal inputs to the cortico-pontine system: diffusion imaging evidence from Macaque monkeys and humans. Cereb Cortex 16(6):811-8.

Watts DJ, Strogatz SH. (1998): Collective dynamics of 'small-world' networks. Nature 393(6684):440-2.