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Structural brain network changes in patients with neurofibromatosis type 1

A retrospective study

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Abstract

We investigated the changes in structural connectivity (using diffusion tensor imaging [DTI]) and the structural covariance network based on structural volume using graph theory in patients with neurofibromatosis type 1 (NF1) compared to a healthy control group. We included 14 patients with NF1, according to international consensus recommendations, and 16 healthy individuals formed the control group. This was retrospectively observational study followed STROBE guideline. Both groups underwent brain magnetic resonance imaging including DTI and 3-dimensional T1-weighted imaging. We analyzed structural connectivity using DTI and Diffusion Spectrum Imaging Studio software and evaluated the structural covariance network based on the structural volumes using FreeSurfer and Brain Analysis Using Graph Theory software. There were no differences in the global structural connectivity between the 2 groups, but several brain regions showed significant differences in local structural connectivity. Additionally, there were differences between the global structural covariance networks. The characteristic path length was longer and the small-worldness index was lower in patients with NF1. Furthermore, several regions showed significant differences in the local structural covariance networks. We observed changes in structural connectivity and covariance networks in patients with NF1 compared to a healthy control group. We found that global structural efficiency is decreased in the brains of patients with NF1, and widespread changes in the local structural network were found. These results suggest that NF1 is a brain network disease, and our study provides direction for further research to elucidate the biological processes of NF1.

Abbreviations: 3D = 3-dimensional, DTI = diffusion tensor imaging, NF1 = neurofibromatosis type 1, ROIs = regions of interest, rs-fMRI = resting state functional magnetic resonance imaging.

Keywords: diffusion tensor imaging, magnetic resonance imaging, neurofibromatosis type 1

1. Introduction

Neurofibromatosis type 1 (NF1), previously known as von Recklinghausen disease, is an autosomal dominant genetic disorder with a prevalence of approximately 1 in 3500 people.[1] NF1 is a neurocutaneous disorder caused by the dysregulation of the production of neurofibromin, a protein with synaptic plasticity functions that is involved in memory and learning.[2]

NF1 is characterized by a variety of symptoms including glioma, café au lait spots, skin wrinkles, bone abnormalities, iris nodules, and cutaneous and plexiform neurofibromatosis.[3] NF1 is also associated with cognitive impairments as well as social and behavioral problems. Cognitive impairments include low intelligence, learning disabilities, visuospatial processing deficits, language problems, and poor executive function. Social and behavioral problems include difficulties in social skills, communication, and forming friendships, and patients may experience social isolation and rejection by their peers.[4–7] Because patients with NF1 have various cognitive impairment symptoms, widespread brain regions may be involved in the pathophysiology.

Recently, neuroimaging has become increasingly vital in understanding the neural basis of these neurological deficits, cognitive impairments, and behavioral problems. In a graph theoretical analysis, the brain network consists of nodes and edges.[8] There are 3 different but related connectivity categories determined by the type of edges: structural, functional, and effective. Structural connectivity involves the anatomical connections linking the neural elements and is usually assessed using diffusion tensor imaging (DTI). It is highly predictive and places constraints on functional interactions across the brain network.[9] Studies on structural connectivity are complemented

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The institutional review board of local institution approved this study and the patients consent was waived.

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by assessments of structural covariance networks based on correlations involving the regional structural volume or thickness. Structural covariance network analysis can detect signs of persistent functional-trophic crosstalk, maturational changes, and common developmental and pathological influences.[10] However, no studies to date have investigated the changes in structural connectivity in patients with NF1 compared to a healthy control group.

Functional connectivity is defined as a time-dependent pattern of neural activation in anatomically isolated brain regions. Changes in functional connectivity related to cognitive, social, and behavioral function have been widely investigated using resting state functional magnetic resonance imaging (rs-fMRI).[11] Research investigating changes in functional connectivity in patients with NF1 compared to a healthy control group has also been conducted, and this demonstrated that positive coupling between the left ventral anterior cingulate cortex and frontal pole, and between the left amygdala and right orbitofrontal cortex, is associated with progression of cognitive impairment.[12] Another study demonstrated the changes in the default mode and visual networks in functional connectivity analysis.[13] Although rs-fMRI studies have been widely used in patients with NF1, the pathophysiology of cognitive impairments in these patients is not fully understood.

Structural changes in patients with NF1 include macrocephaly, corpus callosum enlargement, deep non-tumorous gray and white matter changes, and unidentified bright objects.[14,15] However, there have been no studies on structural connectivity or the structural covariance network in patients with NF1, despite the presence of structural connectivity changes in other neurological diseases.[16–18] Therefore, we investigated changes in structural connectivity (using DTI) and the structural covariance networks based on structural volume using graph theory in patients with NF1 compared to a healthy control group.

2. Material and methods

2.1. Participants

We retrospectively included 14 patients with NF1 in our study, which was approved by the institutional review board of Haeunadae Paik Hospital. Written informed consent to participate in this study was provided by the participants. The inclusion criteria were as follows: the patient was diagnosed with NF1 based on clinical features or genetic testing at the neurology department of our hospital, according to international consensus recommendations[19]; the patient underwent brain MRI including 3-dimensional (3D) T1-weighted sequences and DTI at our hospital between March 2018 and August 2021; and the patient had not been diagnosed with any other medical or neurological diseases.

We included 16 age- and sex-matched individuals with no previous history of medical or neurological diseases in the healthy control group. All healthy individuals had normal brain MRI scans.

2.2. Magnetic resonance imaging acquisition

Participants in both groups underwent brain MRI scans using the same protocols (Achieva 3.0T Tx, Philips Healthcare, Best, Netherlands, with a 32-channel head coil): 3D fluid-attenuated inversion recovery, coronal T2-weighted imaging, 3D T1-weighted imaging, and DTI. Three-dimensional T1-weighted images were obtained using a turbo field-echo sequence (inversion time = 1300 ms, repetition time/echo time = 8.6/3.96 ms, flip angle = 8°, and isotropic voxel size = 1 mm^3). DTI was performed using spin-echo single-shot echo-planar pulse sequences in 32 different diffusion directions (repetition time/echo time = 8620/85 ms, fractional anisotropy = 90°, slice thickness = 2.25 mm, acquisition matrix = 120 × 120, field of view = 240 × 240 mm^2, and b value = 1000 s/mm^2).

2.3. Structural connectivity analysis

We analyzed structural connectivity in both groups using DTI, graph theory, and the Diffusion Spectrum Imaging Studio software (https://dsi-studio.labsolver.org/). We opened DTI source images and created a.scr file. The b-table was checked using an automatic quality-control routine to ensure accuracy. Then, we confirmed the mask coverage on the white matter to filter out the background region, increase the reconstruction efficacy, and facilitate further visualization. This included thresholding, smoothing, and defragmentation. We reconstructed the images using the q-space diffeomorphic reconstruction method, which includes generalized q-sampling imaging, linear registration, normalization, and final reconstruction in the Montreal Neurological Institute space. We conducted fiber tracking by positioning the seeding region to include the entire brain. The anisotropy threshold was 0.188, and the angular threshold was 60°. Tracks <10 mm or >200 mm were discarded. Automated anatomical labeling (AAL 2) was used for brain parcellation, and the connectivity matrix was calculated using the number of connecting tracts. Finally, a graph theoretical analysis was conducted, and the network measures were extracted, including the mean clustering coefficient, characteristic path length, global efficiency, small-worldness index, transitivity, radius of graph, diameter of graph, assortativity coefficient for global structural connectivity, and betweenness centrality for local structural connectivity.

2.4. Structural covariance analysis

We calculated the structural covariance network based on the structural volumes using 3D T1-weighted imaging with FreeSurfer (https://surfer.nmr.mgh.harvard.edu/) and Brain Analysis Using Graph Theory (BRAPH) software (http://braph.org/software/).[20] The detailed methods are described in our previous research.[16,21] We obtained 81 structural volumes of the regions of interest (ROIs) using the FreeSurfer cortical reconstruction function, and selected "recon-all." All images were visually inspected by a neurologist to ensure that obvious errors in skull stripping and tissue segmentation did not occur, in which spatial overlapping extent were identified between overlaid segmented gray or white matter structures and underlaid raw T1-weighted images. Then, we created a non-directional weighted connectivity matrix; the node was defined as the volume of the ROIs, and the edge was defined as the partial correlation among the volumes of ROIs corrected for age and sex. Finally, we extracted the network measures from the matrix using graph theory.

2.5. Statistical analysis

We evaluated the statistical significance of the differences in structural connectivity between patients with NF1 and the healthy control group using an independent Student t test (MedCalc software, version 19.6.4, MedCalc Software, Mariakerke, Belgium). Furthermore, we tested the statistical significance of the differences in the structural covariance network between the 2 groups using a nonparametric permutation test (with BRAPH software)[20] so that we could obtain the network measures at group level. Statistical significance was set at $P < .05$. We applied multiple corrections using a false discovery rate and calculated the adjusted P values. In the case of local network measures, structural connectivity was corrected 120 times and structural covariance network was corrected 81 times by the number of ROIs.

3. Results

3.1. Demographic and clinical characteristics of the participants

Table 1 shows the demographic and clinical characteristics of the patients with NF1 and those in the healthy control group. Age and sex did not differ between the groups.

3.2. Differences in structural connectivity between patients with neurofibromatosis and the healthy control group

Table 2 shows the differences in global structural connectivity between the 2 groups. There were no significant differences in the global structural connectivity between the groups, including that in the mean clustering coefficients, characteristic path lengths, global efficiencies, small-worldness indexes, transitivity, radii of graphs, diameters of graphs, and assortativity coefficients.

However, several regions showed significant differences in local structural connectivity between the groups (Table 3 and Supplementary Digital Content 1, http://links.lww.com/MD/K414). The betweenness centrality in the left anterior cingulate and paracingulate gyri, left posterior cingulate gyrus, right anterior orbitofrontal gyrus, right precentral gyrus, and left lobule 9 of the cerebellar hemisphere was lower, whereas the right cuneus, medial and medio-orbital parts of the right superior frontal gyrus, left superior parietal gyrus, right supplementary motor area, lobules 4 and 5 of the vermis, and left lobules 4 and 5 of the cerebellar hemisphere were higher in the patients with NF1 than that of the healthy control group.

Table 1

Demographic and clinical characteristics of the patients with neurofibromatosis type 1.

	Patients with neurofibromatosis (N = 14)	Healthy controls (N = 16)	*P* value
Age, yr (±SD)	34.0 (±15.8)	38.0 (±15.5)	.485
Male, n (%)	7 (50.0)	8 (50.0)	1.000
Café-au-lait macules, n (%)	10 (71.4)		
Neurofibromas, n (%)	14 (100)		
Optic pathway glioma, n (%)	1 (7.1)		
NF1 gene mutation	7 (50)		

NF1 = neurofibromatosis type 1.

3.3. Differences in the structural covariance network between patients with neurofibromatosis and the healthy control group

Table 4 shows the differences in the global structural covariance network between the patients with NF1 and the healthy control group. There were significant differences in the global structural covariance network between the groups, including differences in the characteristic path lengths and small-worldness indexes. The characteristic path length was longer (2.174 vs 1.639, $P = .001$), while the small-worldness index was lower (0.924 vs 0.983, $P = .001$) in the patients with NF1 than that of the healthy control group. However, other network characteristics, including the mean clustering coefficients, global efficiencies, transitivity, radii of graphs, diameters of graphs, and assortativity coefficients did not differ between the groups.

Several regions also showed significant differences in the local structural covariance network between the groups (Table 5 and Supplementary Digital Content 2, http://links.lww.com/MD/K415). The betweenness centrality in the right inferior parietal cortex and right pericalcarine cortex was lower, whereas the left caudate nucleus, right lateral orbitofrontal cortex, right pars orbitalis cortex, right superior frontal cortex, left caudal middle frontal cortex, left postcentral cortex, and left posterior cingulate cortex were higher in patients with NF1 than that of the healthy control group.

4. Discussion

We first analyzed the changes in structural connectivity and covariance networks in patients with NF1 compared to those of the healthy control group. The main finding of this study was that there were significant differences between the groups in the local structural connectivity and global and local structural covariance networks. These structural brain network changes may be related to the pathophysiology and symptoms of patients with NF1.

Although no differences in the global structural connectivity between that in the patients with NF1 and the healthy control group were found, we observed changes in the global structural covariance network in patients with NF1. The characteristic path length was longer, and the small-worldness index was lower in the patients with NF1 than that of the healthy control group. The lower small-worldness index in patients with NF1 might be caused by the long mean characteristic path length and low clustering coefficient, despite no statistical difference in the mean clustering coefficient being found in this study.[22] The long characteristic path length means that the number of short-distance connections between the nodes is decreased, with an increased average number of minimum connections between nodes in patients with NF1, which results in a reduced capacity

Table 2

Differences in the global structural connectivity between the patients with neurofibromatosis type 1 and the healthy control group.

	Patients with neurofibromatosis (N = 14)		Healthy controls (N = 16)			
Network measures	**Mean**	**SD**	**Mean**	**SD**	**Difference**	***P* value**
Mean clustering coefficient	0.218	0.077	0.221	0.098	0.003	.872
Characteristic path length	4.419	0.485	4.380	0.416	−0.039	.719
Global efficiency	1.524	0.178	1.573	0.154	0.049	.221
Small-worldness index	0.237	0.098	0.248	0.119	0.010	.685
Transitivity	0.259	0.093	0.251	0.109	−0.008	.742
Radius of graph	1.712	0.318	1.656	0.236	−0.056	.399
Diameter of graph	3.227	0.605	3.097	0.407	−0.130	.293
Assortativity coefficient	0.167	0.100	0.139	0.122	−0.027	.299

Table 3

Differences in the betweenness centrality for local structural connectivity between the patients with neurofibromatosis type 1 and the healthy control group.

	Patients with neurofibromatosis (N = 14)		Healthy controls (N = 16)			
Nodes	**Mean**	**SD**	**Mean**	**SD**	**Difference**	***P* value**
Lt. anterior cingulate and paracingulate gyri	50.823	27.697	80.474	33.243	29.651	.033
Lt. posterior cingulate gyrus	37.630	22.636	76.493	46.978	38.863	.030
Rt. cuneus	95.348	45.504	43.906	42.597	–51.443	.010
Rt. superior frontal gyrus (medial orbital)	62.828	51.668	19.757	11.049	–43.071	.004
Rt. superior frontal gyrus (medial)	133.195	97.746	61.313	47.258	–71.882	.020
Rt. anterior orbitofrontal gyrus	38.300	41.315	86.962	49.916	48.662	.021
Lt. superior parietal gyrus	218.013	133.062	128.495	63.427	–89.518	.031
Rt. precentral gyrus	110.025	80.496	271.119	203.282	161.093	.033
Rt. supplementary motor area	194.020	142.494	91.925	46.842	–102.095	.014
Lobule IV, V of vermis	139.186	80.698	80.690	51.050	–58.495	.036
Lt. lobule IV, V of cerebellar hemisphere	226.183	182.873	108.994	68.196	–117.189	.029
Lt. lobule IX of cerebellar hemisphere	47.401	45.572	137.013	118.973	89.612	.042

Table 4

Differences in the global structural covariance network between the patients with neurofibromatosis type 1 and the healthy control group.

	Patients with neurofibromatosis (N = 14)	Healthy controls (N = 16)				
Network measures	**Mean**	**Mean**	**Difference**	**CI lower**	**CI upper**	***P* value**
Mean clustering coefficient	0.473	0.630	0.157	–0.298	0.336	.516
Characteristic path length	2.174	1.639	–0.535	–0.149	1.088	.001
Global efficiency	0.529	0.651	0.122	–0.251	0.250	.468
Small-worldness index	0.924	0.983	0.059	–0.072	0.011	.001
Transitivity	0.726	0.948	0.221	–0.460	0.503	.530
Radius of graph	3.662	2.419	–1.243	–1.917	1.755	.336
Diameter of graph	5.833	4.313	–1.519	–3.389	3.143	.571
Assortativity coefficient	–0.001	–0.026	–0.024	–0.058	0.050	.421

CI = 95% confidence interval of the difference between the groups.

Table 5

Differences in the betweenness centrality for local structural covariance network between the patients with neurofibromatosis type 1 and the healthy control group.

	Patients with neurofibromatosis (N = 14)	Healthy controls (N = 16)				
Nodes	**Mean**	**Mean**	**Difference**	**CI lower**	**CI upper**	***P* value**
Lt. caudate nucleus	0.0063	0.0001	–0.0062	–0.0060	0.0055	.048
Rt. inferior parietal cortex	0.0001	0.0033	0.0032	–0.0044	0.0028	.041
Rt. lateral orbitofrontal cortex	0.0231	0.0005	–0.0226	–0.0177	0.0155	.021
Rt. pars orbitalis cortex	0.0233	0.0072	–0.0161	–0.0137	0.0122	.036
Rt. pericalcarine cortex	0.0002	0.0012	0.0010	–0.0009	0.0011	.049
Rt. superior frontal cortex	0.0102	0.0001	–0.0101	–0.0098	0.0082	.044
Lt. caudal middle frontal cortex	0.0038	0.0001	–0.0037	–0.0023	0.0014	.029
Lt. postcentral cortex	0.0065	0.0012	–0.0053	–0.0050	0.0041	.038
Lt. posterior cingulate cortex	0.0154	0.0004	–0.0150	–0.0111	0.0094	.022

CI = 95% confidence interval of the difference between the groups.

for information transmission in the brain network. Due to such changes, some information may not be expressed in one node or may be expressed weakly, while the transmission to other nodes may be further strengthened, leading to more than the expression of general functions.[8,22] Similar results have also been confirmed in other neurological disorders, such as epilepsy[23] and Alzheimer disease,[24] suggesting the presence of disrupted topological organization of the brain network in patients with neurological disorders.[22]

Furthermore, our study demonstrated differences in the local structural connectivity between patients with NF1 and the healthy control group. The differences in the local structural connectivity could explain the characteristic behavioral findings of each patient disability. Significant changes in local structural connectivity were found in areas spread across the brain. Decreased betweenness centrality in the anterior cingulate and paracingulate gyri may be associated with abnormalities in emotional control and motivation in patients with NF1.[25] A previous study of these patients also confirmed changes in the anterior cingulate cortex, demonstrating that these changes were associated with changes in the patient social and cognitive function. The cingulate gyrus also acts as a hub for information

processing,[26] and reduced network connectivity in this area may be related to lack of attention.[27] The precentral gyrus is an important region for motor control, and abnormalities in this area are associated with motor skill disorders and reduced communication capacity, which are found in patients with autism spectrum disorder.[28] These changes are consistent with the decreased centrality of lobule 9 of the cerebellar hemisphere, which may explain the decrease in motor function in these patients. The cuneus conveys information from the attention network to the visual area,[29] is a major region in the visual network, and is involved in visual selective attention.[30] A previous study showed that abnormal activation of the default mode network by visual stimuli is present in patients with NF1.[31] The superior parietal gyrus is involved in the perceptual aspects of attention and spatiotemporal space, including the concept and manipulation of objects. All these findings suggest that various behavioral cognitive impairment symptoms in patients with NF1 could originate from changes in local structural connectivity in widespread brain areas.

The local structural covariance network also showed statistically significant changes in many brain areas. The caudate nucleus, the area of change in betweenness centrality in patients with NF1, plays a role in working memory and other superior executive functions, including attention and impulse control. A previous study identified morphological abnormalities in this area, and it is believed that these changes may be associated with working memory-related symptoms in patients with NF1.[32] A significant difference was also observed in the inferior parietal cortex, which is the region associated with executive function, as well as self-referential and emotional processes. Differences in the lateral orbitofrontal cortex could be related to social and antisocial behavior,[33] and differences in this area are considered to be the cause of the executive impairments that can be seen in patients with NF1.[34] The pars orbitalis cortex is related to connections in language processing,[35] and the alterations of connectivity in this area may explain the language disability in these patients. Network differences in the pericalcarine cortex could explain the low-level visual processing ability seen in patients with NF1.[34]

In this study, we demonstrated changes in structural connectivity (using DTI) and the structural covariance network based on structural volume using graph theory in patients with NF1 compared to a healthy control group. However, our study had several limitations. First, we included only a small number of patients with NF1 who presented at a tertiary hospital. However, it was difficult to include more patients with NF1 because neurofibromatosis is not a common disease. Second, we were unable to conduct detailed neuropsychological tests on the patients with NF1. Additionally, since the sample size was small, we could not conduct a subgroup analysis according to the patients' cognitive and behavioral phenotypes. If the analysis were divided into subgroups according to cognitive and behavioral functions, it would be possible to explain the relationship between structural connectivity changes and various symptoms in patients with NF1. In a previous study using rs-fMRI, functional connectivity was found to be associated with cognitive, social, and behavioral impairments in patients with NF1.[12] Further studies with larger numbers of patients with NF1 are needed to confirm our findings.

We observed changes in structural connectivity and covariance networks between patients with NF1 and a healthy control group. Global structural efficiency was decreased in the brains of patients with NF1, and widespread changes in the local structural network were found. These results suggest that NF1 is a brain network disease, and our study provides direction for further research to elucidate the biological processes of NF1.

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