이학석사 학위논문

# Behavioral Significance of Altered Resting State Network in Fibromyalgia

# 섬유근육통 증후군에서의 휴지기 네트워크의 변화와 행동적 중요성

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# Abstract

## Behavioral Significance of Altered Resting State Network in Fibromyalgia

Fibromyalgia (FM) is a chronic widespread pain syndrome characterized by increased sensitivity to painful stimuli (hyperalgesia) as well as nonpainful stimuli (allodynia). Neuroimaging studies have demonstated that fibromyalgia is characterized by augmented sensory processing mediated by abnormal central nervous system, although the underlying mechanism of pain is not fully understood. Recent studies have revealed intrinsic connectivity alteration during resting state associated with clinical symptoms in FM patients. However, the network construction is inherently affected by thresholding, which is operator-dependent. In this study, we employed persistent brain network homology which is a multiple scale network modeling framework building the brain network at every threshold, thus not requiring thresholding to understand the topological features of brain network in fibromyalgia (FM).

Spontaneous MEG activity was analyzed for 200 seconds in 17 healthy controls (HCs) and 18 FM patients. All participants were

instructed to close their eyes at rest. Resting MEG data were filtered into theta (4−7 Hz), alpha (8−12 Hz), beta (13−30 Hz), and gamma (31−48 Hz) bands, and we constructed source activities in 76 nodes based on Automated Anatomical Labeling (AAL) in each frequency band using a beamformer. To construct brain network using persistent brain network homology, the distance matrix (1 – absolute value of the correlation coefficient) was calculated. Then, barcode, single linkage dendrogram and single linkage matrix (SLM) were generated for each subject in two groups based on the proposed modeling framework. Barcode represents the global topological change at every threshold. Single linkage dendromgram represents the local network features that show what regions could be merged over different thresholds. Single linkage distance (SLD) is the component of single linkage dendrogram and used to estimate functional connectivity.

In theta band, the slope of decrease in the number of connected components in barcodes showed steeper in HC, suggesting FM patients had decreased global connectivity than the healthy controls.

Patients with FM had reduced connectivity within default mode network region (mPFC, ACC, PCC, and precuneus). They also disclosed longer SLDs between middle temporal lobule and visual area (calcarine fissure, cuneus, lingual gyrus, superior occipital cortex, and fusiform gyrus) in theta. The longer SLDs between MTG and visual cortex were correlated with pain duration.

Our results provided disrupted intrinsic connectivity within

resting state network of FM patients in theta band. Moreover, our findings suggest that the persistent pain in FM patients would be associated with the connectivity within the DMN and sensory network.

**Keyword** : Fibromyalgia (FM), Resting state network, Chronic pain, Persistent brain network homology, Magnetoencephalography (MEG).

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# Chapter 1. Introduction

## 1.1. Study Background

Fibromyalgia (FM) is a chronic widespread pain syndrome characterized by augmented sensitivity to painful stimuli as well as nonpainful stimuli (hyperalgesia, allodynia). Although the pathophysiology of pain in FM is not clearly understood, recent neuroimaging studies demonstrated that development and maintance of FM are characterized by augmented central nervous system processing (Clauw, Arnold et al. 2011).

Chronic pain patients experiences continuous pain in the absence of external stimulation, which is the most general symptom of chronic pain (Apkarian, Hashmi et al. 2011). Investigating the brain functional organization in the absence of any input (i.e. resting state) is critical in that it would disclose the fundamental aspect of spontaneous nature of chronic pain in FM patients.

Neuroimaging studies have observed disruptions of functional brain network during rest state in fibromyalgia and other kinds of chronic pain (i.e. chronic back pain, migraine, and complex regional pain syndrome) (Bolwerk, Seifert et al. 2013, Kim, Kim et al. 2013, Tessitore, Russo et al. 2015).

The default mode network (DMN) is the major component of

resting state network (RSN) shown to be more active at rest and most thoroughly studied RSN in central nervous system disease (i.e., chronic pain, schizophrenia, and dementia) (Farmer, Baliki et al. 2012). The DMN reflects organization of the intrinsic brain network in chronic pain condition (Baliki, Chang et al. 2014). Recent studies have disclosed alterations of the DMN and relation between disruption of the DMN and symptoms in chronic pain syndromes (Baliki, Geha et al. 2008, Napadow, LaCount et al. 2010).

Sensory related networks (SMN; somatosensory network, AN; auditory network, VN; visual network) are also crucial networks in resting state. In addition to aberrant processing of painful stimuli, abnormal sensory processing of non-painful events has been also demonstrated in chronic pain studies. FM patients showed altered brain responses in sensory related network regions to non-nociceptive sensory stimuli which were correlated with FM symptoms (Lopez-Sola, Pujol et al. 2014). Previous resting state fMRI studies also showed aberrant functional connectivity in fibromyalgia within sensory related regions (Dhond, Yeh et al. 2008, Pujol, Macia et al. 2014). Taken together, these findings suggest that resting state networks in FM patients would be altered and associated with spontaneous pain of FM.

Graph theoretical approach deals with analysis of topological characteristics of complex systems in network and provides the critical insights into structural and functional brain networks in complex systems (Bullmore and Sporns 2009, Sporns 2011). Most

network studies based on graph theory use binary networks since weighted network is difficult to interpret (Bullmore and Sporns 2009). Analysis of the brain network uses thresholding to generate binary network, which is operator-dependent. To overcome this limitation, we employed persistent brain network homology to understand the network disruption in fibromyalgia (FM), which is a multiple scale network modeling framework building the brain network at every threshold, thereby inherently thresholding insensitive (Lee, Kang et al. 2012).

## 1.2. Purpose of Research

In this study, we used magnetoencephalography (MEG) during resting state to investigate abnormal characteristics of resting state network in FM patients within each of four frequency bands (theta, alpha, beta, and gamma). Employing persistent network homology, we would estimate invariant topological features of the network at each of these frequency bands. We hypothesized that resting state network in fibromyalgia (FM) would be disrupted and brain regions of disrupted network would be involved in spontaneous pain of FM.

# Chapter 2. Methods

## 2.1. Participants

Eighteen right-handed female patients (age: mean = 45, SD = 8.5 years) were recruited from the outpatient clinics of the rheumatology departments of the Seoul National University Hospital and the Hallym University Sacred Heart Hospital. All examinations except for the diagnosis and self-report questionnaires, were conducted at the Seoul National University Hospital to ensure reliable result. Eligibility criteria for patients with FM were as follows: 1) meeting the American College of Rheumatology 1990 criteria for primary FM (Wolfe, Smythe et al. 1990), 2) disease duration of at least 3 months, but less than 10 years, 3) score of ≥ 40 mm on the 0 to 100 mm pain visual analogue scale (VAS) over the previous week, 4) age between 30 and 60 years, 5) willingness to limit medications, such as, analgesics, antidepressants, and anticonvulsants, at least 3 days prior to assessments. Patients with FM were excluded if they had: 1) secondary FM associated with inflammatory arthritis, 2) history of substance abuse, 3) symptoms of peripheral neuropathy, 4) concomitant acute pain in the upper extremities, 5) hearing loss or use of hearing aids, 6) being pregnant or breastfeeding, 7) contraindications with MEG and MRI

procedures. Seventeen healthy control subjects matched to the age and sex of patients with FM (age: mean = 45.2, SD = 8.9 years) were recruited by local advertisements. The exclusion criteria for the HC group were the same as those for FM patients. The study protocol was approved by the Institutional Review Boards at Seoul National University Hospital and Hallym University Sacred Heart Hospital and was conducted in compliance with the Declaration of Helsinki. All participants in the study provided written informed consent.

## 2.2. Clinical questionnaires

In this study, all participants were asked to complete clinical questionnaires. The Beck Depression Inventory (BDI) (Beck, Ward et al. 1961), the Beck Anxiety Inventory (BAI) (Beck, Epstein et al. 1988), and the Fibromyalgia Impact Questionnaire (FIQ) (Burckhardt, Clark et al. 1991) were assessed. The short-form McGill Pain Questionnaire (SF-MPQ) (Melzack 1987) were also completed to assess the sensory and affective components of pain. The resting MEG recordings and the clinical measurements of pain were acquired on the same day, excepting 9 subjects. The demographic and clinical characteristics of the subjects are displayed in Table 1.

## 2.3. MEG acquisition

The MEG signals were acquired on a VectorView™ 306-channel whole-head neuromagnetometer (Elekta Neuromag, Helsinki, Finland), organized in 204 planar gradiometers and 102 magnetometers. The participants sat comfortably beneath the helmet-shaped sensory array. They were instructed to stay relaxed and not to think about anything. Data were collected inside a magnetically shielded room for 200 seconds in an eye-closed condition. The positions of four indicator coils placed on the scalp with respect to three anatomical landmarks, the nasion and two preauricular points were measured by three-dimensional digitizer (FASTRAK, Polhemus, Colchester, VT). The x-axis of the head coordinate system passed through the two preauricular points from left to the right. The positive y-axis passed through the nasion, and the z-axis pointed up. The magnetic signals were band-pass filtered between 0.1 and 300 Hz, and were digitized at a sampling frequency of 1 kHz. The spatiotemporal signal space separation method using MaxFilter software (version 2.2.10; Elekta Neuromag, Helsinki, Finland) were applied to remove environmental and biological noise (Taulu and Simola 2006, Lim, Kim et al. 2016).

## 2.4. MRI acquisition

MRI images were acquired using a using a Magnetom TrioTim 3T scanner (Siemens, Erlangen, Germany). The following parameters were used: sagittal acquisition with a 256 256 matrix; field of view = 250 mm; voxel size = 1 1 1 mm; slice thickness = 1.0 mm with no gap; repetition time/echo time = 1,670/1.89 ms; flip angle = 9°; 1 excitation (Kim, Lim et al. 2014, Lim, Kim et al. 2016).

## 2.5. Data preprocessing

MEG data were analyzed with MATLAB 2008b (MathWorks, Natick, MA, USA), the Fieldtrip open source software package (the Donders Institute for Brain, Cognition and Behaviour, Centre for Cognitive Neuroimaging, Nijmegen, The Netherlands, http://fieldtrip.fcdonders.nl) (Oostenveld, Fries et al. 2011). To calculate the distance using power correlation, continuous MEG data was split into 200 trials (1sec per trial). After cutting up continuous data into trials, artifact such as EOG and ECG prior to source analysis were rejected using independent component analysis (ICA).

## 2.6. Spectral analysis

Before the frequency decomposition, the data for each trial was multitapered by Discrete Prolate Spheroidal Sequences (DPSS) (Slepian 1978). Each tapered data was Fourier transformed in

various frequency bands: Theta (4−7 Hz), Alpha (8−12 Hz), Beta (13−30 Hz), and Gamma (31−48 Hz).

## 2.7. Source analysis

Beamformer analysis based on Dynamic Imaging of Coherent Sources (DICS) (Gross, Kujala et al. 2001) was performed to reconstruct neuronal source in the frequency domain. The beamforming is a signal transmission of the sensor signal using a spatial filter formed from the lead field and cross spectral density matrix. In order to localize source activity, we constructed head model and leadfield matrix. To construct the head model, the brain surface was extracted from each subject's MRI, which is termed segmentation. The volume conduction model was constructed and then grid points were discretized into the brain. The regular grid in MNI template was spatially deformed to the each subject's brain. The lead field matrix was computed for each grid point. Neural activity on the source level was localized by applying the filter to the Fourier transformed data.

## 2.8. Network filtration

### 2.8.1. Network construction

The 76 nodes covering whole brain except for subcortical and cerebellar regions were defined based on the Automated Anatomical

Labeling (AAL) atlas (Table 2) (Tzourio-Mazoyer, Landeau et al. 2002). The AAL atlas is typically used for the brain anatomical parcellation and has been used in fMRI studies (He, Wang et al. 2009, Wang, Zhu et al. 2009) and MEG studies (Jin, Jeong et al. 2013, Tewarie, Schoonheim et al. 2013, Jin, Jeong et al. 2014) to obtain neuroanatomical labels of the brain network nodes. We interpolated AAL atlas onto source grid to extract source activity. Maximum power values of the whole-brain ROIs were extracted from each trial, and then trials-by-ROIs power matrices in various frequency bands (theta, alpha, beta, and gamma) were estimated per subject. To construct brain network, distance matrix was calculated through Pearson's correlation coefficient. The correlation coefficient between source activities in ROIs for each of trials was estimated per subject. We defined the distance between neuronal activities of each ROIs as 1 – absolute value of the correlation coefficient, yielding the distance matrix per subject and frequency domain.

2.8.2. Graph filtration

Based on persistent homology which is a multi-scale network modeling framework, we generated the brain network at every threshold. In the previous study (Lee, Kang et al. 2012) which described persistent homology, the node $i$ and $j$ are connected if the distance between $i$ and $j$ is less than the threshold distance ($\varepsilon$). Increasing the threshold changes the network within nodes. Those

multiple scale networks over the threshold are called graph filtration and the threshold distance (ε) is termed to filtration value. The topological feature over filtration is visualized by barcode and single linkage dendrogram. The barcode shows the number of the connected components in the network when the filtration value changes. It represents the global topological feature. The slope of barcode was calculated for each group to estimate how fast ROIs are clustered, and it can measure the global connectivity of brain network. The single linkage dendrogram visualizes hierarchical clustering and shows what subnetworks could be merged during graph filtration. The dendrogram represents the local network feature in that it contains anatomical information. Single linkage matrix is the matrix representation of the dendrogram and used for statistical group comparison. Single linkage distance (SLD) is the minimum distance between nodes $i$ and $j$ and the component of the SLM (Fig. 1). Comparing the distances of single linkage matrix, we identify the statistical difference of brain network between fibromyalgia and healthy control.

## 2.9. Statistical analysis

To compare between slopes of barcodes in fibromyalgia and healthy control group, the independent t test was applied. Statistical significance was considered at $p < 0.05$. Permutation test (10,000 replications) was performed for intergroup comparisons of single

linkage matrix between the groups. Significant difference was set at uncorrected $p < 0.001$. Correlation between SLDs and clinical symptoms in FM patients were assessed using Pearson's correlation coefficient. P values of $< 0.0083$ (0.05/6) were taken as statiscally significant after Bonferroni correction.

# Chapter 3. Results

## 3.1. Decreased global network connectivity in fibromyalgia measured by barcode

The barcode visualizes the change in the number of connected components as the thresholds of distance are increased. It represents topological features of the network change over filtration. The healthy control group had a steeper decreasing slope of the barcode than the fibromyalgia group, which suggests that fibromyalgia patients showed decreased global connectivity while the filtration value was increased in theta frequency ($p < 0.05$). There was no significant difference between FM patients and healthy controls in alpha, beta, and gamma bands (Fig. 2).

## 3.2. Alterations of local network in fibromyalgia measured by single linkage dendrogram

The single linkage dendrogram represents the local network features that shows which regions could be merged over different

thresholds. The component of the dendrogram is the single linkage distance (SLD), which is the functional distance between two specific nodes. The single linkage matrix (SLM) is the matrix form of the dendrogram used to investigate the statistical difference of network between groups. To disclose alteration of local network properties in fibromyalgia, we observed the difference in SLMs between FM group and HC group.

In theta frequency band, FM patients showed longer SLDs between following pairs: left precuneus and left medial part of superior frontal gyrus, left precuneus and right medial part of superior frontal gyrus, left precuneus and right precuneus, left precuneus and right anterior cingulate gyrus, left posterior cingulate gyrus and right medial part of superior frontal gyrus, left posterior cingulate gyrus and right precuneus, right medial part of superior fontal gyrus and right posterior cingulate gyrus, and right anterior cingulate gyrus and right posterior cingulate gyrus. Patients with FM mainly had longer SLDs within default mode network (DMN) regions. Moreover, the SLDs of FM group were longer than those of HC between right middle temporal cortex and right visual regions (calcarine fissure, cuneus, lingual gyrus, superior occipital cortex, and fusiform gyrus). The SLD in FM was also longer between left dorsolateral part of superior frontal gyrus and left middle frontal gyrus. In alpha frequency, FM subjects showed longer SLDs between the left precentral gyrus and calcarine fissure. There was no significant difference between FM patients and healthy controls

in beta and gamma bands (Fig. 3, Table 3).

The longer distance means later coupling during network filtration representing weaker connectivity (Kim, Kang et al. 2014). In the fibromyalgia patients, the tendency for weak connectivity was found within the regions of default mode network in theta frequency band. Moreover, FM patients also represented decreased connectivity between temporal lobule and visual cortex in theta bands.

## 3.3. Clinical correlation

Clinical relationship between single linkage distance (SLD) and clinical symptoms were assessed. No significant correlation between SLD and pain VAS, SF-MPQ, FIQ, BAI, or BDI was found in the FM patients. In FM group, a longer SLD between right middle temporal gyrus and right cuneus was significantly associated with longer disease duration of FM ($R = 0.605$, $P = 0.008$). Longer SLD between right middle temporal gyrus and right superior occipital gyrus was also found to be associated with longer disease duration of FM ($R = 0.605$, $P = 0.008$) (Fig. 4).

# Chapter 4. Discussion

## 4.1. Summary

In this study, we first investigated brain network changes during the resting state in fibromyalgia. On persistent brain network homology which we used, barcode and single linkage distance (SLD) represent the network characteristics. The barcodes of FM group displayed slower decrease in theta band than those of healthy controls, indicating that FM had weaker global connectivity. In theta frequency, FM patients showed longer SLD between left dorsolateral part of superior frontal gyrus and left middle frontal gyrus. They showed longer SLDs between left precuneus and left medial part of superior frontal gyrus, left precuneus and right medial part of superior frontal gyrus, left precuneus and right precuneus, left precuneus and right anterior cingulate gyrus, left posterior cingulate gyrus and right medial part of superior frontal gyrus, left posterior cingulate gyrus and right precuneus, right medial part of superior fontal gyrus and right posterior cingulate gyrus, and right anterior cingulate gyrus and right posterior

cingulate gyrus. They also disclosed longer SLDs between right middle temporal lobule and right visual regions (calcarine fissure, cuneus, lingual gyrus, superior occipital cortex, and fusiform gyrus) in theta. The longer SLDs between MTG and visual cortex were correlated with disease duration. Overall, the result suggests that FM had weak connectivity within DMN region and multisensory region. In alpha band, FM subjects showed longer SLDs between the left precentral gyrus and calcarine fissure. There was no significant difference between FM patients and healthy controls in beta and gamma bands.

## 4.2. Global connectivity feature of resting network in FM using barcode.

The barcode means the change in the number of connected components according to increasing single linkage distance. It visualizes global network feature. The slower decrease of the number of connected components means later network coupling, representing weaker network connectivity. Therefore, the slower decrease of the barcode in FM patients shows weaker global feature of resting state network in theta frequency. The results may be interpreted as global information processing in FM was disrupted.

## 4.3. Alteration of default mode network in FM

association with affective aspect of pain.

The single linkage matrix (SLM) and single linkage dendrogram indicate the local network characteristics, representing which nodes could be merged. The single linkage distance (SLD) means the component of SLM and represents the functional distance of brain network. The functional distances within default mode network (DMN) regions (medial prefrontal cortex, precuneus, anterior cingulate cortex, and posterior cingulate cortex) in FM patients were longer than the distances in healthy controls. These results disclose that FM group showed the decreased functional connectivity of DMN.

Previous neuroimaging studies disclosed disrupted connectivity among DMN regions in chronic pain syndromes (Baliki, Geha et al. 2008, Bolwerk, Seifert et al. 2013, Baliki, Chang et al. 2014). Some studies suggested that the disruption of DMN in chronic pain could be related to cognitive impairments (Baliki, Geha et al. 2008, Martucci, Shirer et al. 2015). The medial prefrontal cortex (mPFC), precuneus, anterior cingulate cortex (ACC), posterior cingulate cortex (PCC) are the major components of default mode network (Buckner, Andrews-Hanna et al. 2008, de Pasquale, Della Penna et al. 2012, Agcaoglu, Miller et al. 2015). The mPFC is a component region of the brain's emotion circuitry and related to subjective intensity of chronic pain (Vachon-Presseau, Centeno et al. 2016). One study showed decreased connectivity between mPFC and

precuneus. The precuneus has been known to be the crucial region in integrating information rather than directly processing stimuli (Baliki, Mansour et al. 2014). Balenzuela et al. disclosed the altered connectivity between frontal lobule and ACC in chronic back pain (CBP) patients, suggesting that ACC is involved in the elaboration of sensory, emotional aspects of pain (Balenzuela, Chernomoretz et al. 2010). The PCC is primarily involved in the emotional aspect of pain perception to painful stimuli (Martucci, Shirer et al. 2015). Taken together, the regions which showed decreased connectivity in this study contribute to affective processing of pain. Theta band has been known to be involved in the wide span of cognitive function (i.e., attention, memory function, and pain perception) (Mu, Fan et al. 2008, Wang, Cao et al. 2015). Therefore, our finding of decreased connectivity within DMN regions in theta band indicates the impairment of affective processing of pain.

## 4.4. Functional connectivity between sensory regions related to sensory dysfunction in FM patients

In theta band, the SLDs between middle temporal gyrus (MTG) and visual cortex (calcarine fissure, cuneus, lingual gyrus, superior occipital cortex, and fusiform gyrus) were longer in FM patients than those of HC. In previous studies on the sensory processing of chronic pain, FM patients showed attenuated response to auditory

stimuli in temporal lobule. The results indicated impaired auditory information processing such as attention and habituation (Choi, Lim et al. 2015, Choi, Lim et al. 2016). Patients with FM disclosed disrupted neural response in sensory regions to non-nociceptive sensory stimuli (Lopez-Sola, Pujol et al. 2014). Brain networks among sensory related regions were altered in fibromyalgia (Dhond, Yeh et al. 2008, Pujol, Macia et al. 2014). In the present study, the disruptied functional connectivity between auditory related region (temporal lobule) and visual cortex would indicate that the more pervasive dysfunction of sensory processing in chronic pain. It may not be confined to auditory processing, rather pointing more prevalent dysfunction including visual processing.

## 4.5. Widespread disruption of resting state network in FM arising from persistent pain

We observed positive relationship between reduced connectivity among sensory regions and disease duration. Previous studies found altered resting state networks such as DMN and suggested that ongoing pain may disrupt the brain function (Baliki, Geha et al. 2008, Cifre, Sitges et al. 2012). In this context, our results suggest that the persistent pain of FM would be related to reduction of functional connectivity in resting state. Moreover, the widespread disruptions of RSNs may cause aberrant affective

processing of pain and dysfunction of sensory processing for non-painful stimuli.

## 4.6. Limitation

There are several caveats in this study. First, the participants were asked to refrain from medications three days before MEG acquisition to exclude medication effects. However, this may not be sufficient to minimize the medication effects. However, the further discontinuation of medications would be unethical. Second, the changes in functional connectivity within DMN and sensory regions have been found in other neurological disease and chronic pain (Baliki, Chang et al. 2014). It is of concern that this result is insufficient to suggest the specific feature only for fibromyalgia. Additional studies are necessary to reveal fibromyalgia-specific characteristic. Third, the causal relationship between the altered connectivity of RSN and fibromyalgia is not unclear. Altered RSN connectivity with chronic pain may be an epiphenomenon. Finally, although the sample size in this study is sufficient for analysis, more subjects would allow for detailed analysis of the relationship between symptoms of FM patients and connectivity of RSN in FM. Future study using intervention such as brain stimulation would reveal the relation between behavioral characteristics and the longitudinal recovery of connectivity in fibromyalgia.

## 4.7. Conclusion

In the present study, we showed that reduced functional connectivity within DMN regions and between auditory and visual related regions. Aberrant connectivity within sensory areas has positive correlation with disease duration. These results suggest that persistent pain in fibromyalgia would disrupt brain network at rest and may cause abnormal affective processing to pain and sensory processing of non-painful stimuli.

This study is the first study which investigated resting state network of fibromyalgia syndrome in various frequency bands using MEG. Using the persistent network homology, we investigated the intrinsic topological feature of FM patients at every threshold.

# Bibliography

Agcaoglu, O., R. Miller, A. Mayer, K. Hugdahl and V. Calhoun (2015). "Lateralization of resting state networks and relationship to age and gender." Neuroimage 104: 310-325.

Apkarian, A. V., J. A. Hashmi and M. N. Baliki (2011). "Pain and the brain: specificity and plasticity of the brain in clinical chronic pain." Pain 152(3 Suppl): S49-64.

Balenzuela, P., A. Chernomoretz, D. Fraiman, I. Cifre, C. Sitges, P. Montoya and D. R. Chialvo (2010). "Modular organization of brain resting state networks in chronic back pain patients." Front Neuroinform 4: 116.

Baliki, M. N., P. C. Chang, A. T. Baria, M. V. Centeno and A. V. Apkarian (2014). "Resting-sate functional reorganization of the rat limbic system following neuropathic injury." Sci Rep 4: 6186.

Baliki, M. N., P. Y. Geha, A. V. Apkarian and D. R. Chialvo (2008). "Beyond feeling: chronic pain hurts the brain, disrupting the default-mode network dynamics." J Neurosci 28(6): 1398-1403.

Baliki, M. N., A. R. Mansour, A. T. Baria and A. V. Apkarian (2014). "Functional reorganization of the default mode network across chronic pain conditions." PLoS One 9(9): e106133.

Beck, A. T., N. Epstein, G. Brown and R. A. Steer (1988). "An inventory for measuring clinical anxiety: psychometric properties." J Consult Clin Psychol 56(6): 893-897.

Beck, A. T., C. H. Ward, M. Mendelson, J. Mock and J. Erbaugh (1961). "An inventory for measuring depression." Arch Gen Psychiatry 4: 561-571.

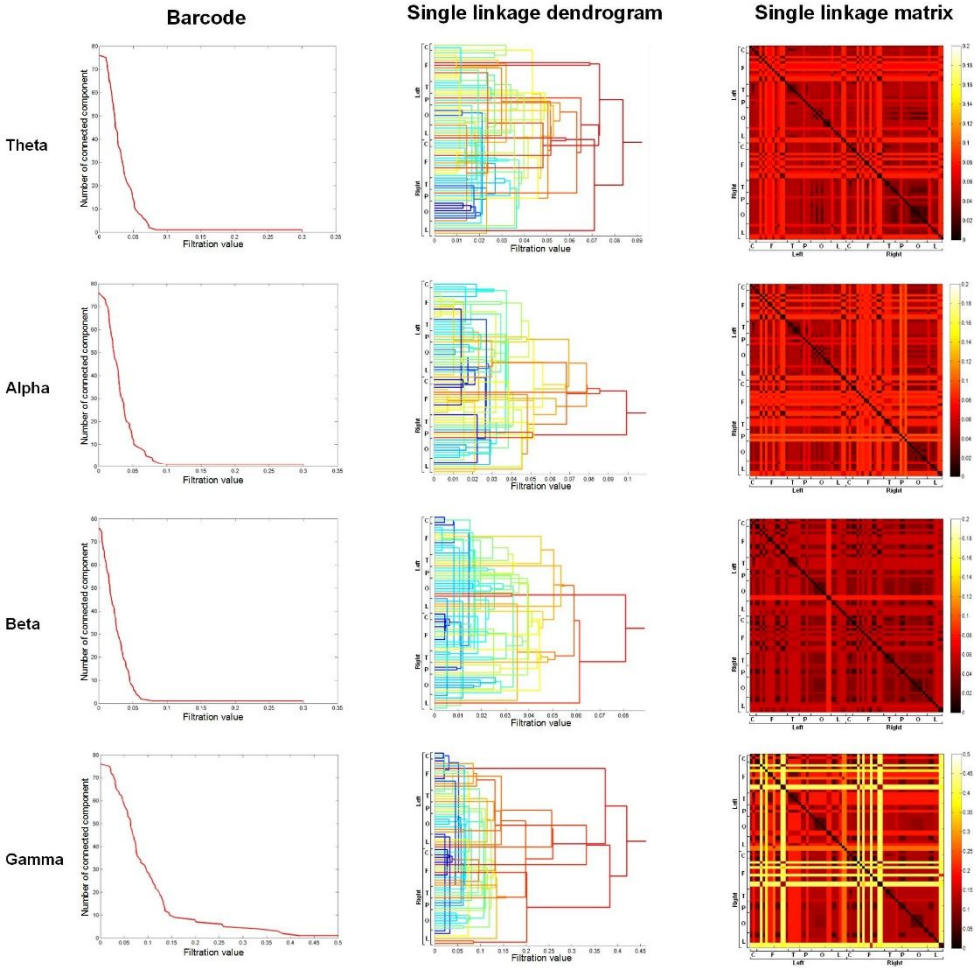
Bolwerk, A., F. Seifert and C. Maihofner (2013). "Altered resting-state functional connectivity in complex regional pain syndrome." J Pain 14(10): 1107-1115 e1108.
Buckner, R. L., J. R. Andrews-Hanna and D. L. Schacter (2008). "The brain's default network: anatomy, function, and relevance to disease." Ann N Y Acad Sci 1124: 1-38.
Bullmore, E. and O. Sporns (2009). "Complex brain networks: graph theoretical analysis of structural and functional systems." Nat Rev Neurosci 10(3): 186-198.
Burckhardt, C. S., S. R. Clark and R. M. Bennett (1991). "The fibromyalgia impact questionnaire: development and validation." J Rheumatol 18(5): 728-733.
Choi, W., M. Lim, J. S. Kim and C. K. Chung (2016). "Habituation deficit of auditory N100m in patients with fibromyalgia." Eur J Pain.
Choi, W., M. Lim, J. S. Kim, D. J. Kim and C. K. Chung (2015). "Impaired pre-attentive auditory processing in fibromyalgia: A mismatch negativity (MMN) study." Clin Neurophysiol 126(7): 1310-1318.
Cifre, I., C. Sitges, D. Fraiman, M. A. Munoz, P. Balenzuela, A. Gonzalez-Roldan, M. Martinez-Jauand, N. Birbaumer, D. R. Chialvo and P. Montoya (2012). "Disrupted functional connectivity of the pain network in fibromyalgia." Psychosom Med 74(1): 55-62.
Clauw, D. J., L. M. Arnold, B. H. McCarberg and FibroCollaborative (2011). "The science of fibromyalgia." Mayo Clin Proc 86(9): 907-911.
de Pasquale, F., S. Della Penna, A. Z. Snyder, L. Marzetti, V. Pizzella, G. L. Romani and M. Corbetta (2012). "A cortical core for dynamic integration of functional networks in the resting human brain." Neuron 74(4): 753-764.
Dhond, R. P., C. Yeh, K. Park, N. Kettner and V. Napadow (2008). "Acupuncture modulates resting state connectivity in default and sensorimotor brain networks." Pain 136(3): 407-418.
Farmer, M. A., M. N. Baliki and A. V. Apkarian (2012). "A dynamic network perspective of chronic pain." Neurosci Lett 520(2): 197-203.
Gross, J., J. Kujala, M. Hamalainen, L. Timmermann, A. Schnitzler and R. Salmelin (2001). "Dynamic imaging of coherent sources: Studying neural interactions in the human brain." Proc Natl Acad Sci U S A 98(2): 694-699.
He, Y., J. Wang, L. Wang, Z. J. Chen, C. Yan, H. Yang, H. Tang, C. Zhu, Q. Gong, Y. Zang and A. C. Evans (2009). "Uncovering intrinsic modular organization of spontaneous brain activity in humans." PLoS One 4(4): e5226.
Jin, S. H., W. Jeong, D. S. Lee, B. S. Jeon and C. K. Chung (2014). "Preserved high-centrality hubs but efficient network reorganization during eyes-open state compared with eyes-closed resting state: an MEG study." J Neurophysiol 111(7): 1455-1465.
Jin, S. H., W. Jeong, J. Seol, J. Kwon and C. K. Chung (2013). "Functional cortical hubs in the eyes-closed resting human brain from an electrophysiological perspective using magnetoencephalography." PLoS One 8(7): e68192.
Kim, D. J., M. Lim, J. S. Kim, K. M. Son, H. A. Kim and C. K. Chung (2014). "Altered white matter integrity in the corpus callosum in fibromyalgia patients identified by tract-based spatial statistical analysis." Arthritis

Rheumatol 66(11): 3190-3199.
Kim, E., H. Kang, H. Lee, H. J. Lee, M. W. Suh, J. J. Song, S. H. Oh and D. S. Lee (2014). "Morphological brain network assessed using graph theory and network filtration in deaf adults." Hear Res 315: 88-98.
Kim, J. Y., S. H. Kim, J. Seo, S. H. Kim, S. W. Han, E. J. Nam, S. K. Kim, H. J. Lee, S. J. Lee, Y. T. Kim and Y. Chang (2013). "Increased power spectral density in resting-state pain-related brain networks in fibromyalgia." Pain 154(9): 1792-1797.
Lee, H., H. Kang, M. K. Chung, B.-N. Kim and D. S. Lee (2012). "Persistent brain network homology from the perspective of dendrogram." Medical Imaging, IEEE Transactions on 31(12): 2267-2277.
Lim, M., J. S. Kim, D. J. Kim and C. K. Chung (2016). "Increased Low- and High-Frequency Oscillatory Activity in the Prefrontal Cortex of Fibromyalgia Patients." Front Hum Neurosci 10: 111.
Lopez-Sola, M., J. Pujol, T. D. Wager, A. Garcia-Fontanals, L. Blanco-Hinojo, S. Garcia-Blanco, V. Poca-Dias, B. J. Harrison, O. Contreras-Rodriguez, J. Monfort, F. Garcia-Fructuoso and J. Deus (2014). "Altered functional magnetic resonance imaging responses to nonpainful sensory stimulation in fibromyalgia patients." Arthritis Rheumatol 66(11): 3200-3209.
Martucci, K. T., W. R. Shirer, E. Bagarinao, K. A. Johnson, M. A. Farmer, J. S. Labus, A. V. Apkarian, G. Deutsch, R. E. Harris, E. A. Mayer, D. J. Clauw, M. D. Greicius and S. C. Mackey (2015). "The posterior medial cortex in urologic chronic pelvic pain syndrome: detachment from default mode network-a resting-state study from the MAPP Research Network." Pain 156(9): 1755-1764.
Melzack, R. (1987). "The short-form McGill Pain Questionnaire." Pain 30(2): 191-197.
Mu, Y., Y. Fan, L. Mao and S. Han (2008). "Event-related theta and alpha oscillations mediate empathy for pain." Brain Res 1234: 128-136.
Napadow, V., L. LaCount, K. Park, S. As-Sanie, D. J. Clauw and R. E. Harris (2010). "Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity." Arthritis Rheum 62(8): 2545-2555.
Oostenveld, R., P. Fries, E. Maris and J. M. Schoffelen (2011). "FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data." Comput Intell Neurosci 2011: 156869.
Pujol, J., D. Macia, A. Garcia-Fontanals, L. Blanco-Hinojo, M. Lopez-Sola, S. Garcia-Blanco, V. Poca-Dias, B. J. Harrison, O. Contreras-Rodriguez, J. Monfort, F. Garcia-Fructuoso and J. Deus (2014). "The contribution of sensory system functional connectivity reduction to clinical pain in fibromyalgia." Pain 155(8): 1492-1503.
Slepian, D. (1978). "Prolate Spheroidal Wave-Functions, Fourier-Analysis, and Uncertainty .5. Discrete Case." Bell System Technical Journal 57(5): 1371-1430.
Sporns, O. (2011). "The human connectome: a complex network." Ann N Y Acad Sci 1224: 109-125.
Taulu, S. and J. Simola (2006). "Spatiotemporal signal space separation method for rejecting nearby interference in MEG measurements." Phys Med Biol 51(7): 1759-1768.

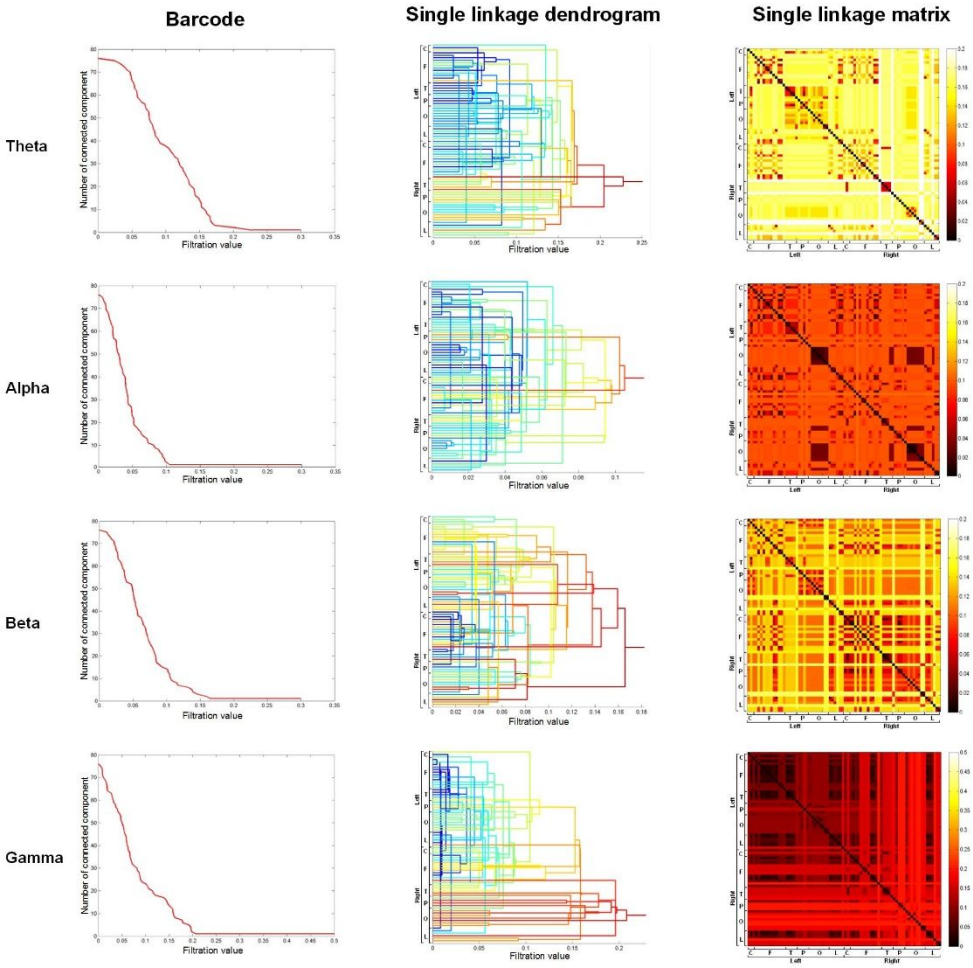
Tessitore, A., A. Russo, F. Conte, A. Giordano, M. De Stefano, L. Lavorgna, D. Corbo, G. Caiazzo, F. Esposito and G. Tedeschi (2015). "Abnormal Connectivity Within Executive Resting-State Network in Migraine With Aura." Headache 55(6): 794-805.
Tewarie, P., M. M. Schoonheim, C. J. Stam, M. L. van der Meer, B. W. van Dijk, F. Barkhof, C. H. Polman and A. Hillebrand (2013). "Cognitive and clinical dysfunction, altered MEG resting-state networks and thalamic atrophy in multiple sclerosis." PLoS One 8(7): e69318.
Tzourio-Mazoyer, N., B. Landeau, D. Papathanassiou, F. Crivello, O. Etard, N. Delcroix, B. Mazoyer and M. Joliot (2002). "Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain." Neuroimage 15(1): 273-289.
Vachon-Presseau, E., M. V. Centeno, W. Ren, S. E. Berger, P. Tetreault, M. Ghantous, A. Baria, M. Farmer, M. N. Baliki, T. J. Schnitzer and A. V. Apkarian (2016). "The Emotional Brain as a Predictor and Amplifier of Chronic Pain." J Dent Res.
Wang, J., B. Cao, T. R. Yu, B. Jelfs, J. Yan, R. H. Chan and Y. Li (2015). "Theta-frequency phase-locking of single anterior cingulate cortex neurons and synchronization with the medial thalamus are modulated by visceral noxious stimulation in rats." Neuroscience 298: 200-210.
Wang, L., C. Zhu, Y. He, Y. Zang, Q. Cao, H. Zhang, Q. Zhong and Y. Wang (2009). "Altered small-world brain functional networks in children with attention-deficit/hyperactivity disorder." Hum Brain Mapp 30(2): 638-649.
Wolfe, F., H. A. Smythe, M. B. Yunus, R. M. Bennett, C. Bombardier, D. L. Goldenberg, P. Tugwell, S. M. Campbell, M. Abeles, P. Clark and et al. (1990). "The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee." Arthritis Rheum 33(2): 160-172.

# List of Figures

## A. Healthy control

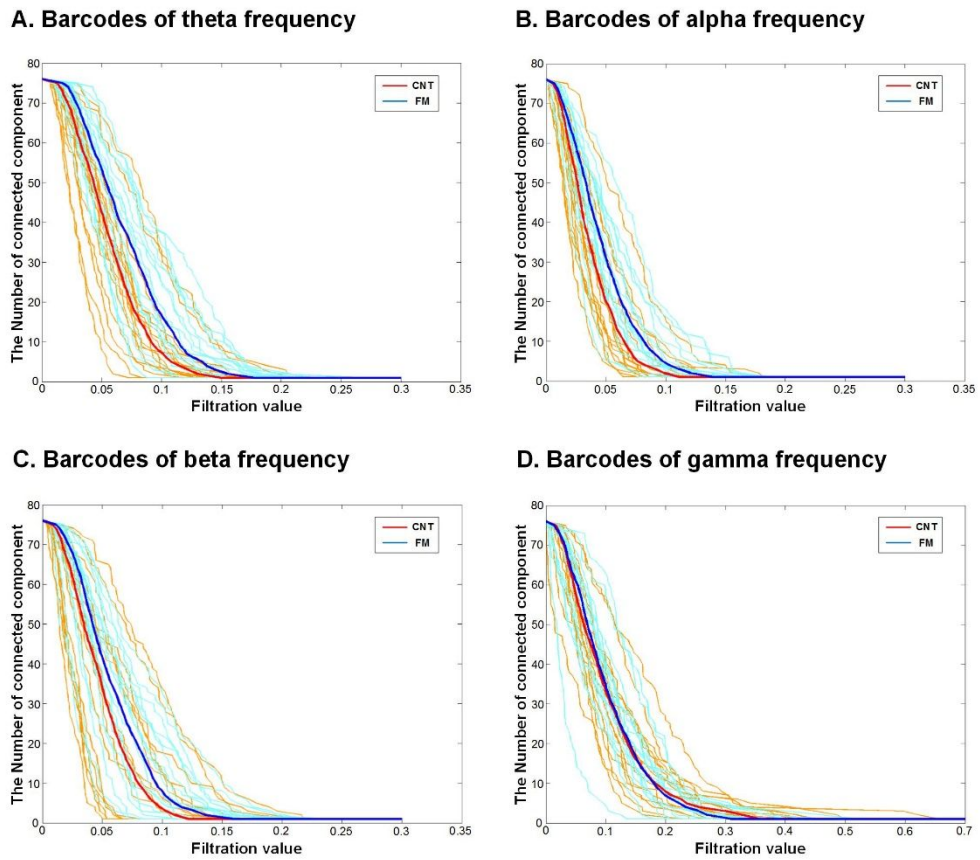


**B. Fibromyalgia**



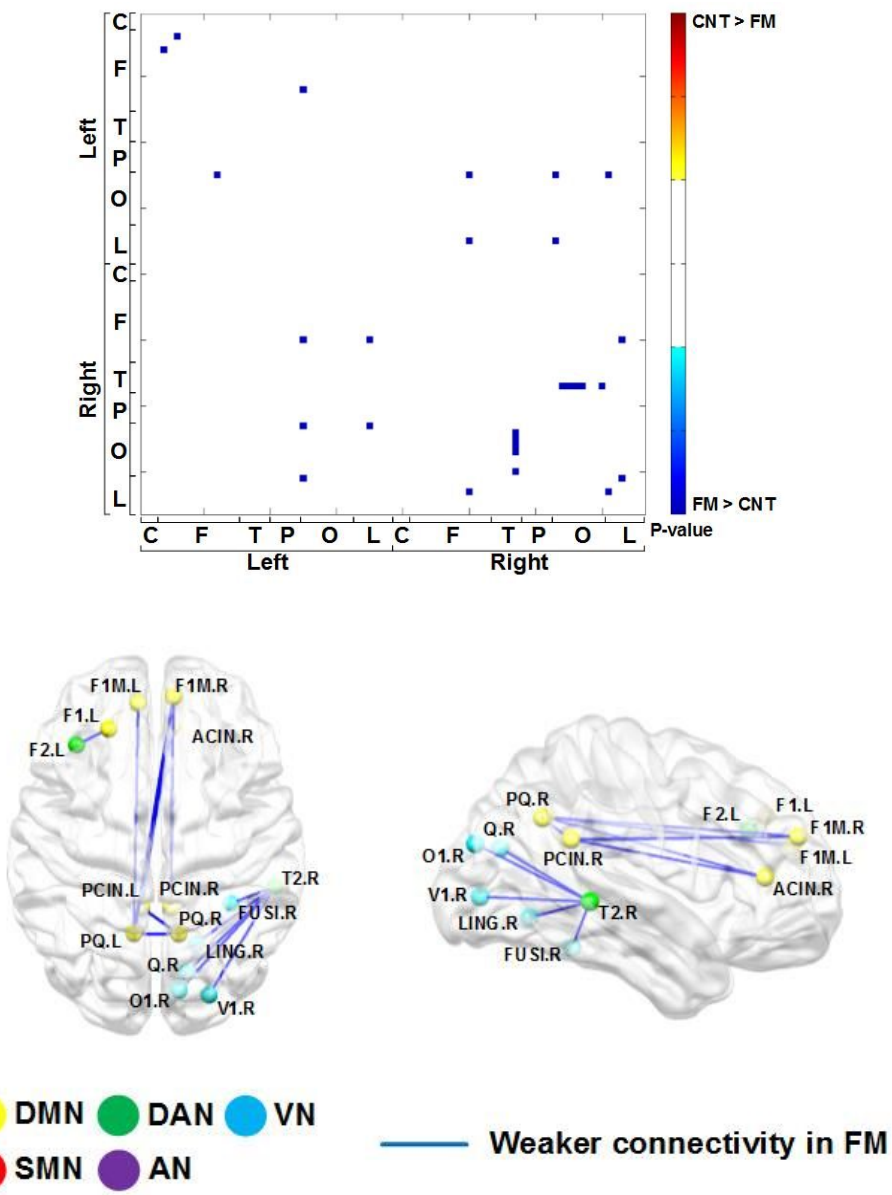

The barcode, Single linkage dendrogram and Single linkage matrix for a single subject of the fibromyalgia patients and healthy controls in 4 frequency bands (theta, alpha, beta and gamma) as example. (A) The barcode, dendrogram and matrix of the fibromyalgia patients. (B) The barcode, dendrogram and matrix of the healthy controls.

# Figure 2.



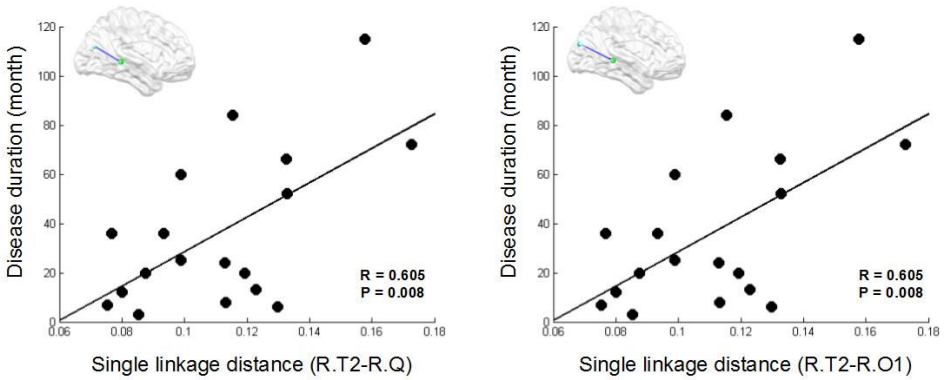

The barcode of the fibromyalgia and healthy controls over increasing filtration values. (A) The barcodes of theta frequency. (B) The barcodes of alpha frequency. (C) The barcodes of beta frequency. (D) The barcodes of gamma frequency. Azure ones indicate that the barcodes of FM subjects, and yellow-orange ones indicate that the barcodes of HC subjects. The blue one is the mean of barcode for FM group, and the red one is the mean of barcode for HC group.

**Figure 3.**




Local network properties based on persistent homology in theta band. (*upper*) Comparison of single linkage matrix (SLM) between FM patients and healthy controls. (*lower*) Difference in the resting state network between FM and HC ($p < 0.001$). L, left; R, right; F1, superior frontal gyrus, dorsolateral; F2, middle frontal gyrus; F1M, superior frontal gyrus, medial; PQ, precuneus; ACIN, anterior cingulate gyrus; PCIN, posterior cingulate gyrus; T2, middle temporal gyrus; V1, calcarine fissure; Q, cuneus; LING, lingual gyrus; O1, superior occipital gyrus; FUSI, fusiform gyrus; AN, auditory network; DAN, dorsal attention network; DMN, default mode network; SMN, somatosensory network; VN, visual network.

**Figure 4.**




Relationship between Single linkage distance (SLD) and disease duration in patients with fibromyalgia. R, right; Q, cuneus; O1, superior occipital gyrus.

# List of Tables

## Table 1. Characteristics of the study subjects

| Variable | FM | HC | Group difference |
|---|---|---|---|
| | n = 18 | n = 17 | *p*-value |
| *Demographic* | | | |
| Age | 45 (8.5) | 45.2 (8.9) | 0.98 |
| Education | 13 (2.3) | 13 (2.4) | 0.76 |
| Edinburgh score | 82 (19.9) | 88 (13.6) | 0.31 |
| *Clinical* | | | |
| Pain duration | 37 (31.7) | N.A. | N.A. |
| FIQ | 62 (13.4) | N.A. | N.A. |
| SF-MPQ (sensory) | 14 (6.8) | N.A. | N.A. |
| SF-MPQ (affective) | 6 (2.6) | N.A. | N.A. |
| SF-MPQ (total) | 20 (9.0) | N.A. | N.A. |
| *Psychological* | | | |
| BAI | 19 (7.0) | 3 (3.5) | < 0.001 |
| BDI | 24 (10.9) | 1 (1.2) | < 0.001 |

All the values are expressed as mean (standard deviation), unless otherwise indicated. N.A., not applicable; FIQ, Fibromyalgia Impact Questionnaire; SF-MPQ, Short-Form McGill Pain Questionnaire; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory.

## Table 2. List of the anatomical regions of interest

| Anatomical description | Label | MNI coordinates (left) | | |
|---|---|---|---|---|
| | | x | y | z |
| *Central* | | | | |
| Precentral gyrus | PRE | -43 | -7 | 46 |
| Rolandic operculum | RO | -44 | -22 | 47 |
| Postcentral gyrus | POST | -47 | -5 | 12 |
| *Frontal* | | | | |
| Superior frontal gyrus, dorsolateral | F1 | -22 | 36 | 38 |
| Superior frontal gyrus, orbital part | F1O | -18 | 43 | -18 |
| Middle frontal gyrus | F2 | -37 | 29 | 32 |
| Middle frontal gyrus, orbital part | F2O | -34 | 52 | -10 |
| Inferior frontal gyrus, opercular part | F3OP | -45 | 13 | 11 |
| Inferior frontal gyrus, triangular part | F3T | -46 | 29 | 8 |
| Inferior frontal gyrus, orbital part | F3O | -35 | 29 | -15 |
| Supplementary motor area | SMA | -8 | 9 | 55 |
| Superior frontal gyrus, medial | F1M | -8 | 48 | 25 |
| Superior frontal gyrus, medial orbital | F1MO | -7 | 51 | -10 |
| Gyrus rectus | GR | -7 | 35 | -22 |
| Paracentral lobule | PCL | -7 | -26 | 63 |
| *Temporal* | | | | |
| Insula | IN | -35 | 5 | -1 |
| Heschl gyrus | T2 | -44 | -22 | 9 |
| Superior temporal gyrus | T1 | -55 | -20 | 3 |
| Middle temporal gyrus | T2 | -54 | -34 | -1 |
| Inferior temporal gyrus | T3 | -52 | -28 | -26 |
| *Parietal* | | | | |
| Superior parietal gyrus | P1 | -26 | -58 | 55 |
| Inferior parietal, but supramarginal and angular gyri | P2 | -45 | -45 | 44 |
| Supramarginal gyrus | SMG | -55 | -32 | 29 |
| Angular gyrus | AG | -49 | -58 | 38 |
| Precuneus | PQ | -10 | -57 | 37 |
| *Occipital* | | | | |
| Calcarine fissure and surrounding cortex | V1 | -11 | -84 | 2 |
| Cuneus | Q | -14 | -75 | 23 |
| Lingual gyrus | LING | -18 | -63 | -7 |
| Superior occipital gyrus | O1 | -24 | -84 | 26 |

| | | | | |
|---|---|---|---|---|
| Middle occipital gyrus | O2 | -39 | -77 | 15 |
| Interior occipital gyrus | O3 | -41 | -75 | -11 |
| Fusiform gyrus | FUSI | -34 | -46 | -20 |
| *Limbic* | | | | |
| Anterior cingulate and paracingulate gyri | ACIN | -6 | 32 | 10 |
| Median cingulate and paracingulate gyri | MCIN | -8 | -16 | 38 |
| Posterior cingulate gyrus | PCIN | -7 | -46 | 27 |
| Parahippocampal gyrus | PHIP | -26 | -25 | -18 |
| Temporal pole: superior temporal gyrus | T1P | -37 | 10 | -26 |
| Temporal pole: middle temporal gyrus | T2P | -33 | 8 | -40 |

**Table 3. The significant difference of single linkage distance between FM and HC groups. (p < 0.001, permutation test, uncorrected for multiple comparison)**

| Single Linkage Distance | Region 1 | Region 2 | Region 1 Coordinates | | | Region 2 Coordinates | | | *p*-value |
|---|---|---|---|---|---|---|---|---|---|
| | | | x | y | z | x | y | z | |
| *Theta* | | | | | | | | | |
| FM > HC | | | | | | | | | |
| | L.F1 | L.F2 | -22 | 36 | 38 | -37 | 29 | 32 | 0.0005 |
| | L.F1M | L.PQ | -8 | 48 | 25 | -10 | -57 | 37 | 0.0008 |
| | L.PQ | R.F1M | -10 | -57 | 37 | 8 | 51 | 28 | 0.0099 |
| | L.PQ | R.PQ | -10 | -57 | 37 | 10 | -58 | 36 | 0.0007 |
| | L.PQ | R.ACIN | -10 | -57 | 37 | 7 | 37 | 11 | 0.0007 |
| | L.PCIN | R.F1M | -7 | -46 | 27 | 8 | 51 | 28 | 0.0009 |
| | L.PCIN | R.PQ | -7 | -46 | 27 | 10 | -58 | 36 | 0.0007 |
| | R.F1M | R.PCIN | 8 | 51 | 28 | 7 | -46 | 27 | 0.0007 |
| | R.ACIN | R.PCIN | 7 | 37 | 11 | 7 | -46 | 27 | 0.0009 |
| | R.T2 | R.V1 | 54 | -37 | -1 | 10 | -84 | 3 | 0.0004 |
| | R.T2 | R.Q | 54 | -37 | -1 | 14 | -75 | 23 | 0.0005 |
| | R.T2 | R.LING | 54 | -37 | -1 | 18 | -63 | -7 | 0.0099 |
| | R.T2 | R.O1 | 54 | -37 | -1 | 24 | -86 | 25 | 0.0002 |
| | R.T2 | R.FUSI | 54 | -37 | -1 | 34 | -45 | -20 | 0.0099 |
| *Alpha* | | | | | | | | | |
| FM > HC | | | | | | | | | |
| | L.PRE | L.V1 | -43 | -7 | 46 | -11 | -84 | 2 | 0.0009 |

FM, fibromyalgia; HC, healthy control; L, left; R, right; F1, superior frontal gyrus, dorsolateral; F2, middle frontal gyrus; F1M, superior frontal gyrus, medial; PQ, precuneus; ACIN, anterior cingulate gyrus; PCIN, posterior cingulate gyrus; T2, middle temporal gyrus; V1, calcarine fissure; Q, cuneus; LING, lingual gyrus; O1, superior occipital gyrus; FUSI, fusiform gyrus; PRE, precentral gyrus.

# Abstract in Korean

섬유근육통 (fibromyalgia)는 만성 통증 질환으로, 통증 자극 혹은 무통증 감각 자극에 대한 통증을 느끼는 증상을 보인다. 섬유근육통의 통증 기전에 대해서는 완벽히 알려지지 않았지만, 중추 신경에서 유래한 감각 증폭이 섬유근육통의 증상과 연관이 있음이 기존 연구에서 밝혀진 바 있다. 최근 휴지기 상태의 뇌 네트워크 연구에 의하면, 뇌 연결성의 차이가 섬유근육통 환자의 증상과 연관이 있음이 알려졌다. 일반적인 뇌 연결성 연구에 의해 밝혀진 네트워크 특성은 연구자의 주관이 개입된 임계점 (threshold)의 지정에 따라 영향을 받는다. 퍼시스턴트 네트워크 호몰로지 (Persistent network homology)는 모든 임계점에 대한 네트워크 특성을 봄으로써, 연구자 주관적인 임계점 설정에 따른 네트워크 특성 변화라는 문제점을 해결할 수 있다. 본 연구에서는 퍼시스턴트 네트워크 호몰로지를 도입하여 섬유근육통 환자의 휴지기 상태의 네트워크 특성을 다양한 주파수 대역에 따라 규명하고, 이들의 차이와 환자의 증상과의 연관성을 연구하고자 하였다.

본 연구에서는 나이와 성별이 일치한 17명의 정상인과 18명의 섬유근육통 환자를 대상으로, 휴지기 상태의 뇌자도 (magnetoencephalography, MEG)를 측정하였다. 측정된 뇌파는 세타 (4-7 Hz), 알파 (8-12 Hz), 베타 (13-30 Hz), 감마 (31-48 Hz) 대역별로 필터링을 하였고, 자동해부학적표지 (Automated Anatomical Labeling, AAL) 템플릿을 기준으로 하여, 모든 뇌 영역의 노드를 설정하고 빔포밍을 이용해 각 영역에서의 뇌 활성을 계산하였다. 퍼시스턴트 호몰로지를 적용하기 위해 피어슨 상관관계를 이용하여

기능적 거리를 계산한 후, 바코드 (barcode), 단일접합계통수 (single linkage dendrogram, SLD)와 단일접합행렬 (single linkage matrix, SLM)를 구하였다.

세타 영역에서 바코드의 기울기는 섬유근육통 환자에게서 완만하게 감소됨을 나타내었고, 이는 전체적인 네트워크 연결성이 섬유근육통 환자에게서 낮음을 의미한다. 어느 영역에서 기능적 연결성이 감소하는지는 단일접합계통수를 통해 알 수 있다. 섬유근육통 환자에서 디폴트 모드 네트워크 (default mode network, DMN) 영역간 연결성의 감소가 나타났으며, 청각과 관련된 측두엽과 시각 영역 간의 낮은 기능적 연결성이 관찰되었다. 측두엽과 시각 영역의 낮은 연결성은 환자군의 통증 기간과 양적인 상관관계를 보였다.

본 연구에서는 세타 대역에서 섬유근육통 환자의 휴지기 네트워크의 연결성이 변화가 있었음을 밝혀냈다. 나아가, 섬유근육통의 만성화는 휴지기 네트워크의 부분인, 디폴트 모드 네트워크와 감각 네트워크의 연결성을 재구성하는데 영향을 주었음을 반영한다.

**주요어**: 섬유근육통, 휴지기 네트워크, 만성통증, 퍼시스턴트 네트워크 호몰로지, 뇌자도

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