Changes in Structural and Functional Neural Networks in Central Post-stroke Pain following Intracerebral Hemorrhage

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Directed by Professor Ji-Cheol Shin

The Doctoral Dissertation submitted to the Department of Medicine, the Graduate School of Yonsei University in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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ABSTRACT

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Central post-stroke pain (CPSP) is one of the most refractory neuropathic pains following stroke. Injury in the spinothalamic pathway appears to be critical in the development of CPSP, but changes in activity in multiple brain regions may also be related to its development. Various distinct pain syndromes have accordingly been linked to specific patterns of alteration in the brain's structural and functional connectivity. However, it is not clearly understood whether CPSP is also associated with cortical plasticity. To determine this, the functional and anatomical integrity of thalamo-cortical network and pain-processing network in patients with CPSP following intracerebral hemorrhage (ICH) were investigated using functional magnetic resonance imaging (fMRI) and diffusion tensor imaging probabilistic tractography.

Forty-three patients with ICH were examined. Probabilistic tractography was performed with five cortical seeds (prefontal, parieto-occipital, motor, somatosensory and temporal) to examine thalamocortical pathways for structural connectivity. Group differences in asymmetry of mean fractional anisotropy, mean diffusivity, and tract volume were measured. A laterality index (LI) was used to determine the asymmetry of diffusion tensor tractography parameters between brain hemispheres. Resting-state fMRI scans

were made to investigate the functional connectivity of the thalamocortical network. In addition, the functional connectivity of the pain-processing regions was explored. Data were analyzed using a seed voxel correlation analysis.

In comparison to the non-CPSP group, the CPSP group exhibited significantly higher mean diffusivity LI levels and lower fractional anisotropy LI levels in the thalamo-occipitoparietal tract. Significantly increased functional connectivity was found between the ipsilesional insula and the ipsilesional orbitofrontal cortex, paracingulate gyrus, dorsolateral prefrontal cortex, superior frontal gyrus and the contralesional cerebellar lobule VIII. The fractional anisotropy LI levels of in the thalamo-occipitoparietal tract were shown to be significantly negatively correlated with resting state functional connectivity of the ipsilesional insula to the ipsilesional orbitofrontal cortex. Pain intensity was significantly correlated with the functional connectivity of the ipsilesional insula to the ipsilesional dorsolateral prefrontal cortex.

This study showed that CPSP was accompanied by the disruption of white matter properties in the thalamocortical pathway including spinothalamic tract and changes in functional connectivity between brain regions processing the cognitive-affective aspect of pain.

Key words: diffusion tensor tractography, resting state connectivity, brain functional MRI, central post-stroke pain, hemorrhage, stroke

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I. INTRODUCTION

Central post-stroke pain (CPSP) is defined as a constant or intermittent pain arising as a direct consequence of a cerebrovascular lesion.[1] The distribution of pain can range from a part of the body to the entire hemibody, with or without negative or positive sensory signs.[2] CPSP occurs in up to 8% of patients with stroke and could be long-lasting, even life-long.[3] It is a great burden to the patient,[2] associated with an increase in functional dependence,[4] and reduces quality of life.[5] The management of CPSP remains challenging; no beneficial effects of any therapies have been found in randomized controlled trials.[6] Identification of the underlying pathophysiology is required to develop an appropriate strategy of treatment.

CPSP is assumed to be the result of a lesion of the normal pain pathways. Classically, sensory deafferentation and thalamic hypoactivity are thought to play an important role in CPSP.[1,7] Disruption of the spinothalamic pathway or its target regions are associated with a considerable risk for the development of CPSP.[8] The volume of the spinothalamic tract was significantly decreased in the affected hemisphere in the patients with CPSP.[9] A lesion in the posterior thalaus, where a major portion of the afferents of the spinothalamic tract are known to terminate, seems to be crucial in the development CPSP.[10,11] Thalamic hypoactivity is observed in a variety of neuropathic pains, as well as in CPSP.[7] However, not all lesions of the spinothalamic tract induce pain. In addition, CPSP could be made

to disappear following additional lesion affecting thalamocortical connections.[12,13] While the spinothalamic tract mainly targets the posterior insula, medial parietal operculum and mid-cingulate cortex,[14] previous studies focused on the spino-thalamo-primary somatosensory cortical pathway.[9,15] Extensive thalamocortical connectivity needs to be investigated in CPSP.

Recent studies suggest that CPSP results from not only damage to a specific region, but also a maladapted network reorganization problem following a stroke.[16,17] Several pieces of evidence support this hypothesis. CPSP usually arises from weeks to months after a stroke rather than immediately.[5,18] Partial injury rather than complete injury and asynchrony transmission rather than abolition in the spinothalamic tract may contribute to the prevalence of CPSP.[15,19] The improvement of symptoms was related to a change of activity in the distributed brain regions in CPSP.[20] In addition, decreases of gray matter volume have been revealed in a wide range of the cortical region including the secondary somatosensory cortex, ventrolateral prefrontal and temporal cortex in CPSP patients compared with nonpain patients.[13] These results suggest that CPSP is a consequence of network reorganization. To our knowledge, however, no study has investigated the network organization in CPSP.

Developments in neuroimaging techniques enable non-invasive analysis of the structural and functional status of the brain. Diffusion tensor imaging (DTI) is used to identify alterations of brain white matter. Functional magnetic resonance imaging (fMRI) is applied to explore temporal correlations of neural activity between brain regions. Previous studies have reported structural and functional reorganization associated with neuropathic pain,[21-24] and it has been proposed that these changes reflect the maladaptive physiology of various types of pain.[25]

In this study, we investigated changes in structural and functional neural networks in central post-stroke pain following intracerebral hemorrhage (ICH) using DTI and resting-state fMRI. We hypothesized that

1. compared to patients without CPSP, specific thalamocortical networks are differently affected in patients with CPSP;
2. functional connectivity of brain regions involved in the processing of pain is also altered in patients with CPSP; and
3. alteration of thalamocortical networks and pain networks are related in patients with CPSP.

II. MATERIALS AND METHODS

1. Subjects

Patients with ICH were consecutively recruited from a tertiary inpatient rehabilitation hospital from 2013 to 2017. The inclusion criteria were: 1) first-event stroke, 2) unilateral solitary subcortical ICH (thalamus or basal ganglia) confirmed by brain computed tomography (CT) or magnetic resonance imaging, 3) aged 18 years or older, and 4) no severe cognitive deficits (Mini-Mental Status Examination (MMSE) scores $\geq$ 20 points).

Each patient underwent a clinical examination, including medical history, stroke severity, sensorimotor impairment, pain characteristics, a pain drawing, and depressive mood. The National Institute of Health Stroke Scale (NIHSS) was used to assess stroke severity. The motor and sensory subscales of the Fugl-Meyer (FM) assessment were administered to measure sensorimotor impairment; each of which is graded on a three-point scale; with the motor score ranging from 0 to 100 and the sensory score from 0 to 24. Other causes of pain, such as spasticity and shoulder pain, were also examined. To exclude the possible impact of medication, which could be related to pain and brain metabolism, such as anticonvulsants, antidepressants, sedative hypnotics, benzodiazepines, antipsychotics, and muscle relaxants; drug consumption was quantified using the Medication Quantification Scale (MQS).[26] Depressive symptoms were measured using the Geriatric Depression Scale (GDS).

CPSP was defined as spontaneous pain within an area of the body

corresponding to the brain lesion that emerged at or after the onset of stroke.[1] According to these criteria, patients were assigned to a CPSP or non-CPSP (control) group. Patients with CPSP were asked to rate the median pain intensity during the previous 48 hours on a numeric rating scale (NRS, 0 ‘‘no pain,’’ and 10 ‘‘worst imaginable pain’’). Demographic and clinical data were analyzed using SPSS Statistics software, v. 23.0 (IBM, Armonk, NY, USA). For categorical variables, the chi-squared test and Fisher’s exact test were used. The Mann-Whitney U test was used for continuous variables. To assess possible confounding factors, correlations among all continuous variables and the NRS were evaluated using Spearman’s rank correlation coefficient. P values < 0.05 were considered significant.

All patients or their family members gave informed consent, and all procedures were performed with the approval of the Institutional Review Board for Clinical Studies of Yonsei University College of Medicine, Seoul, Republic of Korea. The protocols conformed to the ethical standards of the Declaration of Helsinki for the protection of human subjects.

2. Brain MR imaging acquisition

For structural imaging, high-resolution T1-weighted MRI volume data were obtained using a Philips 3T scanner (Intera Achieva, Philips Medical System, Best, The Netherlands) with a SENSE head coil. The scanning parameters of the 3-dimensional magnetization-prepared rapid gradient echo (3D MPRAGE) sequence were an axial acquisition with a 224 × 256 matrix, field of view = 220 mm, voxel size = 0.98 × 0.98 × 1.2mm^3, echo time = 4.6 ms, repetition time = 9.6 ms, flip angle = 8 and slice gap = 0 mm. The T2-weighted images were acquired axially with a 400 × 319 matrix, field of view = 230 mm, voxel size = 0.45 × 0.45 × 5mm^3, echo time = 80 ms, repetition time = 3000 ms, flip angle = 90 and slice gap = 2 mm. The T2-weighted and fluid attenuation inversion recovery images were acquired axially with a 352 × 238 matrix, field of view = 230 mm, voxel

size = 0.45 × 0.45 × 5mm^3, echo time = 125 ms, repetition time = 11000 ms and slice gap = 2 mm.

Diffusion tensor images (DTI) were obtained using a single-shot echo-planar acquisition with the following parameters: 112 × 112 acquisition and a 128 × 128 reconstructed matrix, field of view = 220 mm, voxel size = 1.72 × 1.72 × 2mm^3, SENSE factor 2, echo time = 70 ms; shortest repetition time = 13000 ms, flip angle = 90, slice gap = 0 mm, two averages per slice, b-factor = 600 s/mm^2, non-cardiac gating and 70 axial slices. We acquired diffusion-weighted images from 45 non-collinear, non-coplanar directions with a baseline image without diffusion weighting.

We acquired 165 axial volume scans of resting state fMRI from each subject using a T2-weighted single shot echo planar imaging sequence using a 3T Philips MRI scanner with the following parameters: voxel size = 2.75 × 2.75 × 4.8mm^3, slice number = 29 (interleaved), matrix = 80 × 80, slice thickness = 4.8 mm, repetition time = 2000 ms, echo time = 30 ms, field of view = 209 × 220 mm^2. Foam pads were used to reduce head motion during echo planar imaging data acquisition. During each scan, subjects were instructed to keep their eyes closed, rest without moving and attempt to sleep for 5 minutes.

3. Lesion mapping and analysis

Lesions were delineated manually from raw T1-weighted images by means of the MRIcro software (http://www.mricro.com; University of South Carolina, Columbia, SC, USA). Each lesion was registered, resampled to a voxel size of 2 × 2 × 2 mm^3, and normalized to a standard brain template using Statistical Parametric Mapping 12 software (http://www.fil.ion.ucl.ac.uk/spm/; Wellcome Department of Cognitive Neurology, London, UK). We performed a direct statistical comparison of lesions to identify the difference in lesion distribution between patients with CPSP and without CPSP, using voxel-by-voxel χ^2 analyses for each voxel that was damaged in at least one patient.[27] Statistical

significance was defined as false discovery rate (FDR)-corrected $p < 0.05$.

4. DTI processing and probabilistic tractography

The analysis of the DTI was conducted using the FMRIB Software Library (http://www.fmrib.ox.ac.uk/fsl). Image artefacts due to eddy current distortions and head movements were corrected by registering the diffusion tensor images to the first $b = 0$ image. The diffusion tensor was estimated at each voxel. Maps of the diffusion indices such as mean diffusivity (MD) and fractional anisotropy (FA) were obtained. The probability distributions on 2 fiber directions at each voxel were calculated. Diffusion-weighted images were co-registered to the anatomical image using a rigid-body six-parameter transformation, and anatomical image co-registered to the standard MNI 152 template using a non-linear transformation.

Regions of interests (ROI) were extracted from FSL's Harvard–Oxford Cortical and Subcortical Structural probabilistic atlases thresholded at 50%.[28] Five cortical ROIs in each hemisphere were defined according to differential connectivity with thalamus, consistently reported in previous studies as follows:[29-31] prefrontal, motor and premotor, somatosensory, temporal and occipital and parietal lobes (Figure 1).

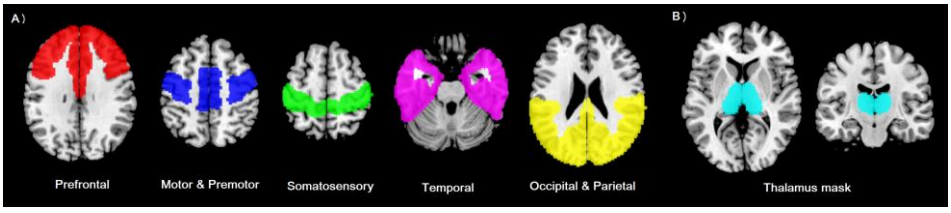

Figure 1. (A) The cortex is partitioned on the basis of major anatomical landmarks into five nonoverlapping regions using a surface-based ROI. (B) Thalamus ROI mask. All masks are shown overlaid on the standard MNI brain.

An exclusion mask was also created to investigate only direct pathways from

the thalamus to the target cortices. The exclusion mask consisted of the contralateral hemisphere, the brain stem and the other cortical regions on the ipsilateral hemisphere. ROIs in standard space were transformed to diffusion space.

Probabilistic tractography was performed from the thalamus to the target cortical regions for each hemisphere. For each tract, 5000 streamlines were generated from all voxels within the seed masks, with a 0.5 mm step length, a curvature threshold of 0.2 and 2000 steps. Raw tracts were thresholded at least at 20 samples in order to remove voxels with very low connectivity probability (Figure 2).

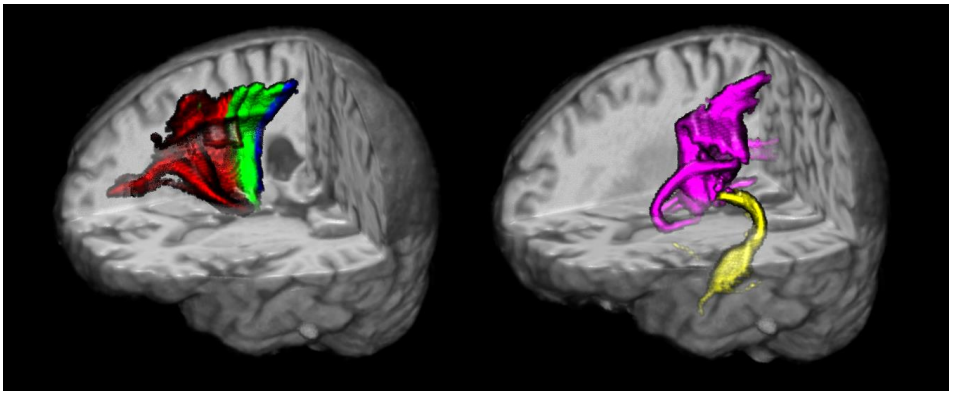

Figure 2. Examples of probabilistic fiber-tracking results. The right thalamo-prefrontal pathway, the right thalamo-motor pathway, the right thalamo-somatosensory pathway, the right thalamo-temporal pathway, and the left thalamo-parieto-occipital pathway are shown in red, green, blue, yellow and violet, respectively.

A laterality index (LI) of mean values of FA and MD was measured to determine the asymmetry of parameters between the hemispheres: LI = (the value of a tract in the affected hemisphere - the value of a tract in the unaffected hemisphere) / (the value of a tract in the affected hemisphere + the value of a tract

in the unaffected hemisphere). The differences of in the LI between the patients with CPSP and the patients without CPSP were analyzed using the independent t-test.

5. fMRI processing and analysis

Data analysis was performed using the Functional Connectivity (CONN) toolbox version 17 (http://web.mit.edu/swg/software.htm) implanted Statistical Parametric Mapping (SPM) version 12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Anatomical and functional datasets were flipped from right to left in patients with a right-sided lesion to ensure that all lesions were located on the same (left) side of the brain.

The functional images were adjusted for head motions, segmented white matter and cerebrospinal fluid images, coregistered to T1-weighted images, spatially normalized to a template space using non-linear transformation and smoothed using an 8mm full-width half-maximum Gaussian kernel. The preprocessed images were band-pass filtered to 0.008Hz~0.09Hz. White matter, cerebrospinal fluid (CSF), and physiological noise source reduction were taken as confounds, following the implemented CompCor strategy.[32] In addition to cortical ROIs defined to examine thalamocortical connectivity, we also investigated the functional connectivity of the 11 brain regions which are consistently reported to be involved in the pain process:[7] bilateral primary somatosensory cortex (S1), bilateral parietal operculum including secondary somatosensory cortex, bilateral posterior parietal cortex (PPC), bilateral lateral prefrontal cortex, bilateral insula and anterior cingulate cortex (ACC). All ROIs were derived from the FSL-Harvard-Oxford Atlas (Harvard Center for Morphometric Analysis, Charlestown, MA, USA) or CONN's ICA analysis of HCP dataset provided by the CONN toolbox.

Functional connectivity maps for each of the ROIs were created for each patient by computing the temporal correlation between the BOLD signals from a

given voxel to all other voxels in the brain using a multiple regression general linear model. Subsequently, connectivity analysis at the group level was performed. Functional connectivity strengths were generated by converting the correlation coefficients to Fisher transformed z-scores. Independent-sample t-tests for between-group differences were performed with a significance threshold using a voxel level threshold of $p < 0.001$ and a cluster-level FDR-corrected $p < 0.05$ for multiple comparisons. Age, sex, onset duration and MQS were always used as nuisance variables.

6. Correlational analysis among the thalamocortical network, pain network and pain severity

In cases in which a significant group difference in seed-voxel connectivity, connectivity values were extracted. Correlation analysis was performed among the factors showing group differences. Additionally, we conducted correlation analysis between connectivity and NRS scores to evaluated the relationship of the functional connectivity and pain severity.

III. RESULTS

1. Demographic and clinical characteristics

A total of 43 patients were finally enrolled in the study (Figure 3). 21 patients had CPSP. 16 patients were administered at least one agent that could be classified as pain medication. There were no statistically significant differences between patients in the CPSP and non-CPSP group in age, gender, duration since stroke onset, injured side, lesion volume, NIHSS, FM motor, FM sensory, MMSE, GDS, and MQS scores ($P \geq 0.05$ for all; Table 1). For the CPSP group, the median of the mean pain intensity was 5.0 (NRS score; range, 2 - 6).

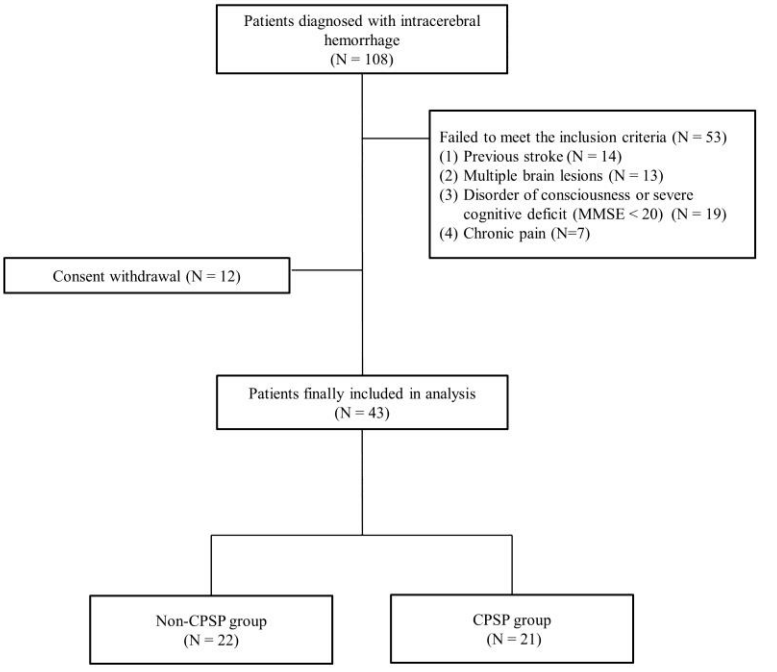

Figure 3. Flow chart showing patient selection according to inclusion/exclusion criteria

Table 1. Clinical characteristics of patients with intracerebral hemorrhage

	Non-CPSP (N=22)	CPSP (N=21)	*P* value
Age	61 (13)	55 (17.5)	0.11
Gender			
Male	10 (47.6)	13 (61.9)	0.54
Female	11 (52.4)	8 (38.1)	
Onset duration (month)	1.3 (2.4)	1.5 (32.3)	0.25
Lesion location			0.34
Left	6 (28.6)	15 (71.4)	
Right	10 (47.6)	11 (52.4)	
Lesion volume (cc)	2.7(4.0)	4.4(5.1)	0.40
NIHSS	6 (8.5)	3 (5.0)	0.12
FM motor	47 (67.0)	86 (46.0)	0.07
FM sensory	18 (4.0)	18 (5.0)	0.66
MMSE	26 (5.5)	28 (2.0)	0.08
GDS	10 (16.5)	12 (14.0)	0.82
MQS	0 (3.4)	0 (6.2)	0.29
Mean pain intensity (NRS)	0	5 (2)	<0.001*

Values are presented as median (interquartile range) or number (%)

NIHSS = National Institute of Health Stroke Scale (0 - 42)

FM motor = Fugl-Meyer motor assessment (0 - 100)

FM sensory = Fugl-Meyer sensory assessment (0 - 24)

MMSE = Mini Mental State Examination (0 - 30)

GDS = Geriatric Depression Scale (0 - 30)

MQS = Medication Quantification Scale

NRS = Numeric Rating Scale (0 - 10)

CPSP = Central Post-stroke Pain

*p < 0.001

2. Group differences in lesion location

The overlay of lesions for all patients is shown in Figure 4A. In patients without CPSP, the maximum lesion overlap was observed in the ventral posterior lateral nucleus of the thalamus (Figure 4B, n = 16 out of 22 lesions; MNI coordinate -18/-22/4), whereas lesions in the pulvinar nucleus of the thalamus were observed mainly in patients with CPSP (Figure 4C, n = 10 out of 21 lesions; MNI coordinate -18/-24/-6). However, there were no statistically significant differences between groups, as identified by a $\chi 2$ analysis.

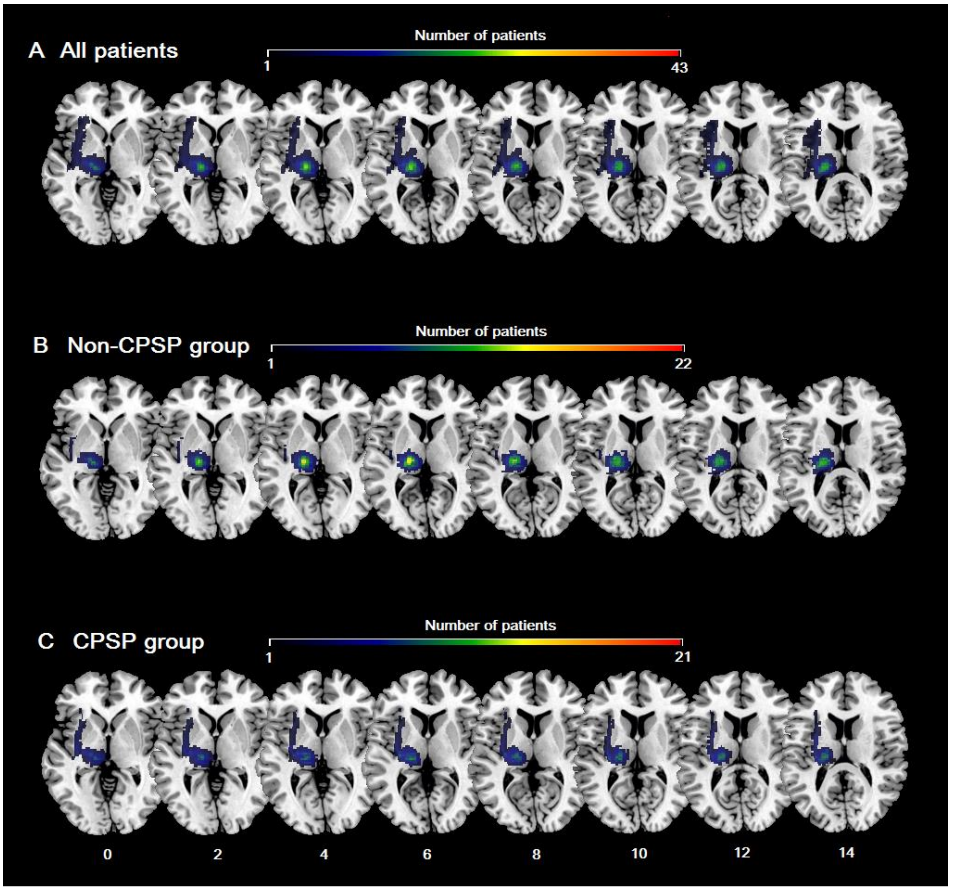

Figure 4. Overlay lesion plots for (A) all 43 patients included in our study, (B) a subgroup of 22 patients without CPSP, and (C) a subgroup of 21 patients with CPSP. Color bars indicate the number of lesion overlaps.

3. Group differences in structural and functional thalamocortical connectivity

The CPSP group demonstrated significantly decreased LI of FA and increased LI of MD of the thalamo-occipitoparietal tract. No other group difference in FA and MD within the regional thalamocortical tracts was found (Table 2).

There was no significant difference in functional thalamocortical connectivity between the CPSP and the non-CPSP group.

Table 2. Group comparison of the laterality index for individual thalamo-cortical pathways

	FA			MD		
	Non-CPSP (N=22)	CPSP (N=21)	*P* value	Non-CPSP (N=22)	CPSP (N=21)	P value
Thalamo-prefrontal	-0.26(0.04)	-0.19(0.06)	0.930	0.004(0.05)	-0.004(0.06)	0.734
Thalamo-motor	-0.05(0.06)	-0.03(0.04)	0.505	0.022(0.08)	0.02(0.05)	0.263
Thalamo-somatosensory	-0.07(0.13)	-0.05(0.09)	0.443	0.01(0.09)	0.01(0.08)	0.372
Thalamo-temporal	-0.01(0.08)	-0.02(0.08)	0.890	0.016(0.07)	-0.02(0.08)	0.148
Thalamo-occipitoparietal	-0.03(0.08)	-0.04(0.05)	0.036*	0.004(0.07)	0.04(0.10)	0.046*

Values are presented as median (interquartile range)
*P < 0.05

4. Group differences in the functional connectivity of pain-processing regions

The ROI to voxel analysis showed significant group differences in the functional connectivity of ipsilesional insula and ipsilesional PPC. Compared with patients without pain, patients with CPSP displayed significantly increased connectivity between the ipsilesional insula and ipsilesional orbitofrontal cortex (OFC), paracingulate gyrus (PCG), dorsolateral prefrontal cortex (DLPFC), superior frontal gyrus (SFG) and contralesional cerebellar lobule VIII (Figure 5A, Table 3). In addition, the CPSP group showed significantly increased connectivity between ipsilesional PPC and ACC/PCG (Figure 5B, Table 3). None of the other seed regions showed any significant differences in functional connectivity.

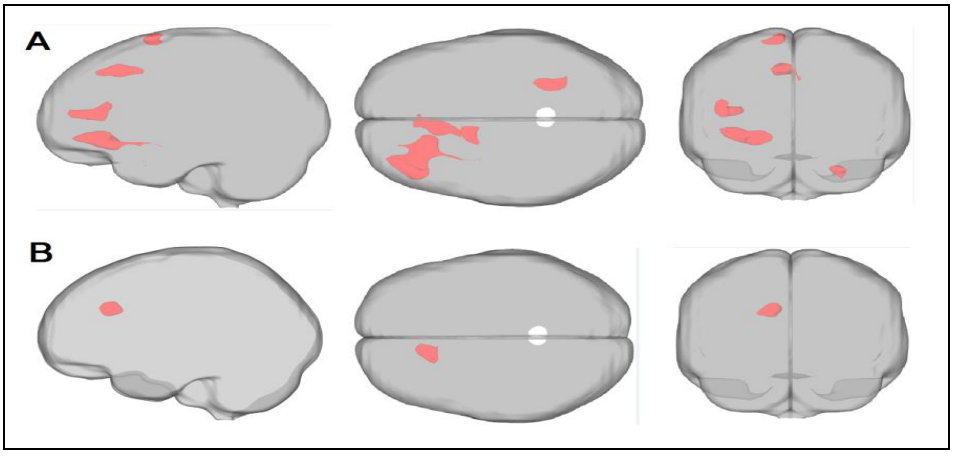

Figure 5. Brain regions show significant differences in resting state functional connectivity between the CPSP and non-CPSP group. (A) Brain regions exhibiting enhanced resting state functional connectivity with the ipsilesional insula in the CPSP group compared with the non-CPSP group. (B) Brain regions exhibiting enhanced resting state functional connectivity with the ipsilesional posterior parietal cortex in the CPSP group compared with the non-CPSP group. All statistical images are thresholded at a voxel level threshold of $p < 0.001$ and a cluster-level FDR-corrected $p < 0.05$.

Table 3. Peak MNI coordinates for regions with significant increased resting state functional connectivity in the CPSP patients compared with the non-CPSP patients

Anatomical Area		MNI coordinate			T-value	Volume (voxels)
		x	y	z		
With left insula seed						
OFC	Ipsi	-18	30	-14	7.52	885
PCG	Ipsi	-2	24	46	4.87	409
	Ipsi	-46	36	10	5.11	390
DLPFC						
SFG	Ipsi	-6	2	74	4.59	184
cVIII	Con	26	-48	-42	5.62	236
With left PPC seed						
ACC	Ipsi	-14	26	28	6.00	277

MNI, Montreal Neurological Institute; OFC, orbitofrontal cortex; PCG, paracingulate gyrus; DLPFC, dorsolateral prefrontal cortex; SFG, superior frontal gyrus; cVIII, cerebellar lobule VIII; PPC, posterior parietal cortex; ACC, anterior cingulate cortex; Ipsi, ipsilesional; Con, contralesional.

5. The relationship between the thalamocortical network and the pain network

In the CPSP group, a significant negative correlation was found between the LI of the FA of the thalamo-occipitoparietal tract and the resting state functional connectivity of the ipsilesional insula to the ipsilesional orbitofrontal cortex (Spearman's rho = - 0.462, p = 0.035; Figure 6). In contrast, no significant correlation was found in the non-CPSP group between the LI of white matter properties and the resting state functional connectivity of ROIs.

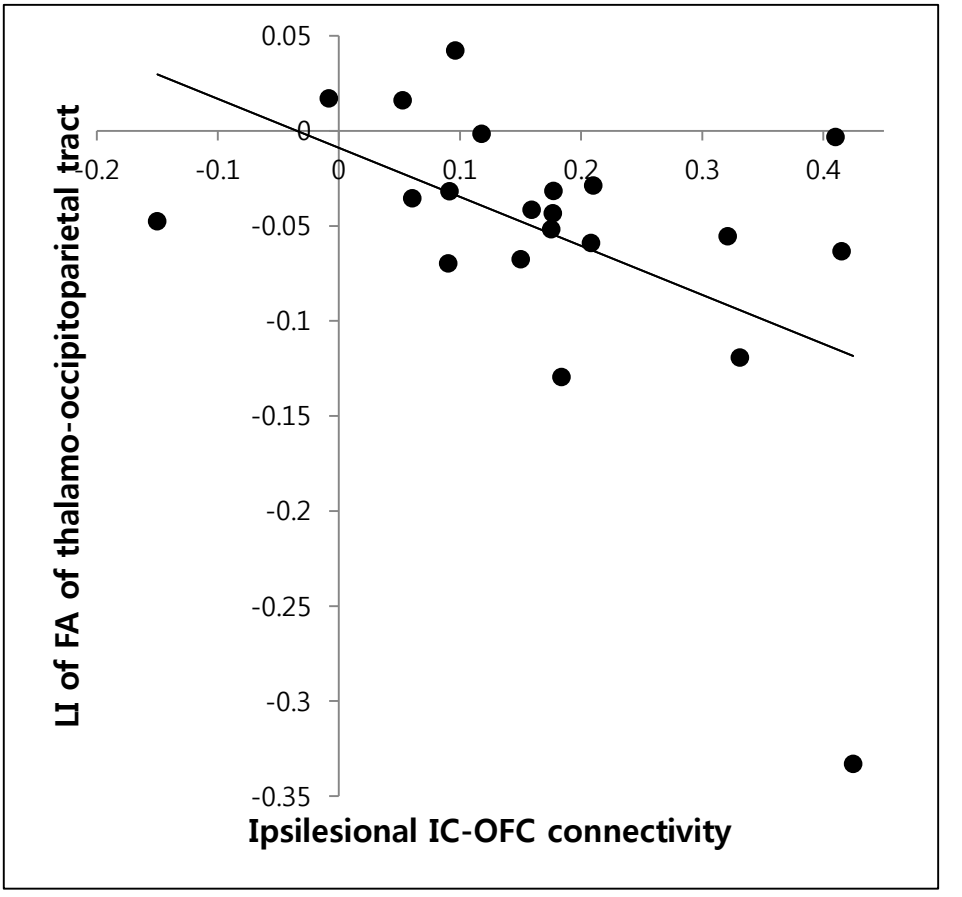

Figure 6. Correlation between LI of FA of the thalamo-occipitoparietal tract and the resting state functional connectivity of the ipsilesional insula to the ipsilesional OFC in patients with CPSP

6. The relationship between the severity of CPSP and resting-state functional connectivity

In the CPSP group, pain severity measured by NRS showed a significantly negative correlation with the resting state functional connectivity of iplesional insula to the ipsilesional DLPFC (Spearman's rho = - 0.588, p = 0.005; Figure 7).

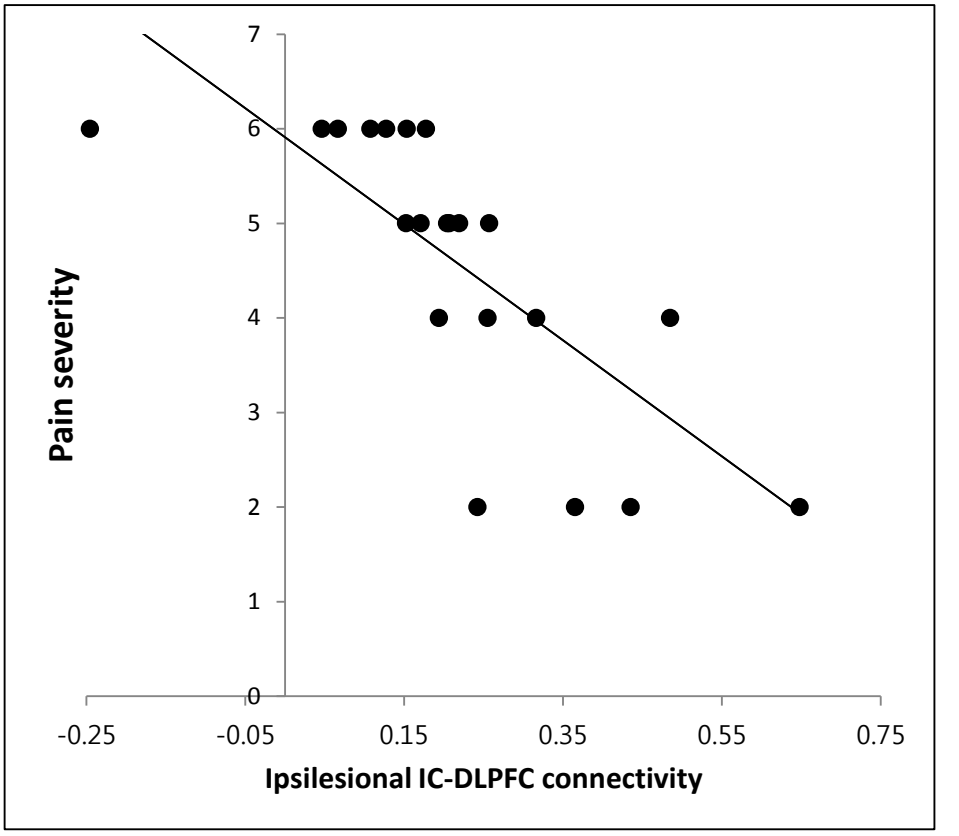

Figure 7. Correlation between the severity of CPSP and the resting state functional connectivity of the iplesional insula to the ipsilesional DLPFC in patients with CPSP

IV. DISCUSSION

In this study, there were no statistically significant differences between the patients with and those without CPSP in clinical characteristics, lesion volume and lesion location. Compared with the non-CPSP group, significant asymmetry was found in the microstructure of the thalamo-occipitoparietal tract in the CPSP group. Increased functional connectivity of ipsilesional insula and ipsilesional PPC with various brain regions were revealed in patients with CPSP. Furthermore, a correlation among structural connectivity and functional connectivity and the intensity of pain was detected.

Our results are well in line with findings from previous studies which suggested that a lesion on the pulvinar nucleus of the thalamus and dysfunction of the spinothalamic tract is a key feature of CPSP.[10,19] The thalamo-occipitoparietal tract contains the third order neuron of the spinothalamic tract arising from the pulvinar nucleus of the thalamus to the parietal cortex.[14,29,31] Decreased FA and increased MD could result from axonal degeneration or edema[33] and it could affect neuronal transmission. In addition, as the asymmetry of the FA of the thalamo-occipitoparietal tract increased, the functional connectivity between pain-processing regions increased only in patients with CPSP. Further work is needed to determine the precise physiological changes which contribute to these processes.

Previous studies have revealed that the insula is functionally connected to brain regions known for affective and cognitive processing such as the frontal cortex and ACC.[34,35] It has been suggested that this network, referred to as the ‘salience network’, integrates information about the significance of a stimulus into perceptual decisions in the context of pain.[36] Aberrant resting-state functional connectivity of the insula was reported in diverse pain syndromes,[37-39] demonstrating that an altered state of the salience network may play a pathogenic role in the conscious perception of pain. Voxels with increased functional connectivity to the ipsilesional insular were also found in

contralesional cerebellar lobule VIII, which constitutes the somatosensory network.[40] Activation of the posterior cerebellum was reported during the anticipation of pain yet it was, dissociated with the area involved in the pain experience itself.[41]

On the other hand, increased functional connectivity between the ipsilesional insula and the DLPFC is presumed to serve antinociception. Since Lorenz et al.[42] proposed that the DLPFC controls pain perception via top-down modulation, growing evidence has shown that the activation of the DLPFC has analgesic effects.[43-45] This would explain why those patients with less connectivity showed higher pain scores.

We also found increased functional connectivity between ipsilesional PPC and ACC in patients with CPSP. It has been suggested that PPC integrates sensory inputs with learning and memory and this information converges on cortical and subcortical limbic structures such as ACC, the insular cortex and amygdala.[46] This pathway affects the emotional dimension of pain, encoding pain unpleasantness.[46,47] It contributes to the subjective experience of pain and alteration of pain perception.[48] Pain unpleasantness could be dissociated from actual stimulus intensity.[49] PCC is also linked to the perception of sense without an external stimulus, such as a phantom sensation[50] and empathy of another's pain.[51] Thus, the alteration of the functional connectivity between PPC and ACC may be involved in the development of CPSP.

A few limitations of our study should be noted. First, we conducted a cross-sectional study; the possibility of late development of pain and its association with structural and functional changes to the brain in patients without CPSP could not be completely ruled out. Although CPSP is expected to develop within the first month after the stroke in most patients, its onset could be delayed.[1] In addition, the range of time that elapsed from the stroke was wide, especially in patients with CPSP. There was no statistical difference between the two groups in terms of the onset duration, and we included it as a

confounding factor in fMRI analysis, but there is a possibility that it influenced the results. Second, twenty-two of our patients had lesions extending to extra-thalamic areas. Damaged white matter may impact brain metabolism. Ideally, only patients with a hemorrhage limited within the thalamus would have been investigated, which is difficult to implement in practice as mentioned in previous studies.[11,19] Third, an influence of pain medication on functional connectivity cannot be completely ruled out. Although a minimal relationship was observed between drug consumption and resting-state functional connectivity in patients with chronic pain due to various causes,[32] different kinds of medications with distinct mechanisms of action may have influenced resting-state functional connectivity. Future studies are needed to have an adequate washout period after discontinuing medication, or to stratify the categories of medication.

V. CONCLUSION

In summary, CPSP is accompanied by structural disruption of the thalamocortical pathway, including the spinothalamic tract and changes in functional connectivity between brain regions involved in the cognitive-affective aspect of pain. This might further disentangle the pathophysiology of CPSP.

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ABSTRACT(IN KOREAN)

뇌출혈 후 중추신경병성 통증에서 구조적, 기능적 뇌 신경 연결망의 변화

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뇌졸중 후 중추신경병성 통증은 뇌혈관 병변에 의해 발생하며, 치료에 잘 반응하지 않는 통증이다. 척수시상로의 손상이 뇌졸중 후 중추신경병성 통증 발생의 주 요인으로 제시되어 왔으나, 뇌 전체 신경망의 부적응적 재구성도 관계가 있는 것으로 여겨진다. 그러나, 뇌졸중 후 중추신경병성 통증에서 신경 연결망의 구조적, 기능적 변화는 아직 밝혀진 바가 많지 않다. 이에, 본 연구에서는 확산텐서영상을 이용하여 신경섬유로를 재건하고 기능적 자기공명영상을 분석하여, 뇌출혈 후에 중추신경병성 통증이 발생한 환자는 특정한 시상피질성 신경망의 구조적, 기능적 손상이 있을 것이며, 통증을 처리하는 뇌 영역들 간의 기능적 연결성에도 변화가 생기고, 이러한 변화는 서로 연관되어 있을 것이라는 가설을 검증하고자 하였다.

총 43명의 환자를 대상으로 연구를 진행하였으며, 뇌졸중 후 중추신경병성 통증이 있는 환자와 없는 환자로 나누어 그룹간 비교를 시행하였다. 먼저, 대뇌 피질을 다섯 가지 구역으로 구분하여 시상과 각 구역들 간의 구조적, 기능적 연결성을 조사하였다. 병변 측 반구와 비병변 측 반구의 각 시상피질로의 확산 지표를 산출 후, 편측성 지표를 계산하여 확산 지표의 비대칭성을 수치화 한 후, 구조적 연결성의 차이를 추산하였다. 기능적 연결성은 기능적 자기공명영상을 분석하여 시드 구역의 활성도와 시간적 연관성이 높은 복셀을 조사하는 방법을 사용하였다. 추가적으로, 통증을 처리하는 뇌 영역의 기능적 연결성도 조사하였다.

뇌졸중 후 중추신경병성 통증이 없는 환자와 비교하였을 때, 통증이 있는 환자는 시상과 두정-후두엽을 연결하는 신경섬유로의 분획이방성의 편측성 지표가 통계적으로 유의하게 감소되어 있었으며 평균 확산성의 편측성 지표는 통계적으로 유의하게 증가되어 있었다. 또한 병변측 섬엽과 병변측 안와 전두피질, 대상회, 배외측 전전두피질, 상전두회와 병변의 반대측 소뇌의 VIII소엽과의 기능적 연결성이 현저히 증가되어 있었으며, 병변측 후두정피질과 대상회의 기능적 연결성도 유의한 증가를 보였다. 시상과 두정-후두엽을 연결하는 신경섬유로의 분획이방성의 편측성 지표는 병변측 섬엽과 병변측 안와 전두피질의 기능적 연결성과 음의 상관관계를 보였다. 통증의 강도는 병변측 섬엽과 병변측 배외측 전전두피질의 기능적 연결성과 음의 상관관계를 보였다.

결론적으로, 본 연구는 뇌졸중 후 중추신경병성 통증은 시상과 두정-후두엽을 연결하는 신경섬유로의 구조적 손상과 통증의 감정적인 측면을 처리하는 영역들 사이의 기능적 연결성의 변화를 동반한다는 것을 밝히었다. 또한, 구조적 변화는 기능적 변화와 관련성이 있으며, 통증의 강도 역시 기능적 연결성과 관련성이 있음을 보여주었다.

핵심되는 말 : 확산 텐서 영상, 기능적 자기공명영상, 휴지 상태연결성, 뇌졸중 후중추신경병성 통증, 뇌출혈, 뇌졸중

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