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Original contribution

7 Tesla magnetic resonance imaging of caudal anterior cingulate and posterior cingulate cortex atrophy in patients with trigeminal neuralgia

Hyeong Cheol Moon[a], Chan-A Park[b], Yeong-Jae Jeon[c], Soon Tae You[a], Hyun Man Baek[d], Youn Joo Lee[e], Chul Beom Cho[f], Chae Joon Cheong[b], Young Seok Park[a,g,*]

[a] Department of Medical Neuroscience and Neurosurgery, College of Medicine, Chungbuk National University, Cheongju, Republic of Korea
[b] Bioimaging Research Team, Korea Basic Science Institute, Ochang, Cheongju, Republic of Korea
[c] Department of Bio-Analytical Science, University of Science and Technology, Daejeon, Republic of Korea
[d] Department of health sciences technology, Gachon University, Republic of Korea
[e] Department of Radiology, Daejoen St. Mary's Hospital, Republic of Korea
[f] Department of Neurosurgery, Suwon Vincent Hospital, The Catholic University of Korea, Republic of Korea
[g] Department of Neurosurgery, Chungbuk National University Hospital, Cheongju, Republic of Korea

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ABSTRACT

The cingulate cortex (CC) is a brain region that plays a key role in pain processing, but CC abnormalities are not unclear in patients with trigeminal neuralgia (TN). The purpose of this study was to determine the central causal mechanisms of TN and the surrounding brain structure in healthy controls and patients with TN using 7 Tesla (T) magnetic resonance imaging (MRI). Whole-brain parcellation in gray matter volume and thickness was assessed in 15 patients with TN and 16 healthy controls matched for sex, age, and regional variability using T1-weighted imaging. Regions of interest (ROIs) were measured in rostral anterior CC (rACC), caudal anterior CC (cACC) and posterior CC (PCC). We also investigated associations between gray matter volume or thickness and clinical symptoms, such as pain duration, Barrow Neurologic Institute (BNI) scores, offender vessel, and medications, in patients with TN. The cACC and PCC exhibited gray matter atrophy and reduced thickness between the TN and control groups. However, the rACC did not. Cortical volumes were negatively correlated with pain duration in transverse and inferior temporal areas, and thickness was also negatively correlated with pain duration in superior frontal and parietal areas. The cACC and PCC gray matter atrophy occurred in the patients with TN, and pain duration was associated with frontal, parietal, and temporal cortical regions. These results suggest that the cACC, PCC but not the rACC are associated with central pain mechanisms in TN.

1. Introduction

Trigeminal neuralgia (TN), an unusual facial pain syndrome affecting the trigeminal nerve, can become a recurrent and chronic disorder. Symptoms of TN mainly include sudden, severe, shock appearing on one side of the face that persists for a few minutes.

Facial pain is often accompanied by negative emotional stimuli involving a broad network of brain regions including the cingulate cortex (CC). The CC is a part of the limbic system, which highly interconnected structures for processing the affective component of pain [1–3]. The CC receives input from the thalamus, and projects to the entorhinal cortex from the cingulum. The CC can be anatomically divided into the anterior CC (ACC), which associated with emotional controls, and posterior CC (PCC), which is associated with pain and memory [4,5]. The ACC is a pain processing region that interferes with cortical activity and can affect pain perception [6,7]. The guiding principle of ACC function is that cognitive and emotional information is processed differently [8]. An inspiring view divided the ACC inti the caudal ACC (cACC), which is associated with cognition and experiencing pain, and the rostral ACC (rACC), which has been reported in pain-induced pain-conditioned avoidance and electrophysiological studies and has affective subdivisions [9–11]. The PCC may play a key role in supporting internally directed cognition and contribute to current knowledge regarding brain disease [12–14].

Gray matter (GM) is closely associated with pain perception under chronic pain [15,16]. Pathological characteristics of GM include focal regions of demyelination, apoptotic neurons and atrophy of cortical volume and thickness [17–19]. Brain regional atrophy related to pain

* Corresponding author at: Department of Neurosurgery, NeuroFuture Lab, Chungbuk National University, College of Medicine, Chungbuk National University Hospital, 776, 1 Sunhwan-ro, Gaesin-dong, Sewon-gu, 28644 Cheongju, Republic of Korea.
E-mail address: youngseokparkmd@gmail.com (Y.S. Park).

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duration and intensity such as abnormalities encompasses emotional, autonomic, and pain perception regions [20,21]. Recently, GM cortical atrophy was investigated using high-resolution magnetic resonance imaging (MRI) at 7 Tesla (T). The development of advanced techniques with increased inherent MR sensitivity and signal-to-noise (SNR) provides anatomical detail in clinical 7 T MRI.

Accumulating brain structural imaging studies have demonstrated that chronic pain can induce changes in cortical thinning and reduce cortical volume in patients with TN [22,23]. In 3 T MRI, TN is associated with GM abnormalities in specific areas involved in pain perception, pain modulation and motor function [24]. However, these areas have not been investigated in 7 T MRI. Brain morphometric studies have revealed anatomical evidence for brain cortical atrophy in phantom-limb pain [25], chronic complex regional pain syndrome (CRPS) [20], headache [26], fibromyalgia [27], and spinal cord injury (SCI) [28,29]. However, the morphometric brain structure underlying TN and how TN affects cortical areas including the CC remain unknown.

In this study, we investigated the parcellation of human cortical structures and provided corrected reconstructions using 7 T MRI. Cortical thickness and volume differences in each cerebral hemisphere were compared between patients with TN and healthy-controls. After confirming GM changes in the CC, we investigated association between cortical areas and clinical symptoms using general linear model (GLM) methods in the patients with TN.

2. Materials and methods

2.1. Patients

A total of 15 patients (30 hemispheres; 4 males and 11females; age range, 36–64 years old; median age, 49.0 years old) who had been previously diagnosed with TN were enrolled in the study. General characteristics including sex, age, symptom duration, laterality, branches (V1, V2, V3), and Carbamazepine response were recorded. Pain characteristics were assessed with the Barrow Neurologic Institute (BNI) pain score [30]. A total of 16 health controls (32 hemispheres; 4 males and 12females; age range, 25–62 years old; median age, 43.5 years old) were used to provide a baseline comparison to the patients group in terms of abnormalities in the cortical thickness and volumes. All study protocols were approved by Chungbuk National University Hospital (IRB number: 2015-04-016-00 2, CBNUH) and informed consent was obtained from all patients in the TN and control groups.

2.2. MRI acquisition

All subjects underwent MRI scans using a 7 T MR system (Philips Healthcare, Cleveland, OH, USA) with 32-channel phased-array head coil (Nova Medical, Wilmington, MA, USA). Three-dimensional (3D) anatomical brain scans were acquired using MP-RAGE (magnetization prepared rapid acquisition gradient echo) sequence-induced T1-weighted image with the following setting: repetition time (TR) = 4.6 ms, echo time (TE) = 2.3 ms, flip angle (FA) = 110°, slice thickness = 0.5 mm, in-plane resolution = 0.5 × 0.5 mm^2, matrix size = 488 × 396, number of axial slices = 320, and acquisition time (TA) = 5 min 53 s. All images with motion artifacts were excluded.

2.3. Image data processing

High resolution images required modification to the default reconstruction using the N3 algorithm for inhomogeneity correction for 7 T MRI with optimized parameters. Cortical reconstruction and volumetric segmentation were performed using FreeSurfer software version 6.0 (http://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurfer). Previous publications of high resolution data (< 1 mm) were used to modify the default stream and inhomogeneity correlation by division before data processing [31,32]. The data of each subject were subjected to standard manual processing in FreeSurfer high resolution data processing. After cortical reconstruction, the GM cortex was parcellated with allocations for labeling with the neuroanatomical atlas by Desikan-Killiany-Tourville (DKT), which divided the cortex into 31 cortical regions per hemisphere. GM volume and thickness were calculated as a vertex of the pial surface. Regions of interests (ROIs) in the CC were automatically processed by morphology labeling, as shown in Fig. 1.

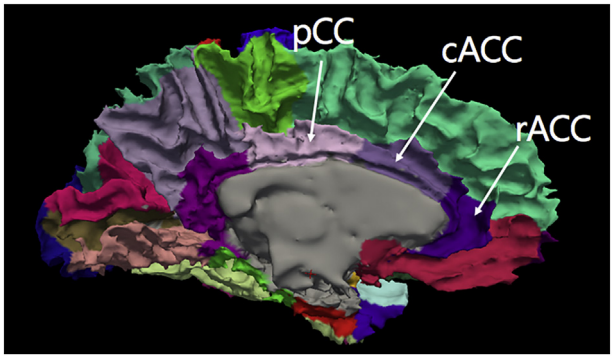

Fig. 1. Brain structure in sagittal views of the rostral anterior cingulate cortex (rACC), caudal anterior cingulate cortex (cACC), and posterior cingulate cortex (PCC).

The GLM was used to assess each subject's vertex in the whole brain to investigate cortical regions significantly associated with clinical symptoms in the patients with TN (with controlled ages) using FreeSurfer's mri_glmfit (http://surfer.nmr.mgh.harvard.edu/fswiki/mri_glmfit). All the data were separately processed for the right and left hemispheres, and thresholds were set at $P < 0.05$ (correlated for multiple comparison problems using false discovery rate (FDR)). Cluster-wise correction for multiple comparisons was performed using FreeSurfer's mri_glmfirt-sim (http://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/GroupAnalysis) to precompute a Z Monte Carlo simulation, with a vertex threshold of 1.3 (*P-value* < 0.05).

2.4. Statistical analysis

Statistical evaluations were performed using GraphPad Prism 6 (GraphPad Software, San Diego, CA, USA). Data are shown as the mean ± SD. Unpaired *t*-test (Wilcoxon matched-pairs test) was performed to compare between groups: age, and sex were assessed using Chi-squared tests. Multiple analysis of covariance (MANOVA) for statistical computations in SPSS 20.0 (SPSS Inc., Chicago, Illinois, USA) performed with relating of age and sex on GM thickness and volume in CC as covariates. We investigated that cortical atrophy is correlated with clinical symptoms controlled for age in Freesurfer Group Descriptor (http://surfer.nmr.mgh.harvard.edu/fswiki/FsgdExamples). The data for pain duration were log-transformed, which is a simple logarithmic (z = log to base 10 y) transformation used to normalize distributions. The threshold of significant difference was *P-value* < 0.05.

3. Results

3.1. Demographic and clinical characterization

There were no significant differences in age and sex between the patients with TN and the controls. Detailed subject characteristics are shown in Table 1. The statistical comparisons shown in Table 1 were performed with unpaired *t*-test for age and Chi-squared tests for sex. The results were significantly different at $P < 0.05$. The median age did not vary significantly between the patient and control groups.