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ORIGINAL RESEARCH

Preliminary Investigation of Pain-Related Changes in Cerebral Blood Volume in Patients With Phantom Limb Pain

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Abstract

Objective: To investigate changes in the pain network associated with phantom limb pain, magnetic resonance imaging (MRI) was used to measure cerebral blood volume (CBV) in patients who had undergone unilateral arm amputation after electrical injury.

Design: Case-controlled exploratory MRI study of CBV via MRI.

Setting: University hospital.

Participants: Participants (N=26) comprised patients with phantom limb pain after unilateral arm amputation (n=10) and healthy, age-matched persons (n=16).

Interventions: Not applicable.

Main Outcome Measures: The intensity of phantom limb pain was measured using the visual analog scale (VAS). Depressive mood was assessed using the Hamilton Depression Rating Scale, and cognitive function was assessed using the Korean version of the Mini-Mental State Examination. Voxel-wise comparisons of relative CBV maps were made between amputees and controls over the entire brain volume. The relationship between individual participant CBV (measured in voxels) and VAS score was also examined.

Results: Compared with control participants, amputees exhibited greater degrees of depression; significantly higher CBV in the bilateral medial frontal area (orbitofrontal cortex [OFC] and pregenual anterior cingulate cortex [pACC]); and significantly lower CBV in the right midcingulate cortex, posterior cingulate cortex, and primary somatosensory cortex. CBV increased in the contralateral and ipsilateral hemispheres of the amputated arm, regardless of the amputation side. This CBV increase in the OFC and pACC was strongly correlated with pain intensity in all amputees.

Conclusions: We observed increased CBV in regions associated with emotion in the cerebral pain network of patients who had undergone unilateral arm amputation after electrical injury. This study suggests that CBV changes were related to neuroplasticity associated with phantom limb pain.

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Amputation is a striking driver of plasticity because it induces both deafferentation from limb amputation and loss of motion.[1] Additionally, previous studies have revealed that depression after amputation is highly predictive of phantom limb pain.[2] Research has indicated that both brain structure and function are altered in the presence of chronic pain[3,4] and depression.[5,6] Therefore, investigation of the neural network involved in the

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perception of phantom limb pain is required to better understand the underlying sensorimotor mechanisms, emotional aspects, chronicity, and severity of pain after limb loss. Such an understanding is paramount to successful rehabilitation after amputation. Previous neuroimaging studies involving patients with phantom limb pain have revealed that alterations in pain network neural activity occur in both the sensory-perceptive[1,7] and emotional domains,[8] both of which play different roles in the experience of pain. The sensory-perceptive domain of the pain network is responsible for pain sensation in the presence of noxious body stimuli and involves the thalamus, primary somatosensory cortex, secondary somatosensory cortex, and insula. The emotional domain of the pain network is responsible for reacting to pain with negative emotional events and memories, and involves the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), amygdala, and insula.[9]

Cerebral blood volume (CBV) is a hemodynamic variable that is highly correlated with oxygen metabolism, representing the fraction of cerebral tissue volume occupied by blood at a given time point.[10-12] Given that the pain network is made up of tiny neural structures, high-resolution neuroimaging tools are required to study phenomena involving these structures. Basal-state functional-imaging studies provide images with spatial resolution superior to those offered by deoxyhemoglobin functional magnetic resonance imaging (MRI) or positron emission tomography, particularly when the contrast agent gadolinium is used to map changes in CBV during MRI. In the present study, we used MRI to measure CBV in patients who had undergone unilateral arm amputation after electrical injury in order to investigate changes in the pain network associated with phantom limb pain.

Methods

Participants and clinical assessments

Ten patients (9 men, 1 woman) with phantom limb pain were enrolled in the present study (table 1). The mean ± SD patient age was 43.8±3.4 years (range, 37−48y), and the mean ± SD duration of pain was 44.8±35.1 months (range, 16−115mo). Patients were considered for study inclusion if all the following were true: (1) aged <50 years; (2) unilateral upper limb amputation after electrical injury; (3) phantom limb pain duration longer than 12 months; and (4) uncontrolled pain despite medication use and physical therapy. Patients were excluded from the study if any of the following were true: (1) history of cardiac arrest resulting from the electrical injury; (2) history of neurologic disease or brain surgery; (3) unstable heart disease or presence of a cardiac pacemaker; (4) pain resulting from other possible causes (eg, stump pain caused by bone spurs, skin lesions, neuroma, circulatory insufficiency, osteomyelitis, and/or abscess) as confirmed via imaging (radiography, ultrasonography, computed tomography, or MRI); (5) other forms of persistent pain lasting >3 months; (6) diabetes mellitus; (7) abnormal renal function; (8) contraindications for MRI; or (9) pregnancy. We also recruited 16 healthy, age-matched control participants (9 men, 7 women; mean age ± SD, 41.7±2.2y; age range, 39−46y) using the same exclusion criteria. Before their participation in the study, none of the control participants had experienced persistent pain for >1 week. This study protocol was approved by the Institutional Review Board of Hallym University Sacred Heart Hospital, and written informed consent was obtained from all participants.

The percentage of amputation was calculated using the following formula:

$$(\text{Nonamputated arm length} - \text{Residual limb length}) / (\text{Nonamputated arm length}) \times 100$$

where the nonamputated arm length was defined as the distance between the acromion and third fingertip of the nonamputated arm. Participants were asked to describe the average intensity of phantom limb pain over the last week using the visual analog scale (VAS). Depressive mood was assessed using the previously validated Korean version of the Hamilton Depression Rating Scale (HDRS).[13] Cognitive function was assessed using the Korean version of the Mini-Mental State Examination (MMSE-K). Both the HDRS and MMSE-K were administered to all participants by a single licensed psychologist. The VAS, HDRS, and MMSE-K assessments were administered on the same day that the MRI was obtained. Age, HDRS scores, and MMSE-K scores were compared between groups using independent *t* tests. The sex distribution was compared between study groups using the Pearson chi-square test. Spearman correlation tests were used to analyze relationships between pain severity (VAS score) and potentially contributing factors, including age, upper limb amputation percentage, phantom limb pain duration, HDRS score, and MMSE-K score. All statistical analyses were performed using SPSS Statistics version 20.[a]

MRI acquisition and CBV mapping

All MRI images were obtained using a 1.5T magnetic resonance scanner[b] using a previously established steady-state gadolinium-enhanced MRI technique.[12,14] Two high-resolution T1-weighted images (repetition time/echo time [TR/TE]=2000ms/3.4ms, flip angle=15°, in-plane resolution=1×1mm, section thickness=1mm) were acquired for each participant, with one obtained before administration of a standard intravenous dose of gadolinium contrast agent (0.1mmol/kg Dotarem[c]) and one obtained 4 minutes after gadolinium administration. Two structural images from each participant were processed following routines specified in SPM8 software.[d] The postenhanced image was coregistered to the pre-enhanced image, and both images were normalized to the same coordinate frame as the Montreal Neurological Institute template brain. The precontrast image was then subtracted from the postcontrast image, and this subtracted image was then divided by the contrast-induced signal difference in the top 4 voxels of the superior sagittal sinus and multiplied by 100. Image processing ultimately produced a map of relative CBV. For patients who had undergone amputation of the left arm (patients 1, 5, 7, 10; see table 1), the map was flipped around the midsagittal axis to uniformly connect the amputated arm to the left hemisphere.

List of abbreviations:

ACC	**anterior cingulate cortex**
CBV	**cerebral blood volume**
HDRS	**Hamilton Depression Rating Scale**
MCC	**midcingulate cortex**
MMSE-K	**Korean version of the Mini-Mental State Examination**
MRI	**magnetic resonance imaging**
OFC	**orbitofrontal cortex**
pACC	**pregenual anterior cingulate cortex**
VAS	**visual analog scale**