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Brain alteration in chronic pain and the relationship with pain score



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ABSTRACT

Brain volume alteration in chronic pain has been studied in many studies. Most of the reviews were reported that the brain volume decrease in chronic pain, although there were some studies reported that the brain volume increased. The alteration mechanism of brain volume was certain unknown, maybe it caused by nerve hyperactivity

in the pain pathway, from nociceptor to post-central gyrus. The alteration of substantia grisea volume decreased is interested to know, which it is occurring in the location of the pain pathway of substantia grisea in the brain. This mechanism was one of the body's ways to reduce the pain score, which then it makes the painless.

Keywords: Brain alteration, chronic pain, pain score.

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INTRODUCTION

Chronic pain is one of major health problems in the world, with high incidence rate reaching 100 million cases per year in United States,¹ and 64% chronic pain growth.² The problem with chronic pain is it causes disruption physically and mentally that eventually impair social activity.³ Moreover, chronic pain often followed by anxiety and depression, physical fatigue, and cognitive impairment,^{1,4} with the expensive cost of chronic pain treatment. Total cost of chronic pain treatment can reach 600 million US dollar annually.^{1,2,5,6}

Pain defined by The International Study of Pain (IASP) is pain without apparently biological value that has persisted beyond the normal tissue healing time, this time interval is often indicated as 3 until 6 months.^{2,5,6} It is well known that chronic pain causes changes in central and peripheral nervous system.^{1,7} Brain volume, both white and gray matter, will increase due to chronic pain in central nervous system.⁸ The mechanism is still unclear whether it is caused primarily by chronic pain or secondarily by prolonged nociceptive impulse input.² This paper will explain about brain volume changes in chronic pain and the effect on pain perception.

CHRONIC PAIN MECHANISM

The basic mechanism of chronic pain is inability of self-healing on cellular level which lead acute pain to chronic. Repeated stimuli caused upregulated mechanism called sensitization. There are two types of sensitization, central and peripheral sensitization. Sensitization act as an amplifier to intensify

process of pain mechanism, resulted with allodynia and hyperalgesia. Sensitization holds an important role in treating chronic pain and plasticity in central and peripheral nervous system,⁵ causing changes in anatomy and physiology of central and peripheral nervous system. One of the changes in brain volume, both white and gray matter.¹ A side of sensitization, chronic pain is also affected by other factors such as lack of inhibition or increased excitation of central nervous system (spinal cord, brainstem and or cortex).^{1,5}

Because of chronic pain complex cellular mechanism is not yet completely understandable, treatment of chronic pain is far from satisfactory and was considered failed to be cured comprehensively.^{2,9} Cellular complexity continues to unclear neural mechanism on chronic pain, with research on neuroimaging of chronic pain giving new insight to neural mechanism complexity, it also give new strategies on treating chronic pain.¹

The animal and human testing result shows that chronic pain induces dramatic event in structural reorganization of brain anatomy and physiology and its sequence.⁸ In chronic pain, brain remodels or reorganize its structure. Mechanism of chronic pain in central nervous system is more apparent than in acute pain mechanism, this proves why patient still feel pain even without prolonged nociceptive input.¹⁰ Chronic pain is not just functional alteration status from acute pain, but more about other consequence occur in the brain, that is plasticity in brain.¹¹

Brain alterations on chronic pain

Since the founding of neuroimaging as diagnostic tool, research related to changes of cortical and

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subcortical anatomy made big progress.^{1,12} There are 2 ways of measurement often used, those are: 1) Voxel-based morphometry (VBM) this method can measure density, volume, and thinning of gray matter, 2) Fractional anisotropy (FA), to measure white matter in fiber density, axonal diameter and myelination integrity.^{1,12,13}

According to recent research, brain volume changes found in almost all forms of chronic pain, including chronic back pain (CBP),^{7,14} fibromyalgia (FM),^{1,7} complex regional pain syndrome (CRPS),^{1,7,15} osteoarthritis (OA),^{7,16} irritable bowel syndrome (IBS),^{7,17} headaches,^{7,17,18} chronic visceral pain,⁷ menstrual pain,⁷ chronic pelvic pain¹⁹ also in animal models of chronic pain.²⁰ Some of the research only focus on grey matter changes as trends nowadays,¹⁰ others focus on white matter changes, some focus about functional or structural connection changes.¹⁰

Although it is not fully understood on how brain volume changes in chronic pain, in two animal model research model with first group induced with spared nerve injury and the second group induced with sham-operated found significant differences on 2/3 pyramidal neuron layer in the contralateral prefrontal cortex and basal dendrite in the first group are longer and has more branch compared to control group. The result match with this paper topic which highlight apparent changes in grey matter volume at the contralateral prefrontal cortex and white matter increased volume proved with elongation of basal dendrite from the first group. Grey matter volume increasement is likely through neurogenesis process, neuronal morphology/cerebral vascular changes and non-neural cell genesis and morphology, while white matter volume increasement is likely caused by myelination and changes in axon.¹²

Grey matter volume changes in chronic pain

Changes in grey matter volume revealed first time by Apkarian et al.³¹ as grey matter atrophy in chronic back pain. Reduced density was found in prefrontal

dorsolateral bilateral cortex and right thalamus area (Figure 1).⁷ Gray matter volume changes depending on the type of chronic pain, meaning a different type of chronic pain involves different area (increased or decreased) (Table 1). However, reduced volume of grey matter not only happen in traditionally considered area to be involved in pain processing, but also in areas that do not seem to be specifically involved in pain processing.¹⁰ Changes in grey matter volume according to types of chronic pain in brain area are shown in Table 1 below.^{1,12}

In the table 1 show that brain region involved in decreased volume of grey matter are region

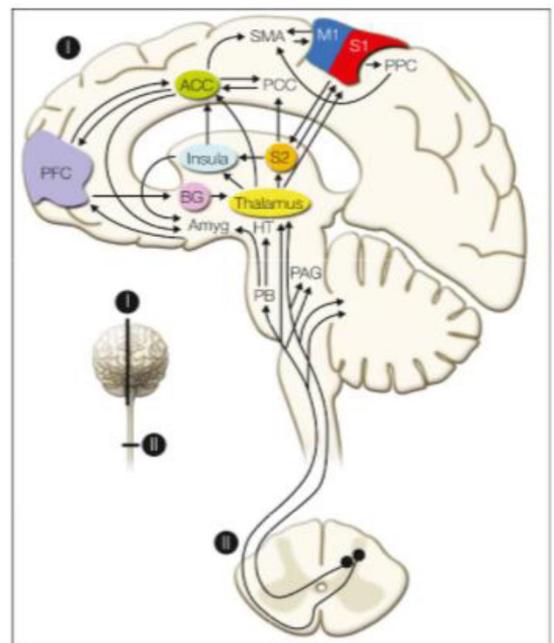


Figure 1 Schematic of ascending pathway, subcortical structure, and cerebral cortical structure involved in processing pain. ACC, anterior cingulate cortex. Amygdala; BG, basal ganglia; MI primary motor cortex, perception and regulation in health and disease⁸

Table 1 Regions of decreased substantia grisea in chronic pain syndromes

Syndrome	Cing. Cortex	Thalamus	Ins. Cortex	Temporal lobes	Brain stem
Migraine	√		√	√	
CTTH	√		√	√	
CBP	√	√		√	
Phantom Pain	√				
FM		√	√		
IBS	√	√	√		
CRPS			√		
Pain Disorder	√		√		
CPP	√	√	√		

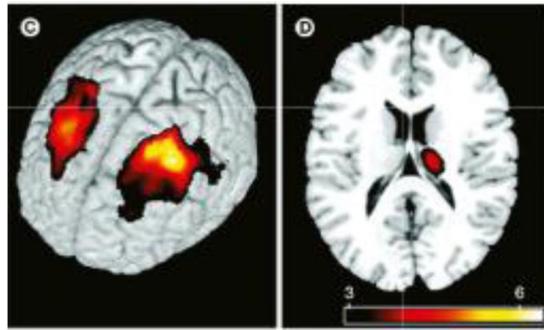


Figure 2 Regional decreases in substantia grisea density in patients with CBP. Substantia grisea density is the left-right dorsolateral prefrontal cortex (C), as well as in the thalamus (D). Decreases were observed in the right thalamus, although the left and right sides of the body were similarly affected across patients. Chronic back pain is associated with decreased prefrontal and substantia grisea density^{8,31}

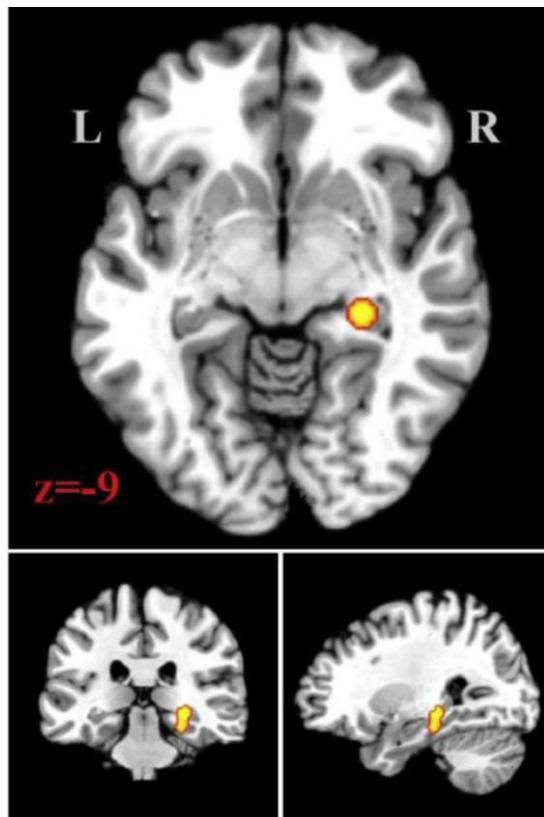


Figure 3 Region where grey matter volume was greater in patients than control subjects displayed on the Colin27 template brain. Number indicates z slice and is displayed in MNI coordinates. Results were taken at cluster level $p < 0.05$, with a cluster forming threshold of $p < 0.01$ uncorrected²³

involved in pain processing, including sensory, motoric, affective and emotional region. The regions are somatosensory cortex, insular cortex, thalamus, basal ganglia, parietal cortex, prefrontal dorsolateral cortex.^{1,7,9,10,14,21,22}

Research shows that grey matter volume changes in chronic pain are either increasing or decreasing, but most of the research resulted in reduced grey matter volume, the following research that show decreasement are Apkarian et al.³¹ Dragnanski et al.³² The contradictive outcome of these research was caused by different type of chronic pain categorizing and underlying etiology, there is also bias such as depression and anxiety contributing to the result (Figure 2 and 3).¹

White matter changes in chronic pain

Changes in white matter were currently considered apparent in neurodegenerative diseases such as Alzheimer, multiple sclerosis and dementia, or mental illness such as depression and schizophrenia.¹² So far several types of chronic pain have been researched for changes in white matter, those are CPRS, migraine, IBS, also urological chronic pelvic pain syndrome (UCPPS), trigeminal neuralgia (TN), chronic musculoskeletal pain.²⁴⁻²⁶

Similar to grey matter, white matter volume changes found increasing and decreasing in research, but the books and journals discussing and researching about white matter volume changes in chronic pain is not as many as grey matter and will be discussed below.

In CPRS, the researcher found no differences in whole-brain skeletal FA between CPRS and control group, no correlation was found between whole-brain skeletal FA and grey matter volume. However, correlation was found in control group. This proves disruption between white and grey matter in CPRS.^{12,15} FA decrease meant were found in right frontal cortex white matter in control group on migraine.¹² An increasing FA volume in fornix and adjacent external capsule to the right posterior insular on IBS.^{12,24} In Trigeminal Neuralgia, based on univariate statistic calculation, abnormality occurs in both white and grey matter, as well as in the multivariate revealed that the structural connectivity pattern could distinguish the healthy controls (HCs) and the trigeminal neuralgia (TN), which is the fibre connection in this region that related with associative and affective dimension of pain in TN is decreased, but the fibre connection in both somatosensory and higher-order cognitive is increased.^{25,27,28} In CPRS, using diffusion imaging technique, the first researcher that found increase-ment of white matter in CPRS, Huang et al.²⁴ concluded that FA increase-ment was found in anterior thalamus radiate tractus and corticospinalis.

Chronic musculoskeletal pain research conducted by Van Riper et al.²⁶ in on war veterans concluded that there were differences between the veteran who suffer musculoskeletal pain group and the group who did not in white matter volume, the veteran who experience musculoskeletal pain with damaged of white matter.²⁶

Understanding of white and gray matter changes in volume of chronic pain is established helpful in other research that related CRPS and FM disease by measuring volume changes both in white and gray matter.¹

The correlation of brain volume changes to chronic pain in pain perception

Subjective pain perception is affected by several factors, such as pain modality, simulated body site, and situational factor.^{1,29} There is no gold standard on measuring pain sensitivity, and pain assessment require certain conditions. A research reported that there is a positive relationship between grey matter changes and chronic pain in pain sensitivity, despite weak-linked.²⁹ Volume of grey matter in left interior temporal gyrus correlated negatively with current pain intensity and duration of the disease, and connectivity of the right insula/SA-ACC correlated negatively with pain intensity, level of depression and anxiety.²⁸ In pain perception, somatosensory cortex plays a bigger role on location and duration of pain, specifically for a spatial, temporal, and intensive aspect of innocuous dan noxious somatosensory stimuli. Subcortex, limbic dan paralimbic such as ACC and IC contribute in emotional process and motivational aspects of pain.¹ Different with changes in the volume of grey matter in chronic pain, so far there are no journals that discuss the effect of change in volume of substantia alba with pain perception.

Chronic pain still persists despite the fact that the source of pain is healed. This raises a question on whether or not chronic pain treatment requires neuroprotection agent. So far, there is no report on research about pain perception level with neuroprotection agent as adjuvant for chronic pain.³⁰

CONCLUSION

1. Chronic pain can induce brain functional and anatomical structure reorganization.
2. Hence chronic pain can increase or decrease gray and white matter volume, despite can not explained of mechanism.
3. Despite weak-linked, there is a correlation between grey matter changes and pain perception.
4. Neuroimaging brain alteration in chronic pain is very useful modality for diagnosis.

CONFLICT OF INTEREST

The author declares there is no conflict of interest regarding publication of the current review.

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