

The Interaction of the Brain and Nervous System in Chronic Pain Conditions

Evidence Based Project

The University of Wyoming

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PICOT Question

Are chronic pain patients who have either neuropathic pain or nociceptive (musculoskeletal) pain at an increased risk for neurologic grey matter atrophy compared with people without chronic pain within 0-14 months of the start of each study discussed below?

Introduction

Pain is felt by all humans, however only a portion of the population develops a chronic pain syndrome (Rodriquez-Raecke, et. al, 2013). Though the reason for this is unclear, the effects of chronic pain on the brain are becoming more evident. In the sections to follow there are a few examples of the many different types of chronic pain syndromes. Each of these examples seek to determine whether grey matter atrophy can be found in the brains of chronic pain patients. One study found that patients with neuropathic pain had significantly decreased grey matter volume in the anterior insula, primary somatosensory cortex, and thalamus on the side ipsilateral to the ongoing pain when compared with control subjects (Henderson et., al, 2013). Another article explored the effects of the reversible chronic pain caused by hip osteoarthritis (OA). Over the course of the longitudinal study, the researchers noted changes in neurologic grey matter in patients with hip OA which were partially reversed when the patient was free of chronic pain post orthopedic surgery (Rodriquez-Raecke, et. al, 2013). As the alterations in grey matter were partially reversible, the authors believe that atrophy is not responsible for the differences seen in pain subjects. On the other hand, a study of chronic back pain (CBP) patients determined that grey matter atrophy of the brain in CBP is equal to 10-20 years of normal aging, with normal grey matter atrophy occurring at a rate of 0.5% per year (Apkarian, et. al, 2004). A fourth study examined the brains of patients diagnosed with chronic regional pain syndrome after trauma to a limb or other portion of the body. These patients were

found to have a distinct area of atrophy in the ventromedial prefrontal cortex (VMPFC), an area involved in the processing of pain intensity and duration (Geha, P. Y, et. al, 2008). Finally, Obermann et. al (2013) determined that trigeminal neuralgia patients showed an alteration in grey matter in several areas of the brain as compared to healthy controls. Thus, it is clear, chronic pain patients experience some type of neurological alteration in their grey matter. Chronic pain is difficult to manage, and can be detrimental to the quality of life of affected patients. As such, research and understanding of this topic is essential for nurses in clinical practice.

Collection of Evidence

In order to answer the PICOT question, sources were compiled using two different databases: Academic Search Premier and PubMed. In the search for relevant articles, the keywords used were, “chronic pain,” “chronic pain syndromes,” “grey matter,” “atrophy,” “neuropathic,” and “nociceptive.” Exclusion criteria included studies that examined patients outside of the 0-14 month window. There are many different types of illnesses that can be classified as chronic pain syndromes, and so disease processes that did not fall under either neuropathic or nociceptive were also excluded.

Synthesis and Review: Types of Chronic Pain and Their Causes

Involvement of the Thalamus in Neuropathic pain

Four decades ago researchers suggested that neuropathic pain may be controlled in a distinct central location, possibly located in the thalamus. Henderson et., al. (2013), explored the more detailed hypothesis that neuropathic pain will be associated with volume loss in the ventral posterior thalamus, decreased thalamic reticular nucleus (TRN) blood flow, as well as decreased

GABAergic content¹ of the thalamus, and altered connectivity. In order to look at the anatomy, connectivity, chemistry, and activity of the thalamus, the researchers used voxel-based morphometry² (VBM), quantitative arterial spin labeling³, magnetic resonance spectroscopy, and functional MRI technology.

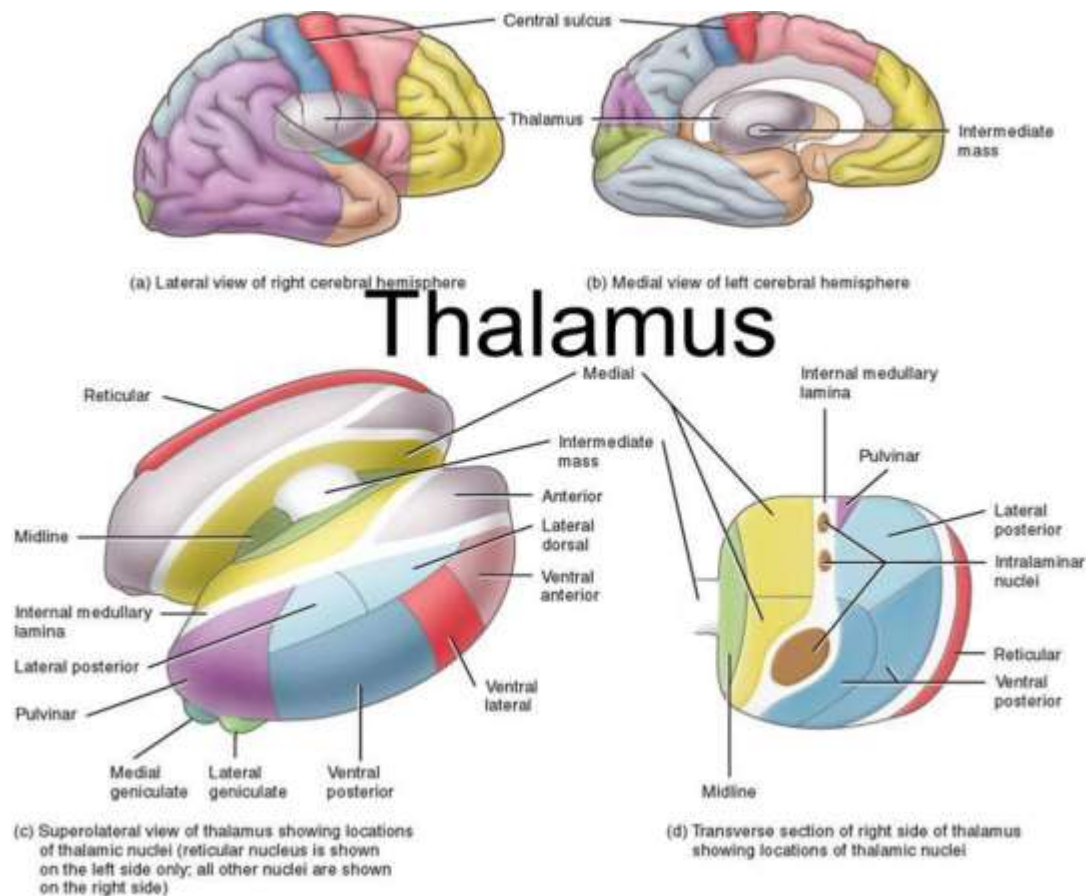


Figure 1. Different views of the thalamus highlighting the various nuclei (Thomas, et. al, 2017).

The sample recruited for this study consisted of 23 participants suffering from trigeminal neuropathy and 43 pain free control subjects (Henderson et., al, 2013). The neuropathic pain

¹ Decreased GABAergic content of the thalamus results in a decreased inhibitory effect causing an increase in connectivity.

² Voxel-based morphometry: method of comparing the local concentration of grey matter between two groups of subjects (Ashburner & Friston, 2000).

³ Quantitative arterial spin labeling: MRI-based technique used to take quantitative blood flow measurements in arteries (Williams, 2016).

group were diagnosed using the same specific criteria, and were asked to keep a pain diary for the week leading up to their MRI scans. The pain levels recorded in the diary were averaged and used to determine if there was a relationship between the pain level and the long term grey matter volume of the participant's brain.

When analyzing the results of VMB techniques, Henderson and his team added the age, gender, and total brain size of the participant as nuisance variables (Henderson et., al, 2013). They found that neuropathic pain participants had significantly decreased grey matter volume in the anterior insula, primary somatosensory cortex, and thalamus on the side ipsilateral to the ongoing pain. It was also found that there was a reduced grey matter volume in the contralateral thalamus in the pain subjects. Furthermore, 18 of neuropathic pain participants were found to have significantly decreased cerebral blood flow (CBF) to the contralateral thalamus and primary somatosensory cortex. The decrease in CBF was found to be in the vicinity of the TRN on the lateral side of the thalamus. Additionally, it was found that the greater the ongoing pain of the person, the greater the reduction in TRN blood flow.

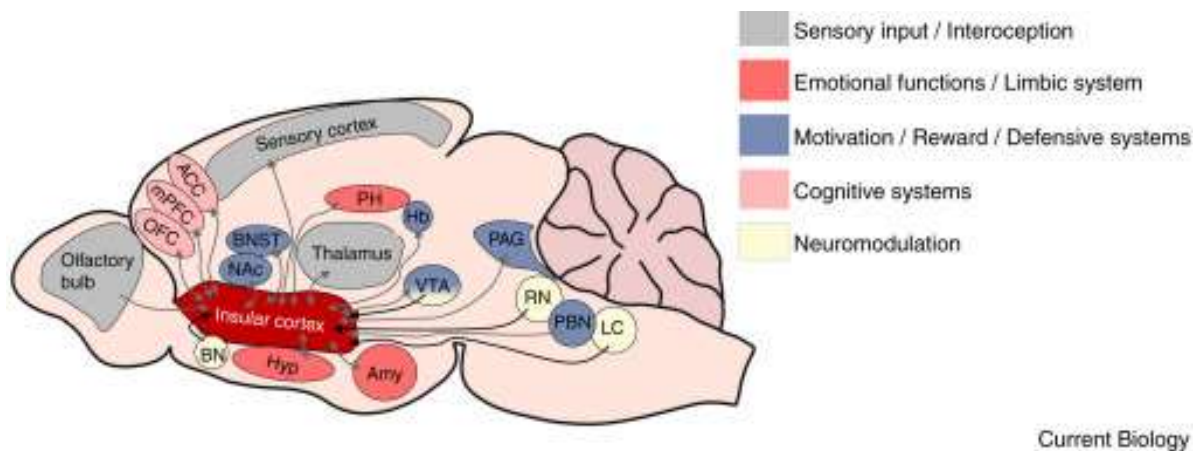


Figure 2. Connectivity of the insular cortex (Gogolla, 2017)

Results also showed that neuropathic pain participants had significantly lower GABA levels in the thalamus as compared with the control group (Henderson et., al, 2013). The

researchers noted that the subjects who were regularly taking pain medication had no significant difference in the GABA content of the thalamus compared to those who took no analgesic medication. In 12 of the neuropathic pain group participants, it was found that the thalamic GABA content was significantly negatively correlated with the connectivity of the ventral posteromedial nucleus (VPN) in both sides of the primary somatosensory/motor cortex. Therefore, in the participants with chronic pain, the greater the decrease in GABA content, the greater the variation in thalamocortical connectivity.

In recent years, it has been hypothesized that neuropathic pain results from an alteration of activity in the thalamus (Henderson, et. al, 2013). Evidence has shown that neuropathic pain is consistently associated with a decrease in thalamic activity on the side contralateral to the chronic pain. Additionally, chronic neuropathic pain has been found to be associated with reduced blood flow within the TRN, and significant reduction in grey matter volume in the somatosensory thalamus. There is also a positive correlation between reduction of blood flow to the TRN and intensity of the neuropathic pain.

The data collected in this study supports the hypothesis that after a peripheral nerve injury, the loss of thalamic somatosensory grey matter results in a change in TRN activity, causing reduced GABA activity, and an altered thalamocortical connectivity (Henderson, et. al, 2013). The effect of these three changes for some patients is ultimately a constant perception of pain. Currently, the mechanism attributed to decreased VP thalamic volume is unknown. However, it is known that blocking neuronal cell apoptosis using a caspase inhibitor after a nerve injury can prevent neuronal loss and reduce pain behaviors in animal models (Scholz, et. al, 2005). Therefore, this research raises the possibility that preventative treatment could be utilized in the future to prevent the development of chronic pain after a peripheral nerve injury.

This study directly relates to the PICOT question as it explored patients experiencing neuropathic pain and determined that there was a significant grey matter volume loss in the experimental group compared to the control group. This study is informative, well organized, and relevant. The results are reported in a manner that is clear and easy to follow. One limitation of this study is the sample size. The experimental group consisted of 23 people, and the control group contained 43 people. Though this is a large enough sample to produce a clear pattern, it may not be large enough to allow this data to be generalized to the whole of the chronic pain population.

Structural Brain Changes in Chronic Pain

In this study, the authors explored one of the few chronic pain syndromes that is highly reversible: OA of the hip. This condition is considered curable as many patients are pain free after recovering from the acute pain that follows a total hip replacement (THR). The sample consisted of 20 patients who had hip OA in one of their hips (Rodriquez-Raecke, et. al, 2013). The group was seen at four different intervals: preoperatively, 6-8 weeks, 12-18 weeks and 10-14 months postoperatively. All the patients involved in the study had chronic pain lasting longer than 12 months, and all were otherwise healthy. MRI scans were done at each appointment (4 total for each participant) to analyze regional differences in grey matter.

All patients were recorded as experiencing chronic hip pain prior to the surgery (Rodriquez-Raecke, et. al, 2013). However, after the surgery, all were free of chronic pain, and were instead feeling the acute pain of the THR. Compared to healthy controls, the preoperative scan of patients with hip OA showed a reduction of grey matter in the anterior cingulate cortex (ACC), the dorsolateral prefrontal cortex (DLPFC), the insular cortex, the right temporal pole, and the cerebellum (Figure 3). In conducting a longitudinal analysis, the researchers found that

there was a significant increase in the grey matter of the ACC, insular cortex, and cerebellum from comparing scan 1 (preoperative) and scan 2 (6-8 weeks post-operative) to scan 3 (12-18 weeks post-operative) and scan 4 (10-14 months postoperative).

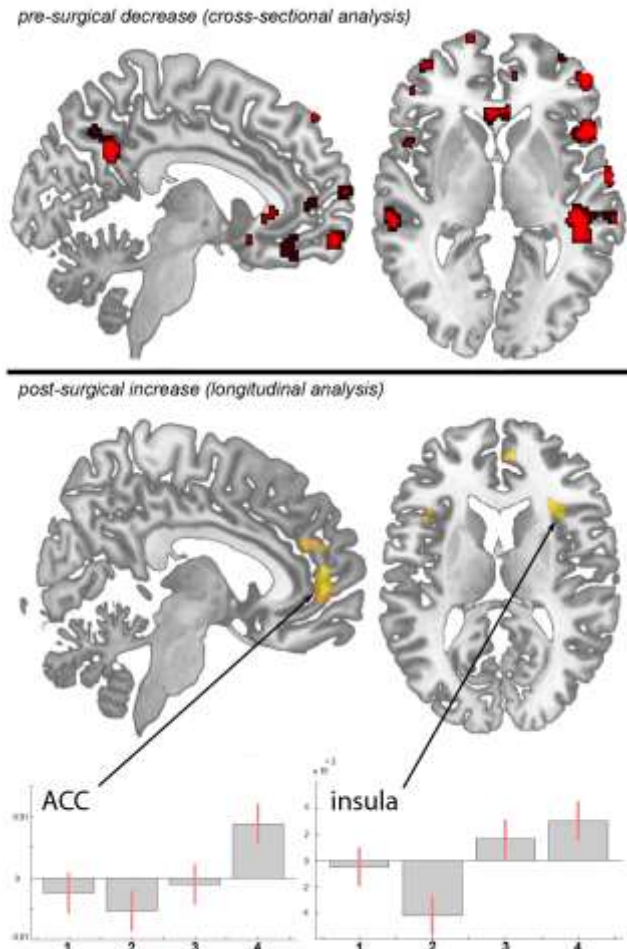


Figure 3. Statistical Parametric maps demonstrating the structural differences in grey matter in patients with chronic pain due to primary hip OA compared to controls and longitudinally compared to themselves over time (Rodriquez-Raecke, et. al, 2013).

Overall, the researchers noted changes in neurologic grey matter in patients with hip OA which were partially reversed when the patient was free of chronic pain post orthopedic surgery (Rodriquez-Raecke, et. al, 2013). The data suggests that the decrease in grey matter during a chronic pain state is not a result of any damage or atrophy to neuronal cells. The authors note that not all areas of decreased grey matter recovered, but suggested that the time spent in the

chronic pain state could affect the time it takes to reverse the changes. In addition, researchers also saw changes to the motor and premotor areas possibly due to patients requiring less restriction in mobility. It is unknown if this variable could have an impact on the grey matter density.

This study related directly to the PICOT question as the patients who were evaluated for grey matter decrease were experiencing chronic musculoskeletal pain. The authors provide evidence that brain grey matter does not atrophy in a chronic pain state. The article was clear and well written; however, the experimental design was broad. The researchers did not aim to discover what factors might change the brain in chronic pain, they focused solely on the neuroplasticity of the brain. It would be interesting to see the results of a scan 5 and scan 6 of the same patients in this study to see if the decrease in atrophy continued to reverse. Though the data presented was significant, this study was limited by a sample size of 20 participants.

Chronic Back Pain (CBP)

Back pain makes up 25% of all disabling workplace injuries and is particularly prevalent among healthcare workers (Apkarian, et. al, 2004). Prior to this study, chronic pain has been studied by investigating changes in the nervous system in animal models. These studies found a reorganization of nociceptive stimuli perception and indicate the occurrence of apoptosis of spinal cord cells. It was previously assumed that the effects of chronic pain were reflected onto the cerebral cortex, but that the cerebral cortex would return to its previous state after the termination of the pain. However, the authors of this study hypothesized that in CBP, neocortical grey matter would atrophy at a rate that is beyond that of normal aging. Based on previous research, the researchers also hypothesized that the thalamus would also atrophy. Both hypotheses were confirmed by the data collected.

The authors compared a study group of 26 CBP patients, with a control group of 26 volunteers (Apkarian, et. al, 2004). CBP patients were diagnosed by experienced practitioners with the most current guidelines from the International Association for the Study of Pain (IASP). Causes of the CBP were not identified, however 15 patients were identified as having musculoskeletal pain, 5 had radiculopathic (neuropathic) pain, and 6 had a mixture of the two. All participants were given brain MRI scans, and the images were used to determine normalized cortical grey matter volume, and normalized lateral ventricular volumes. VBM was used to evaluate grey matter density of specific regions. Pain, anxiety, and depression were determined using a 0-10 scale and questionnaires.

Result analysis indicated that the grey matter volume of the whole brain was dependent on age, gender, and duration of pain (Apkarian, et. al, 2004). After correcting for these confounding variables, CBP patients were found to have an 11% grey matter volume decrease compared to the control group. In CBP patients, it was found that bilaterally, the DLPFC was the main location for regional decrease in grey matter. Additionally, the CBP group showed a significant decrease in grey matter density in the right anterior thalamus. Based on pain changes in DLPFC, the authors concluded that the grey matter changes are strongly related to the characteristics of pain. Specifically, the neuropathic CBP patients were found to have a larger decrease in DLPFC density compared to the CBP patients with musculoskeletal pain. Finally, lateral ventricle analysis concluded that lateral ventricle size and pain intensity have a statistically significant positive correlation. Negative affectivity and sensory components of CBP were also found to have a positive correlation with the change in lateral ventricle size.

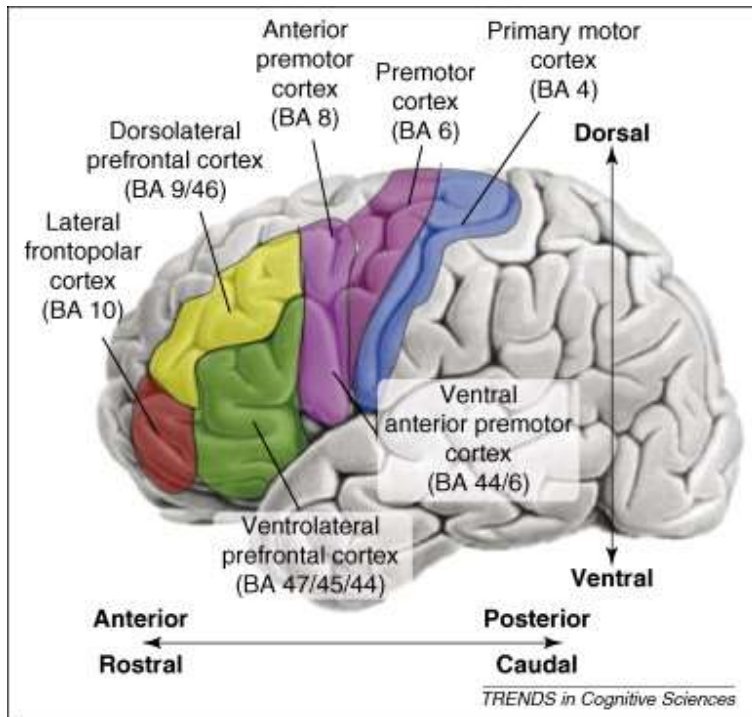


Figure 4. Schematic of major anatomical subdivisions in the frontal lobes (Badre, 2008).

In their discussion, the authors note that only a histological analysis could confirm the presence of atrophy in spinal cord cells (Apkarian, et. al, 2004). However, based on the magnitude of brain volume in participants, they could conclude that grey matter atrophy of the brain in CBP is equal to 10-20 years of normal aging, with normal grey matter atrophy occurring at a rate of 0.5% per year. Apkarian, et. al noted that in their data, only 18% of inconsistency in grey matter could be attributed to pain duration. This implies that there are other variables such as environment and genetics that contribute to the atrophy seen in these patients. The scientists note that some of the decrease in grey matter could be due to shrinking tissues as a result of an increase in extracellular volume. If this is the case, proper treatment could reverse this process. However, the decrease in grey matter could be a result of neurodegeneration. The authors feel as though the latter is the more likely option as the DLPFC does show decreased N-acetyl-aspartate (which is a phenomenon noted in most neurodegenerative processes).

Based on the finds of their research, the authors could infer other relationships resulting in neurological changes (Apkarian, et. al, 2004). Though CBP is often associated with anxiety and depression, the pattern of atrophy observed is much different than that of anxiety and depression. Therefore, this pattern appears to be unique to CBP, particularly since the DLPFC and thalamus are involved in the perception of pain. Recent research on the DLPFC showed a limiting effect on the amount of pain perceived in the cortex. Therefore, atrophy in this region could alter the perception of pain states in chronic pain patients. The authors end by further suggesting that atrophy to the neurologic signals responsible for pain perception could impose on the characteristics of the pain state, leading it to become more permanent, and less treatable.

This study directly relates to the PICOT question as the findings presented significant grey matter loss in the brain, particularly in the DLPFC. This study is organized in a clear and concise manner. The results and discussion are well organized, and the discussion expands nicely on the implications of this research. Like the previous study, this article has a small sample size. The experimental group consisted of 26 people, and the control group contained 26 people. Though it is clear that the data obtained is statistically significant, I believe a larger sample size would be valuable.

Complex Regional Pain Syndrome (CRPS)

CRPS most commonly develops after trauma or injury to a limb (Geha, P. Y, et. al, 2008). The condition is characterized by an inflammatory or neuropathic response, and presents with painful sensations that are often exaggerated, abnormal blood flow to the region, diuresis, edema, disruption of motor function, and other changes to the skin and subcutaneous tissues. CRPS develops in only 5% of limb trauma cases, but can be debilitating to those who experience it.

In this study, researchers examined the structure of the brain in patients with CRPS using VBM (Geha, P. Y, et. al, 2008). Additionally, the authors studied the relationship between grey matter atrophy and changes in connectivity of the white matter using diffusion tensor magnetic resonance imaging and made efforts to explain the clinical presentation of CRPS. Prior research has shown that CRPS patients perform poorly on emotional decision making tasks compared to CBP patients. The impairment of the CRPS patients is similar to that seen in patients with lesions in the VMPFC. Therefore, based on previous findings, this group of researchers hypothesized that CRPS can be defined by atrophy of grey matter in the VMPFC (Figure 5). Participants in this study included a group of 26 CRPS patients, and a control group of 28 healthy individuals. The pain group was diagnosed with CRPS using criteria defined by the IASP.

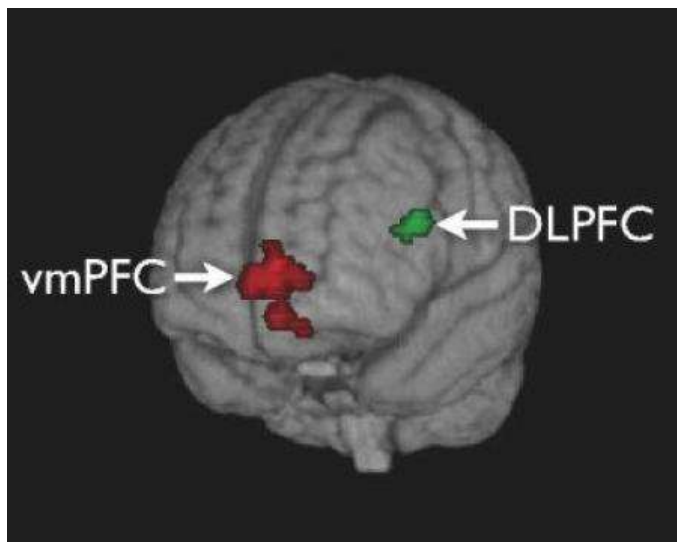


Figure 5. 3-D projection of a transparent brain showing regions of activation: the ventral medial prefrontal cortex (vmPFC) is in red, and the DLPFC is in green (Oliwenstein, L., 2009).

Ultimately, the study found no difference in neocortical grey matter volume or lateral ventricle size between CRPS patients, and the healthy control group (Geha, P. Y, et. al, 2008). However, whole-brain skeletal fractional anisotropy⁴ (FA) revealed a significant positive

⁴ Whole-brain skeletal FA: measure of the diffusion of water across the white matter of the brain reflecting the integrity of the white matter (Geha, P. Y, et. al, 2008).

correlation with grey matter volume of the whole brain in healthy control subjects. The researchers evaluated this data as evidence for a disruption in the relationship between grey and white matter in CRPS patients. In the imaging of the regional grey matter of the VMPCF in CRPS patients, it was observed that there is a small area of atrophy containing the right VMPCF, a portion of the agranular insular area (AI), and the nucleus accumbens (NAc). Additionally, the CRPS patients exhibited a localized decrease in white matter anisotropy, as well as alterations in connectivity between white and grey matter regions. The data presented clearly showed a disruption in the relationship between white matter skeletal FA, and grey matter volume in CRPS patients. The scientists inferred a reorganization of white matter connections on a whole brain level in a manner that differs completely from that of the healthy subjects.

One of the goals of this study was to use the data acquired to help explain some of the clinical presentations of CRPS (Geha, P. Y, et. al, 2008). The atrophy noted in clinical subjects in the right VMPCF, a portion of the AI, and the (NAc) was found to be related to pain duration and pain intensity. When these three separate anatomical regions were divided, the atrophy in the AI related specifically to the duration of the pain response as it is one of the parts of the brain that is most activated in result to acute pain. The interaction between pain intensity and duration was found to be directly related to atrophy in the VMPCF suggesting that the “emotional load (Geha, P. Y, et. al, 2008)” of CRPS falls on the VMPCF. This finding supported the main hypothesis of this study. In contrast to CBP patients showing atrophy of the thalamus and the DLPFC, CRPS patients do not show an increase in performance on emotional decision making tasks when a temporary reduction in pain is achieved. CBP patients however, show improvement and learning of these tasks over a period of time. This comparison suggests that the differences

in the regions of atrophy lie beneath the ability of a patient to perform emotional decision making tasks.

The results of this study are directly related to the PICOT question, as specific areas of grey matter atrophy were found to be the result of CRPS. Like the articles preceding it, the sizes of the pain and control groups were small, however the results achieved were found to be statically significant. The way this article is organized and written made it a challenging read. The experimental procedures section is located after the conclusion, and many statements thorough the article could be written in a more concise manner.

Grey Matter Reduction in Trigeminal Neuralgia (TN)

Traditionally, TN is thought to be a result of compression of the trigeminal nerve in the root entry zone close to the brainstem (Obermann, et. al, 2013). Researchers debate the presence of central involvement, but recent findings have pointed towards central grey matter loss in TN patients. The objective of this study was first to discover which areas of the brain are involved in the development and continuation of TN pain by comparing grey matter volume in TN and healthy subjects. Second, the researchers hoped to determine the differences between TN patients with persistent background pain and those with intermittent neuralgic attacks.

The sample size consisted of 60 TN patients from the same headache center recruited between 2007 and 2010 (Obermann, et. al, 2013). Diagnosis of TN was confirmed per the standards set by the International Classification of Headache Disorders (ICHD). None of the patients had any other remarkable neurological history or been treated invasively for TN. The pain group was compared to 49 healthy controls. Data was obtained through VBM imaging, and all images we evaluated by an experienced neuro-radiologist.

Cross sectional data analysis displayed regional discrepancy in grey matter volume between TN patients and healthy subjects (Obermann, et. al, 2013). The pain group was noted to have decreased brain matter in the primary somatosensory cortex, orbitofrontal cortex, anterior cingulate cortex, insula, secondary somatosensory cortex, thalamus, putamen, caudate nucleus, DLPFC, and cerebellum (Figure 6). The comparison between the two different TN groups showed no differences.

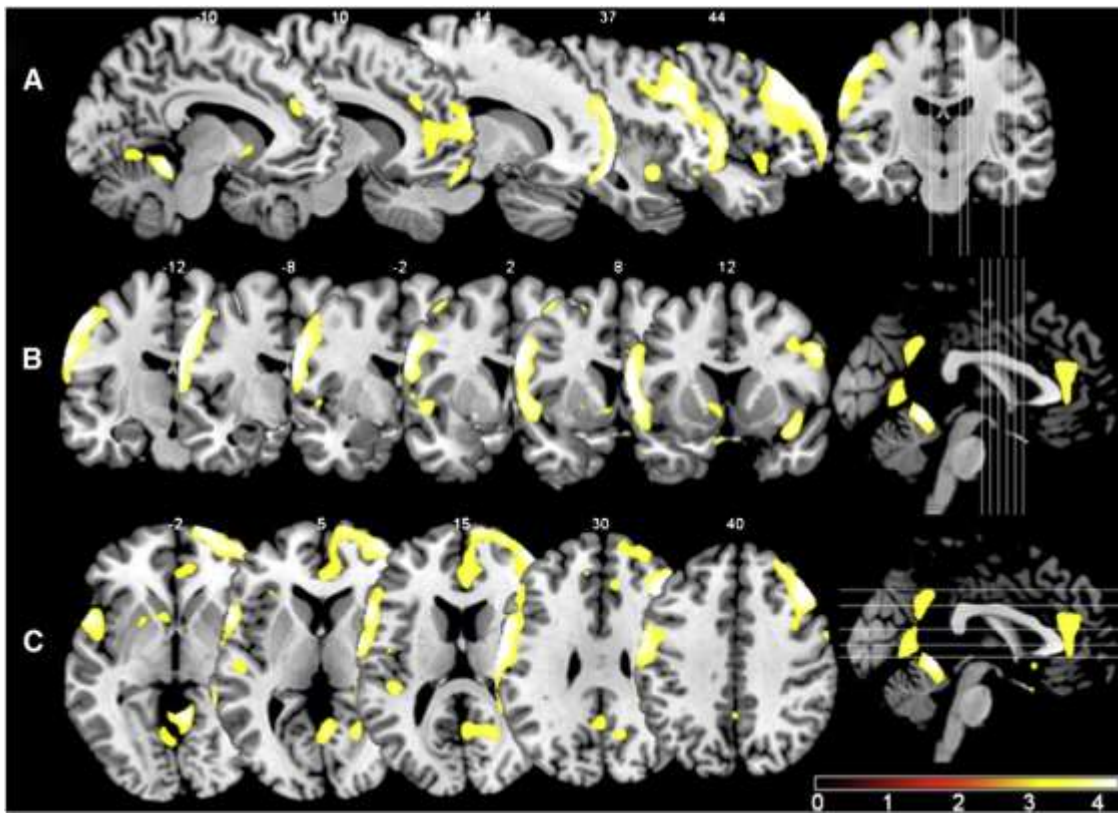


Figure 6. Structural brain changes related to trigeminal neuralgia associated facial pain (Obermann, et. al, 2013).

The regions in which grey matter reduction was noted are areas that have known connections with the processing and perception of pain (Obermann, et. al, 2013). The researchers also note that their findings on grey matter decrease are consistent with those found in other chronic pain conditions. This grey matter alteration also seems to be a reflection of neurological

adaptation to a pain perception that is high level and frequent. This data provides the information needed to complete the first objective of this study.

Unlike what the researchers expected, there was no notable difference in grey matter between the two different categories of TN patients: those with constant background pain and those with intermittent attacks (Obermann, et. al, 2013). The scientists explain that the most logical reason for this finding is that the repeated attacks, though they are short, provide an amount of stimulation that is enough to cause grey matter changes in the brain.

As other studies have mentioned, it is unclear whether grey matter changes are due to atrophy of cells, changes in interstitial fluid, blood flow, or a change in cell size. VBM imaging does not allow scientists to determine the cause of grey matter decrease, only that it has occurred. The authors note that they cannot determine whether alterations in grey matter are due to a reversible process or an irreversible process without a histological analysis.

This study directly relates to the PICOT question because the researchers were able to link TN to a decrease in grey matter volume, but were not able to definitively say that it was a result of atrophy. The sample size recruited for this study was larger than some of the previous studies with 60 pain participants and 49 healthy controls. Though this study did determine that there was a change in grey matter with this chronic pain condition, their data didn't reveal anything that previous research hadn't already. This article was organized, easy to read, and well written.

Gaps in Literature

At this time, this is no definitive research on the cause of grey matter decrease in chronic pain conditions. Though many articles refer to this decrease as atrophy, further research is needed to determine the true cause. There are many studies on this topic that have been

published in the last 20 years, however the most recent article that I discussed above was published in 2013. There is still much to be discovered on the deficits that chronic pain patients experience, why some patients will develop a chronic pain syndrome while others do not, and whether neurological changes in the chronic pain brain are permanent or reversible.

Conclusion

Chronic pain can be difficult to manage and in many cases, has a large impact on the quality of a patient's life. For nurses and other providers to give the best care possible, it is important to know as much as possible about the origins and effects of chronic pain conditions. Based on the research available today, it is obvious that chronic pain influences the grey matter volume of the brain. There is still much to be learned about how this happens, what the long-term effects are, and if the changes are permanent. Some authors state that the changes in grey matter are the result of atrophy, while others have shown that if the cause of the pain is taken away, that the effects partially reverse (Rodríguez-Raecke, et. al, 2013). With more insight into the causes of chronic pain conditions, there are opportunities for experts to develop new, and more effective treatment methods for patients in need.

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