ISSN: 3029-0708

Review Article

Journal of Clinical Psychology and Neurology

Hippocampal Abnormalities as a Biological Mechanism in Chronic Pain: A Critical Review

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Received: February 20, 2024; **Accepted:** February 26, 2024; **Published:** March 04, 2024

ABSTRACT

Chronic pain is a common medical issue that impacts the daily lives of more than 50 million Americans making it the leading cause of disability in the United States and the most common reason people seek medical care. Studies have shown that the limbic system plays an important part in the experience of chronic pain, however, of all the components of the corticolimbic system, the hippocampus has been studied less systematically in terms of its impact on chronic pain. This paper analyzed four studies that were published between 2019 and 2023 that examined the role of hippocampal abnormalities in chronic pain patients to provide a critical review of the emerging literature on this topic. The focus of the papers included in this critical review encompasses a variety of chronic pain disorders and sources of pain. For each study, an overview of the methodology, main findings, and limitations was provided.

Keywords: Hippocampus, Hippocampal Volume, Chronic Pain, Pain

Chronic pain is a common medical issue that impacts the daily lives of more than 50 million Americans making it the leading cause of disability in the United States and the most common reason Americans seek medical care [1]. Chronic pain occurs when acute pain, or pain that brings attention to injury or harm, persists beyond the healing process [2]. The common timespan used to define the typical healing process is three months and, therefore, chronic pain is defined as pain that lasts longer than three months [3]. The impact of chronic pain is often extreme and deleterious, greatly impacting the quality of life of those who suffer from this condition. Moreover, the impact of chronic pain is often felt not only by the individuals who live with it, but also by their families, communities, and society as a whole [4]. For individuals, living with chronic pain means persistent physical and psychological discomfort. For society as a whole, chronic pain is one of the largest causes of disability and healthcare costs today, with the current annual cost of chronic pain estimated to range between $261 and $300 billion [5,6]. The cost of chronic pain to society is greater than the cost of cancer and diabetes combined [6].

In an attempt to address the major public health burden of chronic pain, many animal and human studies have investigated the biological mechanisms that influence the experience of persistent pain [2,7]. There is a large body of literature that links chronic pain with activity in the central nervous system (CNS) and chronic pain is often conceptualized as a CNS disorder [2]. Housed within the CNS, the corticolimbic system is the focus of much of the literature on the underlying biological mechanisms of chronic pain with the thalamus, amygdala, anterior cingulate cortex, and ventral tegmental area just some of the corticolimbic system components that have been associated with the perception of pain [2,8,9].

However, of all the components of the corticolimbic system, the hippocampus has been studied less systematically in terms of its impact on chronic pain [10]. Some studies have established a link between chronic pain and the hippocampus in both human patients and laboratory animals [2]. Moreover, brain imaging studies have identified the key brain regions that are involved in pain processing, one of those areas is the hippocampus [5]. Abnormalities in the hippocampus that have been linked to chronic pain include reduced hippocampal volume, neurogenesis, and synaptic plasticity [10]. These findings have been shown across several different types of pain including osteoarthritis, back pain, complex regional pain syndrome, and chronic pain in the elderly [7,10,11]. This paper aims to review recent literature that focuses on the role of hippocampal abnormalities

Citation: Madeline Foster, Meaghan Donnelly, Tiffany Field. Hippocampal Abnormalities as a Biological Mechanism in Chronic Pain: A Critical Review. J Clin Psychol Neurol. 2024. 2(1): 1-7. DOI: doi.org/10.61440/JCPN.2024.v2.12

as a biological mechanism involved in chronic pain. Four recent studies from the last five years will be critically reviewed to develop a deeper understanding of the role the hippocampus plays in the experience of chronic pain.

Brain Structures Involved in Chronic Pain

Several human and animal studies have investigated the underlying cellular and molecular mechanisms behind chronic pain in an effort to inform interventions that minimize the significant impact pain has on individuals, as well as society as a whole. The biological pathways that have been identified as facilitators of chronic pain are complex and interdependent, however, the centrality of the CNS is consistent throughout the literature on this topic [2,12,13]. The CNS is made up of the brain and the spinal cord, which are responsible for detecting noxious stimuli and transmitting pain signals through the spinal cord to the brain. The detection of noxious stimuli is made through sensory receptors called nociceptors [12]. Messages from the nociceptors are transported via various neurotransmitters including glutamate to signal the location and intensity of the pain [14]. Once the messages reach the brain they are transmitted to areas involved in affect and memory such as the amygdala, hypothalamus, periaqueductal grey matter, and nucleus accumbens [2].

Neurological Models of Chronic Pain

The most dominant model for chronic pain throughout the scientific community is the biopsychosocial model [15]. This model posits that the interconnectedness between biological, psychological, and social factors is the foundation for the experience of chronic pain. Within the biological component of the biopsychosocial model sit several neurological models of pain. Melzack and Wall's Gate Control Theory suggests that pain is controlled by a mechanism in the spinal cord that allows or blocks pain from traveling to reach the brain [16]. The model states that pain originates from a malfunctioning gate that allows pain signals to continue traveling up the spinal cord to the brain despite the absence of acute tissue or nerve damage [17]. In 1999, Melzack expanded on the Gate Control Theory proposing that the neuromatrix, a network of neurons in the brain, generates the perception of pain [18,19]. Essentially, Neuromatrix Theory suggests that the neuromatrix determines the experience of pain. The neuromatrix can be triggered by a stimulus that causes pain, or it can be stimulated by external factors like chronic stress.

In addition to the Gate Control and Neuromatrix theories, several other models have also been proposed to explain the biological foundations of persistent pain. Central Sensitization Theory proposes that when the CNS becomes overly sensitive to pain, through prolonged or repeated exposure to painful stimuli, the perception of pain can be amplified through a pathophysiologic process [20]. Over time, the pain threshold of an individual is lowered because of the sensitization of the CNS. Another theory, referred to as the Wind-Up Phenomenon, proposes a similar neurological pain model suggesting spinal neurons that are subjected repeatedly to nociceptive impulses become more easily excitable [21]. In this model even when the pain stimulus is removed, spinal neurons continue to be stimulated.

Critical Review

Over the past five years, several studies have looked at hippocampal abnormalities and chronic pain. Four key studies, published since 2019, have been identified and will be critically reviewed in this paper. The first study, by Zhao and colleagues, looked at elevated dementia risk, cognitive decline, and hippocampal atrophy in individuals living with multisite chronic pain [22]. The study was conceptualized based on previous research findings that chronic pain prevalence increases with age and that many chronic pain patients report pain in multiple anatomical locations. The literature review cited several studies that reported increased cognitive decline and dementia risk as a result of chronic pain compared to the normal aging population [23-25]. Moreover, the study also highlighted the increasing literature base that recognizes chronic pain rarely exists at a single site with more than half of the chronic pain population experiencing pain at multiple sites [26]. This is important because when multiple pain conditions coexist it has been shown to create additional health burdens [27]. The authors emphasize the dearth of literature that addresses multisite chronic pain, despite the prevalence rate being so high, and state this as a motivator for conducting their study [22].

Literature has made a number of associations in terms of biological mechanisms for individuals with chronic pain who develop dementia [22]. For example, inflammation, genetic risk factors, and brain function and structure have all been identified in such patients [27,28]. However, Zhao and colleagues point out there is less literature that explores the potential biological mechanisms that are common between chronic pain and dementia [22]. One observation the authors make is that hippocampal abnormalities, particularly hippocampal volume are known to be common in patients with dementia [29]. Similarly, hippocampal atrophy has also been frequently observed in chronic pain patients [30].

Ultimately, the study aimed to link neural mechanisms that underpin chronic pain with increased dementia risk [22]. By linking literature that found hippocampal abnormalities in chronic pain patients, the study hypothesized that the hippocampus may play a role in the development of dementia for patients living with chronic pain. The study also hypothesized that the risk of dementia would be greater, and the hippocampal atrophy would be more severe, in those with multisite chronic pain compared to single-site or no chronic pain. The first research question asked whether multisite chronic pain was associated with an increased risk of dementia, the second asked whether multisite chronic pain was associated with more rapid cognitive decline, and the third asked whether multisite chronic pain was accompanied by hippocampal volume loss.

The study utilized both longitudinal and cross-sectional data taken from the UK Biobank database [22]. Longitudinal data was taken from 354,943 individuals aged between 39 years and 73 years. Within this longitudinal sample, there were 188,746 controls without chronic pain, 76,206 participants with single-site chronic pain (SCP), and 89,991 with multi-site chronic pain (MCP). The mean follow-up time for this group was 11.8 years (SD = 1.7). In addition to the longitudinal data, a subset of participants (N = 19,116) completed a brain MRI to explore the differences in hippocampal volume between those with no chronic pain (N = 9,558), SCP (N = 5,597), and MCP (N = 3,961). Sociodemographic information was collected from all participants and those with MCP were more likely to be female, non-White, currently smoke, have lower socio-economic status, lower education attainment,

higher body mass index (BMI), greater risk of psychological comorbidities, and have more disease history.

Chronic pain status was collected via self-report, no clinical evaluations were conducted to determine the course and severity of participants' pain. Participants answered a single question related to their experience of pain in the last month "In the last month have you experienced any of the following that interfered with your usual activities?" [22]. If they responded yes, they were asked to report whether their pain had lasted more than three months. Participants were asked to select which pain categories applied to them out of the following "back pain, facial pain, headaches, knee pain, stomach/abdominal pain, hip pain, neck/shoulder pain, none of the above, prefer not to answer, or pain all over the body." Those who identified pain at more than one site for more than three months were categorized as the MCP group, those with only one site were placed in the SCP group, and those with no pain were defined as the pain-free (PF) controls. Individuals who selected "pain all over the body" were excluded. Dementia was measured using the International Classification of Diseases-10 (ICD-10) codes in the UK Biobank. Cognitive tests were administered via a touchscreen at the UK Biobase Assessment Center to assess cognitive abilities and structural MRI data was used to determine total hippocampal gray matter volume (GMV).

The results of the study were broken down into three main findings [22]. The first was that MCP was associated with increased dementia risk as determined by Cox proportional hazards regression models. Compared to participants in the control group, individuals with SCP were 1.19 times more likely to develop dementia and those with MCP were 1.55 times more likely to develop dementia. After being controlled for potential cofounders including education status, BMI, smoking status, alcohol consumption, chronic condition history, and psychological conditions, the risk of dementia was 1.15 times greater for those with SCP and 1.36 times greater for those with MCP. Moreover, it was found that dementia risk increased significantly with the number of chronic pain sites, with those with pain at five or more sites 2.12 times more likely to develop depression than those without chronic pain. The second key finding was that MCP was associated with accelerated cognitive decline. Those with MCP had significantly accelerated aging trajectories as evidenced by their significantly worse performance on a majority of cognitive tests administered.

The main finding of the study was that both SCP and MCP were accompanied by significant hippocampal GMV loss [22]. Those in the SCP had significantly lower hippocampal GMV compared to PF controls. Moreover, the number of chronic pain sites further exacerbated hippocampal GMV loss. For example, from PF to SCP the change in GMV was -9.795 mm^3 in the left hippocampal GMV and -8.272 mm^3 in the right hippocampal GMV. For those in the MCP group who reported two chronic pain sites, this went up to 25.852 mm^3 in the left hippocampal GMV and 22.202 mm^3 in the right hippocampal GMV. Notably, for those with five or more chronic pain sites, GMV loss jumped to 100.330 mm^3 and 87.522 mm^3 in the left and right sides of the hippocampus respectively. Ultimately, the results of this study were important in establishing that hippocampal abnormalities increase with the number of chronic pain sites.

There are several methodological limitations of this study. The first was that the classification of participants into chronic pain groups was based entirely on self-report [22]. There were no clinical evaluations to determine the course and severity of each participant's chronic pain. Self-reporting can be problematic as it may lead to response bias which contributes to over or underreporting of pain [31]. Moreover, data related to the use of pain medication was not collected and, therefore, it is not possible to understand the impact this may have had on the results [22]. Additionally, the data that was used to determine the impact of multisite chronic pain on cognition and hippocampal GMV was cross-sectional, therefore, it is not possible to make casual relationships. Finally, the limited number of dementia cases meant it was not possible to establish an association between dementia and hippocampal GMV.

The findings of Zhao and colleague's study underscore the need for future research to consider the overlapping nature of chronic pain conditions and the compounding impact of multi-site chronic pain [22]. Moreover, given the limitations of the cross-sectional design, future longitudinal studies would be beneficial for establishing a causal relationship between multi-site chronic pain and hippocampal atrophy. Clinically, this study underscores the importance of factoring in the number of chronic sites when treating individuals with chronic pain.

A 2023 study by Neumann and colleagues looked at GMV in the anterior cingulum, anterior and posterior insula, and hippocampus in individuals living with chronic pain. The study focused on three specific chronic pain conditions, chronic back pain, migraine, and craniomandibular disorder. In their literature review, Neumann and colleagues emphasized the fact that changes in GMV have been observed in several studies that focus on a diverse representation of chronic pain experiences [32]. Ultimately, these studies suggest that the reorganization of grey matter may be a diagnostic marker for chronic pain. However, there is a limitation in the literature in that many studies have small sample sizes and there is a lack of clarity as to which specific chronic pain conditions share biological mechanisms with one another [33].

Therefore, this study aimed to investigate the association between GMV in the anterior cingulum, anterior and posterior insula, and hippocampus across three unique pain conditions [32]. Pain conditions were defined by location within the body, rather than pain mechanism and were representative of three unique pain experiences. The first research question asked whether there were differences between demographic and clinical scores between pain groups and control participants, the second asked whether there was a significant difference between GMV across pain conditions, the third asked whether depression was a mediator of GMV in individuals with chronic pain, and the forth asked whether chronic pain could be predicted by GMV.

The study used data collected between 2008 and 2012 by the Study of Health in Pomerania (SHIP) project [32]. The original project for which the data were collected aimed to recruit a large representative sample of the population in northern Germany. The study excluded those who did not have MRI data available, had more than one pain condition, had clinical abnormalities, and those who currently used opioids or benzodiazepines. This left a final sample size of 601. Of the total sample, 174

had chronic back pain, 92 had chronic migraines, 39 had the craniomandibular disorder, and 296 made up the control group. The study design was cross-sectional, with data being collected via a single MRI scan using a 1.5T Siemens MRI scanner. Classification into a chronic pain condition group was based on self-report. Those in the chronic back pain (CBP) group reported having back pain that lasted more than three months within the last 12 months. The migraine group reported having physician-diagnosed migraines within the last 12 months. The craniomandibular disorder (CMD) group reported pain in the fast, ear, masseter, or mandibular joint in the last 6 months. All participants had not recovered from their pain at the time of examination. The control group reported no or little limitation of daily activities because of pain in the last month.

For the first research question, it was reported that there was a significant difference in age, sex, depression scores, stressors, and alcohol consumption between all four groups [32]. There were no significant differences found between groups in terms of education, income, or smoking status. In terms of pain intensity, there was a significant difference between groups with those in the CBP group reporting an average pain intensity (measured on a scale of 1-10) of 5.23, those in the migraines group reporting 3.18, and those in the CMD group reporting 2.82. Similarly, in terms of limitations to daily activities attributed to pain, there was also a significant difference between groups with those in the CBP group reporting 2.74, migraines reporting 2.16, and CMD reporting 1.24.

In terms of GMV, at a macro level, there was a significant difference between those with a chronic pain condition (all pain groups combined) and those in the control group [32]. Whole-brain analysis revealed that the left hippocampus had less GMV across all chronic pain groups in comparison to the control group. More specifically, examining the differences between the three distinct pain groups included in the study, there was no overall significant difference found in GMV between groups. Moreover, the results of a linear regression analysis between GMV and pain intensity were also not statistically significant and there was no mediating effect found for mild depression. In terms of hippocampal volume specifically, GMV in the left hippocampus and left anterior insula/temporal pole significantly predicted chronic pain. Ultimately, the results of the study showed less hippocampal GMV in individuals with chronic pain compared to those in the control group who did not live with chronic pain. Notably, this finding was replicated across all three pain groups. The findings of this study highlight the recent shift towards focusing on the importance of hippocampal GMV as a key biological mechanism for the development of chronic pain.

As is the case for many studies on chronic pain, this study was limited by the fact that chronic pain status was based entirely on self-report [32]. Additionally, this study restricted its inclusion criteria for chronic pain to only three conditions, meaning that the diverse nature of chronic pain may not be adequately represented by only three common conditions. Moreover, the collection of the data used in this study was not gathered specifically to investigate pain, rather it was taken from a large population-based survey. Therefore, while the control group was somewhat comparable to the pain groups, there were some variables that they differed on. To address this limitation, the authors of the study used these variables as covariates and possible mediators. Finally, the pain conditions that were included in the study may have different underlying major mechanisms, therefore it is not possible to generalize the findings of this study to chronic pain in general or specific mechanisms of pain like neuropathic or nociceptive origin pain.

Future research could build on this study to include more chronic pain conditions and to look at hippocampal GMV in terms of specific mechanisms. Additionally, since this study only used data from northeast Germany and did not report racial or ethnic data, it would be beneficial for the study to be replicated in more diverse geographic, racial, and ethnic populations. Additionally, cognitive assessment in addition to MRI imaging may be a suitable complement to the assessment of those with chronic pain.

Another study that examined the role of hippocampal abnormalities in individuals with chronic pain and depression was published in 2019 by Ezzati and colleagues. Chronic pain is often comorbid with depression, with a large body of literature on both human and animal subjects highlighting the shared symptoms and complex interplay between the two conditions [34]. Therefore, it has been suggested that the two conditions share a neurobiological substrate [35]. However, the literature available that links chronic pain and depression in terms of neurobiological mechanisms is lacking [36]. Research has linked the hippocampus with both depression and chronic pain in isolation, with it being known to play a pivotal role in mood, cognition, stress, and the perception of pain [37]. Moreover, it has been found that within the hippocampus, the left and right sides play unique roles, with the left side being involved in verbal and declarative memory and the right being more closely linked to depression, pain, and stress [36].

In light of this, the study aimed to examine whether chronic pain and depressive symptoms are mediated by hippocampal volume [36]. More specifically, the study also aimed to determine whether left or right hippocampal volume had a stronger association with chronic pain and depressive symptoms. Therefore, the two research questions posed were whether chronic pain and depressive symptoms are mediated by hippocampal volume and which side of the hippocampus has a stronger association with chronic pain and depressive symptoms. Referencing the already published literature on this topic, it was hypothesized that the hippocampus would play a mediating role and that right-side hippocampal atrophy would be more pronounced in individuals with chronic pain and higher depressive symptoms.

The study utilized data from the Einstein Aging Study which utilized systematic recruiting methods to capture greater racial diversity that is representative of the Bronx community [36,38]. All participants were residents of the Bronx, New York, English-speaking, and non-institutionalized. The study included 131 non-demented individuals who participated in an MRI scan using a 3.0 T MRI scanner with a 32-channel head coil [36]. MRI imaging was used to determine overall hippocampal volume, as well as left and right side hippocampal volume. Depressive symptoms were measured using the Geriatric Depression Scale (GDS) with clinically significant depression being considered ≥ 5 on a 0 to 15-point scale. Chronic pain was based on a self-report of the presence of pain for at least three months that was moderate to severe in at least one anatomical location. The total

sample had a mean age of 78.9 years (SD = 5.18), were mostly women (58.8%), and were predominantly white (54.2%).

Results of the study revealed that, after controlling for demographic covariates, chronic pain was associated with significantly higher depressive symptoms [36]. Notably, while depressive symptoms were associated with significantly smaller hippocampal volume for both the left and right sides of the hippocampus, chronic pain was only significantly associated with less volume on the right side. Since hippocampal volume was only significantly associated with chronic pain on the right side of the hippocampus, the subsequent path analysis only included the right side. The results revealed a good fit (X2 = 17.7, degree of freedom = 3, comparative fit index = 0.99, and root mean square error of approximation = 0.19). Moreover, there was a significant direct effect of chronic on depressive symptoms and a significant indirect effect of chronic pain on depressive symptoms when mediated by hippocampal volume. These results highlight the unique and important role of the right side of the hippocampus on pain perception and depressive symptoms.

Several limitations were identified in this study. The first is the lack of detail as to how the sample of 131 participants was selected from the larger population study in which this data was taken [36]. Additionally, as has been pointed out in the other limitations of the previously discussed studies, the cross-sectional design limits the ability of these findings in terms of confirming causal relationships. Moreover, the evaluation of pain was specific only to the three months before the data was collected, and therefore, it is not possible to assess the cumulative effects of pain in this study. Specific pain mechanisms, anatomical locations, and differing levels of severity were not addressed in this study, and therefore, given the diversity in the experiences of those living with chronic pain, it is difficult to generalize these findings to all individuals with chronic pain.

Future studies may expand on the findings of this study by replicating the study design with cohorts who are representative of specific pain mechanisms or types of pain. Additionally, since this sample was taken from one inner-city New York City community, it may be useful to answer these same research questions with a larger, more generalizable population. Finally, the impact of pain medications was not assessed in this study and therefore future research may look at the effect of medication on chronic pain, depressive symptoms, and hippocampal volume.

Taking a slightly different approach than the previously discussed studies, a 2022 study by Noorani and colleagues looked at the effect of pain relief on hippocampal abnormalities in chronic pain patients with a specific chronic pain disorder. Citing literature that links chronic pain with poor memory and concentration, Noorani and colleagues emphasized the importance of the hippocampus in memory in their literature review [25,39-41]. As a result of this association, recent research has linked persistent stressors, like chronic pain, to adverse memory and therefore investigated the hippocampus as a potential underlying biological mechanism of chronic pain. This relationship has been explored in several different chronic pain conditions [36,42,43].

In their study, Noorani and colleagues use trigeminal neuralgia as a model pain disorder that is representative of chronic neuropathic pain [39]. The decision to use trigeminal neuralgia specifically was justified by the fact that it is unilateral, severe in nature, has a largely consistent presentation, and is not associated with other sensory deficits [44]. Trigeminal neuralgia is a severe condition characterized by severe, debilitating chronic facial pain that typically occurs in shock-like pain episodes [45]. One unique feature of trigeminal neuralgia is the fact that it is one of the few chronic pain disorders that is highly responsive to pain relief interventions like medication and surgery [46].

While there is a body of literature that highlights the reversibility of neurological abnormalities in individuals with chronic pain following pain relief interventions, the study by Noorani and colleagues is the first to focus on the reversal of hippocampal abnormalities [39]. Therefore, this study aimed to investigate whether the structure of the hippocampus differed in trigeminal neuralgia patients pre and post-pain relief intervention. Based on their literature review, the authors hypothesized that pain relief would increase hippocampal volume leading to the normalization of previous hippocampal abnormalities. The primary research question was whether hippocampal volume improved post-treatment. Other research questions posed included whether neurogenesis was negatively impacted by chronic pain and whether there would be a sex difference in hippocampal neurogenesis in trigeminal neuralgia patients.

The sample used in the study consisted of 61 trigeminal neuralgia patients who were being treated at Toronto Western Hospital in Canada [39]. Those in the intervention group received Gamma Knife Radiosurgery (GKRS) to treat their trigeminal neuralgia. Inclusion criteria included a diagnosis of trigeminal neuralgia according to ICHD-3 criteria, no prior surgical GKRS treatment for the disorder, availability of an MRI scan before and after treatment, and clinical follow-up six months post-surgery. A group of 61 healthy controls, matched in terms of age and sex, were also recruited from the Cambridge Centre for Aging. Pain was measured using two assessments, a Numeric Rating Scale (NRS) and the Barrow Neurological Institute (BNI) scale. Both scales were selected given their frequent use in similar literature.

Six months following the survey, 47 individuals in the intervention group were identified as treatment responders, reporting at least a 75% pain reduction. Pre-treatment brain scans revealed that the hippocampus was significantly smaller in those with trigeminal neuralgia compared to healthy controls. Notably, reversal of hippocampal abnormalities was reported for individuals with trigeminal neuralgia who received the GKRS procedure. While baseline assessments showed that those with trigeminal neuralgia had smaller hippocampal sizes, after treatment at six-month follow-up, there was no significant difference in terms of hippocampal size for those with trigeminal neuralgia and healthy controls. The study also looked closely at the subfields of the hippocampus including the subiculum, cornu ammonis, and dentate gyrus, and found that hippocampal subfields also normalized following the pain relief procedure. Breaking down the responses by sex, female participants in the intervention group experienced significantly greater hippocampal volumic increase compared to their male peers ($p = 0.031$).

The limitations of this study included the fact that trigeminal neuralgia is typically diagnosed over the age of 50, therefore,

it was difficult to recruit the control group onsite hence the use of the differing database [39]. Additionally, the number of individuals in the intervention group who did not respond to treatment was relatively small. Therefore, it was not possible to perform analysis and the paper was only able to focus solely on responders. Moreover, most trigeminal neuralgia patients are treated with medications and anti-convulsant drugs which may impact hippocampal volume. Due to the severity of trigeminal neuralgia, it is not possible to collect a sample of participants who are not using pain medication that would be large enough. Further, the brain scans for the control and intervention groups were done using different machines. While the authors cite there is little evidence that this difference may impact findings, there is literature that highlights potential discrepancies between machines [47]. Finally, trigeminal neuralgia is limited in its ability to represent all chronic pain given it is one of the few chronic pain conditions that can be effectively treated.

Several avenues for future research are available. Firstly, a study with a greater sample size may be able to recruit enough participants who are not treatment-responders to explore the differences in this group before and after treatment [39]. Moreover, future studies may repeat the study design to include participants who are more representative of diverse chronic pain conditions. Of particular importance would be examining the difference for those who have a disorder that is more complex to treat. Future research may also look at the correlation between hippocampal size change and change in pain intensity which was not addressed by this study.

Conclusion and Recommendations

While the biological mechanisms that underpin the experience of chronic pain have been heavily researched, the hippocampus is one structure that has received less attention [1,2,5,10]. However, in recent years, the centrality of the hippocampus in the experience of chronic pain has become the focus of a growing body of literature. This paper looked at four studies published in the last five years that explored the role of the hippocampus through a variety of methods. In all four studies, the hippocampus was identified as a key structure that differs significantly between pain-free controls and chronic pain patients. Throughout the papers examined, a number of chronic pain conditions were investigated with results consistent between diagnoses that vary in terms of anatomical location and pain categories. In Zhao and colleagues, Neumann and colleagues, and Ezzati and colleagues the hippocampus was observed to have a significantly smaller GMV in those with a chronic pain condition compared to healthy controls [22,36,39]. The final study by Noorani and colleagues also found smaller GMV in those with a chronic pain condition, however, their findings also revealed that this loss of volume may be reversible with pain relief treatment [39].

A number of methodological limitations were consistent across the research examined in this critical review. Firstly, the overreliance on self-reporting of chronic pain across the literature is potentially problematic. Future research could utilize physician diagnosis or other clinical tests to determine those with chronic pain. Moreover, common to most of the included studies in this critical review was a cross-sectional design. The lack of longitudinal research in this area is apparent and there is a great need for future studies to conduct longitudinal research so that causality in terms of hippocampal volume and chronic pain can be better understood. Finally, this critical review has highlighted the need for more diverse representation in the research on this topic. Future research should include more diverse populations with a variety of pain disorders to understand the unique relationship between chronic pain and hippocampal volume across the broad population who are impacted by this condition.

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