The Efficacy of Limbic System Retraining and Neuroplasticity in the Management of Chronic Pain and Disease: A Systematic Review

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The Efficacy of Limbic System Retraining and Neuroplasticity in the Management of Chronic Pain and Disease: A Systematic Review

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Abstract

**Background:** Chronic pain and disease are prevalent, affecting 51.6 million people in 2023. Therefore, due to the high complexity of chronic disease, many providers try different interventions to alleviate pain and improve their patient's quality of life. The limbic system is a critical component of the brain involved in pain perception and emotional regulation. With an overactive limbic system, the perception of pain is enhanced and continues to cause discomfort for the patient. By retraining the limbic system to alter the fight or flight response, a significant reduction in pain can be achieved, which results in better emotion regulation. The primary interventions considered for limbic system retraining are neurofeedback and electrical stimulation.

**Purpose:** This review aims to evaluate the efficacy of limbic system retraining and neuroplasticity in managing chronic pain and disease.

**Methods:** The author conducted an extensive literature review to evaluate the evidence and conducted a thorough annotated bibliography. Inclusion criteria for this study included articles that contained the key terms, were original research, could be obtained freely, and were published later than 2019. Any articles that didn’t meet the inclusion criteria were excluded. Data was collected using these key terms: amygdala neuromodulation, amygdala and insula retraining, limbic system neuromodulation, amygdala and chronic pain, limbic system retraining, neuroplasticity, and chronic pain management. Further, the following search engines were used to obtain articles: PubMed, Google Scholar, Jane Biosematic, National Institute of Health (NIH), UpToDate, and Science Direct. Data gathered was synthesized by evaluating the study's sample size and the statistical significance of the results while considering any potential bias. A limitation of the data collection was that only freely available articles through Augsburg Library sources were reviewed.

**Results:** After a thorough literature review, evidence supports the efficacy of limbic system retraining and neuroplasticity using neurofeedback and electrical stimulation. Of the articles reviewed, 19 met inclusion criteria, with 11 supporting neuromodulation using neurofeedback and eight for electrical stimulation. Studies ranged in sample size, and of the 11 articles supporting neurofeedback for neuromodulation, all were randomized controlled studies, with three not randomized. Further, of the eight randomized controlled studies, two were double-blind studies. Additionally, of the eight papers supporting the use of electrical stimulation, all were randomized controlled, with three being double-blinded. Evidence to support limbic system retraining using neurofeedback included amygdala plus insula retraining with MBSR and using real-time fMRI and amygEFP. These articles have shown efficacy in reducing pain and overall functional impairment. For patients with post-traumatic stress disorder, a significant reduction in
symptoms of 75% continued for up to 6 months. When considering articles supporting electrical stimulation, the results indicated that transcutaneous direct stimulation is effective for neuromodulation and reduced abdominal pain for inflammatory bowel disease. Additionally, 73% of participants noted reduced pain for patients who underwent electrical intramuscular stimulation. Further, transcutaneous vagus nerve stimulation also proved effective in modulating pain and reducing the number of chronic migraine attacks.

**Discussion:** A review of the literature and studies noted a few limitations. Across multiple papers, the primary limitation was the small sample size. Additional considerations were specific to each modality. The primary limitation of articles supporting neurofeedback for neuromodulation included the time to learn neurofeedback techniques. However, other limitations had too few fMRI scans, which were noted in two studies, and there was a concern about not considering the control variable of different therapists for teaching MBSR. Additionally, electrical stimulation papers also emphasized the need for research conducted over a more extended period, varied participants, and a greater sample size. Further, for the vagus nerve articles, the primary future consideration was to evaluate the influence of the sham intervention on the overall results. In conclusion, limbic system retraining and neuroplasticity are possible and effective. However, additional research is needed to evaluate the efficacy across a larger population and consider the long-term outcomes and benefits.
Introduction

In a survey conducted by the Centers for Disease Control (CDC), chronic pain and disease were found to be highly prevalent, multifactorial, and significantly impactful on patients’ daily lives.\textsuperscript{1} To understand the implications of chronic pain, it is essential to highlight the definition of pain, how it is classified, and when it becomes chronic. According to the International Association for the Study of Pain, pain is an unpleasant sensory and emotional experience associated with, resembling, or having actual or potential tissue damage.\textsuperscript{2} Further, pain is classified in three ways such as nociceptive, neuropathic, and nociplastic. Nociceptive pain results from either actual or threatened injury to tissues in the body that are not a part of the nervous system. Neuropathic pain results from damage to components of the somatosensory nervous system. Nociplastic pain is often considered the hardest to treat as it arises from an altered pathway that does not have an apparent reason for actual or threatened tissue injury.\textsuperscript{2} Therefore, persistent pain for over three months is then considered chronic.

In 2023, it is estimated that 51.6 million people will suffer from chronic pain.\textsuperscript{1} Additionally, it is commonly understood that patients who suffer from chronic pain and disease are at a higher risk for underemployment, disability, and associated opioid use and dependence.\textsuperscript{2} For patients and providers, this results in more significant difficulties when managing the complexity and chronicity of their condition due to its multifactorial components.\textsuperscript{2} Many different therapies have been considered to help patients manage chronic pain and disease, but each intervention has a varying level of efficacy. This review aims to determine the efficacy of limbic system retraining and neuroplasticity in managing chronic pain and disease by considering two primary interventions. The first intervention considers the limbic system and the
effects of neuromodulation of the amygdala using neurofeedback, and the second is electrotherapy utilizing electrical stimulation.

**Literature Review**

**Anatomical Review**

To understand the role of the limbic system in chronic pain and disease, it is necessary to review the pertinent anatomy. The brain is a complex organ that controls the functions of the human body. It is responsible for varying tasks, but one key component is the interpretation of trauma. As such, when an injury occurs, pathways in the body are turned on and elicit a pain response. Chronic pain and disease develop when these pathways are dysfunctional due to overactivation or injury.

The limbic system is one of the critical parts of the brain that impacts pain regulation. The anatomy of this system is complex, but it is essential to understand the pain pathways fully. The limbic system is located deep in the brain, and its primary function is to monitor an individual’s emotional state and regulate how a person responds to their perception of different stimuli. Understanding the anatomy and physiology of the brain will allow a more thorough comprehension of how pain develops and its impact when it becomes chronic.

As stated previously, the limbic system is in the deep layer of the brain and is primarily linked to modulating memories, emotions, and motivational processes. It is generally found lateral to the thalamus, inferior to the cerebral cortex, and superior to the brain stem. The different regions are separated primarily based on their embryologic origins and include the mesencephalic (visual, auditory, and somatosensory), diencephalic (hypothalamus, anterior thalamic nuclei, and habenular commissure) and telencephalic (olfactory bulbs, hippocampus, parahippocampal gyrus, fornix, septum pellucidum, mammillary body, amygdala, cingulate...
gyrus, and entorhinal cortex.) Each of these structures come in pairs and help regulate responses on either side of the brain.

When considering each of the specific structures, they each have a unique function and can aid in retraining and neuroplasticity. The hippocampus is essential for consolidating information and processing short- and long-term memories. The fornix is part of the hippocampus's output tract, and an associated injury has been shown to affect memory recall.

The amygdala is primarily responsible for regulating emotions, specifically anxiety, fear, and aggression. The amygdala also impacts decision-making, processes memories, and forms associations with adverse stimuli. The cingulate gyrus is primarily responsible for connecting behavior and motivational outcomes. Of these limbic system structures, the hippocampus and amygdala have been primarily assessed for their contribution to neuroplasticity due to their role in emotional regulation and the formation of memories. Future literature in this review will address how the limbic system becomes dysfunctional and how modulation of the amygdala aids in reforming new memories in the hippocampus and, therefore, strives for neuroplasticity as new neural pathways are created.

Limbic System Dysfunction

To answer the research objective, it is essential to understand why and how the limbic system becomes dysfunctional and contributes to chronic pain and disease. In a study by Duan et al., a concept of Notch signaling in the anterior cingulate cortex (ACC) was considered a primary contributor to the neuropathic pain pathway. In this study, the authors concluded that increased synaptic transmission occurred in the ACC. This was discovered after taking rats and applying a constriction injury for a specified amount of time, resulting in a chronic disability and observing their new response to stimuli. The rats with the constriction injury had a reduced tolerance to
painful stimuli. Their brains also had an enlarged ACC, which was then attributed to the increase in neuropathic pain generation. Additional studies have also shown the ACC's impact on limbic system function. In a study by Gu D et al., the research team considered the role of astrocytes (specific glial cells in the neuropathic pain pathway) and their role in chronic post-op pain. Their question considered whether preoperative anxiety would induce chronic postoperative pain. This was evaluated by giving rats a single prolonged stressor and observing the effects on their pain threshold compared to the control group. Their conclusions confirmed that anxiety and stress preoperatively could induce chronic pain by activating and increasing astrocytes in the ACC of the brain.

Further, the ACC is not the only part of the limbic system that can be affected. Stehberg et al., through a study on neuropathic pain, discovered that interleukin-1β is a crucial substrate that induces glycinergic activity in the amygdala. The research team noted increased excitability and reduced inhibitory control of the amygdala's (CeA) central nucleus due to pain. They further noted that neuroplasticity with the CeA appeared to be caused by an imbalance between the inhibitory-excitatory processes rather than the noxious stimuli.

Additionally, when considering the amygdala and its impact on chronic disease, Bao et al. noted altered functional activity in patients with Crohn’s disease. When evaluating the amygdala via functional MRI, the studies showed abnormal gray matter and increased thickness and volume in multiple parts of the brain, including the amygdala, ACC, and thalamus. Their conclusion confirmed that Crohn’s disease patients with high anxiety and depression had increased functional connectivity between their amygdala and thalamus. Further, Coppieters et al. considered the functional connectivity of the amygdala during rest in women with chronic neck pain. This study also confirmed that patients with chronic neck pain at rest had enhanced
left amygdala function compared to their control group. Their findings support that amygdala-ventral frontal circuitry in chronic neck pain is associated with diminished pain inhibition. This further supports understanding of cognitive-affective and sensory alterations in women with chronic neck pain.

Finally, the impact of disease processes such as chronic migraines has the potential to affect limbic structures and alter endogenous μ-opioid neurotransmission. In a study by Jassar et al., a PET scan was used to evaluate patients’ limbic system during the ictal phase, and three primary observations were made. First, patients with > 15 headache days a month may indicate μ-opioid activation in the right amygdala. Additionally, this concept was consistent with the previous understanding that there is an amplification of nociceptive pain and an increased emotional response. This outlines the pathophysiological significance of opioidergic dysfunction. Second, the scan's pain intensity and abnormal area measurements showed sensory aggravation of attacks. Finally, thermal pain indicated that chronic migraine patients significantly increased μ-opioid transmission and effect on the parahippocampal region and the amygdala. The research team concluded that the flawed opioidergic activity in the limbic system explained pain's high emotional and cognitive impact on patients with chronic migraines. Additionally, the research team noted that the enhanced sensitivity to environmental factors for patients with chronic migraines had a higher risk for medication or substance overuse.

Limbic System Neuromodulation Overview

As mentioned, the ability to effectively treat these conditions is complicated due to many factors. However, research has shown that there are effective ways to help patients manage their pain by utilizing the limbic system. The standard approach to chronic pain and disease management is multifactorial and can include pharmacotherapy and lifestyle interventions such
as stress management, diet, and exercise. However, after utilizing these initial interventions and chronic pain is persistent, the question becomes if the problem is within the limbic system and if the body is stuck in a constant state of arousal. Previously, it has been shown that trauma does induce physiologic changes within the brain, specifically the ACC and amygdala. Therefore, strategies to reduce amygdala activity and responsiveness to stimuli is a theory to aid in managing limbic system dysfunction. Currently, some methods evaluate the ability of a patient to control their response to stimuli by modulating their limbic activity. Additionally, the use of electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) have also been used to help patients to be able to see their brain activity visually and try to modulate the response based on the feedback given.

**MBSR and Insula Retraining**

MBSR is a tool used to help patients to monitor their stress response. It has been widely accepted to significantly improve patients' quality of life who use the techniques regularly. In 2020, Sanabria-Mazo et al. conducted a study that utilized a combined therapy approach, including MBSR and techniques designed to retrain the amygdala and insula responses to stimuli. The overall goal was to use a mind-body practice that interrupted the amygdala's chronic over-sensitization and heightened fear response and retrain the conditioned somatic signaling in the brain, which would keep the nervous system in constant arousal. Of the 41 participants, the outcomes noted a significant reduction in functional impairment, anxiety, depression, and notably brain-derived neurotrophic factor (BDNF). To further consider the effects of MBSR, Andrés-Rodríguez et al. evaluated its effects on modulating the immune system by assessing immune-inflammatory markers. This proved informative as it showed efficacy in altering the limbic system activity reducing inflammatory biomarkers.
Emotional Regulation and Positive Memories

While MBSR effectively reduces stress and anxiety among many patient populations, Kober et al. considered the effectiveness of learning mindful acceptance to reduce amygdala responses. Their study considered the effect of teaching acceptance as a strategy in a single moment to down-regulate pain and negative emotions. fMRI was used to observe amygdala responses to stimuli, and participants were instructed to either accept or react. To react meant to respond as they would typically in a similar situation but accept implied allowing the experience to be as it was without trying to answer or avoid it. Additionally, the use of positive memories to modulate the limbic system response and achieve neuroplasticity was considered in a study done with teenagers suffering from depression. The goal was to evaluate the level of amygdala activity and the ability for neuroplasticity by having teenagers recall positive memories and try to recall the exact emotions and feelings at that time. Given that depression typically has reduced amygdala activity, the hope was that by using this strategy, the teenagers would find a reduction in their depression symptoms and an improved affect. The research team concluded that there was a reduction in anxiety and depressive symptoms in the active control group versus the placebo group. These findings outlined that the neurofeedback effects in the amygdala resulted in a unique mechanism of self-processing modification and should be considered as an intervention to evaluate neuroplasticity further.

Real-Time Amygdala Neurofeedback

Interestingly, real-time amygdala neurofeedback has been an intervention that has shown results in helping patients modulate their limbic response and achieve neuroplastic changes effectively. Multiple studies have indicated that patients with access to neuroimaging, such as an EEG or fMRI, have effectively achieved limbic modulation. By utilizing different
neuromodulation strategies and then seeing real-time feedback, outcomes showed enhanced emotional regulation and reduced pain symptoms. Goldway et al. considered volitional neurofeedback, which aimed at helping patients with fibromyalgia achieve better emotional regulation and improved sleep.\textsuperscript{13} The study consisted of five-week biweekly sessions, and the goal was to help participants control neural activity by bridging mental states and, therefore, achieve neural signal modulation.\textsuperscript{13} Further, Fruchtman-Steinbok et al. also considered how using amygdalaEFP (amygEFP) would assist in limbic system neuromodulation.\textsuperscript{14} Their study also showed that real-time neurofeedback was essential to helping patients with post-traumatic stress disorder (PTSD) to modulate their limbic system, resulting in lower responses to stimuli and reduced overall symptoms.\textsuperscript{14} Therefore, these studies suggest that real-time neurofeedback can be a way to help patients achieve neuromodulation. Overall, researchers noted that patient outcomes were impacted by the following factors: the ability to actively see what their brain is doing, practicing techniques to downregulate their limbic system, visually seeing results cemented in their brain, and the motivation to continue practicing techniques on their own as they can see and experience the positive benefits.

\textit{Transcranial Direct Stimulation}

While there is evidence of using neurofeedback for limbic system neuromodulation, electrical stimulation warrants discussion as a treatment for managing chronic pain. Transcranial direct current stimulation (tDCS) modulates the nerve pathway and interrupts the chronic pain signaling response. This was demonstrated to be effective for central pain modulation. In a study by Kold et al., participants had three days of treatment with 20 minutes of tDCS after creating delayed muscle soreness in the participants.\textsuperscript{15} This approach did show that the tDCS did modulate the central nerve processing and modulation of the pain response.\textsuperscript{15}
Additionally, tDCS effectively modulates the pain response of patients with inflammatory bowel disease. Neeb et al. demonstrated that after five days of tDCS treatments, the participants receiving the intervention had higher functional connectivity in the amygdala and insula. These functional changes resulted in reduced pain and better emotional regulation, pain integration, and overall perception of pain among the participants. Notably, similar effects were also seen when Young et al. considered the impact of tDCS on patients with multiple sclerosis. In this randomized, controlled, single-blinded study with five days of tDCS, participants noted reduced pain in bilateral lower extremities for up to two weeks after treatment.

Along with tDCS, intramuscular electrical stimulation (EIMS) has been evaluated as an intervention for chronic myofascial pain. The overall theory for the efficacy of EIMS is the ability to modulate pain pathways. This technique is described as electroacupuncture to achieve pain modulation in a bottom-up fashion. In a study by Angoleri et al., 24 participants had ten sessions with EIMS treatment, and the results were promising, with a 73% reduction in pain, a 30% reduction in analgesic medications, and improved sleep biomarkers of 12.75%. Further, BDNF biomarkers were also considered to evaluate the immune response, and for this study, there was an increase in BDNF.

**Vagus Nerve Stimulation**

Along with tDCS and EIMS, using the vagus nerve pathway has shown promising results in pain modulation. Muthulingam et al. conducted a study considering the effectiveness of using cervical vagus nerve stimulation for patients with chronic pancreatitis with the goal of limbic system modulation and altering cerebral metabolites. The study supported potential beneficial effects when targeting the central nervous system and modulating pain responses. Further, Yakunina et al. considered the effects of vagus nerve stimulation on patients with chronic
tinnitus. In this study, 36 participants with chronic tinnitus received vagus stimulation to the inner tragus and cymba conchae. Interestingly, the results indicated that auditory and limbic structures were sensitized by the vagus nerve stimulation, especially in the parahippocampal gyrus, which is noted as being the primary area to cause tinnitus. Finally, vagus nerve stimulation has also effectively managed chronic migraine attacks. Huang et al. conducted a study with subjects for four weeks, three sessions a week, going through vagus nerve stimulation. The overall results indicated a decreased functional activity in the nucleus tractus solitarius area within the brain, which then projects to the limbic system structures and, therefore, results in modulation of their response.

Methods

The author conducted an extensive literature review to evaluate the evidence, and an annotated bibliography was created based on the data collected. Data was gathered utilizing key terms and specific search engines. Inclusion criteria consisted of articles not older than 2019 containing key terms, were original research, and could be obtained freely from the search engine. Articles that did not meet the above criteria were excluded. Of the articles reviewed, six were used for providing a transparent background and need for interventions, and one outlined the pertinent anatomy. The background articles were taken from PubMed and NIH using the key terms. To answer the research question, ten papers were selected to highlight neurofeedback and eight for electrical stimulation to evaluate the interventions' efficacy. These articles were found using PubMed, Google Scholar, Jane Biosemantic, National Institute of Health(NIH), UpToDate, and Science Direct using the following key terms: amygdala neuromodulation, amygdala and insula retraining, limbic system neuromodulation, amygdala, and chronic pain, limbic system
retraining, neuroplasticity, and chronic pain management. A limitation of the data collection was that only freely available articles through Augsburg Library sources were reviewed.

Results

As noted, managing chronic pain and disease is a multifactorial and complex process with variable outcomes. This creates challenges for patients and providers as they may have to try multiple interventions to determine which are the most effective. Currently, the first line of treatment is lifestyle modification with pharmacotherapy. However, the use of medications has shown to be minimally effective. After a thorough literature review and analysis of the data, there are definite treatment options that have better efficacy and outcomes for patients.

When considering complex disease processes such as fibromyalgia, the use of mind-body training is effective in reducing pain and improving sleep. The primary intervention for fibromyalgia has traditionally been pharmacotherapy and lifestyle interventions. However, both Sanabraia-Mazo et al. and Andrés-Rodríguez have noted that MBSR is highly effective in reducing overall stress levels and inflammatory markers in the body. Further, Sanabria-Mazo et al. added the addition of amygdala and insula retraining to their study, which had promising results despite the small sample size. Of the 41 participants, MBSRI plus amygdala and insula retraining has been shown to add additional benefits and increase the effectiveness of the therapy. This was confirmed by reduced anxiety, depression, functional impairment, and clinical severity scores after treatment for participants. Specifically, 84% of subjects achieved > 20% improvement, which increased the probability of the overall success rate of the intervention to 65%, and 35% noted a > 50% reduction in their functional impairment scores. There was also a decrease in BDNF markers, therefore affirming that MBSR with the amygdala and insula retraining is effective in modulating this immune biomarker and should be considered an
adjunctive therapy to the overall treatment of fibromyalgia. Finally, while the data is precise regarding the effectiveness of the intervention, the results are still preliminary, and additional studies should be conducted to evaluate the effects over time and with a larger sample size.

While MBSR and amygdala retraining are one avenue to modulate limbic activity and reduce pain, another promising intervention is using real-time EEG and fMRI to see how brain activity responds differently when performing relaxation strategies in response to varying stimuli. Specifically, Quevedo K et al. noted that neuromodulation and neuroplasticity of visual self-processing in teenagers suffering from depression is achievable and practical, as seen in Figure 1. In their study, 34 teenagers were asked to modulate their amygdala activity by recalling positive memories and noting the specific details of when, where, and what they felt. Results from this study reported a reduction in anxiety and depressive symptoms and further confirmed the ability for neuroplastic changes within the amygdala, as shown in Figure 2. Additionally, Kober et al. showed the effectiveness of using a concept of acceptance and not reacting to stimuli. The study instructed participants to respond or accept based on the triggers. The research team noted that within the small sample size of 17, mindful acceptance altered the nociceptive response and modulated the intensity of the stimulus. Due to the small sample size, further research should be conducted to see the effects of the intervention on a larger scale, consider the impact of pre-operative pain, and then correlate the pain response post-operatively.

Notably, of all the literature discussing neurofeedback and neuromodulation of the amygdala and limbic system, the study with the most promising effects considered using real-time EEG and neuromodulation in managing both fibromyalgia and post-traumatic stress disorder (PTSD). Goldway et al. illustrated this concept using an amygdala-electrical fingerprint, an fMRI-driven EEG model for patients with fibromyalgia (see Figure 3). While this study is
small, with only 34 participants, the outcomes noted a 40% reduction in pain intensity, which is considerable when comparing the 7.2-8.6% effectiveness of pharmacotherapy such as Duloxetine, Pregabalin, and Milnacipran. The research team outlined that this treatment is a low-cost modality with considerable clinical value as the skills learned can be further integrated into daily life.

Further, Fruchtman-Steinbok et al. outlined the amygdala electrical=fingerprint (amygEFP) as being highly effective for patients with PTSD. In this study, 59 participants were randomized into three groups (Trauma-neurofeedback, Neutral-neurofeedback, and No-neurofeedback.) The research team considered the effectiveness of using the AmygEFP to downregulate the amygdala while reinstating the traumatic memories. After 15 sessions, the results indicated that in the trauma-neurofeedback group, there was a reduction of 35.13% of symptoms compared to baseline, and the fMRI noted a greater amygdala-down regulation and were able to use their own pre-recorded trauma memories compared to the no-neurofeedback groups as indicated in figures 4 and 5. Notably, the intervention's positive effects lasted 3-6 months as participants reported continued benefits at follow-up. Zweering et al. also noted that real-time fMRI is beneficial for PTSD. After their crossover design study with 25 participants, while being small, they found that neurofeedback significantly reduced PTSD symptoms and improved affect from baseline after four weeks of training. Additionally, 75% of participants noted that they learned techniques that can be applied during situations with significant exposures and used them to help reduce the severity of their symptoms.

Overall, the research shows how these techniques can be effective when considering the effectiveness of neurofeedback for limbic system retraining and neuromodulation. The limiting factor is that the sample size is small in many of these studies, so further research should be
conducted to confirm the efficacy for a larger population. Additionally, the feasibility of administering neurofeedback via neuroimaging is considered. Further, the financial cost and time considerations are important, so continued study on how these treatments can be utilized cost-effectively is essential.

To contrast neurofeedback, electrical stimulation was considered to achieve neuromodulation of the limbic system. Of the studies reviewed, the results indicated that electrical stimulation effectively achieves neuromodulation and reduces overall symptoms. Specifically, Neeb et al. noted the effects of transcranial direct current stimulation (tDCS) for patients with inflammatory bowel disease. Their study included 36 subjects and reported a higher functional activity in the right amygdala after the intervention and reduced abdominal pain.\textsuperscript{16} Further, tDCS was evaluated for patients with multiple sclerosis. Again, a small study of 30 participants was assessed, and results showed a 2-week reduction of neuropathic pain after five sessions.\textsuperscript{17} While these results are also promising, larger sample sizes with a focused population would be beneficial in determining the efficacy of the intervention.

While tDCS has shown promise in neuromodulation, stimulation of the vagus nerve and electrical intramuscular stimulation have also had positive results. Transcutaneous vagus nerve stimulation noted reduced symptoms and desensitization of the limbic, auditory, and parahippocampal structures for chronic tinnitus.\textsuperscript{20} Further, this intervention was also used for chronic migraine sufferers. In a study by Huang et al. with 70 participants, the results showed a reduction in chronic migraine attacks and noted a modulation of the limbic system and overall pain perception.\textsuperscript{21} Finally, in a study by Botelho et al., electrical intramuscular stimulation effectively reduced pain for patients with chronic myofascial pain. While the study was small, of the 24 participants, the results showed a 73% reduction of pain after 12 weeks, a 30% reduction
of analgesics needed, and improved sleep by 12.75%. Additionally, the BDNF biomarker was noted to increase from 26.21 to 31.93. This suggests learning and appropriate memory of new neural pathways and likely would predict the long-term effect of the intervention.

Overall, the literature shows promise when considering the results from the data reviewed for electrical stimulation as a viable intervention, just like the neurofeedback interventions. Similarly to the neurofeedback studies, further evaluation should consider larger sample sizes to understand the efficacy on a larger scale and the feasibility from a financial standpoint to implement the therapy.

**Discussion**

Managing chronic pain and disease is complicated due to its multifactorial components. A comprehensive literature review has shown the efficacy of using neurofeedback and electrical stimulation as modalities for limbic system neuromodulation and neuroplasticity to reduce chronic pain and disease symptoms. The methods used to evaluate the effectiveness of these interventions included multiple studies using surveys noting symptoms before the intervention, their quality of life due to their symptoms, a discussion of any relative risk, and surveys post-intervention to evaluate for efficacy. For participants using neurofeedback and amygdala retraining, sessions were done on average 2x a week for four weeks. If the intervention involved real-time EEG of fMRI, the sessions involved debriefing and communication with the participants to see how the intervention was going. When participants did not have real-time EEG or fMRI, they did have a debriefing session conducted at the end of the study along with the post-survey.

To further explain the methodologies used, the studies that did not have real-time neuroimaging also had homework to practice the skills learned, and then they reported the
findings to the research team at the end of the study. Of note, the electrical stimulation studies had varying session lengths and parameters. Both intervention groups had pre- and post-assessment surveys that were included to evaluate symptom severity before and after the intervention and discuss any relative risk.

After considering all the benefits, risks, and outcomes of the studies evaluated in the literature review, evidence supports using limbic system retraining and neuroplasticity to manage chronic pain and disease. Current interventions reviewed have yielded a reduction in symptom severity, better affect, improved sleep, and enhanced quality of life throughout multiple studies. The overall effectiveness of using limbic system neuromodulation through either neurofeedback or electrical stimulation has yielded, at best, a 73% reduction of symptoms using electrical intramuscular stimulation and the long-term benefits seen at six months as seen through the studies utilizing amygEFP for PTSD.\textsuperscript{13,18}

However, additional research is needed to evaluate the effectiveness of the interventions on a larger sample size with an increased length of time for each study to assess the long-term efficacy of the interventions. By continuing the research on limbic system modulation and neuroplasticity, assessed interventions can be further considered on a larger scale and evaluate the effectiveness for more significant populations and disease processes. This would provide additional ways to effectively manage patients' pain, helping reduce chronic disease and improve quality of life.

When considering ways to manage chronic pain and disease, the primary interventions include lifestyle modifications and pharmacotherapy. As stated previously, the interventions described have the potential to be clinically significant, but additional research is needed to evaluate the efficacy of limbic system retraining on a larger scale. By further investigation, the
interventions evaluated could be confirmed as practical and financially reasonable to help patients manage their chronic pain or disease as either an adjunct to their treatments or as an option when refractory to first-line interventions.

Conclusion

As the prevalence of chronic pain and disease continues to grow, there is a greater need for safe and effective interventions. Historically, the primary intervention includes lifestyle modifications and pharmacotherapy-targeted symptom management. However, current research suggests that retraining the limbic system can be a viable option in symptom reduction and improves the outcomes of patients who suffer from chronic pain and disease. The primary interventions considered included neurofeedback and electrical stimulation for modulating the limbic response. The similarity between traditional pharmacotherapy and limbic system retraining is the goal of symptom reduction. When considering the differences between the current treatment protocols and limbic system retraining, the primary differentiating factor is the possibility of physiologically altering the brain pathways to reduce the overall pain response significantly. Of the studies evaluated, there were varying levels of efficacy, but at best, there was a 73% reduction in overall pain response with lasting effects for six months.\textsuperscript{13}

After a thorough review, it can be concluded that neurofeedback and electrical stimulation can effectively retrain the limbic system and reduce chronic pain and disease effects. Multiple studies have shown varying levels of efficacy, but all have at least a 20% reduction in symptoms, with the highest being 73%.\textsuperscript{13} The following studies showed the most promising results: electrical intramuscular stimulation, MBSR with amygdala and insula retraining, and real-time amygdala EFP. These studies showed clinically significant percentages for positive results and sustained benefits for at least three to six months. Finally, among the studies using
amygdala EFP and MBSR with amygdala retraining, participants noted skills were learned that they felt they could practice during their activities of daily living to help reduce their reactivity to stressful stimuli.

While limbic system retraining to achieve neuroplasticity has multiple studies showing efficacy, more research is needed to show the true effectiveness over a more extended period and with varying populations. Future studies must evaluate a larger sample size, a more focused intervention of either electrical stimulation or neurofeedback, and consider any long-term outcomes greater than six months. The potential benefit of affirming the efficacy of limbic system neuromodulation is a possible reduction in patient use of analgesic medications, improved sleep, better affect, and a reduction in overall symptoms related to their disease processes.

Chronic pain and disease management is complicated and challenging for both patient and provider. As medicine continues to change, the ability to profoundly impact a patient's health is a reality. Limbic system retraining has the potential to be a powerful tool and, if utilized correctly and effectively, will significantly impact many patients by helping them live with less pain and an overall improved quality of life.
Fig 1: This figure notes the effects of neurofeedback on the frontotemporal network. Recalling happy memories showed more significant activity, especially in the postcentral gyrus and inferior parietal lobe.

Fig 2: Highlights that all participants, regardless of demographics, had better emotional regulation with accessing happy memories and neurofeedback when compared to counting backward.

Fig. 3 illustrates the statistical significance and impact of amgEFP for patients with fibromyalgia.
Fig 4: This outlines the overall model and protocol for the study.

Fig 5: This figure outlines the positive effects of using amgEFP for patients with PTSD and notes a significant percentage in symptom reduction compared to the Neutral-NF and No-NF groups.
References


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