REVIEW ARTICLE

Anatomy and Pathophysiology of Chronic Pain and the Impact of Hypnotherapy

Malminder Gill^{1*}

¹96 Harley Street London W1G 7HY

ABSTRACT

Chronic pain is thought to develop from intense repetitive nociceptive (acute) pain. This condition has various forms and can persist for longer than 3 months, such that finding efficacious treatment is challenging in the clinical setting. The essence of this review is to present a selection of studies highlighting anatomical changes in brain activity in acute and chronic pain. An overview of the interaction between pain and psychological conditions will also be examined followed by the physiological effect of hypnosis. The review concludes with recommendations for further work in developing robust pain management in clinical hypnotherapy practice.

Keywords: chronic pain, pain pathway, hypnotherapy, hypnotic suggestions, pain modulation, pathophysiology

INTRODUCTION

According to a survey assessing the impact of chronic pain on the daily lives of patients, 1 in 5 people in Europe are affected by this condition (Breivik et al., 2006). This presents a compelling case to find efficacious treatments that help in the management of chronic pain.

Over the last three decades, numerous studies using an evidence-based approach have validated hypnosis as being efficacious in the treatment of certain chronic pain conditions (Jensen et al., 2009; Goodin et al., 2012; Del Casale et al., 2015).

Chronic pain

Chronic pain is often described as pain that persists longer than 3 months (Ginzburg, Merskey and Lau, 1988). There are many types of chronic pain conditions including

phantom pain, neuropathic pain, lower back pain, fibromyalgia, complex regional pain syndrome and post-surgical pain. Unlike acute pain, which subsides after injury heals, chronic pain continues in the absence of any recognizable peripheral damage (Tsay et al., 2015).

It is thought that the inception of chronic pain develops from intense repetitive nociceptive (acute) pain (Voscopoulos and Lema, 2010).

Nociceptive pain

Acute pain is usually referred to as nociceptive pain that occurs during and after tissue injury to the skin, joints or viscera. Under normal conditions, the body's reaction to this peripheral damage usually follows the pain pathway of transduction, conduction, transmission, perception and modulation. As soon as the injury has healed, acute nociceptive pain usually subsides (Voscopoulos and Lema, 2010).

Pathophysiology of normal (acute) pain – The pain pathway

Nociceptors are free sensory nerve endings located in the skin, joint and walls of organs. They are activated upon tissue injury and are responsible for converting

*Correspondence: info@hypnosis-in-London.com
Malminder Gill, 96 Harley Street London W1G 7HY
Phone: 02036375877, Mobile: 44 7848458351

harmful stimulus into electrical currents. The process of conversion is known as transduction.

The electrical signal is conducted through the axon to the dorsal root ganglion and onto the dorsal horn in the spinal cord where it arrives at the presynaptic nerve. At this point, the electric signal triggers the release of neurotransmitters, namely glutamate. If the insult to the tissue is particularly intense, Substance p is also released (Voscopoulos and Lema, 2010). These neurotransmitters diffuse into the synaptic gap and synapse with postsynaptic dorsal horn neurons, also known as second order neurons.

The electric signal then continues through the ascending spinothalamic and spinoreticular tracts to the thalamus (Steeds, 2013). From here, the signal is then transmitted to various areas of the cerebral cortex such as the anterior cingulate cortex, insular cortex, primary somatosensory (S1), secondary somatosensory (S2) and prefrontal cortex. It is in these brain regions that the electrical signal is perceived as pain (Zhuo, 2008). Thereafter, transmission of pain signals is modulated by the periaqueductal gray and nucleus raphe magnus in the midbrain. Essentially, projecting neurons from these locations either invoke the inhibition or facilitation of pain.

Pathophysiology of chronic pain

The area of chronic pain and its exact pathology is still a relatively new topic. Emerging results from MRI scans from the 1990's have started to piece together some initial ideas behind the mechanics of chronic pain. Recent findings have been able to show that changes in neural plasticity, activation of certain cortical regions, gray matter density and the release of chemical substances are unique to chronic pain.

Glutamate and substance P

It is thought that intense persistent acute pain leads to the development of chronic pain (Tsay et al., 2015). The heightened intensity causes an exaggerated prolonged reaction from C-fibre nociceptors. This in turn leads to the release of substance P into the synaptic gap and by extension, an activation of mast cells that release calcitonin

gene-related peptide (CGRP). Additionally, glutamate (the major excitatory neurotransmitter) is also released into the synaptic gap (Voscopoulos and Lema, 2010). In the synaptic gap, a process of diffusion of these substances occurs, which triggers a cascade of events leading to a vicious cycle of chronic pain. Once glutamate is released, it reacts with certain post-synaptic receptors, namely N-methyl-D-aspartic acid (NMDA) and α -amino-3-hydroxy-5-methyl-4-isoazolepropionic acid (AMPA).

In the normal pathophysiology of pain, where pain is considered to be short-lived and acute, glutamate only acts on the AMPA receptors. However, in chronic pain, where the initial intensity and duration of acute pain is heightened, glutamate acts on NMDA receptors. This latter action is known as "wind-up".

The activation of NMDA receptors results in further inflammatory process causing central sensitization of pain and subsequently to chronic pain state (Voscopoulos and Lema, 2010).

As a response to heightened pain intensities, glutamate along with substance P are released by c-fibre nociceptors. This concurrent release plays an important role in the development of chronic pain. When substance P is released, it activates genes within glial cells. This causes the release of an inflammatory concoction of cytokines, interleukin-1, interleukin-6 and tumor necrosis factor- α (TNF- α). These inflammatory mediators increase excitability in the surrounding area and more neurotransmitters are subsequently released in the synaptic gap. In turn, the higher concentration of substance P and glutamate exert their effect on glial cells and NMDA receptors respectively. This process is known as a positive feedback loop and describes chronic pain (even after the initial injury has healed) in allodynia, hyperalgesia and hyperpathia.

Activation of cortical regions

Studies show that the cortical areas affected during perception of pain include primary somatosensory cortex (S1), secondary somatosensory cortex (S2), insular cortex, anterior cingulate cortex, amygdala, prefrontal cortex and the thalamus. In particular, studies have also been able to show that the cognitive and emotional pain processing

areas such as the anterior cingulate cortex, display heightened activity amongst chronic pain patients (Henry, Chiodo and Yang, 2011). These findings could begin to explain why distraction techniques employed by cognitive behavioural and relaxation therapists help in the management of chronic pain states (Mahrer and Gold, 2009).

Further studies have demonstrated the key role the anterior cingulate cortex plays in the perception of the unpleasantness of pain. In particular, the landmark study by Foltz and White in the 60's showed that patients who had cingulotomy had little emotional response to pain they experience (Henry, Chiodo and Yang, 2011). Therefore, it can be hypothesized that increased ongoing activity in the anterior cingulate cortex plays a key role in differentiating between chronic pain patients and acute pain subjects (Henry, Chiodo and Yang, 2011).

Changes in plasticity

Neural plasticity refers to the physical changes to the neuronal anatomy and physiology in response to the environment. In a normal healthy non-pain state, one can expect plasticity to occur at various levels in the central nervous system due to ongoing life experiences (Henry, Chiodo and Yang, 2011). Plasticity affects both the function and structure of the central nervous system, which can significantly alter neuronal behaviour.

In the development of ongoing pain states, the heightened intensity of acute pain and the subsequent barrage of cascading events are thought to initiate the development of neuroplasticity.

Neuroplasticity occurs in response to intense prolonged pain states to help facilitate the over-active cascading events, thus creating the chronic pain cycle (Voscopoulos and Lema, 2010). The process of neuroplasticity starts when over-stimulation and ultimate death of the inhibitory secondary neurons (which serve to modulate nociceptive pain) occurs. Simultaneously, the cycle of pain transmission continues due to alteration of the genetic profile of glial cells by substance P. This leads to plasticity changes in the sensory pathway including the nociceptors, dorsal horn and the higher cortical and subcortical centres (Zhuo, 2008). Studies have shown

changes in cortical areas of the brain including motor and sensory alterations with patients suffering from chronic pain (Henry, Chiodo and Yang, 2011).

Changes in gray matter

Nerve cell bodies make up the gray matter in the spinal cord and the brain. Recent studies show changes in the density of gray matter of the cingulate cortex, insular cortex and dorsolateral prefrontal cortex in patients suffering from chronic pain (Henry, Chiodo and Yang, 2011). Interestingly, gray matter changes differ according to the type of chronic pain condition.

In the study performed by Apkarian (2004), patients with chronic lower back pain showed a reduced amount of gray matter in the prefrontal and thalamic regions of the brain. Kuchinad et al., 2007 were able to show a reduction in gray matter in the anterior cingulate cortex and insular cortex in patients suffering from fibromyalgia. The reason for changes in gray matter density remains uncertain, however it could be linked to the death of inhibitory secondary neurons, which serve to modulate pain in the spinal cord (Zhuo, 2008). Researchers have hypothesized that the reduction and absence of chronic pain should lead to an increased and thus normal level of gray matter density over time, however, this still process remains unclear (May, 2008).

The interaction between psychological and physical systems in chronic pain

Chronic pain is usually comorbid with a number of psychological conditions such as depression, anxiety, cognitive dysfunction, somatization and self-efficacy, amongst others (Burke, Mathias and Denson, 2015). The link between the physicality of chronic pain and psychological conditions is an ongoing field of inquiry. The following section will discuss recent developments between psychological and physical systems of pain in relation to gray matter, executive function and depression.

Influence on gray matter

Recent studies suggest that change in gray matter often seen in patients suffering from chronic pain has a direct impact on their psychological wellbeing. These

changes directly reflect the level of anxiety and depression experienced by chronic pain sufferers (Bushnell et al., 2015). In fact, reduction in gray matter exacerbates and extends pain sensation (Apkaria, 2004; Geha et al., 2008, Bushnell et al., 2015). Moreover, it is suggested that the experience of ongoing pain further reduces gray matter density (Bushnell et al., 2015). Reduced gray matter in the cingulate and frontal cortices have shown varying degrees of cognitive dysfunction amongst chronic pain patients (Luerding et al., 2008).

The influence of reduced gray matter density is further demonstrated in studies that have examined decreased level of concentration and attention capabilities of chronic pain patients (Bushnell et al., 2015).

Influence on executive function

Executive function is the overarching term used to describe various mental processes including time and task management, decision making and working memory (Berryman et al., 2014). A pool of evidence from a recent meta-analytical review suggests that chronic pain patients suffer from reduced executive function (Berryman et al., 2014). This could largely be due to patients focusing on their chronic pain symptoms rather than the tasks presented in tests that recorded their cognitive aptitude, thus demonstrating the impact chronic pain can have on normal psychological functioning (Berryman et al., 2014).

Influence on depression

It is a widely held belief among health professionals and current literature that chronic pain is comorbid with depression (Burke, Mathias and Denson, 2015). However, the underlying mechanics of this association still remains to be investigated. It is uncertain whether chronic pain influences depression or whether ongoing depression influences chronic pain (Bair et al., 2003).

One study in the literature review has revealed that depressed patients show heightened awareness of pain intensities, bordering on allodynia (Bair et al., 2003), suggesting that a depressive state of mind can lead to chronic pain.

Additionally, Bair et al., (2003) found that long-term depressives usually have uncategorized pain symptoms,

further adding to the literature evidence stating that depression is linked to chronic pain. This differs from an earlier meta-analysis showing that chronic pain is often the precursor of depression (Dworkin and Gitlin, 1991).

Based on the discussion so far concerning the pathophysiology of chronic pain, the meta-analysis by Dworkin and Gitlin (1991) fits in with the traditional idea of chronic pain developing from acute nociceptive pain. Contrary to the more recent study by Bair et al., (2003) that alludes chronic pain to a psychological condition. With more research needed to identify which condition triggers the other, it is clear that depression influences chronic pain and vice versa.

It has been proposed that there is a common link in the physiology of the brain with patients who have depression and chronic pain (Fasick et al., 2015). In particular, it has been suggested that the hippocampus, which is responsible for learning and memory, plays a key role in the maintenance of ongoing chronic pain, stress and depression (McEwen, 2006). Additionally, studies have revealed that both depressed and chronic pain patients express a disruption in the hypothalamic-pituitary-adrenal (HPA) axis. This system is largely responsibly for the fight-or-flight response to stress. Given that stress is a major contributing factor to depression and chronic pain, this could explain the physiological link that has been discovered between depression and chronic pain (Fasick et al., 2015).

Physiological effects of hypnotherapy in chronic pain patients

In the early 70's, Hilgard experimented with pain perception and hypnosis using specific hypnotic neodissociation methods. The results of this study sparked wider interest to further investigate the use of hypnosis in pain management (Hilgard, 1973). Since then, numerous studies have revealed various levels of efficacy for the use of hypnosis in experimental and clinical pain conditions. However, the underlying technicalities of the physiological impact of hypnosis with pain patients have remained somewhat a mystery. Recently, PET and fMRI scans, have shed some light to this discussion (Goodin et al., 2012; Del Casale et al., 2015).

Although there is still much to be investigated, especially in the domain of chronic pain and hypnosis, the following section will discuss recent findings that have reported on changes in physiology of chronic and experimental pain via hypnosis.

Potential impact on HPA and Cytokines

The hypothalamic-pituitary-adrenal (HPA) axis is usually activated during responses to stress, but it is also known to play a role in the development of chronic pain. The stimulation of the HPA axis coupled with saturation of cytokines is responsible for pain perception. A recent study evaluated the impact hypnosis had on the HPA axis and cytokines in subjects undergoing experimental pain (Goodin et al., 2012). Although the results showed a significant reduction in pain unpleasantness and moderate reduction in pain intensity compared to the control group, the biomarkers assessing HPA axis and cytokine activity showed little change. The outcome of this study differs from an earlier review, which implied the shielding effect of hypnosis on stress and related immune functions (Gruzelier, 2002).

As yet, it is unclear whether hypnosis impacts the HPA and cytokines, however, the marked reduction in experimental pain unpleasantness and pain intensity warrants further research in this area.

Impact on cortical and subcortical regions

The anterior cingulate cortex plays a central role in the pain matrix, and especially in the maintenance of chronic pain. A number of recent studies have shown heightened activity in this area of the brain in chronic pain patients who were subjected to hypnotic analgesic input. In particular, a study of patients with fibromyalgia undergoing hypnosis showed an increased activity in the middle cingulate cortex during fMRI scan (Derbyshire, Whalley and Oakley, 2009).

Hypnotic suggestion for pain modulation has been seen to also impact other areas of the brain including prefrontal, insular and somatosensory regions (Del Casale et al., 2015). A study using PET scans demonstrated

increased activity in insular and cingulate cortices of chronic back pain patients when exposed to hypnotic analgesic suggestions (Del Casale et al., 2015).

Another fMRI study revealed that differing hypnotic suggestions impacted different brain regions and subsequently altered pain outcomes. In particular, the anterior cingulate cortex was activated under fMRI scans when the patient received suggestions for pain affect. However, when the patient received suggestions for alterations in pain intensity, the anterior cingulate cortex and sensory cortices were both activated (Goodin et al., 2012).

These recent studies demonstrate a promising start to the discovery of how hypnosis impacts the pathophysiology of pain. However, more research is needed in the area of chronic pain to validate the efficacy of hypnosis to the wider clinical community.

CONCLUSIONS

Various studies discussed in this paper have demonstrated the pathology of chronic pain, the impact it has on psychology and the reductions in pain unpleasantness amongst pain patients undergoing hypnosis. More importantly, the studies related to hypnosis reveal the significant nature of the impact of various hypnotic suggestions and their subsequent influence on different regions in the brain. PET and fMRI scans have shown the areas of the brain that are activated via hypnotic suggestion, however this does not necessarily point to the efficacy of hypnosis or provide enough evidence for hypnosis to be viewed as an efficacious treatment in the wider clinical community. Whilst these studies provide a good foundation for further research, the clinical applicability is sparse. It is hoped that future studies will add to the existing literature and provide robust methods for pain management in hypnotherapy practice that is applicable in general clinical setting.

Conflict of interest

The author does not declare any conflict of interest

References

- Apkarian, A. (2004). Chronic Back Pain Is Associated with Decreased Prefrontal and Thalamic Gray Matter Density. *Journal of Neuroscience*, 24(46), 10410-10415.
- Bair, M., Robinson, R., Katon, W. & Kroenke, K. (2003). Depression and Pain Comorbidity. *Archives of Internal Medicine*, 163(20), 2433-2445.
- Berryman, C., Stanton, T., Bowering, K., Tabor, A., McFarlane, A. & Moseley, G. (2014). Do people with chronic pain have impaired executive function? A meta-analytical review. *Clinical Psychology Review*, 34(7), 563-579.
- Breivik, H., Collett, B., Ventafridda, V., Cohen, R. & Gallacher, D. (2006). Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment. *European Journal of Pain*, 10(4), 287-287.
- Burke, A., Mathias, J. & Denson, L. (2015). Psychological functioning of people living with chronic pain: A meta-analytic review. *British Journal of Clinical Psychology*, 54(3), 345-360.
- Bushnell, M., Case, L., Ceko, M., Cotton, V., Gracely, J., Low, L., Pitcher, M. & Villemure, C. (2015). Effect of environment on the long-term consequences of chronic pain. *Pain*, 156, 42-49.
- Del Casale, A., Ferracuti, S., Rapinesi, C., Serata, D., Caltagirone, S., Savoia, V., Piacentino, D., Callovin, G., Manfredi, G., Sani, G., Kotzalidis, G. & Girardi, P. (2015). Pain Perception and Hypnosis: Findings From Recent Functional Neuroimaging Studies. *International Journal of Clinical and Experimental Hypnosis*, 63(2), 144-170.
- Derbyshire, S., Whalley, M. & Oakley, D. (2009). Fibromyalgia pain and its modulation by hypnotic and non-hypnotic suggestion: An fMRI analysis. *European Journal of Pain*, 13(5), pp.542-550.
- Dworkin, R. and Gitlin, M. (1991). Clinical aspects of depression in chronic pain patients. *The Clinical Journal of Pain*, 7(2), 79-94.
- Fasick, V., Spengler, R., Samankan, S., Nader, N. and Ignatowski, T. (2015). The hippocampus and TNF: Common links between chronic pain and depression. *Neuroscience & Biobehavioral Reviews*, 53, 139-159.
- Geha, P., Baliki, M., Harden, R., Bauer, W., Parrish, T. & Apkarian, A. (2008). The Brain in Chronic CRPS Pain: Abnormal Gray-White Matter Interactions in Emotional and Autonomic Regions. *Neuron*, 60(4), 570-581.
- Ginzburg, B., Merskey, H. and Lau, C. (1988). The relationship between pain drawings and the psychological state. *Pain*, 35(2), 141-146.
- Goodin, B., Quinn, N., Kronfli, T., King, C., Page, G., Haythornthwaite, J., Edwards, R., Stapleton, L. & McGuire, L. (2012). Experimental Pain Ratings and Reactivity of Cortisol and Soluble Tumor Necrosis Factor- α Receptor II Following a Trial of Hypnosis: Results of a Randomized Controlled Pilot Study. *Pain Medicine*, 13(1), 29-44.
- Gruzelier, J. (2002). A Review of the Impact of Hypnosis, Relaxation, Guided Imagery and Individual Differences on Aspects of Immunity and Health. *Stress*, 5(2), 147-163.
- Henry, D., Chiodo, A. & Yang, W. (2011). Central nervous system reorganization in a variety of chronic pain states: A review. *PM&R*, 3(12), 1116-1125.
- Hilgard, E. (1973). The domain of hypnosis: With some comments on alternative paradigms. *American Psychologist*, 28(11), 972-982.
- Jensen, M., Barber, J., Romano, J., Hanley, M., Raichle, K., Molton, I., Engel, J., Osborne, T., Stoelb, B., Cardenas, D. & Patterson, D. (2009). Effects of Self-Hypnosis Training and EMG Biofeedback Relaxation Training on Chronic Pain in Persons with Spinal-Cord Injury. *International Journal of Clinical and Experimental Hypnosis*, 57(3), 239-268.
- Kuchinad, A., Schweinhardt, P., Seminowicz, D., Wood, P., Chizh, B. & Bushnell, M. (2007). Accelerated Brain Gray Matter Loss in Fibromyalgia Patients: Premature Aging of the Brain? *Journal of Neuroscience*, 27(15), 4004-4007.
- Luerding, R., Weigand, T., Bogdahn, U. & Schmidt-Wilcke, T. (2008). Working memory performance is correlated with local brain morphology in the medial frontal and anterior cingulate cortex in fibromyalgia patients: structural correlates of pain-cognition interaction. *Brain*, 131(12), 3222-3231.
- Mahrer, N. & Gold, J. (2009). The use of virtual reality for pain control: A review. *Current Science*, 13(2), 100-109.
- May, A. (2008). Chronic pain may change the structure of the brain. *Pain*, 137(1), 7-15.
- McEwen, B. (2006). Plasticity of the Hippocampus: Adaptation to Chronic Stress and Allostatic Load. *Annals of the New York Academy of Sciences*, 933(1), 265-277.
- Steeds, C. (2013). The anatomy and physiology of pain. *Surgery (Oxford)*, 31(2), 49-53.
- Tsay, A., Allen, T., Proske, U. & Giummarra, M. (2015). Sensing the body in chronic pain: A review of psychophysical studies implicating altered body representation. *Neuroscience & Biobehavioral Reviews*, 52, 221-232.
- Voskopoulou, C. & Lema, M. (2010). When does acute pain become chronic? *British Journal of Anaesthesia*, 105(Supplement 1), i69-i85.
- Zhuo, M. (2008). Cortical excitation and chronic pain. *Trends in Neurosciences*, 31(4), 199-207.