Implications on hypnotherapy: neuroplasticity, epigenetics and pain

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ABSTRACT

We provide a brief review about the significance of hypnosis with respect to applications and physiological processes in hypnotherapy. Our review concludes that hypnosis is a promising method to manage acute and chronic pain. In addition, we discuss indications pointing toward the view that hypnosis can induce changes in neuroplasticity possibly involving epigenetic mechanisms.

Keywords: hypnotherapy, neuroplasticity, epigenetics, pain

1. INDRODUCTION

Hypnosis has been used to manage diverse types of pain since centuries and across different cultures (Pintar and Lynn, 2008). Although hypnosis has been controversial and is currently not a part of mainstream clinical practices, there is increasing evidence that hypnosis can indeed be an effective non-pharmacological and cost-effectiveness method for the treatment of various health conditions like pain, anxiety, mood disorders, sleep problems, stress associated with medical and surgical procedures, cancer treatment-related side effects or irritable bowel syndrome (Anbar and Slothower, 2006; McCann and Landes, 2010; Coelho et al., 2008; Schnur et al., 2008; Lindfors et al., 2013; Kravits, 2013; Yeh et al., 2104).

While a uniform definition of hypnosis still not exists, hypnosis can be considered to be an altered state of consciousness (i.e. a trance-like state) resembling sleep induced by another person. It allows to recall memories or to be guided to change a specific behavior (Wagstaff, 2013).

Although the neurophysiological mechanisms underlying hypnosis are far from sufficiently understood, neuroimaging studies revealed that subjective changes in response to hypnotic suggestion are associated with corresponding changes in brain areas related to the specific psychological function (Demertzi et al., 2011, 2015; Jensen et al. 2017). Furthermore, neuroimaging studies found that altered functional connectivity is associated with hypnosis (Schulz-Stübner et al., 2004; Jiang et al., 2017; Pyka et al., 2011). In addition, hypnotherapy may also be associated with hypnosis-induced epigenetic changes (Sawni and Breuner, 2017; Cozzolino et al., 2021; Rossi, 2005).

Here we review the relevant literature and explain why we conclude that hypnosis is a promising method to manage acute and chronic pain. In addition, it is also proposed that hypnosis could induce changes in neuroplasticity and that epigenetic mechanisms may underlie these changes of synaptic plasticity.

2. HYPNOTISABILITY

Hypnotisability refers to the degree to which individuals follow suggestions during hypnosis. Standardized tests like the “Stanford Hypnotic Susceptibility Scale, Form C” (SHSS:C; Weitzenhoffer and Hilgard, 1962) and the “Harvard Group Scale of Hypnotic Susceptibility scale, Form A” (HGSHS:A; Shor and Orne, 1962) have been developed to measure and predict hypnotic suggestibility (Gamsa, 2003). Since then, about 60 years have passed and most hypnotisability models focus on biological, psychological and social factors. Such biological factors include genetics, brain morpho-functional characteristics, the hemispheric prevalence (asymmetries) and the working memory (De Pascalis and Santarcangelo, 2015). Psychological factors include attitudes, beliefs and expectancies about hypnosis, imaginative abilities, hypnotic suggestions, how participants interpret suggestions, and the actual mental state of subject. Social factors include the rapport, verbal information and context effects. In an interesting study, Gandhi and Oakley (2005) found that the hypnotic technique produces a modest increase in suggestibility when it was called relaxation, but a significant increase if it was called hypnosis. This study is an excellent example how much a single factor, like verbal information, can have on the outcome of hypnosis. The

biopsychosocial model of hypnosis tries to integrate and organize biological, psychological and social factors, as well as their interactions (Jensen et al. 2015; Buckner et al., 2013). Biological, psychological and social factors of hypnotisability cannot be separated in reality. Jensen et al. (2015) emphasize that no single factor appears primary and that various factors may contribute more or less to the outcome in different subsets of individuals or for different conditions. Thus, models of hypnosis that incorporate all biological, psychological and social factors can be more useful than restrictive models that focus on only one factor or a few factors (Jensen et al., 2015). It is feasible that the interconnectedness of the factors of hypnotizability may play an important role in explaining apparent contradictions published study results about the neural correlates of hypnosis, hypnotizability and hypnotic responses.

3. HYPNOTHERAPY FOR VARIUS HEALTH CONDITIONS

Numerous studies have showed that hypnosis can be an effective and safe approach for the treatment of pain, wound healing, emotional stress, haemorrhage, depression, anxiety, sleeping disorders or stressful events like surgical procedures or tooth extraction. Furthermore, hypnosis has been applied in the context of bone marrow aspiration, colonoscopy and for psychotherapy (Chester et al., 2016; Rogovik and Goldman, 2007; Evans et al., 2008; Iserson, 2014; Schnur et al., 2008; Fuhr et al., 2017; Chiu et al., 2018; Golden, 2012; Milling et al., 2018; Moser et al., 2013; Mackey, 2018; Abdeshahi et al., 2013; Chen et al., 2018; Wobst, 2007).

4. HYPNOTHERAPY AND ACUTE PAIN

Feeling pain is a stressful and often induces anxiety. The stress is sufficient to trigger the perception of pain (Rome and Rome, 2000). Our nervous system controls how we process and feel pain, although there is no single “pain center” in the body that is responsible for the processing of pain. Pain perception is associated with interactions between various regions of the peripheral and central nervous systems that contribute to the overall experience of pain. Pain by itself is a complex, biopsychosocial phenomenon that arises from the interaction of numerous neuroanatomic and neurochemical systems with a number of cognitive and affective mechanisms (Garland, 2012).

Landolt et al. (2011) analyzed 13 studies and found that hetero-hypnosis (i.e. a hypnotic state induced by another person) and self-hypnosis (i.e. a self-induced hypnotic state) reduced pain during labor and delivery and was even more effective compared with

standard medical care. A systematic review and meta-analysis by Provençal et al. (2018) concluded that hypnosis reduced pain intensity and anxiety in adults undergoing burn wound care. Another systematic review by Flynn (2018) indicated that hypnotherapy and relaxation methods are effective in reducing short-term and long-term headache incidence in migraine sufferers. During the course of cancer, hypnosis can reduce patients' perception of pain, cancer procedure-related pain, disease-related stress, anxiety and insomnia (Tomé-Pires and Miró, 2012; Wortzel and Spiegel, 2017; Carlson et al., 2018; Montgomery et al., 2013). Thompson et al. (2019) performed the largest meta-analysis based on 85 controlled studies that investigated the efficiency of hypnosis as a method for pain reduction. They found strong evidence that hypnosis can produce substantive analgesia, with optimal pain relief delivered when direct analgesic suggestions are used in a target population of individuals with high suggestibility. The authors also concluded that hypnosis may represent a potentially effective and safe alternative or adjunct to pharmacological intervention for acute pain.

Recently, Billot et al. (2020) revealed that a 12-week long hypnosis home care program was effective to manage pain perception in an elderly population. Madden et al. (2016) analyzed the effectiveness of hypnosis for pain management during labour and childbirth based on evaluating nine trials comprising 2954 women. The authors suggested that hypnosis may reduce the overall use of analgesia during labour, but not epidural use. Dorfman et al. (2013) demonstrated that hypnosis can be efficient for the management of painful human immunodeficiency virus (HIV) distal sensory polyneuropathy (HIV-DSP), the most common nervous system disorder in HIV patients. Hypnosis reduced pain levels in HIV patients and improved their quality of life. These benefits lasted for seven weeks following the intervention. The authors stated that although hypnosis is a proven pain method for acute pain, its efficacy non-malignant chronic pains is not well documented and large clinical trials are missing which could assess the long-term effects of hypnotic treatments.

5. HYPNOTHERAPY AND CHRONIC PAIN

Although most of the earlier researchers focused on acute pain reduction by hypnotic analgesia induced in laboratory settings or pain associated with medical procedures, there is a constantly growing interest in applying the efficacy of hypnosis for chronic pain conditions. Chronic pain affects hundreds of millions of people worldwide, resulting in great personal suffering and social burden in terms of lost productivity and financial cost. A survey of developed and developing countries revealed that the prevalence of chronic pain among adults is about 41% in developing countries and about 37% in developed countries (Tsang et al.,

2008). Approximately 100 million Americans suffer from chronic pain which is one of the leading causes of reduced quality of life. The economic impact of pain is greater than most other health condition (Gaskin and Richard, 2012).

Pain that persists for more than three months is termed chronic pain (Merskey and Bogduk 1994; Keefe, 1982). Chronic pain is a complex phenomenon that requires a multimodal treatment approach (Elkins et al., 2007). Since most of the chronic diseases involve multiple physical, cognitive and emotional factors, researchers and clinicians normally use the biopsychosocial model which considers the pain as a multidimensional, dynamic interaction among physiological (biological), psychological and social factors that can reciprocally influence one another, and can eventuate chronic and complex pain syndrome (Gatchel et al., 2007, 2014).

Genetic factors can also play an important role in the development of chronic pain and individual differences in pain sensitivity, but the general understanding of the genetic contribution of pain is still vague (Meng et al., 2020; Diatchenko et al., 2013; Diatchenko et al., 2005). Hocking et al. (2012) revealed that severe chronic pain has a heritability of 30%. In addition, various pain phenotypes can be associated with depression, anxiety and neuroticism (Ashina et al., 2017; Tsuji et al., 2016; Walter et al., 2013). Neuroticism is a personality trait with long-term tendency to be in a negative emotional state like depression, anxiety, panic, aggression or phobic fears (Sauer-Zavala et al., 2017; Ormel et al., 2013). People with neuroticism are particularly sensitive to environmental stress. Joint deterioration and associated chronic pain are common in people with haemophilia. Perede et al. (2019) found that hypnosis reduced pain and promoted health-related quality-of-life in people with haemophilia. Ardigo et al. (2016) investigated the efficacy of hypnosis and self hypnosis in the management of chronic pain in older hospitalized patients with multiples co-morbidities. The authors found that hypnosis and self-hypnosis significantly decreased pain intensity and had a positive effect on mood in older hospitalized patients. However, there was no effect three months later after the patients were discharged from the hospital. In a study by Mazzola et al. (2017), patients with fibromyalgia (FM) and chronic migraine (CM) were treated during five weekly hypnosis sessions, each lasting 60 minutes. They found that hypnosis could be effective for chronic pain and reducing anxiety and depression in the greater part of CM patients and in a minority of the FM patients. According to Jensen and Patterson (2014),”chronic pain management remains one of the largest challenges in health care, and

hypnosis is an undeveloped but highly promising intervention that can help to address this problem."

Chronic pain is usually associated with strong emotional reactions like increased anxiety, depression and reduced quality of life. The stress itself is sufficient to generate pain perception (Rome and Rome, 2000). It was observed that in numerous cases the emotional suffering is maintained even though the peripheral signs of the injury, and thus the possible source of nociceptive activity disappeared. Mansour et al. (2004) suggested that chronic pain produces changes in the cortical-limbic circuitry, involving learning and memory formation. This new emotional information associated with pain is continuously reinforced and thus cannot be abolished. Namely, the abnormal chronic pain sensation can be an association learned process that resulting from central sensitization enhanced by anxiety and depression induced stress (Aytur et al., 2021). In addition, it was also suggested that central sensitization may be driven by neuroinflammation in the peripheral and central nervous system that causes widespread chronic pain (Ji et al., 2018). Furthermore, neuroimaging experiments suggested that chronic pain can be also due to an unusual hyper-connectivity of brain networks associated with self-reflection (default-mode network, DMN), emotion (salience network, SN) and cognitive control (fronto-parietal network, FPN) networks (Hemington et al., 2016; van Ettinger-Veenstra et al., 2019; Aytur et al., 2021).

Furthermore, recent studies indicate that epigenetic mechanisms can play a central role in the development and maintenance of chronic pain by the modulation of the stress axis and the FKBP5 gene (FKBP5 responds to stress and glucocorticoids) (Géranton, 2019). It is likely that both epigenetic regulation and genetic pre-dispositions drive vulnerability (resilience) in the context of mood/emotional disorders related to subjective perception of chronic pain (Descalzi et al., 2015; Géranton, 2019; D'Agnelli et al., 2019; Johnston et al., 2021).

If we know something cognitively it does not mean necessarily that we are able to control our emotions such as fear, depression and anxiety. When patients are very anxious, they are operating at more emotional than cognitive (Williamson, 2019). During hypnosis there is increased access to the emotional level. Hypnosis can not only be used to decrease emotional stress but also may have a direct effect on the patient's experience of pain (Jensen and Patterson, 2014).

We agree that many more standardized experiments are needed to assess the effect of hypnosis on chronic pain (Dorfman et al. 2013). Nevertheless, several studies indicated that in

many areas, including chronic pain relief, it would be important to use this method (Elkins et al., 2007; Tomé-Pires and Miró, 2012; Jensen and Patterson, 2014; Célestin-Lhopiteau, 2014; Mazzola et al., 2017; Taylor and Genkov, 2020; Juel et al., 2018; Adachi et al., 2014; Jensen and Patterson, 2006; Dillworth and Jensen, 2010; Dillworth et al., 2012).

6. BRAIN ACTIVITY AND FUNCTIONAL CONNECTIVITY ASSOCIATED WITH HYPNOSIS

The human brain is an extremely complex system that can be represented as a structurally interconnected and functionally synchronized network, which provide the segregation and integration of information processing. The human brain is topologically arranged into spatially distributed and functionally specific networks. The most extensively studied networks are the DMN, executive-control network (ECN) and SN since they have essential roles in cognitive functions (Liang et al., 2016). However, little is known about how cognitive demands could modulate and modify interactions within these three networks.

The DMN includes the medial prefrontal cortex (MPFC), the posterior cingulate cortex (PCC), the anterior cingulate cortex (ACC), precuneus, inferior parietal lobule, lateral temporal cortex (LTC), and hippocampal formation, among others (Washington and VanMeter, 2015; Mars et al., 2012). DMN is implicated in episodic memory retrieval, self-reflection, mental imagery, and stream-of-consciousness processing (Xu et al., 2016). The DMN presents increased activity during rest that is associated with internal processes, such as self-referential thinking, autobiographical memory, and thinking about the future (Philippi et al., 2015). In contrast, the DMN is deactivated when it performs externally-oriented complex cognitive processing. Recently Yeshurun et al. suggested (2021) that ”the DMN is an active and dynamic ‘sense-making’ network that integrates incoming extrinsic information with prior intrinsic information to form rich, context-dependent models of situations as they unfold over time.”

The ECN plays important roles in the integration of sensory and memory information, regulation of cognition and behavior and also contributes in the maintenance in working memory of relevant information necessary for action preparation (Chan et al., 2008). The ECN is a functionally linked system that includes the prefrontal cortex (PC), frontopolar cortex (FP), dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), posterior parietal cortex (PPC), cuneus, supplementary motor area (SMA), motorrelated nodes, cingulo-opercular nodes, cerebellum and subcortical nuclei (Shen et al., 2020).

The SN takes part in various complex functions like communication, social behavior, and self-awareness by means of the integration of sensory, emotional, and cognitive information (Menon, 2015). The cortical hubs of the SN are the insula, the anterior cingulate cortex, paralimbic areas (three-layered cortex) like dorsal anterior cingulate cortex (DACC), limbic regions like the amygdala, hypothalamus, ventral striatum, thalamus and specific brainstem nuclei (Seeley, 2019; Sevinc et al., 2017).

The most important imaging methods to investigate the neurophysiological effects of hypnosis are functional magnetic resonance imaging (fMRI; measuring changes in blood flow in the brain and spinal cord), electroencephalography (EEG; measuring cortical electrical activity) and positron emission tomography (PET; measuring cortical metabolic activity). The use of functional near-infrared spectroscopy (fNIRS) has been also reported (Halsband et al., 2019). fNIRS allows to non-invasively detect cerebral changes in tissue oxygenation and hemodynamics (Scholkmann et al., 2014).

Numerous neuroimaging studies found various altered functional connectivity in the brain during hypnosis. Schulz-Stübner et al. (2004) investigated the activation of brain areas in response to thermal pain with and without hypnosis. The authors observed decreased activity in the primary sensory cortex, the middle cingulate gyrus, precuneus and the visual cortex. The authors also observed increased activation in the anterior basal ganglia and the left anterior cingulate cortex. But there was not activation in the brainstem and thalamus under either condition. Schulz-Stübner et al. (2004) proposed that hypnosis may prevent nociceptive inputs from reaching the higher cortical structures responsible for pain perception. Recent fMRI experiments by Jiang et al. (2017) found decreased activity in the DACC, increased functional connections between the dorsolateral prefrontal cortex (DLPFC) and the insula, and reduced connections between the DLPFC and the DMN. These changes - in very high hypnotizability healthy people - imply the focused attention, enhanced somatic and emotional control, as well as a lack of self-consciousness characterize hypnosis. In PET experiments by Faymonville et al. (2003) subjects got a hot noxious or warm non-noxious stimulation of the right hand during resting state, mental imagery and hypnotic state. It was observed that during the hypnotic condition there was an increase in functional modulation between midcingulate cortex and a large neural network encompassing bilateral insula, pregenual anterior cingulate cortex, pre-supplementary motor area, right prefrontal cortex and striatum, thalamus and brainstem. In a PET study, Maquet et al. (1999) found that during hypnotic state, the pattern of changes in cerebral blood flow was different compared to the changes observed in subjects

performing a control task (a simple evocation of autobiographical memories). The authors emphasized that there are several similarities with mental imagery, from which it differs by the relative deactivation of the precuneus. Pyka et al. (2011) investigated human brain function during hypnotic paralysis by resting-state fMRI, focusing on two core areas of the DNM and the representation of the paralysed hand in the PMC. They found increased connectivity of the precuneus with the right DLPFC, angular gyrus and a dorsal part of the precuneus. Functional connectivity of the medial frontal cortex and the primary motor cortex were unchanged. The authors suggested that the precuneus plays a pivotal role during maintenance of an altered state of consciousness. Cojan et al. (2009) performed a go-nogo task while subjects underwent fMRI in three conditions: normal state, hypnotic left-hand paralysis and feigned paralysis. They observed that hypnotic paralysis differs from active voluntary motor inhibition. Different patterns of brain activity were found in brain regions involving self-monitoring and attentional control. Decreased functional connectivity of the PMC with premotor areas was noted and increased connectivity with regions in precuneus that are associated with mental imagery and self representations. Hypnosis thus induced the control of action by internal representations produced by suggestion and imagery, mediated by precuneus activity, and reconfigures the executive control of the task implemented by frontal lobes. Jensen et al. (2015) reviewed EEG studies regarding the associations between hypnosis and brain oscillations. They pointed out that hypnosis is most closely linked to power in the theta band and changes in gamma activity. Jensen et al. (2015) hypothesized that theta oscillations help hypnotic responding and that theta-gamma phase-locked oscillations may offer a physiological explanation for hypnosis by suggesting linking of limbic and neocortical circuits. Hypnosis is frequently used in dental practice as an alternative treatment or instead of sedation or general anaesthetics. Halsband and Wolf (2015) studied the effects of a brief dental hypnosis on the fear processing structures of the brain in dental phobics (DP) by fMRI. In the DP group, major effects of fear condition were found in the left amygdala and bilaterally in the ACC, insula, and hippocampus. During hypnosis DP presented reduced activation in all of these regions. No amygdala activation was detected in healthy subjects in the two experimental conditions. Lately, Halsband and Wolf (2019) reviewed various fMRI, PET and EEG studies of brain-plasticity changes in hypnosis. They concluded that hypnosis can be a successful method that inhibits the reaction of the fear circuitry structures.

There is increasing evidence that the hypnotic state involves the ACC, insular cortex, tthalamus, ponto-mesencephalic brainstem, as well as increased activation in occipital and DLPFC and decreased activation in the precuneus (Rainville et al., 2002; Del Casale et al.,

2012).

Table 1. A summary of key neuroimaging studies about brain activity and functional connectivity associated with hypnosis.

Study	Objectives of the study	Results
Schulz-Stübner et al. (2004) (fMRI)	Activation of brain areas in response to thermal pain during hypnosis	Decreased activity in the primary sensory cortex, the middle cingulate gyrus, precuneus, and the visual cortex. Increased activation in the anterior basal ganglia and the left anterior cingulate cortex. No activation in the brainstem and thalamus.
Jiang et al. (2017) (fMRI)	Investigation of activity and functional connectivity among DMN, ECN and SN networks in hypnosis	Decreased activity in the DACC, increased functional connections between the dorsolateral prefrontal cortex (DLPFC) and the insula, and reduced connections between the DLPFC and the DMN. These changes - in very high hypnotizability healthy people – imply that focused attention, enhanced somatic and emotional control and lack of self-consciousness characterizes hypnosis.
Faymonville et al. (2003) (PET)	Reaction to hot noxious or warm non-noxious stimulation to the right hand during resting state, mental imagery and hypnotic state	The hypnotic condition, compared to normal alertness, increased the functional modulation between midcingulate cortex and a large neural network encompassing bilateral insula, pregenual anterior cingulate cortex, pre-supplementary motor area, right prefrontal cortex and striatum, thalamus and brainstem.
Pyka et al. (2011) (fMRI)	Human brain functions during hypnotic paralysis	Increased connectivity of the precuneus with the right DLPFC, angular gyrus and a dorsal part of the precuneus. Functional connectivity of the medial frontal cortex and the primary motor cortex were unchanged. These results suggest that the precuneus plays a pivotal role during maintenance of an altered state of consciousness.
Halsband and Wolf (2015) (fMRI)	Effects of a brief dental hypnosis on the fear processing structures of the brain in dental phobics	Major effects of fear condition were found in the left amygdala and bilaterally in the ACC, insula, and hippocampus. During hypnosis DP presented reduced activation in all of these regions. No amygdala activation was detected in healthy subjects in the two experimental conditions.
Maquet et al. (1999) (PET)	Investigation of the distribution of regional cerebral blood flow during the hypnotic state in humans	The pattern of activation was different from those induced in normal subjects via the simple evocation of autobiographical memories. Authors emphasized that there are several similarities with mental imagery but the relative deactivation of precuneus was different.
Cojan et al. (2009) (fMRI)	Analysis involving a go-nogo task while subjects underwent fMRI in three conditions: normal state, hypnotic left-hand paralysis, and feigned paralysis	Hypnosis induced the control of action by internal representations produced by suggestion and imagery, mediated by precuneus activity, and reconfigures the executive control of the task implemented by frontal lobes.
Halsband and Wolf (2019) (review)	Review about various fMRI, PET and EEG studies of brain-plasticity changes in hypnosis	Hypnosis can be a successful method that inhibits the reaction of the fear circuitry structures.
Jensen et al. (2015) (review)	Review about hypnosis induced changes in theta and gamma activity	Hypnosis most closely linked to power in the theta band and changes in gamma activity. Theta oscillations may help hypnotic responding and that theta-gamma phase-locked oscillations may offer a physiological explanation for hypnosis by suggesting linking of limbic and neocortical circuits.

7. GENETIC AND EPIGENETICS ASPECTS OF HYPNOSIS

Epigenetics is a discipline that studies heritable and reversible changes in gene expression that do not involve altering the DNA sequence. Most essential epigenetic mechanisms are DNA methylation, histone post-translational modifications (methylation, acetylation, phosphorylation, and ubiquitination), and regulatory non-coding RNAs (ncRNAs), such as micro-RNA (miRNA), Piwi-interacting RNA (piRNA) and long noncoding RNA (lncRNA), and chromatin organization (Clark et al., 2016; Zhang et al., 2019; Peschansky et al., 2014). NcRNAs can control the expression of proteins at the transcriptional and translational levels (Pagiatakis et al., 2019). DNA methylation is generally down regulating, although histone epigenetic modifications can be positive or negative, depending on which amino acid is affected by methylation, phosphorylation, ubiquitination (Kimura, 2013). The telomere length is a significant regulator of gene expression and cellular signaling, and its length is heritable and can increase or decrease reversibly, similar to other epigenetic processes. The three-dimensional structure of chromatin is also under epigenetic control (Kim and Kaang, 2017). Epigenetic modifications are not separated mechanisms, but these regulations could interact and regulate each other at multiple levels (Marczylo et al., 2016; Vaissière et al., 2008). Epigenetic regulations take essential roles in behavior plasticity, memory, cancer, autoimmune diseases, addiction, aging, psychological disorders and age-related neurodegenerative disorders like Alzheimer's and Parkinson's disease (Moosavi and Motevalizadeh Ardekani, 2016; Lardenoije et al., 2018; Borodinova et al., 2020; Ye et al. 2016; Levenson and Sweatt, 2005).

There is increasing evidence that genetic factors may explain partially the interindividual variability in hypnotizability. Catechol-O-methyltransferase (COMT) is one of various enzymes that is involved in the inactivation of the catecholamine neurotransmitters, such as dopamine, epinephrine and norepinephrine. In humans, the COMT protein is encoded by the COMT gene. Dopamine (DA) signaling presents various neural functions. Dopaminergic afferents from the midbrain DA nuclei innervate the striatum, amygdala, hippocampus and PFC (Schacht, 2019). Various studies proposed that dopaminergic systems are involved in hypnotizability associated with the COMT Val(158)Met single nucleotide polymorphism (SNP, rs4680) (Rominger ert al., 2014; Szekely et al., 2010). Lichtenberg et al. (2004) found that highly hypnotizable subjects have a more effective fronto-limbic attentional system and that suggested the involvement of dopaminergic systems in hypnotizability. Another possible gene associated with the hypnotizability may be the 5-HTTLPR variable number tandem

repeat polymorphism of the serotonin transporter (SERT) gene (gene, SLC6A4; variant, 5HTTLPR) (Katonai et al., 2017). However, Rominger et al. (2014) did not found a link between serotonin-related 5-HTTLPR polymorphisms and hypnotizability. It was also suggested that the expression of oxytocin receptor gene (OXTR encodes oxytocin, a neuropeptide hormone that increases trust and social bonding, synthesized in the hypothalamus) may be associated with hypnotizability (Bryant et al., 2013; Bryant and Hung, 2013). When subjects received oxytocin by nasal spray, their level of hypnotic responding increased significantly (Bryant et al., 2013).

In a pilot study by Rossi et al. (2008) studied three highly susceptible hypnotic volunteers experiencing therapeutic hypnosis following a protocol called "The Creative Psychosocial Genomic Healing Experience". Analysis of peripheral blood by DNA microarrays revealed that the therapeutic hypnosis changed expression of 15 early response genes within one hour that induced a further cascade of 77 genes 24 hours later. In a study by Cozzolino et al. (2015), peripheral blood was collected before and immediately following administration of the Mind-Body Healing (MHE) protocol to 18 subjects. After 1 hour the expression of 46 genes was altered and after 24 hours 154 genes were differentially expressed. The genes expressed in response to the MHE were found to be related to a variety of Gene Ontology (GO) term pathways associated with reduced cellular stress and inflammation while supporting immune system functioning. Recently, Presciuttini et al. (2018) studied whether hypnotizability is associated with the presence of the OPRM1 polymorphism (The OPRM1 gene encodes the μ1 opioid receptor that plays a key role in pain perception and addiction). The authors found hypnotizability-related activity of μ1 receptors presented a higher frequency of the G allele of the 118 single nucleotide polymorphism (SNP) of the OPRM1 gene in highly hypnotizable subjects compared to low hypnotizable subjects and to the general population. Presciuttini et al. (2018) also suggested that hypnotic assessment could be a potential method for screening patients' responsiveness to opioid treatments.

Mental stress can produce endothelial dysfunction, an early event in atherogenesis and a risk factors for cardiovascular diseases. Interestingly, mental stress has been found to not produce endothelial dysfunction in people that are highly susceptible to hypnosis in the waking as well as in hypnotic state (Jambrik et al., 2004). In Jambrik et al. (2004) experiments the nociceptive painful stimulation in high and low hypnotizability subjects caused decreased flow-mediated dilation (FMD is a dilation of an artery when blood flow increases in that artery), although it was less pronounced in high hypnotizability subjects.

Presciuttini et al. (2009) studied the association between genetic polymorphisms of NOS3 (NOS3, Nitric Oxide Synthase 3 encodes Endothelial NOS (eNOS) protein) involved in NO blood levels and hypnotizability in high and low hypnotizability subjects during nociceptive stimulation. The authors analyzed SNPs of NOS3 in high and low hypnotizability subjects, and newborns. Haplotype analysis revealed that the newborns were in linkage equilibrium for these SNPs, while high and low hypnotizability subjects presented linkage disequilibrium. They proposed that the lower FMD reduction found in high hypnotizability subjects during nociceptive stimulation show a higher NO availability. The promoter polymorphisms of the NOS3 may therefore have an important role in hypnotizability. Rossi et al. (2008) studied if a creatively oriented positive human experience of therapeutic hypnosis could change gene expression. They found that an ideoplastic (intuitive creativity) mechanism of hypnotherapy could upregulation of genes necessary for stem cell growth, reduction of cellular oxidative stress and chronic-inflammation. Rossi (2005) recommended that “hypnotic susceptibility scales of the future incorporate gene expression data to include the concept of "embodied imagination" and the "ideo-plastic faculty" on a molecular-genomic level as well as the psychological and behavioral level of ideomotor and ideosensory responses that are currently assessed.” Furthermore, positive psychosocial experiences, including psychotherapeutic interventions and therapeutic mind-body protocols like clinical hypnosis, mediation, guided imagery, can alter the expression of genes associated with inflammatory response and stress-related pathways, leading to an improved mind-body health (Sawni and Breuner, 2017; Cozzolino et al., 2021). Although we are still in the early stages of linking hypnosis to hypnosis-induced epigenetic changes, research into this can greatly enhance our understanding of the biological underlying hypnosis.

8. EPIGENETIC MECHANISMS UNDERLIE NEURAL PLASTICITY AND LONG-TERM MEMORY

Neuroplasticity (also termed “neural plasticity”) refers to the brain's ability to change its activity in response to extrinsic or intrinsic stimuli through dynamically reorganizing its structure, functions or connections (Mateos-Aparicio and Rodríguez-Moreno, 2019). While it was first thought that neural plasticity is limited to a phase when the nervous system is developing, the current knowledge is that neural plasticity is not restricted to infancy but retained by the individual throughout the lifespan. It seems that neural plasticity changes over the lifespan with different speeds of change in different individuals (Oberman and Pascual-

Leone, 2013). Brain aging is associated with altered glutamatergic neurotransmission, Ca2+ dysregulation, a decline in synaptic mitochondrial function, neuroinflammation, apoptosis and epigenetic changes (Kumar A, Foster 2019; Espino de la Fuente-Muñoz et al., 2020). Thus, neurogenesis and synaptic plasticity are reduced with age, which is associated with age-related cognitive decline (Bettio et al., 2017).

To date, the synaptic plasticity hypothesis is generally considered to be the neurobiological basis of learning and memory (Langille et al., 2018; Abraham et al., 2019; Cajal, 1984). Namely, traces of memory are stored by means of modifications in the strength of synaptic connections, resulting in formations of new patterns of neural activity. On the other hand, numerous studies challenged the synaptic plasticity hypothesis. Cognitive functions can for example determined by means of the specific properties of individual neurons and are therefore likely to occur also (or even primarily) at the intracellular level (Arshavsky, 2017). Arshavsky (2006) concluded: “Memory that can last throughout an entire lifespan should be "etched in stone." The only "stone-like" molecules within living cells are DNA molecules. Therefore, I advocate an alternative, genomic hypothesis of memory, which suggests that acquired information is persistently stored within individual neurons through modifications of DNA, and that these modifications serve as the carriers of elementary memory traces.” Recent advances in chromatin biology have revealed the key role of epigenetic mechanisms in the regulation of neuronal gene expression changes, a necessary process for proper synaptic plasticity and memory formation (Lubin et al., 2011). Epigenetic processes like DNA methylation and demethylation, protein acetylation and deacetylation, small ncRNAs and miRNA activity, are all essential for the regulation of neuronal plasticity (Ortuño-Sahagún et al., 2019).

Numerous studies suggested that miRNAs can be master regulators of gene expression in the nervous system where they contribute to proper neuronal function, neuronal network plasticity, brain development and plasticity (Salta and De Strooper, 2012; Sun et al., 2013; Arai et al., 2016). miRNAs probably play a role in the onset and maintenance of neurological diseases (Mehta et al., 2020). Elramah et al. (2014) proposed that chronic pain can be considered as a form of maladaptive plasticity in which changes in gene expression and miRNAs can play important roles.

Epigenetic mechanisms have also a central role in autophagy of nerve cells (Hwang et al., 2019). Autophagy is essential to appropriate axon guidance, dendritic spine architecture,

vesicular release, spine pruning and synaptic plasticity. It is possible that there is a complex bidirectional signal communication between the epigenetic system and long-term neural plasticity (Bronfman et al., 2014). Recent experiments by Bédécarrats et al. (2018) challenged the synaptic plasticity notion of memory storage in particular. The authors demonstrated successful transfer of memory from a trained to an untrained Aplysia (a large sea slug) via RNA injection. Their results indicate that RNA is sufficient to produce an engram for long-term sensitization in Aplysia and are consistent with the assumption that RNA-induced epigenetic changes underlie memory storage in Aplysia. Qureshi and Mehler (2014) emphasize that epigenetic regulations are fundamental for brain complexity and flexibility, including neural development and aging, neurogensis, cellular differentiation, homeostasis, stress responses, as well as synaptic and neural network connectivity and plasticity.

Epigenetic regulations are not only essential for activity-dependent and long-term neural and synaptic plasticity but also play a fundamental role in impaired neuronal plasticity, development of mental diseases, and the pathogenesis of neurodevelopmental and neurodegenerative disorders (Salta and De Strooper, 2017; Karpova et al., 2017). The view of Nobel laureate Francis Crick (Crick, 1984) could turn out to be true with respect to long-term memory storage by epigenetic processes. We wrote: „Yet it is believed that almost all the molecules in our bodies, with the exception of DNA, turn over in a matter of days, weeks or at the most a few months. How then is memory stored in the brain so that its trace is relatively immune to molecular turnover? Several possible solutions of the problem suggest themselves. For example, memory might be coded in alterations to particular stretches of chromosomal DNA." The activity-dependent synaptic plasticity - such as LTP and LTD via strengthening or weakening synaptic connections - is the major proposed cellular mechanism that underlies learning and memory (Queenan, et al., 2017**;** Hebb, 1949). However, there are many new concepts about this and numerous cognitive scientists are increasingly skeptical about the notion that synapse are the sole locus of memory in the brain. Neuroepigenetics may be the next evolution and the most suitable candidate in our understanding of the molecular mechanisms underlying learning and memory (Marshall and Bredy, 2016). However, the concept of synaptic plasticity (neural networks) does not contradict the influence of epigenetics. Neural networks can operate as variable information channels among neurons while long-term memory can have an epigenetic basis in individual neurons.

9. SUMMARY AND CONCLUSIONS

According to Gandhi and Oakley (2005), “Despite its intrinsic interest, its potential as an adjunctive procedure in therapy and more than 200 years of scientific investigation, hypnosis has remained an elusive concept for science and on the periphery of mainstream psychology.”

As we reviewed, there are numerous and interconnected hypnotisability factors that play elementary roles in the contradictions in diverse experiments regarding to neural correlates of hypnosis, hypnotisability and hipnotic responses. Despite these contradictions, there is increasing evidence that hypnosis can be useful therapy for various conditions like acute and chronic pain, anxiety and mood disorders, sleep problems, irritable bowel syndrome, medical and surgical procedures and cancer treatment-related side effects.

In spite of subjective and methodological differences, numerous studies suggested that the hypnotic state involves the ACC, insular cortex, the thalamus, the ponto-mesencephalic brainstem, increased activation in occipital and DLPFC, and decreased activation in precuneus (Rainville et al., 2002; Del Casale et al., 2012).

In the case of acute pain, many studies have observed the efficacy of hypnosis. However chronic conditions may require a comprehensive plan that targets various aspects besides the pain experience (APA, 2004). Jensen and Patterson (2014) emphasized that ”chronic pain management remains one of the largest challenges in health care, and hypnosis is an undeveloped but highly promising intervention that can help to address this problem.”

Positive psychosocial experiences like clinical hypnosis, mediation and guided imagery can alter the expression of genes associated with inflammatory response and stress-related pathways and improve the mind-body health (Presciuttini et al., 2009; Bryant et al., 2013; Rominger ert al., 2014; Sawni and Breuner, 2017; Katonai et al., 2017; Cozzolino et al., 2021). Epigenetic mechanisms are essential for brain complexity and flexibility, including neural development and aging, neurogenesis, cellular differentiation, homeostasis, stress responses, and synaptic and neural network connectivity and plasticity (Qureshi and Mehler, 2014).

Since hypnosis could alter the expression of genes and epigenetic mechanisms may be underlie neural network connectivity and synaptic plasticity, it suggests that hypnotic state make it possible that given patient could access to his/her emotional level i.e. to cortical-limbic circuitry (Mansour et al., 2004) via top-down induced processes. As a result, harmful chronic pain associated learned emotional memory (with hyper-connectivity of brain networks associated with DMN, SN, and FPN network (van Ettinger-Veenstra et al., 2019; Aytur et al., 2021) may be reduced, which finally could decrease the subjective pain perception and stress-related inflammatory response.

One could argue that the neuroplasticity/epigenetics aspects of hypnosis are overestimated because of the lack of data based on animal models (Liu et al., 2020; McKinstry-Wu et al., 2019; Salort et al., 2019; Álvaro-Bartolomé et al., 2015). However, it needs to be appreciated that hypnosis is a complex psychological treatment without any application of a substance (drug) (i.e. a non-pharmacological method), acting via psychological processes at the first place. Thus, for example, in animal experiments, Ketamine (which is an antidepressant and hypnotic drug) or azi-medetomidine (which is an A2 adrenergic agonist that produces anxiolysis, hypnosis, and analgesia) induced hypnotic effects are more than likely to work through other biological and molecular processes compared to psychological hypnosis induced hypnotic mechanisms. If we really want to study the effects of psychological hypnosis, we must do this without the use of any drugs. In addition, since hypnosis is considered as a complementary or alternative therapy in science, research on psychological hypnosis has been neglected and not taken seriously this method. Hence, so far, few standardized epigenetic and neuroimaging experiments have been performed regarding psychological hypnosis without the use of any drugs.

Furthermore, most experiments investigated the adverse effects of diverse external and internal factors on epigenetic processes (for example: Császár et al., 2021; Lewandowska et al., 2019; Hart and Tadros, 2019; Franzago et al., 2019; Chmielewska et al., 2019; Császár and Bókkon, 2017). However, in reality, epigenetic regulations operate uninterruptedly from conception to birth to the end of our lives (Feinberg 2008; Kanherkar et al, 2014). There is continuous interaction between the external and internal environments that is essential for normal development and health maintenance as well as for influencing disease load and resistance (Kanherkar et al, 2014). The epigenome integrates the information encoded in the genome via dynamic and flexible mechanisms and can form an individual both physically and mentally (Kanherkar et al, 2014). Although we are still in the early stages of linking hypnosis

to hypnosis-induced epigenetic changes, since epigenetic regulations respond continuously to external and internal factors, hypnosis cannot be an exception, i.e., it should be accompanied by epigenetic changes.

In summary, the following ones could be concluded:

- hypnosis is a non-pharmacological and cost-effectiveness method,
- although hypnosis has been controversial and is currently not a part of mainstream clinical practices, there is increasing evidence that hypnosis can be an effective method for various conditions,
- countless and interconnected hypnotisability factors play a fundamental role in the contradictions in diverse experiments regarding to neural correlates of hypnosis, hypnotisability and hypnotic responses,
- hypnosis allows for individualized treatment,
- hypnosis is an useful method to help patients manage diverse conditions, especially anxiety and pain,
- hypnosis can induce altered functional connectivity and change neuroplasticity,
- hypnosis can be successful treatment that inhibits the fear circuitry structures,
- hypnosis may be associated with epigenetic changes,
- hypnosis induced epigenetic changes may underlie hypnosis induced changes in neuroplasticity,
- chronic pain can be associated with learned emotional memory that maintaining sensation of chronic pain,
- hypnosis increases access to the emotional level (via cortical-limbic circuitry) that could decrease the subjective pain perception and stress-related inflammatory response.

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REFERENCES

Abdeshahi, S. K., Hashemipour, M. A., Mesgarzadeh, V., Shahidi Payam, A., Halaj Monfared, A. 2013. Effect of hypnosis on induction of local anaesthesia, pain perception, control of haemorrhage and anxiety during extraction of third molars: a case-control study. J. Craniomaxillofac. Surg. 41, 310-315.

Abraham, W. C., Jones, O. D., Glanzman, D. L. 2019. Is plasticity of synapses the mechanism of long-term memory storage? NPJ Sci. Learn. 4, 9.

Adachi, T., Fujino, H., Nakae, A., Mashimo, T., Sasaki, J. 2014. A meta-analysis of hypnosis for chronic pain problems: a comparison between hypnosis, standard care, and other psychological interventions. Int. J. Clin. Exp. Hypn. 62(1), 1-28.

Álvaro-Bartolomé, M., García-Sevilla, J.A. 2015. The neuroplastic index p-FADD/FADD and phosphoprotein PEA-15, interacting at GABAA receptor, are upregulated in brain cortex during midazolam-induced hypnosis in mice. Eur. Neuropsychopharmacol. 25(11), 2131-244.

Anbar, R. D., Slothower, M. P. 2006. Hypnosis for treatment of insomnia in school-age children: a retrospective chart review. BMC Pediatr. 6, 23.

APA. (2004). Hypnosis for the Relief and Control of Pain July 2, 2004 https://www.apa.org/research/action/hypnosis

Arai, M., Genda, Y., Ishikawa, M., Shunsuke, T., Okabe, T., Sakamoto, A. 2013. The miRNA and mRNA changes in rat hippocampi after chronic constriction injury. Pain Med. 14, 720–729.

Ardigo, S., Herrmann, F. R., Moret, V., Déramé, L., Giannelli, S., Gold, G., Pautex, S. 2016. Hypnosis can reduce pain in hospitalized older patients: a randomized controlled study. BMC Geriatr. 16, 14.

Arshavsky, Y. I. 2006. "The seven sins" of the Hebbian synapse: can the hypothesis of synaptic plasticity explain long-term memory consolidation? Prog Neurobiol. 80, 99-113.

Arshavsky, Y. I. 2017. Neurons versus networks: The interplay between individual neurons and neural networks in cognitive functions. Neuroscientist 23, 341-355.

Ashina, S., Bendtsen, L., Buse, D. C., Lyngberg, A. C., Lipton, R. B., Jensen, R. 2017. Neuroticism, depression and pain perception in migraine and tension-type headache. Acta Neurol. Scand. 136, 470–476.

Aytur, S. A., Ray, K. L., Meier, S. K., Campbell, J., Gendron, B., Waller, N., Robin, D. A. 2021. Neural mechanisms of acceptance and commitment therapy for chronic pain: A network-based fMRI approach. Front Hum Neurosci. 15, 587018.

Bédécarrats, A., Chen, S., Pearce, K., Cai, D., Glanzman, D. L. 2018. RNA from trained *Aplysia* can induce an epigenetic engram for long-term sensitization in untrained *Aplysia*. eNeuro *5*(3), ENEURO.0038-18.2018.

Bettio, L. E. B, Rajendran, L, Gil-Mohapel, J. 2017. The effects of aging in the hippocampus and cognitive decline. Neurosci. Biobehav. Rev. 79, 66-86.

Billot, M., Jaglin, P., Rainville, P., Rigoard, P., Langlois, P., Cardinaud, N., Tchalla, A., Wood, C. 2020. Hypnosis program effectiveness in a 12-week home care intervention to manage chronic pain in elderly women: A pilot trial. Clin Ther. 42, 221-229.

Borodinova, A. A., Balaban, P. M. 2020. Epigenetic regulation as a basis for long-term changes in the nervous system: In search of specificity mechanisms. Biochemistry (Mosc). 85, 994-966.

Bronfman, Z. Z., Ginsburg, S., Jablonka, E. 2014. Shaping the learning curve: epigenetic dynamics in neural plasticity. Front Integr Neurosci. *8*, 55.

Bryant, R. A., Hung, L. 2013. Oxytocin enhances social persuasion during hypnosis. PLoS One 8, e60711

Bryant, R. A., Hung, L., Dobson-Stone, C., Schofield, P. R. 2013. The association between the oxytocin receptor gene (OXTR) and hypnotizability. Psychoneuroendocrinology 38, 1979-1984.

Buckner, J. D., Heimberg, R. G., Ecker, A. H., Vinci, C. 2013. A biopsychosocial model of social anxiety and substance use. Depress Anxiety. 30, 276-284.

Cajal, S. R. 1984. La fine structure des centres nerveux. Proc. R. Soc. Lond. 55, 444-468.

Carlson, L. E., Toivonen, K., Flynn, M., Deleemans, J., Piedalue, K. A., Tolsdorf, E., Subnis, U. 2018. The role of hypnosis in cancer care. Curr. Oncol. Rep. 20, 93.

Célestin-Lhopiteau, I. 2014. Hypnosis for chronic pain of children. Soins Pediatr Pueric. 277, 36-38.

Chan, R. C., Shum, D., Toulopoulou, T., Chen, E. Y. 2008. Assessment of executive functions: review of instruments and identification of critical issues. Arch. Clin. Neuropsychol. 23, 201-216.

Chen, X., Yuan, R., Chen, X., Sun, M., Lin, S., Ye, J., Chen, C. 2018. Hypnosis intervention for the management of pain perception during cataract surgery. J Pain Res. 11, 1921-1926.

Chester, S. J., Stockton, K., De Young, A., Kipping, B., Tyack, Z., Griffin, B., Chester, R. L., Kimble, R. M. 2016. Effectiveness of medical hypnosis for pain reduction and faster wound healing in pediatric acute burn injury: study protocol for a randomized controlled trial. Trials 17, 223.

Chiu, L., Lee, H. W., Lam, W. K. 2018). The effectiveness of hypnotherapy in the treatment of chinese psychiatric patients. Int. J. Clin. Exp. Hypn. 66, 315-330.

Chmielewska, N., Szyndler, J., Maciejak, P., Płaźnik, A. 2019. Epigenetic mechanisms of stress and depression. Psychiatr. Pol. 53(6), 1413-1428.

Clark, S.J., Lee, H.J., Smallwood, S.A., Kelsey, G., Reik, W. 2016. Single-cell epigenomics: powerful new methods for understanding gene regulation and cell identity. Genome Biol. 17, 72.

Coelho, H. F., Canter, P. H., Ernst, E. 2008. The effectiveness of hypnosis for the treatment of anxiety: A systematic review. Prim Care Community Psychiatr. 12, 49-63.

Cojan, Y., Waber, L., Schwartz, S., Rossier, L., Forster, A., Vuilleumier, P. 2009. The brain under self-control: modulation of inhibitory and monitoring cortical networks during hypnotic paralysis. Neuron 62, 862-875.

Cozzolino, M., Cicatelli, A., Fortino, V., Guarino, F., Tagliaferri, R., Castiglione, S., De Luca, P. Napolitano, F., Celia, G, Iannotti, S., Raiconi, S., Rossi, K., Rossi, E. 2015. The mind-body healing experience (MHE) is associated with gene expression in human leukocytes. IJPSS 5, 1-31.

Cozzolino, M., Cocco, S., Piezzo, M., Celia, G., Costantini, S., Abate, V., Capone, F., Barberio, D., Girelli, L., Cavicchiolo, E., Ascierto, P. A., Madonna, G., Budillon, A., De Laurentiis, M. 2021. A psychosocial genomics pilot study in oncology for verifying clinical, inflammatory and psychological effects of mind-body transformations-therapy (MBT-T) in breast cancer patients: Preliminary results. J. Clin. Med. 10, 136.

Crick, F. 1984. Memory and molecular turnover. Nature 312, 101.

Császár, N., Bókkon, I. 2017. Mother-newborn separation at birth in hospitals: A possible risk for neurodevelopmental disorders? Neurosci. Biobehav. Rev. 84, 337-351.

Császár, N., Kapócs, G., Erdöfi-Szabó, A., Bókkon, I. 2021. Modern environmental and lifestyle risk factors, oxidative stress, perturbed epigenetic processes, and increasing incidence of neurodevelopmental, neurodegenerative and neurological disorders. IRJMMS 9(3), 68-93.

D'Agnelli, S., Arendt-Nielsen, L., Gerra, M. C., Zatorri, K., Boggiani, L., Baciarello, M., Bignami, E. 2019. Fibromyalgia: Genetics and epigenetics insights may provide the basis for the development of diagnostic biomarkers. Mol Pain. 15, 1744806918819944.

De Pascalis, V., Santarcangelo, E. L. 2020. Hypnotizability-related asymmetries: A review. Symmetry 12, 1015.

Del Casale, A., Ferracuti, S., Rapinesi, C., Serata, D., Sani, G., Savoja, V., Kotzalidis, G. D., Tatarelli, R., Girardi, P. 2012. Neurocognition under hypnosis: findings from recent functional neuroimaging studies. Int. J. Clin. Exp. Hypn. 60, 286-317.

Demertzi, A., Soddu, A., Faymonville, M. E., Bahri, M. A., Gosseries, O., Vanhaudenhuyse, A., Phillips, C., Maquet, P., Noirhomme, Q., Luxen, A., Laureys, S. 2011. Hypnotic modulation of resting state fMRI default mode and extrinsic network connectivity. Prog. Brain Res. 193, 309-322.

Demertzi, A., Vanhaudenhuyse, A., Noirhomme, Q., Faymonville, M. E., Laureys, S. 2015. Hypnosis modulates behavioural measures and subjective ratings about external and internal awareness. J. Physiol. Paris. 109, 173-179.

Descalzi, G., Ikegami, D., Ushijima, T., Nestler, E. J., Zachariou, V., Narita, M. 2015. Epigenetic mechanisms of chronic pain. Trends Neurosci. 38, 237-246.

Diatchenko, L., Fillingim, R. B., Smith, S. B., Maixner, W. 2013. The phenotypic and genetic signatures of common musculoskeletal pain conditions. Nat. Rev. Rheumatol. 9, 340-350.

Diatchenko, L., Slade, G. D., Nackley, A. G., Bhalang, K., Sigurdsson, A., Belfer, I., Goldman, D., Xu, K., Shabalina, S. A., Shagin, D., Max, M. B., Makarov, S. S., Maixner, W. 2005. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. Hum. Mol. Genet. 14, 135–143.

Dillworth, T., Jensen, M.P. 2010. The role of suggestions in hypnosis for chronic pain: A review of the literature. Open Pain J. 3(1), 39-51.

Dillworth, T., Mendoza, M.E., Jensen, M.P. 2012. Neurophysiology of pain and hypnosis for chronic pain. Transl. Behav. Med. 2(1), 65-72.

Dorfman, D., George, M. C., Schnur, J., Simpson, D. M., Davidson, G., Montgomery, G. 2013. Hypnosis for treatment of HIV neuropathic pain: a preliminary report. Pain Med. 14, 1048-1056.

Elkins, G., Jensen, M. P., Patterson, D. R. 2007. Hypnotherapy for the management of chronic pain. Int. J. Clin. Exp. Hypn. 55, 275-287.

Elramah, S., Landry, M., Favereaux, A. 2014. MicroRNAs regulate neuronal plasticity and are involved in pain mechanisms. Front. Cell. Neurosci. 8, 31.

Espino de la Fuente-Muñoz, C., Rosas-Lemus, M., Moreno-Castilla, P., Bermúdez-Rattoni, F., Uribe-Carvajal, S., Arias, C. 2020. Age-dependent decline in synaptic mitochondrial function is exacerbated in vulnerable brain regions of female 3xTg-AD mice. Int. J. Mol. Sci. 21, 8727.

Evans, S., Tsao, J. C., Zeltzer, L. K. 2008. Complementary and alternative medicine for acute procedural pain in children. Altern. Ther. Health Med. 14, 52-56.

Faymonville, M. E., Roediger, L., Del Fiore, G., Delgueldre, C., Phillips, C., Lamy, M., Luxen, A., Maquet, P., Laureys, S. 2003. Increased cerebral functional connectivity underlying the antinociceptive effects of hypnosis. Brain Res. Cogn. Brain Res. 17, 255-262.

Feinberg, A.P. 2008. Epigenetics at the epicenter of modern medicine. JAMA 299(11), 1345-1350.

Flynn, N. 2018. Systematic review of the effectiveness of hypnosis for the management of headache. Int. J. Clin. Exp. Hypn. 66, 343-352.

Franzago, M., Fraticelli, F., Stuppia, L., Vitacolonna, E. 2019. Nutrigenetics, epigenetics and gestational diabetes: consequences in mother and child. Epigenetics 14(3), 215-235.

Fuhr, K., Schweizer, C., Meisner, C. Batra, A. 2017. Efficacy of hypnotherapy compared to cognitive behavioural therapy for mild-to-moderate depression: Study protocol of a randomised-controlled raterblind trial (WIKI-D). BMJ Open, 7, e016978.

Gandhi, B., Oakley, D. A. 2005. Does 'hypnosis' by any other name smell as sweet? The efficacy of 'hypnotic' inductions depends on the label 'hypnosis'. Conscious. Cogn. 14, 304-315.

Garland, E. L. 2012. Pain processing in the human nervous system: a selective review of nociceptive and biobehavioral pathways. Prim. Care. 39, 561-571.

Gaskin, D. J., Richard, P. 2012. The economic costs of pain in the United States. J. Pain. 13, 715-724.

Gatchel, R. J., McGeary, D. D., McGeary, C. A., Lippe, B. 2014. Interdisciplinary chronic pain management: past, present, and future. Am. Psychol. 69, 119-130.

Gatchel, R. J., Peng, Y. B., Peters, M. L., Fuchs, P. N., Turk, D. C. 2007. The biopsychosocial approach to chronic pain: Scientific advances and future directions. Psychol. Bull. 133, 581–624.

Géranton, S. M. 2019. Does epigenetic 'memory' of early-life stress predispose to chronic pain in later life? A potential role for the stress regulator *FKBP5*. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 374, 20190283.

Golden, W. L. 2012. Cognitive hypnotherapy for anxiety disorders. Am. J. Clin. Hypn. 54, 263-274.

Halsband, U., Wolf, T. G. 2015. Functional changes in brain activity after hypnosis in patients with dental phobia. J. Physiol. Paris. 109, 131-142.

Halsband, U., Wolf, T. G. 2019. Functional changes in brain activity after hypnosis: Neurobiological mechanisms and application to patients with a specific phobia-limitations and future directions. Int. J. Clin. Exp. Hypn. 67, 449-474.

Hart, K., Tadros, N.N. 2019. The role of environmental factors and lifestyle on male reproductive health, the epigenome, and resulting offspring. Panminerva Med. 61(2), 187-195.

Hebb, D. 1949. The Organization of Behavior. New York: Wiley.

Hemington, K. S., Wu, Q., Kucyi, A., Inman, R. D., Davis, K. D. 2016. Abnormal cross-network functional connectivity in chronic pain and its association with clinical symptoms. Brain Struct. Funct. 221, 4203–4219.

Hocking, L. J., Generation Scotland., Morris, A. D., Dominiczak, A. F., Porteous, D. J., Smith, B. H. 2012. Heritability of chronic pain in 2195 extended families. Eur. J. Pain 16, 1053-1063.

Hwang, J. Y., Yan, J., Zukin, R. S. 2019. Autophagy and synaptic plasticity: epigenetic regulation. Curr. Opin. Neurobiol. 59, 207-212.

Iserson, K. V. 2014. An hypnotic suggestion: review of hypnosis for clinical emergency care. J. Emerg. Med. 46, 588-596.

Jambrik, Z., Santarcangelo, E. L., Rudisch, T., Varga, A., Forster, T., Carli, G. 2005. Modulation of pain-induced endothelial dysfunction by hypnotisability. Pain 116, 181-186.

Jensen, M. P., Adachi, T., Hakimian, S. 2015. Brain oscillations, hypnosis, and hypnotizability. Am. J. Clin. Hypn. 57, 230-253.

Jensen, M. P., Adachi, T., Tomé-Pires, C., Lee, J., Osman, Z. J., Miró, J. 2015. Mechanisms of hypnosis: toward the development of a biopsychosocial model. Int. J. Clin. Exp. Hypn. 63, 34-37.

Jensen, M. P., Jamieson, G. A., Lutz, A., Mazzoni, G., McGeown, W. J., Santarcangelo, E. L., Demertzi, A., De Pascalis, V., Bányai, É. I., Rominger, C., Vuilleumier, P., Faymonville, M. E., Terhune, D. B. 2017. New directions in hypnosis research: strategies for advancing the cognitive and clinical neuroscience of hypnosis. Neurosci. Conscious. *3*(1), nix004.

Jensen, M. P., Patterson, D. R. 2014. Hypnotic approaches for chronic pain management: clinical implications of recent research findings. Am. Psychol. 69, 167-177.

Jensen, M., Patterson, D.R. 2006. Hypnotic treatment of chronic pain. J. Behav. Med. 29(1), 95-124.

Ji, R. R., Nackley, A., Huh, Y., Terrando, N., Maixner, W. 2018. Neuroinflammation and central sensitization in chronic and widespread pain. Anesthesiology 129, 343-366.

Jiang, H., White, M. P., Greicius, M. D., Waelde, L. C., Spiegel, D. 2017. Brain activity and functional connectivity associated with hypnosis. Cereb. Cortex 27, 4083-4093.

Juel, J., Abrahamsen, R., Olesen, S.S., Drewes, A.M. 2018. A pilot-study of hypnotherapy as complementary treatment for pain in chronic pancreatitis. J. Complement. Integr. Med. 15(4).

Kanherkar, R.R., Bhatia-Dey, N., Csoka, A.B. 2014. Epigenetics across the human lifespan. Front. Cell. Dev. Biol. 2, 49.

Karpova, N. N., Sales, A. J., Joca, S. R. 2017. Epigenetic basis of neuronal and synaptic plasticity. Curr. Top. Med. Chem. 17, 771-793.

Katonai, E. R., Szekely, A., Vereczkei, A., Sasvari-Szekely, M., Bányai, É. I., Varga, K. 2017. Dopaminergic and Serotonergic Genotypes and the Subjective Experiences of Hypnosis. Int. J. Clin. Exp. Hypn. 65, 379-397.

Keefe, F. J. 1982. Behavioral assessment and treatment of chronic pain: current status and future directions. J Consult Clin Psychol. 50, 896-911.

Kim, S., Kaang, B.K. 2017. Epigenetic regulation and chromatin remodeling in learning and memory. Exp. Mol. Med. 49, e281

Kimura, H. 2013. Histone modifications for human epigenome analysis. J. Hum. Genet. 58, 439-445.

Kravits, K. 2013. Hypnosis: adjunct therapy for cancer pain management. J. Adv. Pract. Oncol. 4, 83-88.

Kumar, A., Foster, T. C. 2019. Alteration in NMDA receptor mediated glutamatergic neurotransmission in the hippocampus during senescence. Neurochem. Res. 44, 38-48.

Landolt, A. S., Milling, L. S. 2011. The efficacy of hypnosis as an intervention for labor and delivery pain: a comprehensive methodological review. Clin. Psychol. Rev. 31, 1022-1031.

Langille, J. J., Brown, R. E. 2018. The synaptic theory of memory: A historical survey and reconciliation of recent opposition. Front. Syst. Neurosci. 12, 52.

Lardenoije, R., Pishva, E., Lunnon, K., van den Hove, D. L. 2018. Neuroepigenetics of aging and age-related neurodegenerative disorders. Prog. Mol. Biol. Transl. Sci. 158, 49-82.

Levenson, J. M., Sweatt, J. D. 2005. Epigenetic mechanisms in memory formation. Nat. Rev. Neurosci. 6, 108e18.

Lewandowska, A.M., Rudzki, M., Rudzki, S., Lewandowski, T., Laskowska, B. 2019. Environmental risk factors for cancer - review paper. Ann. Agric. Environ. Med. 26(1), 1-7.

Liang, X., Zou. Q., He, Y., Yang, Y. 2016. Topologically Reorganized Connectivity Architecture of Default-Mode, Executive-control, and salience networks across working memory task loads. Cereb. Cortex 26, 1501-1511.

Lichtenberg, P., Bachner-Melman, R., Ebstein, R. P., Crawford, H. J. 2004. Hypnotic susceptibility: multidimensional relationships with Cloninger's Tridimensional Personality Questionnaire, COMT polymorphisms, absorption, and attentional characteristics. Int. J. Clin. Exp. Hypn. 52, 47-72.

Lindfors, P., Ljótsson, B., Bjornsson, E., Abrahamsson, H., Simrén, M. 2013. Patient satisfaction after gut-directed hypnotherapy in irritable bowel syndrome. Neurogastroenterol. Motil. 25, 169-e86.

Liu, C., Huang, Z., Li, Z., Li, J., Li, Y. 2020. Muscone reduced the hypnotic and analgesic effect of ketamine in mice. J. Chin. Med. Assoc. 83(2), 148-155.

Lubin, F. D., Gupta, S., Parrish, R. R., Grissom, N. M., Davis, R. L. 2011. Epigenetic mechanisms: critical contributors to long-term memory formation. Neuroscientist 17, 616-632.

Mackey, E. F. 2018. An extension study using hypnotic suggestion as an adjunct to intravenous sedation. Am. J. Clin. Hypn. 60, 378-385.

Madden, K., Middleton, P., Cyna, A. M., Matthewson, M., Jones, L. 2016. Hypnosis for pain management during labour and childbirth. Cochrane Database Syst. Rev. 2016(5), CD009356.

Mansour, A. R., Farmer, M. A., Baliki, M. N., Apkarian, A. V. 2014. Chronic pain: the role of learning and brain plasticity. Restor. Neurol. Neurosci. 32, 129-139.

Maquet, P., Faymonville, M. E., Degueldre, C., Delfiore, G., Franck, G., Luxen, A., Lamy, M. 1999. Functional neuroanatomy of hypnotic state. Biol. Psychiatry. 45, 327-333.

Marczylo, E.L., Jacobs, M.N., Gant, T.W. 2016. Environmentally induced epigenetic toxicity: potential public health concerns. Crit. Rev. Toxicol. 46, 676-700.

Marshall, P., Bredy, T. W. 2016. Cognitive neuroepigenetics: the next evolution in our understanding of the molecular mechanisms underlying learning and memory? NPJ Sci. Learn. 1, 16014.

Marsm, R. B., Neubertm, F. X., Noonan, M. P., Sallet, J., Toni, I., Rushworth, M. F. 2012. On the relationship between the "default mode network" and the "social brain". Front. Hum. Neurosci. 6, 189.

Mateos-Aparicio, P., Rodríguez-Moreno, A. 2019. The impact of studying brain plasticity. Front. Cell. Neurosci. 13, 66.

Mazzola, L. A., Calcagno, M. L., Obdrzalek, A., Pueyrredón, J. H., Cavanagh, S., Shubaroff, P., Goicochea, M. T., Procopio, A., Daud, M. L. Salvat, F. 2017. Hypnosis for chronic pain management. Physiother. Rehabil. 2, 1000128.

McCann, B. S., Landes, S. J. 2010. Hypnosis in the treatment of depression: considerations in research design and methods. Int. J. Clin. Exp. Hypn. 58, 147-164.

McKinstry-Wu, A.R., Woll, K.A., Joseph, T.T., Bu, W., White, E.R., Bhanu, N.V., Garcia, B.A., Brannigan, G., Dailey, W.P., Eckenhoff, R.G. 2019. Azi-medetomidine: Synthesis and Characterization of a Novel α2 Adrenergic Photoaffinity Ligand. ACS Chem. Neurosci. 10(11), 4716-4728.

Mehta, S. L., Dempsey, R. J., Vemuganti, R. 2020. Role of circular RNAs in brain development and CNS diseases. Prog. Neurobiol. 186, 101746.

Meng, W., Adams, M. J., Reel, P., Rajendrakumar, A., Huang, Y., Deary, I. J., Palmer, C.N.A, McIntosh, A. M., Smith, B. H. 2020. Genetic correlations between pain phenotypes and depression and neuroticism. Eur. J. Hum. Genet. 28, 358-366.

Menon, V. 2015. Salience Network. In: Arthur W. Toga (Ed.) Brain Mapping: An Encyclopedic Reference, vol. 2, pp. 597-611. Academic Press: Elsevier.

Merskey, H., Bogduk, N. 1994. Classification of chronic pain. 2nd ed. Seattle: IASP Press, p. 1.

Milling, L. S., Valentine, K. E., McCarley, H. S. LoStimolo, L. M. 2018. A meta-analysis of hypnotic interventions for depression symptoms: High hopes for hypnosis? Am. J. Clin. Hypn. 61, 227-243.

Montgomery GH, Schnur JB, Kravits K. 2013. Hypnosis for cancer care: over 200 years young. CA Cancer J. Clin. 63, 31-44.

Moosavi, A., Motevalizadeh Ardekani, A. 2016. Role of Epigenetics in Biology and Human Diseases. Iran Biomed. J. 20, 246-258.

Moser, G., Trägner, S., Gajowniczek, E. E., Mikulits, A., Michalski, M., Kazemi-Shirazi, L., Kulnigg-Dabsch, S., Führer, M., Ponocny-Seliger, E., Dejaco, C., Miehsler, W. 2013. Long-term success of gut-directed group hypnosis for patients with refractory irritable bowel syndrome: A randomized controlled trial. American J. Gastroenterology 108, 602-609.

Oberman, L., Pascual-Leone, A. 2013. Changes in plasticity across the lifespan: cause of disease and target for intervention. Prog. Brain Res. 207, 91-120.

Ormel, J., Jeronimus, B. F., Kotov, R., Riese, H., Bos, E. H., Hankin, B., Rosmalen, J.G.M., Oldehinkel, A. J. 2013. Neuroticism and common mental disorders: meaning and utility of a complex relationship. Clin. Psychol. Rev. 33, 686-697.

Ortuño-Sahagún, D., Schliebs, R., Pallàs, M. 2019. Editorial: Epigenetic mechanisms regulating neural plasticity. Front Cell Neurosci. 13, 118.

Pagiatakis, C., Musolino, E., Gornati, R., Bernardini, G., Papait, R. 2019. Epigenetics of aging and disease: a brief overview. Aging Clin. Exp. Res. doi: 10.1007/s40520-019-01430-0.

Paredes, A. C., Costa, P., Fernandes, S., Lopes, M., Carvalho, M., Almeida, A., Pinto, P. R. 2019. Effectiveness of hypnosis for pain management and promotion of health-related quality-of-life among people with haemophilia: a randomised controlled pilot trial. Sci. Rep. 9(1), 13399.

Peschansky, V.J., Wahlestedt, C. 2014. Non-coding RNAs as direct and indirect modulators of epigenetic regulation. Epigenetics 9, 3-12.

Philippi, C. L., Tranel, D., Duff, M., Rudrauf, D. 2015. Damage to the default mode network disrupts autobiographical memory retrieval. Soc. Cogn. Affect. Neurosci. 10(3), 318-326.

Pintar, J., Lynn, S. J. 2008. Hypnosis: A brief history. Malden, MA: Wiley-Blackwell.

Presciuttini, S., Curcio, M., Chillemi, R., Barbuti, S., Scatena, F., Carli, G., Ghelarducci, B., Santarcangelo, E. L. 2009. Promoter polymorphisms of the NOS3 gene are associated with hypnotizability-dependent vascular response to nociceptive stimulation. Neurosci Lett. 467(3), 252-255.

Presciuttini, S., Curcio, M., Sciarrino, R., Scatena, F., Jensen, M.P., Santarcangelo, E.L. 2018. Polymorphism of opioid receptors μ1 in highly hypnotizable subjects. Int. J. Clin. Exp. Hypn. 66(1), 106-118.

Provençal, S. C., Bond, S., Rizkallah, E., El-Baalbaki, G. 2018. Hypnosis for burn wound care pain and anxiety: A systematic review and meta-analysis. Burns 44(8),1870-1881.

Pyka, M., Burgmer, M., Lenzen, T., Pioch, R., Dannlowski, U., Pfleiderer, B., Ewert, A. W., Heuft, G., Arolt, V., Konrad, C. 2011. Brain correlates of hypnotic paralysis-a resting-state fMRI study. Neuroimage 56(4), 2173-2182.

Queenan, B. N., Ryan, T. J., Gazzaniga, M. S., Gallistel, C. R. 2017. On the research of time past: the hunt for the substrate of memory. Ann. N. Y. Acad. Sci. 1396(1), 108-125.

Qureshi, I. A., Mehler, M. F. 2014. An evolving view of epigenetic complexity in the brain. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 369(1652), 20130506.

Rainville, P., Hofbauer, R. K., Bushnell, M. C., Duncan, G. H., Price, D. D. 2002. Hypnosis modulates activity in brain structures involved in the regulation of consciousness. J. Cogn. Neurosci. 14(6), 887-901.

Rogovik, A. L., Goldman, R. D. 2007. Hypnosis for treatment of pain in children. Can. Fam. Physician. 53(5), 823-825.

Rome, H. P. Jr., Rome, J. D. 2000. Limbically augmented pain syndrome (LAPS): kindling, corticolimbic sensitization, and the convergence of affective and sensory symptoms in chronic pain disorders. Pain Med. 1(1), 7-23.

Rominger, C., Weiss, E. M., Nagl, S., Niederstätter, H., Parson, W., Papousek, I. 2014. Carriers of the COMT Met/Met allele have higher degrees of hypnotizability, provided that they have good attentional control: a case of gene-trait interaction. Int. J. Clin. Exp. Hypn. 62(4), 455-482.

Rossi, E. L. 2005. Prospects for exploring the molecular-genomic foundations of therapeutic hypnosis with DNA microarrays. Am. J. Clin. Hypn. 48(2-3), 165-182.

Rossi, E., Iannotti, S., Cozzolino, M., Castiglione, S., Cicatelli, A., Rossi, K. 2008. A pilot study of positive expectations and focused attention via a new protocol for optimizing therapeutic hypnosis and psychotherapy assessed with DNA microarrays: The creative psychosocial genomic healing experience. Sleep Hypn. 10, 39-44.

Rossi, E., Iannotti, S., Cozzolino, M., Castiglione, S., Cicatelli, A., Rossi, K. 2008. A pilot study of positive expectations and focused attention via a new protocol for optimizing therapeutic hypnosis and psychotherapy assessed with DNA microarrays: The creative psychosocial genomic healing experience. Sleep and Hypnosis 10(2), 39-44.

Salort, G., Álvaro-Bartolomé, M., García-Sevilla, J.A. 2019. Ketamine-induced hypnosis and neuroplasticity in mice is associated with disrupted p-MEK/p-ERK sequential activation and sustained upregulation of survival p-FADD in brain cortex: Involvement of GABAA receptor. Prog. Neuropsychopharmacol. Biol. Psychiatry. 88, 121-131.

Salta, E., De Strooper, B. 2012. Non-coding RNAs with essential roles in neurodegenerative disorders. Lancet Neurol. 11(2), 189-200.

Salta, E., De Strooper, B. 2017. Noncoding RNAs in neurodegeneration. Nat. Rev. Neurosci. 18(10), 627-640.

Sauer-Zavala, S., Wilner, J. G., Barlow, D. H. 2017. Addressing neuroticism in psychological treatment. Personal. Disord. 8(3), 191-198.

Sawni, A., Breuner, C. C. 2017. Clinical hypnosis, an effective mind-body modality for adolescents with behavioral and physical complaints. Children (Basel) 4(4), 19.

Schacht, J. P. 2016.COMT val158met moderation of dopaminergic drug effects on cognitive function: a critical review. Pharmacogenomics J. 16(5), 430-438.

Schnur, J. B., Kafer, I., Marcus, C., Montgomery, G. H. 2008. Hypnosis to manage distress related to medical procedures: A meta-analysis. Contemp. Hypn. 25(3-4), 114-128.

Scholkmann, F.S., Kleiser, S., Metz, A.J., Zimmermann, R., Mata Pavia, J., Wolf, U., Wolf, M. 2014. A review on continuous wave functional near-infrared spectroscopy and imaging instrumentation and methodology. Neuroimage 85, 6-27

Schulz-Stübner, S., Krings, T., Meister, I. G., Rex, S., Thron, A., Rossaint, R. 2004. Clinical hypnosis modulates functional magnetic resonance imaging signal intensities and pain perception in a thermal stimulation paradigm. Reg. Anesth. Pain Med. 29(6), 549-556.

Seeley, W. W. 2019. The salience network: A neural system for perceiving and responding to homeostatic demands. J. Neurosci. 39(50), 9878-9882.

Sevinc, G., Gurvit, H., Spreng, R. N. 2017. Salience network engagement with the detection of morally laden information. Soc. Cogn. Affect. Neurosci. 12(7), 1118-1127.

Shen, K. K., Welton, T., Lyon, M., McCorkindale, A. N., Sutherland, G. T., Burnham, S., Fripp, J., Martins, R., Grieve, S. M. 2020. Structural core of the executive control network: A high angular resolution diffusion MRI study. Hum. Brain Mapp. 41(5), 1226-1236.

Shor, R. E., Orne, E. C. 1962. Harvard group scale of hypnotic susceptibility, Form A. Palo Alto, CA: Consulting Psychologists Press.

Sun, A. X., Crabtree, G. R., Yoo, A. S. 2013. MicroRNAs: regulators of neuronal fate. Curr. Opin. Cell Biol. 25(2) 215-221.

Szekely, A., Kovacs-Nagy, R., Bányai, E. I., Gosi-Greguss, A. C., Varga, K., Halmai, Z., Ronai, Z., Sasvari-Szekely, M. 2010. Association between hypnotizability and the catechol-O-methyltransferase (COMT) polymorphism. Int. J. Clin. Exp. Hypn. 58(3), 301-315.

Taylor, D.A., Genkov, K.A. 2020. Hypnotherapy for the treatment of persistent pain: A literature review. J. Am. Psychiatr. Nurses. Assoc. 26(2), 157-161.

Thompson, T., Terhune, D. B., Oram, C., Sharangparni, J., Rouf, R., Solmi, M., Veronese, N., Stubbs, B. 2019. The effectiveness of hypnosis for pain relief: A systematic review and meta-analysis of 85 controlled experimental trials. Neurosci. Biobehav. Rev. 99, 298-310.

Tomé-Pires, C., Miró, J. 2012. Hypnosis for the management of chronic and cancer procedure-related pain in children. Int. J. Clin. Exp. Hypn. 60(4), 432-457.

Tsang, A., Von Korff, M., Lee, S., Alonso, J., Karam, E., Angermeyer, M. C., Borges, G. L., Bromet, E. J., Demytteneare, K., de Girolamo, G., de Graaf, R., Gureje, O., Lepine, J. P., Haro, J. M., Levinson, D., Oakley Browne, M. A., Posada-Villa, J., Seedat, S., Watanabe, M. 2008. Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. J. Pain 9(10), 883-891.

Tsuji, T., Matsudaira, K., Sato, H., Vietri, J. 2016. The impact of depression among chronic low back pain patients in Japan. BMC Musculoskelet. Disord. 17, 447.

Vaissière, T., Sawan, C., Herceg, Z. 2008. Epigenetic interplay between histone modifications and DNA methylation in gene silencing. Mutat. Res. 659(1-2), 40-48.

van Ettinger-Veenstra, H., Lundberg, P., Alföldi, P., Södermark, M., Graven-Nielsen, T., Sjörs, A., Engström, M., Gerdle, B. 2019. Chronic widespread pain patients show disrupted cortical connectivity in default mode and salience networks, modulated by pain sensitivity. J. Pain Res. 12, 1743-1755.

Wagstaff, G.F. 2013. On the centrality of the concept of an altered state to definitions of hypnosis. J. Mind–Body 2, 90-108.

Walter, S. A., Jones, M. P., Talley, N. J., Kjellström, L., Nyhlin, H., Andreasson, A. N., Agréus, L. 2013. Abdominal pain is associated with anxiety and depression scores in a sample of the general adult population with no signs of organic gastrointestinal disease. Neurogastroenterol. Motil. 25, 741-e576.

Washington, S. D., VanMeter, J. W. 2015. Anterior-posterior connectivity within the default mode network increases during maturation. Int. J. Med. Biol. Front. 21(2), 207-218.

Weitzenhoffer, A. M., Hilgard, E. R. 1962. Stanford hypnotic susceptibility scale, Form C. Palo Alto, CA: Consulting Psychologists Press.

Williamson, A. 2019. What is hypnosis and how might it work? Palliat Care 12, 1178224219826581.

Wobst, A. H. 2007. Hypnosis and surgery: past, present, and future. Anesth. Analg. 104(5), 1199-208.

Wortzel, J., Spiegel, D. 2017. Hypnosis in cancer care. Am. J. Clin. Hypn. 60(1), 4-17.

Xu X, Yuan H, Lei X. Activation and Connectivity within the Default Mode Network Contribute Independently to Future-Oriented Thought. Sci Rep. 2016 Feb 12;6:21001

Ye, Y., Xu, H., Su, X., He, X. 2016. Role of MicroRNA in governing synaptic plasticity. Neural. Plast. 2016, 4959523.

Yeh, V. M., Schnur, J. B., Montgomery, G. H. 2014. Disseminating hypnosis to health care settings: Applying the RE-AIM framework. Psychol. Conscious (Wash D C). 1(2), 213-228.

Yeshurun, Y., Nguyen, M., Hasson, U. 2021. The default mode network: where the idiosyncratic self meets the shared social world. Nat. Rev. Neurosci. doi: 10.1038/s41583-020-00420-w.

Zhang, P., Wu, W., Chen, Q., Chen, M. 2019. Non-Coding RNAs and their integrated networks. J. Integr. Bioinform. 16(3), 20190027.