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Multidisciplinary Approach to Hypnosis: Psychiatric Basis, Neuroimaging and Genetic Findings

Hipnoza Multidisipliner Yaklaşım: Psikiyatrik Temeli, Nörogörüntüleme ve Genetik Bulgular

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ABSTRACT

Hypnosis, a practice often misunderstood and surrounded by misconceptions, has a rich historical lineage dating back to ancient civilizations. Our review explores the relationship between neuroanatomy, genetics, and hypnotic susceptibility, investigating organic factors influencing an individual's responsiveness to hypnosis. This review highlights the importance of hypnosis as a high-level cognitive activity, especially in pain and anxiety management, and emphasizes the potential benefits of integrating hypnosis into healthcare practices. Recent advancements in neuroimaging have provided insights into the neurological mechanisms of hypnosis, while genetic research has expanded its applications. However, persistent misconceptions hinder its acceptance. This article offers a multidisciplinary basic exploration of hypnosis, focusing on its origins, historical development related to psychiatry, the basic neuroimaging findings mainly affecting the limbic system responsible for emotion, and genetic underpinnings. We aim to inspire clinicians, social scientists, and healthcare professionals to effectively integrate the scientific basics of hypnosis into therapeutic practice, contributing to a better understanding of its role in augmenting outcomes.
Keywords: Hypnosis, psychiatric basis, neuroimaging, genetics, multidisciplinary approach

ÖZ

Hipnoz, sıklıkla yanlış anlaşılan ve çeşitli yanılgılarla çevrili bir uygulama olup, antik uygarlıklara kadar uzanan köklü bir tarihi geçmişe sahiptir. Bu derleme, bireyin hipnoza yanıt verme yeteneğini etkileyen organik faktörleri inceleyerek, nöroanatomi, genetik ve hipnotik duyarlılık arasındaki ilişkiyi keşfetmektedir. Bu derleme, özellikle ağrı ve kaygı yönetiminde, hipnozun yüksek düzeyde bilişsel bir aktivite olarak önemini vurgulamakta ve hipnozun sağlık uygulamalarına entegre edilmesinin potansiyel faydalarını belirtmektedir. Son zamanlarda nörogörüntüleme alanındaki ilerlemeler, hipnozun nörolojik mekanizmalarına dair içgörüler sunarken, genetik araştırmalar uygulama alanlarını genişletmiştir. Ancak, süregelen yanılgılar kabulünü engellemektedir. Bu makale, hipnozun kökenleri, psikiyatriyle ilgili tarihsel gelişimi, esas olarak duygulardan sorumlu limbik sistemi etkileyen temel nörogörüntüleme bulguları ve genetik alt yapısına odaklanarak, hipnozu multidisipliner bir şekilde keşfetmeyi amaçlamaktadır. Amacımız, klinisyenleri, sosyal bilimcileri ve sağlık profesyonellerini hipnozun bilimsel temellerini terapötik uygulamalara etkili bir şekilde entegre etmeye teşvik ederek, sonuçları iyileştirmedeki rolünü daha kapsamlı şekilde anlamalarına katkıda bulunmaktır.
Anahtar sözcükler: Hipnoz, psikiyatrik temeli, nörogörüntüleme, genetik, multidisipliner yaklaşım

Introduction

Hypnosis, a term and practice with its roots entwined deeply in ancient civilizations, continues to mystify, captivate, and prove instrumental in modern medical and social disciplines (Bernheim 1980). Its multidimensional nature, encompassing neuroanatomy, genetics, and cognitive psychology, presents a complex web of interactions that have only begun to be untangled with recent scientific advancements.

Traditionally, hypnosis has been perceived as an enigmatic phenomenon, often surrounded by myth and misunderstanding. However, as a high-level cognitive activity, its importance in the realms of pain management, anxiety control, and therapeutic intervention cannot be understated. From its ancient beginnings to the

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groundbreaking theories of the modern centuries, hypnosis has evolved to become an essential tool, not only in psychiatry but also in various other healthcare and social fields, such as advertising (Chan et al. 2023).

Recent years have witnessed unprecedented insights into the neurological foundations of hypnosis, enabled largely by advances in neuroimaging techniques. The unveiling of genetic factors influencing hypnotic susceptibility has broadened our understanding and allowed for more personalized and targeted interventions. Yet, despite these strides, misconceptions persist, causing hesitance and underutilization of hypnosis in clinical practice (Lifshitz et al. 2013, Landry and Raz 2015).

Our objective is to comprehensively examine hypnosis from an interdisciplinary perspective, focusing primarily on its application in various health fields, including psychiatry, as well as in social domains such as advertising. We strive to elucidate the organic scientific foundations of hypnosis in an easily comprehensible manner. In this context, our work seeks to provide comparative information on how and why different communities, notably including Turkish society, are influenced by hypnosis. We believe that our study is both original and particularly beneficial from an interdisciplinary standpoint, as it aims to address public health and socioeconomic issues caused by social hypnosis and to propose solutions to these challenges.

Our exploration highlights the vital role of hypnosis as an essential cognitive process, summarizing its prevalence, influence on individuals, and findings from functional brain imaging, particularly concerning pain and anxiety. We believe this perspective will shed light on potential benefits, inspire healthcare professionals, and contribute to the growing body of evidence supporting the integration of hypnosis into diverse therapeutic practices. By probing the depths of this complex subject, we hope to dispel prevailing myths, illuminate the rich tapestry of hypnosis's history and application, and pave the way for its more widespread recognition and utilization in enhancing therapeutic outcomes across various disciplines. Through a lens that stretches back to antiquity, this exploration reaffirms hypnosis's longstanding presence in human culture and its promising future in contemporary healthcare practices (Mikail and Mamman 2020).

Over the years, hypnosis has evolved, and various phenomena related to it have been observed and explored, contributing to understanding the unconscious mind and developing different therapeutic techniques. From the debate between Charcot and Bernheim's respective schools of thought to the contributions of Milton Erickson, hypnosis has been instrumental in shaping modern-day psychotherapy and therapeutic interventions (Ellenberger 1970, Green et al. 2014)

In recent years, advances in neuroimaging techniques have provided insights into the neurological underpinnings of hypnosis, enabling researchers to better understand its mechanisms and potential applications. Additionally, exploring genetic factors related to hypnotic susceptibility has broadened the scope of the field and paved the way for tailored interventions. Despite these advancements, misconceptions surrounding hypnosis persist, leading to clinical practitioners hesitating to implement hypnotic methods in their practice (Halsband and Wolf 2021).

This article aims to offer a comprehensive review encompassing the origins, historical development, neuroimaging findings, and genetic underpinnings of hypnosis. We will delve into the organic basis of hypnosis, emphasizing neuroimaging and genetic perspectives, to elucidate the scientific evidence supporting hypnosis. Through this, we aim to dispel prevailing myths and misconceptions related to hypnosis, inspiring clinicians to recognize and utilize the potential of hypnosis in augmenting therapeutic outcomes.

History of Hypnosis and Its Place in Psychiatry

Hypnosis, often clouded by misconceptions and myths, boasts a significant and intricate historical lineage. Its roots can be traced back to ancient civilizations, where rituals performed by shamans, healers, and priests demonstrated striking similarities with modern hypnotic practices (Wolberg 1948, Mac Hovec 1975, Bernheim 1980). Its evolution continued in the 18th century with Franz Anton Mesmer's theory of Animal Magnetism, laying the foundation for future therapeutic interventions and the development of psychotherapy(Peter 2005, Green et al. 2014). A significant shift occurred in 1784 with a Royal Inquiry into Animal Magnetism, dismissing the concept of magnetic fluid and recognizing socio-psychological factors as fundamental to the therapy (Ellenberger 1970, Laurence and Perry 2015). This highlighted the influence of imagination, imitation, and tactile interaction in the outcomes observed.

The 19th century, he witnessed further developments in understanding unconscious phenomena such as somnambulism and magnetic analgesia, culminating in James Braid's coining of the term "hypnosis" in 1843 (Braid 1843, Ellenberger 1970, Trochu 2008). The divergent views of Charcot and Bernheim in the late 19th century fueled the development of hypnotic interventions and the shaping of psychotherapy (Ellenberger 1970). Milton Erickson's utilization technique has been instrumental in shaping contemporary psychotherapy, representing a radical departure from traditional methods by emphasizing the real-time acceptance of the patient's thoughts, emotions, and convictions(Green et al. 2014). His innovative approach involved techniques that leveraged patient resistance, humor, metaphors, and surprise. This revolutionary work laid the foundation for integrating hypnotic methods into various psychotherapeutic approaches (Pintar 2008)

Since the late 1950s, hypnosis has been merged with behavioral therapies such as Wolpe's systematic desensitization, and it later found application in cognitive-behavioral treatment during the 1970s and 1980s (Goldfried and Davison 1976, Kanfer 1986). The method has not only regained attention in psychodynamic therapies but has become a staple in treatments for significant psychopathology (Fromm and Nash 1997, Nash 2008). In contemporary psychiatric practice, hypnosis is often synergized with cognitive-behavioral or psychodynamic techniques, reflecting Erickson's lasting impact on the field (Lynn et al. 2012).

Hypnosis leverages the flexibility of consciousness to allow suggestions, mental images, memories, and focused associations to channel and modify the mind, achieving therapeutic objectives (Yapko 2010). Highly hypnotizable individuals, making up roughly 15% of the population, have been found to benefit significantly from hypnotic treatments, including suggestions for relaxation, calmness, and mental imagery (Barnier et al. 2014). Understanding individual differences in hypnotic susceptibility could inform the development of tailored interventions for individuals with varying levels of hypnotizability (Kirsch and Lynn 1999)

Hypnotic suggestions have been employed to enhance treatments for posttraumatic conditions and depression, showing promise in alleviating symptoms and improving established therapeutic approaches (Spiegel et al. 1988, Ponniah and Hollon 2009). Combining hypnosis with cognitive-behavioral therapy (CBT) for depression has been shown to promote positive expectancies, mood regulation, and problem-solving abilities (Yapko 2010, Alladin 2012, Kirsch and Low 2013). A meta-analysis supports the effectiveness of hypnosis in reducing depressive symptoms (Shih et al. 2009). Hypnosis has effectively addressed a range of psychological and somatic concerns (Lynn and Kirsch 2006, Alladin and Alibhai 2007).

Despite these advantages, many clinical practitioners may be hesitant to implement hypnotic methods due to enduring misconceptions surrounding hypnosis(McConkey 1986, Green 2003). Dispelling myths regarding hypnosis is crucial for optimizing outcomes with hypnotic interventions (Nash 2001, Green et al. 2006). As our understanding of hypnosis and its organic foundations grows, it becomes increasingly important for clinicians to embrace its potential for therapeutic change across various treatment modalities. Therefore, the following section of our paper will focus on elucidating the organic basis of hypnosis, with particular emphasis on neuroimaging and genetic perspectives.

Limbic Brain Regions Affected in Hypnosis: Neuroanatomy

In hypnosis, the brain's limbic system is primarily responsible for emotional activity (Casiglia et al. 2018). On the other hand, although the limbic system a has pivotal role in processing the hypnotic mechanism, hypnosis is a complex phenomenon that likely involves multiple cortical brain regions and networks including the sensorimotor cortex, visual cortex and parietal lobe. We will mainly discuss the functional anatomy of the limbic system responsible for emotions and body control and leave higher cortical parts of the brain region for another review for a basic understanding of primary mechanism to avoid too much complexity for comprehension of other disciplines of health professionals such as social sciences and supportive health professionals.

The limbic system is the part that is especially responsible for motivation, satisfaction, memory, fear, hunger, aggression, and sexuality (Klein and Spiegel 1989, Pugnaghi et al. 2011, Casiglia et al. 2018). The limbic system controls the parasympathetic and sympathetic systems and manages the whole body. The most important of these areas are the anterior cingulate cortex (ACC.), olfactory nerve, hypothalamus, hippocampus, and amygdala (Picture 1). According to functional Magnetic Resonance Imaging (fMRI) and P.E.T. studies, the limbic system is the leading actor in hypnosis, and the conductor in the limbic system is the Cingulate cortex, especially the Anterior Cingulate Cortex (ACC) located just above the anterior part of the corpus callosum. During hypnosis, connectivity between the D.L.P.F.C. and dACC activation is increased (De Benedittis 2021). Previous literature have suggested a common network of brain regions underlying the connection of the dorsolateral prefrontal cortex (DLPFC), the ventrolateral prefrontal cortex (VLPFC), the dorsal cingulate (dACC), and the parietal cortex (PC). Specially, dACC is important for monitoring the conflicting information (Blasi et al. 2006).

Depending on the task at hand, The prefrontal areas, cingulate, and precuneus are mainly activated, along with the cerebellum. The right hemisphere is more affected than the left. As commonly known, the right hemisphere is responsible for creativity, intuition, non-analytical thinking, abstract concepts, metaphors, and stories. Furthermore, corticolimbic system, the prefrontal cortex and the sensorineural cortex are among the most affected areas (Wolf et al. 2022). The limbic system, encompassing the brain's inner, middle, and anterior parts, is expected to all mammals, including humans. This system, along with the hippocampus and parahippocampal gyrus, is responsible for memory. The Cingulate Gyrus serves as the conductor and director of our attention, and through the hypothalamus, it regulates heart rate, blood pressure, emotions, attention, pain, and hypnosis. The limbic system includes the hormone-controlling hypothalamus, the fear and anxiety-regulating amygdala, the attention-regulating anterior thalamic nuclei, and the reward and satisfaction center, the Nucleus Accumbens, which is responsible for addiction. The olfactory nerve is the only nerve that is part of the limbic system. According to the literature, the anterior part of the insula, responsible for the body's survival functions, emotions, sexuality, and empathy, is also considered part of the limbic system (Pugnaghi et al. 2011, Vigliocco et al. 2013, Moseley et al. 2015, Uddin et al. 2017).

Notably, the ACC, is rich in gabaergic, dopaminergic, noradrenergic, serotoninergic receptors, and beneficial neuropeptides. Hence it is a crucial area that takes place in numerous psychiatric and neurodegenerative sickness such as Parkinson's disease. The insula, which also responsible for empathy and essential vital functions, and the sensory cortex, responsible for our emotional perceptions, are the areas most affected in hypnosis. These areas also overlap with pain pathways.

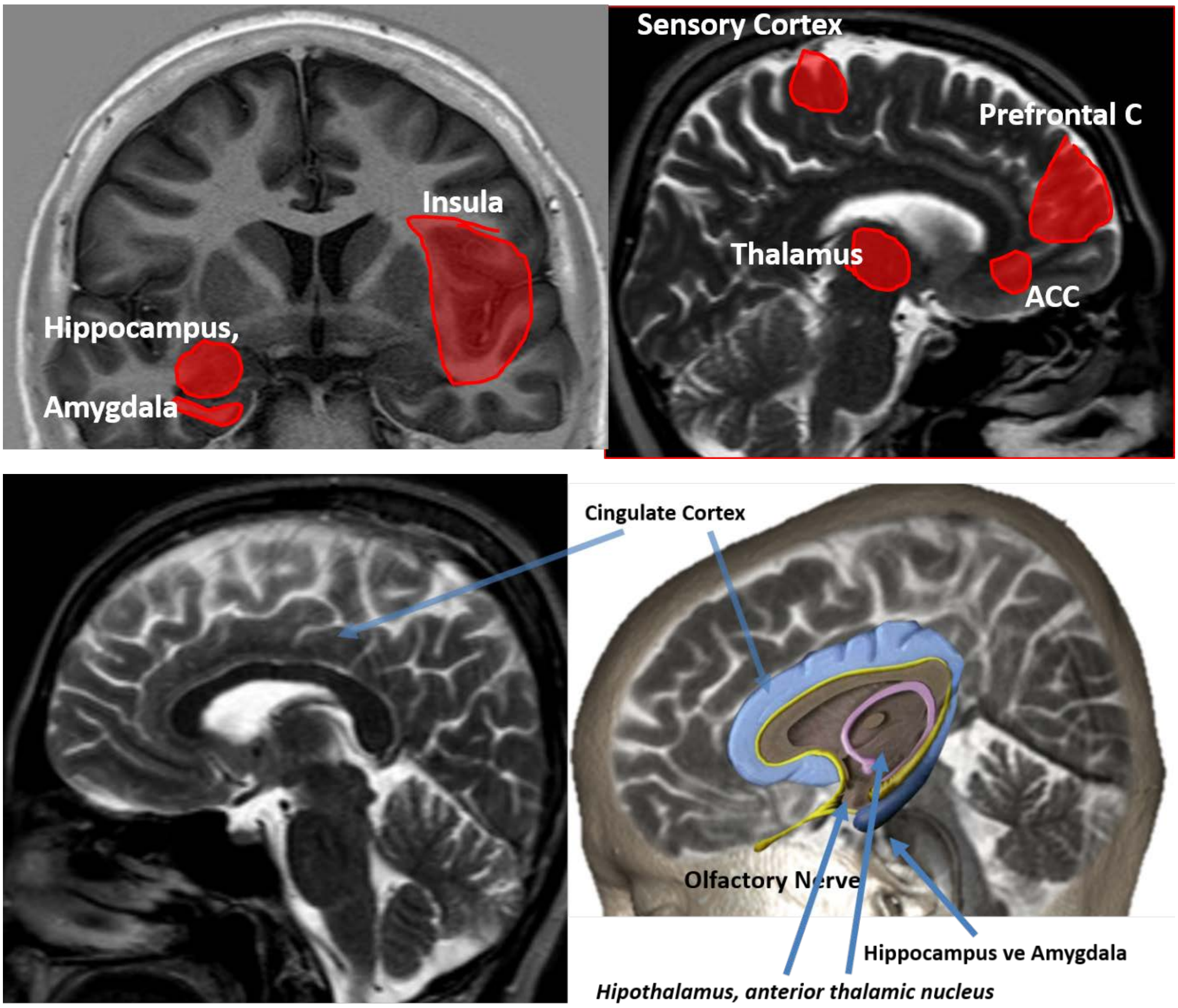

Figure 1. Main anatomical regions of lymbic system shown on Coronal T1(upper right) and sagittal T2 (upper left), Sagital T2 (lower images) MR images of the brain.

Significant Functional Findings in Imaging of Hypnosis

Neuroimaging findings in hypnosis have gained momentum, particularly since the 1980s. While PET imaging, based on brain glucose consumption using ionizing radiation, was used in the early years, fMRI studies, also known as the BOLD technique, which relies on brain oxygen consumption and does not involve radiation, have become widespread in recent years. fMRI has revolutionized the diagnosis and pathophysiology of neurological and psychiatric disorders. It has been beneficial for distinguishing organic psychiatric diseases and revealing crucial neural connections. In connectivity studies, a subcategory of this method, individual brain imaging, is uncovered, much like fingerprints. The goal is to differentiate an individual's brain within the population based on various features, assess changes over time, and evaluate responses to functional and psychiatric treatment methods.

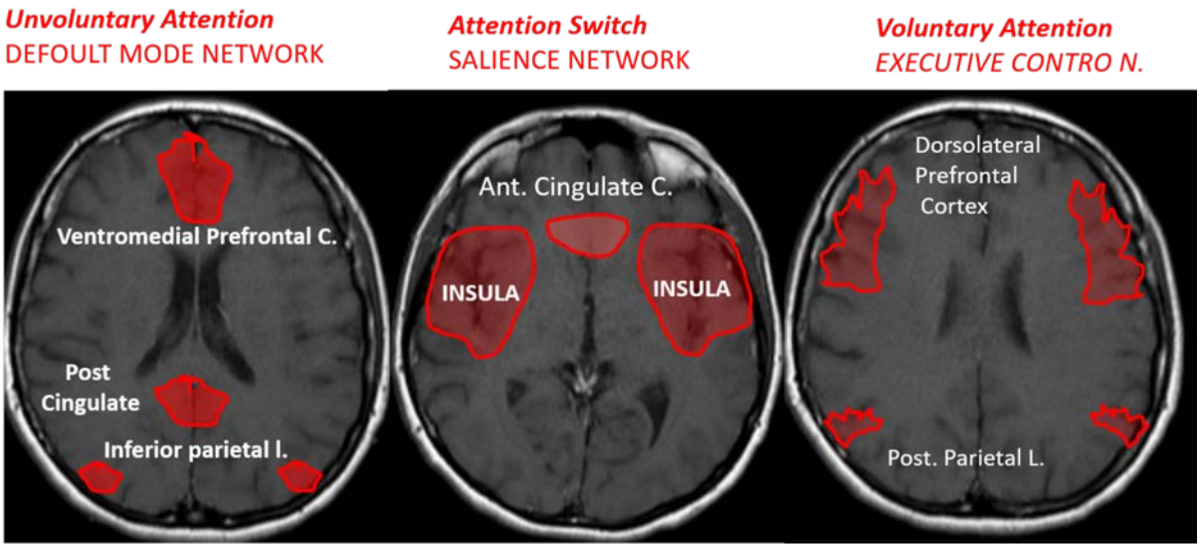

Figure 2. Basic neural networks of the brain (Far right: Involuntary attention, Middle: Attention selective, Left: Voluntary attention network) are shown on T1W MR images.

In resting-state fMRI examinations, which involve taking images without any assigned task while the patient lies in the MRI device, the goal is to uncover connectivity or network relations, which refers to the communication between specific brain regions. Recent resting-state fMRI findings have identified approximately ten fundamental neural network connections, three of which are particularly significant in terms of hypnosis. These networks also disclose stable and essential pattern relationships responsible for the brain's core neurocognitive connections. The networks and their functions can be summarized as follows:

Salience Network (SN): The switch Button of Selective Attention

The SN is a crucial component of the limbic system, primarily composed of the bilateral anterior insula (AI) and the dorsal anterior cingulate cortex (dACC). It is responsible for detecting disruptions to internal and external homeostasis, resolving contradictions, focusing attention, and identifying and filtering stimuli. It acts as the observer and conductor in our minds, selectively directing attention, activating other networks, and focusing on specific tasks. In this regard, it plays a significant role in hypnosis, pain modulation, and memory encoding. (Seeley et al. 2007)

This function is always available voluntarily or involuntarily. In short, it can be described as the switch button of attention. Disturbances in this network lie at the root of many neuropsychiatric, neurodevelopmental diseases, and degenerative diseases such as dementia (Kapur 2003, Klin et al. 2003, Seeley et al. 2012, Uddin 2015, Wang et al. 2017). Since this area is rich in dopaminergic, serotoninergic, and noradrenergic receptors, the dysfunctioning of this neural network increases abnormally in delusions and hallucinations. Hence it is tried to be controlled with antipsychotics (Kapur 2003, Klin et al. 2003, Seeley et al. 2012, Uddin 2015, Wang et al. 2017).

Default Mod Network (DMN): Involuntary Attention

The DMN is a neural network that functions as an autopilot in the brain and is responsible for crucial functions such as insight, self-awareness, and autobiographical memory. This network consists of the posterior cingulate cortex (PCC), inferior parietal lobe (IPL), and medial prefrontal cortex (MPFC), with contributions from the bilateral precuneus, left fusiform gyrus, and right medial temporal lobe. For instance, when we perform routine tasks like washing dishes or engage in daily activities that do not require heavy selective attention, the DMN becomes the dominant neural network. Its activity is regulated by the SN. In cases of addiction and dementia, DMN activity and dopaminergic, glutamatergic, and GABAergic signaling is reduced (Andrews-Hanna et al. 2010, Zhang and Volkow 2019). A stronganti-correlation exist with attentional executive control network compared to ventral PCC (Chen et al. 2017). Overall, the hypnotic state is associated with reduced activity in DMN and increased activity in prefrontal attentional systems. The further information can be found in the related literature (McGeown et al. 2009b, Deeley et al. 2012)

Executive Control Network (CEN; Voluntary attention)

Executive Control Network (CEN) mainly covers the dorsolateral prefrontal cortex (DLPFC) and posterior parietal lobule, located in the back and outer part of the brain. High cognitive functions such as decision-maker, controller, supervisor, attention, processor memory, decision making, complex memory processes, and mental activities, in short, intellectual functions and motor planning take place in this area. Imbalanced stimulation causes stress and pathologies (Figure 2) (Diamond 2013, Hertrich et al. 2021).

Individual fMRI Findings in Hypnosis

The fMRI findings in hypnosis have been shown to vary depending on an individual's susceptibility to hypnosis. In other words, individuals who are highly hypnotizable can be differentiated from those who are not based on functional brain imaging findings.

Individuals with high hypnotic susceptibility also possess an enhanced ability to focus which in turn increases their hypnotic capacity. These individuals are generally more open to suggestions when they trust the hypnotist, and the hypnotic state can evoke positive emotions such as motivation and relaxation. Besides fMRI, such individuals can be distinguished using methods like the Stanford Hypnotic Clinical Scale (SHCS)(Morgan and Hilgard 1978) ,Hypnosis Induction Profile (HIP), or the Stroop test. There is evidence that distraction, relaxation, and hypnotic suggestions can reduce pain perception in these "highly hypnotizable" individuals (Santarcangelo and Consoli 2018).

As is known, the Stroop interference (SI) test uses the interfering and conflicting effect feature at the time of conflict resolution. Accordingly, those who are prone to hypnosis are less affected by the Stroop effect, in other words, the brain slows down less than those who are not sensitive. This function is called lexical process. The rostrum of the corpus callosum is also effective in this function. In other words, people who are highly sensitive to hypnosis do not show any delay in verbal reactions under hypnosis or while awake (Nordby et al. 1999).

Depending on the degree of sensitivity to hypnosis, fMRI findings vary. For instance, some studies have reported increased ACC activity during hypnosis (Rainville et al. 1999, Egner and Hirsch 2005), while others have observed decreased activity (Raz et al. 2005, McGeown et al. 2009a, Deeley et al. 2012). While there is an increase in activity in the ACC in the area responsible for focus and attention, called the "Salience network" in those who are sensitive to hypnosis, there is a decrease in activity in this region in those who are not sensitive to hypnosis. The connection between the dorsolateral prefrontal cortex and involuntary attention (Default Mode Network), in other words, the activity in medial prefrontal and post cingulate cortex is reduced. Thus, the person under hypnosis becomes less aware of what they are doing. Again in those who are sensitive to hypnosis, the connection between the ACC and the Executive Control Network becomes stronger with hypnosis(Hoeft et al. 2012). Therefore, selective attention (Salience Network) and voluntary attention (Executive Control Network) activities are higher in those who are sensitive to hypnosis. In these individuals, the activity between the dorsolateral prefrontal cortex (DLPFC) and the anterior cingulate cortex (ACC) increases further with hypnosis (Greicius et al. 2004, Seeley et al. 2007). In addition, the connection between the dorsolateral prefrontal cortex and the insula; in other words, the brain-body connection is strengthened.

Although relationship between lateralization and hypnosis has not been well-established, there is a growing data for right brain dominancy at the hypnotic state. . Specially, the right parieto-temporal region show more electric power than the left one in highly susceptible subjects. The activity increase in the right parieto-temporal associative characterizing Ericsonian hypnotic state (Mészáros and Szabó 1999). According to scientific studies o the Pulvinar Nucleus and Fusiform Gyrus demonstrate increased activity in individuals experiencing hypnotic trance (Lifshitz and Raz 2015). Particularly in those who are more susceptible to hypnosis, the capacity for selective attention is heightened, involving the activation of the right prefrontal cortex and the anterior cingulate cortex (ACC) (Cojan et al. 2015). These people can use the volitional attention (Executive network) more effectively and reduce the left medial frontal gyrus activity in the involuntary attention (Default mode network) more effectively. In these people, the attention-seeking conductor (Salience network) is more dynamic and faster; connectivity is stronger (Hoeft et al. 2012).

Examination of MR images from easily hypnotizable individuals and those who are non-hypnotizable reveals significant differences in the corpus callosum, particularly in the rostrum region. Hypnosis-sensitive individuals exhibit a thicker rostrum. The rostrum, in conjunction with the frontal cortex, plays an important role in modulating attention and inhibition, as well as identifying emotional expressions on faces (Horton et al. 2004). Studies suggest that a smaller rostrum correlates with reduced verbal functions in autistic patients (Paul et al. 2007, Edwards et al. 2014, J and Geetha 2023). In summary, while hypnosis is commonly understood as submission to suggestion, it has been found that individuals with high hypnotic susceptibility exhibit enhanced control over their sensory, motor, and somatic functions (Hoeft et al. 2012). Studies have demonstrated that high hypnotic susceptibility boosts treatment success and increases the effectiveness of combined therapies (Montgomery et al. 2000) (De Pascalis et al. 2000, De Pascalis et al. 2008). Several assessment methods, such as the Harvard Group Hypnotic Sensitivity Scale and the Stanford Hypnotic Sensitivity Scale, have been developed to measure this predisposition and treatment management, significantly contributing to research findings in this field (Nadon et al. 1987).

The effects of genetics; treatment of antidepressants and placebo are also affected by these responses and show individual differences. It has been stated that genetic characteristics are an important factor in determining a person's susceptibility to hypnosis and that the revision of the susceptibility tests used in accordance with gene variants will provide more accurate results (Lichtenberg et al. 2004, Raz 2008) . In addition, it has been found that the increased connection between DLPFC and ACC in individuals with high hypnosis is associated with dopamine (Mier et al. 2010, Montag et al. 2012). The relationship between the COMT gene and dopamine was examined by fMRI, and it was shown that with the increase of dopamine activation in the brain, internal attention increased and attention to external stimuli decreased. It has been reported that dopamine plays an important role in hypnotherapy due to its effects on increasing attention in diseases with decreased memory and attention (Mier et al. 2010, Dang et al. 2012, Montag et al. 2012). Those who are sensitive to hypnosis have better control of their motor, sensory and somatic functions. The coupling between dACC and DLPFC in these individuals is very strong. Therefore, suggestions that reduce the feeling of pain are accompanied by a decrease in activity in the ACC and sensory cortex (Stoelb et al. 2009). Conversely, ACC, insula, thalamus, parietal cortex, and DLPFC were found to increase pain sensation created by hypnosis (Szechtman et al. 1998, Maquet et al. 1999).

Relationship between Neuroanatomy and Cognitive Diseases Affected By Hypnosis

Medial Prefrontal Cortex

As a principal area for involuntary attention and a part of the Default Mode Network, this region can be likened to a security door. It plays an essential role in aspects of personality and social relationships such as internal attention, autobiographical thoughts, interactions with the external world, coordination, socialization, self-awareness, motivation, decision-making, and self-control, and is significantly influenced during hypnosis (Ozsunar and Kayhan 2021).

Anterior Cingulate Cortex (ACC)

Considering the features mentioned above from an integrative perspective, the cingulate cortex, a vital component of the limbic system located on the corpus callosum, holds significant importance and functions as an orchestra conductor in attention modulation. This region also serves as a gateway for numerous cognitive, emotional, and autonomic functions (Vogt et al. 2013), including pain and placebo responses. The dorsal ACC (dACC), in particular, is abundant in opioid, dopaminergic, serotoninergic, and noradrenergic receptors, as well as peptides involved in the mechanisms of action for antidepressant and antipsychotic medications. The dACC plays crucial roles in selective attention, recognition of written words, and processing memory (Cabeza and Nyberg 2000). This area has been linked to various psychological and mental disorders, such as attention deficit, Parkinson's disease, major depression, bipolar disorder, obsessive-compulsive disorder, post-traumatic stress disorder, autism, and schizophrenia (Bush et al. 1999, Yücel et al. 2003, Maletic et al. 2007, Bush et al. 2008, Fornito et al. 2009).

Consequently, the heightened activity in this region, particularly among individuals with high hypnotic susceptibility, is theorized to boost the production of these advantageous neurochemicals, thereby positively impacting overall bodily health.

In summary, the dACC, a key region involved in hypnosis and pain modulation, functions in conjunction with the prefrontal cortex, amygdala, insula, and thalamus. The dACC primarily serves to identify contradictions by inhibiting automatic responses governed by involuntary attention, or the default mode network. During hypnosis, this region is suppressed in individuals with low hypnotic susceptibility, while its activity is heightened in those with high hypnotic susceptibility. Hypnosis leads to the shutting down of decision-making mechanisms associated with voluntary attention, known as the central executive network. Concurrently, dopamine secretion increases (Cabeza and Nyberg 2000, Egner and Hirsch 2005, Bush et al. 2008, Vogt et al. 2013).

Overall, although we discusses fMRI findings related to hypnosis briefly, the reader might find the confusing findings in the literature regarding the activity in the ACC during hypnosis, We would like to underline genetic factors to this conflicting finding although a more in-depth discussion of the possible reasons for these discrepancies and the potential methodological limitations of the studies. Overall, the literature addres a contrasting fMRI findings of high versus low hypnozibility. The following section will give a brief explanation and ling between fMRI versus genomic features.

Hypnosis and Genetics

The fact that not every person can be hypnotized at the same level has raised the suspicion that there may be a relationship between hypnotic susceptibility and genetic factors, as well as environmental factors, and studies have been conducted in this regard (Lichtenberg et al. 2000, Lichtenberg et al. 2004, Szekely et al. 2010, Presciuttini et al. 2014, Rominger et al. 2014, Storozheva et al. 2018). Lichtenberg et al. reported that a single nucleotide polymorphism (Val158Met) in the Catechol-O-methyltransferase (Catechol-O-Methyltransferase, COMT) gene is associated with hypnosis tendency (Lichtenberg et al. 2000). In his study, in which 48 male and 57 female samples were tested, a significant relationship was found only in females and showed that subjects with heterozygous COMT(Val/Met) genotype had a higher susceptibility to hypnosis (Lichtenberg et al. 2000). However, there is no consistency regarding the effects of functional polymorphisms in the COMT gene.

There are also studies with inconsistent results. For example, in the study of Raz et al. with healthy volunteers, consistent with Lichtenberg's findings, the hypnotic propensity in individuals with the heterozygous (Val/Met) COMT genotype was higher than both homozygous Val/Val and homozygous Met/Met subjects were found to be higher (Raz et al. 2006). However, Szekely et al. showed that issues with the Val/Val genotype had the highest hypnotizability scores (subjects with the Val/Met and Met/Met alleles followed the Val/Val genotype).

Catechol-O-methyltransferase (called COMT for short), encoded by the COMT gene, catalyzes the transfer of the methyl group to catecholamines, including dopamine, epinephrine, and norepinephrine, thereby limiting their activity. Therefore, functional changes in the enzyme cause the balance of these neurotransmitters to change. Indeed, changes in COMT activity have been associated with schizophrenia (Table 1) (Zammit et al. 2007).

The COMT gene encodes two COMT protein variants. One is the S-COMT (Soluble form) of 221 amino acids, and the other is the MB-COMT (Membrane-Bound- able to bind to the membrane) isoform, which contains an additional 50 amino acids and can attach to the membrane. The S-COMT protein, which cannot bind to the membrane, is present in greater amounts, predominant in tissues such as the liver, kidneys, and blood, as well as in glial cells. It has been reported that MB-COMT plays a fundamental role in the prefrontal cortex, where dopamine inactivation occurs (Tunbridge et al. 2007). The functional polymorphism mentioned above is at codon 108 of S-COMT; It takes place at codon 158 of MB-COMT. At these points, a change from guanine to adenine (G>A) causes methionine to replace the valine amino acid, and therefore a more unstable protein is formed. This means that it has lower activity. Therefore, there are higher dopamine levels in the anterior cingulate cortex (Blasi et al. 2005) and the prefrontal (Roussos et al. 2008) cortex (Table 1). Increased activity of COMT (Val/Val isoform or GG genotype) accelerates the degradation of dopamine in synaptic clefts. It reduces reuptake in presynaptic neurons, thereby increasing the regeneration rate of dopamine. When it comes to dopamine levels, it is possible to talk about an inverted U-shape in terms of results (Meyer-Lindenberg and Weinberger 2006). However, other point mutations in the COMT gene also affect the outcome (Meyer-Lindenberg and Weinberger 2006). These mutations can increase the ability to learn and focus. Inverted U means that the Val/Val variant of COMT and if there is a stress condition, the Met/Met variant of COMT also causes low dopamine levels (Meyer-Lindenberg and Weinberger 2006). In a stressful situation, the isotype with the highest level of dopamine is the Val/Met COMT isotype, while the other two homozygous isotypes cause low dopamine levels. Without stress, the Met/Met variant causes higher dopamine accumulation, and higher dopamine levels provide advantages such as faster learning, higher brain activity, and better memory. However, under stress, high dopamine levels become a disadvantage, causing a decrease in brain activity and an increase in the risk of chronic pain, schizophrenia, anger and violence, anxiety, and paranoia. Considering that it is very likely to encounter stress in the course of life, it is quite possible that dopamine levels may drop for this reason.

Apart from COMT, there have been other genes whose association with hypnotic susceptibility has been investigated. These include DRD3 and DRD4 dopamine receptors, the monoamine oxidase gene (MAOA), the SLC6A4 gene encoding the serotonin transporter protein (Serotonin Transporter, SERT, alias 5HTT), and the dopamine transporter (DAT) genes. However, polymorphisms in the DRD3, DRD4, MAOA, and DAT genes were not found to be significantly associated with hypnosis (Katonai et al. 2017).

Tablo 1. Polymorphism in the COMT gene and its effects

Amino acid	**Valine/Valine**	**Valine/ Methionine**	**Methionine / Methionine**	**References**
Allele frequency	Asians: 58.5%, Caucasians: 25% Turks: 34% Americans: 24% Germans: 24% Norwegians: 21% Japanese: 54% Chinese: 60% Filipinos: 67%	Asians: 37.25%, Caucasians: 50% Turks: 53% Americans: 51 Germans: 52% Norwegians: 47% Japanese: 39% Chinese: 37% Filipinos: 32%	Asians: 4.25%, Caucasians: 25% Turks: 13% Americans: 25% Germans: 24% Norwegians: 32% Japanese: 7% Chinese: 3% Filipinos: 1%	(Kocabaş et al. 2002, Baclig et al. 2012)
Variant	Homozygous-Valine	Heterozygous (Valine/Methionine)	Homozygous-Methionine	(Lichtenberg 2000)
Durability	***	**	*	
Activity (H: high, L: low)	*** HH	** HL	* LL	(Lichtenberg 2000)
Effects	Dopamine can be metabolized 4 times more (the activity of dopamine is limited)	The optimal level of dopamine	*In vivo,* in the brain, COMT enzyme activity is reduced by 40% (Dopamine activity cannot be adequately limited)	(Männistö and Kaakkola 1999)
Dopamine levels	*	**	*** But in case of stress, it drops: (*)	(Männistö and Kaakkola 1999, Meyer-Lindenberg and Weinberger 2006)
Hypnotizability	*	***	*	(Lichtenberg et al. 2004, Raz 2005, Szekely et al. 2010, Farrell et al. 2012)
Other results:	The pain threshold is low. Impulsivity. Depression and risk-taking behavior may occur. There may be an anger management problem.	It may play a role in the development of bipolar disorder and migraine. There is also a risk in the development of schizophrenia. It has been reported that this genotype has a protective effect from Parkinson's disease in Asians. No association was found in Caucasians.	Anxiety, Chronic pain High blood pressure, Insomnia, Paranoia It has been associated with Schizophrenia/Psychosis. It can play a role in panic disorder, A relationship was found with violence and suicidal behavior. Asians have an increased risk of Parkinson's disease.	(Glatt et al. 2003, Goldberg et al. 2003, Rujescu et al. 2003, Meyer-Lindenberg and Weinberger 2006, Varma et al. 2011, Baclig et al. 2012, Lechun et al. 2013)

* denotes relatively lowest level; ** intermediate level; *** the highest level

Another important candidate, the SLC6A4 gene, has a polymorphic region called the SERT-linked polymorphic region (serotonin-transporter-linked polymorphic region, 5-HTTLPR). In this region, two different alleles of serotonin (5-hydroxytryptamine, 5-HT), which arise due to polymorphisms, play a decisive role in the level of use in the synapses. 5-HTTLPR contains a variable number of tandem repeats (VNTR, variable number of tandem repeats). The polymorphism created by these repeating sequences is in the gene's promoter region. After all, there are two variations: the short ("S") version with 14 repeats and the long ("L") version with 16 repeats. The protein encoded by the short allele has a much lower transcriptional activity compared to the one encoded by the long allele (Lesch et al. 1996). Thus, the long variant produces much more SERT (another name is 5-HTT) mRNA and hence protein. More SERT means more serotonin can reach cell synapses. Serotonin is a hormone that gives happiness, vitality, and enthusiasm. Its deficiency can lead to malaise, aggression, depression, and increased appetite. It has been reported that the presence of the short SERT variant may be associated with neuroticism, depression, and suicidality (Benjamin et al. 1996, Caspi et al. 2003). A study showed that susceptibility to hypnosis may be associated with COMT and 5-HTTLPR polymorphism(Katonai et al. 2017). However, in this study, the tested serotonergic 5-HTTLPR polymorphism played an essential role in promoting intimacy between the subject and the hypnotist during hypnosis, and the level of familiarity of the interaction resulted in a significantly higher intimacy score (Dyadic Interactional Adaptation questionnaire) in carriers of the "Short" allele (14′) has been reported.

Despite all these determined data, hypnotic responsiveness is a complex trait that is influenced by both genetic and environmental factors. Although genetic factors, such as the COMT gene, which produces the COMT enzyme that breaks down catecholamines, i.e., dopamine; the 5-HTTLPR gene, which determines the length of the serotonin transporter protein (SERT), factors affect hypnotizability, environmental factors can be as effective as genetic factors. While it was previously thought that neural plasticity could occur during the development of the nervous system, it is now accepted that neural plasticity can occur throughout a person's lifetime (Császár et al. 2021). Epigenetic changes (methylation, acetylation, phosphorylation, ubiquitination, regulatory small non-coding RNAs, etc.) determine the level of expression of genes and can occur with environmental effects such as early childhood experiences, parental bonding, and exposure to stress.

In addition to the factors mentioned above, some other factors may influence hypnotic responsiveness, such as age, gender, and cultural background. For example, research suggests that children may be more susceptible to hypnosis than adults and that women may be more sensitive than men (Page and Green 2007, Kayhan 2021). However, more research is needed to confirm these findings.

Conclusion

In summary, hypnosis is one of the most important networks of the (real) brain that can be visualized. It is a high-level cognitive activity that requires (network) modulation. Many psychosomatic diseases, especially pain, can be cured with the brain-body (top-down) control mechanisms in hypnosis. In particular, pain and anxiety can be significantly reduced with hypnosis. Pain pathways are almost the same areas of the brain as those affected by hypnosis. Many fMRI studies on critical areas, especially the limbic system, where hypnosis, our perception of reality in the brain, takes place in the brain will become more frequent. Genetic findings also support brain imaging findings. At the point reached so far, it has been determined that individuals with heterozygous (Val/Met) COMT genotype have a higher susceptibility to hypnosis. However, working memory is higher than those with other variants. It is understood from the studies that the heterozygous (Val/Met) genotype also provides advantages for conditions such as pain threshold/chronic pain, anger control, violence tendency, risk-taking behavior, and suicidal tendencies. Dopamine levels are low in the Val/Val COMT variant low in the Met/Met COMT variant if stress conditions are present; however, Val/Met is highest in the COMT variant (Meyer-Lindenberg and Weinberger 2006). Therefore, the heterozygous COMT variant provides the optimum dopamine level and an advantage in hypnotic susceptibility. These findings show that hypnosis is a scientific, down-to-earth, provable scientific fact. However, it is a fact that different perspectives in the literature vary according to the genetic characteristics sampled. There is a need for scientific studies and holistic interpretations that exemplify western but also eastern and Asian societies. Current medicine practiced today often neglects the emotional aspect of pain, which is easily affected by hypnosis. We think that raising awareness and informing healthcare professionals will increase the use of hypnosis, a low-cost method with almost no side effects in pain control. For these reasons, we should use hypnotic suggestions, which are already part of daily life, more as healthcare professionals for pain, anxiety control, and healing.

Despite its scientific validation, hypnosis is under-recognized or misconstrued by healthcare professionals and society. This article seeks to illuminate the scientific basis of hypnosis through a summary of critical neuroscientific and neuroimaging findings, emphasizing functional neuroimaging. Educating healthcare professionals about hypnosis is essential, a technique dismissed as unscientific in medicine for years but used covertly in advertising and politics. This article aims to raise awareness among healthcare professionals and promote their informed application of this cost-effective, safe, and beneficial technique, particularly for pain management. There is a call for the broader acceptance of hypnosis in the health sector, including its integration into undergraduate medicine, psychology, and dentistry programs.

The limitations of this review are the following. Overall, the sample sizes of some studies in the liare relatively small, and the results may need to be more generalizable to broader populations. Moreover, the complex interplay of genetic and environmental factors in determining hypnotic responsiveness must be fully addressed with further studies. Therefore, we avoid drawing definitive conclusions solely based on the current genetic research. We would like to further analyze the current literature in with next studies to seek out the other factors effecting the hypnotic state.

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