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Review

Implications on Irritable Bowel Syndrome, Fibromyalgia, Chronic Pain, and Infantile Behaviour

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Abstract

The enteric nervous system (ENS) can function independently of the central nervous system (CNS) in regulating complex gastrointestinal processes and may possess forms of learning and memory. Recently, we have proposed that maternal stress, depression, or anxiety during pregnancy may induce stress-related long-term epigenetic implicit memory (SLEIM) in the foetal ENS via mechanisms distinct from those of the CNS. These stress imprints may persist throughout life. Through the bidirectional microbiota–gut–brain axis (MGBA), SLEIM signals originating in the embryonic ENS may influence the CNS. Because these signals are implicit and unrelated to conscious representation, the CNS cannot directly interpret them, yet it must regulate their physiological consequences. This interaction may activate stress-response systems, including the hypothalamic–pituitary–adrenal (HPA) axis and immune pathways, leading to cortisol release, mast cell activation, and cytokine imbalance. A self-reinforcing cycle may thus develop between the ENS and CNS. The frequent comorbidity of fibromyalgia (FM) and irritable bowel syndrome (IBS) suggests shared pathogenic mechanisms, particularly central sensitization and MGBA dysfunction. Clinically, patients with FM often display childlike behavioural traits. We hypothesize that early developmental influences—potentially linked to maternal SLEIM effects on the foetal ENS—may contribute to personality immaturity in FM, similarly to IBS. Under varying biopsychosocial conditions, IBS-related mechanisms may later manifest as systemic symptoms characteristic of FM.

Keywords: maternal mental stress; enteric nervous system (ENS); microbiota-gut–brain axis (MGBA); long-term epigenetic implicit memories (SLEIM); irritable bowel syndrome; fibromyalgia

1. Introduction

We recently presented a hypothetical model where maternal mental stress (depression, anxiety, etc.) may cause stress-induced long-term epigenetic implicit memory (SLEIM) in the foetal enteric nervous system (ENS) during pregnancy, which may last throughout a person's entire life (see hypothetical model in Figure 1) [1,2]. During pregnancy, maternal stress can change the mother's gut microbiota (dysbiosis) by perturbing the hypothalamic–pituitary–adrenal (HPA) axis and increasing cortisol levels [1]. As a result, the foetus's circulatory cortisol levels also rise when maternal cortisol passes across the placental barrier. This dysregulation of the HPA axis in the foetus produces gut dysbiosis by perturbing the gut microbiota, microbial metabolites, and intestinal permeability. Epigenetic regulation in the ENS cells is affected by mainly short-chain fatty acids (SCFAs), as well as other metabolites from the foetus's gut microbiota. Therefore, SLEIM may be imprinted onto the ENS during pregnancy and may induce a number of disorders through epigenetic modifications, like irritable bowel syndrome (IBS).

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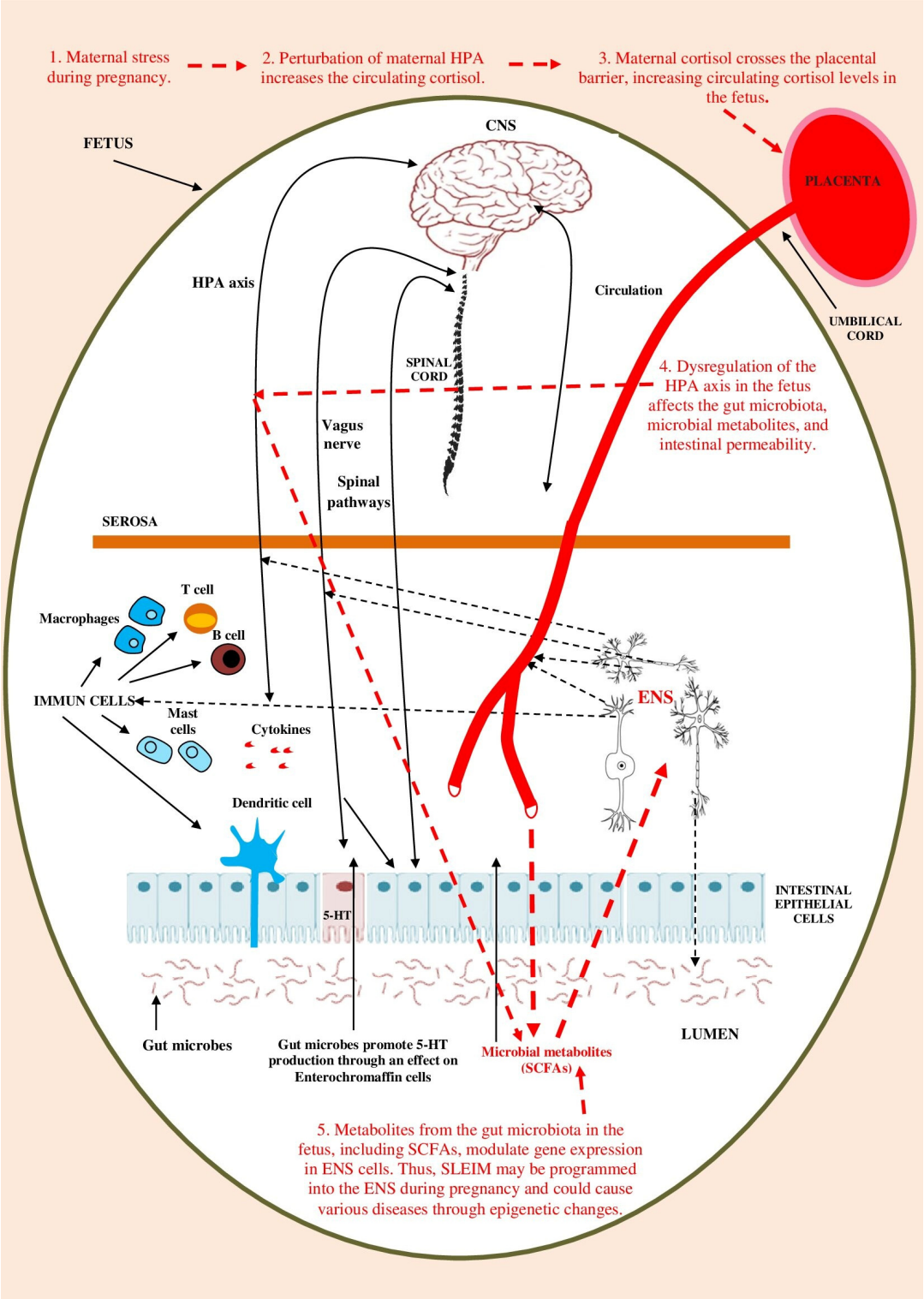

Figure 1. Our simplified hypothesis regarding the potential programming of stress-induced long-term epigenetic memory (SLEIM) into the foetal ENS during pregnancy is represented by parts in red. The additional processes shown are intricate intestinal functions that may also be involved in these processes. Our open-access paper is the source of this figure [1]. Abbreviations: Enteric nervous system (ENS) Short-chain fatty acids (SCFAs) Stress-induced long-term epigenetic implicit memory (SLEIM) Hypothalamic–pituitary–adrenal (HPA) axis.

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There is strong evidence that SCFAs produced by the intestinal microbiota have important roles in host metabolism, gastrointestinal physiology, immunological response, and the development and homeostasis of the central nervous system (CNS) [3]. SCFAs have the ability to control CNS functions directly and indirectly, which means that they can influence behaviour and cognitive function. SLEIM signals from the ENS can enter the CNS through the microbiota–gut–brain axis (MGBA), which suggests that they could disturb pain and emotional mechanisms [4–8].

Boem et al. [9] suggested a new theory about the existence primordial emotions [10] (proto-cognition) in the ENS. This theory [9] could explain why stress-related gut issues like IBS are difficult to treat as their origin involves deep, implicit, non-cognitive gut memories. Based on this new theory, we assert that SLEIM pertains to non-representational primordial emotional memory in the ENS [11]. In other words, the foetal ENS records SLEIM during pregnancy as primordial and non-representational emotional information. In contrast, the CNS processes representational emotional information through complex networks across multiple brain areas: the anterior cingulate, insula, and ventromedial, prefrontal, and subcortical structures, such as the amygdala, ventral striatum, putamen, caudate nucleus, and ventral tegmental area [12].

However, the CNS is responsible for managing the inflow of SLEIM signals from the gut, which perturb intestinal functions by initiating stress-response systems such as the HPA and the immune system. As a result, an endless cycle develops between the ENS and the CNS via cortisol release, mast-cell activation, and cytokine dysregulation, among other processes. MicroRNAs (miRNAs) play also an important role in foeto-maternal communication. Maternal stress can produce alterations in microRNAs, which can also enter the placenta and foetus through the bloodstream and influence epigenetic processes related to foetal development and maternal stress in the ENS [13,14].

Very often, fibromyalgia (FM) and IBS coexist, which suggests the possibility of both disorders sharing similar pathogenic mechanisms—most notably central sensitization and dysfunction in the MGBA [15–17]. We hypothesize that SLEIM signals from the ENS may play an important role in the development of both IBS and FM. Whether IBS develops into FM may depend on a number of individual biopsychosocial factors, and personal epigenetic processes may have an important role. We also discuss our observation that patients with FM frequently have a childlike mentality in our clinic. These personality developmental impairments in patients with FM may arise very early in intrauterine or perinatal development.

2. The Enteric Nervous System

From an evolutionary perspective, the ENS predates the development of the CNS [18]. The ENS is a complicated and autonomous neural system that developed earlier and independently of the CNS and can be considered as the “first brain” [19]. The ENS plays a key role as an integrative hub for regulating gastrointestinal physiology [20,21].

The ENS and the CNS can communicate bidirectionally through the MGBA, which is a complex bidirectional communication system that links the gut microbes, gut, and CNS. The MGBA includes the gut microbes (viruses, bacteria, fungi, and archaea) and their metabolites, the autonomic nervous system (ANS), the immune system, the neuroendocrine system, the CNS, and the ENS [22,23]. The ANS includes the sympathetic and parasympathetic systems, and the vagus nerve is a key parasympathetic pathway. The neuroendocrine system includes the HPA axis, which is considered the core stress-efferent axis that coordinates the adaptive responses of an organism to stressors. The ENS has the ability to function completely independently of the CNS.

The structure and neurochemistry of the ENS and CNS are similar, and nearly all CNS neurotransmitters are also present in the ENS, which is home to a variety of neurons and glia [24,25]. The ENS and CNS share a significant amount of cellular and molecular similarity, and many developmental pathways that are involved in CNS formation are also involved in ENS ontogeny [26]. Although the ENS can operate independently of the CNS, this is not typically the case. In actuality, 90% of the vagal fibres that connect the gut to the brain are afferent, indicating that in terms of brain–gut communication, the brain is more of a receiver than a transmitter [26].

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Epigenetics has been proposed as a molecular mechanism that is involved in encoding long-term memories. Growing research has demonstrated that epigenetic changes, such as DNA methylation, histone acetylation, and non-coding RNAs (miRNAs), are essential for the formation and maintenance of long-lasting memories in neurons. Their roles include controlling gene expression, enhancing the physical durability of experiences in the brain, and even impacting age-related memory decline [27–33]. Genetic , epigenetic, and other signalling pathways control the development of the millions of neurons and glial cells that make up the ENS from neural crest cells (NCCs) [34], and epigenetic regulation is an essential component of the ENS's operation [35–39].

Studies suggest that the ENS might also have capacities for learning and memory [40–42]. Similar to CNS processes like long-term potentiation (LTP), the ENS exhibits forms of gut-specific habituation and plasticity that allow it to "remember" past gut experiences like inflammation or nutrient exposure, which influence gut function via the gut–brain axis and the vagus nerve [43].

3. Maternal Stress in Pregnant Women

Various risk factors influence the composition of the gut microbiota and MGBA during pregnancy and impact foetal development and long-term health. These factors include nutrition, maternal obesity, infections, medications (antibiotics and antidepressants), environmental toxins (pesticides and pollution), smoking, alcohol, psychological stress (anxiety and depression), genetic (epigenetic) predisposition, and maternal age [44–49]. In addition, prenatal maternal stress responses are complex and multifactorial, they can vary significantly from individual to individual, and they can affect foetal development and later life [50].

Maternal psychological stress (depression and anxiety) that arises during the prenatal period affects millions of pregnant women worldwide each year [51]. Such stress during pregnancy may be a key determinant of foetal development [52,53]. Maternal mental stress may be the most important stressor as it disrupts the development of the foetus, affects its later life, and predisposes it to various diseases. Additionally, gut dysbiosis and dysregulation of the HPA axis in children are linked to maternal psychological stress during pregnancy [54–56].

Pregnancy-related changes may make expectant mothers more vulnerable to mental health issues like stress, anxiety, and depression. Up to 20% of pregnant women may experience depressive symptoms during pregnancy, and 10% have symptoms that fit the criteria for a major depressive disorder [57]. A recent study by Kiyak [58] examined 301 pregnant women and found that 40.9% had symptoms of stress, 52.8% had symptoms of anxiety, and 37.2% had symptoms of depression. Kiyak [58] also showed that pregnancy symptoms and emotion-focused coping are positively associated with depression, anxiety, and stress. In contrast, problem-focused coping is negatively associated.

According to other studies, up to 25% of pregnant women report high levels of stress, which was linked to a higher risk of poor delivery outcomes and poor mental health after giving birth [59,60]. Additionally, pregnant women report similar anxiety to those who had anxiety during childbirth before their first pregnancy [61]. Al-Abri et al. analysed 128 systematic reviews and found that the mean overall prevalence of perinatal depression, antenatal depression, and postnatal depression was 26.3%, 28.5%, and 27.6%, respectively [62].

One in five women suffer from peripartum anxiety disorders, which are more common than previously believed [63]. Thongsomboon et al. examined 403 pregnant women and found that the prevalence of perceived stress symptoms among antenatal pregnant women was 23.6% [64]. Perceived stress symptoms were significantly associated with divorce, separation from one's spouse, physical or psychological trauma from family, marital conflict, and family conflict. Several diverse risk factors play a role in the development of maternal depression and anxiety during pregnancy, such as lack of social support, living alone, marital problems, an unintended pregnancy, having numerous children, age, and a personal or family history of affective disease, which are risk factors for the development of depression during pregnancy [65,66].

Almost 80% of pregnant women have been found to experience varying levels of pregnancy stress [67]. Therefore, early mental health screening plays an important role for health care providers

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in identifying women at risk of adverse pregnancy outcomes. Unfortunately, recent research has suggested that the risk of developing antenatal depression is understated due to the inadequacies of the instruments used [68].

One of the main processes of foetal programming caused by maternal prenatal stress and negative affect is thought to be changes in the structure and function of the foetal brain [69]. Maternal prenatal stress increases cortisol levels and abnormal neurotransmitter signalling, which may interfere with foetal brain development. The HPA is the central stress-response system, and increased cortisol and glucocorticoids cross the placenta and disrupt foetal brain regions such as the hippocampus and amygdale [51]. These disruptions can impair cognitive function, emotional regulation, and later stress resilience. Imaging studies have revealed reduced left hippocampal volume and altered neural connectivity in infants exposed to high prenatal anxiety [70]. On a molecular level, chronic stress modifies DNA methylation patterns in glucocorticoid receptor genes (NR3C1) and predisposes offspring to anxiety and depression [71].

3.1. Stress Before and During Pregnancy and Impact on the Foetus

Before conception and during pregnancy, mothers should reduce stress through various mindfulness, hypnosis, and meditation techniques, such as prenatal yoga, cognitive behavioural therapy, hypnosis, meditation, deep breathing techniques, improving sleep quality, exercise, healthy diet, and lifestyle changes (avoiding smoking, alcohol, and drugs) [51,72–81]. It is also important to build strong social and emotional support (with the partner, family, or groups) and to talk to healthcare providers about overwhelming feelings as stress can impact pregnancy outcomes [72]. Mothers who persistently feel sad, anxious, or overwhelmed should talk to their healthcare providers immediately.

4. IBS as a Hallmark of Psychological Stress in Women

IBS is a prevalent chronic illness of the gut–brain connection, and its hallmarks include recurrent abdominal pain and changes in bowel habits, such as constipation, diarrhoea, or both. According to contemporary epidemiological data, IBS affects about 11.2% of the world's population, making it one of the most common functional gastrointestinal illnesses [82]. Numerous factors have been connected to potential pathophysiological pathways underlying IBS. Examples include genetic and epigenetic factors, compromised immune systems, stress-induced effects on the nervous and endocrine systems, dysregulation of the HPA axis, disorders in the brain-gut axis interaction, dysbiosis, altered gastrointestinal motility, visceral hypersensitivity, infections, food sensitivity, malabsorption of carbohydrates, and abnormalities in serotonin metabolism. Nevertheless, the precise cause of the IBS is still unknown [83–85].

In recent years, the tight connection between psychological factors and IBS has drawn more attention from scientists. Women with IBS report higher levels of psychological distress compared to men [86], and there is a strong association between psychological distress and psychosocial factors in IBS symptoms [87]. Psychological factors seem to play a pivotal role. Anxiety, depression, and stress have high rates of comorbidity with IBS and exacerbate its clinical presentation while perpetuating gut–brain communication disturbances [88]. In particular, women with IBS often exhibit heightened visceral hypersensitivity, dysregulated gut motility, and altered microbiota composition, which may interact with psychological distress and perpetuate symptoms [86].

There is strong evidence that gut bacteria affect the ENS, which could help with brain afferent communication [89]. It is believed that dysregulation of the MGBA in modulating both bowel function and pain perception could be a key factor in the development of IBS [86]. In addition, it seems that psychological comorbidities are more prevalent among pregnant and postpartum patients with IBS [86,90]. In other words, IBS may serve as a hallmark of psychological distress in women.

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5. Fibromyalgia

FM is a chronic syndrome that causes widespread pain all over the body and mainly affects women. The pain is often accompanied by cognitive dysfunction, sleep disturbances, fatigue, and psychiatric symptoms such as anxiety and depression, as well as digestive disorders, including IBS [91,92]. FM is a heritable syndrome with estimated frequency in the general population ranging from 0.5% to 12% [93]. The incidence of FM is 13.6 times higher among first-degree relatives of patients with FM [94]. The exact way that genes are passed down is still unknown, but a polygenic process is the most likely explanation [95].

Triadafilopoulos et al. found that 73% of patients with FM had bowel dysfunction [96]. Recently, a review by Erdrich et al. confirmed previous reports that IBS is common in people living with FM and suggests that the mixed and constipation types of IBS predominate [16]. Cai et al. demonstrated that when germ-free mice received a transplant of the faecal microbiota from patients with FM led to discomfort and a variety of molecular characteristics that are known to occur in patients with FM, such as immunological activation and changes in metabolomic profiles [97]. These effects did not occur with transplants from healthy controls. When the authors replaced the FM microbiota with a healthy microbiota, pain was significantly reduced in mice. More research needs to be done on the link between FM and functional gastrointestinal problems other than IBS [16].

Although the real causes of FM are still unknown, various pathophysiologies have been suggested. It has been hypothesized to stem from a combination of factors, including genetic and environmental factors, physical and emotional trauma, infections, and CNS disorders where the brain and nerves process pain signals abnormally and produce hypersensitivity [98]. Central sensitization is currently considered the key pathological mechanism in FM [99,100].

6. The Strong Relationship Between IBS and FM

The fact that FM and IBS often occur together suggests the possibility that both disorders may share similar pathogenic mechanisms—most notably central sensitization and dysfunction in the MGBA [15–17]. It is probable that systemic symptoms seen in FM may develop later as a consequence of IBS [101]. Berstad et al. examined 1100 consecutive patients with IBS over 9 years and suggested that it may develop earlier on, while systemic symptoms like FM and myalgic encephalopathy (ME) may appear years later [101]. De Palma et al. used the faecal microbiota of healthy controls or patients who had IBS with diarrhoea (IBS-D) with or without anxiety and transplanted it into germ-free mice [117]. They found that transplantation from patients with IBS-D and anxiety altered the gut function and behaviours of the mice, including faster gastrointestinal transit, low-grade inflammation, and anxiety-like behaviour.

In experiments by Lin et al., treatment using faecal microbiota transplantation from healthy donors successfully reduced the anxiety and depressive behaviours of patients with IBS-D [118]. According to Garofalo et al., increasing evidence suggests that dysbiosis may be an upstream mechanism that influences the emergence of symptoms, especially neurological ones, seen in FM and IBS [15]. As shown in Table 1, there is much research supporting the existence of a strong relationship between FM and IBS. A possible explanation is that FM may develop later as a consequence of IBS, and dysbiosis and epigenetics play a key role. When and how FM develops from IBS and with what symptoms depend on several biopsychosocial factors, and personal epigenetic processes may play a key role. Therefore, it is difficult to determine the exact mechanism of FM development as there are significant biopsychosocial differences between individuals.

Table 1. Clinical characteristics and significant overlap of symptoms suggesting that irritable bowel syndrome (IBS) and fibromyalgia (FM) may have a common aetiology.

Both FM and IBS are classified as functional pain syndromes.	[102].
In both FM and IBS, there is altered pain sensitivity	[15].

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In both FM and IBS, there is autonomic nervous system (ANS) dysregulation.	[15,103].
Both FM and IBS are more prevalent in women.	[16].
FM and IBS have common associated factors, such as stress, fatigue, hypersensitivity, pain, depression, and anxiety.	[104].
Gut dysbiosis might be a common leading cause of the onset of both FM and IBS.	[101].
There is high prevalence of IBS in patients with FM, and vice versa. 70% of patients with FM have IBS, and 65% of patients with IBS have FM.	[105].
Increased psychological stress is a key factor for the development of IBS and FM.	[106,107].
Both FM and IBS are characterized by sympathetic dysfunction with central sensitization.	[100,108].
Individuals with both FM and IBS frequently have comorbid psychiatric illnesses (mainly depression and anxiety disorders).	[109,110].
A key physiological similarity is the concept of central sensitization and disturbance of the gut–brain axis in both FM and IBS.	[111,112].
The immunological and inflammatory processes in IBS and FM share similarities, such as initiation of the HPA axis by stress, leading to cortisol release, mast-cell activation, and cytokine dysregulation.	[104].
Drugs and other therapies used for IBS and FM are common for both conditions.	[15].
The intestinal microflora of patients with IBS or FM differs from that of healthy subjects.	[97,113].
Various therapies may reduce symptoms and improve quality of life rather than offer a full recovery from both IBS and FM.	[114–116].

7. Chronic Pain and Childlike Behaviour with FM

We have observed that patients with FM in our clinic often exhibit childlike (infantile) behaviour. We have found that patients with FM are significantly dependent on the outside world, social assistance, and support in every way such that the outside world can compensate for their missing mental and social functions and enable them to exist. They exist in a childlike, helpless state and lack the ability and means to cope. They behave in a more childlike, rule-abiding manner without internal motivation. Their emotional processing is incomplete, and their intellectual integration skills are also at a lower level. Their comprehensive perspective and level of abstract thinking are lower than those of individuals without FM.

7.1. Chronic Pain

Chronic pain is a common and complex illness that is defined by continuous pain lasting more than 3 to 6 months [120,121]. Chronic pain is a common ailment that affects an estimated 20% of individuals worldwide [121]. Around 51.6 million Americans (20.9% of the adult population) had chronic pain in 2021 [122]. Chronic pain can result from an injury, illness, or disease, but in many cases, the cause is unknown.

Each of the several varieties of chronic pain problems has distinct symptoms and traits, and there are numerous risk factors, such as biological, psychological, clinical, and sociodemographic factors

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[123]. According to the biopsychosocial model, chronic pain is a multifaceted experience impacted by social, psychological, and biological aspects rather than merely being a biological problem. In other words, chronic and complex pain syndromes are the outcome of a multifaceted dynamic interaction of physiological, psychological, and social elements that mutually impact one another according to the biopsychosocial approach [124,125].

7.2. Childlike Behaviour in Patients with FM

As mentioned, we noticed that patients with FM in our clinic frequently present childlike behaviour. "Coping" refers to methods—whether conscious or unconscious—for controlling and minimizing negative emotions [126,128]. "Non-conscious coping" refers to automatic, unintentional mental and emotional processes that manage stress and conflict without conscious awareness. According to Galvez-Sánchez et al. [128], FM syndromes are characterized by high neuroticism and low conscientiousness (high impulsivity), negative body image, passive coping strategies, and low self-efficacy. In addition, FM syndrome and other chronic illnesses like chronic fatigue syndrome may be preceded by dysregulation of stress response pathways. Stress pathways may be altered by early maternal (prenatal) stress in human development, which increases susceptibility to stress-related illnesses [128].

We hypothesize that adequate coping cannot develop in the foetus due to non-conscious, non-representational, and primordial stress memory (SLEIM) in the foetal ENS. Furthermore, the CNS does not have access to stress information independently recorded in the foetal ENS, which may be the reason why there has been no way to cure IBS or FM thus far [101]. A lack of adequate coping may cause patients with FM to often present childlike behaviour as they cannot manage chronic pain, which is caused by continuous SLEIM signals from the ENS that disturb the central processes for emotional and pain regulation.

8. Summary

Based on our previous theoretical research [1,2,11], the aim of this study was to highlight the possible role of the maternal ENS in the development of IBS in the foetus in relation to maternal psychological stress (depression, anxiety) during pregnancy. That is, maternal stress can produce SLEIM in the foetal ENS through epigenetic mechanisms that are distinct from those of the CNS, which might persist throughout life. SLEIM during gestation could induce gut dysbiosis, alter microbial metabolites, increase intestinal permeability, and increase the risk of disorders such as IBS in the foetus. SLEIM signals could also be transmitted via the bidirectional MGBA from the embryonic ENS to the CNS, which may cause malfunction of the central affective and pain control systems.

The substantial correlation between FM and IBS is another significant issue. There is strong evidence that FM and IBS are strongly associated (Table 1). Dysbiosis and epigenetics play a significant role in FM, which can arise later due to IBS. When, how, and what FM symptoms develop from IBS can depend on a number of biopsychosocial factors, including individual epigenetic processes. It is difficult to identify the exact mechanism of FM development because there are significant biopsychosocial differences among individuals.

Additionally, patients with FM may exhibit infantile behaviour due to inadequate coping. SLEIM in the ENS prevents the foetus from developing an appropriate coping mechanism. Furthermore, the lack of a remedy for IBS or FM may be due to the CNS's lack of access to stress data independently recorded in the ENS [9,101].

For example, hypnosis [2,129,130] likely affects the central emotional and pain regulations to ease the symptoms and improve quality of life because it allows access to conscious and unconscious CNS processes [131]. Nevertheless, hypnosis cannot stop SLEIM signals produced by maternal stress during the foetal period from being continuously sent from the ENS to the CNS. It is important for mothers reduce stresses that impact foetus development before conception and during pregnancy.

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We suspect that childlike behaviour may occur in both patients with FM and those with IBS. Dąbek-Drobny et al. found a significant effect of personality, perceived self-efficacy, resilience, and coping strategies in patients with IBS [132]. Patients with IBS presented lower levels of adaptive coping skills, a higher level of neuroticism, and lower levels of extraversion, perceived self-efficacy, and resilience than individuals without IBS. According to Torkzadeh et al., compared to control groups, patients with IBS use avoidant and problem-focused coping mechanisms more frequently [133]. Furthermore, the severity of IBS symptoms shows a direct correlation with the use of maladaptive coping strategies. We suggest that in the future, childlike behaviour should also be monitored when examining both patients with FM and those with IBS.

Currently, there is still little experimental and theoretical evidence for our proposed hypothetical model. Nevertheless, the function and role of the ENS, which is associated with numerous diseases, still holds many "surprises" for us, and future research will likely require new approaches since the ENS is evolutionarily much older than the CNS system. However, the knowledge that could be obtained could lead to many possibilities for the treatment of various diseases in the future.

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