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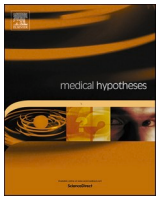

Neuroinflammation as a possible link between attention-deficit/hyperactivity disorder (ADHD) and pain

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) and pathological pain are two complex syndromes of multifactorial origin. Despite their prevalence and broad impacts, these conditions are seldom recognized and managed simultaneously. The co-existence of neuropsychiatric conditions (such as ADHD) and altered pain perception and chronic pain has been noted in children, and the comorbidity of ADHD and chronic pain is well documented in adults. Pathophysiological studies have suggested dysfunction of the dopaminergic system as a common neurochemical basis for comorbid ADHD and pain. Considerable evidence supports the role of neuroinflammation in the pathophysiology of both.

We suggest that central neuroinflammation underlies altered pain perception and pain sensitization in persons with ADHD.

Based on our hypothesis, targeting neuroinflammation may serve as a potential new therapeutic intervention to treat ADHD and comorbid pain in children and adolescents and a preventive strategy for the development of chronic pain in adults with ADHD.

Introduction

The present hypothesis considers the coexistence of somatic and mental health complaints and the relationship between them. In other words, the whole affects the parts just as much as the parts affect the whole. This is in line with a holistic (rather than reductionistic) way of thinking.

Attention-deficit/hyperactivity disorder (ADHD) and chronic pain are complex syndromes of multifactorial origins. ADHD is a neurodevelopmental disorder associated with cognitive, emotional, and behavioral deficits. It is one of the most common psychiatric pathologies, with an estimated prevalence ranging from 5 to 29% in children (depending on country, year of study, and method of diagnosis) [1] and 2–5% in adults [2] worldwide.

Chronic pain is a major health problem that negatively impacts quality of life. In the USA, approximately 100 million people suffer from pain, costing about $600 billion per year in health care and lost productivity [3]. The prevalence of chronic pain is approximately 8% in the general population [4]. In clinics, patients with ADHD report alterations to perceptual functions, particularly impairment of pain perception [5,6]. In turn, chronic pain causes increased impulsivity [7] and induces attentional and cognitive deficits, both in human patients [8,9] and in preclinical animal models of peripheral nerve injuries [10].

Currently, pharmacological treatment of ADHD implies chronic administration of psychostimulants (e.g., methylphenidate), which raises important concerns regarding potentially harmful long-term effects [11,12], including addiction [13] and anxiety [14]. Patients with ADHD also often suffer from coexisting complaints such as social disabilities and emotional deficits [15,16]. Therefore, in line with a holistic vision, elucidating common mechanisms between ADHD and common comorbidities may aid in providing novel therapeutical strategies to also alleviate core and minor symptoms of ADHD itself. Despite their prevalence and broad impacts, ADHD and pain conditions are seldom recognized and managed simultaneously. In general, investigations of ADHD and pain are conducted separately in specialized settings. Improved knowledge regarding the interactions between neuronal circuits underlying cognitive, affective, and pain pathologies is key to developing better treatment strategies and ensuring patient-centered care.

Our hypothesis focuses on an issue that affects the growing

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proportion of children and adolescents who experience deviations from the "average" in regard to both somatic and mental health measures. This hypothesis brings together persistent/chronic pain in combination with a psychiatric syndrome—ADHD. At present, there are no established health care routines for examining psychiatric symptoms when investigating functional pain conditions in a somatic care setting, nor is there any knowledge of offering patients with ADHD or other neuropsychiatric diagnoses adapted treatments for pain conditions. Since ADHD and pain sensitization are mutually worsening neurological and psychiatric disorders, a better understanding of fundamental pathophysiological pathways and their interactions may provide a broadly applicable conceptual framework and subsequent means of therapeutic interventions.

Background to hypothesis

Attention-deficit/hyperactivity disorder (ADHD)

ADHD is a neurodevelopmental disorder that is recognized today by the number and severity of its core symptoms—inattention and hyperactivity/impulsivity [17]. It is a complex and heterogenous disorder that originates in early childhood and continues throughout the lifespan for most people [18]. In adults, untreated ADHD symptoms can lead to lower quality of life and a higher likelihood of developing drug and alcohol abuse [19].

The underlying neurobiological background of ADHD is not yet fully elucidated, but it has been shown to include morphological, functional, and neurotransmitter alterations in the brain. Cortical deficits have been proposed as a hallmark of ADHD pathophysiology. In particular, reduced volume, gray matter density, and cortical thickness have been identified in the prefrontal, frontal, parietal, temporal, and entorhinal cortices [20,21]. The prefrontal cortex is of particular interest for the understanding of the neurobiology of ADHD; several subdivisions have been implicated (e.g., dorsolateral, ventrolateral, and anterior cingulate areas) [22–25]. Neuronal connectivity is also altered in individuals with ADHD. Neuroimaging studies in patients with ADHD have identified structural and functional abnormalities in networks comprising the fronto-striatal, cingulate, fronto-parietal, fronto-cerebellar, and parieto-occipital tracts [26–29]. It was initially proposed that deficits in monoaminergic transmission within the fronto-striatal network were associated with ADHD [30,31]. In fact, several monoamines-related genes have been proposed as potential candidates in the etiology of ADHD [32]. These deficits result in insufficient cortical regulation of subcortical structures. Later, this view was expanded to other regions [33].

Indeed, in addition to cortical abnormalities, ADHD has been linked with early morphological alterations in the subcortical and limbic regions [34]. A major mega-analysis spanning 60 years highlighted key structural differences between the brains of participants with and without ADHD [35]. This study showed bilateral decreased volume in various regions, including the nucleus accumbens, amygdala, caudate, hippocampus, and putamen, with no difference in the volume of the pallidum or thalamus. Interestingly, some alterations showed gender-specific differences (e.g., changes in caudate volume were reported only in male patients with ADHD) [36]. Other studies confirmed that several areas of the limbic system, including the hippocampus [35], amygdala [37], and nucleus accumbens [38], displayed specific structural features in patients with ADHD. At a functional level, it has been proposed that disinhibition of the nucleus accumbens accounts for locomotor hyperactivity [38].

In combination, these data support the roles of the cortical, subcortical, and limbic regions in the hypothesis of delayed brain maturation in patients with ADHD.

Neuropsychological studies have revealed several well-documented differences in executive function and motivation domains between patients with ADHD and healthy control patients [39]. Strong evidence points to dopamine system dysfunction at the onset of ADHD [40]. According to the dopamine theory, children without ADHD experience an immediate anticipatory dopamine signaling, while children with ADHD have a delay. This would explain the sensitivity to a delay in reinforcement—in other words, as seen in preclinical models, children with ADHD choose small immediate reinforcements over large, delayed ones [41–43]. For this reason, ADHD has also been classified as a subtype of a general condition known as Reward Deficiency Syndrome [44,45]. This syndrome is characterized by altered neurotransmitter signaling, resulting in aberrant reward-related behavior [44]. Primarily, the altered neurotransmitter is dopamine. A change in dopamine transfer underlies deficits in attention networks, resulting in reduced learning ability and motivation [46] and increased risk for the development of substance use disorder [47]. For that reason, since oral methylphenidate administration can increase extracellular dopamine in the brain, it is used as a treatment for ADHD [48].

Altered pain perception and chronic pain

Acute pain is often elicited by acute inflammation, and its biological significance is to protect wounded tissue. Nociceptive pain represents a normal response to noxious injury of tissues such as skin, muscles, visceral organs, joints, tendons, or bones. Noxious pain is often initiated in the periphery and follows the ascending pain pathways to cortical areas, where the conscious perception of pain develops. Alterations of these pain pathways may cause hypersensitivity such that pain loses its usefulness as an acute warning system and instead becomes chronic and debilitating. At some level, this can be considered as an extension of the normal healing process, promoting guarding and recovery of the injured area. In some pathological processes, however, this sensitization does not resolve, leading to chronic, pathological pain. Chronic pain may even persist long after the primary cause of the injury has disappeared.

It is important to recognize that there is not one overarching, singular condition called chronic pain; rather, there are multiple etiologies of pain, each resulting from a different pathology and differing in its clinical presentation [49]. Chronic pain is usually subcategorized based on the mechanism of injury. Inflammatory pain results in activation and sensitization of the nociceptive pain pathway by a variety of mediators released at the site of tissue inflammation. Neuropathic pain is caused by damage to the nervous system itself, central or peripheral, either from disease, injury, or pinching. Other types of pain (e.g., cancer pain or dysfunctional pain) are indicated when no biological cause is identified.

It is generally believed that neuronal plasticity of the somatosensory system in response to activity, inflammation, and neural injury results in chronic pain [50]. Neuronal plasticity consists of peripheral sensitization in primary sensory neurons of dorsal root ganglia and trigeminal ganglia [51] and central sensitization of pain-processing neurons in the spinal cord and brain [52]. The International Association for the Study of Pain describes central sensitization as increased responsiveness of nociceptive neurons in the central nervous system to the normal or subthreshold afferent input [53]. Central sensitization first referred to the process through which a state of hyperexcitability is established in the central nervous system, leading to enhanced processing of nociceptive (pain) messages [54]. Persistent nociceptive input leads to the increased release of neurotransmitters, neuropeptides, and growth factors from the primary afferent central terminals in the spinal cord and trigeminal nucleus. Through signal transduction, these neurotransmitters induce a state of neuronal hyperactivity and hyperexcitability in the spinal cord and brain, known as central sensitization [55]. More recently, central sensitization was characterized as increased synaptic efficacy in the dorsal horn of the spinal cord following intense peripheral noxious stimuli, tissue injury, or nerve damage [56]. The current definition is broader, and central sensitization is now defined as enhancement of the function of neurons and circuits in nociceptive pathways caused by increases in membrane excitability and synaptic efficacy [57]. Therefore, central sensitization may also include conditions like

increased central responsiveness due to dysfunction of the endogenous pain control system (e.g., reduced inhibition [58–59] and glial-neuronal interactions [3,60].

Coexistence of altered pain perception/pathological pain and ADHD

Individuals with severe ADHD are more likely to have a greater symptom burden, greater functional impairment, and several psychiatric co-morbidities [61], such as anxiety and mood and/or antisocial personality disorders [62–64]. In a 2016 national parent survey, the US Centers for Disease Control and Prevention identified frequent concomitant disorders that accompanied ADHD [65]. Their study showed that two thirds of children diagnosed with ADHD also suffered from mental, emotional, or behavioral disorders [65]. Interestingly, recent studies have indicated an association between attention deficits and altered sensory processing [66,67]. Attentional processes have been shown to regulate pain transmission through the modulation of brain networks [68] and descending pathways [69,70]. A high prevalence of neuropsychiatric conditions, including ADHD, has been documented in children and adolescents with chronic pain [71]. Rare yet existing evidence suggests interplay between pain perception and the manifestation of ADHD in children and adolescents [72–74]. Clinical studies have reported a high prevalence of pain among adults with ADHD, suggesting an increased risk of pain disorder in patients with ADHD [75–79]. Moreover, recent clinical studies have highlighted the link between childhood ADHD and an increased risk of developing chronic pain in adulthood [80]. The increasing use of stimulants and opioids were associated with the diagnosis of pain in patients with ADHD, putting this population at risk with regard to the current opioid crisis [81]. ADHD is also highly comorbid with other psychiatric conditions (e.g., anxiety and depression) [82], which, in turn, are strongly associated with pain [83]. These disorders may contribute to pain sensitization but are not sufficient to fully explain the development of pain pathologies in ADHD patients [79]. Conversely, chronic pain causes cognitive impairments and worsens ADHD symptoms in humans [8,9,84,85] and animal models [10]. As ADHD is frequently underdiagnosed [86–88], this co-morbidity represents an important issue for pain specialists.

Numerous experimental studies, as well as clinical observations, have provided strong evidence that cognitive (particularly attention-related) tasks are highly effective in modulating the pain experience, demonstrating how cognitive processes can interfere with pain perception [69,89]. Various neuroanatomical structures are at the crossroads of cognition and pain processing in the brain. Studies on attentional control of pain demonstrated that the responsiveness of neurons in primary somatosensory cortices (S1 and S2) to both nonpainful and painful stimuli is altered by the direction of attention in monkeys [90] and humans [91]. An opiate-sensitive descending pathway from the frontal cortex to the amygdala, periaqueductal grey matter, rostral ventral medulla, and spinal cord dorsal horn may also be involved in attentional and/or emotional modulation of pain [70,92]. Several areas of the brain that are involved in ADHD physiopathology also subserve the influence of affectivity on pain processing. The amygdala is a key neural substrate for pain integration in the brain [93–96] and may be at the crossroads of ADHD pathophysiology and pain processing [37,97]. Reciprocal connections exist between the amygdala and the entorhinal cortex and could jointly influence ADHD symptoms and the modulation of pain [21,98]. The cingulate cortex is involved in sustained attention and the psychopathology of ADHD [25,99,100], and it is also a central hub [101] for both the sensory-discriminative [102,103] and emotional components of pain [104–106].

Dysfunction of the thalamo-cortical ascending pathways is also implicated in comorbidity between pathological pain and psychiatric disorders. Indeed, the thalamocortical dysrhythmia model—which proposes that specific oscillatory pattern alterations underlie both neurological (Parkinson's disease, tinnitus, neuropathic pain) and psychiatric (depression) syndromes [107,108]—has long been accepted. Furthermore, recent studies based on this model have confirmed that an imbalance in the oscillatory patterns between descending pain inhibitory pathways and ascending pain pathways exists in patients with chronic pain [109]. Interestingly, the treatment with antidepressant desvenlafaxine (which targets the serotine and norepinephrine systems) were found to reduce pain symptoms compared to placebo controls, possibly due to decreased functional connectivity in the thalamo-cortical-periaqueductal pathway [110].

The reward systems, and particularly the nucleus accumbens, are also implicated in alterations of partially overlapping circuits (e.g., between the nucleus accumbens and the caudate putamen) controlling both ADHD symptoms [38] and pain processing [111,112]. Reduced nucleus accumbens activity underlies alterations of reward circuits [113] and pain-induced negative affect [114]. Impairment of nucleus accumbens activity has also been proposed as a signature of chronic pain states [115]. The reward system being controlled by dopaminergic innervation, it is interesting to notice that also in healthy humans, polymorphisms in dopaminergic pathway genes are associated to increased pain perception [159].

Decreased brain dopamine levels, especially in the frontal and prefrontal cortices, are often associated with pain sensitization [69,116] and the etiology of ADHD [117,118]. Therefore, lesions of the dopaminergic system are of great interest for modeling ADHD in preclinical animal models. Accordingly, neonatal intracerebroventricular injection of 6-hydroxydopamine (6-OHDA) in rodents [119] generates ADHD-like animal models that display good face and predictive validity. One preclinical study demonstrated that neonatal dopamine depletion in rats caused a hyperalgesic behavioral response (specifically to tonic chemical stimuli) and motor hyperactivity during adolescence [120]. We recently developed this 6-OHDA lesion model in mice and proposed a comprehensive assessment of ADHD-like symptoms [121,122]. Interestingly, the 6-OHDA mouse model also exhibited changes to pain sensitivity for both basal and inflammatory pain conditions. These studies confirmed that developmental alterations of dopaminergic transmission may disrupt overlapping brain circuits involved in pain transmission and ADHD-like physiopathology. They further suggest possible interactions between these comorbid pathologies and offer the opportunity to manipulate neuronal circuits in animal models to test this hypothesis.

Neuroinflammation as a link between ADHD and pain sensitization

Neuroinflammation is associated with a broad range of psychiatric disorders, including depression [123], schizophrenia [124], bipolar disorder [125], and post-traumatic stress disorder [126].

As previously described, the pathophysiology of ADHD is still poorly understood. Evidence from human studies and animal models, while still incomplete, support the potential role of oxidative stress and neuroinflammation [127–129], especially during early neurodevelopment [130]. Epidemiological studies, including meta-analyses, have revealed that patients with ADHD are more likely than control patients to suffer from well-known inflammatory conditions such as asthma, allergic rhinitis, atopic dermatitis, and allergic conjunctivitis [128,131–133]. Moreover, maternal inflammatory status (eg obesity, asthma, autoimmune disease, infection and psychosocial stress) can trigger the incidence of neurodevelopmental diseases, including autism spectrum disorder and ADHD in offspring [134]. This is in line with intergenerational psychiatry hypothesis suggesting that the mental problems observed in children are rooted in the exposure to adversity in the previous generation [135]. One prospective study with more than 23,000 participants revealed that a maternal history of autoimmune disease was associated with an increased risk of ADHD [136]. Other observational data point to a strong association between ADHD and inflammatory and autoimmune disorders [132,133]. Neuroinflammation is associated with increased reactive oxygen species. Neurons are considered particularly vulnerable to oxidative damage, as

they have a comparatively high oxygen utilization [137]. Elevated maternal expression of the pro-inflammatory cytokine interleukin (IL)-13 has been linked to the occurrence of ADHD [138]. Pro-inflammatory cytokines also regulate beside tryptophan metabolism the dopaminergic pathways [139]; therefore, neuroinflammation could play a role in dopamine deficits.

In summary, neuroinflammation involves glial activation, increased oxidative stress, and altered neurotransmitter metabolism [128].

Several reports have also indicated the role of neuroinflammation in pain [140]. Acute inflammation, which generally results in the perception of pain, serves an important protective and/or survival role by removing harmful stimuli, initiating the healing process, and restoring tissue integrity [141]. Thus, acute inflammation induces acute pain sensitization; this phenomenon is mostly peripheral. However, chronic neuroinflammation alters neural networks in the central nervous system and triggers central sensitization [109,141]. In turn, central sensitization processes may also affect partially overlapping circuits that underlie different neurological functions [3,142].

Pro-inflammatory mediators released by activated microglia contribute to hypersensitivity to pain and provoke central sensitization. This has been particularly well studied in the spinal cord [60,143]. Pro-inflammatory cytokines, including IL-1β, IL-6, and tumor necrosis factor-α, have been shown to accelerate pain sensitization, while inhibitors of these cytokines reduce neuropathic pain [144]. The microglial inhibitor minocycline also decreases hypersensitivity to pain in a number of different models, including burns, spinal cord injuries, and chronic constriction lesions [145]. In addition, treatment of pain with cytokine inhibitors shows encouraging results in patients [141]. Interestingly, beyond the spinal cord, numerous pain-related areas of the central nervous system that are also implicated in ADHD (e.g., the cingulate cortex [146] and nucleus accumbens [114,147] are often altered by neuroinflammation.

Furthermore, dysfunction of the dopaminergic system has been shown to contribute significantly to the development of neuroinflammation [148]. For example, dopamine affects the ability of microglia to secrete cytokines [149], and dopamine receptor activation directs the shift toward specific microglial pro-inflammatory phenotypes, a phenomenon at the origin of inflammatory processes [150]. The current evidence suggests that high dopamine levels stimulate the low-affinity dopamine receptors, inducing an anti-inflammatory effect in microglia, while low dopamine levels selectively stimulate the high-affinity dopamine receptors, triggering inflammation [151].

The hypothesis

We suggest a link between altered pain perception and a higher risk of developing chronic pain in ADHD, and we propose that this link is neuroinflammation. This may also open possibilities to develop new treatment strategies.

The previously described relationships between lifelong ADHD, altered pain perception, the development of chronic pain, and the common inflammatory pathologies behind ADHD and pain conditions led us to the formation of this hypothesis (Fig. 1).

Our hypothesis includes two stages. First, we make the hypothesis that pain and ADHD are commonly associated. This has been suggested by several studies, especially in adults with ADHD, but not yet unambiguously established and still debated for children. Importantly, the underpinning mechanisms have not been studied also far. The second stage of our hypothesis is that neuroinflammation is at the origin of ADHD and pain comorbidity. We propose that the persistence of neuroinflammatory processes leads to the development of ADHD and comorbid pain sensitization. Neuroinflammation triggers neuronal dysfunction in cortical, subcortical, and/or limbic structures that, in turn, may impair circuits involved in social cognition, impulse control, and attention. These areas overlap with those involved in pain processing. Furthermore, from a neurochemical perspective, neuroinflammation has the capacity to disrupt dopaminergic regulatory circuits and a dysfunctional dopaminergic system could explain the concomitance of ADHD and altered pain processing.

We have excluded other neurodevelopmental psychiatric conditions potentially coupled to dopaminergic dysfunction and altered pain procession such as the Autism Spectrum Disorder (ASD), mainly for two reasons. Firstly, the role of dopamine in ASD is not yet clearly established, as some authors propose hyperactivity while others propose hypoactivity of dopaminergic pathways [152]. Moreover, beside dopamine alterations, several other important neurochemical alterations

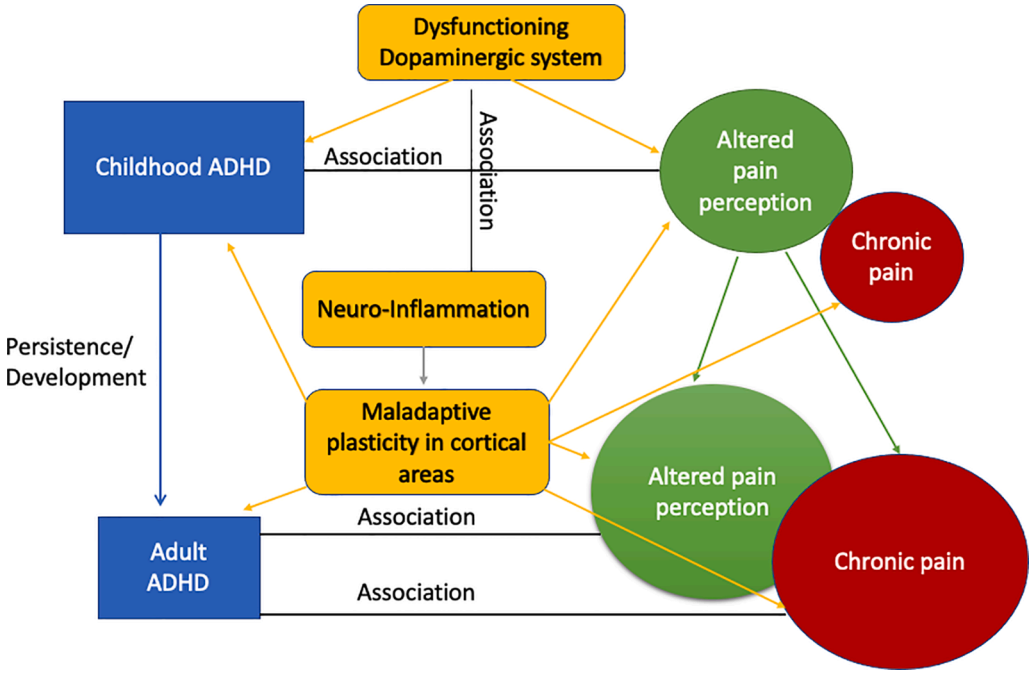

Fig. 1. A summative schematic representation of the previously described relationships between ADHD, pain, and neuroinflammation that form the basis of our hypothesis.

(GABA and glutamate, serotonin, N-acetyl aspartate, oxytocin and arginine-vasopressin, melatonin, vitamin D, orexin, endogenous opioids, and acetylcholine) are associated to ASD [153]. Secondly, regarding the pain comorbidity, although increased autism traits have been reported in children with chronic pain [71], patients with ASD most often show hypoalgesia. Furthermore, in a recent study no systematic dysfunction of pain modulation could be detected in adults with ASD compared to matched control participants [154]. Therefore, our hypothesis remains focused on ADHD and pain, proposing that dopamine-dependent neuroinflammatory processes in specific brain areas lead to these comorbid pathological conditions. Consequently, our hypothesis also suggests that early targeting of neuroinflammation may result in decreased phenotypic manifestation of inattention, impulsivity, and increased pain sensitivity while also contributing to the prevention of chronification of these pathologies (such as chronic pain disorders and adult ADHD).

Evaluation of the hypothesis

In support of our hypothesis, it is well accepted that attention and pain are intimately related. Attention can modulate pain perception; this is demonstrated by studies in which subjects who were engaged in a task requiring attention perceived less pain to the same stimulus than subjects not doing such a task [69]. Contrarily, (chronic) pain reduces attention span [9]. In humans, recent evidence indicates that the presence of ADHD alters (increases) pain perception [76], and the prevalence of generalized pain is higher in patients with ADHD (up to 80%) than in control patients (17%) [75]. Interestingly, methylphenidate treatment for ADHD (stabilizing the dopaminergic function) can partially reduce nociception in adults [6]. To date, while an increased prevalence of ADHD symptoms has been found in children with chronic pain [71], sparse and inconsistent findings exist regarding the alteration of pain perception in children with ADHD.

Moreover, neuroinflammation has been reported as a common denominator for the co-occurrence of pain and depression, and other psychiatric condition (for review, see [155]). Therefore, it is safe to speculate that neuroinflammation may be implicated in pain concomitant with ADHD.

A distinctive aspect of neuroinflammation is the activation of glial cells that results in the release of pro-inflammatory cytokines. Several reports have indicated that elevated levels of central cytokines can induce hyperalgesia and allodynia by sensitization—that is, increase the neuronal response of specific pathways involved in pain perception [156]. Sensitization is driven by changes in synaptic plasticity. Neuroinflammation is a strong modulator of synaptic plasticity [157], inducing synaptic loss [158].

Thus, this evidence supports that neuroinflammation affecting synaptic function is a risk factor for the development of ADHD symptoms and altered pain perception, leading to chronic pain.

Consequences of the hypothesis and discussion

Posner et al. [18], upon reviewing recent major discoveries about ADHD, emphasized the need for new knowledge about the pathophysiology of ADHD—inviting innovative thoughts and hypotheses challenging our current ways of thinking about ADHD, which may give rise to new and potentially more effective clinical treatment strategies.

The implications of our hypothesis in science and health advances would have an impact on patients with ADHD and pain.

Based on our hypothesis, targeting neuroinflammation would be a new potential therapeutic intervention in patients with ADHD and comorbid pain as well as a preventive strategy for adults with ADHD to avoid developing chronic pain.

The hypothesis must be proven utilizing preclinical and clinical means. To do that, the experimental work will resolve the following: 1) The association between altered pain perception and ADHD needs to be specified in patients stratified by gender, ADHD type, and age (separating children and adolescents). 2) As ADHD commonly occurs alongside other psychiatric conditions, it is necessary to define whether (and how) comorbid conditions (and which ones) may alter the relationship between pain and ADHD. 3) Studies must demonstrate unquestionably that (neuro)inflammation etiology underlies ADHD and coexisting altered pain perception. 4) Cellular and molecular studies should focus on the relationship between neuroinflammation and synaptic plasticity in the dopaminergic connections and neuronal mechanisms involved in ADHD and pain. 5) The effects of anti-inflammatory substances on symptoms of ADHD and altered pain perception and central sensitization should be tested at the cellular, molecular, and clinical levels.

A better understanding of the fundamental pathophysiological pathways of ADHD and pain, their interaction, and their links with neuroinflammation may provide a broadly applicable conceptual framework and subsequent means of new therapeutic interventions.

Consent statement/Ethical approval

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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