**UNIVERSITÀ DI PADOVA**

**Department of General Psychology**

Bachelor's Degree Course in
Techniques and Methods in Psychological Science (TEMPS)

# ADHD from a Psychoneuroimmunology Perspective: The Role of Chronic Stress and Neuroinflammation

Final Dissertation

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Academic Year 2024/2025

# ACKNOWLEDGEMENT

First and foremost, I offer my deepest and most enduring gratitude to my parents. You have sacrificed everything for my siblings and I, giving up your own comfort, dreams, and time so that we could chase ours. Your strength is the foundation upon which this work, and my entire life, has been built. It is because of you that I now find myself in rooms, at tables, and among opportunities I could have only once dreamed of. Every page of this thesis is a tribute to your resilience, love, and unwavering belief in me.

Moreso, to my girlfriend, thank you for being present with me throughout this journey. Your love made the difficult days feel lighter and the good days even more meaningful. You understood the weight of this work, and you supported me without hesitation. Your faith in who I am and who I am becoming shaped the way I carried myself through this process. This achievement is yours as much as it is mine. I appreciate you, deeply.

To my friends, thank you for being the family I chose along the way. Your humor, encouragement, and companionship made even the most challenging days bearable. From late-night talks to shared laughter and gentle reminders that life exists beyond deadlines, you've each added light to this chapter of my life in your own unique way.

I would also like to express my sincere gratitude to **Dr. Elisabetta Patron**, my thesis supervisor, for her guidance, precision, and patience throughout this work. Her feedback not only strengthened this thesis but also helped me grow as a researcher and as a thinker.

My appreciation also extends to **Dr. Laura Miola**, my internship supervisor, whose support and insight enriched my professional development during this academic journey.

Finally, to the University of Padova and the Department of General Psychology, I extend my heartfelt appreciation for providing an environment that fostered growth, curiosity, and intellectual discovery. The professors, mentors, and colleagues I have encountered here have inspired a lifelong commitment to learning and empathy.

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# ABSTRACT

Attention-Deficit/Hyperactivity Disorder (ADHD) is typically conceptualized as a neurodevelopmental condition marked by persistent inattention, hyperactivity, and impulsivity. While cognitive and neurochemical models have advanced understanding and treatment, they do not fully explain the marked variability in symptom expression, emotional dysregulation, or inconsistent treatment outcomes. Emerging evidence suggests that biological responses to chronic stress may play a meaningful role in these patterns.

Drawing on psychoneuroimmunology (PNI), this thesis examines how chronic stress–related immune activation interacts with dopaminergic systems implicated in ADHD. Particular focus is placed on hypothalamic–pituitary–adrenal (HPA) axis dysregulation, altered diurnal cortisol secretion, and elevations in pro-inflammatory cytokines such as IL-6, TNF-α, and CRP. These pathways may disrupt prefrontal and striatal dopamine signaling, contributing to attentional difficulties and emotional dysregulation.

Integrating current evidence from stress physiology, neuroimmunology, and dopamine research, this work proposes that ADHD can be understood, in part, as a pattern of allostatic dysregulation, in which chronic stress and low-grade inflammation reinforce neural vulnerability. This perspective highlights the relevance of neuroimmune markers for explaining symptom heterogeneity and suggests potential benefit in extending ADHD management to include approaches that target stress regulation and inflammatory processes.

# INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most frequently diagnosed neurodevelopmental disorders, particularly in children and adolescents. It is typically characterized by persistent patterns of inattention, hyperactivity, and impulsivity that impair academic, emotional, and social functioning. However, despite decades of research and treatment advancement, important questions remain unanswered. Why do symptoms vary so significantly between individuals? Why do some patients show poor or inconsistent responses to treatment? And why does emotional dysregulation persist even after improvements in attentional control?

These gaps point to a fundamental limitation in how ADHD is typically understood. Dominant cognitive and behavioral models often neglect how environmental and physiological stressors—such as chronic emotional strain, early adversity, or inflammation—interact with neurodevelopmental vulnerabilities to influence symptom trajectories. Psychoneuroimmunology (PNI) offers a broader lens by examining the complex interactions between the brain, immune, and endocrine systems under stress. Recent research suggests that neuroinflammatory responses may interfere with dopaminergic signaling, contribute to cognitive fatigue, and intensify emotional reactivity—all features commonly seen in ADHD and often resistant to standard treatment approaches.

**Research problem**

While research into PNI has expanded in fields like depression and PTSD, **ADHD has received far less attention** from this perspective. Yet individuals with ADHD show evidence of altered stress responses, HPA axis dysregulation, and systemic inflammation—pointing to biological pathways that may be central to symptom development and variability.

**Research Objective**

This thesis aims to address this gap by investigating how chronic stress and neuroimmune dysregulation—particularly neuroinflammatory signaling—affect the dopaminergic systems underlying ADHD symptoms. The central objective is:

> To examine, through a PNI framework, how chronic stress–driven immune activation (e.g., IL-6/CRP elevation and altered cortisol rhythms) affects dopaminergic signaling and contributes to emotional and attentional dysregulation in ADHD.

**Research question.**

Does chronic stress–induced immune activation, indexed by alterations in cytokine levels (e.g., IL-6, CRP) and diurnal cortisol patterns, contribute to dopaminergic dysfunction and subsequent emotional and attentional dysregulation in individuals with ADHD?

**Hypothesis.**

Chronic stress and low-grade systemic inflammation are associated with dysregulated dopaminergic signaling and greater emotional and attentional impairment in ADHD. Individual differences in stress reactivity are expected to contribute to symptom heterogeneity.

# CHAPTER 1: Understanding ADHD - Background and Theoretical Models

## 1.1 Defining ADHD: A Neurodevelopmental Disorder

### 1.1.1 Overview of ADHD

It often begins as a pattern, subtle at first: a mind that races from thought to thought, unable to settle, or a body driven by an irresistible urge to move, speak, or act, even when stillness is expected. For some, it shows up as frequent forgetfulness, losing track of a conversation or misplacing important details. For others, it's the difficulty of following through—starting multiple tasks with enthusiasm, only to leave them unfinished. What may outwardly look like disorganization, carelessness, or even defiance stems from something deeply rooted: a neurodevelopmental condition known as Attention-Deficit/Hyperactivity Disorder, or ADHD.

ADHD is one of the most commonly diagnosed neurodevelopmental conditions seen in individuals of all ages. The symptoms of ADHD vary widely from person to person in both severity and presentation, but the core difficulties usually involve challenges in attention regulation, impulse control, and activity levels (American Psychiatric Association, 2013). These patterns extend beyond behavior and reflect underlying differences in brain development, emotional regulation, and how people interact with their environment (Thapar et al., 2013).

#### 1.1.1a Functional Neural Circuits in ADHD

Research using brain imaging has found that individuals with ADHD often show structural and functional alterations in both **cortical and subcortical** brain regions involved in executive functioning, reward processing, and motor regulation (Castellanos & Proal, 2012). These include the **prefrontal cortex**, which is responsible for attention control, planning, and inhibition; the **basal ganglia**, which play a central role in initiating movement and evaluating reward; the **anterior cingulate cortex**, linked to decision-making and emotional regulation; the **cerebellum**, which contributes to coordination and timing of both physical and cognitive processes; and the **corpus callosum**, which enables communication between the brain's hemispheres.

The brain regions implicated in ADHD are functionally organized into large-scale circuits that support key cognitive and behavioral processes. These include the **fronto-striatal circuit**, which governs response inhibition and motor control; the **fronto-cerebellar circuit**, which supports timing and coordination; and the **reward circuit**, which regulates motivation and delay gratification. Additional involvement of the **attentional network** and the **executive function**

**system** links ADHD to deficits in sustained focus, task-switching, and working memory (Castellanos & Proal, 2012).

As shown in Figure 1, these circuits involve key brain structures such as the prefrontal cortex, basal ganglia, cerebellum, parietal lobes, and corpus callosum.

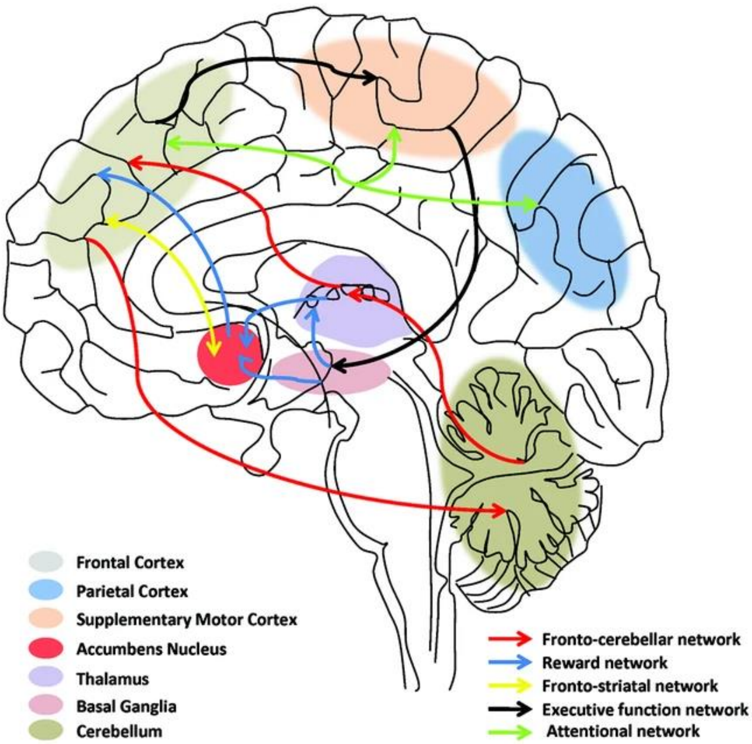


***Figure 1:*** *Functional circuits involved in ADHD pathophysiology. The diagram illustrates key networks: attentional (green), fronto-striatal (yellow), executive function (black), fronto-cerebellar (red), and reward (blue). Affected brain regions include the frontal and parietal cortices, basal ganglia, cerebellum, hippocampus and corpus callosum. Adapted from Purper-Ouakil et al. (2011).*

ADHD is also associated with dysregulation of catecholaminergic neurotransmitters, particularly dopamine and norepinephrine. These neurotransmitters help regulate arousal, attention, and motivation. Dopamine, for instance, is central to reward-based learning and delay gratification, while norepinephrine influences alertness and responsiveness to stimuli (Arnsten, 2009; Volkow et al., 2009). Alterations in these systems may result in the observed difficulty with sustaining attention, and preference for immediate rewards, which are commonly seen in individuals with ADHD.

These neurobiological features offer an important insight into the underlying mechanisms of ADHD. However, even with these findings, ADHD remains a complex condition that cannot be fully understood through brain imaging or neurotransmitter imbalances alone. The clinical presentation is highly heterogeneous, and symptoms may shift in the form or intensity overtime, influenced by factors such as stress exposure, environmental demands, and developmental stage which will be elaborated in the next chapters (Biederman et al., 2010; Thapar et al., 2013).

### 1.1.2 Diagnosis and DSM-5 Criteria

The diagnosis of ADHD is based primarily on clinical evaluation rather than biological tests. According to the **Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)**, ADHD is characterized by the presence of symptoms in two core domains: **inattention** and **hyperactivity-impulsivity**. For a formal diagnosis, children must exhibit **at least six symptoms** from either or both domains, persisting for **a minimum of six months**, to a degree that is inconsistent with developmental level and that negatively impacts social, academic, or occupational functioning. In adolescents aged 17 and older, **only five symptoms** are required. Additionally, several symptoms must have been present **before the age of 12**, and the presentation must not be better explained by another mental disorder, such as anxiety, mood disorders, or autism spectrum disorder (American Psychiatric Association, 2013; Barkley, 2015).

Clinicians typically rely on **multiple sources of information** to assess ADHD, including clinical interviews, behavioral observations, and standardized rating scales. For example, **Conners' Rating Scales** are questionnaires used to assess behavioral symptoms of ADHD and related issues like oppositional behavior, anxiety, and mood dysregulation. These scales are often completed by parents and teachers to capture behavior across different settings. Similarly, the **ADHD Rating Scale-IV** is a widely used instrument aligned with DSM criteria, used to quantify the frequency of inattention and hyperactivity symptoms. These tools provide standardized scores that can support diagnosis but must be interpreted within the broader clinical context (DuPaul et al., 2016).

The DSM-5 also distinguishes between three clinical presentations of ADHD:

- **Predominantly Inattentive Presentation**: Individuals may appear forgetful, easily distracted, disorganized, or mentally "elsewhere," often failing to complete tasks or follow instructions.
- **Predominantly Hyperactive/Impulsive Presentation**: Individuals may fidget, talk excessively, interrupt others, or struggle with waiting their turn.
- **Combined Presentation**: A mix of symptoms from both domains is present.

These presentations are not fixed and may shift over time. For example, a child initially diagnosed with hyperactive/impulsive symptoms may, as they grow older, transition to a predominantly inattentive profile. This shifting presentation reflects both developmental changes and the influence of environmental demands (Willcutt, 2012).

In addition to the DSM-5, the **International Classification of Diseases, 11th Revision (ICD-11)** also provides diagnostic criteria for ADHD. While similar in structure, ICD-11 uses the term "**attention deficit hyperactivity disorder**" but places a slightly greater emphasis on developmental and contextual factors. National health systems may adapt or modify these criteria, which can result in variation in how ADHD is diagnosed across countries. For instance, some European countries use narrower criteria or emphasize comorbidities more heavily, which influences both diagnosis rates and treatment approaches.

### 1.1.3 ADHD as a Spectrum condition

Although ADHD is traditionally categorized into distinct subtypes—**predominantly inattentive**, **predominantly hyperactive/impulsive**, and **combined**—growing evidence suggests that it may be more accurately conceptualized as a **spectrum condition**. This perspective reflects the wide variability in symptom type, severity, age of onset, and functional impact (Faraone et al., 2015; Thapar & Cooper, 2016). For example, two individuals with the same diagnosis might differ significantly in attention regulation, emotional reactivity, or executive functioning. These differences suggest that ADHD is not a single uniform disorder, but rather a cluster of symptoms that exist along a continuum (Nigg et al., 2020).

This variability complicates both diagnosis and treatment. While some individuals show stable symptom patterns over time, others experience shifting presentations, especially during key developmental stages such as adolescence or adulthood. Such changes are not random; they often occur in response to environmental pressures, emotional stress, or physiological changes. For instance, a child with primarily hyperactive symptoms may evolve into an adolescent or adult whose difficulties center around disorganization, distractibility, or emotional impulsivity (Willcutt, 2012; Franke et al., 2018). These developmental shifts can make it harder to track ADHD across the lifespan using static categories.

From a **psychoneuroimmunology (PNI)** perspective, chronic stress and immune system dysregulation are potential contributors to this heterogeneity. These systems are deeply interconnected with brain development and emotional regulation, which suggests that variability in stress exposure or immune functioning may partly explain why ADHD can look so different from person to person. For example, early exposure to environmental adversity or prolonged stress may affect how symptoms develop and persist across life stages (Castellanos & Proal, 2012; Saccaro et al., 2021).

A more detailed exploration of these underlying mechanisms will be presented in the following chapter, with a focus on their neurobiological, immunological, and psychophysiological contributions to ADHD's heterogeneity.

### 1.2 Theoretical Models of ADHD

#### 1.2.1 Classic Cognitive Models

Several traditional theories have shaped our understanding of ADHD. The **Executive Dysfunction Model** emphasizes impairments in working memory, planning, and inhibitory control, which are believed to stem from underdeveloped prefrontal cortical circuits (Barkley, 1997). The **Delay Aversion Theory** suggests that individuals with ADHD have an increased sensitivity to delay, leading them to prefer immediate over delayed rewards, even when the latter may be more beneficial (Sonuga-Barke et al., 1992). The **Dopamine Deficit Hypothesis**, one of the most widely studied biological models, proposes that disruptions in dopaminergic pathways—particularly in the prefrontal cortex and striatum—underlie core symptoms such as inattention and impulsivity (Volkow et al., 2009). While these models differ in scope, they all contribute valuable insights into ADHD's cognitive and neurobiological features. Readers interested in a more detailed overview of these theories are encouraged to consult comprehensive reviews such as Thapar et al. (2013) and Barkley (2015).

#### 1.2.2 PNI-Based Theoretical Models of ADHD

While ADHD has long been understood through behavioral and cognitive models, newer approaches grounded in **psychoneuroimmunology (PNI)**—or **psychoneuroendocrinoimmunology** (PNEI)—offer a broader and more biologically integrated perspective. PNI is the study of how the **nervous system (the brain and nerves)**, the **endocrine system (hormones like cortisol)**, and the **immune system (especially the inflammatory responses)** interact with each other, especially under conditions of chronic stress. These systems are deeply interconnected and capable of influencing behavior, cognition, and emotional regulation, therefore,disruptions in one system can lead to dysregulation in the others.

Applying this framework to ADHD suggests that symptoms like inattention, impulsivity, and emotional dysregulation may not just result from neurological or behavioral causes alone, but also from chronic imbalances in the body's stress and immune responses. In this section, two key

PNI-based models are explored: the **Allostatic Load Model**, which focuses on how chronic stress biologically "wears down" the body and brain, and the **Neuroimmune Dysregulation Model**, which examines how inflammation and immune overactivation may influence ADHD symptoms.

### The Allostatic Load Model

The Allostatic Load Model describes how the body adapts to stress through a process called *allostasis*—the ability to maintain stability through change. In the short term, stress activates protective systems like the hypothalamic-pituitary-adrenal (HPA) axis, which releases cortisol, a hormone that helps the body respond to challenges. This process is normal and adaptive.

However, when stress is chronic—due to social, emotional, or environmental pressures—the body's stress systems remain activated for too long. This leads to allostatic load, which refers to the cumulative biological burden exacted on the body and brain over time (McEwen & Stellar, 1993). In children and adolescents with ADHD, repeated exposure to stressors may increase physiological vulnerability to stress.

This chronic activation of the HPA axis can disrupt the normal rhythm of cortisol secretion. Studies have found blunted or erratic cortisol levels in some individuals with ADHD, which may reflect a malfunctioning stress response system (Saccaro et al., 2021). Cortisol imbalance affects several brain regions, including the prefrontal cortex, responsible for attention and impulse control; the amygdala, involved in emotion processing; and the hippocampus, which plays a role in memory and stress regulation. These alterations may contribute directly to core ADHD symptoms like poor emotional control, difficulty focusing, and impulsivity (O'Connor et al., 2014).

While the Allostatic Load Model was not developed specifically for ADHD, it offers a compelling explanation of how persistent stress can lead to physiological changes that impact cognitive functioning and self-regulation—two of the most affected domains in ADHD.

### The Neuroimmune Dysregulation Model

The **Neuroimmune Dysregulation Model** focuses on how chronic stress affects the immune system. Under conditions of prolonged stress, immune cells begin releasing **pro-inflammatory cytokines**, such as **interleukin-6 (IL-6)**, **tumor necrosis factor-alpha (TNF-α)**, and **C-reactive protein (CRP)**. These molecules are part of the body's defense system, but in excessive amounts, they can become harmful—especially to the brain (Leffa et al., 2018). In fact, these cytokines are capable of crossing the blood-brain barrier and influencing brain function. When they reach the brain, they can interfere with dopamine and norepinephrine activity (Del Campo et al., 2011). Disruptions in these systems can impair working memory, attention regulation, reward processing, and emotional stability—all of which are key areas of dysfunction in ADHD (Chang et al., 2021; Cortese et al., 2019).

What makes this model especially relevant is that neuroimmune dysregulation can begin early in development. For instance, exposure to maternal stress during pregnancy, early childhood trauma, or even infections may "prime" the immune system to react more aggressively later in life. Once primed, the body may overproduce inflammatory cytokines in response to minor stressors, increasing vulnerability to ADHD symptoms or worsening their severity (O'Connor et al., 2014). This may also help explain the high rate of comorbidity between ADHD and disorders like anxiety, depression, and autoimmune conditions.

These immune-driven changes are not only about inflammation—they reshape how the brain functions over time. For example, inflammation can reduce neuroplasticity (the brain's ability to adapt), affect the development of critical white matter pathways, and disrupt synaptic communication in areas responsible for planning, reward, and self-monitoring. As a result, neuroimmune dysregulation becomes a self-reinforcing loop: stress increases inflammation, which worsens brain function, which then leads to greater dysregulation of behavior and emotion (Saccaro et al., 2021).

## CHAPTER 2: Biological Mechanisms : The "Stress–Neuroinflammation–ADHD" Cycle

### 2.1 The Psychoneuroimmunology of ADHD

#### 2.1.1 Overview of Psychoneuroimmunology (PNI) and Its Relevance to ADHD

**Psychoneuroimmunology (PNI)** is an interdisciplinary field that explores how the **nervous system**, the **endocrine system**, and the **immune system** interact to influence health, disease, and behavior. Emerging in the late 1970s through the pioneering work of **Robert Ader**, **Nicholas Cohen**, and **David Felten**, PNI challenged the traditional view that the immune system functioned independently of psychological and neurological processes. Instead, it proposed that the brain, through hormones and neural pathways, could shape immune responses—and that immune activity could, in turn, influence brain function (Ader & Cohen, 1993; Ader, Felten, & Cohen, 1991). PNI research has since demonstrated that stress, emotions, and cognition are closely linked to inflammatory markers, hormonal changes, and even vulnerability to illness. (Irwin & Cole, 2011; Maes et al., 2012). While traditional models of ADHD have focused on dysfunction in executive systems or dopamine pathways, a PNI-informed approach asks: *What happens to the developing brain when the stress response system is persistently overactivated? What role does inflammation play in shaping attention, emotion regulation, or impulsivity?*

Growing evidence suggests that ADHD is not only characterized by dysregulation of neurotransmitters like dopamine and norepinephrine, but also by altered immune signaling. Studies have shown that individuals with ADHD may exhibit elevated levels of pro-inflammatory cytokines, including IL-6, TNF-α, and CRP, which are known to influence brain circuits involved in motivation, arousal, and emotional reactivity. PNI helps explain how environmental stressors—such as trauma, academic pressure, or social conflict—can become biologically embedded, shaping neurodevelopment through repeated activation of the HPA axis and the immune system (Segerstrom & Miller, 2004; Slavich & Irwin, 2014).

#### 2.1.2 How Chronic Stress Triggers Neuroinflammatory Responses

When the brain perceives a stressor, the hypothalamus activates the stress response through the HPA axis, initiating the release of corticotropin-releasing hormone (CRH). This stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH), which in turn prompts the adrenal glands to release cortisol, the body's primary stress hormone. Cortisol is designed to help the body cope with immediate challenges by mobilizing energy in several body systems and dampening the immune response.

One key effect of chronic stress is the activation of microglia, the brain's resident immune cells. Under persistent stress conditions, microglia shift from a "surveillance" mode into a pro-inflammatory state, releasing cytokines such as IL-1β, IL-6, and TNF-α. These cytokines, in turn, contribute to neuroinflammation, characterized by increased blood-brain barrier permeability, oxidative stress, and reduced neurogenesis in regions like the prefrontal cortex and hippocampus (Dantzer et al., 2008; Miller & Raison, 2016).

In addition, systemic stress may alter sympathetic nervous system (SNS) output, increasing the release of norepinephrine, which can bind to immune cell receptors and further amplify cytokine production. This bidirectional communication means that stress not only originates in the brain but also feeds back to influence immune activity in a **cyclical, self-reinforcing loop**.

### 2.1.3 The HPA Axis and Cortisol Dysregulation in ADHD

The HPA axis plays a central role in the body's response to stress, coordinating the release of cortisol, a glucocorticoid hormone that helps mobilize energy and regulate immune function. Under normal conditions, the HPA axis operates on a **negative feedback loop**: once cortisol levels rise in response to a stressor, they eventually signal the brain to reduce further production, returning the system to baseline. However, in individuals exposed to chronic stress, this regulatory loop may become dysregulated, leading to abnormal patterns of cortisol secretion that can disrupt brain development and behavior (McEwen, 2007; Gunnar & Quevedo, 2007).

In ADHD, several studies have reported altered diurnal cortisol rhythms, suggesting that the HPA axis may not function optimally in this population. For instance, some children with ADHD show blunted cortisol responses to stress, while others exhibit elevated baseline levels or delayed peak secretion. These inconsistent cortisol profiles are thought to reflect long-term adaptation—or maladaptation—of the stress response system, particularly in individuals exposed to early life adversity, chronic psychosocial stress, or emotional dysregulation. *Figure 2* illustrates this blunted diurnal cortisol rhythm observed in ADHD. As shown, individuals with ADHD display a flatter decline in cortisol levels across the day, reflecting reduced HPA axis reactivity and impaired stress regulation (Saccaro et al., 2021; Sciberras et al., 2017).

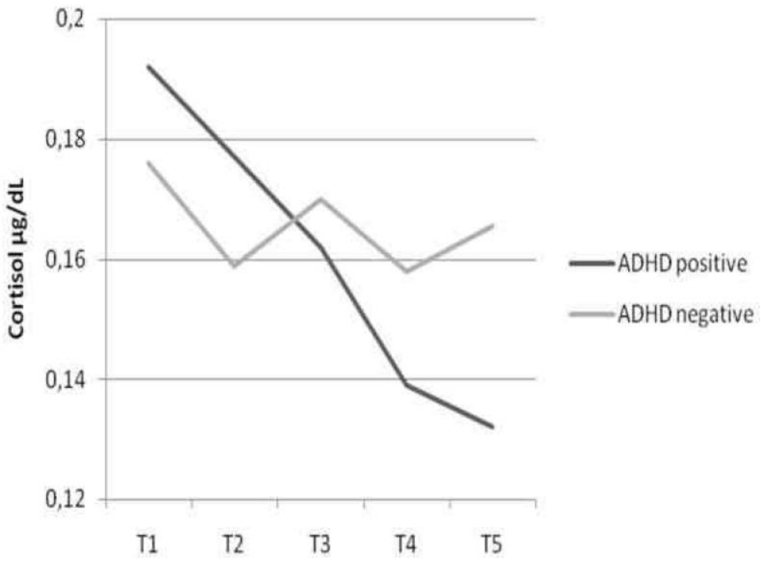


***Figure 2:*** *Diurnal cortisol secretion patterns in ADHD. The graph shows a flatter diurnal cortisol slope, indicating reduced HPA axis reactivity. Adapted from Saccaro et al. (2021).*

The consequences of HPA axis dysregulation are particularly relevant for the neurocognitive and emotional symptoms of ADHD. Cortisol receptors are densely distributed in brain regions associated with ADHD, including the prefrontal cortex, hippocampus, and amygdala. Chronic or dysregulated cortisol exposure can impair synaptic plasticity in the prefrontal cortex, shrink hippocampal volume, and sensitize the amygdala, contributing to increased emotional reactivity, cognitive fatigue, and difficulty adapting to changing demands (Liston et al., 2009; Arnsten, 2009).

Interestingly, cortisol abnormalities in ADHD are not uniform across individuals or age groups. Some research suggests that younger children with ADHD may show hyper-responsivity to stress, while adolescents and adults may display a flatter, more blunted stress response. This developmental variability supports the idea that ADHD is not a fixed neurobiological state, but one that interacts dynamically with the environment, particularly through stress-related systems like the HPA axis (van Goozen et al., 2007).

From a PNI perspective, these alterations in HPA axis function are not isolated. Cortisol also modulates immune system activity, meaning that its dysregulation can trigger or amplify neuroinflammatory processes. A failure to suppress pro-inflammatory cytokines effectively—either due to cortisol resistance or inadequate secretion—can lead to sustained immune activation, further disrupting neural circuits involved in attention (Miller et al., 2002; Slavich & Irwin, 2014). Thus, cortisol abnormalities may serve as a biological link between chronic stress, immune dysregulation, and ADHD symptomatology.

## 2.2 Chronic Stress and ADHD

### 2.2.1 The Stress-Diathesis Model and ADHD

The stress-diathesis model is a widely accepted framework in psychopathology that explains how psychological disorders can emerge when a person with an underlying biological vulnerability (diathesis) is exposed to chronic or acute stressors (Ingram & Luxton, 2005; Walker & Diforio, 1997). In the case of ADHD, this model helps account for why some individuals develop more severe or persistent symptoms than others, even when their initial neurobiological profiles may be similar. ADHD has long been associated with heritable neurodevelopmental traits—such as reduced executive functioning, altered dopamine transmission, and differences in cortical maturation (Biederman et al., 2004; Thapar et al., 2013). However, these vulnerabilities alone are often not sufficient to produce clinically significant impairment without the presence of environmental stressors.

Research suggests that chronic psychosocial stress—whether from academic failure, peer conflict, family instability, or internal emotional dysregulation—can amplify core ADHD symptoms such as distractibility, irritability, impulsivity, and emotional lability (Seymour et al., 2012; Sciberras et al., 2017). This symptom exacerbation appears to be more pronounced in individuals with existing cognitive vulnerabilities. Stress activates the HPA axis and other neuroendocrine systems that influence attentional control and emotional regulation (Arnsten, 2009; Saccaro et al., 2021). When these systems are overactivated repeatedly, they may amplify pre-existing ADHD-related impairments by increasing cognitive fatigue, reducing frustration tolerance, and heightening sensitivity to external demands. For example, a child with ADHD may show more severe attentional problems or aggressive outbursts during periods of family stress or social rejection—not because their core symptoms have changed, but because their **stress threshold has been exceeded** (Shaw et al., 2014).

Evidence also suggests that individuals with ADHD may be more biologically reactive to stress than their neurotypical peers. Several studies report that individuals with ADHD exhibit heightened physiological arousal—such as reduced heart rate variability (HRV), prolonged cortisol secretion, and exaggerated limbic system activation—during tasks involving uncertainty, delay, or social judgment (Saccaro et al., 2021). This heightened sensitivity may make it harder for them to "bounce back" from stress, leading to prolonged stress responses that interfere with self-regulation (Shaw et al., 2014). Moreover, the same cognitive deficits that define ADHD—such as poor working memory or inhibition—may also impair a person's ability to use adaptive coping strategies, making stressors feel more overwhelming and harder to manage on a day-to-day basis (Seymour et al., 2012; Barkley, 2015).

This prolonged stress reactivity creates a **feedback loop** in which stress impairs regulation, impaired regulation leads to more stress exposure, and stress exposure worsens the original symptoms. Over time, this cycle may contribute not only to worsening ADHD symptoms, but also to the development of comorbid disorders, including anxiety, depression, and behavioral problems.

### 2.2.2 The Impact of Stress on Cognitive and Emotional Regulation in ADHD

Cognitive and emotional regulation are core areas of impairment in ADHD, and both appear to be highly sensitive to the effects of stress. Chronic stress can impair the functioning of the prefrontal cortex, which is crucial for executive processes such as working memory, attention allocation, inhibition, and goal management. Under prolonged stress exposure, cortisol and other stress mediators disrupt the neurochemical balance required for optimal prefrontal activity, shifting regulatory control to more emotion-driven limbic regions, including the amygdala. This shift compromises the individual's ability to remain focused, resist distractions, and moderate emotional responses. As a result, individuals with ADHD may become more impulsive, emotionally reactive, and mentally fatigued under stress—behaviors that resemble or exacerbate their baseline symptoms (Arnsten, 2009; Liston et al., 2009).

The emotional dysregulation seen in ADHD—ranging from mood swings and irritability to frustration intolerance and sensitivity to rejection—is also closely tied to how stress alters neural circuitry. Stress increases activity in the amygdala and reduces connectivity between the prefrontal cortex and limbic system, undermining the brain's ability to modulate emotional responses. This imbalance is compounded by deficits in neurotransmitter systems like dopamine and norepinephrine which are further impaired under stress conditions. These effects are particularly relevant in socially or academically demanding settings, where performance expectations are high and emotional self-control is essential.

### 2.2.3 Neuroendocrine Alterations in ADHD Under Chronic Stress

Neuroendocrine systems, particularly the HPA axis and the sympatho-adrenal medullary (SAM) system, play essential roles in regulating the body's arousal, alertness, and stress reactivity. While the HPA axis governs long-term stress adaptation via cortisol, the SAM axis is responsible for the immediate "fight or flight" response through the release of adrenaline and noradrenaline.

Closely linked to this system is the locus coeruleus–norepinephrine (LC-NE)[1] pathway, which mediates arousal, vigilance, and attention by influencing both prefrontal and limbic structures. Under normal conditions, norepinephrine release enhances alertness and cognitive flexibility. However, in ADHD—especially under chronic stress—this signaling may become excessive, erratic, or inefficient, contributing to emotional volatility, hyperarousal, and poor impulse control (Arnsten, 2009; Benarroch, 2009). This dysregulation is further compounded by weaknesses in dopaminergic tone, resulting in a neurochemical environment that undermines reward sensitivity and sustained attention.

These neuroendocrine imbalances also influence the body's adaptive thresholds for coping with change, novelty, or social stressors. When stress is persistent, altered feedback mechanisms between the brain and endocrine glands may reduce the ability to switch between different levels of arousal. This may result in a blunted response to positive feedback, lower stress tolerance, and difficulty modulating behavior in response to environmental cues. In daily life, this could manifest as emotional shutdown in the face of mild criticism, impulsive task-switching, or avoidance of effortful tasks—behaviors often attributed solely to ADHD's cognitive features, but increasingly understood as the result of stress-related neurohormonal dysfunction.

### 2.3 Neuroinflammatory Mechanisms in ADHD

#### 2.3.1 The Role of Pro-inflammatory Cytokines (IL-6, TNF-α, CRP) in ADHD

Pro-inflammatory cytokines such as IL-6 and TNF-α are signaling proteins released by immune cells in response to sustained physical or psychological stress, often mediated through activation of the HPA axis and sympathetic nervous system. In turn, IL-6 stimulates the production of CRP, an acute-phase protein synthesized by the liver that serves as a broader marker of systemic inflammation. These molecules are key mediators of peripheral inflammation, a systemic immune response that occurs outside the brain, often triggered by stress, infection, gut dysbiosis, or environmental toxins. Elevated peripheral cytokines can circulate through the bloodstream and

[1] The locus coeruleus–norepinephrine (LC-NE) system is the brain's primary source of norepinephrine and plays a critical role in regulating arousal, attention, alertness, and stress adaptation. It originates in the brainstem and sends widespread projections to the prefrontal cortex, limbic system, and other brain regions involved in cognitive control and emotion regulation. Dysregulation of LC-NE activity, particularly under chronic stress, has been linked to impaired executive function, heightened emotional reactivity, and the core symptoms of ADHD (Berridge & Waterhouse, 2003; Arnsten, 2009).

communicate with the central nervous system through multiple pathways, including direct crossing of the blood–brain barrier (BBB), activation of vagal afferents, or modification of BBB permeability. In individuals with ADHD, several studies have reported increased levels of IL-6 and CRP, suggesting a persistent low-grade inflammatory state that may influence the severity and variability of symptoms (Cortese et al., 2019; Leffa et al., 2018).

Once cytokines reach the brain, they can activate microglia initiating a localized immune response known as central (neuro)inflammation. Unlike peripheral inflammation, which occurs systemically, neuroinflammation involves the release of cytokines and chemokines[2] directly within the central nervous system, affecting neuronal communication, synaptic pruning, and neurotransmitter regulation. IL-6 and TNF-α have been shown to modulate dopamine transmission by altering the function of dopamine transporters and receptors, particularly in regions implicated in ADHD such as the prefrontal cortex and striatum (Felger & Miller, 2012; Saccaro et al., 2021). These mechanisms are of particular relevance for ADHD, given the disorder's hallmark deficits in attentional control, executive functioning, and emotional regulation.

Moreover, the interaction between peripheral and central inflammation appears to follow a feed-forward dynamic. Persistent peripheral immune activation primes microglia to become hyper-reactive, lowering the threshold for neuroinflammatory responses even to minor stressors. This mechanism may underlie the chronic emotional and cognitive dysregulation observed in some individuals with ADHD, particularly those who exhibit heightened stress sensitivity. The presence of elevated CRP and IL-6 in children with ADHD has been associated with increased behavioral impulsivity and emotional reactivity, reinforcing the view that immune activity is not merely a peripheral phenomenon but one that directly alters brain function (Chang et al., 2020). As shown in Figure 3, the immune–brain feedback loop involves complex communication through cytokine release, vagal signaling, and BBB modulation, ultimately leading to sustained changes in neural activity and behavior.

[2] Chemokines are a subclass of cytokines that direct immune cells—such as microglia and astrocytes—to inflammatory sites via chemotaxis, and they can be produced by glia and neurons in the brain. Notably, CCL2 (MCP-1) is actively transported across the blood–brain barrier during systemic inflammation and contributes to CNS immune signaling (Ransohoff, 2009; Shkundin & Halaris, 2024).

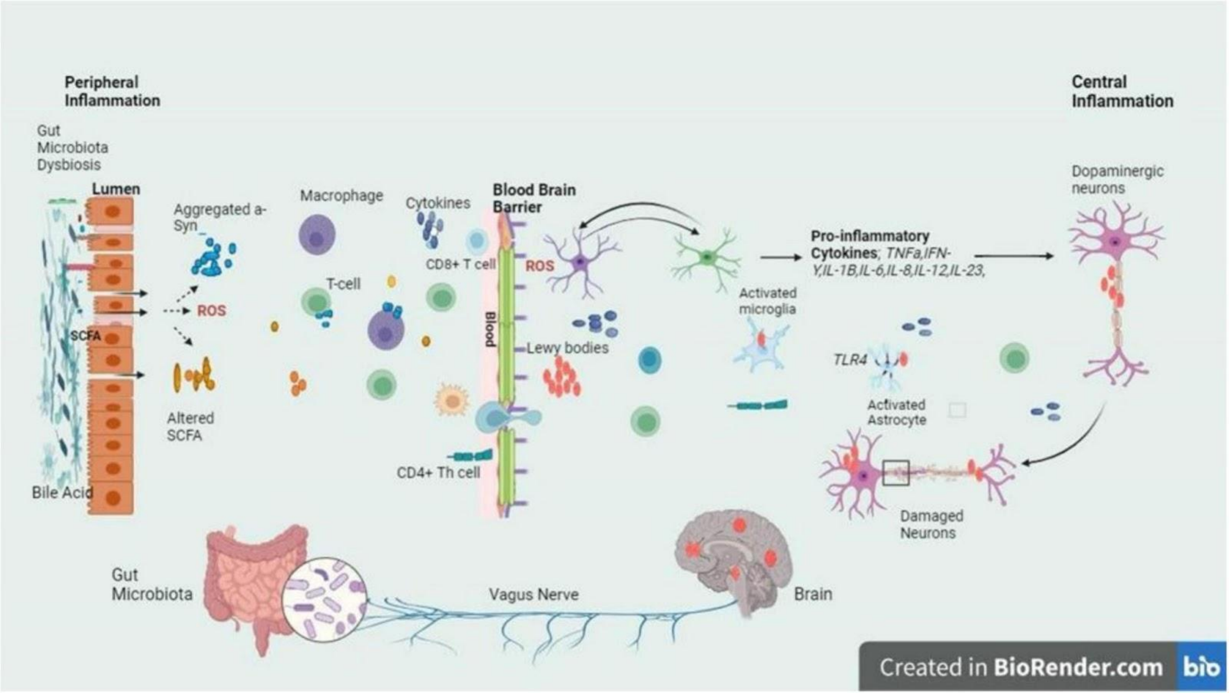


***Figure 3:*** *Bidirectional model of peripheral and central inflammation, highlighting the role of systemic cytokines, the blood–brain barrier, and neuroimmune signaling pathways. Adapted from Frontiers in Aging Neuroscience (Zhao, Zhan, & Wang, 2024).*

As shown in Figure 3, the process begins in the gut, where dysbiosis (an imbalance in gut microbiota) triggers the release of reactive oxygen species (ROS) and altered short-chain fatty acids (SCFAs), initiating peripheral inflammation. Immune cells such as macrophages and T-cells release cytokines, including IL-6 and TNF-α, into the bloodstream. These circulating cytokines can cross or alter the permeability of the BBB and activate the vagus nerve, signaling the brain to initiate a central immune response. Within the brain, microglia and astrocytes become activated, releasing additional pro-inflammatory cytokines that can disrupt neuronal integrity—especially dopaminergic neurons in regions such as the prefrontal cortex and striatum. This bidirectional communication between the periphery and the central nervous system establishes a chronic neuroinflammatory loop, which may contribute to the dopaminergic dysregulation and cognitive-emotional symptoms observed in ADHD.

### 2.3.2 How Neuroinflammation Affects Dopamine Function and Cognitive Performance

Inflammation has a profound effect on dopaminergic signaling, particularly in brain regions critical for attention, reward processing, and executive function. Pro-inflammatory cytokines such as IL-6 and TNF-α can disrupt dopamine function by interfering with key enzymes responsible for its production and regulation. These disruptions result in reduced dopamine availability in areas like the prefrontal cortex, nucleus accumbens, and striatum, all of which are central to regulating motivation, behavioral inhibition, and working memory—functions that are consistently impaired in individuals with ADHD (Miller et al., 2009).

The impact of these inflammatory processes on cognition is both direct and indirect. Neuroinflammation impairs synaptic plasticity, reduces long-term potentiation (a key mechanism for learning and memory), and promotes oxidative stress, further compromising neural efficiency. In ADHD, this can translate into slower cognitive processing speed, increased mental fatigue, and lower cognitive flexibility, particularly in high-demand situations. Studies have shown that inflammatory markers correlate with poorer performance on neuropsychological tasks requiring sustained attention and inhibitory control, suggesting that inflammation may play a modulatory role in the expression and variability of ADHD symptoms (Felger & Treadway, 2017; Chang et al., 2021).

## CHAPTER 3: Rethinking ADHD Through a PNI Lens

### 3.1 The importance of studying ADHD beyond behavioral and cognitive symptoms

For decades, ADHD has been framed as a disorder defined by behavioral output and executive functioning deficits. These models have been clinically useful, yet they have unintentionally confined ADHD to the brain, and sometimes even just to behavior. What they fail to explain is the striking heterogeneity of the condition: why some individuals experience intense emotional lability, why stress dramatically shapes symptom severity, and why two people with the same diagnosis respond so differently to the same treatment.

PNI offers a compelling way to interpret these inconsistencies. Rather than conceptualizing ADHD purely as a deficit of neural circuitry, PNI situates the disorder within a network of physiological systems that respond to and shape lived experience. Studies reporting elevated pro-inflammatory cytokines (e.g., IL-6, TNF-α) in subsets of individuals with ADHD suggest that immune activation may contribute to attentional instability or emotional dysregulation in a meaningful subset of patients. These markers correlate more closely with irritability and mood instability than with core attentional deficits, implying that inflammation may help explain symptom clusters that traditional cognitive models do not (Sciberras et al., 2017; Saccaro et al., 2021).

Moreover, chronic stress — a variable historically relegated to psychosocial context — becomes central in this biological story. Through repeated HPA-axis activation, stress alters cortisol rhythms, changing how flexibly the organism adapts to daily challenges. These disruptions are not just consequences of ADHD; they may help drive symptom persistence. The importance of this perspective is not that ADHD becomes "an immune disorder," but that immune and stress biology interact with neural function in ways that make symptoms fluid, environmentally dependent, and physiologically contextual.

### 3.2 Integrating PNI into ADHD management

If stress physiology and immune activity actively shape ADHD expression, then management must expand beyond targeting dopamine transmission alone. Stimulants improve attention by enhancing catecholamine signaling, but their effects are inconsistent across individuals — perhaps reflecting biological heterogeneity. A PNI-informed model recognizes that differences in immune or stress profiles may interact with how medications are metabolized or how neural circuits respond.

This does not mean replacing medication; rather, it means contextualizing it. For individuals with elevated inflammatory markers, for example, stimulants may be less effective until systemic inflammation is reduced. Preliminary work suggests that regular aerobic exercise — through effects on vagal tone and microglial activation — can reduce inflammatory load while simultaneously improving executive functioning. Nutritional strategies, particularly increasing omega-3 fatty acids and dietary polyphenols, may support neuronal membrane integrity and attenuate cytokine signaling (van der Oord et al., 2020). Though these approaches are not cures, they act on biological pathways that medications overlook.

### 3.3 How a PNI-based framework offers a more comprehensive ADHD treatment model.

Traditional ADHD treatment models focus primarily on cognitive symptoms and neurotransmitter regulation, yet clinical variability and inconsistent treatment responses suggest that these approaches capture only part of the disorder's biology. A psychoneuroimmunological framework provides a broader lens by showing how inflammation, oxidative stress, and chronic stress physiology interact with dopamine and norepinephrine pathways central to ADHD. When inflammatory markers rise or cortisol rhythms become dysregulated, dopaminergic signaling in prefrontal and striatal circuits becomes less efficient, which can intensify emotional reactivity, reduce reward sensitivity, and limit the effectiveness of standard pharmacological interventions.

By highlighting the biological pathways linking stress, immune activation, and neurotransmission, a PNI-oriented model also clarifies why individuals with ADHD respond so differently to treatment. Elevated cytokines, increased oxidative stress, or persistent sympathetic activation may create neurochemical conditions in which stimulant medications alone cannot fully restore functioning. This framework therefore shifts the focus from symptom suppression toward supporting physiological regulation. Interventions that reduce inflammatory load, improve sleep and circadian stability, enhance antioxidant capacity, or support stress recovery (e.g., through physical activity, omega-3 fatty acids, N-acetylcysteine, or mindfulness-based stress reduction) may complement traditional treatment by directly targeting the systems that modulate attention and emotional control.

This integrative perspective supports a more personalized approach to ADHD by recognizing that individuals differ not only in symptom profiles but in the underlying biological mechanisms driving those symptoms. Some may present with inflammation-driven dopaminergic inefficiency, others with HPA-axis dysregulation or heightened oxidative stress. A PNI framework encourages matching interventions to these patterns rather than assuming a universal pathway. The model illustrated in **Figure 4** summarizes these interactions, showing how genetic predispositions, environmental adversity, inflammation, oxidative stress, and catecholaminergic dysregulation converge in ADHD, and how a multi-target therapeutic approach may help address these interconnected systems.

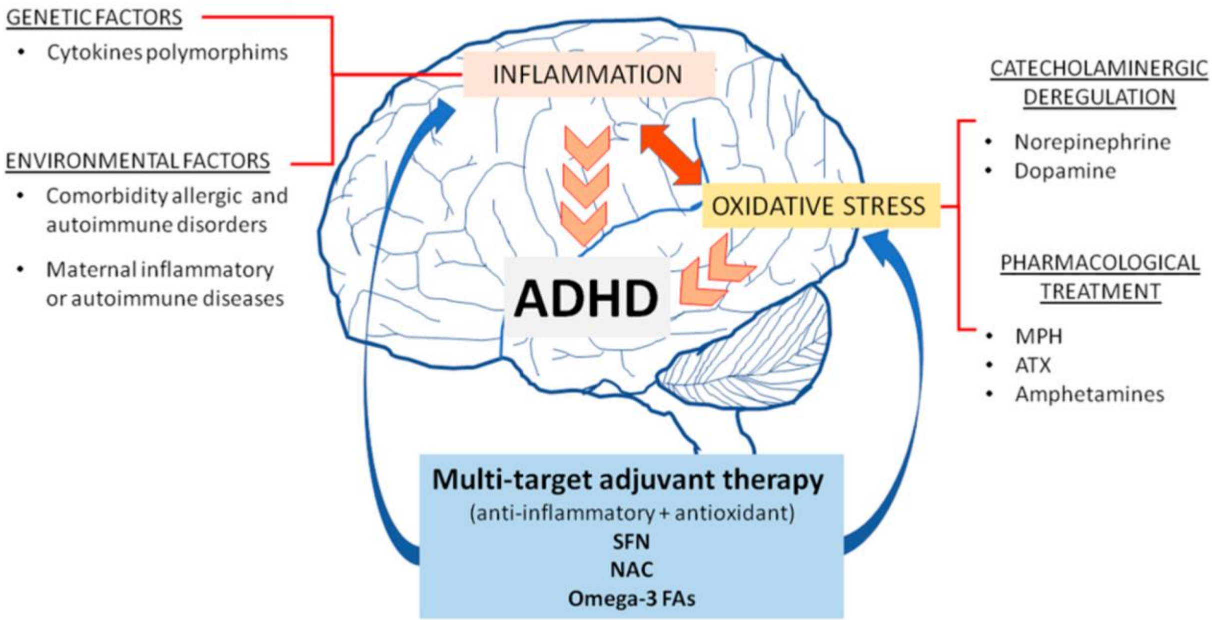


***Figure 4:*** *Model illustrating how inflammation and oxidative stress contribute to ADHD symptoms, and potential adjuvant treatments such as sulforaphane (SFN), N-acetylcysteine (NAC), and omega-3 fatty acids. Adapted from Alvarez-Arellano et al. (2020).*

### 3.4 Conclusion

This thesis explored ADHD through a psychoneuroimmunological perspective, asking whether chronic stress–induced immune activation contributes to dopaminergic dysregulation and, in turn, to attentional and emotional difficulties. Taken together, the reviewed literature provides support for this hypothesis. Studies consistently show that individuals with ADHD exhibit altered HPA-axis activity, flattened cortisol rhythms, and elevated inflammatory markers such as IL-6, TNF-α, and CRP. These biological patterns align with models describing how chronic stress can influence immune signalling and modulate dopaminergic function in prefrontal and striatal circuits that are central to ADHD.

At the same time, evidence also shows that these biological mechanisms do not act in isolation. Variability in stress reactivity, environmental adversity and emotional regulation, contributes to heterogeneity in symptom presentation and treatment response. This indicates that while the hypothesis is supported, the mechanisms are complex and likely differ across individuals. Rather than pointing to a single causal pathway, the findings suggest that chronic stress and low-grade inflammation may amplify or maintain a vulnerability already present in ADHD, helping explain why some individuals experience more severe emotional dysregulation or respond differently to treatment.

By integrating these strands of evidence, the thesis supports the value of a PNI-based framework for understanding ADHD. This perspective highlights the need for approaches that consider stress regulation, inflammation, and lifestyle factors alongside traditional cognitive and pharmacological interventions. Future work should further investigate biomarkers of stress and immune function in ADHD and test interventions that target these systems directly.

Overall, the research question guiding this thesis can be answered positively: chronic stress-related immune activity appears to contribute meaningfully to the neural and emotional processes underlying ADHD. The hypothesis is supported by current literature, though the extent of these effects varies across individuals and remains an important direction for future research.

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