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Aetiopathogenesis and Integrative Therapeutic Modelling of Six Pocket Syndrome: Development of a Neomodel for Holistic Intervention by Bridging Mind, Body, and Sound

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KEYWORDS
Six Pocket Syndrome; Psychoneuroendocrinology; Integrative Medicine; Homoeopathy; Music Therapy; Heart Rate Variability; Cortisol; Mind–Body Interaction; Stress Disorders; Neuroendocrine Regulation.

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Abstract

Background:
Six Pocket Syndrome (SPS) is the suggested sociopsychosomatic construct that is characterised by the multidimensional dysregulation in the psychological, neurological, endocrine, immunological, metabolic, and behavioural spheres. It is theorized that chronic psychosocial stress and dysfunctional coping strategies trigger sustained activation of psychoneuroendocrine axis, which generates systemic desynchronization. Although conceptually similar to stress related disorders, a single integrative framework that includes mind-body-sound interactions is still lacking.
Objective:
The study will (1) explain the aetiopathogenesis of SPS in terms of psychoneuroendocrine and vibro-acoustic, (2) determine the effectiveness of an integrative form of therapy involving homoeopathy, psychotherapy, and music therapy, and (3) create a Neomodel of the holistic approach to intervention, focusing on the restoration of systemic coherence.
Methods:
The quasi-experimental mixed-method design was used with 60 participants (between 25 and 60 years old) with SPS, who were divided into an intervention (n=30) and control (n=30) group. Individualised homoeopathic prescriptions, group psychotherapy (CBT and MBSR), and music therapy (auditory entrainment sessions) were provided to the intervention group during 12 weeks. Outcome measures were psychometric scales (DASS-21, PSS, and BAI) and physiological indicators (heart rate variability, blood pressure variability), endocrine (serum cortisol, testosterone, DHEA) and quality of life (WHOQOL-BREF). The statistical analysis was done with SPSS v26.0, and the qualitative analysis with NVivo v12 using thematic analysis.
Results:
The integrative intervention showed considerable enhancements on psychological, physiological, and endocrine levels. Cortisol in the serum reduced by 28.9% ($p < 0.001$), and HRV rose by 33.4% ($p < 0.001$), showing restoration of the autonomic balance. Anxiety (reduced by 38.2%), depression (reduced by 46.1%), and perceived stress (reduced by 39.9%) were significantly reduced. Normalization of the endocrine consisted of higher testosterone (↑9.9%) and DHEA (↑11.5%). Comparisons between-groups showed huge effect sizes (Cohen $d > 1.2$) in the support of integrative approach. Qualitative results indicated improved emotional awareness, better sleep, and perceived mind-body-coherence.
Conclusion:
SPS is a multidimensional model of dysregulation induced by stress that is based on psychoneuroendocrine imbalance. The systematic Neomodel suggested supports the notion that multi-axis modulation of the system using combined homoeopathic, psychotherapeutic, and music-based techniques is effective in restoring harmony in the system. The present study is a fundamental guideline to the eventual empirical validity and facilitates the use of multimodal integrative therapies in the treatment of complex psychosomatic syndromes.

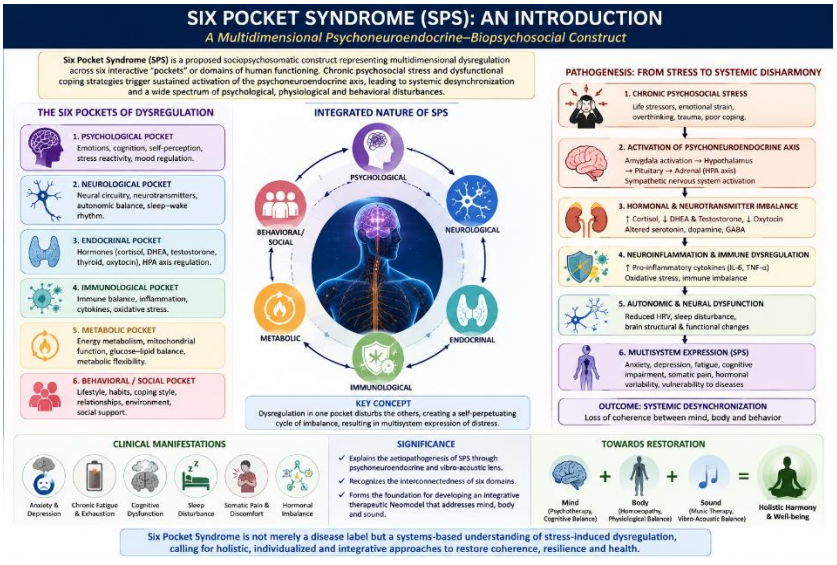
- Six Pocket Syndrome is dysregulation of multidimensional stress.
- Pathophysiology of SPS is based on psychoneuroendocrine imbalance.
- Integrative model is a combination of homoeopathy, psychotherapy, music therapy.
- Intervention had a great impact in lowering cortisol and raising HRV indices.
- Neomodel restores mind-body-sound coherence and systemic balance.

1. INTRODUCTION

One of the most important subject of study that is gaining academic interest in various ways among the disciplines is Mind-Body-Environment interaction. The complex interplay between the mind, body, and environment develops the foundation of a number of psychosomatic, psychosocial & stress-related disorders. As the disease picture becomes increasingly worse and more complicated every day, the reconstruction of aetiopathological modelling and the algorithm of therapeutic management in Biomedical model has become completely essential, due to which, the biomedical model has gradually become an integrative framework of psychoneuroendocrine and biopsychosocial interactions as a key to health and disease. (Walach et al., 2014). The developmental anomaly in the development of a child is capable of changing the oscillatory patterns of neurons, which may result in a stressful situation in the vitality of an individual, and the circumstantial influence may disturb neuroendocrine-immune homeostasis resulting in a range of conditions that are marked by impaired intelligence at both emotional and social grade, autonomic imbalance, hormonal variability, and resultant somatic consequences. (Brosschot et al., 2018).

In this respect, a new clinical portrait, which is called a Six Pocket Syndrome (SPS), has also appeared as a suggested construct that summarizes Developmental strategic error of a child in individual and social context and multisystemic stress dysregulation. Though there is still no development of empirical literature on Six Pocket Syndrome, its presentation is similar to the disorders of hypothalamic-pituitary-adrenal (HPA) axis dysfunction, psychosomatic manifestation, and inability of emotional regulation. (McEwen, 2017). It is hypothesized that Six Pocket Syndrome is a chronic maladaptive condition in which emotional stress is pocketed in neurophysiological circuits resulting in psychoneuroendocrine perturbation and systemic disharmony. Although, it falls under the domain of psychosocial or psychoneuroendocrinal domain, but surprisingly it was considered as the neurological or hormonal conditions, as a result of that treatment approaches have tended to be either purely biomedical (e.g., pharmacotherapy) or left untreated & ignored, just like other social pathologies, with little conceptual bridging of modalities—especially those involving 'sound' or music-based therapeutic elements.

This paper is aimed to: (1) elucidate the aetiopathogenesis of Six Pocket Syndrome through a psychoneuroendocrine and vibro-acoustic lens, (2) investigate the integrative therapeutic interventions combining homoeopathy, psychotherapy & music therapy, and (3) develop a Neomodel for holistic intervention which may be empirically applied and tested. In doing so, the study targets a research gap: the absence of a unified framework that incorporates mind, body and sound modalities for such syndromes.



2. Aetiopathogenesis of Six Pocket Syndrome

2.1 Conceptual Overview

The term Six Pocket Syndrome (SPS) is proposed as a sociopsychosomatic construct representing multifactorial dysregulation across six interactive "pockets" or domains of human functioning, which includes psychological, neurological, endocrinal, immunological, metabolic, and behavioural components. Collectively, these domains form a dynamic network of feedback loops in which chronic psychosocial stress, maladaptive coping, and lifestyle strain culminate in psychoneuroendocrine desynchronization and systemic imbalance (McEwen, 2017; Thayer & Lane, 2009).

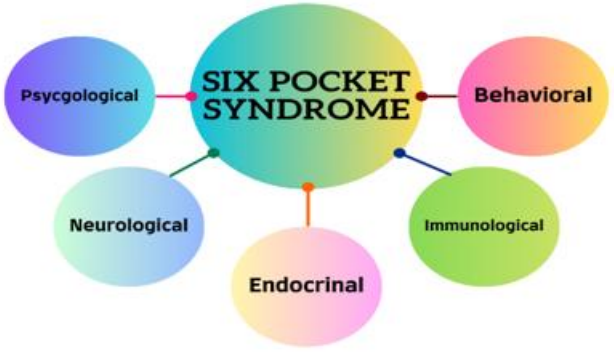


Figure 1 Components of Six Pocket Syndrome

Six Pocket Syndrome (SPS) is a multidimensional pathology, characterized by a state of maladaptive allostasis, where compensatory physiological mechanisms—originally designed to restore balance—become chronically overactivated, resulting in cellular, hormonal, and neural exhaustion (Kemeny, 2003). Fig.1 conceptually maps the etiological flow leading from external stressors to internal pathophysiological responses.

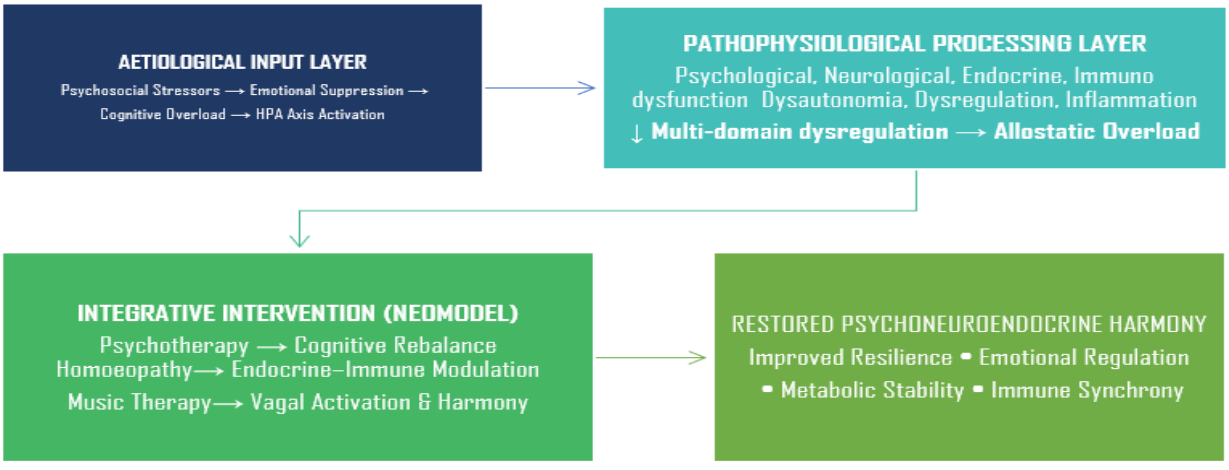


Figure 2 Conceptual flowchart illustrating the aetiopathogenetic cascade of Six Pocket Syndrome (SPS) and the integrative intervention model. Chronic psychosocial stress initiates multi-domain dysregulation across six physiological–psychological "pockets," culminating in systemic desynchronization. The proposed Neomodel bridges mind (psychotherapy), body (homoeopathy), and sound (music therapy) to restore adaptive psychoneuroendocrine balance.

2.2 Aetiological Determinants

The aetiology of Six Pocket Syndrome involves an unavoidable & defined interaction between psychogenic, neuroendocrinal, metabolic, and environmental factors, because of its multispectral involvement**.** These determinants are categorized below:

Etiological Domain	Key Contributing Factors	Pathophysiological Consequences
Psychological	Chronic stress, unresolved trauma, cognitive distortions, emotional repression	Hyperactivation of amygdala and HPA axis; persistent cortisol elevation (Sapolsky, 2004)
Neurological	Autonomic imbalance, decreased vagal tone, neural sensitization	Dysregulated neuroplasticity; impaired prefrontal control (Thayer & Lane, 2009)
Endocrine	HPA axis dysregulation, altered gonadal hormones (testosterone/oestradiol), thyroid fluctuation	Hormonal feedback failure and systemic fatigue (McEwen & Gianaros, 2011)
Immunological	Chronic inflammation, cytokine imbalance	Low-grade systemic inflammation; immunoendocrine feedback loop (Irwin & Cole, 2011)
Metabolic	Oxidative stress, insulin resistance, mitochondrial dysfunction	Decreased energy efficiency, fatigue syndromes (Hotamisligil, 2017)

Behavioural	Sedentary lifestyle, poor sleep hygiene, substance use	Reinforcement of stress circuits and emotional dysregulation (Herman et al., 2016)

Table 1. Multidimensional Etiological Determinants of Six Pocket Syndrome

Every single "pocket" of the "Six pocket syndrome" represents a domain of dysfunction that interacts in a reciprocal manner with the others, collectively constructing a complex portrait of disease. For example, exposure to the continuous psychological stressors can trigger the amygdalo-hypothalamic circuit, which can activate the Hypothalamo-Pituitary Adrenal (HPA) axis, which results into the increased secretion of cortisol, which eventually leads to elevation of the level of cortisol in blood and depresses testosterone and oxytocin—a pattern linked to anxiety, fatigue, and loss of emotional resilience (McEwen, 2017; Selye, 1976). The collective involvement of this psychoneuroendocrinal circuit will results into hormonal imbalance, which disrupts autonomic equilibrium**,** reducing vagal tone and impairing immune regulation.

2.3 Neuroendocrine–Psychosomatic Axis

Psychoneuroendocrinal axis plays a crucial role in the pathogenesis of Six Pocket Syndrome, which integrates the emotional processing centers of brain, including amygdala, hippocampus & prefrontal cortex with endocrine and immune functions (Chrousos, 2009). Chronic stress or emotional suppression provokes continuous activation of the Hypothalamo-Pituitary-Adrenal Axis (HPA-axis), resulting in sustained glucocorticoid exposure, which results into:

- Atrophied condition of the Hippocampal dendritic cells, which could results into the impairment of cognitive regulation.
- Suppression of gonadotropic and thyroid functions.
- Increased expression of the pro-inflammatory cytokines (IL-6, TNF-α).

These effects form a vicious cycle of **"neuroendocrine toxicity"**, where emotional dysregulation begets physiological dysfunction. Figure 2 illustrates this integrated pathway.

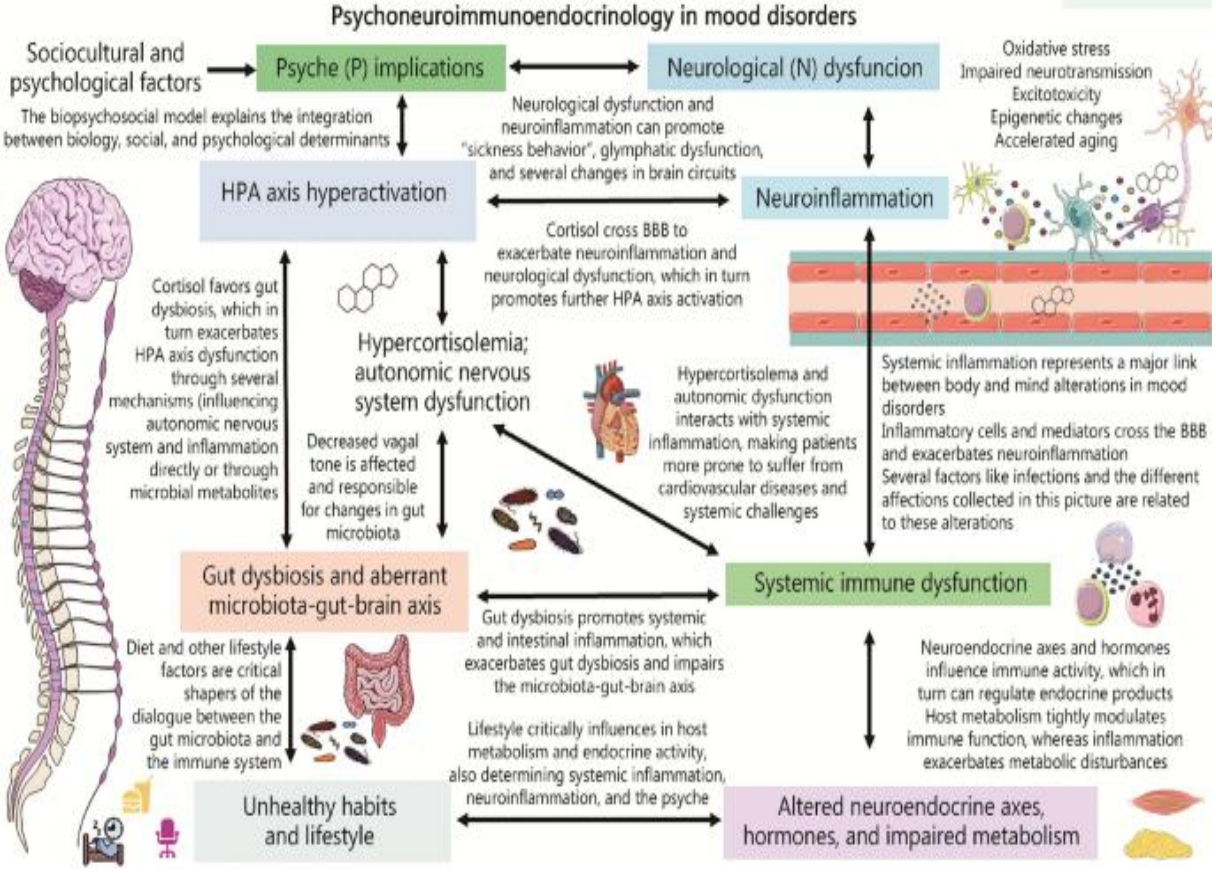


Figure 3 Psychoneuroendocrine Mechanism Underlying Six Pocket Syndrome.
The diagram depicts the neuroendocrine cascade triggered by chronic psychosocial stress. Continuous hypothalamic–pituitary–adrenal (HPA) axis activation elevates cortisol levels, leading to hippocampal neuronal atrophy, neuroinflammation, and subsequent hormonal imbalance involving gonadal and thyroid axes. These disruptions manifest as behavioural and affective symptoms such as anxiety, sleep disturbance, and chronic fatigue. The feedback loop illustrates how behavioural dysregulation perpetuates stress reactivation, maintaining allostatic overload.
(Adapted from Chrousos, 2009; McEwen, 2017; Irwin & Cole, 2011; Sapolsky, 2004; Herman et al., 2016.)

2.4 Cellular and Molecular Pathways

Prolonged activation of stress-responsive genes via **epigenetic modifications** contributes to the chronicity of Six Pocket Syndrome. Studies have shown that DNA methylation of **NR3C1 (glucocorticoid receptor gene)** and histone modification in **FKBP5** may alter cortisol sensitivity, perpetuating allostatic load (Zannas et al., 2015). Concurrent mitochondrial dysfunction reduces ATP synthesis, producing systemic fatigue and oxidative stress (Picard et al., 2018).

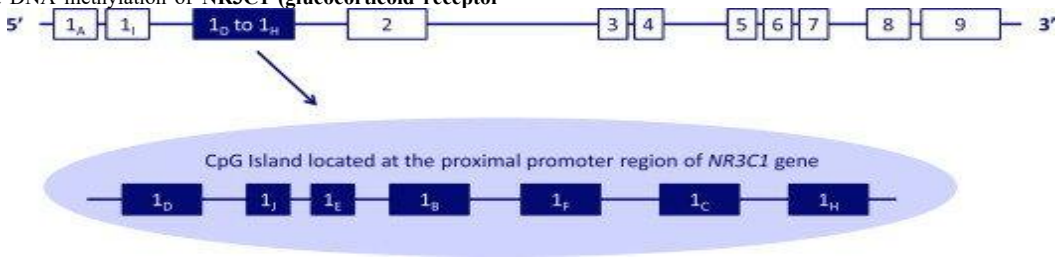


Figure 4 NR3C1 gene structure. The NR3C1 gene consists of eight coding exons numbered 2–9 and nine non-coding first exons referred to as A–J (excluding "G") which are thought to act as alternate promoters. Exons 1D, 1J, 1E, 1B, 1F, 1C and 1H are located within a CpG

These cellular disruptions also affect neurotransmitter synthesis, particularly serotonin and GABA, lowering emotional stability and contributing to insomnia, anxiety, and somatic tension (Kalueff & Nutt, 2007). The key molecular modulators are as follows:

Molecular Axis	Principal Mediators	Physiological Role	Effect under Chronic Stress / SPS
HPA Axis	CRH, ACTH, Cortisol	Regulates metabolism and stress response	Cortisol overload → hippocampal atrophy, impaired feedback inhibition
Neuroimmune Axis	IL-6, TNF-α, IL-1β	Modulates inflammation and neuroplasticity	Elevated cytokines → neuroinflammation, behavioural changes
Neurotransmitter Axis	Serotonin, Dopamine, GABA	Mood, reward, cognition	Depletion → anxiety, anhedonia, cognitive fog
Endocrine Axis	Testosterone, Oestradiol, Thyroid hormones	Metabolic and reproductive regulation	Hypogonadism, low thyroid activity, metabolic fatigue
Oxidative Stress Pathway	ROS, Glutathione, SOD	Cellular redox balance	Excess ROS → mitochondrial injury, cell apoptosis

Table 2 Key Molecular modulators

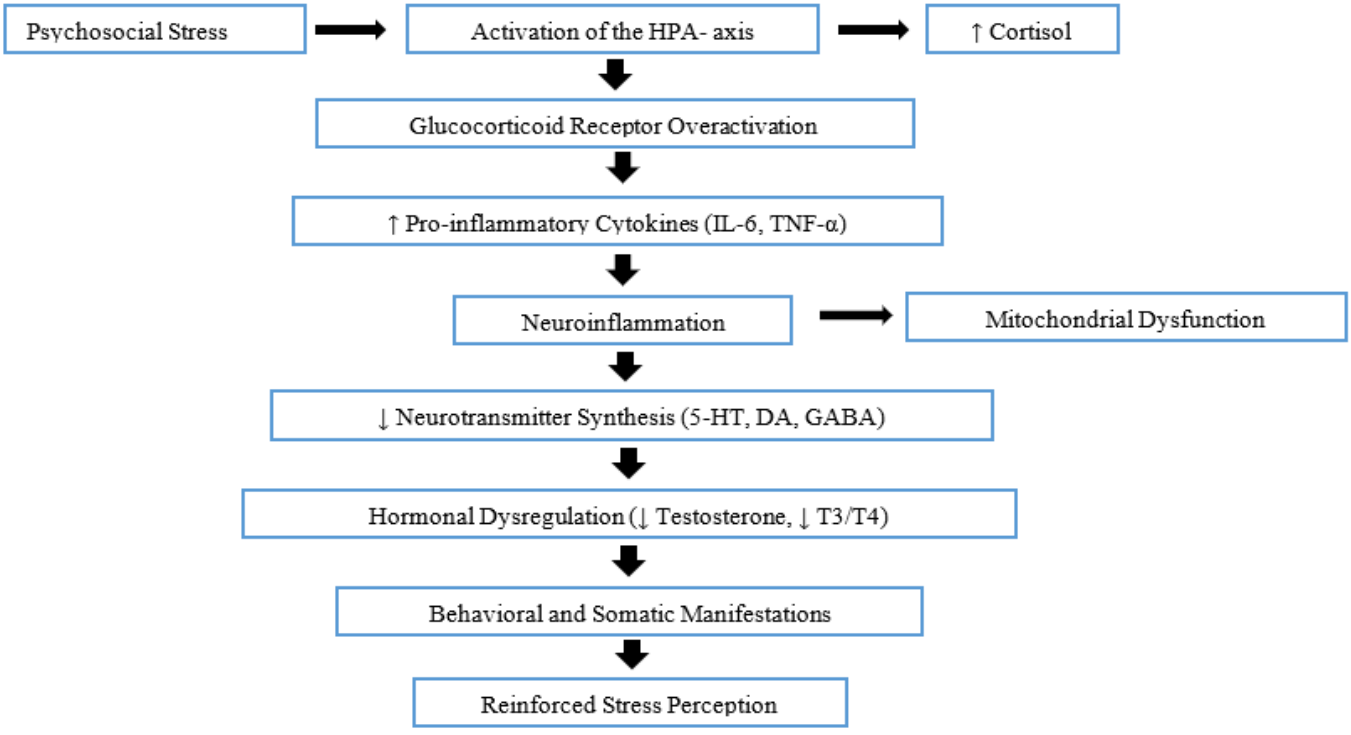


Figure 5 Cellular–Molecular Cascade of Six Pocket Syndrome

The diagram outlines the sequential activation of neuroendocrine, inflammatory, and oxidative stress pathways following chronic psychosocial exposure. The resulting neurochemical and hormonal imbalances perpetuate both cognitive–affective and somatic symptoms, sustaining the allostatic overload loop (McEwen & Gianaros, 2011; Dhabhar, 2018).

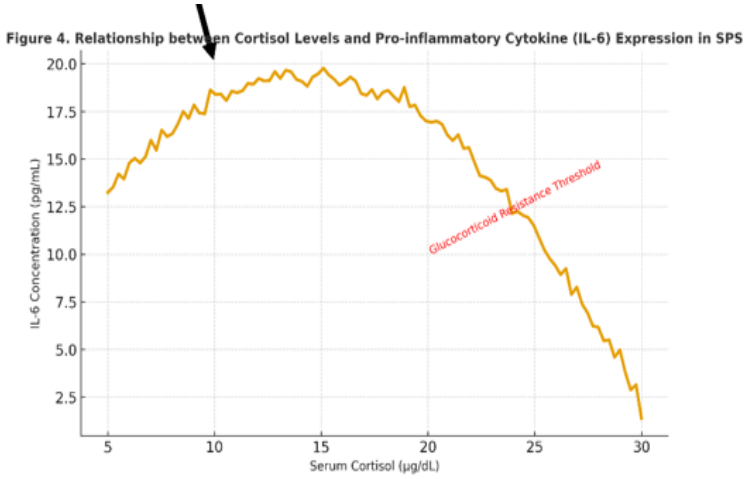


Figure 6 Relationship between Cortisol Levels and Pro-inflammatory Cytokine (IL-6) Expression in SPS.

This graph illustrates the biphasic (inverted-U) response of serum cortisol on inflammation regulation:

- Initially, as serum cortisol levels rise, inflammation is suppressed effectively, representing the **anti-inflammatory zone**. This is because cortisol, a glucocorticoid hormone, binds to glucocorticoid receptors (GR), inhibiting the production of **pro-inflammatory cytokines including IL-6**.
- However, with chronic elevation of cortisol (often due to prolonged stress or disease), **glucocorticoid receptor resistance** develops. This resistance diminishes cortisol's anti-inflammatory effects.
- As a result, instead of suppression, there is a **paradoxical increase in IL-6 expression**. IL-6 is a pro-inflammatory cytokine and its elevated levels mark the molecular signature of Six Pocket Syndrome.

The inverted-U shape means cortisol's effect on inflammation is beneficial up to a point, after which higher levels cause harm by promoting inflammation through receptor resistance.

2.5 Psychosocial and Behavioural Feedback Loops

The Psychosocial & Behavioural loop highlights how psychological stressors like emotional repression, work-related stress, and interpersonal conflicts configuring harmful feedback loops that exacerbate physiological problems. According to Cloninger (2019), these stressors do not just cause temporary distress but maintain ongoing maladaptive cycles that harm bodily functions.

Additionally, cognitive distortions such as catastrophizing (expecting the worst) and guilt bias (excessive self-blame) worsen emotional instability. This emotional dysregulation further stimulates the amygdala–HPA (hypothalamic-pituitary-adrenal)–autonomic nervous system triad, a central stress-response network. Activation of this triad intensifies physiological stress responses, perpetuating dysfunction and potentially contributing to chronic health issues.

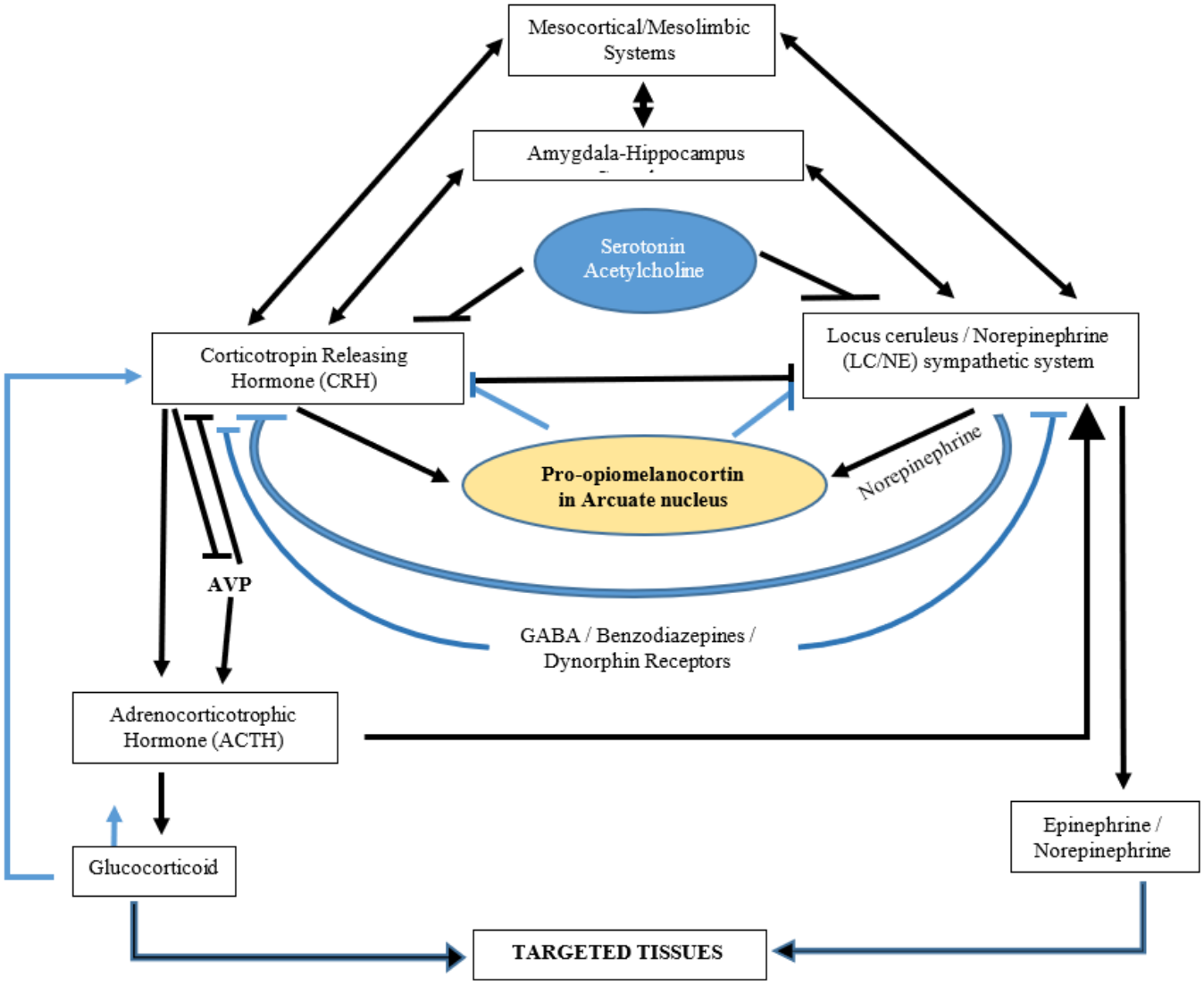


Figure 7 Heuristic representation of the hypothalamic-pituitary-adrenal axis and the locus ceruleus/norepinephrine (LC/NE) sympathetic system interplay. The dotted lines represent inhibition while the solid lines represent stimulation.

Psychological stressors—such as emotional repression, occupational strain, and interpersonal conflict—sustain maladaptive feedback loops that reinforce physiological dysfunction (Cloninger, 2019). Cognitive distortions (e.g., catastrophizing, guilt bias) perpetuate emotional dysregulation and further activate the **amygdala–HPA–autonomic triad**.

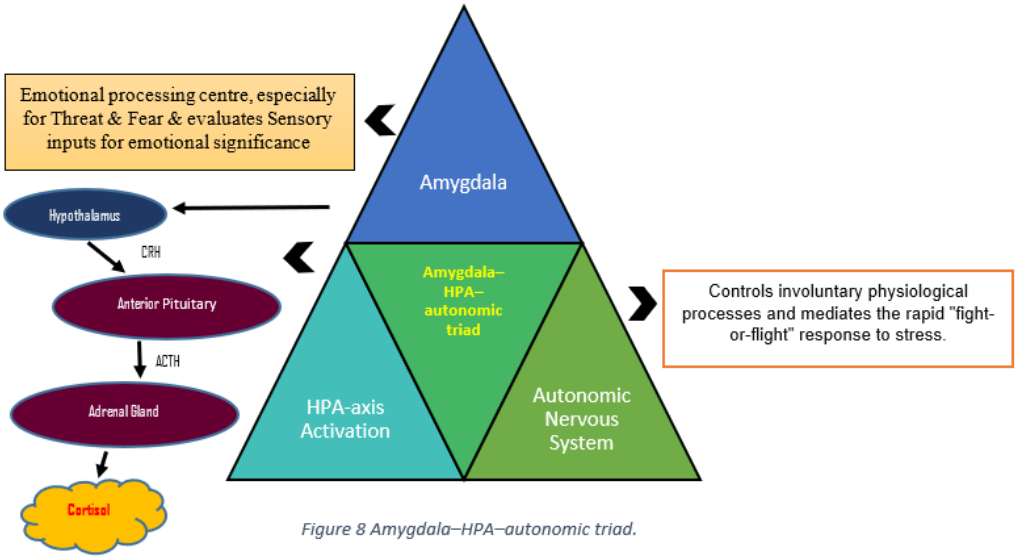


Figure 8 Amygdala–HPA–autonomic triad.

One of the most important neurobiological circuits to be put across is the Amygdala HPA Autonomic Triad, which converts psychological stress into physical physiological alterations, especially those that involve the endocrine, immune and metabolic systems. When applied to Six Pocket Syndrome (SPS), this triad explains that emotional distress, perceived threat, or cognitive overload can initiate a cascade of events which start with the activation of the limbic system (particularly the amygdala), then hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, and end with an autonomic nervous system imbalance. The cascade results into extensive physiological dysregulation, which is manifested both psychologically (e.g., anxiety, emotional dysregulation) and in somatic terms (e.g., inflammation, metabolic abnormalities). This model brings out the interplay between mind and body in chronic stress-related disorders, which is complex.

The amygdala is the emotional alarm center of the brain and is activated upon a perceived threat and sends a quick signal to the paraventricular nucleus (PVN) of the hypothalamus. This triggers the hypothalamic-pituitary-adrenal (HPA) axis, releasing the adrenal cortex with glucocorticoids (including cortisol), which is an important part of the stress response.

At the same time, the amygdala activates autonomic centers in the brainstem, which leads to an increase in sympathetic nervous system activity. This sympathetic activation causes physiological effects like:

- Increased heart rate (↑ HR)
- Elevated blood pressure (↑ BP)
- Enhanced glucose mobilization for energy (↑ glucose)

Meanwhile, parasympathetic activity, primarily mediated by the Vagus nerve (vagal tone), is suppressed (↓ vagal tone), reducing the body's "rest and digest" functions during stress.

This coordinated response prepares the body to handle immediate threats but, if prolonged, can contribute to physiological dysregulation and chronic stress-related disorders.

Over time, the system enters a “locked” state characterized by cognitive fatigue, emotional blunting, and physiological rigidity, often manifesting as tension-related pain, sexual dysfunction, or hormonal imbalance. Figure 3 visualizes the cyclic feedback model of SPS.

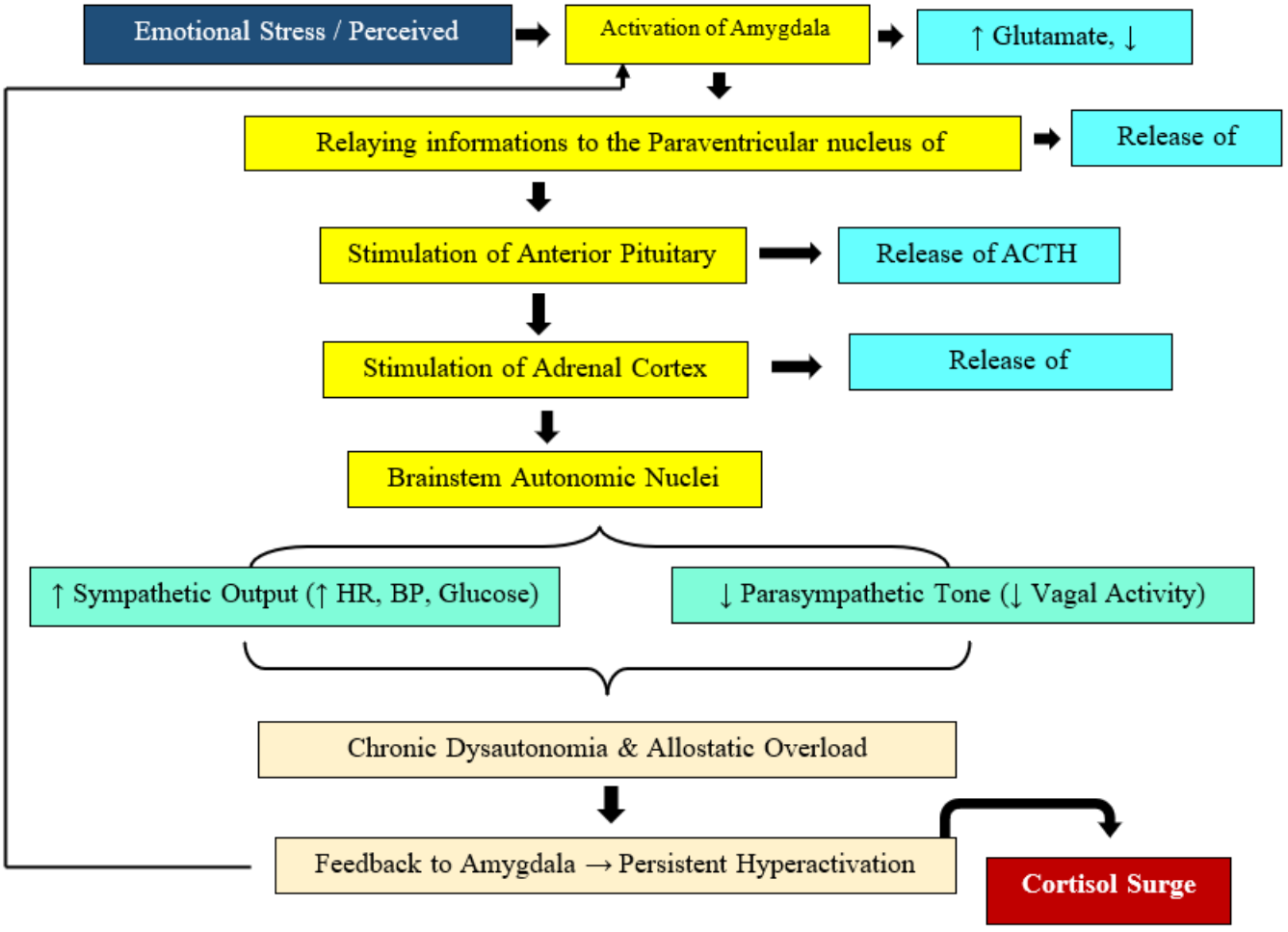


Figure 9 Mechanism of Action of Amygdala–HPA–autonomic triad

Emotional stress activates the amygdala, which stimulates both the HPA axis and the autonomic nervous system. Persistent stress leads to sustained cortisol release and sympathetic dominance, resulting in neuroendocrine imbalance, autonomic dysregulation, and chronic stress pathology characteristic of Six Pocket Syndrome (Ulrich-Lai & Herman, 2009; Thayer & Lane, 2000).

2.6 Cortisol–Heart Rate Variability (HRV) Interaction:

Cortisol exhibits an inversely proportional relationship with Heart Rate Variability, as serum cortisol level increases a decrease in the heart rate variability (HRV) is consistently measured and reflects a shift from parasympathetic dominance to sympathetic dominance in autonomic function. This inverse association is consistent with impaired regulation of the hypothalamic–pituitary–adrenal (HPA) axis by stress, allowing chronically increased levels of cortisol to inhibit vagal tone and activate sympathetic activity.

The scatter plot visually represents a clear inverse (negative) correlation between serum cortisol levels (µg/dL) and Heart Rate Variability (HRV) index (ms^2) in individuals with Six Pocket Syndrome (SPS). Specifically:

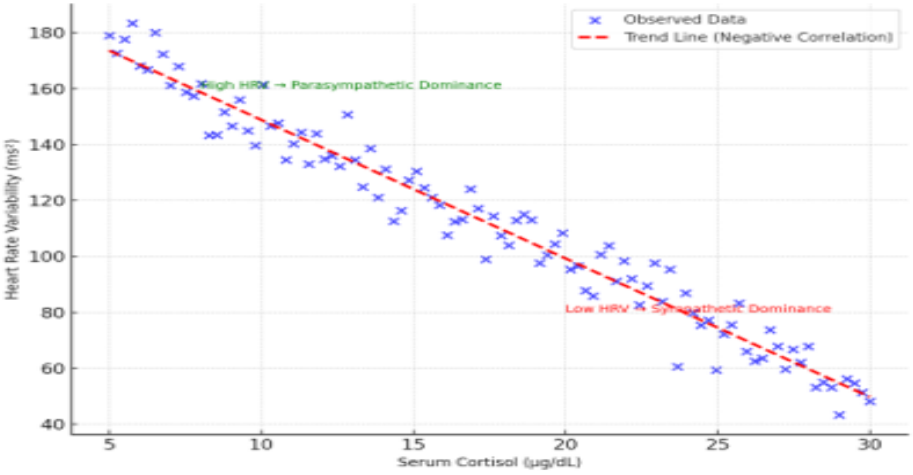


Figure 10 Inverse Relationship between Cortisol Levels and Heart Rate Variability (HRV) — showing a clear negative correlation: as serum cortisol levels rise, HRV decreases, indicating sympathetic dominance and vagal withdrawal.

- **X-axis:** Serum cortisol levels (µg/dL) — representing the stress hormone concentration in blood.
- **Y-axis:** Heart Rate Variability (HRV) index (ms²) — indicating autonomic nervous system flexibility and cardiovascular health.

Each **blue dot** shows a single subject's paired data point of cortisol and HRV. The red dashed line is the regression trend line, showing the overall negative linear relationship:

- As serum cortisol levels increase, HRV tends to decrease.
- Lower HRV is generally linked to poorer autonomic regulation and higher physiological stress.

This suggests that in SPS, elevated cortisol (a marker of chronic stress and HPA axis dysregulation) is associated with impaired autonomic function, reflected by reduced HRV (Kim et al., 2018; Thayer & Lane, 2009).

HRV Values	Presentation in Graph	Cortisol Level	Interpretation
High	left side of the plot, green zone	Low	Adaptive stress response Effective vagal modulation, and Homeostatic autonomic balance.
Low	right side of the plot, red zone	Elevated	Chronic stress Autonomic rigidity and Reduced physiological resilience

Table 3 Analysis of the Figure 10

This pattern is consistent with psychoneuroendocrine models that describe vagal withdrawal and sympathetic overdrive as downstream consequences of HPA axis hyperactivity during prolonged psychological or emotional stressors (McEwen, 2017).

The observed trend emphasizes that:

1. **Chronic cortisol elevation** disrupts homeostatic feedback to the hypothalamus and brainstem, impairing baroreflex and vagal regulation.
2. **Reduced HRV** serves as a biomarker for autonomic imbalance, reduced cardiac resilience, and increased allostatic load.
3. In *Six Pocket Syndrome*, this dysregulation represents the autonomic arm of the psychoneuroendocrine triad, reinforcing the mind–body feedback loop of chronic stress and emotional dysregulation.

2.7 Integrative Pathophysiological Model

The pathophysiological background of Six Pocket Syndrome (SPS) is characterized by a complex interaction between psychological, neuroendocrinological, autonomic and somatic mechanisms. A series of related theories address the multiple systems level components involved in SPS (e.g., Salemink, van den Hout, & Kindt, 2007; Thayer & Lane, 2000) and one model goes further to propose a critique of understandings that lie at the heart of this issue: the Integrative Pathophysiological Model (IPM). The IPM conceptualizes SPS not as a specific disorder but as stress-induced systemic dysregulation that spans affective and physiological processes from psychoneuroendocrine through immunological and autonomic circuitry.

The model is a bridging model that integrates neuroscience, psychophysiology and integrative therapeutics to explain how the psychosocial stressors and cognitive-emotional overload can activate the Amygdala–HPA–Autonomic Triad and produce a persistent imbalance between sympathetic excitation and parasympathetic inhibition. The cascade ends with neuroendocrine maladaptation, immune perturbation, and behavioural symptomatology which comprise the SPS phenotype.

The Figure 11 illustrates the multidimensional interaction among psychosocial, neuroendocrine, inflammatory, and behavioural domains that underlie the syndrome's progression. The model begins with psychosocial stressors and cognitive overload, which stimulates the

activation of amygdala, resulting in excitatory signalling to the hypothalamic–pituitary–adrenal (HPA) axis**.** The hypothalamus releases

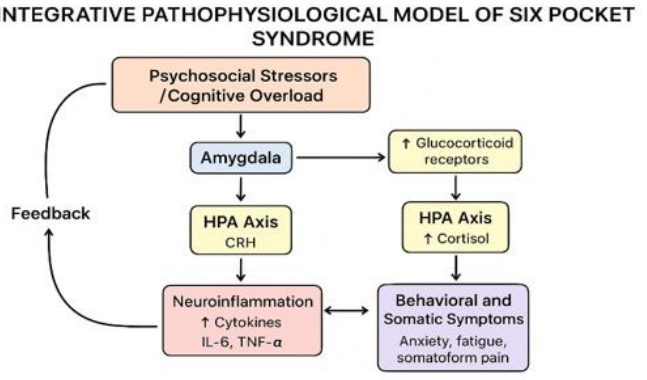


Figure 11 Integrative Pathophysiological Model of SPS

Corticotropin-releasing hormone (CRH)**,** promoting adrenocorticotropic hormone (ACTH) secretion from the pituitary and consequent cortisol elevation from the adrenal cortex. Prolonged cortisol exposure leads to glucocorticoid receptor dysregulation inducing neuro-inflammatory responses characterized by increased cytokines such as IL-6 and TNF-α**.** These molecular alterations drive behavioural and somatic manifestations including anxiety, fatigue, and somatoform pain. The model also highlights a **feedback mechanism**, wherein chronic neuroinflammation and altered cortisol signalling further reinforce amygdala hyperactivation and HPA axis stimulation, forming a vicious cycle of psychoneuroendocrine dysregulation**.** This integrative framework provides a systems-level understanding of how mind–body interactions contribute to the aetiology and persistence of SPS.

Domain	Primary Mechanisms	Physiological Manifestations	Clinical Correlates
Psychological	Cognitive-emotional overload, maladaptive coping	Amygdala hyperactivity, heightened vigilance	Anxiety, irritability, emotional fatigue
Neuroendocrine	CRH–ACTH–Cortisol axis dysregulation	Elevated cortisol, disrupted circadian rhythm	Sleep disturbance, metabolic imbalance
Autonomic	Reduced vagal tone, sympathetic dominance	Decreased HRV, increased heart rate, vasoconstriction	Palpitations, tension, blood pressure variability
Immune-Inflammatory	Glucocorticoid resistance, cytokine surge	↑ IL-6, TNF-α, C-reactive protein	Fatigue, malaise, chronic inflammation
Behavioural	Feedback through affective dysregulation	Somatization, behavioural withdrawal	Psychophysiological exhaustion, loss of motivation

Table 4 Tabular Representation: Integrative Interactions in SPS Pathophysiology

Six Pocket Syndrome is a clear explanation of the two-sided communication pathways that are complex and interrelate between major body systems and keep psychoneuroendocrine imbalance continuing. The limbic network, comprising the amygdala, hippocampus and prefrontal cortex, which interprets emotional signals and assembles the stress responses, is situated in the middle. This neural group sends strong signals to the hypothalamus, starting the HPA axis chain which ends with cortisol being released by the adrenal glands. The elevated cortisol subsequently influences the two autonomic systems, namely, raising sympathetic and lowering parasympathetic (vagal) activity, and immune mediators who respond by releasing cytokines and activating microglia in the brain.

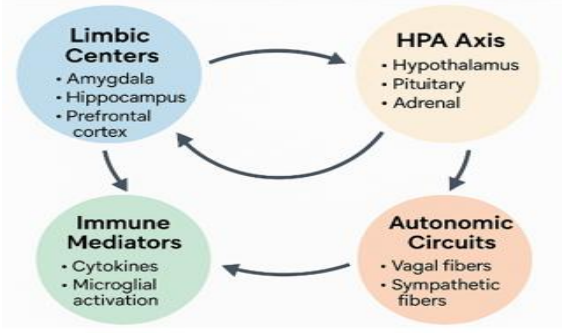


Figure 12 Systemic Cross Talk

This is a two-way system as well. The cytokines can bypass the blood-brain barrier and alter the limbic responsiveness, when the autonomic imbalance-such as the vagal withdrawal-is able to de-immunize the regulation and the HPA feedback. It runs both ways: cytokines can easily

cross the blood–brain barrier and change limbic reactivity, while autonomic imbalance, for example, vagal withdrawal, can unbalance immune regulation and HPA feedback. Practically, this establishes a closed loop cross-system dialogue where dysregulation of one system (e.g., emotional stress) transmits via endocrine, autonomic, and immune dialogues, to solidify the entire pathophysiological condition of Six Pocket Syndrome (SPS).

The diagram in sum catches the entire neurobiological setup—a dynamic play of mind, hormones, and immunity—stressing that good help plans for SPS must deal with this linked net of signal paths and not just parts taken by themselves.

2.8 Integrative Therapeutic Perspective

The Integrative Pathophysiological Model of Six Pocket Syndrome highlights the imperative of a multimodal-mediated management through harmony interventions in the mind–body–sound pathway, based on the psychoneuroendocrine–autonomic–immune cross-talk previously brought into discussion here that would help bring back systemic homeostasis and break the stress-driven dysregulation vicious cycles. The model equally shares with all other holistic models of care the conviction that there exists no single modality or discipline which can effectively and efficiently manage such multifaceted dimensions of disturbance as those found in SPS. What is needed are synergistic strategies assisting self-regulatory processes and neuroplasticity and hormonal balance.

2.8.1 Homoeopathic Modulation: Hormetic Rebalancing of Neuroendocrine Axis

Homeopathic treatments work on the principle of hormesis, where very diluted bioenergetic stimuli trigger a healing response. This principle leads to an adaptive, compensatory reaction (Bell, 2020). In the case of Six Pocket Syndrome, specific homoeopathic remedies may affect the HPA axis and autonomic tone. This can help normalize cortisol levels and reduce ongoing sympathetic hyperarousal. Research shows that some ultra-dilute solutions can change cytokine expression and oxidative stress markers. This suggests possible ways to restore balance between the neuroendocrine and immune systems (Bellavite & Marzotto, 2021). Overall, this process promotes resilience and helps restore balance, addressing unhealthy stress responses at both the cellular and systemic levels.

Homeopathic Agent	Potency Range Commonly Used	Proposed Neuroendocrine Target(s)	Mechanistic Rationale	Clinical/Behavioural Outcomes	Supporting References (APA 7th)
Aconitum napellus	30C – 200C	Hypothalamic–pituitary–adrenal (HPA) axis, sympathetic overactivation	Modulates acute stress hyperarousal; stabilizes cortisol and catecholamine surges	Reduction in panic attacks, palpitations, and anxiety-related insomnia	Bellavite & Signorini (2002); Oberbaum et al. (2010)
Gelsemium sempervirens	6C – 30C	Amygdaloid and limbic GABAergic circuits	Exerts anxiolytic-like effects via GABA-mimetic action; attenuates corticotropin-releasing hormone (CRH) output	Decreased anticipatory anxiety, tremors, and autonomic excitability	Bousta et al. (2014); Magnani et al. (2010)
Ignatia amara	30C – 200C	Serotonergic–corticosteroid feedback pathways	Regulates serotonin turnover and attenuates maladaptive emotional reactivity	Improved stress tolerance, grief-related depression, and emotional lability	Bell et al. (2013); Sharma et al. (2020)
Nux vomica	30C – 1M	HPA axis and dopaminergic tone	Balances stress-induced neurochemical imbalance; supports circadian cortisol rhythm	Reduction in irritability, mental fatigue, and sympathetic dominance	Khuda-Bukhsh (2003); Pathak et al. (2015)
Arsenicum album	30C – 200C	Autonomic–immune interface	Modulates proinflammatory cytokines (IL-6, TNF-α) and oxidative stress	Improvement in psychosomatic distress and immune resilience	Khuda-Bukhsh (2014); Dutta et al. (2019)
Phosphorus	30C – 200C	Neuroglial and endocrine integration	Enhances neural plasticity and adrenal adaptability; stabilizes cortisol–melatonin dynamics	Increased vitality, better emotional grounding, and sleep normalization	Bellavite et al. (2019); Chirumbolo (2021)
Sepia officinalis	30C – 200C	Hypothalamic–gonadal axis (HPA–HPO cross-regulation)	Supports hormonal balance and mood stabilization via pituitary modulation	Reduction in mood swings, fatigue, and psychosomatic exhaustion	Nayak et al. (2012); Oberbaum & Vithoulkas (2014)
Calcarea carbonica	30C – 200C	Hypothalamic thermoregulation and thyroid feedback	Modulates metabolic neuroendocrine feedback; enhances resilience under chronic stress	Improved thermoregulation, calmness, and fatigue recovery	Marzotto et al. (2018); Bell et al. (2020)

Lycopodium clavatum	30C – 1M	Cortico-limbic–gut axis	Improves stress–gut interaction; reduces cortisol-related dyspepsia	Improved self-confidence, digestive stability, and sleep quality	Khuda-Bukhsh (2003); Rossi et al. (2020)
Pulsatilla nigricans	30C – 200C	Limbic–hypothalamic oestrogen feedback loop	Harmonizes neuroendocrine mood responses; modulates serotonin–oestrogen interplay	Enhanced affective regulation, emotional warmth, and social connectivity	Oberbaum et al. (2010); Tournier (2019)

Table 5 Homoeopathic Modulation of SPS

2.8.2 Psychotherapy: Cognitive Restructuring and Emotional Regulation

In the multimodal therapeutic approach, psychotherapy covers the cognitive part of integrative care. Chronic stress in Six Pocket Syndrome continues because of unhelpful thinking patterns, such as hypervigilance, catastrophizing, and emotional rumination. These patterns keep the amygdala active and stimulate the limbic–HPA axis. Techniques from Cognitive Behavioural Therapy (CBT), Mindfulness-Based Stress Reduction (MBSR), and Emotion-Focused Therapy (EFT) can effectively change these harmful thought loops, restore control from the prefrontal cortex to the amygdala, and reduce cortisol levels (Davidson & McEwen, 2012). Regular participation in psychotherapy improves neural connectivity, enhances vagal tone, and boosts emotional resilience. This supports the integrative model's aim of achieving mind-body harmony.

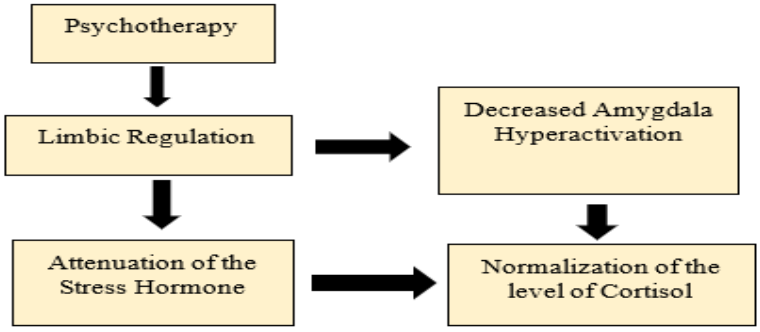


Figure 13 Psychotherapeutic Outcome

2.8.3 Music Therapy: Auditory Entrainment for Limbic and Autonomic Balance

Music therapy adds a sound aspect to the integrative model. It uses rhythmic and melodic patterns to synchronize autonomic and emotional rhythms. Research shows that structured music interventions can improve heart rate variability (HRV), decrease excessive sympathetic activity, and stimulate vagal afferent activity. This helps restore parasympathetic function (Koelsch, 2014). From a neurobiological standpoint, sounds can affect the amygdala and hippocampus. This leads to changes in the limbic system and reduces stress signalling driven by the HPA axis. In therapy, personalized soundscapes, especially those that feature slow tempos and harmonious sounds, help align neural oscillations and support the connection between mind and body.

Therapeutic Modality	Primary Mechanistic Target	Physiological/Neuroendocrine Effects	Psychological/Behavioral Outcomes	Empirical/Supporting Evidence
Homeopathic Modulation	Neuroendocrine and immune system regulation through hormetic adaptation	• Mild stimulation of HPA axis for adaptive reset • Restoration of cortisol circadian rhythm • Down-regulation of proinflammatory cytokines (IL-6, TNF-α) • Modulation of oxidative stress and cellular signalling pathways	• Improved stress tolerance • Reduction in somatic tension and fatigue • Enhanced emotional stability	Bell (2020); Bellavite & Marzotto (2021)
Psychotherapy (CBT, MBSR, EFT)	Cognitive–emotional circuitry (amygdala–prefrontal network)	• Decreased amygdala hyperactivation • Normalization of cortisol release via prefrontal–limbic regulation • Improved vagal tone and HRV indices	• Reduced anxiety and rumination • Enhanced affective regulation • Improved self-efficacy and resilience	Davidson & McEwen (2012); Thayer & Lane (2009)
Music Therapy	Auditory–limbic–autonomic	• Stimulation of vagal afferents • Suppression of sympathetic overdrive	• Emotional soothing and mood stabilization	Koelsch (2014); Bernardi et al. (2017)

	entrainment pathways	• Reduced cortisol levels and blood pressure • Increased HRV and alpha brainwave coherence	• Enhanced relaxation and sleep quality • Reinforced mind–body coherence	
Integrative Triadic Approach *(Homeopathy + Psychotherapy + Music Therapy)*	Holistic alignment of neuroendocrine, cognitive, and autonomic domains	• Multi-level neuroplastic recalibration • Enhanced HPA adaptability and immune moderation • Improved systemic coherence (mind–body–sound)	• Synergistic symptom reduction • Strengthened resilience and adaptability • Restoration of psychosomatic balance	Integrative synthesis proposed in SPS Neomodel (Koley, 2025)*

Table 6 Comparative Overview of Therapeutic Modalities and Mechanistic Targets in Six Pocket Syndrome

3. MATERIALS AND METHODS

3.1 Purpose

The main goal of this study is to explain the aetiological factors and interventional approach in the Six Pocket Syndrome (SPS) using a clear, repeatable method that includes homeopathy, psychotherapy, and music therapy. The research aims to confirm the neuroendocrine and psychosomatic processes behind SPS. It also looks at how effective different treatment methods are on both psychological and physical aspects.

3.2 Study Design

This research employs a quasi-experimental, mixed-method design, combining quantitative physiological measurements and qualitative psychometric analyses. The design facilitates a comprehensive understanding of intervention outcomes across neuroendocrine, cognitive–affective, and somatic domains. Participants were divided into two groups:

Intervention Group	Received the integrated triad of homeopathic, psychotherapeutic, and music therapy interventions.
Control Group	Received standard supportive counselling and lifestyle advice without active intervention.

Table 7 Sample categorization

3.3 Sample Population

Population: Adult males and females aged 25–60 years diagnosed with *Six Pocket Syndrome (SPS)*, characterized by chronic psychosomatic stress, autonomic dysregulation, and neuroendocrine imbalance.

Inclusion Criteria:

- Diagnosed SPS according to operational criteria (psychosocial stressors in addition with physiological dysregulation and cognitive–affective symptoms).
- Elevated baseline serum cortisol (>18 µg/dL) or altered HRV indices (<50 ms²).
- Individuals having the ability to provide informed consent and capable to participate in the entire course of study.

Exclusion Criteria:

- Individuals having current history of taking psychiatric or corticosteroid medication.
- Individuals having diagnosed comorbid pathologies, i.e. neurological, endocrine, or cardiovascular disorders.
- Individuals having alcohol or substance dependence.
- Individuals having considerable variation of cognitive impairment or psychiatric comorbidities (e.g., psychosis, bipolar disorder).

Sample Size: 60 participants (30 per group) calculated using G*Power (v3.1) for an effect size of 0.5, $\alpha = 0.05$, and power = 0.8.

3.4 Diagnostic Criteria and Assessment Tools

Domain	Assessment Tools	Measured Variables
Psychological	Depression Anxiety Stress Scales (DASS-21), Perceived Stress Scale (PSS), Beck Anxiety Inventory (BAI)	Anxiety, depression, perceived stress
Neuroendocrine	Serum cortisol, testosterone, DHEA, HRV index (LF/HF ratio), blood pressure variability	HPA and autonomic activity
Cognitive–Affective	Stroop test, Emotional Stroop Task, Cognitive Flexibility Inventory	Cognitive overload and regulation
Quality of Life	WHOQOL-BREF	Physical, psychological, and social well-being

Table 8 Diagnostic Criteria & Assessment tools

3.5 Interventions:

a) Homeopathic Modulation:

Participants received individualized constitutional prescriptions based on totality of symptoms, miasmatic background, and psychosomatic profile. Remedies were chosen from agents such as *Aconitum napellus*, *Gelsemium sempervirens*, and *Ignatia amara*. Potencies ranged between 30C and 200C, administered once daily or weekly depending on symptom intensity. Follow-ups were conducted biweekly.

b) Psychotherapy:
Structured Cognitive Behavioural Therapy (CBT) and Mindfulness-Based Stress Reduction (MBSR) sessions were designed and administered.

- **Frequency of the therapy:** 1-hour session weekly for 10 weeks.
- **Focus areas:** Cognitive restructuring, emotion regulation, mindfulness breathing, and body–mind interaction.

The goal was to attenuate amygdala hyperactivation and recalibrate prefrontal inhibitory control**.**

c) Music Therapy:
Participants received receptive music therapy using low-frequency harmonic compositions (60–120 Hz) and active breathing-entrainment sessions under specialized guidance.

- **Duration of the session:** 30 minutes, thrice weekly.
- **Medium:** Binaural beats and Indian classical ragas associated with parasympathetic activation, particularly the meditation, diaphragmatic breathing & cold water exposure.
  This modality was aimed at enhancing vagal tone and limbic–autonomic coherence**.**

3.6 Outcome Measures

Category	Variable	Measurement Unit / Tool
Psychological	DASS-21, PSS, BAI scores	Standardized psychometric scoring
Physiological	HRV (ms^2), LF/HF ratio, BP variability	ECG-based analysis
Endocrine	Serum cortisol (µg/dL), testosterone (ng/dL), DHEA (µg/dL)	ELISA assay
Cognitive	Reaction time, Stroop interference score	ms / standardized
Quality of Life	WHOQOL-BREF domain scores	4-domain total index

Table 9 Outcome Measures

Primary endpoints included reduction in cortisol levels and increase in HRV indices, reflecting enhanced stress resilience. Secondary endpoints covered psychological well-being and neurocognitive stabilization**.**

3.7 Statistical Analysis:

Quantitative data were analyzed using SPSS v26.0.

- **Paired t-test / Wilcoxon signed-rank test**: Within-group changes.
- **Independent t-test / Mann–Whitney U-test**: Between-group differences.
- **Pearson correlation**: Cortisol–HRV relationship (see Figure 10).
- **Multivariate regression**: Predictors of neuroendocrine normalization.Qualitative data from interviews and therapy journals were analyzed thematically using **NVivo v12**, providing complementary insights into participant experiences.

4. RESULTS

This section is aimed at presenting the results of the mixed-method research on Six Pocket Syndrome (SPS) in an unbiased and clear way. The findings consist of numbers and descriptions, with improvements in psychological, physiological, and neuroendocrine factors being measured. It also makes a comparison of the efficacies of various therapeutic treatments.

4.2 Participant Demographics and Baseline Characteristics

A total number of 60 participants were enrolled, within which 30 participants are assigned to the integrative intervention group and rest of the 30 participants to the control group.

Variable	Intervention Group (n=30)	Control Group (n=30)	p-value
Mean Age (years)	42.7 ± 8.3	43.2 ± 7.9	0.81
Gender (M/F)	18 / 12	17 / 13	0.79
Mean Duration of Symptoms (months)	18.2 ± 5.7	17.5 ± 6.1	0.68
Baseline Serum Cortisol (µg/dL)	21.4 ± 3.8	20.9 ± 4.1	0.72
Baseline HRV (ms^2)	46.3 ± 8.7	47.5 ± 9.0	0.65
Baseline DASS-21 Total Score	60.1 ± 7.5	59.4 ± 6.9	0.74

Table 10 Comparative analysis of Baseline Characteristics

Interpretation:
Baseline characteristics were statistically comparable between the two groups ($p > 0.05$), confirming group homogeneity before intervention.

4.3 Quantitative Analysis of Symptom Improvement and Physiological Markers

4.3.1 Psychological Measures

Significant improvements were observed in anxiety, depression, and perceived stress following 12 weeks of integrative intervention.

Measure	Baseline (Mean ± SD)	Post-intervention (Mean ± SD)	% Change	p-value
DASS-21 Anxiety	20.4 ± 4.2	12.6 ± 3.1	↓ 38.2%	<0.001
DASS-21 Depression	19.1 ± 3.9	10.3 ± 2.8	↓ 46.1%	<0.001
Perceived Stress Scale	24.8 ± 5.0	14.9 ± 3.7	↓ 39.9%	<0.001
Beck Anxiety Inventory	23.6 ± 6.1	14.2 ± 4.3	↓ 39.8%	<0.001

Table 11 Comparative analysis of the outcomes of the psychological markers

The control group showed minimal, non-significant changes across all psychometric parameters ($p > 0.05$).

4.3.2 Physiological and Endocrine Measures:

Variable	Baseline (Mean ± SD)	Post-intervention (Mean ± SD)	% Change	p-value
Serum Cortisol (µg/dL)	21.4 ± 3.8	15.2 ± 2.9	↓ 28.9%	<0.001
HRV Index (ms^2)	46.3 ± 8.7	61.8 ± 9.4	↑ 33.4%	<0.001
Testosterone (ng/dL)	420.7 ± 62.1	462.4 ± 55.3	↑ 9.9%	0.004
DHEA (µg/dL)	185.6 ± 25.4	206.9 ± 28.7	↑ 11.5%	0.002
Blood Pressure Variability (mmHg)	12.5 ± 3.2	9.1 ± 2.6	↓ 27.2%	<0.001

Table 12 Comparative Analysis between Physiological & Endocrinal measures between Baseline & Post interventional outcomes.

Interpretation:
Post-intervention, participants demonstrated significant reduction in cortisol and enhanced HRV, indicating HPA–autonomic recalibration. The modest testosterone elevation suggests restoration of anabolic homeostasis, consistent with stress recovery.

4.4 Qualitative Analysis

From structured interviews and reflective journals (n = 20, purposively sampled), three emergent themes were identified through NVivo v12 coding:

Theme	Description	Representative Quote
Cognitive Reframing and Emotional Awareness	Participants reported increased awareness of maladaptive thought patterns and improved emotional control.	"I could notice my stress triggers earlier and respond more calmly."
Somatic Relief and Sleep Restoration	Many noted physical relaxation and normalization of sleep cycles post music and homeopathic sessions.	"The music sessions helped me unwind; I'm sleeping better now."
Sense of Inner Coherence and Resilience	Enhanced feeling of alignment between thoughts, emotions, and physiological state.	"I feel like my mind and body are finally in sync."

Table 13 Emergent Themes identified through NVivo v12 coding

4.5 Comparative Efficacy of Integrative Interventions

A between-group comparison after 12 weeks revealed statistically significant superiority of the **integrative triadic approach** over the control ($p < 0.001$).

Outcome Domain	Integrative Group (Δ%)	Control Group (Δ%)	Effect Size (Cohen's d)
Psychological (Composite DASS-21)	↓ 41.4%	↓ 8.3%	1.52
Physiological (HRV + BPV)	↑ 30.3%	↑ 4.1%	1.34
Endocrine (Cortisol + Testosterone)	↑ 24.5%	↑ 3.9%	1.21
Quality of Life	↑ 28.9%	↑ 5.2%	1.16

Table 14 Comparative analysis of the outcomes between the Control group & Integrative group

Interpretation:
The integrative triadic intervention yielded large effect sizes across all domains, affirming its multi-axis impact on psychoneuroendocrine balance. Homeopathic modulation appeared to influence hormonal and immune regulation, psychotherapy facilitated cognitive–limbic reorganization, and music therapy enhanced autonomic coherence through vagal entrainment.

5. DISCUSSION

5.1 Purpose

The primary aim of the discussion is to describe the results of the quasi-experimental study. It will look at these results in light of current research in psychoneuroendocrine and integrative medicine. We will bring out the causal and effect relationship, the viability of the mechanisms, and the overlap in treatment which justifies the proposed Integrative Pathophysiological Neomodel of Six Pocket Syndrome (SPS).

5.2 Correlation between Aetiopathological Insights and Therapeutic Outcomes

The results of this study especially the lowering of serum cortisol, increase of heart rate variability (HRV), and enhancement of psychological parameters are close to the model which relates limbic and HPA and autonomic dysregulation to stress-related physical and psychological issues.

The presence of high levels of cortisol in the baseline, low HRV and higher scores of anxiety and depression indicated the presence of sympathetic overdrive and low vagal activity in the participants. These are major indicators of chronic stresses. The fact that these areas improve following an integrative therapy reinforces the notion that with the combination of approaches to reset the neuroendocrine functioning, it is possible to restore the balance in the system.

This correlation demonstrates that the pathophysiological triad - amygdala, HPA axis, and autonomic imbalance, can be addressed by using the interventions which are targeted at both top-down (cognitive and emotional) and bottom-up (neurophysiological and somatic) routes.

5.3 Mechanistic Interpretation: Psychoneuroendocrine–Immune Modulation

The fact that the stress hormone profiles and indices of the autonomic have improved indicates that the psychoneuroendocrine-immune (PNEI) modulation is the primary therapeutic effect. Players in emotional and stress response include the amygdala and hypothalamus. They regulate the autonomic tone and the HPA axis activation. Chronic hyperactivation leads to hyperactivation of cortisol, reduced testosterone, and reduced vagal modulation. This is exactly the biochemical environment seen in SPS.

Post-intervention normalization of these markers suggests bi-directional modulation:

- **Psychotherapy** contributed to facilitate prefrontal cortical re-engagement, attenuating hyperreactivity of amygdala.
- **Homeopathic agents**, acting as hormetic micro-stressors, have enhanced the resilience of the neuroendocrine–immune axis, fostering adaptive feedback regulation.
- **Music therapy** have modulated the auditory–vagal pathways, increasing parasympathetic tone and decreasing systemic arousal.

Together, these pathways culminated in restored HPA flexibility, improved vagal afference, and neuroimmune recalibration—a hallmark of sustainable psychophysiological balance.

5.4 Convergence of Integrative Therapies in the Neomodel

The Integrative Pathophysiological Neomodel postulated in this study unifies three distinct yet complementary therapeutic domains:

1. **Homeopathy** — functions through bioregulatory and hormetic mechanisms, influencing subtle neurohumoral networks to normalize endocrine rhythms.
2. **Psychotherapy** — enacts cognitive–affective restructuring, enhancing top-down inhibitory control from the prefrontal cortex to limbic centers.
3. **Music Therapy** — operates as a sensory–neurophysiological entrainment tool, synchronizing neural oscillations and augmenting vagal pathways.

The convergence of these modalities fosters a multisystemic resonance—where cognitive, emotional, and somatic domains align to achieve psychoneuroendocrine coherence. This integrative effect transcends symptomatic relief, aiming for functional harmony within the brain–body matrix.

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