Review Article

Orexinergic and Hypothalamic Dysfunction in CFS/ME: An Integrative Review with a Focus on Precision Medicine

Noé López-Amador[1]

1. Universidad Veracruzana, Mexico

Background: Chronic fatigue syndrome (CFS), or myalgic encephalomyelitis (ME), manifests as persistent (> 6 months) fatigue, post-exertional malaise and unrefreshing sleep, yet lacks validated biomarkers. We undertook an integrative review to synthesize neuroimaging, endocrine and immunological evidence and to build a unified mechanistic framework.

Methods: Following Whittemore and Knafl's five-stage integrative-review methodology, we searched PubMed, Scopus, Web of Science and OpenAlex (*Last Search*: April 2025). Studies meeting our inclusion criteria (quantitative, qualitative and theoretical) were appraised with an adapted Joanna Briggs tool.

Results: Neuroimaging studies report a 10 ± 3 % reduction in hypothalamic volume ($p < .001$) and a 0.12 ± 0.04 decrease in fractional anisotropy of the inferior frontoparietal fasciculus ($p = .005$). Endocrine assessments demonstrate hypocortisolism (morning cortisol 8.2 ± 1.5 µg/dL) and reduced cerebrospinal fluid orexin-A (250 ± 30 pg/mL). Immunological profiles reveal elevated interleukin-6 and tumor necrosis factor-α ($p < .05$). These findings converge on a model of hypothalamic–pituitary–adrenal axis hypoactivity and orexinergic dysfunction sustained by low-grade neuroinflammation.

Conclusions: This integrative review lead to propose experimental validation protocols—such as pre/post-intervention CSF orexin measurements with orexin-receptor modulators—and outline a precision-medicine roadmap targeting the orexin–HPA–inflammation axis.

 doi.org/10.32388/ZOZBH7.2

1. Introduction

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME) or systemic exertion intolerance disease (SEID), is a debilitating multisystem disorder characterized by persistent or relapsing fatigue lasting for more than six months, post-exertional malaise, and unrefreshing sleep[1]. Annual per-patient healthcare costs exceed USD 8,000, and productivity losses in the United States alone approach USD 24 billion, underscoring the substantial societal and economic burden of CFS/ME[2][3][4].

Diagnosis relies on the combination of (a) a substantial reduction in pre-illness activity levels for at least six months accompanied by profound fatigue not alleviated by rest; (b) post-exertional malaise; and (c) unrefreshing sleep, plus at least one of cognitive impairment or orthostatic intolerance[5][6]. Despite these consensus criteria, clinical evaluation is complicated by overlapping symptomatology in rheumatologic, psychiatric, endocrine, and multisystem conditions, leading to high rates of misdiagnosis and diagnostic delay[7].

Although primarily defined by clinical features, patients with CFS/ME frequently exhibit objective laboratory and neuroimaging abnormalities. Endocrine studies demonstrate blunted HPA-axis activity, with morning serum cortisol levels averaging 8.2 ± 1.5 µg/dL versus 11.0 ± 2.0 µg/dL in controls[8][9]. Pro-inflammatory cytokine profiles—particularly elevated interleukin-6 and tumor necrosis factor-α—are present in approximately 60 % of patients[10]. Neuroimaging techniques reveal a 10 ± 3 % reduction in hypothalamic volume[11][12] and microstructural white-matter disruptions in frontoparietal tracts[13], correlating with fatigue severity and cognitive dysfunction.

Current therapeutic approaches, including graded exercise therapy (GET) and cognitive-behavioral therapy (CBT), offer modest short-term benefit but lack durable efficacy[14][15]. Pharmacologic interventions—such as selective serotonin reuptake inhibitors, stimulants, and metabolic modulators—have produced mixed outcomes, and no gold-standard treatment has emerged[16].

Given these gaps, an integrative review is warranted to synthesize quantitative, qualitative, and theoretical evidence on the role of orexinergic and hypothalamic dysfunction in CFS/ME. By applying Whittemore and Knafl's[17] framework, we aim to[1] *map the spectrum of biomarkers* across neuroimaging, endocrine, and immunological domains;[2] *evaluate methodological rigor* and thematic convergence; and[3] *propose a conceptual model* and candidate biomarkers to guide precision-medicine strategies in CFS/ME.

2. Integrative Review Methods

For methodological rigor, this integrative review followed the Whittemore and Knafl's five-stage framework[17]:

2.1. Problem Identification

We formulated the primary question: "What evidence links orexinergic and hypothalamic dysfunction to CFS/ME pathophysiology?" Secondary objectives included mapping neuroimaging, endocrine, and immunological biomarkers and identifying mechanistic models.

2.2. Literature Search Strategy

Comprehensive searches were performed in PubMed, Scopus, Web of Science, and OpenAlex for publications from February 2000 to April 2025, using combinations of terms: "chronic fatigue syndrome" OR "myalgic encephalomyelitis" AND (orexin OR hypocretin OR hypothalamus OR HPA axis OR cytokine OR neuroimaging OR biomarker). References of included studies and relevant reviews were hand-checked to capture gray literature.

2.3. Eligibility and Study Selection

Peer-reviewed quantitative, qualitative, mixed-methods, and theoretical studies addressing CFS/ME diagnosed by recognized criteria that reported on orexin/hypothalamic metrics, HPA-axis measures, or inflammatory markers was included. Excluded were non-English reports, reviews, editorials, case series with < 5 subjects, and studies with significant comorbidities confounding neuroendocrine data.

2.4. Data Evaluation

Retrieved records were imported into a reference manager with duplicates removed. Titles/abstracts were screened, and full texts were assessed. Methodological quality across diverse designs was appraised using an adapted Joanna Briggs Institute tool[18], rating each study as *low*, *moderate*, or *high* risk of bias. Studies with high risk of bias, were eliminated.

2.5. Data Analysis and Synthesis

We extracted study characteristics, methods, and key findings into a standardized matrix. Quantitative biomarkers (e.g., hypothalamic volume, cortisol, orexin-A, cytokine levels) were tabulated, while

qualitative and theoretical insights (e.g., mechanistic hypotheses) were coded thematically. Findings were integrated to develop a conceptual model of orexin–hypothalamic dysregulation in CFS/ME.

2.6. Presentation of Results

Results are organized into neuroimaging biomarkers, endocrine indicators, immunological profiles, and integrative mechanistic frameworks. Limitations and research gaps are explicitly highlighted to guide future investigations.

3. Results

Table 1 concentrates quantitative results related to the findings of potential biomarkers reported in this integrative review:

Domain	Measure	CFS/ME	Controls	*p*-Value
Neuroimaging	Hypothalamic volume (% change)	−10 ± 3 %	—	< .001
	FA, inferior frontoparietal fasciculus (Δ)	−0.12 ± 0.04	—	0.005
Endocrine	Morning serum cortisol (µg/dL)	8.2 ± 1.5	11.0 ± 2.0	< .01
	CSF orexin-A (pg/mL)	250 ± 30	—	—
Immunology	IL-6 (proportion elevated)	60 %	—	< .05
	TNF-α (proportion elevated)	60 %	—	< .05

Table 1. Quantitative Biomarker Findings Across Physiological Domains in CFS/ME

This table summarizes key quantitative biomarkers identified in patients with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME), spanning neuroimaging, endocrine, and immunological domains. Measures include changes in hypothalamic structure and white matter integrity, reductions in

cortisol and orexin-A levels, and elevated pro-inflammatory cytokines. These findings support the model of hypothalamic–orexin–HPA axis disruption contributing to the clinical manifestations of CFS/ME.

3.1. Neuroimaging Biomarkers

Voxel-based morphometry studies demonstrate a 10 ± 3 % reduction in hypothalamic volume in CFS/ME patients compared with healthy controls[11][12]. Diffusion tensor imaging reveals decreased fractional anisotropy in the inferior frontoparietal fasciculus[13] and corpus callosum[19], correlating with cognitive impairment and fatigue severity.

3.2. Endocrine Indicators

Endocrine assessments indicate HPA-axis hypoactivity: morning serum cortisol averages 8.2 ± 1.5 µg/dL versus 11.0 ± 2.0 µg/dL in controls[8]. Cerebrospinal fluid orexin-A concentrations are reduced[20], supporting orexinergic dysfunction.

3.3. Immunological Profiles

A pro-inflammatory milieu is present in most CFS/ME cohorts. Blundell, Ray, Buckland, and White[10] reported elevated interleukin-6 and tumor necrosis factor-α in 60 % of patients ($p < .05$). Wong et al.[21] corroborated these findings, demonstrating an altered Th1/Th2 balance in CFS/ME relative to controls.

3.4. Synthesis of Convergent Findings

The convergence of structural atrophy, hypocortisolism, orexin-A reduction, and cytokine elevations supports a model in which HPA-axis hypoactivity and orexinergic dysfunction—driven by chronic low-grade neuroinflammation—underpin CFS/ME symptomatology (Table 2).

Theme	Key Findings	Representative Studies
HPA-Axis Hypoactivity	Blunted cortisol responses; altered diurnal rhythm	Di Giorgio et al.[8]; Papadopoulos & Cleare[9]
Orexinergic Dysfunction	Reduced CSF orexin-A; diminished wake-promoting drive	Grafe et al.[20]
Neuroinflammation	Elevated IL-6 and TNF-α creating a pro-inflammatory milieu	Blundell et al.[10]; Wong et al.[21]
Structural Atrophy	Hypothalamic volume loss; microstructural white-matter disruptions	Puri et al.[11]; Finkelmeyer et al.[12]
Feedback-Loop Dynamics	Cytokine-driven impairment of both HPA and orexin networks, perpetuating symptom cycle	Papadopoulos & Cleare[9]

Table 2. Thematic Synthesis of Mechanistic Insights in CFS/ME

This table presents the main physiological and pathophysiological themes identified through integrative synthesis. Each theme is linked to representative empirical findings and supporting studies, reflecting the interplay between hypothalamic–pituitary–adrenal (HPA) axis dysfunction, orexinergic signaling deficits, neuroinflammation, and structural brain changes. Together, these themes form the conceptual framework underlying symptomatology and guide future biomarker and therapeutic research in CFS/ME.

4. Theoretical Framework

4.1. Hypothalamic Anatomy and Homeostatic Regulation

The hypothalamus, located beneath the thalamus around the third ventricle, is subdivided into anterior (preoptic), tuberal, and posterior regions with distinct medial and lateral nuclei that regulate energy balance, thermoregulation, circadian rhythms, autonomic function, and stress responses[22]. In CFS/ME, alterations in lateral hypothalamic and paraventricular nuclei may disrupt these homeostatic processes, contributing to sleep–wake dysregulation and metabolic imbalance[23].

4.2. Orexinergic Signaling Pathways

Orexin-A and orexin-B (hypocretins) are neuropeptides derived from prepro-orexin in lateral hypothalamic neurons, acting via G protein–coupled receptors OX1R and OX2R to activate phospholipase C, protein kinase C, adenylyl cyclase/cAMP, and MAPK cascades. They modulate arousal, feeding, and autonomic tone through widespread projections to brainstem and limbic regions[24][25]. Reduced orexin-A levels in CFS/ME[20] imply impaired excitatory drive on these circuits.

4.3. Integration: Orexin–HPA–Inflammation Feedback Loops

Chronic low-grade neuroinflammation—evidenced by elevated IL-6 and TNF-α in 60 % of patients[10]—can suppress orexin neuron activity and blunt HPA axis responses[9]. Conversely, HPA hypoactivity[8] reduces cortisol's anti-inflammatory feedback, perpetuating cytokine release and further eroding orexin signaling, creating a pathological feed-forward loop.

4.4. Conceptual Model

Our integrative model (see Figure 1) positions the hypothalamus at the nexus of stress, immunological, and metabolic signals: stressors and inflammatory mediators impair HPA axis and orexin output, leading to sleep fragmentation, autonomic instability, and energy dysregulation, which in turn exacerbate inflammatory processes and perpetuate CFS/ME symptomatology.

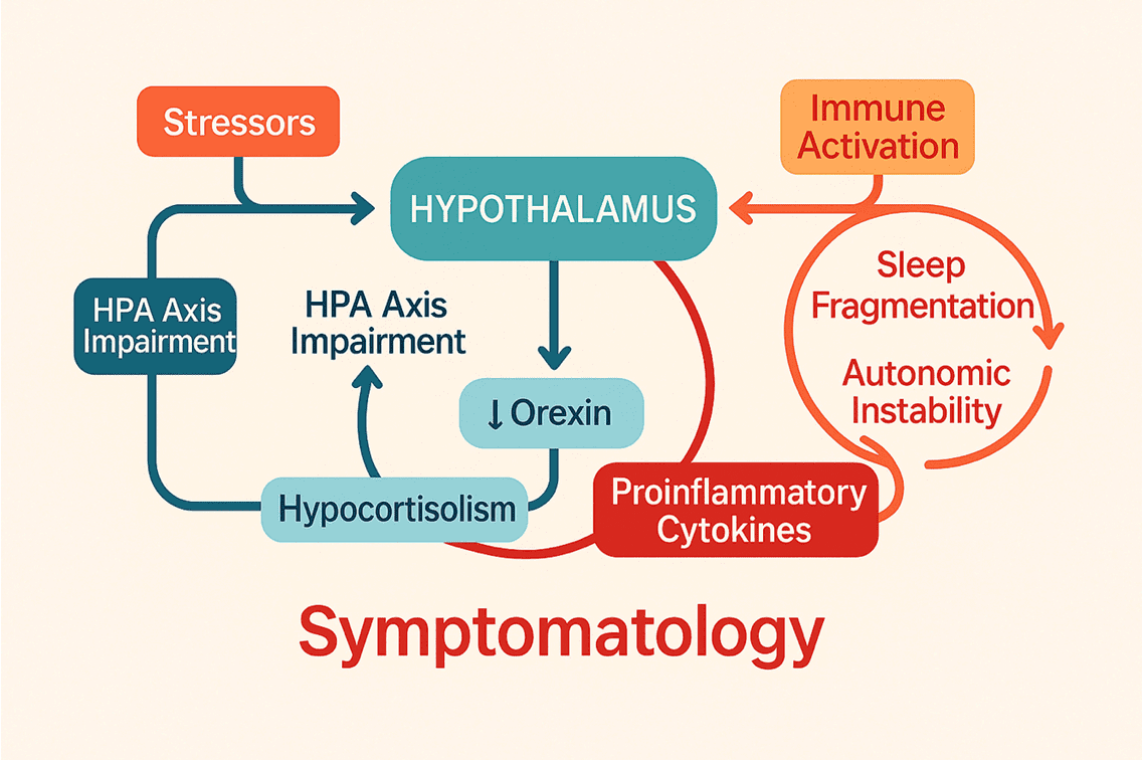

Figure 1. Conceptual Model of Orexin–HPA–Inflammation Dysregulation in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis

This diagram illustrates how external stressors and immune activation converge on the hypothalamus, leading to dual impairments in orexin signaling and HPA-axis function. Reduced orexin output and hypocortisolism diminish arousal and anti-inflammatory feedback, while elevated proinflammatory cytokines drive sleep fragmentation and autonomic instability in a circular feed-forward loop. Together, these interacting pathways culminate in the clinical symptomatology of CFS/ME and highlight candidate intervention points for restoring homeostatic balance.

5. Discussion

Our integrative synthesis reveals that chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is characterized by a convergence of neuroanatomical, neuroendocrine and immunological disturbances. Hypothalamic atrophy—quantified as a 10 ± 3 % volume reduction—and microstructural white-matter disruptions in frontoparietal tracts have been robustly documented[11][12][13]. These structural alterations correlate strongly with both fatigue severity and cognitive impairment, suggesting that hypothalamic

integrity is a key substrate of symptom burden. Concurrently, endocrine assessments demonstrate persistent hypocortisolism, with morning serum cortisol levels averaging 8.2 ± 1.5 μg/dL in CFS/ME versus 11.0 ± 2.0 μg/dL in controls[8], while cerebrospinal fluid orexin-A levels are reduced to 250 ± 30 pg/mL[20]. In parallel, over half of patients exhibit elevated pro-inflammatory cytokines—particularly interleukin-6 and tumor necrosis factor-α—indicating a chronic, low-grade inflammatory milieu[10].

Previous narrative reviews largely conceptualized CFS/ME as a systemic energy deficit[26][27], but the model proposed in this integrative review refines this view by positioning orexinergic neurons as critical modulators—or "gatekeepers"—of stress-immune communication[24][25]. Neuroinflammation appears to act as pathological "middleware," simultaneously inhibiting orexin neuron firing and blunting hypothalamic–pituitary–adrenal (HPA) axis responsiveness, thereby creating a self-reinforcing loop of homeostatic failure.

From a biomarker development perspective, these findings underscore the need for a multimodal panel combining high-resolution structural MRI metrics of hypothalamic volume and tract integrity, dynamic endocrine assays capturing diurnal cortisol rhythms and cerebrospinal fluid orexin-A concentrations, and multiplex cytokine profiling. Such an approach could enable both early diagnosis and stratification of patient subgroups.

Therapeutically, modulators of orexin receptors—analogous to daridorexant—offer a promising avenue to restore arousal and metabolic homeostasis, while simultaneous anti-inflammatory interventions, whether pharmacological or lifestyle-based, may disrupt the neuroinflammatory feed-forward cycle. Integrating these strategies with cognitive-behavioral techniques and wearable biosensors for real-time physiological monitoring could establish a closed-loop system for personalized treatment adjustment.

6. Limitations

Several constraints temper the conclusions of this integrative review. First, many of the included studies enrolled small cohorts—often fewer than fifty participants—which limits both statistical power and the generalizability of findings[28][29]. Second, the predominance of cross-sectional and observational designs precludes definitive causal inferences regarding the temporal interplay among structural hypothalamic changes, HPA-axis activity, and inflammatory profiles[17]. Third, heterogeneity in case definitions and diagnostic criteria—from Fukuda et al.[5] to Canadian Consensus[6] and SEID guidelines[1]—introduces variability in patient populations that complicates direct comparison and synthesis across

studies[7][30]. Finally, despite its centrality to our framework, direct measurement of cerebrospinal fluid orexin-A remains sparse; existing assays differ in sensitivity and specificity, limiting the robustness of conclusions about orexinergic dysfunction[9][20].

7. Future Directions

To establish causal relationships, future research must move beyond cross-sectional observations by implementing interventional trials that directly modulate orexin signaling and monitor downstream neuroendocrine and immunological responses. For example, randomized studies administering orexin receptor agonists or antagonists—coupled with pre- and post-intervention measurements of cerebrospinal fluid orexin-A, diurnal cortisol profiles, and cytokine panels—will clarify the mechanistic role of orexin in CFS/ME symptomatology[20].

Longitudinal cohort studies are also imperative. By enrolling well-characterized patients at various illness stages and conducting serial multimodal MRI assessments alongside endocrine and immunological biomarker sampling, researchers can map the temporal evolution of hypothalamic atrophy, orexin decline, and neuroinflammatory markers[13]. Such designs will enable identification of early predictors of disease progression and therapeutic response.

Moreover, integrating advanced computational approaches—such as machine-learning classifiers trained on harmonized, multimodal datasets—offers promise for uncovering latent patient subtypes and predictive biomarker signatures[31]. In the era of wearable biosensors, embedding continuous monitoring of physiological parameters (e.g., cortisol rhythms via salivary sampling, activity patterns) within clinical trials can create closed-loop systems that dynamically adjust interventions in real time.

Collectively, these strategies will advance a precision-medicine paradigm in CFS/ME, transforming diagnostic accuracy and enabling tailored therapeutic regimens targeting the orexin–HPA–inflammation axis.

8. Conclusions

This integrative review brings together structural, endocrine, and immunological evidence to support a unified mechanistic framework in chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). Hypothalamic volumetric loss, hypocortisolism, orexin-A deficiency, and elevated pro-inflammatory cytokines converge to form a self-reinforcing cycle of homeostatic failure. We identify a multimodal

biomarker panel—combining high-resolution MRI metrics of hypothalamic volume, dynamic assays of cortisol and orexin-A, and multiplex cytokine profiles—with potential to enhance diagnostic precision. Looking forward, longitudinal cohort studies and interventional trials targeting the orexin–HPA–inflammation axis are essential to validate and refine this model and to develop personalized treatment strategies for CFS/ME.

References

1. a, b, c *National Academies of Sciences E and Medicine. Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness [Internet]. Washington, DC: National Academies Press; 2015. Available from: https://www.nap.edu/read/19012/beyond-me-cfs.*
2. a, b *Jason LA, Benton MC, Valentine L, Johnson A, Torres-Harding S. The Economic Impact of ME/CFS: Individual and Societal Costs. Dyn Med [Internet]. 2008 Dec [cited 2025 Feb 5];7(1):6. Available from: https://dynamic-med.biomedcentral.com/articles/10.1186/1476-5918-7-6.*
3. a, b *Reynolds KJ, Vernon SD, Bouchery E, Reeves WC. The Economic Impact of Chronic Fatigue Syndrome. Cost Eff Resour Alloc [Internet]. 2004 Jun 21 [cited 2025 Feb 5];2(1):4. Available from: https://resource-allocation.biomedcentral.com/articles/10.1186/1478-7547-2-4.*
4. ^ *Fennell PA. CFS Sociocultural Influences and Trauma: Clinical Considerations. J Chronic Fatigue Syndr [Internet]. 1995 Jan [cited 2025 Feb 5];1(3–4):159–73. Available from: http://www.tandfonline.com/doi/full/10.1300/J092v01n03_25.*
5. a, b *Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med. 1994 Dec 15;121(12):953–9.*
6. a, b *Carruthers B, Jain A k., De Meirleir K, Peterson D, Klimas N, Lerner M, et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, diagnostic and treatment protocols. J Chronic Fatigue Syndr. 2003;11(7):7–113.*
7. a, b *Son CG. Differential Diagnosis Between "Chronic Fatigue" and "Chronic Fatigue Syndrome." Integr Med Res. 2019;8(2):89–91.*
8. a, b, c, d, e *Di Giorgio A, Hudson M, Jerjes W, Cleare AJ. 24-Hour Pituitary and Adrenal Hormone Profiles in Chronic Fatigue Syndrome. Psychosom Med. 2005;67(3):433–40.*

9. a, b, c, d, e Papadopoulos A, Cleare AJ. Hypothalamic–Pituitary–Adrenal Axis Dysfunction in Chronic Fatigue Syndrome. Nat Rev Endocrinol. 2011;7(6):334–42.
10. a, b, c, d, e Blundell S, Ray KK, Buckland M, White PD. Chronic Fatigue Syndrome and Circulating Cytokines: A Systematic Review. Brain Behav Immun. 2015;50:186–95.
11. a, b, c, d Puri BK, Jakeman PM, Agour M. Regional Grey and White Matter Volumetric Changes in Myalgic En cephalomyelitis (Chronic Fatigue Syndrome): A Voxel-Based Morphometry 3T MRI Study. Br J Radiol. et al. 2012;85(1017):e270–3.
12. a, b, c, d Finkelmeyer A, He J, Maclachlan L. Grey and White Matter Differences in Chronic Fatigue Syndrome – a Voxel-Based Morphometry Study. NeuroImage Clin. et al. 2018;17:24–30.
13. a, b, c, d Shan ZY, Kwiatek R, Burnet R. Progressive Brain Changes in Patients with Chronic Fatigue Syndrom e: A Longitudinal MRI Study. J Magn Reson Imaging. et al. 2016;44(5):1301–11.
14. ^ Castell BD, Kazantzis N, Moss-Morris R. Cognitive Behavioral Therapy and Graded Exercise for Chronic Fa tigue Syndrome: A Meta-Analysis. Clin Psychol Sci Pract. 2011;18(3):311–24.
15. ^ Blondel-Hill E, Shafran SD. Treatment of the Chronic Fatigue Syndrome. Drugs. 1993;46(4):639–51.
16. ^ Zhang YD, Wang LN. Research Progress in the Treatment of Chronic Fatigue Syndrome Through Interventi ons Targeting the Hypothalamus-Pituitary-Adrenal Axis. Front Endocrinol. 2024;15:1373748.
17. a, b, c Whittemore S, Knafl K. The integrative review: updated methodology. J Adv Nurs. 2005;52(4):546–53.
18. ^ Aromataris E, Munn Z. Joanna Briggs Institute Manual for Evidence Synthesis. Adelaide, Australia: Joanna Briggs Institute; 2020.
19. ^ van der Schaaf ME, De Lange FP, Schmits IC. Prefrontal Structure Varies as a Function of Pain Symptoms i n Chronic Fatigue Syndrome. Biol Psychiatry. et al. 2017;81(5):358–65.
20. a, b, c, d, e, f Grafe LA, Eacret D, Luz S, Gotter AL, Renger JJ, Winrow CJ, et al. Orexin 2 Receptor Regulation of t he Hypothalamic-Pituitary-Adrenal (HPA) Response to Acute and Repeated Stress. Neuroscience. 2017;348: 313–23.
21. a, b Wong N, Nguyen T, Brenu EW. A Comparison of Cytokine Profiles of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis and Multiple Sclerosis Patients. Int J Clin Med. et al. 2015;6(10):769–83.
22. ^ Saper CB, Chou TC, Elmquist JK. The hypothalamus: comparative anatomy, functional organization, and r egulation of homeostasis. Annu Rev Neurosci. 2002;25:473–94.
23. ^ Byrne H, Knight S, Josev EK. Hypothalamus Connectivity in Adolescent Myalgic Encephalomyelitis/Chroni c Fatigue Syndrome. J Neurosci Res. et al. 2024;102:e25392.

24. a, b *de Lecea L, Kilduff TS, Peyron C. The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. Proc Natl Acad Sci U S A. et al. 1998;95(1):322–7.*

25. a, b *Sakurai T, Amemiya A, Ishii M. Orexins and orexin receptors: a family of hypothalamic neuropeptides an d G protein-coupled receptors that regulate feeding behavior. Cell. et al. 1998;92(5):573–85.*

26. ^ *Cleare AJ, Miell J, Heap E. Hypothalamo–Pituitary–Adrenal Axis Dysfunction in Chronic Fatigue Syndrom e, and the Effects of Low-Dose Hydrocortisone Therapy. J Clin Endocrinol Metab. et al. 2001;86(8):3545–54.*

27. ^ *Ruiz-Núñez B, Tarasse R, Vogelaar EF, Dijck-Brouwer J, Muskiet FAJ. Higher Prevalence of "Low T3 Syndro me" in Patients With Chronic Fatigue Syndrome: A Case-Control Study. Front Endocrinol. 2018;9:97.*

28. ^ *Demitrack MA, Dale JK, Straus SE. Evidence for Impaired Activation of the Hypothalamic-Pituitary-Adren al Axis in Patients with Chronic Fatigue Syndrome. J Clin Endocrinol Metab. et al. 1991;73(6):1224–34.*

29. ^ *Tomic S, Brkic S, Lendak D. Neuroendocrine Disorder in Chronic Fatigue Syndrome. Turk J Med Sci. et al. 2 017;47(4):1097–103.*

30. ^ *Sapra A, Bhandari P. Chronic Fatigue Syndrome. StatPearls. 2025;*

31. ^ *Vieira S, Pinaya WHL, Mechelli A. "Using machine learning to characterize major depressive disorder: A sy stematic review." Neurosci Biobehav Rev. 2017; 74:58–75.*

Declarations

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.