Review

Chronic MIGRAINE as an emergent Systems Failure: Integrating Upstream Neuroimmunology, Gut–Brain Dysregulation, and Computational Chronification

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Chronic MIGRAINE as an emergent Systems Failure: Integrating Upstream Neuroimmunology, Gut–Brain Dysregulation, and Computational Chronification

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Abstract

Chronic migraine affects 1–2% of the global population and is the leading cause of neurological disability in women younger than 50. Calcitonin gene–related peptide (CGRP)-targeting monoclonal antibodies and gepants represent the first disease-specific preventive therapies, yet real-world registries show that 30–50% of treated patients fail to revert to an episodic phenotype, and medication-overuse headache compounds the problem. The therapeutic ceiling of single-target CGRP pharmacology suggests that chronification is governed by mechanisms upstream of, parallel to, and beyond the trigeminovascular neuropeptide loop. This narrative review synthesises converging evidence from 2020–2026 and proposes a multi-stratum model of chronic migraine as an emergent systems failure. In the trigeminocervical complex, the alarmin high-mobility group box 1 (HMGB1) operates as an upstream catalyst of the Toll-like receptor 4 (TLR4)–NF-κB–CGRP signalling axis; nitroglycerin-induced chronic-migraine models show that HMGB1 silencing attenuates neuroinflammation and central sensitisation. Clinical data from patients with medication-overuse headache reveal elevated circulating lipopolysaccharide, HMGB1, and HIF-1α, consistent with intestinal barrier failure feeding systemic neuroinflammation. Preclinical data from 2026 document sex-specific gut-microbiota and metabolome disruption and more severe allodynia in female chronic-migraine models, while separate work shows that sleep restriction and caffeine synergistically lower the headache threshold in a sex-dependent manner. Functional-neuroimaging synthesis implicates sustained decoupling of the salience, default-mode, and central-executive networks as the neural substrate of interictal cognitive impairment. A complementary computational perspective, grounded in the Free Energy Principle, conceptualises chronification as the formation of pathologically rigid prior beliefs—a hypothesis testable via task-based contingent-negative-variation, mismatch-negativity, and Hierarchical Gaussian Filter modelling of probabilistic-learning tasks. The review concludes that chronic migraine research must move from single-target optimisation to multi-stratum intervention. Priority areas include phase-1–2 trials of upstream neuroimmune modulation with mandatory immunological safety screening, sex-stratified microbiome trials, factorial designs combining sleep and network-level neuromodulation, and ethically calibrated priors-relaxing interventions. Establishing causality requires a longitudinal transitional cohort with integrated neuroimaging, electrophysiological, microbial, and ecological-momentary endpoints.

Keywords: chronic migraine; medication-overuse headache; HMGB1; TLR4; CGRP; gut–brain axis; triple network; Free Energy Principle; predictive coding; sex differences

Key Points

- Chronic migraine is reframed as an emergent systems failure—a distinct state arising from convergent dysregulation across neuroimmune, large-scale network, autonomic and gut–brain axes, rather than a linear progression of episodic migraine.

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- Neuroinflammatory signalling (HMGB1, IL-6, CGRP–immune cross-talk) and triple-network collapse of default-mode, salience and central-executive systems sustain a self-reinforcing chronicity loop that receptor-level models cannot capture.
- Allostatic overload and gut–brain decoupling act as permissive substrates, providing a mechanistic account of why sleep, stress and psychiatric comorbidity so consistently modify disease trajectory—factors usually absent from conventional mechanistic frameworks.
- The framework yields falsifiable predictions: network-restoring, multi-axis interventions (closed-loop neuromodulation, combination pharmacotherapy, circadian- and microbiome-targeted strategies) should outperform single-receptor approaches in preventing and reversing chronification.

1. Introduction

Chronic migraine, defined by the International Classification of Headache Disorders (ICHD-3) as headache on 15 or more days per month for more than three months, with features of migraine on at least eight of those days, imposes a disease burden exceeded by few other neurological conditions [1]. The 2019 Global Burden of Disease study ranks migraine as the second leading cause of years lived with disability worldwide and the first among women aged 15–49 [2]. Chronic migraine accounts for roughly 8% of all migraine diagnoses but generates a disproportionate share of healthcare utilisation, lost productivity, and psychiatric comorbidity [3].

The introduction of CGRP-targeting monoclonal antibodies (erenumab, fremanezumab, galcanezumab, eptinezumab) and oral CGRP-receptor antagonists has been transformative, yet a sober reading of the evidence tempers optimism. In the LIBERTY trial extension—albeit conducted in patients with episodic migraine and 2–4 prior preventive treatment failures—only 33% achieved a 50% or greater reduction in monthly migraine days at 64 weeks [4,44]. Pivotal randomised trials in chronic migraine—including the foundational erenumab trial, [45] HALO-CM with fremanezumab, [46] REGAIN with galcanezumab, [47] and PROMISE-2 with eptinezumab [48]—show 50%-responder rates of approximately 40–60% in chronic-migraine populations, leaving a substantial minority refractory across all CGRP-pathway agents. A 2026 network meta-analysis of 18 randomised trials (n = 7 281 patients with prior preventive treatment failure) confirmed that CGRP-pathway agents are among the most effective pharmacological options in this refractory population, but only with low-to-moderate certainty of evidence and largely on the basis of industry-sponsored trials—underscoring the need for mechanistically broader strategies [43]. Medication-overuse headache complicates outcomes further: an estimated 50–70% of patients referred to specialist centres have concurrent medication overuse [5]. These numbers signal that the CGRP neuropeptide loop, although necessary, is not sufficient to explain chronification.

This review argues that chronic migraine is best understood as an emergent systems failure: a state in which genetic vulnerability, epigenetic fixation, upstream neuroimmune amplification, gut–brain dysregulation, large-scale network reconfiguration, psychosocial load, and computational rigidity reinforce one another across biological scales. We synthesise mechanistic findings from 2020–2026 and propose a research agenda that targets the disorder at multiple strata simultaneously. The search strategy and inclusion criteria underlying this synthesis are detailed in Box 1.

Recent narrative and systematic reviews have addressed neuroimmune signalling, [38] HMGB1-mediated chronification, [39] triple-network disruption in medication-overuse headache, [40] gut–brain dysregulation, [41] and allostatic load [42] as separate mechanistic domains. The contribution of this Review is integrative rather than additive: it argues that these strata are mechanistically coupled and proposes a single computational framework, grounded in the Free Energy Principle, that links them and generates falsifiable predictions testable with existing electrophysiological and computational-psychiatry methods.

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2. Genetic and Epigenetic Vulnerability

Migraine is strongly polygenic. Genome-wide association studies have identified more than 120 risk loci, the majority of which converge on vascular smooth muscle, ion-channel, and synaptic-signalling pathways [6]. Rare monogenic forms—mutations in CACNA1A, ATP1A2, and SCN1A—produce familial hemiplegic migraine and illustrate how constitutive hyperexcitability lowers the threshold for cortical spreading depression [7].

Crucially, the transition from episodic to chronic migraine is mediated not by new mutations but by epigenetic modification. Exogenous stressors—sleep deprivation, medication overuse, early-life adversity—induce DNA-methylation and histone-acetylation changes that can permanently upregulate expression of nociceptive receptors, including CGRP-receptor components (RAMP1, CLR, RCP) and transient receptor potential channels (TRPV1, TRPA1) [8]. The result is a nervous system that is chronically sensitised even in the absence of an acute trigger, which partly explains why remission from a chronic to an episodic state is so difficult to achieve.

3. Upstream Neuroimmunology: HMGB1, TLR4, and the Inflammatory CGRP Loop

The central role of CGRP in trigeminovascular activation is well established, but CGRP release is itself downstream of a neuroimmune cascade whose molecular architecture is now coming into focus. High-mobility group box 1 (HMGB1) is a ubiquitous nuclear protein that, under conditions of neuronal excitotoxicity, metabolic stress, or cortical spreading depression, is actively secreted into the extracellular space and functions as a damage-associated molecular pattern (DAMP) [9,10]. Extracellular HMGB1 binds Toll-like receptor 4 (TLR4) and the receptor for advanced glycation end-products (RAGE), both densely expressed on trigeminal neurons, astrocytes, and microglia [11].

In rodent models of nitroglycerin-induced chronic migraine, HMGB1 translocates from the nucleus to the cytoplasm of trigeminal ganglion neurons, activating the TLR4–NF-κB signalling cascade and driving transcription of inducible nitric oxide synthase and CGRP. Pharmacological inhibition or siRNA silencing of HMGB1 reduces NF-κB activation and attenuates CGRP upregulation, providing direct evidence that HMGB1 functions as an upstream mediator [12]. Activated microglia, locked into a pro-inflammatory M1-like phenotype, secrete TNF-α, IL-1β, and additional HMGB1, creating a self-sustaining feed-forward loop that maintains central sensitisation [11].

Medication-overuse headache may represent the clinical embodiment of this loop. Vuralli and colleagues demonstrated that patients with chronic migraine and medication overuse have significantly elevated circulating lipopolysaccharide (LPS), VE-cadherin, HMGB1, and HIF-1α, consistent with intestinal barrier failure allowing bacterial endotoxins into the systemic circulation and feeding the trigeminocervical inflammatory cascade [13]. This finding is critical for therapeutic design, as discussed below.

4. The Gut–Brain Axis: Sex-Specific Microbiota Dysregulation and Lifestyle Triggers

Migraine is three times more prevalent in women after puberty, and women are disproportionately represented among chronic and medication-overuse phenotypes [14]. Hormonal fluctuation and CGRP sensitivity are established contributors, but a second interacting layer—sex-specific gut–brain dysregulation—is now supported by preclinical evidence.

Chen and colleagues, using a repeated nitroglycerin model of chronic migraine, reported that female rats developed more robust and longer-lasting mechanical and thermal allodynia than males, and that their faecal metabolomes and microbial communities were disproportionately disrupted, with perturbations converging on tryptophan metabolism, short-chain fatty-acid (SCFA) synthesis, and serotonergic precursor pathways [15]. SCFA depletion is mechanistically significant: SCFAs regulate tight-junction proteins in the intestinal epithelium, promote regulatory T-cell differentiation,

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and restrain NF-κB activity in macrophages, so their loss precipitates intestinal hyperpermeability—connecting directly to the elevated circulating LPS observed by Vuralli and colleagues in patients with medication-overuse headache [13,16].

Lifestyle triggers interact with this vulnerability in a sex-dependent manner. De Oliveira and colleagues showed that sleep restriction combined with sub-threshold doses of CGRP or PACAP induced migraine-like allodynia selectively in female rats; addition of caffeine—a non-selective adenosine-receptor antagonist that disrupts purinergic homeostasis—rendered male animals equally vulnerable [17]. These data suggest that caffeine intake and sleep loss do not merely lower a generic headache threshold but interact with sex-specific purinergic and microbiota-mediated pathways to precipitate chronification.

Zheng and colleagues demonstrated that electroacupuncture modulates gut-microbial genera and faecal metabolites and restores circulating serotonin and CGRP levels in a chronic-migraine rat model, implicating vagal and somatosensory pathways in microbiota regulation [18]. Though translation to clinical chronic migraine remains uncharted, the study underscores the therapeutic tractability of the gut–brain axis through peripherally acting interventions. The implication is that microbiome-targeted therapeutics—precision pre- and postbiotics, SCFA supplementation, and evidence-based adjuncts—deserve formal, sex-stratified clinical evaluation in chronic migraine.

5. Triple-Network Dysfunction and Cognitive Morbidity

Patients with chronic migraine consistently report interictal deficits in executive function, working memory, attention, and expressive language—so-called migraine brain fog—that can be more disabling than the headache itself [19]. A 2025 review by Fernandes and Gil-Gouveia in Cephalalgia synthesises evidence that these deficits are present across all phases of the migraine cycle (prodrome, ictal, interictal) and reflect dysfunction in prefrontal, thalamic, and hippocampal circuits, with particular involvement of thalamocortical connectivity [19].

These findings align with the triple-network model proposed by Menon, which describes the dynamic interplay of three large-scale intrinsic connectivity networks: the default-mode network (DMN), the salience network (SN), and the central-executive network (CEN) [20]. In health, the anterior-insula–centred SN operates as a rapid switch: it engages the CEN for goal-directed processing and simultaneously deactivates the DMN. In chronic migraine, continuous nociceptive bombardment—amplified by the HMGB1–CGRP loop and compounded by sleep loss—renders the SN hyper-reactive and decouples it from the CEN [21]. Simultaneously, the DMN becomes hyperconnected with the SN, absorbing the pain signal into autobiographical self-representation [22]. Clinical imaging studies by Schwedt and Androulakis confirm altered resting-state connectivity in these networks in patients with chronic migraine, particularly in women [21,23].

Network-level therapies—fMRI-guided neurofeedback, transcranial direct-current stimulation, and repetitive transcranial magnetic stimulation—can modulate functional connectivity between these networks [24]. Future trials should assess not only headache-day reduction but also objective cognitive endpoints and network-coupling metrics, since cognitive recovery may predict long-term treatment durability.

6. A Computational Framework: Chronification as Pathologically Rigid Priors

The molecular, immunological, and network-level accounts converge but leave a central question unanswered: why does the brain maintain the chronic pain state even when peripheral inflammatory drivers have been pharmacologically attenuated? The Free Energy Principle (FEP), as formulated by Friston, provides a formal framework [25]. The brain is modelled as a hierarchical Bayesian inference engine that constructs top-down predictions (priors) about bodily and environmental states and continuously compares these with incoming sensory evidence. The discrepancy—prediction error—is minimised either by updating the internal model (perceptual inference) or by altering sensory input through behaviour (active inference).

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We propose, consistent with recent predictive-coding accounts of chronic pain, that chronic migraine represents a pathological solution in which the brain has assigned overwhelming precision (confidence) to the prior belief that the body is in pain [26]. Once this high-precision prior is established, genuine afferent signals of tissue safety are systematically down-weighted—analogous to perceptual suppression—and prediction errors signalling recovery are treated as noise.

Crucially, this framework is not mere philosophy: it generates specific, falsifiable predictions that can be tested with existing neuroscientific methods. First, if chronification reflects aberrant precision weighting, patients with chronic migraine should show altered contingent-negative-variation (CNV)—the most extensively replicated electrophysiological marker of cortical excitability and habituation in migraine, with episodic-migraine cohorts consistently demonstrating elevated initial-CNV (iCNV) amplitudes and reduced inter-trial habituation that progress with disease duration; convergent support is expected from mismatch-negativity (MMN) paradigms probing automatic change detection—a more general index of prediction-error signalling—although CNV remains the migraine-specific anchor biomarker [27,49]. Preliminary data in episodic migraine already suggest altered MMN during the interictal phase; we predict that this attenuation will be significantly more pronounced in chronic migraine and will correlate inversely with headache frequency and catastrophising scores. Second, the precision-weighting parameter ω in hierarchical Bayesian belief-updating can be estimated from behavioural data acquired during controlled probabilistic-learning paradigms (for example, perceptual reversal-learning or audio-visual deviance tasks) using computational-psychiatry methods such as the Hierarchical Gaussian Filter (HGF); HGF parameters are derived from trial-by-trial prediction errors generated by such tasks and cannot be recovered from spontaneous resting-state or ambulatory EEG. Within this framework, patients with rigid priors should show reduced learning rates (κ) for safety-related sensory evidence while maintaining normal or supranormal learning for threat-related cues [28]. Third, if priors-relaxation is a genuine therapeutic mechanism, interventions that demonstrably increase cortical entropy—such as 5-HT2A agonists measured via Lempel-Ziv complexity of the EEG signal—should predict clinical improvement in a dose-response manner. A negative result on any of these predictions would constitute strong evidence against the rigid-priors hypothesis, satisfying the Popperian criterion.

A critical dimension absent from earlier formulations is the sex-specific modulation of these computational parameters. A 2024 systematic review by Ruehr and colleagues synthesised 54 neuroimaging studies demonstrating that oestrogen fluctuations across the menstrual cycle modulate resting-state connectivity in the DMN, SN, and limbic circuits, with particular plasticity in hippocampal and amygdalar hubs [37]. We hypothesise that the late-luteal oestrogen trough—a well-established migraine trigger—may directly increase the precision (ω) assigned to nociceptive priors by destabilising SN–DMN coupling, while simultaneously reducing the learning rate (κ) for safety-related prediction errors. If correct, this predicts that perimenstrual chronic-migraine attacks will be preceded by measurable shifts in HGF-derived κ values (assessed via brief task-based assessments at scheduled visits across the menstrual cycle) and in CNV amplitude. This sex-specific computational vulnerability would explain why women are disproportionately represented among chronic phenotypes: they face cyclical destabilisation of the very parameters that maintain flexible inference, making the transition to rigid priors statistically more likely over a lifetime of hormonal fluctuation.

Triple-network dysfunction provides a plausible neural implementation: the hyperactive SN fixates on nociception, the decoupled CEN cannot flexibly reallocate processing resources, and the DMN integrates pain into the autobiographical self, reinforcing the rigid prior at the level of personal narrative [19,20].

The REBUS (relaxed beliefs under psychedelics) model proposes that 5-HT2A agonists such as psilocybin transiently reduce the precision of top-down predictions, opening a window of neuroplasticity during which cognitive-behavioural scaffolding can encode a more flexible perceptual model [29]. Small open-label studies in cluster headache and migraine are suggestive but not conclusive. Any clinical translation must include rigorous placebo control, cardiovascular screening, and structured psychotherapeutic integration. We explicitly note that these remain

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investigational approaches requiring phase-2 safety and efficacy evidence before clinical adoption can be considered.

7. Psychosocial Determinants and Allostatic Load

No multi-stratum model of chronic migraine can be complete without acknowledging the psychosocial dimension. Fear of pain (kinesiophobia) and pain catastrophising are among the strongest psychological predictors of chronification, operating bidirectionally: catastrophising amplifies hypothalamic–pituitary–adrenal (HPA)-axis activation and cortisol release, which suppresses prefrontal top-down inhibition of the limbic system and reinforces central sensitisation [30]. Chronic stress, adverse childhood experiences, low socioeconomic status, and marginalisation translate biologically into high allostatic load—a state of endocrine and immune exhaustion that minimises physiological buffering capacity [31].

A 2026 mediation analysis by Xing and colleagues, using data from the Women's Health Initiative, tested whether systemic inflammatory biomarkers (CRP, TNF-α, IL-6) mediate the association between migraine and ischaemic stroke in postmenopausal women. Contrary to the expected universal inflammation hypothesis, the mediated proportions were negligible and statistically non-significant [32]. This nuance is critical for risk stratification: it suggests that interventions targeting systemic inflammation may improve pain outcomes without necessarily addressing the cerebrovascular risk pathway, and that the two comorbidities require parallel but distinct management strategies.

8. Therapeutic Horizons: From Single Target to Systems Portfolio with Rigorous Safety Constraints

A systems view of chronic migraine demands a portfolio approach to therapeutics. Five directions are especially promising, but each carries specific translational constraints that must be addressed with rigour.

First, upstream neuroimmune modulation. HMGB1 inhibitors, TLR4–RAGE antagonists, and NLRP3-inflammasome blockade have a strong mechanistic rationale as adjuncts to anti-CGRP therapy [9–13]. However, the immunological safety concern deserves explicit acknowledgement. Vuralli and colleagues' data demonstrate that patients with medication-overuse headache have active intestinal barrier failure with circulating LPS [13]. Systemically inhibiting DAMP–TLR4 signalling in the context of ongoing bacterial endotoxaemia creates a genuine risk of impaired innate immune surveillance, potentially precipitating uncontrolled infection or sepsis. We therefore propose the following mandatory safety framework for any phase-1 evaluation: (i) pre-enrolment screening for circulating LPS, intestinal permeability markers (zonulin, intestinal fatty-acid binding protein), and faecal calprotectin—patients with active endotoxaemia should be excluded or first undergo intestinal barrier rehabilitation; (ii) preference for anatomically restricted delivery—peripherally restricted blood–brain-barrier-impermeable small molecules, intranasal nose-to-brain formulations, or cervical-lymph-node-directed administration—over systemic dosing, so that local neuroimmune modulation is achieved while peripheral immune competence is preserved; intrathecal delivery is not a realistic primary-prevention route in migraine and is therefore deprioritised for first-in-human studies; (iii) non-invasive cervical vagus-nerve stimulation (e.g., the gammaCore device, with randomised-controlled-trial evidence in cluster headache and supportive evidence in migraine) as a non-pharmacological alternative that leverages the cholinergic anti-inflammatory pathway to dampen trigeminocervical neuroinflammation without broad immunosuppression—and that, by acting through endogenous neural circuits rather than novel pharmacology, sidesteps both the blood–brain-barrier-penetration challenge and the immunosuppression risk; [33] (iv) continuous immune monitoring (serial CRP, procalcitonin, neutrophil function assays) throughout any trial of TLR4 or HMGB1 antagonism, with pre-specified stopping rules.

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Second, precision pharmacokinetics. Hybrid intranasal nanoparticles encapsulating rizatriptan, recently shown by Kaya and colleagues to bypass the blood–brain barrier via the olfactory and trigeminal routes in an optogenetic cortical-spreading-depression model, achieved rapid CNS delivery with minimal systemic exposure [34]. This approach may eventually transform acute aura management but requires human pharmacokinetic and safety evaluation.

Third, endocannabinoid-system modulation. Enzymatic inhibition of fatty-acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) increases endogenous anandamide and 2-arachidonoylglycerol, and is emerging as a non-opioid analgesic strategy in preclinical headache models [35]. Safety precedent must be noted: the 2016 BIA 10-2474 FAAH inhibitor trial resulted in one death and serious neurological injuries due to off-target effects, underscoring that any clinical programme must incorporate extensive selectivity profiling.

Fourth, network-level neuromodulation. fMRI-guided neurofeedback, transcranial direct-current stimulation, and repetitive transcranial magnetic stimulation can target the SN–CEN–DMN decoupling that underlies cognitive morbidity [19,24]. These are arguably the most immediately translatable interventions, carrying minimal systemic risk.

Fifth, priors-relaxing interventions. Beyond psilocybin-assisted psychotherapy, cognitive-behavioural therapy for insomnia (CBT-I) and structured caffeine restriction already target modifiable chronification drivers at the lifestyle interface and can be implemented without regulatory delay [17,36]. The mechanistic bridge to the computational framework is direct: by restoring slow-wave sleep architecture, CBT-I may re-establish physiological SN–DMN coupling and thereby reduce the pathologically high precision (ω) assigned to nociceptive prediction errors; caffeine withdrawal, in turn, normalises adenosinergic modulation of thalamic gating, plausibly increasing the learning rate (κ) for safety-related sensory evidence. These interventions thus represent low-risk, high-plausibility entry points for testing the rigid-priors hypothesis in routine clinical care.

A recurring methodological concern is the reliance on rodent models that only partially recapitulate the chronic human phenotype. Sex-disaggregated reporting, pre-registration, and harmonised endpoints—including monthly migraine days, the Migraine Disability Assessment, triple-network connectivity metrics, and validated cognitive batteries—are essential.

9. Conclusions

Chronic migraine is not a peripheral nociceptive disorder with central consequences; it is a multi-scale systems failure in which genetic predisposition, epigenetic fixation, upstream neuroimmune amplification, gut–brain dysregulation, large-scale network reconfiguration, psychosocial stress, and computational rigidity form a mutually reinforcing web (Figure 1). The CGRP era has delivered proof-of-concept that mechanism-based therapy can succeed; the next decade must extend that logic from a single neuropeptide to the full architecture of chronification.

A fundamental methodological limitation of the current evidence base must be acknowledged: nearly all data supporting this model derive from cross-sectional comparisons between patients who are already chronic and healthy controls, or between chronic and episodic cohorts. Chronification is, by definition, a temporal process, and establishing causality requires longitudinal observation of the transition itself. We therefore propose, as a core component of the international registry described below, a prospective transitional cohort study enrolling patients with high-frequency episodic migraine (10–14 headache days per month)—the population at highest risk for chronification. Participants would undergo quarterly resting-state fMRI, serial task-based EEG combining contingent-negative-variation and mismatch-negativity paradigms together with brief probabilistic-learning sessions for HGF parameter estimation, intestinal permeability assays (zonulin, I-FABP), and gut-metabolomic profiling, combined with daily ecological momentary assessment (EMA) via smartphone capturing headache burden, sleep, caffeine, stress, and menstrual phase. Only such a design can demonstrate that shifts in CNV amplitude and habituation, alterations in MMN, the divergence in HGF-derived learning rates, the rise in circulating LPS, and the decoupling of SN–CEN

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connectivity actually precede—rather than merely accompany—the transition to a chronic phenotype.

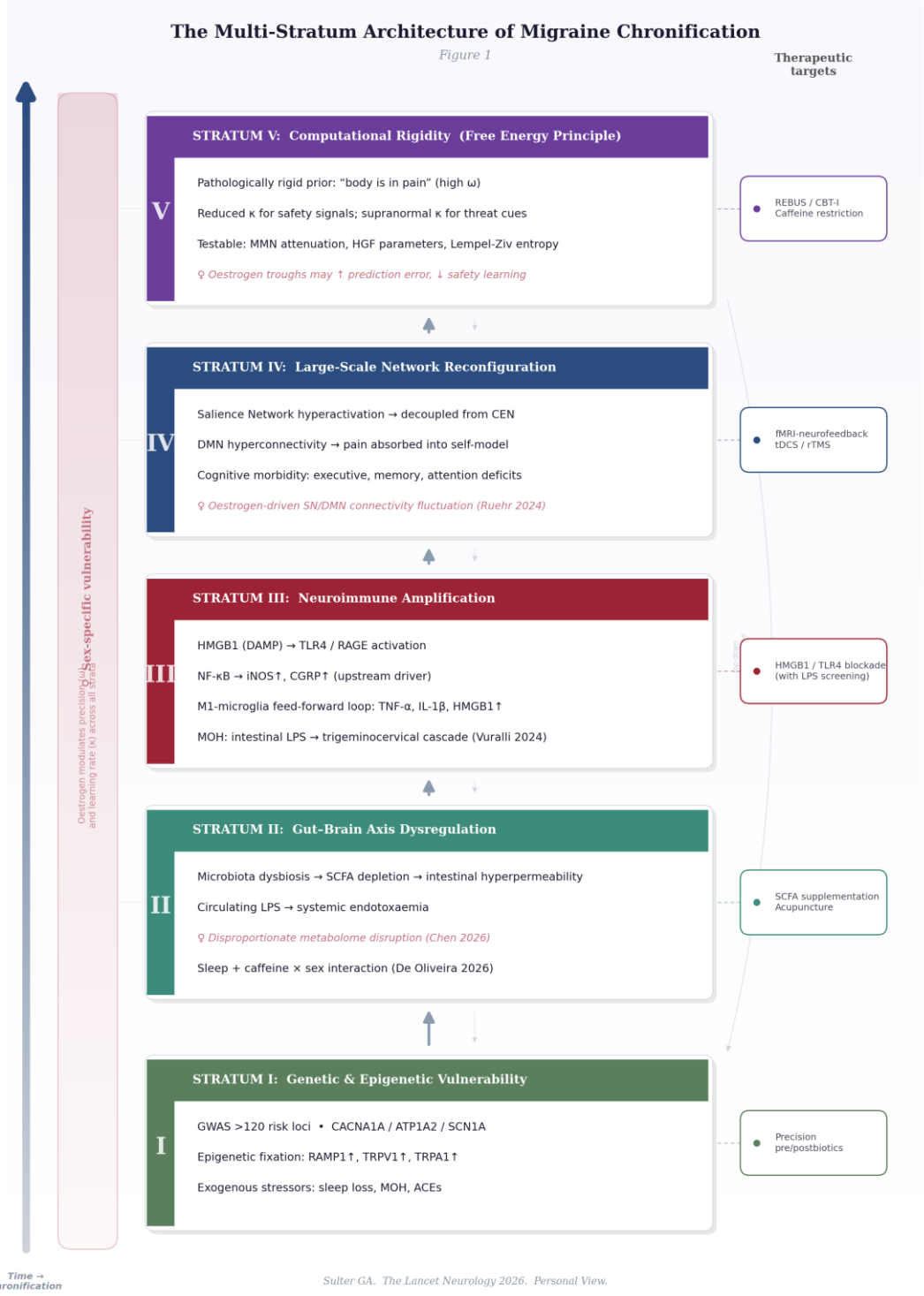

Figure 1. The multi-stratum architecture of migraine chronification. The diagram is organised as a vertical hierarchy representing the temporal and mechanistic progression from genetic vulnerability (bottom) to computational rigidity (top). Stratum I (green) depicts the polygenic and epigenetic foundation: GWAS risk loci, monogenic channelopathies, and stressor-driven epigenetic fixation of nociceptive receptors. Stratum II (teal) shows gut–brain axis dysregulation, including sex-specific microbiota disruption, SCFA depletion, and the resulting intestinal hyperpermeability that feeds systemic endotoxaemia. Stratum III (burgundy) represents the neuroimmune amplification bridge: HMGB1–TLR4/RAGE signalling drives the NF-κB–CGRP feed-forward

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loop, sustained by M1-polarised microglia. Stratum IV (navy) depicts the resulting large-scale network reconfiguration: salience-network hyperactivation decoupled from the central-executive network, with default-mode hyperconnectivity absorbing pain into autobiographical self-representation. Stratum V (purple) represents the computational apex: pathologically rigid prior beliefs under the Free Energy Principle, characterised by elevated precision weighting (ω) for nociceptive priors and reduced learning rates (κ) for safety-related prediction errors. The left vertical band (rose) indicates sex-specific vulnerability running through all strata, with oestrogen fluctuations modulating both gut-microbiota composition and the Bayesian precision parameters that govern network dynamics. Dashed arrows on the right indicate stratum-specific therapeutic targets. The upward temporal arrow emphasises that chronification is a dynamic, longitudinal process requiring prospective study designs to establish causality.

Concretely, we propose (i) this longitudinal transitional-cohort registry as the primary infrastructure investment; (ii) phase-1–2 adaptive trials of upstream neuroimmune modulators with the mandatory safety framework described above; (iii) sex-stratified factorial trials combining microbiome modulation, sleep and caffeine interventions, and network-level neuromodulation; and (iv) ethically calibrated evaluation of priors-relaxing interventions within dedicated academic centres. Chronic migraine will not yield to a single molecule. It is the predictable failure of a multi-layered biological and computational system that has been pushed beyond its buffering capacity, and it will require interventions—and study designs—that match that complexity.

Search approach

This is a narrative integrative review and does not aspire to systematic-review reproducibility. We searched PubMed, Scopus, and Google Scholar for English-language peer-reviewed articles published between January 2020 and April 2026, combining the core terms “chronic migraine”, “medication-overuse headache”, “HMGB1”, “TLR4”, “CGRP”, “gut–brain axis”, “triple network”, “default-mode network”, “salience network”, “Free Energy Principle”, “active inference”, “predictive coding”, and “mismatch negativity”. Selection prioritised mechanistic depth and complementarity across the strata being integrated; when multiple sources made overlapping claims, the most rigorous primary study or most cited review was retained. A complementary 24-month competing-review scan was performed to identify reviews in adjacent mechanistic domains so that the present synthesis could position itself transparently relative to existing scholarship.

Box 2. Key messages

- Chronic migraine is not reducible to CGRP signalling; it is an emergent failure spanning neuroimmune, gut–brain, network, psychosocial, and computational strata.
- HMGB1 is emerging as an upstream catalyst of the TLR4–NF-κB–CGRP loop and a candidate therapeutic target—but safety constraints, including the risk of immunosuppression in patients with intestinal barrier failure, mandate careful trial design.
- Sex-specific gut-microbiota dysregulation and lifestyle triggers (sleep loss, caffeine) interact to lower the chronification threshold disproportionately in women.
- Sustained salience–default-mode–executive network decoupling underlies interictal cognitive morbidity and may entrench chronification via the computational mechanism of rigid priors.
- The Free Energy Principle generates falsifiable predictions: altered contingent-negative-variation amplitude and habituation (the migraine-specific electrophysiological signature) together with convergent mismatch-negativity findings, altered precision-weighting parameters from Hierarchical Gaussian Filter modelling of probabilistic-learning tasks, and dose-dependent entropy increases predicting response to priors-relaxing interventions.
- Establishing causality requires shifting from cross-sectional designs to longitudinal, high-frequency transitional cohorts tracking the episodic-to-chronic transition, combined with sex-

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stratified, multi-stratum factorial trials with mandatory immunological safety screening, embedded in international registries capturing molecular, microbial, network, and psychosocial data.

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