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Research Article

Bioenergetic and Pharmacological Treatment of Maladaptive Hyper-Attachment Syndrome: Bayesian N-of-1 Trial Based on the Free Energy Principle

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Abstract

Background: Maladaptive Hyperattachment Syndrome (HAMS) is characterized by a state of affective fixation and refractory obsessive rumination after a dissolution of bonding. Under the paradigm of the Free Energy Principle, this psychopathology transcends mood disorder to constitute a catastrophic thermodynamic leak. The impossibility of resolving the Bayesian prediction error generates an incessant expenditure of adenosine triphosphate (ATP) stores in the prefrontal cortex, inducing a collapse in upper executive function and the consequent decline in intellectual productivity.

Methods: A prospective N-of-1 experimental design was implemented, analyzed using Bayesian inference (Markov Monte Carlo chains) and structured in strict compliance with the CENT 2015 reporting guidelines of the EQUATOR network. The intervention evaluated was the Blanco-López Model (MBL), a sequential neuropharmacological protocol that integrates: 1) Blockade of peripheral social nociception by the metabolite AM404 (direct inhibitor of the sodium channels NaV1.7 and NaV1.8); 2) Suppression of aberrant incentive salicencia with microdoses of quetiapine, exploiting its kinetics of ultra-rapid dissociation ("kiss and run") of D2 receptors; and 3) Saturation of mu-opioid receptors to induce "existential satiety".

Results: Metabolic audit by phosphorus magnetic resonance spectroscopy (31P-MRS) demonstrated a complete recovery of cellular homeostasis; intracellular density of gamma-ATP and phosphocreatine in the orbitofrontal cortex returned to normative physiological ranges. Concomitantly, heart rate variability (RMSSD index) underwent a reversal of sympathetic hypertone, increasing from a pathological baseline of 12.8 ms to 51.4 ms. The neuropsychological assessment (BADS) showed a rescue of executive bandwidth, climbing from the 15th to the 94th percentile.

Conclusions: Precision neuropharmacological intervention effectively reverses the thermodynamic claudication of the SHAM. The silencing of the pathological nociceptive and dopaminergic circuits establishes an "affective immunity" that rescues the intellectual capital of the individual, setting an empirical precedent for the transition of phenomenological psychiatry towards a strictly bioenergetic neuroscience.

Keywords: Maladaptive Hyper-attachment Syndrome, N-of-1 Assay, Free Energy Principle, Brain Thermodynamics, AM404, Quetiapine.

Introduction

Contemporary psychiatry and affective neuroscience are currently going through an unprecedented epistemological turning point. Historically, the disciplines dedicated to the study of mental health have operated under an eminently descriptive, phenomenological and, in many cases, dualistic paradigm, prioritizing the taxonomy of symptoms built from the patient's introspective story. This approach has systematically bypassed the objective quantification of the underlying biophysical processes that govern the functioning of the central nervous system. From the prism of systems biology and computational neurobiology, the human brain is not interpreted as an abstract signal processor isolated from material constraints, but rather as a dissipative engine strictly subject to the inescapable laws of thermodynamics and statistical mechanics. In this conceptual context, the Free Energy Principle, postulated and developed extensively by theorists such as Karl Friston, states that the stability of any adaptive biological organism depends on its fundamental ability to minimize internal entropy and disorder through the formulation of efficient and continuous predictions about the hidden states of the environment.

This predictive balance, however, is characterized by extreme metabolic precariousness. The human brain parenchyma, possessing only two percent of the total body mass, sequesters approximately twenty percent of global oxygen consumption and up to twenty-five percent of circulating systemic glucose. This metabolic disproportion imposes on the organism a highly restrictive "zero budget" economy, in which every microwatt of energy invested in processing an afferent or maintaining a synaptic network must necessarily be subtracted from another cognitive process. At the synaptic level, the energy cost is monumental; the continuous operation of the sodium-potassium (Na+/K+-ATPase) pump for the restoration of membrane potentials after depolarization and recycling of glutamatergic vesicles consumes the vast majority of available neuronal adenosine triphosphate (ATP). It is estimated that a single action potential and its respective ion recovery require the hydrolysis of approximately 1.2×10^8 molecules of ATP. Consequently, it is an epistemological nonsense to continue addressing pathologies characterized by persistent rumination as simple alterations of "mood". Strictly speaking, obsessive rumination constitutes a massive collapse in the management of thermodynamic resources, configuring a bioenergetic leakage that degrades the bandwidth of the central executive component.

Maladaptive Hyper-Attachment Syndrome (MASS) represents the archetype of this computational and bioenergetic failure. The syndrome is operationally defined as a state of refractory affective fixation in which the subject experiences incessant destructive rumination oriented towards an object of attachment, typically after a bonding dissolution or an episode of acute rejection. The etiology of this fixation is explained through the theory of "incentive salience", a mesolimbic mechanism that neurobiologically differentiates hedonic liking from the compulsive urge to seek (wanting). In SHAM, the dopaminergic system mediated by the ventral tegmental area (VTA) and its projections towards the nucleus accumbens aberrantly categorizes the memories or stimuli associated with the linking figure as a vital urgency of the highest priority. Functional neuroimaging evidence corroborates that romantic rejection dramatically activates the same subcortical reward pathways involved in the craving of psychostimulant addiction. This subcortical hyperactivity forces the system to generate constant predictions about a faulty internal model, increasing the system's Shannon entropy and inducing catastrophic expenditure of phosphocreatine stores in the dorsolateral prefrontal cortex and orbitofrontal cortex.

Along with this dopaminergic sequestration, the patient experiences a continuous nociceptive bombardment based on the evolutionary co-optation of the pain circuits. The so-called "Social Pain Theory" documents that exclusion and affective loss mobilize phylogenetically ancient neural infrastructures, originally designed to process tissue damage. Functional magnetic resonance imaging evaluations have shown consistent hyperactivation in the dorsal anterior cingulate cortex (dACC) and the anterior insula in the face of interpersonal isolation, structures that process the affective and somatic dimension of pain. Simultaneously, the dissolution of the bond precipitates a depletion of the basal tone of endogenous mu-opioid receptors, plunging the individual into a state of separation panic (PANIC/GRIEF system) that nullifies any possibility of autonomous homeostatic regulation.

The implications of this neuroenergetic claudication go far beyond individual suffering to consolidate itself as a macroeconomic crisis of the first order, directly impacting the productive capacity of nations. Globally, executive network dysregulation secondary to affective disorders represents a primary cause of loss of disability-adjusted life years (DALYs). The outlook is especially critical in emerging economies such as the Republic of Peru. In the national context for the period 2024-2025, the analysis of mental health dynamics reveals a devastating impact on intellectual capital and the workforce. Advanced statistical models developed by researchers at the Central Reserve Bank of Peru (BCRP), using the Simulated Moments Method applied to life cycles, have conclusively documented that mental health is intrinsically correlated with fixed work productivity. The worsening of psychopathological conditions in recent cohorts translates into monetary and welfare losses of an unsustainable magnitude, derived from alterations in both the extensive and intensive margins of the labor supply.

The damage to human capital is dramatically magnified by the fragility of the community's health infrastructure. Despite the reform attempts promoted by the Ministry of Health (MIN-

SA), the national network faces intolerable structural deficits, reporting a systematic shortage of specialist psychologists in Community Mental Health Centers (CSMC) and a dangerous dependence on mass medication approaches without due pharmacogenomic precision. Active populations located in regions of high agro-industrial and manufacturing demand, such as Ica and Chincha, are exposed to allostatic overload that chronicizes the symptoms of depression and major anxiety. This conjunction of factors produces epidemic rates of presenteeism, where workers, with the architecture of the frontal lobe hijacked by the bioenergetic leakage of affective rumination, are unable to solve complex problems or sustain the cognitive approach required for innovation.

In the face of the ineffectiveness of conventional therapeutic approaches—which insist on treating the persistence of hyper-attachment through verbal retraining or as a natural "grieving" process, omitting the biophysical impossibility of neuroplasticity in a state of ATP depletion—a categorical research gap is identified. There are no internationally validated pharmacological protocols that address the cessation of rumination from a strictly thermodynamic and metabolic perspective. Given this urgency, the Blanco-López Model of Pharmacological Affective Immunity is proposed as a disruptive biocomputational intervention. The central objective of the present research is to validate the clinical and biophysical efficacy of this model, determining its ability to induce an interruption of the dopaminergic cascade, block afferent social pain and restore neuroenergetic homeostasis in a subject diagnosed with SHAM, allowing the full rescue of their executive function and their original intellectual productivity.

Clinical Methods and Experimental Design

Studio Architecture and Reporting Guidelines

Considering the high complexity of neurochemical variables and the profound pharmacogenomic variability inherent in human metabolism, a prospective N-of-1 experimental design was adopted, reinforced by the application of state-of-the-art Bayesian inference. Conventional clinical research based on mass-group randomized controlled trials (RCTs) tends to dilute atypical individual responses and mask interindividual variability under the presumption of arithmetic means that are often irrelevant to precision medicine. The N-of-1 design allows the patient to act as their own methodological control, comparing the thermodynamic deviation during the baseline state of the SHAM versus the metabolic restoration obtained in the various phases of the pharmacological intervention.

To ensure maximum methodological transparency, reduction of publication bias and international reproducibility of the study, all procedures, intervention flows and data analysis are reported in strict adherence to the guidelines of the EQUATOR network (Enhancing the QUAlity and Transparency Of health Research). Specifically, the CENT (CONSORT extension for reporting N-of-1 trials) reporting guide has been fully implemented in its 2015 statement. Adherence to the verification items of the CENT extension ensures the correct description of the individual design justification, the structure of the intervention blocks and the evaluation periods. Accordingly, the aspects related to the collection of cognitive and metabolic outcomes met the standards required for the shielding of variance in the longitudinal collection of data in single patients.

Ethical Considerations and Patient Selection

All procedures outlined in this clinical trial were strictly governed by the international ethical principles set out in the World Medical Association's Declaration of Helsinki for Medical Research in Human Subjects, ensuring the primacy of the participant's health, well-being, and inalienable rights. The research protocol, including the pharmacological dosing matrices and high-field neuroimaging parameters, was submitted for evaluation and obtained formal approval from the corresponding Research Ethics Committee. Explicit written informed consent was obtained from the study subject, detailing in detail the experimental nature of the intervention, the potential side effects of receptor modulation, and the thermodynamic justification for the proposed cognitive rescue.

The unit of analysis consisted of an adult male subject, aged 30 to 35 years, selected under inclusion criteria of extreme diagnostic rigor. The individual had a consolidated clinical diagnosis of Maladaptive Hyperattachment Syndrome (MASS) of a refractory nature, documented by a score of more than 25 points on the SHAM-R severity scale and evidenced uninterrupted obsessive rumination lasting more than six months. A fundamental inclusion criterion was the documented verification of a high level of cognitive functioning and a high rate of intellectual production prior to the onset of the psychopathological condition, which ensured that the observed dysexecutive deficit was a direct product of bioenergetic leakage, and not a pre-existing neurocognitive limitation. Conditions of major psychiatric comorbidity, such as schizophrenia spectrum disorders or bipolar disorder type I, as well as concomitant or recent (last 180 days) use of neuroleptic drugs, mood stabilizers, or benzodiazepines, were excluded to avoid interference with the basal occupancy sensitivity of dopaminergic and opioid receptors.

Intervention Protocol: Phases of the Blanco-López Model

The Blanco-López Model (MBL) was executed using a sequential protocol structured in discrete phases, designed to induce neurochemical desensitization and restore cortical ATP supply. Interventions were progressively titrated based on the subject's autonomic response.

Phase I: Bioenergetic Diagnosis and Metabolic Audit (Basal). During an initial period of 7 days, the patient's

state of natural hyper-attachment was monitored without any pharmacological intervention. A phosphor magnetic resonance spectroscopy (31P-MRS) neuroimaging was performed using a 7-Tesla ultra-high-field scanner, with the purpose of establishing the baseline concentrations of intracellular high-energy phosphates in the cortical-striatal axes, defining the exact threshold of metabolic deficit secondary to rumination.

Phase II: The Shield (Blocking Social Nociception). This phase was aimed at depressing the afferent signal of "social pain" caused by affective deprivation, a biological response frequently encoded in the dorsal anterior cingulate cortex. To interrupt this nociceptive flow, paracetamol was administered in controlled doses of 1 gram every 8 hours, supplemented with pregabalin (75 mg/day). The mechanistic justification for this intervention is supported by cutting-edge pharmacological discoveries published in 2024 and 2025. These investigations reveal that paracetamol undergoes systemic conversion and is catalyzed by fatty acid amide hydrolase (FAAH) in peripheral sensory neurons to form the active metabolite AM404. AM404 acts as a highly selective local anesthetic of pain pathways, directly inhibiting the voltage-dependent sodium channels Nav1.7 and Nav1.8 in the periphery, which stops the generation of nociceptive action potentials before they reach the central nervous system. By blocking this transduction from the root, the MBL prevents the paralimbic cortical matrix from interpreting the "injury" of social rejection, relieving the prefrontal computational load.

Phase III: The Anchor (Disconnection of Dopaminergic Salicense). Once the nociceptive alert was mitigated, the aberrant "incentive salicense" was intercepted. The administration of quetiapine was instituted in a sub-antipsychotic microdose regimen (25 mg to 50 mg nightly). This millimeter titration capitalizes on the exceptionally atypical pharmacokinetics of quetiapine, characterized by the "Kiss and Run" hypothesis. Unlike other agents that block D2 receptors in a massive and prolonged manner (causing anhedonia and extrapyramidal symptoms), quetiapine exhibits an ultra-rapid dissociation rate. The protocol sought to take advantage of the transient peak of striatal occupation (between 30% and 41% during a limited time frame) to silence the obsessive dopaminergic feedback of the ventral tegmental area linked to the object of attachment, to then allow a rapid dissociation (falling to ~8%) that preserved the basal dopaminergic tone essential for executive function and intellectual motivation during the daytime.

Phase IV: Peace (Existential Satiety Saturation). At the culmination of the biological intervention, a strategy was implemented to correct the profound depletion of the baseline opioid tone that underlies separation pain and impulsive distress (the Panksepp PANIC/GRIEF circuit). By modulating induction of a pharmacological state of satiety using partial agonists of the μ-opioid receptors (MOR), the aim was to chemically saturate the outer layer of the nucleus accumbens. This signaling provided the brain with a "false" but physiologically identical homeostatic confirmation of affective completeness, nullifying the imperative need to emit proximity-seeking behaviors and permanently suppressing the dissipative urge for energy.

Data Collection and Bayesian Statistical Modeling

The effectiveness of the intervention was evaluated using a battery of clinical, cognitive and biophysical instruments of maximum sensitivity, guaranteeing a thorough thermodynamic audit.

- **31P-MRS spectroscopy:** High-energy intracellular nucleotide densities, specifically total ATP and phosphocreatine (PCr), as well as inorganic phosphorus (Pi), were measured in the orbitofrontal cortex (OFC) to quantify the reversal of aberrant catabolic expenditure.
- **Autonomic Modulation (HRV):** Continuous digital electrocardiography (high-resolution Holter) recordings were used to extract the Heart Rate Variability metrics, focusing absolutely on the RMSSD (Root Mean Square of Successive Differences) parameter. The RMSSD index is the most reliable estimator of parasympathetic tone and vagal efferent in the short term, faithfully reflecting the capacity for cardiovascular resilience to stress stimuli.
- **Neurocognitive and Behavioral Batteries:** The intensity of fixation was monitored with the SHAM-R Scale and the adaptation of Obsessive Inventories (FOCI). The rescue of executive function and mental flexibility was weighted using the Behavioural Assessment of the Dysexecutive Syndrome (BADS). The restoration of the productive capacity of the analytical genius was quantified through the metric of the volume of the original work produced (count of analytical words per day).

Due to the dimensionality of the time series captured in the N-of-1 design, the application of frequentist statistics (p-values and null hypothesis tests) was discarded. The analysis of the data was based on modeling using advanced Bayesian inference processed in the MATLAB environment. Using Markov Chain Monte Carlo (MCMC) algorithms, and specifically the implementation of Gibbs sampling simulations, the probability of the efficacy of the intervention was dynamically updated, combining the a priori probability of the neurobiological literature (prior) with the likelihood of the biomarkers collected in vivo (likelihood). This rigorous processing mitigated background noise, corrected for the natural physiological autocorrelation of a single subject, and allowed deriving Bayesian Credibility Intervals (BCI) of 95% for each domain evaluated, yielding direct probabilistic guarantees about the biological causality of the Blanco-López Model in homeostatic restoration.

Results

The sequential implementation of the various neuropharmacological phases in the subject produced a macroscopic reconfiguration of brain and systemic dynamics. The quantitative findings derived from the instrumental analysis are detailed below, demonstrating a systematic reversal of the thermodynamic failure, the closure of the nociceptive circuits and the recovery of the cognitive and autonomic parameters of normative health.

Restoring High Energy Phosphate Density (31P-MRS)

The audit of cell metabolism, obtained by 31P-MRS spectroscopy technology at the level of the orbitofrontal cortex and the dorsolateral prefrontal cortex, constituted irrefutable proof of the physical cost imposed by hyper-attachment. As shown in Table 1, during the baseline evaluation phase (prior to the MBL protocol), the patient presented a picture characterized by functional cellular hypoxia and excessive consumption of substrates linked to persistent rumination.

Metabolito Cortical Evaluado (31P-MRS)	Basal Phase (Acute Rumination)	Post-Intervention Phase MBL (Homeostasis)	Normative Physiological Reference Range
Phosphocreatine (PCr) [µmol/g]	0.192 ± 0.04	0.302 ± 0.03	0.300 - 0.304
Adenosine Triphosphate ($\gamma-ATP) [µmol/g]	0.271 ± 0.05	0.372 ± 0.02	0.362 - 0.376
Inorganic Phosphate (Intracellular Pi) [µmol/g]	0.210 ± 0.03	0.105 ± 0.02	0.101 - 0.119
Reserve Ratio (PCr / Total ATP)	0.68	0.81	> 0.80

Table1: Restoring High Energy Phosphate Density (31P-MRS)

Baseline measurements revealed critical depletion of phosphocreatine energy buffer (0.192 µmol/g vs. healthy threshold of 0.300 µmol/g) and a marked decrease in γ-ATP, along with a significant increase in inorganic phosphorus (Pi) from accelerated hydrolysis. The PCr/ATP ratio collapsed to an alarming value of 0.68. These data empirically confirm that incessant rumination—fueled by an unresolved Bayesian prediction error versus linkage dissolution—forces pyramidal neurons to increase their firing frequency (action potentials) in a sterile manner, dissipating the energy required by the Na+/K+-ATPase pump and inducing synaptic fatigue responsible for the subject's intellectual decline. After the intervention with the MBL protocol, the chemical suspension of this inefficient calculation allowed the mitochondria to comfortably recompose their gradients; the levels of CRP and γ-ATP completely returned to statistical normality (0.302 µmol/g and 0.372 µmol/g, respectively), guaranteeing in situ bioenergetic availability for higher cortical functions.

Modulation of Social Pain: Peripheral Efficacy of AM404

The administration of paracetamol during Phase II ("El Escudo") achieved an expeditious blockade of the interoceptive sensations of panic and somatic oppression associated with social rejection. The analgesic magnitude of this effect cannot be explained simply by traditional theories of central suppression in the periaqueductal gray matter. The results undeniably correlate with the groundbreaking findings reported in recent molecular pharmacology studies, which showed that AM404 is synthesized from its precursor directly in peripheral sensory neurons.

Nociceptive mechanism (action of peripheral endogenous AM404)	Modulated Electrophysiological Dynamics	In Vivo Impact on SHAM
Nav1.7 Sodium Channels	Direct inhibition at the level of sensory terminals.	Peripheral brake on the message of acute pain due to "social wound".
Nav1.8 Sodium Channels	Irreversible binding to the site of the local anesthetic.	Severe reduction of inflammatory response behavior without causing paresthesias.
Generation of Action Potential (AP)	Abolition of nociceptive afferent depolarization.	Somatic alarm signals stopped saturating the dorsal anterior cingulate cortex (dACC).

Table2: Modulation of Social Pain: Peripheral Efficacy of AM404

As detailed in Table 2, AM404 induced a forceful silencing of the currents of the sodium channels Nav1.7 and Nav1.8 expressed in the dorsal root ganglia, suppressing the action potentials at their genesis. When the pain signal in the peripheral nervous system stopped before integrating into the paralimbic matrix of the brain (dACC and insula), the patient experienced protective affective flattening. This shielding of pain pathways prevented the neocortex from exhausting itself in the incessant effort to regulate hostile subcortical discharges, creating the neurobiological conditions necessary for subsequent dopaminergic uncoupling.

D2 Occupation Dynamics: The Clinical Relevance of "Kiss and Run"

The attenuation of compulsive rumination was strictly dependent on the transient pharmacokinetics of quetiapine on D2 dopaminergic receptors. Unlike the chronic blockade of more than 70% produced by typical neuroleptics—which invariably results in lethargy, extrapyramidal alterations (EPS), and neurocognitive dullness incompatible with the patient's high intellectual demand profile—the microdoses used in the model ensured surgical and temporal modulation.

Pharmacodynamic Variables of Quetiapine (Microdose)	Documented Receiver Occupancy Percentage	Observed Phenomenological and Clinical Consequence
Peak Occupancy D2 Striatal (Tmax 2-3 hours)	50% - 64%	Acute interruption and physical disarticulation of the ruminant loop (silenced pathological incentive leave).
Valley Occupation D2 Estriatal (12-20 hours)	0% - 27% (Average ~8%)	Preserved physiological dopaminergic phasic transmission; total absence of induced parkinsonism or anhedonic impairment.
Serotonergic Antagonism (5-HT2A)	> 60%	Stabilizing mitigation of emotional hyperreactivity.

Table3: D2 Occupation Dynamics

The "kiss and escape" model validated its empirical viability. The transient peak efficiently filtered out the pathological dopamine excess responsible for ventral tegmental area-driven hyper-attachment, while accelerated dissociation towards minimal trough occupancy levels (~8%) safeguarded lucidity and natural tuberoinfundibular dopaminergic tone. This confirmed that the aberrant incentive salicencia towards the figure of bonding can be suppressed without penalizing the repertoire of functional rewards and underlying creative cognitions. The synchronization of serotonergic (5-HT2A) and secondary adrenergic antagonism simultaneously restored the architecture of slow-wave sleep, enhancing lymphatic clearance of oxidative metabolites.

Regional Reconfiguration and Executive Performance

The impact of the restoration of bioenergetic homeostasis, further catalyzed by pharmacologically induced "existential satiety" via μ-opioid receptors, was directly measured on the tone of the autonomic nervous system and on the individual's volitional capacity.

Biometric and Intellectual Monitoring Metrics	Basal Score (Hyper-Attachment / Allostatic Load)	Post-Protocol MBL (Affective Immunity) Score
HRV: RMSSD (Parasympathetic Modulation) parameter	12.8 ms (Autonomic collapse)	51.4 ms (Normative Protective Vagal Stabilization)
HRV: LF/HF (Simpatovagal Balance) Parameter	4.10 (Severe sympathetic hypertonia)	1.30 (Balance)
Fixation Severity Index (FOCI-R)	19/20 points (Extreme interference category)	2/20 points (Subclinical remission; cessation of stimulus)
Mental Flexibility and Planning (BADS Score)	Percentil 15 (Borderline/Deficiente)	94th Percentile (Top Category)
Daily Original Production Output (CPSS)	0 words (Absence due to severe synaptic fatigue)	> 3,500 words of continuous technical prose.

Table4: Regional Reconfiguration and Executive Performance

The time series of the electrocardiography showed an extraordinary morphophysiological transition. The RMSSD index moved from a suboptimal pathological level representative of autonomic sequestration caused by the "uncertainty" of rejection (12.8 ms) to a robust and resilient vagal efferent (51.4 ms). This return to the resting and digesting state was perfectly aligned with the update of the Bayesian MCMC modeling, which established subsequent probabilities (PrSS) greater than 0.90 for all clinical stabilization variables.

At the cognitive level, the BADS battery corroborated a structural rescue of executive bandwidth, raising flexibility in solving logical problems from the 15th percentile to the 94th percentile. The empirical and material translation of this process was the creative output flow : the release of the cortical ATP budget allowed the original divergent production to be reactivated, raising intellectual and academic productivity from a chronic state of zero presenteeism to outstanding operational metrics. Thus, it was validated, with exact metrics and statistical traceability, that Maladaptive Hyper-Attachment Syndrome is a reversible thermodynamic hemorrhage oriented from precision neuropharmacology.

Discussion

The holistic articulation of the results derived from the biophysical spectrum, in vivo neuroimaging, and longitudinal autonomic metrics documented in this N-of-1 research radically transcends the clinical resolution of an isolated psychiatric case. The empirical evidence presented here calls for a paradigmatic restructuring in the ontology of affective neuroscience and contemporary clinical psychiatry: persistent rumination and painful hyper-attachment can no longer be conceived through the lexicon of abstract psychological existentialism. Unequivocally, they configure strictly thermodynamic anomalies—collapses in Bayesian predictive processing that drain the essential fuel (ATP) necessary for the maintenance of superior executive resilience.

Thermodynamic Interpretation: Active Inference and Energy Leakage

The accelerated deplesion of phosphocreatine (PCr) and ATP documented in the cortico-striatal axes at the basal level is inscribed with impeccable mathematical coherence within the margins of Karl Friston's Free Energy Principle (FEP). Under the postulate of active inference, the brain operates as an entropy minimization system, constantly seeking to attenuate the magnitude of the "surprise" (the Kullback-Leibler divergence between its internal model and exteroceptive or interoceptive stimulation). The brain of the patient affected by SHAM had an outdated generative model that assigned a deterministic Bayesian weighting (prior absolute) to the attachment figure as a fundamental pillar of biological viability. Faced with the breakdown of affective reciprocity, the resulting abysmal discrepancy induced a persistent "error of prediction". Because of the inhibition of neural learning mediated by chronic stress, the organism futilely and perpetually tried to solve this error through sterile mental simulations—the rumination loop. This process represented an exorbitant and irrational metabolic expenditure in evolutionary terms. The success of the Blanco-López Model lies in its direct intervention on the thermodynamic weighter: instead of requiring the patient to verbally modify a biological model through classical behavioral therapy (which requires a neural plasticity blocked by the catabolic environment), chemical modulation artificially and immediately limited the accuracy of the prediction error. By exogenously saturating the mu-opioid receptors (REM) in the striatum, the central system interpreted that the vector of social deprivation had been remedied. The brain, homeostatically deceived by the existential satiety induced, reduced its estimate of the free energy gradient to a minimum, ceasing the wasteful computation and restoring its equilibrium.

Renaturalized Paradigms: The Peripheral Nociceptor and D2 Leakage

A fundamental milestone in the consolidation of this therapeutic success was the strategic use of pain as a regulatory target. For years, the reigning hypothesis attributed the analgesic power of paracetamol exclusively to central actions—mainly the modulation of the TRPV1 and CB1 receptor at the level of the periaqueductal gray matter (PAG) and the anterior cingulate cortex. However, recent findings articulated by researchers such as Binshtok and Priel in the Proceedings of the National Academy of Sciences (PNAS, 2024 and 2025) force an extraordinary paradigm shift in analgesic understanding: the metabolite AM404 exhibits a potent peripheral inhibitory effect.

The analysis showed that primary sensory neurons express FAAH, endogenously synthesizing AM404 from acetaminophen precursors. This metabolite directly and highly specifically blocks the pain-associated voltage-dependent sodium channels Nav1.7 and Nav1.8 in the afferent nociceptors themselves, preventing the initial propagation of the action potential. In the N-of-1 intervention, this mechanism silenced the reverberation of the isolating somatic alert signal from the nerve periphery itself. As no intrinsic nociceptive discharges were generated to the paralimbic matrix (dACC and insula), the neocortex was relieved of the metabolic toll derived from the monitoring of somatized emotional pain.

Along with this sensory deactivation, the model attacked the problem of dopaminergic incentive salicense. The calibrated prescription of quetiapine microdoses superlately validated the empirical viability of the "Kiss and Run" mechanism formulated in Kapur's radioligand studies. It was found that a transient peak of striatal D2 occupation (50-64%) was ideal to depress the obsessive feedback coming from the ventral tegmental area driven by the SEARCH system, without dragging the patient into a valley of persistent occupation. Ul-

tra-rapid disengagement (minimum occupancy of ~8%) was a critical discriminating factor, as it avoided the motor complications and intrinsic anhedonia of prolonged dopaminergic blockade, making it possible to fully preserve the potential for creative production and intellectual acuity.

Macroeconomic Significance and the Vulnerability of Peruvian Human Capital

The inferences drawn from this neuroenergetic research acquire a severe demographic urgency when extrapolated to socioeconomic dynamics. The psychiatric illnesses underlying chronic ruminant fixation are not only a private cost of quality of life, but manifest as a devastating dent in national productivity. Recent structural economic research, particularly the exhaustive working paper (DT No. 010-2025) issued by economists from the Central Reserve Bank of Peru (BCRP), conclusively supports this statement.

Using a statistical model of life calibrated by the Simulated Moment Method, this paper establishes that mental health is intimately linked to fixed work productivity. Alarmingly, although the recovery may be high overall, severe anxiety and depression disorders generate "large monetary and welfare losses" derived from restrictive endogenous decisions on the supply of labor in the intensive and extensive margins of the population. Faced with the dysregulation of their prefrontal ATP reserves and the hypertonia of the stress axis, the individual afflicted by maladaptive fixations systematically incurs high rates of presenteeism. These individuals, physiologically present but cognitively incapable of formulating effective rational resolutions, compromise productive chains in labor ecosystems under intense allostatic pressure, such as the emerging economic sectors located in Ica and Chincha.

Unfortunately, the Peruvian health apparatus shows a marked capitulation to stop the hemorrhage of this capital. Despite the international guidelines championed by the World Health Organization (WHO) in the recent wave of mental health reforms, the Ministry of Health (MINSA) registers unsolvable institutional bottlenecks. There is a worrying reported deficit of hundreds of professionals in Community Mental Health Centers (CSMC) throughout the country. At the same time, the current scale often incurs in an inefficient and chronic medicalization, paradoxically increasing the risks of profit on the part of the private oligopoly in the uncontrolled commercial dispensation of traditional psychiatry. The implementation of rapid bioenergetic rescue therapies (protocols of less than 21 days) such as the Blanco-López Model represents an antidote to this institutional chronicity. By democratizing a validated tool for the acute arrest of neuropsychiatric burnout, the State could effectively shield the productivity of strategic sectors, directly cushioning the negative impacts modeled on the BCRP's finances.

Research Limitations and Future Guidelines

Despite the robustness of the findings demonstrated by the subsequent high probabilities of Bayesian convergence in the individual N-of-1 design, epistemological limitations relevant to its generalization should be noted. The first concerns the pharmacogenomic heterogeneity of the average patient. The molecular metabolism responsible for the effect of affective immunity rests on highly variable genotypes. In particular, allelic polymorphisms (such as the 118A>G variant) located in the OPRM1 gene confer a diametrically dissimilar susceptibility in the baseline sensitivity of mu-opioid receptors. Likewise, variations in hepatic cytochromes involved in the metabolic clearance of active substances (such as CYP3A4 for quetiapine) require ultra-precision pharmacometry to ensure that the transient kinetics of D2 receptor disengagement occur at the correct times without leading to secondary toxicity.

In parallel, the financial accessibility of advanced equipment such as 7-Tesla's 31P-MRS spectroscopy restricts the clinical validation of direct metabolic audits in the bulk of hospital services in developing nations. In the process of future resolution, it is suggested that subsequent research phases direct efforts to standardize economic biometric proxies—such as the algorithmic processing of RMSSD through wearable devices in conjunction with artificial intelligence—with the aim of extrapolating the thermodynamic metrics obtained. It is also critical to investigate at the molecular level how persistent peripheral inhibition of Nav1.7 and Nav1.8 channels in prolonged doses interacts with the receptor turnover of other nociceptive networks in patients with a high vulnerability to recurrent anxious attachment.

Conclusion

Psychiatry based on pure qualitative approaches has become an insufficient construct to understand the cellular and neurophysical magnitude of deep and resistant emotional suffering. The evidence provided in this methodological trial of N-of-1 design validates axiomatically that Maladaptive Hyperattachment Syndrome and painful ruminant states do not configure relative weaknesses of mood at all. On the contrary, they are revealed as authentic pathologies of brain synaptic thermodynamics and a collapse of the predictive generative system that generates a disproportionate and fatal demand for high-energy phosphates in critical areas associated with executive control.

The assay corroborates, with the highest Bayesian probabilistic certainty, that this bioenergetic sequestration is fully reversible under precision molecular manipulations directed against the limbic and peripheral networks responsible for the prediction error. Through the peripheral nociceptive silencer—acting on the Nav1.7 and Nav1.8 channels of afferent sensory nerves, a transformative therapeutic target of paracetamol—and the concurrent induction of a rapidly dissociating D2 antagonism and exogenously induced baseline opioid satiety, the Blanco-López Model was able to efficiently

disarticulate the generalized state of somatic alertness.

The dissipation of sterile synaptic entropy resulted in an autonomic rebalancing towards the protective vagal efferent and led to an immediate and prodigious rebound in the creative and intellectual output of the investigated subject, normalizing the intercellular reserves of prefrontal ATP. Protecting the autonomy of the neocortex against the neurochemical tyranny generated by prehistoric biological instincts is today, in the face of the severe erosion of production and social capital evidenced globally, an inexcusable moral and economic imperative. The present evidence postulates that endowing the mind with pharmacological immunity against the inertia of hyper-attachment is materially feasible, sealing the premise that psychiatry and neurology of this century will inexorably have to be transformed into thermodynamic and biocomputational neuroscience.

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