The Zero Sleep Project

Toward Accelerated Biological Refresh

Samuel Neymotin, PhD

Lev Neymotin, PhD

A systems neuroscience and bioengineering framework for measuring, accelerating, and selectively reproducing the biological work of sleep

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Executive Summary

Sleep is conventionally treated as an indivisible biological requirement measured by duration and architecture. The Zero Sleep Project advances a different, engineering-oriented formulation: sleep is investigated as a coordinated transformation network that moves an individual from a documented pre-sleep neural and molecular state to a documented post-sleep state through interacting electrical, neuromodulatory, synaptic, metabolic, vascular, endocrine, immune, and repair processes. The long-range objective is to determine whether these operations can be measured, causally controlled, accelerated, parallelized, or partially substituted so that biological refresh can be achieved in substantially less time than a conventional night of sleep.

The framework begins with personalized pre-sleep and post-sleep state vectors and defines their net change as the Difference Vector. Because identical endpoint concentrations can conceal extensive turnover, transport, repair, or spatial reorganization, the framework expands the target to a Difference-plus-Work Vector that includes endpoint change, trajectory, flux, anatomical and cellular localization, functional performance, durability, and absence of cumulative deficit. A Process-to-Difference Matrix maps ten candidate transformation families onto ten major biological outcome domains and identifies candidate control handles, including phase-locked stimulation, pharmacological state control, metabolic support, and vascular or fluid-dynamic modulation.

Because the full biologically relevant brain-and-body state is not presently observable, the near-term program adopts measurement sufficiency rather than exhaustive measurement. It begins with a Minimum Testable Refresh Panel: a prespecified NREM Difference-plus-Work subvector of reproducible variables with demonstrated sensitivity to human sleep, adequate temporal resolution, mechanistic interpretability, and linked functional outcomes. Core electrophysiological, homeostatic, molecular, autonomic, and cognitive measurements are supplemented by nested PET, MRS, CSF, isotope-kinetic, and multi-omic studies. A Biological Refresh Scanner estimates this partially latent state with calibrated uncertainty; a Closed-Loop Restoration System selects a process-specific intervention, measures target engagement, rescans, and either continues, stops at module-level equivalence, abstains, or defaults to conventional sleep.

Current evidence supports control of selected modules but not replacement of sleep as a whole. Human studies demonstrate measurable sleep-wake changes in adenosine A1-receptor availability, SV2A binding, cerebral bioenergetics, blood transcriptomics, plasma metabolomics, cerebrospinal-fluid amyloid-β and tau, endocrine and immune trajectories, tissue-specific molecular programs, and muscle protein synthesis. Closed-loop auditory stimulation is treated as a state- and phase-contingent perturbation of endogenous slow oscillations, not as generic sound exposure; the controller must optimize slow-oscillation response and spindle coupling while suppressing arousal and cross-domain disruption. Dexmedetomidine is prioritized as an initial pharmacological state gate, with sodium oxybate as a comparator, creatine as a metabolic-support probe, orexin-2 agonism as a possible exit switch, and tiagabine and zolpidem as mechanistic counterexamples. Defense use is framed as the Resilient Warfighter: objective, role-specific readiness assessment and protected recovery, not an unbounded “perfect soldier.” The first testable claim is module-specific; complete Difference-plus-Work equivalence without cumulative impairment remains the long-range criterion.

Keywords: sleep homeostasis; systems neuroscience; accelerated biological refresh; measurement sufficiency; biological refresh scanner; closed-loop auditory stimulation; slow-wave activity; synaptic homeostasis; glymphatic transport; mechanistic pharmacology; multi-omics; warfighter readiness

Position. Sleep should be decomposed into measurable biological operations. If the indispensable operations can be identified, controlled, accelerated, safely parallelized, and verified, the duration of conventional behavioral sleep may eventually be reduced. This is a research hypothesis—not a claim that sleep can currently be eliminated.

1. Introduction

Sleep occupies approximately one-third of human life, yet the scientific unit ordinarily optimized is still time: total sleep time, stage duration, sleep efficiency, or the frequency of specific electroencephalographic events. Those quantities are important, but they are proxies. The biologically decisive question is not how long the organism remains behaviorally asleep; it is what work is performed during that interval, in what order, in which compartments, and with what lasting consequence.

The Zero Sleep Project is built around a deliberately provocative objective: to understand the transformation normally achieved during sleep well enough to reproduce progressively larger portions of it in an accelerated mode. The popular phrase “zero-sleep individual” expresses the destination, but it should not be misunderstood. The scientific objective is not to abolish sleep biology while leaving the organism continuously active. It is to decouple essential maintenance and reorganization from a long, consolidated period of conventional sleep. The nearer-term and more defensible term is Accelerated Biological Refresh (ABR).

The project adopts the two-process understanding of sleep regulation—homeostatic sleep pressure interacting with circadian timing—as necessary background rather than a complete mechanistic account [1]. Waking theta activity and subsequent slow-wave activity provide related electroencephalographic markers of homeostatic pressure [2], but neither specifies the full molecular work of sleep. Similarly, multivariable blood signatures can classify acute sleep deprivation with high accuracy under controlled conditions, yet chronic insufficient sleep and realistic mixed states remain substantially harder to identify [3,4]. These observations establish an important distinction between detecting a state and explaining the processes that created it.

The proposed research sequence moves from description to mechanism and then to control. It begins with paired neural and molecular snapshots immediately before verified sleep and immediately after verified awakening. It then reconstructs the transformation network connecting those snapshots, identifies hidden overnight work that endpoint measurements can miss, and determines which components possess plausible control handles. This produces an observer-controller architecture: a Biological Refresh Scanner estimates the residual Difference-plus-Work Vector, and a Closed-Loop Restoration System applies and verifies process-specific interventions. The sequence culminates in a staged research program and a stringent defense-readiness application, in which apparent refresh is never accepted as biological replacement unless state, process, function, durability, and cumulative safety all meet predefined equivalence criteria.

2. Scope, terminology, and falsifiable position

2.1 Actual sleep as the reference condition

Within this framework, “pre-sleep” and “post-sleep” refer to states bracketing objectively documented physiological sleep. Polysomnography (PSG)—including electroencephalography (EEG),

electrooculography, electromyography, respiratory monitoring, and cardiac recording—serves as the audit trail establishing sleep onset, stage composition, arousals, and final awakening. External performance measures are important verification endpoints, but they are not the primary object. The primary object is the paired neural and molecular state of the same individual.

Sedation, anesthesia, quiet wakefulness, stimulant-supported wakefulness, and circadian morning activation are not assumed to be equivalent to sleep. They are experimental states whose biological outputs must be compared with the reference transformation. A sleep-like EEG pattern is likewise not sufficient evidence that the underlying work has been completed.

2.2 State signature, history marker, and biological replacement

A state signature describes what the individual presently resembles. A history marker indicates what probably happened during the preceding interval. These are related but not identical. Circadian phase, morning light, cortisol, temperature, posture, and activity can shift measurements toward a morning pattern even after a sleepless night. Conversely, fragmented sleep may leave a recognizable post-sleep signature while failing to complete all restorative functions.

The project consequently distinguishes five levels of intervention:

1. Masking: suppressing subjective sleepiness or transiently improving performance without performing sleep-dependent work.
2. Compensation: supporting one impaired domain, such as cerebral energy buffering, while sleep debt continues to accumulate.
3. Acceleration: increasing the rate or density of a genuine sleep-dependent operation.
4. Partial replacement: reproducing a defined subset of the Difference-plus-Work Vector in less time than natural sleep.
5. Whole-system equivalence: reproducing all material neural and peripheral outputs without rebound, hidden deficit, or cumulative injury.

2.3 The core hypothesis and its failure conditions

The project's core hypothesis is that the biological work of sleep is modular enough to be mapped and partially controlled, yet coordinated enough that sequence and coupling must be preserved. The hypothesis would be weakened or falsified if one or more indispensable processes proved to have a hard temporal minimum near normal sleep duration; if the processes could not be accelerated without loss of selectivity; if essential NREM and REM operations required mutually incompatible states; or if repeated compression produced cumulative deficits despite normal immediate endpoints.

A negative result would still be scientifically valuable. The project is designed to identify the minimum biologically permissible refresh time, even if that minimum remains several hours and "zero sleep" proves unattainable.

3. Paired neural and molecular snapshots

3.1 State-vector formulation

Let Xpre denote the individual's multidimensional biological state during the final period of wakefulness before verified sleep onset, and Xpost the corresponding state immediately after final awakening. The first descriptive object is the overnight Difference Vector:

$$\Delta night = Xpost - Xpre$$

The vector is personalized. Between-person variation in transcriptomes, receptor availability, sleep architecture, circadian phase, prior sleep history, and responsiveness to deprivation can exceed the within-person overnight effect. This is consistent with evidence that within-subject comparisons improve detection of chronic sleep insufficiency [3]. The initial objective is therefore not a universal "rested" value but a reproducible individual transformation envelope across multiple baseline nights.

3.2 Measurement compartments

Table 1. Proposed paired-snapshot architecture. Invasive measurements would often require matched study nights rather than simultaneous collection.

Compartment or level	Representative measurements	Principal information
Living brain	7-T magnetic resonance spectroscopy; 31P-MRS; PET targets including A1 receptors and SV2A; structural and functional MRI; TMS-EEG	Regional neurotransmitter, energy, receptor, synaptic-vesicle, excitability, and network states
Electrical physiology	High-density EEG; PSG; source-resolved slow oscillations, spindles, ripples where intracranial access is clinically available	Sleep architecture, event density, coupling, propagation, and homeostatic pressure
Cerebrospinal fluid	Targeted proteins; proteomics; metabolomics; lipidomics; albumin and transport markers	Closest practical molecular sample of the human central nervous system; solute movement and compartment exchange
Blood plasma and serum	Proteomics; metabolomics; lipidomics; cytokines; hormones; extracellular vesicles	Systemic state and candidate brain-to-blood or organ-derived signals
Blood cells	RNA sequencing; epigenetic profiling; immune phenotyping; integrin activation	Gene regulation, cellular stress, leukocyte state, and trafficking
Skeletal muscle/adipose	Biopsy multi-omics; stable-isotope protein synthesis; mitochondrial and substrate assays	Direct peripheral-tissue recovery rather than strength or fatigue proxies
Functional phenotype	Psychomotor vigilance; working memory; declarative/procedural/emotional memory; mood; balance; autonomic tests	Verification that molecular equivalence produces usable organism-level equivalence

Human PET studies provide examples of tractable molecular anchors. Extended wakefulness increases A1 adenosine-receptor availability, while recovery sleep returns it toward baseline [5]. A 2026 randomized study found modest but significant regional increases in SV2A binding after approximately 28 hours of wakefulness, including the hippocampus, thalamus, and parietal cortex; the increase correlated with subsequent slow-wave activity [6]. SV2A is a proxy for synaptic-vesicle biology and must not be interpreted as a literal count of functional synapses, but it demonstrates that a central component of the proposed vector is measurable in vivo.

Molecular classifiers further support multidimensional measurement. Blood mRNA panels classified acute sleep loss at 92% accuracy in an independent validation setting, whereas a single between-person sample classified chronic insufficiency at only 57% [3]. A five-metabolite model distinguished 24–38 hours awake from well-rested conditions with 94.7% accuracy in an unseen controlled test set;

performance fell under the more realistic between-person formulation [4]. These are powerful state detectors, not proof that all sleep functions have been completed.

3.3 Measurement sufficiency and the Minimum Testable Refresh Panel

The complete Difference-plus-Work Vector is an aspirational scientific object, not an immediately observable experimental endpoint. The initial program should therefore pursue measurement sufficiency: a bounded panel that is sufficiently informative to predict, control, and verify one specified sleep-transformation module. A variable enters the panel only when (1) human evidence demonstrates sensitivity to sleep, wakefulness, or controlled perturbation; (2) it can be measured reproducibly at the temporal resolution required by the experiment; (3) its biological interpretation and principal confounders are characterized; and (4) it is linked to a defined process or functional outcome. A positive result supports only the measured module, population, exposure, and follow-up interval.

The panel is hierarchical. Core measurements are acquired in every participant and provide real-time control, safety, and functional verification. Secondary measurements characterize systemic and peripheral responses at lower temporal resolution. Nested measurements provide deeper molecular or physiological anchors in smaller subgroups. Exploratory multi-omics may discover future markers, but variables selected after outcome inspection cannot retrospectively establish equivalence.

Table 2. Minimum Testable Refresh Panel for the initial NREM program.

Tier and domain	Candidate measurement	Method	Evidentiary role and principal limitation
Core — electrical coordination	Slow-oscillation phase, amplitude, slope and density; spindle density; slow-oscillation–spindle coupling; traveling propagation; arousal probability	PSG and high-density EEG	Directly measures the process targeted by auditory stimulation [7,8]. EEG pattern alone does not prove memory, repair, or clearance.
Core — homeostatic demand	Waking theta; subsequent NREM slow-wave activity, N3 duration, and slow-wave-pressure dissipation	Waking EEG and subsequent-night PSG	Tests whether an intervention changes the expected homeostatic response [2,21]. Reduced later demand is supportive, not sufficient evidence of whole-system restoration.
Core — functional verification	Psychomotor vigilance, response inhibition, declarative recall, working memory, and next-day learning capacity	Standardized repeated cognitive battery	Independent functional check linked to the NREM module [8,23–25]. Practice, motivation, and stimulant exposure require control.
Secondary — systemic molecular state	Prespecified plasma metabolite and blood-transcript panels	Targeted LC-MS and RNA assays	Feasible sleep-loss state or history markers [3,4]. Peripheral classification cannot independently demonstrate central restoration.
Nested — adenosine reset	Regional cerebral A1 adenosine-receptor availability	[18F]CPFPX PET	Human recovery sleep returns elevated receptor availability toward the rested state [5]. PET is costly, burdensome, and not an operational sensor.
Nested — synaptic-vesicle state	Regional SV2A binding	[18F]SynVesT-1 PET	Human deprivation changes this measurable central marker [6]. SV2A is not a direct count of synapses or synaptic quality.
Nested — cerebral bioenergetics	PCr/Pi, ATP-related measures, cerebral pH, and total creatine/NAA	31P- and 1H-MRS	Measurable and pharmacologically modifiable [25]. Current evidence may represent metabolic compensation rather than completed restoration.
Nested — solute transport	Serial CSF and plasma amyloid-β and tau; CSF-to-plasma relations and kinetic estimates	Immunoassay or mass spectrometry; isotope or compartmental modeling	Research-level process measure supported by human sleep studies [13–15]. Concentrations jointly reflect production, redistribution, transport, and clearance.
Secondary/nested — endocrine and immune	Cortisol, aldosterone, prolactin, circulating T- and B-cell counts, and activation or trafficking measures	Serial blood sampling and flow cytometry	Closed-loop slow-oscillation enhancement changed selected trajectories in a small crossover study [34]. These are nonspecific secondary endpoints.

The first NREM studies should prespecify which entries form the confirmatory subvector and which are safety, nested, or exploratory outcomes. A study may declare module-level equivalence only when all prespecified material components pass their margins; favorable EEG, cognitive, or molecular findings may not compensate for failure in another required domain.

3.4 Timing and perturbation control

The immediate post-sleep state is unstable. Light exposure, standing, conversation, food, hydration, device use, and the cortisol-awakening response begin changing it within minutes. The core post-sleep

sample should therefore be collected while the participant remains supine, in darkness or standardized dim light, before food, drink, speech, exercise, or phone use, and ideally within five minutes of verified final awakening. A preplaced intravenous catheter allows quiet sampling without a new needle stimulus.

A practical temporal series is: pre-sleep at −60 and −10 minutes; post-awakening at 0–5, +15, +30, and +60 minutes. The immediate sample estimates the sleep-produced endpoint; the subsequent series characterizes sleep inertia and the transition into active morning physiology. Lumbar puncture, muscle biopsy, PET, and lengthy imaging cannot all be performed without materially perturbing sleep and should therefore be distributed across randomized, matched study nights.

Circadian time, fasting, posture, ambient temperature, light history, menstrual phase where relevant, prior exercise, medication, alcohol, caffeine, acute stress, and recent sleep history must be standardized or explicitly modeled. A paired snapshot identifies what changed; it does not by itself establish that sleep caused the change. Causal attribution requires sleep-deprivation, constant-routine, circadian-matched, partial-night, and selective-perturbation conditions.

4. From the Difference Vector to the Difference-plus-Work Vector

Endpoint differences are necessary but incomplete. A molecule can be produced and consumed overnight with no net concentration change. A damaged protein can be removed and replaced while total protein remains constant. Synaptic receptors can be redistributed across compartments without changing total abundance. Immune cells can leave the circulation and enter tissues, changing blood counts without changing total cell number. A small or zero Δnight therefore does not imply that little work occurred.

The target must include state, trajectory, and flux. For outcome j and process i, a useful conceptual model is:

$$\Delta Dj = \Sigma i \int 0T \, Mji(X,t) \, Fi(t) \, dt$$

Fi(t) is process activity or flux; Mji describes its state-dependent effect on outcome j; and T is the sleep interval. The expanded Difference-plus-Work Vector should include:

1. Endpoint change: whether the relevant concentration, structure, receptor state, connectivity pattern, or physiological set point reached the individual post-sleep target.
2. Completed flux: the quantity synthesized, degraded, transported, repaired, exchanged, or turned over during the interval.
3. Spatial result: whether the change occurred in the correct region, cell type, synapse, organ, or subcellular compartment.
4. Functional result: whether cognition, judgment, mood, autonomic control, immunity, and physical performance are equivalent.
5. Durability: whether equivalence persists throughout the next waking interval rather than disappearing after transient stimulation.
6. Accumulation: whether repeated refresh cycles avoid progressive rebound sleep, molecular drift, inflammation, metabolic dysfunction, memory error, or tissue injury.

Acceptance principle. No intervention qualifies as biological refresh because it produces wakefulness, a sleep-like EEG, a normal morning hormone level, or a favorable single biomarker. It must reproduce the required process package and pass durability and accumulation tests.

5. The Sleep Transformation Network

Normal sleep is not a transition between two static equilibria. It is a sequence of operating modes in which NREM and REM cycles repeatedly reorganize electrical activity, neuromodulator concentrations, vascular tone, autonomic output, metabolism, and peripheral signaling. The transformation is better represented as:

$$Xpost = \Phi[Xpre, S(t), C(t), E(t)]$$

S(t) is the time-ordered NREM–REM sequence; C(t) represents circadian influences; E(t) represents fasting, posture, temperature, light, and other environmental conditions; and Φ is the still-incompletely known biological transformation. The following ten process families provide a working ontology.

Table 3. Principal transformation-process families and engineering constraints.

Process family	Representative biological work	Critical engineering requirement
P1 Electrical coordination	Slow oscillations, spindles, hippocampal ripples, REM rhythms, and regional firing patterns coordinate information processing and network communication.	Event density, phase coupling, propagation, and regional selectivity—not delta power alone.
P2 Neuromodulatory switching	Norepinephrine, acetylcholine, serotonin, histamine, orexin, GABA, adenosine, and related systems change by stage and microstate.	Correct trajectories and switching order; low or high static concentrations are insufficient.
P3 Synaptic remodeling	Selected connections are strengthened, weakened, stabilized, or down-selected; receptors and scaffolding proteins traffic among compartments.	Preserve useful learning while preventing saturation, interference, or pathological excitation.
P4 Memory replay and reconsolidation	Hippocampal–cortical replay, integration, abstraction, emotional processing, and procedural reorganization occur across NREM and REM.	Content selectivity and correct disposition of individual memories.
P5 CSF, vascular, and solute transport	Neural activity, cerebral blood volume, vasomotion, CSF movement, interstitial exchange, and barrier transport are rhythmically coupled.	Clearance must be distinguished from production, dilution, redistribution, and blood–brain transport.
P6 Glial, ionic, and energy regulation	Ion gradients, neurotransmitter recycling, glycogen/lactate dynamics, substrate delivery, mitochondrial readiness, and redox balance change.	Active wakefulness creates simultaneous demand that may oppose restoration.
P7 Proteostasis and cellular repair	Protein folding, ubiquitination, autophagy, damaged-component removal, RNA regulation, and candidate DNA-repair processes operate.	Many pathways may have rate limits and narrow safe operating ranges.
P8 Autonomic and endocrine programming	Sympathetic/parasympathetic balance, blood pressure, temperature, growth hormone, cortisol, prolactin, and metabolic hormones follow time-dependent programs.	Pulses and trajectories matter more than a single morning concentration.
P9 Immune regulation	Leukocyte redistribution, adhesion, cytokine signaling, antigen presentation, and immune-memory support change during sleep.	Blood values reflect both cellular state and trafficking between compartments.
P10 Peripheral-tissue recovery	Muscle, adipose, liver, and other organs execute tissue-specific transcriptional, epigenetic, protein-turnover, and substrate programs.	Peripheral modules may be parallelizable, but their signals may conflict across tissues.

Human intracranial recordings show sequential coupling of slow oscillations, spindles, and ripples with stepwise increases in local firing, assembly correlation, and cross-regional medial-temporal communication [7]. Phase-locked auditory stimulation can enhance slow oscillations, coupled spindle activity, and selected declarative-memory outcomes [8]. These findings support controllability of P1, but replication is not universal and increased oscillatory power is not synonymous with complete biological efficacy.

At the molecular level, mouse studies identify plausible links between sleep state and synaptic change. Homer1a-dependent signaling drives removal and dephosphorylation of AMPA-type glutamate receptors during sleep [9]. Synaptic phosphoproteomics shows extensive sleep–wake organization of

phosphorylation, with sleep deprivation eliminating most rhythmic phosphorylation in the studied mouse forebrain synapses [10]. These mechanisms are compelling candidates for P3 and P7 but cannot yet be assumed to operate identically, at the same scale, in the living human brain.

Fluid and vascular processes illustrate superposition. Simultaneous human EEG-fMRI measurements demonstrate coupled slow electrical, hemodynamic, and macroscopic CSF oscillations during NREM sleep [11]. In freely sleeping mice, infraslow norepinephrine oscillations drive vasomotion and predict glymphatic transport; zolpidem suppressed these oscillations and tracer flow despite promoting sleep [12]. Human isotope-kinetic and randomized studies show sleep-associated changes in CSF amyloid-β and tau [13,15] and increased morning plasma biomarkers consistent with brain-to-blood transport [14]. These results strengthen P5 while emphasizing that EEG-defined sleep can coexist with disruption of a specific restorative mechanism.

Peripheral tissues cannot be represented by blood alone. Acute sleep loss produces tissue-specific DNA-methylation, transcriptomic, proteomic, and metabolic changes in human adipose tissue and skeletal muscle [16]. In a randomized crossover study of 13 healthy adults, one night of total sleep deprivation reduced postprandial muscle protein synthesis by 18%, increased cortisol, and reduced testosterone [17]. Human T-cell studies demonstrate that sleep regulates integrin activation through Gαs-coupled receptor signaling [18]. The body snapshot must therefore be built compartment by compartment.

Candidate nuclear and mitochondrial mechanisms remain less mature. Sleep increased chromosome dynamics and facilitated reduction of neuronal DNA double-strand breaks in zebrafish [19]. Work in Drosophila links sleep pressure to mitochondrial electron-flow imbalance and neuron–glia lipid metabolism [20]. These findings justify mechanistic investigation, but they should remain hypotheses for human whole-brain refresh until direct human evidence exists.

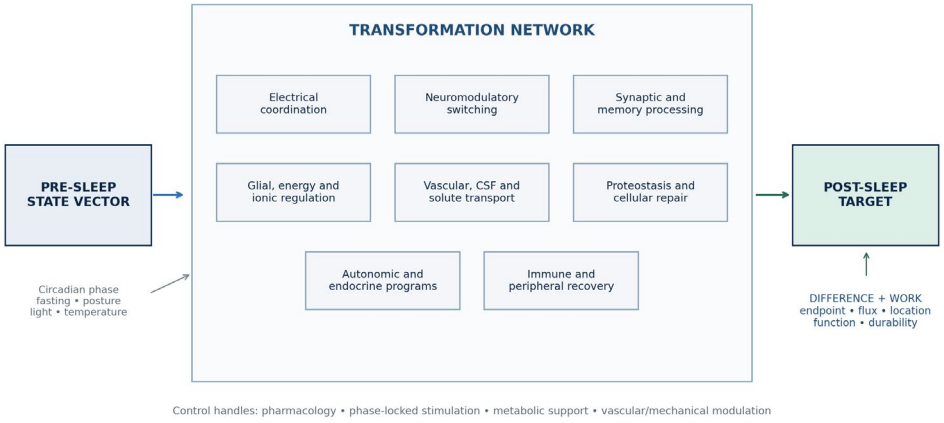

Figure 1. Systems architecture of the Zero Sleep Project. The project targets the transformation network and its hidden work, not merely the appearance of wakefulness at the endpoint.

6. Process-to-Difference Matrix

The Difference Vector is organized into ten outcome domains: D1 sleep pressure and arousal readiness; D2 neural excitability and synaptic balance; D3 learning and declarative memory; D4 emotional and procedural processing; D5 brain solute transport and proteostasis; D6 cellular energy, redox balance,

and repair; D7 autonomic and cardiovascular reset; D8 endocrine and metabolic state; D9 immune state; and D10 muscle and peripheral-organ recovery.

The Process-to-Difference Matrix maps each process family onto these outcomes. A filled circle denotes a primary proposed contribution, an open circle a secondary or coordinating contribution, and a blank cell indicates that no material relationship is proposed. The matrix is a testable research map, not a settled causal graph. Each filled cell should ultimately carry an evidence grade, effect size, temporal window, anatomical location, control handle, and falsification test.

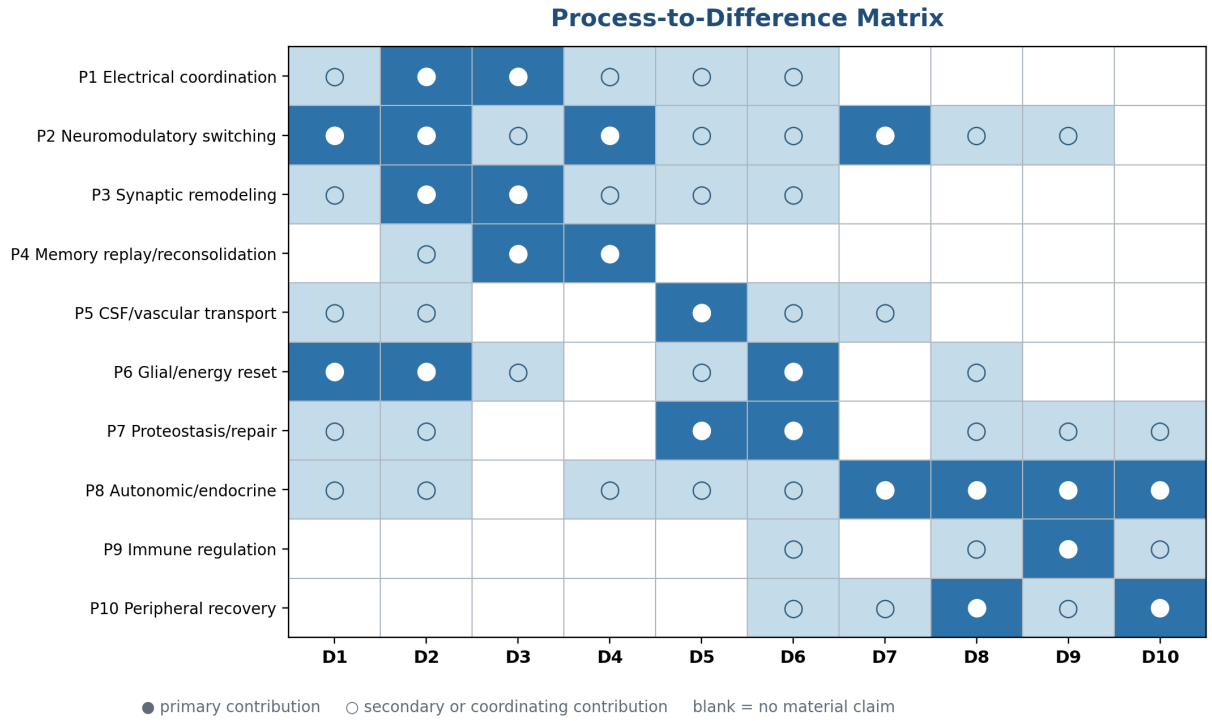

Figure 2. Process-to-Difference Matrix. D1–D10 are defined in the text. The dense mapping makes clear that no major post-sleep outcome is generated by one isolated mechanism.

The matrix is intentionally many-to-many. D2, for example, may reflect electrical coordination, neuromodulator switching, receptor trafficking, glial ion and transmitter cycling, and molecular repair. D5 may involve altered production, extracellular mobility, vascular/CSF transport, receptor-mediated uptake, degradation, blood–brain transfer, and peripheral clearance. A successful intervention must therefore reproduce the relevant package rather than maximize one visible surrogate.

7. The engineering objective: acceleration, parallelization, and substitution

7.1 Control formulation

For each indispensable process i, the engineering objective is to reproduce the normal sleep-integrated work over a shorter interval T*:

$$\int_0^{T^*} F_i^*(t)\,dt \approx \int_0^{T_{sleep}} F_i(t)\,dt, \quad \text{with } T^* \ll T_{sleep}$$

Equivalent integrated activity is not sufficient if sequence, localization, selectivity, or safety differ. Increasing the rate of synaptic down-selection could erase useful learning; increasing autophagy could damage healthy components; increasing vascular pulsatility could compromise perfusion or barrier integrity; forcing endocrine concentrations could imitate an endpoint without reproducing their temporal information. The correct optimization problem is to minimize refresh time subject to state, work, function, and safety constraints.

$$\textit{minimize } T^* \textit{ subject to } Y(T^*) \in Epost \textit{ and } Risk_{acute}, Risk_{cumulative} \leq \textit{predefined limits}$$

Y is the complete Difference-plus-Work Vector and Epost is the individual's validated post-sleep equivalence region. If compatible processes can be safely parallelized, the minimum duration will be determined by the slowest indispensable nonparallelizable process or sequence.

7.2 Three engineering strategies

Acceleration increases the number or rate of useful events per unit time—for example, correctly coupled slow oscillation–spindle events, solute transport, or selected repair flux. Parallelization moves processes that do not require global brain offline time into wakefulness or runs compatible peripheral programs simultaneously. Substitution achieves the same functional and biological output through a different mechanism, such as externally controlled substrate delivery or vascular dynamics.

These strategies should not be conflated. A wake-promoting drug is not an accelerator if it leaves restorative work undone. A metabolic buffer is not a replacement if it merely postpones failure. A sedative is not a substitute for sleep if it changes EEG appearance but disrupts spindle coupling, memory, or clearance.

7.3 Three routes toward ABR

Table 4. Candidate system architectures.

Route	Concept	Scientific assessment
A. Compressed global refresh	A short, controlled sleep-like interval with higher density or efficiency of essential NREM and REM operations.	Most plausible first route; begins by reducing rather than eliminating conventional sleep.
B. Rotating regional refresh	Selected brain regions enter local maintenance modes while the rest of the brain remains functionally awake.	Conceptually attractive but high-risk; local sleep-like events during deprivation are associated with degraded neuronal responses and cognitive lapses [28].
C. Fully awake molecular emulation	Electrical, chemical, metabolic, and mechanical interventions reproduce all sleep work during continued wakefulness.	Ultimate form of "zero sleep," presently least plausible because active information processing may conflict with remodeling and maintenance.

The likely architecture is hybrid: substantial peripheral maintenance is moved into waking life, while the brain undergoes a short, intensified, globally or regionally organized refresh interval. A successful project may therefore eliminate long conventional sleep without eliminating sleep-like biological modes.

8. Candidate control handles

8.1 Closed-loop stimulation and state control

Auditory stimulation should not be conceptualized as an externally imposed restorative signal. During stable NREM sleep, a low-intensity sound can perturb an already active thalamocortical oscillator. When

the stimulus reaches the cortex near the predicted depolarizing up-state of an endogenous slow oscillation, it may reinforce the succeeding wave and increase the probability that a spindle is correctly nested within the oscillation. In-phase stimulation has enhanced slow oscillations, coupled spindle activity, and selected memory outcomes [8]; a separate small crossover study found accompanying changes in cortisol, aldosterone, and circulating lymphocyte trajectories [34]. These findings support causal controllability of a limited process package, not generic efficacy of sound or proof of biological refresh.

8.1.1 Adaptive auditory inner loop

The relevant intervention is therefore state- and phase-contingent modulation, not sound exposure during sleep. A technically credible controller contains the following seven operations:

1. **State gate.** Confirm stable N2 or N3 sleep, adequate signal quality, and acceptable respiratory, cardiovascular, and artifact conditions.
2. **Phase estimator.** Detect the current slow oscillation and predict the next cortical up-state with an uncertainty estimate.
3. **Stimulus scheduler.** Deliver a brief, individualized, low-intensity acoustic pulse or pulse pair only when predicted phase and safety conditions are satisfied.
4. **Immediate-response estimator.** Quantify phase error, evoked slow-wave response, spindle nesting, spatial propagation, and arousal probability.
5. **Adaptive update.** Adjust phase delay, intensity, pulse spacing, and repetition according to the individual response rather than imposing a fixed population pattern.
6. **Safety inhibition.** Suspend stimulation during arousal, apnea or hypopnea, phase instability, excessive autonomic response, degraded coupling, or loss of signal integrity.
7. **Module stopping rule.** Stop when additional stimulation ceases to improve the prespecified composite process measure, the target subvector enters its equivalence region, or another domain begins to deteriorate.

The controller should optimize a composite biological objective rather than delta power alone:

$$J = \alpha R\_SO + \beta C\_SO\text{-}spindle - \gamma P\_arousal - \delta L\_cross\text{-}domain$$

Here R_SO represents the evoked slow-oscillation response, C_SO-spindle represents physiologically timed coupling, P_arousal is arousal probability, and L_cross-domain is a penalty for respiratory, autonomic, cognitive, or other disruption. Published human experiments have used brief pink-noise pulses, including 50-ms pulses delivered from frontal EEG timing [8,34], but pulse form, level, latency, and stopping thresholds should be treated as historical starting conditions to be individualized and experimentally re-estimated—not as a universal prescription.

Electrical and magnetic stimulation, sensory cueing, targeted memory reactivation, respiratory or autonomic entrainment, and mechanical or vascular modulation are plausible additional control classes. Their development should follow the same closed-loop principle: estimate the current state, intervene only within a validated physiological window, observe target engagement and process execution, and stop when the relevant Difference-plus-Work target has been reached. Open-loop stimulation risks increasing event count while degrading temporal organization. Section 9 formalizes the broader observer-controller architecture.

8.2 Mechanistic pharmacology

Available evidence supports a pharmacological branch of the project, but only if molecules are classified by the biological role they actually perform. Four categories are required: process actuators initiate a genuine sleep-like operation; process accelerators increase its rate or density; process supports supply substrates or protection; and state maskers or switches alter sleepiness or wakefulness without demonstrated restorative work.

Table 5. Pharmacological and molecular candidates relevant to Accelerated Biological Refresh. Readiness refers to the Zero Sleep objective, not clinical approval for another indication.

Candidate	Proximal mechanism	Project role	Relevant evidence	Interpretation
Dexmedetomidine	α2-adrenergic agonism suppresses locus-coeruleus noradrenergic arousal and recruits endogenous sleep-promoting circuitry [22].	Actuator / state gate	With closed-loop acoustic stimulation, reduced subsequent N3 duration and slow-wave-pressure dissipation in 13 healthy adults [21].	Strongest direct signal of partial NREM homeostatic work; small study, not whole-system replacement.
Dexmedetomidine + vascular support	Central noradrenergic suppression combined with maintenance of systemic arterial pressure.	Actuator + transport support	A 2026 preprint reports greater slow waves, vascular pulsatility, reduced parenchymal resistance, and ~9–10% higher Aβ/tau clearance indices during a shortened sleep opportunity [29].	Highly relevant but not peer-reviewed; requires independent replication and safety analysis.
Sodium oxybate	GHB/GABAB-related inhibitory signaling intensifies slow-wave sleep and changes architecture.	Sleep intensifier	During restricted sleep, increased SWS and reduced some later alertness and attention deficits and the homeostatic response [23].	May suppress or alter other modules, including REM; controlled-substance and respiratory/misuse risks.
Creatine	Phosphocreatine buffers ATP through reversible phosphate transfer.	Metabolic support	A controlled sleep-deprivation study detected MRS changes in PCr/Pi, ATP-related measures and pH with improved selected cognitive outcomes [25].	Evidence for compensation, not memory consolidation, clearance, or full restoration.
Orexin-2 agonists	Directly activate OX2 receptors in wake-promoting circuits.	Wake switch / masker	IV danavorexton increases wakefulness in sleep-deprived healthy people [26]; oral oveporexton improves wakefulness in narcolepsy type 1 [27].	Useful as a controlled exit from refresh, but no evidence that restorative work is performed.
Tiagabine	GAT-1 inhibition increases extracellular GABA and slow-wave activity.	EEG-state modifier	Increased slow-wave sleep but reduced phase-locked spindles and failed to improve memory; procedural performance worsened [24].	Critical counterexample: more slow-wave activity can be biologically incomplete or adverse.
Zolpidem	GABAA positive allosteric modulation promotes sleep.	Sedative / architecture modifier	In mice, dampened norepinephrine, vascular, and CSF oscillations and reduced glymphatic flow [12].	Demonstrates that sleep promotion can interfere with a candidate restorative process.
Caffeine, modafinil, stimulants	Adenosine antagonism or other arousal-promoting mechanisms improve alertness and selected performance.	Masker / compensator	Substantial evidence for short-term vigilance support; no demonstration of full sleep-work replacement.	Must not be counted as refresh; may obscure accumulating biological debt.

8.2.1 Initial molecule hierarchy

For the initial NREM-compression program, dexmedetomidine is the lead pharmacological state-gating candidate because its proximal α2-adrenergic mechanism is established and its combination with closed-loop acoustic stimulation has altered subsequent N3 homeostatic demand in humans [21,22]. Sodium oxybate should initially serve as a pharmacological sleep-intensification comparator; creatine as a metabolic-support probe; and orexin-2 agonists as candidate exit switches rather than restorative agents [23,25–27]. Midodrine-supported clearance remains hypothesis-generating because the human report is a preprint [29]. Tiagabine and zolpidem are mechanistic counterexamples, not candidate

restorative treatments [12,24]. This hierarchy prioritizes causal interpretability and measurable process engagement rather than the ability to produce sedation, wakefulness, or a favorable single biomarker.

Dexmedetomidine is the most consequential existing actuator because its proximal pathway is mechanistically characterized and a human intervention altered subsequent sleep homeostasis. It activates α2-adrenergic receptors, reduces locus-coeruleus output, disinhibits ventrolateral preoptic sleep-promoting circuitry, and produces a controllable NREM-like state [22]. In the 2024 CLASS-D study, daytime dexmedetomidine sedation paired with closed-loop acoustic stimulation reduced subsequent N3 duration by approximately 17 minutes and altered slow-wave-pressure dissipation [21]. This does not establish complete restoration, but it crosses the boundary between making a person feel awake and apparently satisfying part of a homeostatic NREM demand.

The 2026 glymphatic preprint is even closer to the project's mechanistic logic. It reports that dexmedetomidine combined with oral midodrine increased EEG slow waves, cerebrovascular pulsatility, and biomarker indices of brain-to-blood amyloid-β and tau clearance during a 4-hour-15-minute sleep opportunity [29]. Because the report has not yet been peer reviewed, it should be treated as a high-priority replication target rather than established fact. If independently confirmed, it would provide a direct example of pharmacologically manipulating a defined process package—neuromodulation, vascular dynamics, and solute transport—rather than merely altering sleep appearance.

Tiagabine and zolpidem provide equally important negative evidence. Tiagabine demonstrates that increasing slow-wave activity without preserving spindle coordination may fail to improve memory [24]. Zolpidem demonstrates in mice that a hypnotic state can suppress norepinephrine-driven vascular/CSF dynamics [12]. These results support the matrix approach: a candidate must be evaluated across all linked difference domains, not only the one used to select it.

9. Biological Refresh Scanner and Closed-Loop Restoration System

9.1 Observability: estimating a partially latent refresh state

The science-fiction image of a body-and-brain scanner is useful if translated into a rigorous systems problem. The device would not directly observe "restoration" as one physical quantity. It would infer a partially latent biological state from multiple noisy, incomplete, and differently sampled measurements. In control-theory terms, the first question is observability: whether the components of the Difference-plus-Work Vector that matter for safety and function can be reconstructed with adequate accuracy from accessible signals.

$$z(t) = h[Y(t), C(t)] + \varepsilon(t)$$

Here Y(t) is the evolving Difference-plus-Work state; C(t) contains circadian phase, prior sleep history, posture, fasting, light, stress, illness, medications, and other covariates; h is the measurement function; and ε(t) is sensor and assay error. A personalized estimator uses the complete measurement history and the individual's calibration data to produce Yhat(t), together with uncertainty. The residual refresh vector is then the domain-by-domain distance from the person's verified post-sleep equivalence region Epost:

$$R(t) = d[Yhat(t), Epost]$$

R(t) must remain a vector. A single readiness score could conceal an unacceptable deficit in memory integrity, vascular function, judgment, immune state, or tissue recovery behind strong performance in

another domain. The operational output should be a Biological Refresh Profile reporting each domain's estimated status, confidence interval, trajectory, and whether the model can make a reliable classification. The permissible classifications are post-sleep equivalent, residual deficit detected, and indeterminate. Abstention is a safety function, not an algorithmic failure.

9.2 Two-level measurement architecture

No portable instrument can presently verify the complete Difference-plus-Work Vector. The defensible design is therefore hierarchical. A research scanner performs deep, burdensome measurements on repeated reference and perturbation nights. Those data train and periodically recalibrate a lower-burden operational scanner. The portable system estimates the deep state; it does not replace the laboratory measurements that establish biological meaning.

Table 6. Proposed Biological Refresh Scanner architecture and evidentiary role.

System layer	Representative inputs	Primary output and limitation
Research scanner	PSG and high-density EEG; MRI/MRS, PET, fMRI, or TMS-EEG; blood and CSF multi-omics; tissue and isotope-flux substudies; autonomic physiology; comprehensive cognitive testing	Establishes the personalized post-sleep equivalence region and links accessible surrogates to deep biology. Too burdensome, costly, or invasive for routine use.
Operational physiology	Wearable EEG or ear-EEG; ECG/PPG and HRV; respiration and oxygen saturation; skin and core-temperature estimates; electrodermal activity; movement; pupil and oculomotor measures	Provides continuous trajectories and detects arousal instability, autonomic recovery, local sleep propensity, and state transitions. Signals are nonspecific and artifact-prone.
Rapid biochemical adjunct	Small-volume blood, saliva, or interstitial-fluid panels for metabolites, hormones, inflammatory signals, and validated history markers	Improves specificity for metabolic, endocrine, and immune domains. Peripheral values do not directly prove brain repair, memory processing, or regional clearance.
Functional challenge layer	Psychomotor vigilance, working memory, response inhibition, declarative and procedural recall, balance, and mission-relevant decision tasks	Tests whether estimated biological equivalence produces usable performance. Practice, motivation, and stimulants can confound results.
State-estimation layer	Personalized multimodal model; circadian and exposure covariates; sensor-quality checks; uncertainty calibration; longitudinal drift detection	Produces the Biological Refresh Profile, residual vector, and go/indeterminate/not-ready classification. Must be externally validated and capable of abstaining.

Human blood-transcriptomic and metabolomic studies already demonstrate that multivariable classifiers can identify acute sleep loss under controlled conditions [3,4]. Their weaker performance in chronic or between-person formulations is not a reason to abandon the scanner; it is evidence that personalization, longitudinal calibration, and explicit uncertainty are necessary. Deep central markers such as A1-receptor and SV2A PET measurements [5,6] should be treated as research anchors for model validation rather than imagined as field sensors.

9.3 The repairer as a safety-constrained biological controller

The proposed repairer or modifier is best formulated as a Closed-Loop Restoration System. It does not deliver a universal treatment. It maps the estimated residual vector onto a validated process module, applies an intervention within defined physiological limits, observes the response, and updates the state estimate. In discrete form:

$$u(k) = safety\_filter\{\pi[\hat{Y}(k), R(k), context]\}; \quad Y(k+1) = f[Y(k), u(k), w(k)]$$

The control policy π selects among phase-locked acoustic, photic, electrical, or magnetic stimulation; pharmacological state gates; autonomic, temperature, respiratory, or vascular modulation; metabolic support; a short NREM-like or REM-like interval; and conventional sleep. The safety filter constrains dose, timing, hemodynamics, respiratory state, seizure risk, arousal stability, and prohibited

combinations. The disturbance term w(k) represents ongoing waking demand, environmental stress, illness, and unmodeled biological variability.

Control must be hierarchical. A fast loop regulates stimulation phase or drug effect-site state over seconds to minutes. A module loop evaluates whether the intended rhythm, transport event, metabolic trajectory, or memory endpoint has occurred. A supervisory loop integrates all domains, detects adverse cross-effects, and decides whether to continue, change modules, terminate, or require natural sleep. No controller should use a wake-promoting output as evidence that restorative work is complete.

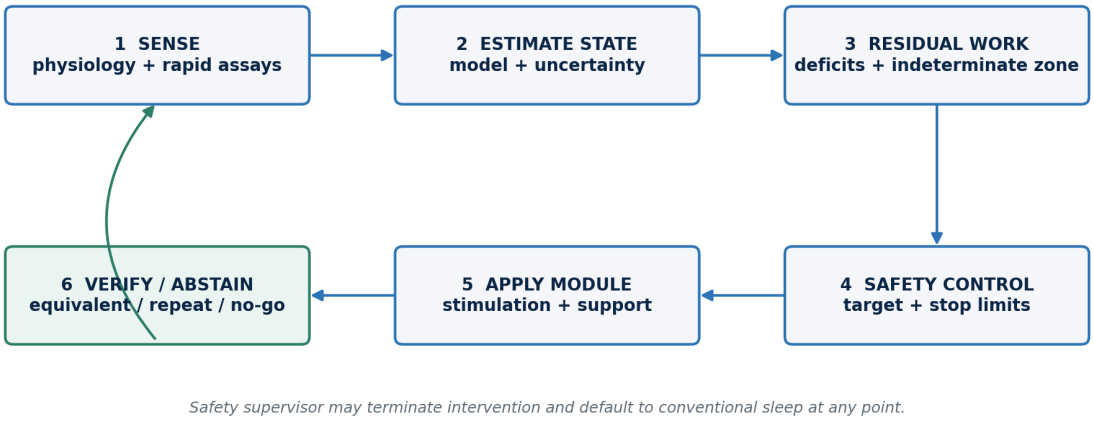

Figure 3. Closed-loop restoration architecture. The system is an observer-controller with a safety supervisor; it either continues intervention, declares verified equivalence, or defaults to conventional sleep and a not-ready output.

9.4 Acceptance logic: restoration before optimization or enhancement

Three objectives must remain distinct. Restoration returns an individual to that person's validated healthy post-sleep baseline. Optimization places the person near the best-performing region of the natural healthy envelope. Enhancement intentionally changes performance or traits beyond the validated baseline. The Zero Sleep Project should begin and remain, through its early stages, a restoration program. Optimization may become scientifically defensible after long-term safety is established. Enhancement of fear, aggression, memory selection, pain response, or other identity-relevant traits is outside the sleep-replacement objective and requires a separate ethical and regulatory framework.

Release from the system requires more than a low residual score. The intended process must show target engagement and execution; the linked Difference-plus-Work subvector must be equivalent; safety-critical domains must individually pass; the estimator must be within its validated operating range; and no adverse cross-domain trajectory may be present. If these conditions are not met, the correct output is additional protected recovery or conventional sleep. The scanner must be permitted to say not ready.

10. Research program

10.1 Stage 0: measurement ontology, research scanner, and reproducibility

The first program should establish a standardized ontology, sampling sequence, data model, biorepository, and research-scanner protocol. Healthy adults would complete multiple baseline nights under controlled conditions to estimate within-person variance, cross-night reproducibility, and the temporal stability of each measurement. PSG-defined sleep architecture, high-density electrophysiology, blood multi-omics, immediate morning sampling, cognition, autonomic measures, and noninvasive brain measurements form the core. PET, CSF, stable-isotope, and tissue-biopsy measurements form nested substudies that provide deep anchors for the portable estimator.

The primary deliverable is not a universal classifier but a personalized post-sleep equivalence region and a validated state estimator. Models must be trained and tested on separate nights and challenged with partial sleep, naps, extended wakefulness, caffeine, alcohol, illness, stress, circadian displacement, fragmented sleep, and sensor failure. The classifier must return three zones: post-sleep equivalent, residual deficit detected, and indeterminate. The indeterminate category and calibrated confidence bounds are scientifically essential.

10.2 Stage 1: causal process mapping and observability

Two snapshots do not reveal mechanism. Stage 1 reconstructs the overnight path using continuous physiology, stage-locked sampling where feasible, stable-isotope flux measurements, and selective perturbations. Early-night NREM-rich sleep can be compared with late-night REM-rich sleep; closed-loop stimulation can enhance or disrupt selected oscillatory events; and pharmacological probes can alter a defined neuromodulatory or metabolic process under formal clinical oversight. This stage must also determine which deep variables are observable from portable signals and under which conditions the operational scanner must abstain.

For every matrix cell, the program should ask: what produced the change; when; where; whether the signal is a driver, mediator, moderator, or consequence; what fails when the process is selectively altered; and whether reproducing the process reproduces the expected endpoint. Causal mediation should supplement—but not replace—direct perturbation.

10.3 Stage 2: the NREM Core compression prototype

10.3.1 Experiment 2A: natural-sleep controller validation

Experiment 2A should use natural sleep to validate the inner auditory controller before any pharmacological state gate is introduced. In a randomized within-subject design, individualized up-state stimulation should be compared with sham and a prespecified phase-control condition chosen to test timing specificity without creating excessive arousal. Primary process endpoints are phase error, evoked slow-oscillation response, slow-oscillation–spindle nesting, traveling-wave propagation, and arousal probability. Declarative-memory retention, next-day learning, psychomotor vigilance, cardiorespiratory safety, and selected endocrine or immune trajectories provide independent functional and cross-domain checks. The controller advances only if it improves the composite process objective without degrading a required secondary domain.

10.3.2 Experiment 2B: pharmacologically gated NREM model

Experiment 2B should compare dexmedetomidine plus adaptive closed-loop stimulation with dexmedetomidine plus sham, while replicated natural sleep supplies the biological reference. The primary endpoints are execution of the prespecified EEG process package and subsequent N3/SWA demand; a lower later demand is interpreted only together with module-level electrophysiological, functional, and safety equivalence. Nested substudies should assess A1-receptor availability, cerebral bioenergetics, endocrine and immune trajectories, and selected solute-transport markers. Pharmacokinetic and pharmacodynamic state, hemodynamics, respiration, arousability, and residual sedation require continuous measurement. The prior CLASS-D result in 13 healthy adults justifies this experiment but does not define its outcome [21].

Stage 2 advances only when both experiments meet prespecified process, function, safety, and subsequent-sleep-demand criteria. A successful natural-sleep controller does not validate pharmacological gating; a favorable drug-plus-stimulation EEG does not establish memory, molecular, or whole-system refresh. The confirmatory claim remains reproduction of the prespecified NREM Difference-plus-Work subvector.

10.4 Stage 3: REM, emotional, and procedural modules

REM-related functions should be studied as a separate but interacting module. Candidate endpoints include emotional-memory recalibration, fear extinction, procedural learning, creative integration, cholinergic state, autonomic variability, and network reconfiguration. A NREM-compressed intervention cannot be declared a global refresh if it shifts or eliminates essential REM work.

10.5 Stage 4: peripheral parallelization and hybrid refresh

Endocrine, immune, muscle, adipose, liver, and cardiovascular programs may not all require global unconsciousness. Stage 4 evaluates which peripheral operations can be supported or executed during wakefulness through timing, nutrition, activity, temperature, autonomic modulation, or pharmacological support. Tissue-specific multi-omics and isotope flux—not subjective energy—must verify completion. This stage also attempts to compress the research scanner into an operational system without losing the ability to detect safety-critical residual deficits.

The resulting system is likely to be hybrid: peripheral maintenance operates continuously or in parallel, while the brain enters a shorter controlled offline interval. At this stage an orexin-2 agonist or another arousal actuator might be studied as an exit switch only after process-completion criteria are met, never as proof of refresh.

10.6 Stage 5: repeated-cycle validation

A single successful morning is insufficient. Repeated-cycle studies should progress conservatively from isolated exposure to 7-, 30-, and 90-cycle evaluation only after independent safety review. Outcomes should include sleep rebound, cognition, memory accuracy, mood, autonomic function, metabolic control, endocrine rhythms, immune competence, muscle protein turnover, neuroinjury markers, imaging, estimator drift, classification error, and participant-reported symptoms. Longer surveillance is required before any claim of chronic replacement or operational readiness use.

Table 7. Staged development program and advancement gates.

Stage	Primary product	Advancement gate

Stage	Primary product	Advancement gate
0. Baseline atlas and research scanner	Personalized pre/post state vectors; assay reproducibility; deep-to-portable measurement map	Independent-night classification with calibrated uncertainty and a prespecified indeterminate zone
1. Causal mapping and observability	Stage- and process-specific trajectories, fluxes, perturbation responses, and validated accessible surrogates	Replicable causal links for priority matrix cells and documented limits of operational estimation
2. NREM Core closed loop	Experiment 2A validates natural-sleep auditory control; Experiment 2B tests dexmedetomidine-gated compression against sham and natural sleep	Prespecified process, functional, and safety equivalence together with reduced subsequent NREM demand
3. REM module	Defined emotional, procedural, and integrative transformation package	No loss of REM-linked outputs when combined with NREM compression
4. Hybrid refresh and operational scanner	Parallel peripheral support, short central refresh, portable estimation, and controlled awakening	Whole-day equivalence without masking, rebound, or unsafe false-ready classification
5. Repeated cycles and field validation	Cumulative-safety, durability, estimator-drift, and context-generalization dataset	No progressive deficit across molecular, functional, clinical, or safety-critical operational domains

11. Experimental design and analytical standards

11.1 Study architecture

The default design should be randomized, controlled, within-subject, and crossover wherever washout and feasibility permit. Within-subject design is critical because trait-like biological variation is large. Natural-sleep reference nights must be replicated; intervention order must be counterbalanced; circadian phase and prior sleep must be stabilized; and analysis plans should be preregistered. Scanner development must use temporally separated training, calibration, and validation nights so that repeated measurements from one participant do not leak across data partitions.

A nested architecture balances depth and burden. The core cohort receives repeated PSG, wearable physiology, blood multi-omics, autonomic measures, and cognitive testing. Imaging subgroups receive MRS, functional MRI, PET, or TMS-EEG on matched visits. Deep-tissue subgroups receive CSF or muscle/adipose measurements under protocols designed to minimize procedure-induced sleep disruption. These measurements constitute the research scanner and provide labels for the operational estimator. No single compartment is assumed to represent the whole organism.

11.2 Equivalence analysis

Success should be tested with equivalence or noninferiority statistics, not failure to detect a difference. Each outcome requires a biologically justified margin, measurement reliability estimate, and multiplicity strategy. Multivariate state-space distance—such as a regularized Mahalanobis distance from the individual post-sleep distribution—can complement domain-specific endpoints, but a favorable composite score must not conceal failure in a safety-critical domain. Scanner performance additionally requires sensitivity to incomplete recovery, specificity for true equivalence, calibration of predicted probabilities, abstention performance, and false-ready error rates under distribution shift.

Discovery and validation sets must be separated by participant and night. Models should be calibrated, externally validated, and stress-tested against mixed states, sensor loss, environmental artifacts, illness, medications, and previously unseen operational conditions. Process-completion metrics should include dose–response, temporal mediation, and reversibility. Biomarker panels must distinguish sleep-specific change from circadian time, fasting, posture, and stress. A controller may advance only when both the biological endpoint and the estimator-controller pair have been validated.

11.2.1 Withheld-variable challenge

A controller can appear successful if it is judged only by the variables it was trained to optimize. Each equivalence study should therefore prespecify deep biological and functional measurements that are withheld from model training, controller feedback, hyperparameter selection, and stopping decisions. After the core panel declares module-level equivalence, blinded analysis of these withheld variables should test whether natural sleep and the accelerated intervention remain distinguishable. A reproducible difference in a withheld safety-relevant variable constitutes evidence that the measurement panel is incomplete, even when the controller's own endpoints appear normal.

The withheld challenge should include both mechanistically adjacent variables, which test whether the controller reproduced the intended process package, and orthogonal variables, which search for unanticipated cross-domain disruption. Any marker discovered exploratorily must be confirmed on an independent participant-and-night dataset before it can modify the advancement decision.

11.3 Required proof-of-replacement hierarchy

1. Target engagement: the intervention reaches and modulates the intended receptor, circuit, rhythm, transporter, vascular mechanism, or metabolic pathway.
2. Process execution: the expected trajectory or flux occurs in the correct region and temporal window.
3. Subvector equivalence: the intended Difference-plus-Work components match natural sleep within prespecified limits.
4. Functional equivalence: cognition, affect, autonomic control, immune function, and physical performance are noninferior.
5. Durability: equivalence persists through the subsequent waking day.
6. Cumulative safety: repeated use does not produce rebound, drift, hidden injury, or progressive loss.

A project that reaches only the first or second level has identified a control handle; it has not replaced sleep.

12. Defense application: the Resilient Warfighter

12.1 Scientific rationale and terminology

Defense is a logical but unusually demanding application. Military personnel operate under sleep restriction, circadian displacement, sustained attention, physical load, environmental extremes, and consequential decision pressure. Walter Reed Army Institute of Research training material states that soldiers receiving five hours of sleep are twice as likely to make a mission-critical mistake as those receiving seven hours and identifies vigilance, problem solving, situational awareness, decisive action, and moral reasoning among the affected functions [31]. These are precisely the domains in which a false-ready classification would be dangerous.

The phrase "perfect soldier" is powerful as speculative language but is not a scientifically coherent objective. Different roles require different readiness profiles: an infantry soldier, medic, pilot, vehicle operator, intelligence analyst, cyber operator, and commander do not require identical balances of vigilance, patience, motor precision, memory, empathy, risk tolerance, and physical recovery.

Maximizing one trait can degrade another. The formal defense objective should therefore be the Resilient Warfighter: a service member whose physiological and cognitive readiness is objectively estimated, whose incomplete recovery can be selectively and conservatively accelerated, and who is protected from deployment when equivalence has not been demonstrated.

A 2026 DARPA SBIR topic, Engineering Sleep for Cognitive Performance, called for a wearable, non-invasive, closed-loop system that monitors neurophysiological signals and delivers precisely timed auditory or photic stimulation to improve restorative sleep under restriction [30]. It specifically requested physiological target engagement and cognitive-performance evidence. The Zero Sleep architecture is broader: it seeks a multimodal body-and-brain state estimate, maps residual deficits to several intervention classes, and demands whole-system Difference-plus-Work equivalence. The DARPA topic nonetheless demonstrates that a narrower observer-controller concept is already recognized as a defense-relevant engineering problem.

12.2 Operational concept and readiness outputs

The military system should not be designed primarily to extend time awake. Its primary functions are readiness measurement, allocation of protected recovery, acceleration of validated restoration modules, and prevention of deployment under hidden biological debt. The Army has separately solicited wearable technologies that monitor real-time physiology to assess operational health, cognitive resilience, illness, and readiness [32], providing an existing implementation context for the sensing layer.

Table 8. Proposed defense-use functions and non-negotiable safeguards.

Operational phase	System function	Required safeguard
Pre-mission readiness	Estimate a role-specific Biological Refresh Profile and classify ready, conditionally ready, indeterminate, or not ready.	No favorable composite may override failure in judgment, vigilance, autonomic stability, or another role-critical domain.
Constrained rest planning	Estimate which modules are incomplete and the minimum protected recovery interval likely to reduce residual risk.	The output allocates sleep or recovery; it must not become a quota for maximizing duty hours.
Controlled refresh	Apply a validated closed-loop NREM, REM, autonomic, metabolic, or peripheral module while monitoring target engagement and adverse cross-effects.	Use only within the intervention's validated population and operating envelope; conventional sleep remains the default fallback.
Post-mission recovery	Quantify residual and newly accumulated debt after operational stress, stimulants, injury risk, or circadian disruption.	A normal subjective state or stimulant-supported performance cannot erase a biological recovery requirement.
Longitudinal surveillance	Detect estimator drift, repeated-cycle molecular deviation, sleep rebound, mood change, or declining reserve.	Health-protective trends require independent medical review and must not be repurposed as disciplinary or promotion metrics.

Readiness must be represented as a role-conditioned vector and a probability of unacceptable error, not a generic peak-performance score. Required endpoints include psychomotor vigilance, response inhibition, working and prospective memory, decision quality under surprise, moral reasoning, motor coordination, autonomic reserve, metabolic and inflammatory state, injury risk, and task-specific performance. A command-facing display may summarize these results, but the underlying medical system must retain uncertainty and explain which domains produced the classification.

12.3 Validation pathway and failure authority

Validation should proceed from controlled laboratory sleep restriction to high-fidelity simulation, supervised field exercises, and only then limited operational evaluation. Each occupational class requires separate task models and error costs. The primary safety metric is not average performance gain; it is the rate of false-ready decisions—instances in which the system authorizes duty despite a material

residual deficit. Rare-event testing, adversarial conditions, sensor dropout, heat, dehydration, altitude, infection, analgesics, stimulants, and acute stress must be included before deployment.

The scanner must possess protected failure authority. An indeterminate or not-ready output should trigger sleep, medical evaluation, reassignment, or reduced-risk duty according to protocol. If commanders can routinely override the biological safety output to meet operational demand, the system becomes a mechanism for concealing fatigue rather than reducing it. Operational doctrine must therefore specify when a no-go determination is binding, who may review it, and how emergency exceptions are documented and followed by mandatory recovery.

12.4 Consent, privacy, and limits on enhancement

Military hierarchy creates a distinctive risk of coercion. DoD Instruction 3216.02 requires command approval for research involving DoD-affiliated personnel but prohibits supervisors and the chain of command from influencing subordinates to participate or being present during recruitment and consent; it also requires disclosure of fitness-for-duty and data-breach risks [33]. Zero Sleep research should adopt these protections as minimum requirements and add independent medical oversight, nonparticipation protection, and a clear separation between research consent and operational evaluation.

Brain-state, biochemical, genomic, behavioral, and longitudinal readiness data are unusually sensitive. Access should follow least-privilege rules. Clinicians and safety officers may require detailed data; commanders should ordinarily receive only the minimum readiness classification and operational restrictions necessary for immediate safety. Secondary use for discipline, promotion, security adjudication, or trait selection should be prohibited unless separately authorized by law, supported by validated evidence, and subject to due process. The system's first obligation is restoration and protection, not enhancement beyond baseline.

13. Safety, ethics, and governance

ABR research involves healthy-person exposure to sedatives, arousal modulators, sleep restriction, invasive sampling, algorithmic readiness classification, and potentially interacting neurophysiological interventions. Early studies therefore belong in specialized clinical research units with continuous cardiorespiratory monitoring, emergency capability, independent data and safety monitoring, formal regulatory review, conservative stopping rules, cybersecurity controls, and explicit post-study recovery requirements. The pharmacological and device interventions described here are mechanistic research candidates, not a dosing protocol or a basis for self-experimentation.

Risk is not limited to acute hemodynamic or respiratory events. Incorrect memory selection, emotional dysregulation, seizure susceptibility, altered blood–brain barrier function, impaired proteostasis, immune misprogramming, endocrine desynchronization, and cumulative neurobiological debt must be treated as foreseeable categories even when evidence is incomplete. Apparent alertness can increase risk by hiding impairment.

The social implications also require governance. A technology that reduces sleep could be coercively demanded by employers, militaries, caregivers, or educational institutions; could deepen inequity; and could redefine normal productivity in ways that transfer benefit to institutions while concentrating risk in individuals. Participation must remain voluntary, informed consent must explicitly address uncertainty and cumulative risk, and occupational use should not precede independent evidence of long-term

safety. Biological-state data should be separated from disciplinary and personnel systems except for narrowly defined, immediate safety requirements.

The phrase “Zero Sleep” is valuable as an intellectual challenge but can encourage premature commercialization or self-experimentation. Public communication should consistently pair the title with the scientific term Accelerated Biological Refresh and the statement that no existing medication, supplement, stimulation device, or combination has demonstrated complete or chronic replacement of sleep.

14. Limitations and unresolved questions

The framework has five principal limitations. First, direct access to the living human brain is constrained; blood and CSF are imperfect proxies, PET targets are selective, MRS has limited molecular specificity, and most cellular mechanisms come from animal models. Second, sleep functions may be more strongly coupled than the modular framework assumes. Third, many Difference-plus-Work components may be only partially observable from portable signals, creating irreducible uncertainty and false-ready risk. Fourth, endpoints that appear normal immediately after intervention may conceal turnover deficits or rare errors that emerge only over weeks or years. Fifth, intervention and estimator performance will likely vary with age, sex, chronotype, genotype, prior sleep debt, vascular health, neuropsychiatric status, medication exposure, occupational context, and sensor environment.

Several decisive questions remain open: Which sleep operations have hard rate limits? Which require global disconnection from sensory input? Can synaptic renormalization be accelerated without indiscriminate weakening? Can memory replay be densified without false association or interference? Can solute transport be increased without compromising perfusion or pressure? Which peripheral programs can safely run during wakefulness? Is REM work compressible, transferable, or fundamentally time-dependent? Which deep biological variables are sufficiently observable from operational sensors? What false-ready rate is acceptable in a safety-critical role? What biomarker changes predict cumulative failure before clinical symptoms appear?

These uncertainties do not invalidate the project; they define it. The project is scientifically useful precisely because it converts the vague ambition to “need less sleep” into a set of measurable, falsifiable, and safety-gated questions.

15. Conclusion

The Zero Sleep Project proposes a change in the unit of analysis. Sleep duration is not itself the biological product. The product is a coordinated transformation of the brain and body: electrical rhythms organize timing; neuromodulators open and close operating gates; synapses and memories are selectively remodeled; glial and metabolic systems restore ionic and energetic readiness; vascular and CSF dynamics transport solutes; cellular machinery repairs and renews; and endocrine, autonomic, immune, and peripheral-tissue programs distribute the transformation throughout the organism.

The project now has a corresponding engineering architecture. The Biological Refresh Scanner addresses observability by estimating the individual’s latent Difference-plus-Work state from deep research measurements and portable operational signals. The Closed-Loop Restoration System addresses controllability by mapping residual process deficits to validated intervention modules, measuring target engagement, updating the state estimate, and stopping only when equivalence and safety conditions are satisfied. The scanner is not a single machine and the repairer is not a universal treatment; together

they form a hierarchical observer-controller with uncertainty, abstention, and conventional sleep as the mandatory fallback.

Current evidence is sufficient to justify an actionable first program, but not a claim of feasibility for complete sleep elimination. The Minimum Testable Refresh Panel identifies human-measurable electrophysiological, homeostatic, functional, molecular, endocrine, immune, bioenergetic, synaptic, and solute-transport variables and assigns each to a core, secondary, nested, or exploratory role. Mechanistically selected molecules provide state gates, comparators, supports, or exit switches; an adaptive auditory inner loop supplies a noninvasive control handle over endogenous NREM timing. Negative examples show that increasing a sleep-like signal can disrupt another essential process, and no operational scanner can yet verify the complete post-sleep state.

Ultimate research question. What is the shortest safe sequence of global, regional, and peripheral biological operations that reproduces the complete post-sleep state—and can that sequence be controlled well enough to make long conventional sleep unnecessary?

Defense provides a stringent application, not a license to relax the evidence standard. The scientifically defensible objective is the Resilient Warfighter: role-specific readiness that can be measured, incomplete recovery that can be selectively accelerated, and a protected not-ready determination when biological restoration has not been achieved. A “perfect soldier” is neither a coherent biological target nor an ethically acceptable substitute for individualized health protection.

The first actionable objective is therefore not measurement of the entire brain state or elimination of sleep. It is reproduction of a prespecified NREM Difference-plus-Work subvector using mechanistically selected interventions, an adaptive closed-loop auditory controller, independent functional endpoints, withheld biological measurements, and subsequent-sleep-demand testing. Progressively broader claims become permissible only as additional modules and repeated-cycle safety are validated. The ultimate endpoint remains reproduction of the complete post-sleep Difference-plus-Work Vector in the shortest biologically permissible time without cumulative impairment.

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Appendix A. Operational definitions

Table A1. Terms used as programmatic controls.

Term	Operational definition
Pre-sleep state	The final waking neural and molecular state before objectively verified sleep onset under standardized conditions.
Post-sleep state	The state sampled immediately after final awakening from objectively verified sleep, before material morning exposure or activity.
Difference Vector	The personalized net change from the pre-sleep to post-sleep multidimensional state.
Difference-plus-Work Vector	The Difference Vector augmented by flux, localization, functional output, durability, and cumulative-safety components.
Transformation Network	The time-ordered, interacting electrical, chemical, molecular, vascular, endocrine, immune, and peripheral processes producing the post-sleep state.
Accelerated Biological Refresh	A controlled intervention that reproduces a predefined portion of the Difference-plus-Work Vector in less time than reference sleep.
Whole-system equivalence	Prespecified noninferiority of all material state, work, function, durability, and cumulative-safety endpoints relative to natural sleep.
Zero Sleep	Aspirational program label; scientifically, elimination of long conventional sleep through verified reproduction of its essential biological operations—not elimination of sleep biology.
Biological Refresh Profile	A domain-specific, uncertainty-calibrated estimate of current neural and peripheral recovery, residual process deficits, trajectory, and classification confidence.
Biological Refresh Scanner	A multiscale measurement and state-estimation architecture that compares current brain-and-body status with the individual's validated post-sleep equivalence region.
Closed-Loop Restoration System	A safety-constrained observer-controller that selects process-specific interventions, measures target engagement and execution, rescans, and stops, repeats, or defaults to natural sleep.
Minimum Testable Refresh Panel	A prespecified set of core, secondary, and nested variables sufficient to predict, control, and test equivalence for one defined sleep-transformation module.
Resilient Warfighter	A defense application centered on role-specific readiness assessment, selective restoration, cumulative-debt detection, and protected not-ready decisions—not unbounded wakefulness or trait enhancement.
Withheld-variable challenge	A blinded test using prespecified outcomes excluded from scanner training and controller feedback to detect hidden or unmodeled differences from natural sleep.

Appendix B. Readiness scale

The following scale should be applied separately to every process–difference link and intervention. No current intervention has reached R4 for sleep replacement.

Level	Definition
R0	Biologically plausible hypothesis supported primarily by theory or nonhuman evidence.
R1	Measurable in living humans with acceptable reliability.
R2	Causally modifiable in humans, at least partially, with target engagement demonstrated.
R3	A meaningful Difference-plus-Work endpoint reproduced in a shortened human protocol.
R4	Whole-system replacement demonstrated safely across repeated cycles with long-term follow-up.