Measuring Dynamic CB1 Regulatory State During Sleep

A non-invasive proof-of-concept biomarker framework for longitudinal assessment of inferred CB1 regulatory dynamics

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Core proposition
CB1 biology is dynamic, but current receptor-level methods are not suited to frequent longitudinal measurement. This white paper evaluates whether repeated sleep EEG and sleep-stage autonomic physiology can provide a non-invasive physiological estimate of CB1-associated regulatory state and, importantly, how that state changes during perturbation and recovery.

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Executive Summary

Making a dynamic regulatory state measurable

Cannabinoid type 1 receptor (CB1) signaling is a major neuromodulatory component of the endocannabinoid system. CB1 is widely expressed in the central nervous system, regulates neurotransmitter release, and is dynamically modified by sustained receptor stimulation [1-5]. In humans, PET imaging has shown that chronic daily cannabis exposure can be associated with lower cortical CB1 receptor availability and that this change can reverse during monitored abstinence [6]. These observations establish a central premise for biomarker development: CB1-related biology is not a fixed trait; it can move through measurable regulatory states.

The practical problem is measurement. PET can provide receptor-level information, but radiotracer imaging is costly and poorly suited to dense, repeated monitoring. Circulating endocannabinoid concentrations provide complementary biochemical information but do not directly report receptor responsiveness or its functional expression. A scalable longitudinal method would therefore fill a different measurement niche: repeated estimation of how CB1-associated physiology changes over time.

Sleep provides a potentially useful observation window. During sleep, thalamocortical oscillations, sleep-stage transitions, and autonomic regulation are repeatedly organized under relatively standardized conditions. Experimental evidence supports a role for endocannabinoid/CB1 signaling in sleep-wake regulation and NREM stability, and recent preclinical work shows that CB1 agonism can alter spindle-rich and REM-related oscillatory organization [7-10]. Sleep spindles themselves reflect thalamocortical circuit dynamics, while heart-rate variability changes systematically across NREM and REM sleep [11-14]. The human evidence linking specific sleep EEG features to receptor-level CB1 state remains incomplete; that gap is precisely what the present framework is designed to test.

What this proof-of-concept evaluates

- Whether an EEG-derived CB1 Availability Index (CB1AI) changes during a biologically meaningful cannabinoid-exposure transition.
- Whether the direction of CB1AI change reverses after sustained cannabinoid stimulation is reduced.
- How inferred CB1 state relates conceptually to sleep restoration and autonomic physiology within a broader Functional Sufficiency Score (FSS) framework.
- Whether different perturbation contexts produce distinguishable regulatory trajectories.
- Whether those trajectories can be described using dynamic features such as response amplitude, transition velocity, and post-transition variability.

Proof-of-concept findings

1. CB1AI showed a marked longitudinal state transition during changing estimated cannabinoid exposure (Figure 1).
2. After exposure reduction, the CB1AI slope changed from negative to positive, while individual physiological features such as spindle density followed different kinetics (Figure 2).
3. The multimodal framework separated inferred CB1 state from sleep-restoration and autonomic dimensions; the relationships shown in Figure 3 illustrate the internal architecture of the composite rather than independent external validation.
4. Pre-specified perturbation windows produced different trajectory patterns depending on biological context and starting inferred state (Figure 4).

5. The same trajectories could be summarized as dynamic regulatory profiles using response amplitude, transition velocity, and post-transition variability (Figure 5).

Interpretation boundary
These observations support feasibility and biological plausibility. They do not establish that CB1AI directly measures CB1 receptor abundance, occupancy, or signaling efficacy; they do not establish clinical validity; and they do not yet demonstrate generalizability beyond the current longitudinal dataset.

1. The Measurement Gap

Most clinical biomarkers are optimized to identify a state at a particular time: glucose concentration, inflammatory activity, receptor binding, structural imaging, or a molecular genotype. Regulatory systems create a different challenge because their most informative property may be the trajectory itself: how the system changes when demand, exposure, or physiological context changes.

CB1 is a useful example. It is a Gi/o-coupled receptor that modulates presynaptic neurotransmitter release and participates in neural, metabolic, stress-related, and behavioral regulation [1-3]. Like other GPCRs, CB1 is subject to desensitization, internalization, trafficking, and pathway-specific regulation after agonist stimulation [4,5]. Human PET data further are consistent with that chronic cannabis exposure can be associated with reversible changes in cortical CB1 receptor availability [6].

A single receptor measurement can therefore answer 'what is measurable now?' but not necessarily 'how is the system adapting?'. The measurement opportunity addressed here is longitudinal: infer a CB1-associated physiological state frequently enough to observe transitions, recovery, and stabilization.

2. Why Sleep Is an Attractive Observation Window

Sleep is a repeated physiological state in which neural and autonomic systems reorganize in structured, stage-dependent patterns. NREM sleep contains slow oscillations and sleep spindles generated within coordinated thalamocortical networks, while REM sleep has a distinct oscillatory and autonomic profile [11,12]. These patterns provide multiple physiological readouts from the same overnight recording.

The endocannabinoid system is not a generic 'sleep system', and the available literature does not justify treating any single sleep metric as CB1-specific. However, experimental studies support a regulatory role for endocannabinoid/CB1 signaling in sleep-wake organization and NREM stability [7-9]. Preclinical CB1 agonism has also been shown to alter spindle architecture and REM-related oscillatory activity [10]. Human cannabinoid-sleep studies remain heterogeneous, and systematic reviews emphasize substantial limitations in the clinical evidence base [15].

This combination makes sleep scientifically useful for biomarker discovery: it is biologically rich, repeatedly measurable, and mechanistically connected to CB1 signaling, while still leaving an unresolved translational question about which multivariate physiological patterns, if any, track receptor-level regulatory state.

3. The ECS Restore Biomarker Framework

ECS Restore treats CB1 regulatory state as a latent variable. The platform does not attempt to infer CB1 state from one EEG feature or one heart-rate metric. Instead, it integrates complementary physiological dimensions and evaluates how they change longitudinally.

3.1 CB1 Availability Index (CB1AI)

CB1AI is an EEG-derived research index built from sleep features selected for their relationship to network organization and their hypothesized sensitivity to CB1-regulated physiology. The current implementation incorporates information from spindle dynamics, slow-wave and spectral organization, sleep-stage transitions, and cortical network coordination.

Terminology
The word 'Availability' in CB1 Availability Index is a project-specific physiological term. CB1AI must not be conflated with PET receptor binding availability. It is an inferred index designed for within-person longitudinal tracking.

3.2 Sleep restoration and autonomic expression

The framework deliberately separates inferred CB1 state from broader physiological expression. REMRepair summarizes selected features of restorative sleep organization. Sleep-stage autonomic measures, including NREM2 RMSSD, provide an independent cardiovascular domain. Sleep-stage HRV is appropriate for this purpose because autonomic balance changes substantially across NREM, REM, wake, and arousal states [13,14].

3.3 Functional Sufficiency Score (FSS)

FSS is an exploratory composite that integrates CB1AI with sleep-restoration and autonomic dimensions. It is not a diagnostic score and is not an independent validation target for CB1AI. Its purpose is architectural: to ask whether an inferred regulatory state is expressed in a physiological context that also shows coordinated restorative and autonomic features.

Because CB1AI, REMRepair, and autonomic variables contribute to the construction of FSS, correlations among these quantities are partly expected by design. They should therefore be interpreted as internal coherence of the framework, not evidence that CB1AI has been externally validated.

4. Methods and Analytical Framework

4.1 Study design

The initial evaluation used a longitudinal within-person observational design. The objective was not to establish clinical validity, but to examine whether the candidate biomarker framework exhibits measurable temporal behaviour consistent with biological adaptation and receptor regulation.

The analytical strategy focused on repeated overnight measurements, within-person trajectories, defined physiological transition periods, and temporal relationships between inferred CB1 regulatory state and functional physiological measures.

4.2 Data acquisition and computational pipeline

Sleep EEG data were acquired using the Muse S Athena EEG headband (InteraXon Inc.), a commercially available wearable EEG device designed for longitudinal neurophysiological monitoring during sleep.

Raw EEG recordings were collected using the MindMonitor application, which provides access to continuous EEG signal streams and associated physiological data.

To transform raw recordings into analytical variables, a proprietary Python-based computational pipeline was developed. The pipeline performs signal processing, feature extraction, and generation of derived physiological metrics used within the ECS Restore framework.

The analytical workflow includes preprocessing of raw EEG recordings, extraction of sleep-related neurophysiological features, quantification of sleep microarchitecture, and integration with sleep-stage autonomic measures. The resulting framework is designed to identify longitudinal changes in coordinated physiological organization rather than provide direct measurement of CB1 receptor biology.

The analytical innovation resides in the integration of wearable physiological signals, computational feature extraction, and longitudinal state estimation, rather than in any single measurement modality alone.

4.3 CB1 Availability Index (CB1AI)

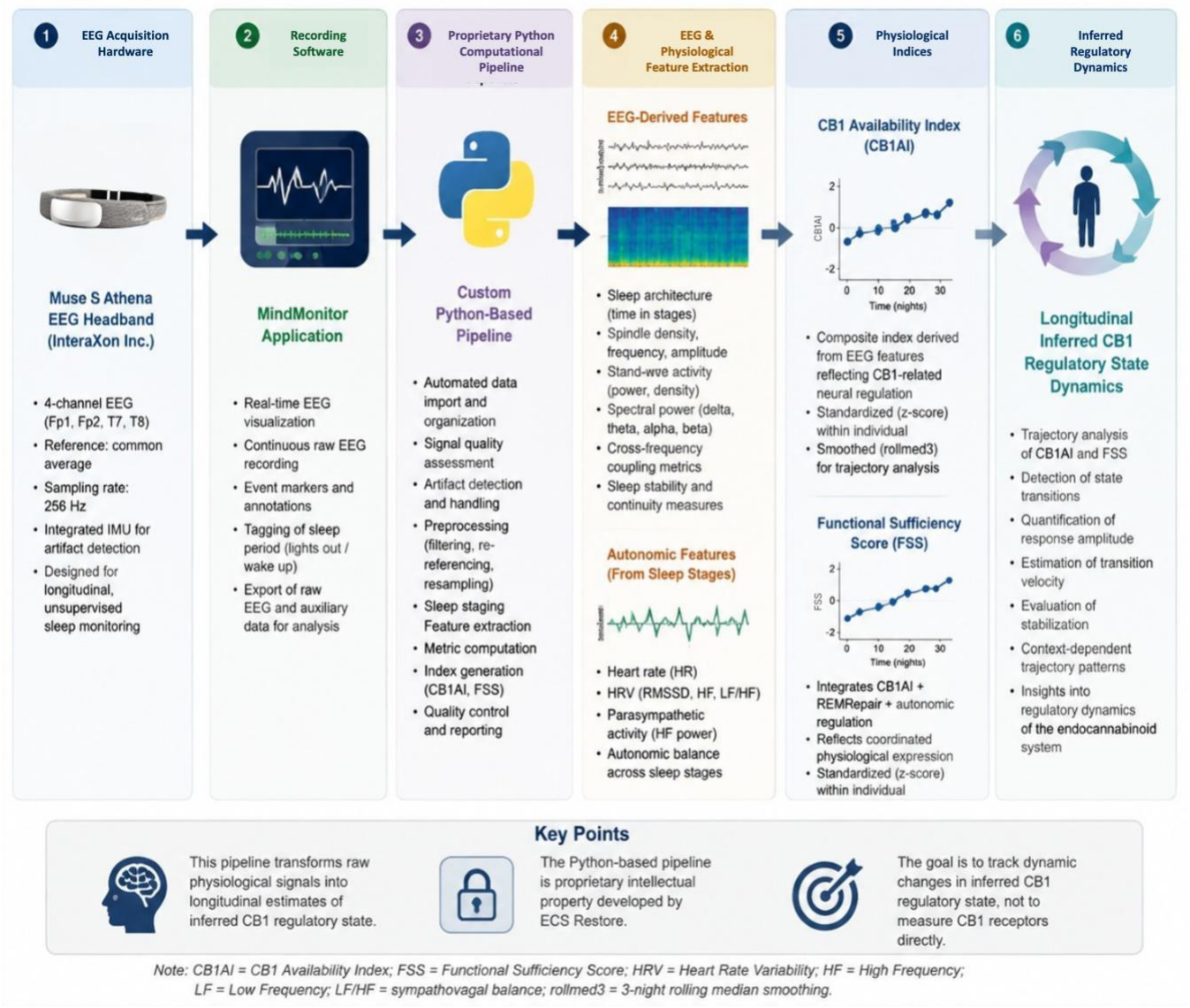
CB1AI is a composite physiological index derived from multiple sleep EEG features selected based on biological plausibility as downstream signatures of CB1-related neural regulation. CB1AI is not a direct measurement of receptor abundance, occupancy, or PET-derived availability. It is intended to estimate longitudinal changes in inferred CB1 regulatory state. Trajectory analyses included raw values and three-observation rolling median smoothing (rollmed3).

4.4 Functional Sufficiency Score (FSS)

FSS integrates CB1AI, REMRepair, and autonomic regulation to explore whether inferred regulatory state is accompanied by coordinated physiological expression. Because CB1AI contributes to FSS, correlations between these measures are interpreted as framework coherence rather than independent validation.

4.5 Temporal and statistical analysis

Analyses focused on longitudinal trajectories and transition behaviour. Exploratory analyses included trajectory visualization, transition analysis, response amplitude, transition velocity, stabilization metrics, Spearman correlations, and exploratory regression modelling. No claims of population-level generalization are made from the current dataset.



Supplementary Figure S1. Computational Pipeline Overview. Raw physiological recordings are transformed through a multi-stage computational workflow to generate longitudinal indices of inferred CB1 regulatory state. Sleep EEG data are acquired using the Muse S Athena EEG headband and recorded through the MindMonitor application. Raw recordings are processed through a proprietary Python-based computational pipeline involving signal preprocessing, feature extraction, and derivation of sleep neurophysiological metrics. These features are integrated with sleep-stage autonomic measures to generate composite physiological indices, including the CB1 Availability Index (CB1AI) and Functional Sufficiency Score (FSS). The resulting framework enables analysis of temporal trajectories, state transitions, and regulatory dynamics. CB1AI and FSS represent inferred physiological constructs and do not constitute direct measurements of CB1 receptor abundance, occupancy, or PET-derived receptor availability.

5. Proof-of-Concept Human Dataset and Analytical Approach

The current dataset consists of repeated overnight recordings collected longitudinally, with an emphasis on within-person change rather than cross-sectional group classification. The central analytical unit is a trajectory: the individual serves as their own reference across defined perturbation and recovery periods.

5.1 Measurement inputs

- Sleep EEG and derived sleep microarchitecture features.
- N2/N3 spindle density and related oscillatory measures.

- REM-related restorative features.
- Sleep-stage autonomic physiology derived from beat-to-beat cardiac intervals.

5.2 Exposure and perturbation alignment

For the cannabinoid-transition analyses, the exposure series represents recorded estimated cannabinoid exposure expressed as THC-equivalent units. It is an exposure estimate, not a plasma THC measurement. Analyses were aligned to biologically defined exposure-reduction or perturbation-removal points.

A second longitudinal perturbation context was used to test whether the framework could resolve a different response architecture outside the cannabinoid-reduction trajectory. The identity of that intervention is not disclosed in this public white paper. Consequently, that analysis is presented only as a feasibility demonstration of context dependence and is not independently reproducible from this document.

5.3 Smoothing and exploratory statistics

Night-to-night physiological data are inherently variable. A three-night rolling median (rollmed3) was used as a descriptive smoothing method because it reduces sensitivity to isolated nights while preserving short-timescale transitions. Raw nightly values are retained where informative. Reported correlations and slopes are exploratory; no correction for repeated-measures autocorrelation or confirmatory hypothesis testing is claimed.

6. Proof-of-Concept Findings

6.1 Can the platform detect a known CB1-related state transition?

Figure 1 places estimated cannabinoid exposure, CB1AI, and one underlying EEG feature on the same calendar axis. During sustained high estimated exposure, CB1AI occupied a lower range. As exposure was reduced, CB1AI moved upward into a distinct longitudinal state. Spindle density also changed over the observation period, but its trajectory was not identical to the composite index.

This is the first proof-of-concept requirement: the candidate index should be sensitive to a biological transition with a strong prior rationale. Human PET studies provide that rationale by demonstrating reversible CB1 downregulation in chronic daily cannabis users during abstinence [6]. The present data do not establish equivalence between CB1AI and PET; they show that a sleep-derived index changes in a direction that is compatible with a known CB1 adaptation paradigm.

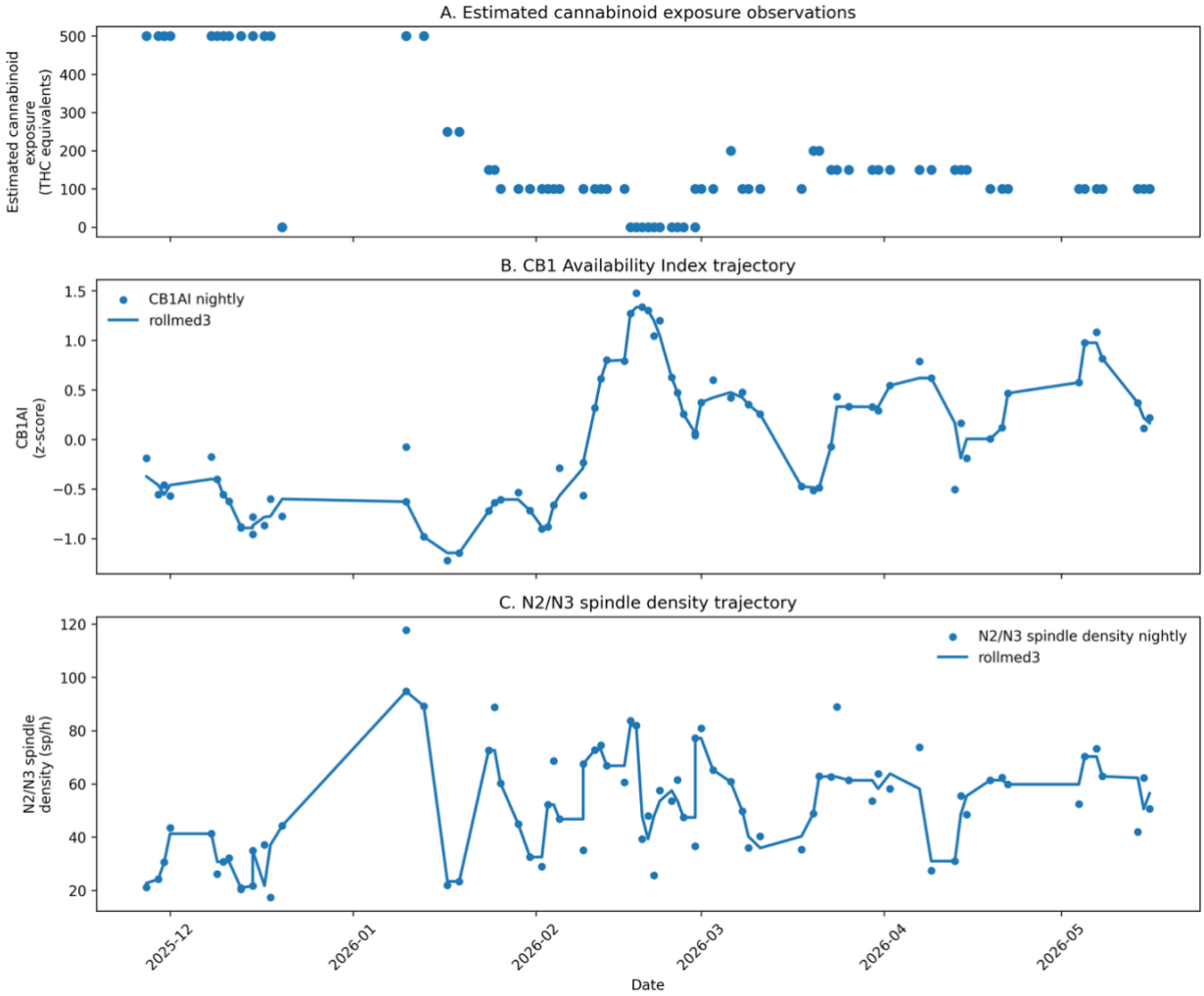


Figure 1. Detection of a longitudinal CB1-associated state transition. **(A)** Recorded estimated cannabinoid exposure observations expressed as THC-equivalent units. **(B)** Nightly CB1 Availability Index (CB1AI) with three-night rolling median. **(C)** N2/N3 spindle density shown as an individual EEG feature. The figure illustrates a change in CB1AI during a major exposure transition and, separately, the non-identical kinetics of a constituent physiological feature. The analysis is descriptive and within-person; it does not represent direct receptor measurement.

6.2 Does inferred CB1 regulatory state recover after reduced stimulation?

Figure 2 re-expresses the primary trajectory relative to the exposure-reduction point. The CB1AI slope was negative before reduction and positive afterward (approximately -0.0039 versus +0.0068 z-score units/day in the exploratory linear fits). This directional reversal is more informative than a simple pre/post mean because it asks whether the trajectory itself changes after the perturbation.

The spindle-density trajectory behaved differently: it increased strongly before the defined transition and then showed little continued slope afterward. This supports the rationale for a composite biomarker architecture. A dynamic regulatory state need not be represented by one feature moving monotonically in parallel with all others.

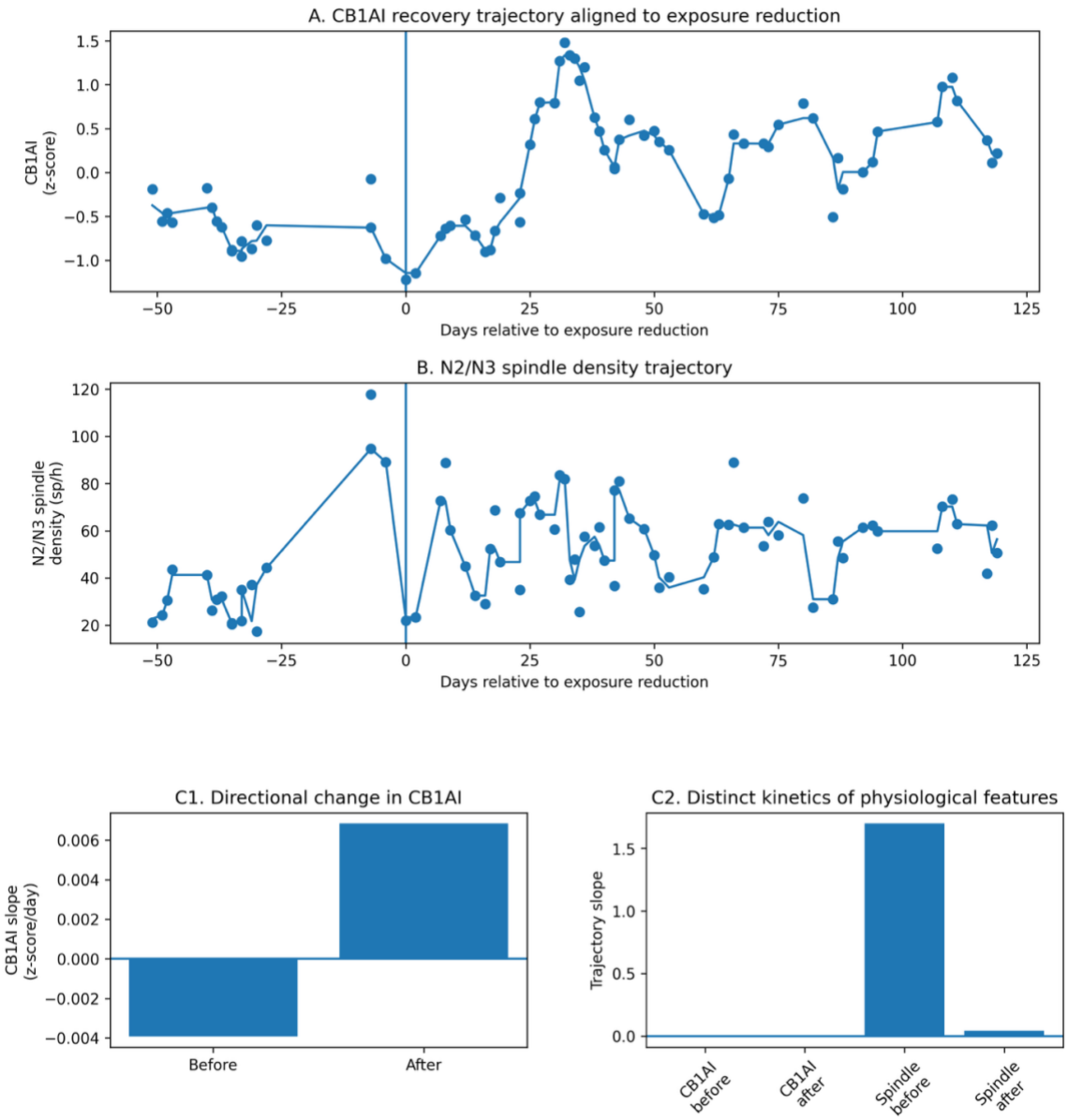


Figure 2. Recovery of inferred CB1 regulatory state following reduced stimulation. **(A)** CB1AI trajectory aligned to the exposure-reduction point (day 0). **(B)** N2/N3 spindle-density trajectory aligned to the same transition. **(C1)** Exploratory pre/post slope comparisons are consistent with a directional reversal in CB1AI. **(C2)** Spindle density shows distinct kinetics, illustrating why a multifeature index may capture information that is not present in a single sleep metric. These slopes are descriptive and should not be interpreted as causal estimates.

6.3 How does inferred CB1 state relate to broader physiological expression?

Figure 3 addresses a different question: once a CB1-associated state is estimated, how should its physiological expression be represented? CB1AI was strongly associated with FSS in the current longitudinal dataset (Spearman rho approximately 0.85). That association is expected because CB1AI contributes directly to the construction of FSS.

Residual analyses were then used to illustrate the additional role of the other FSS dimensions. After accounting for the CB1AI-FSS relationship, residual FSS was positively associated with REMRepair (Spearman rho approximately 0.76) and with N2 RMSSD (rho approximately 0.63). These relationships are also partly structural because the modifiers contribute to the FSS framework. Their value is conceptual

rather than confirmatory: they show how the platform separates inferred regulatory state from sleep-restoration and autonomic expression.

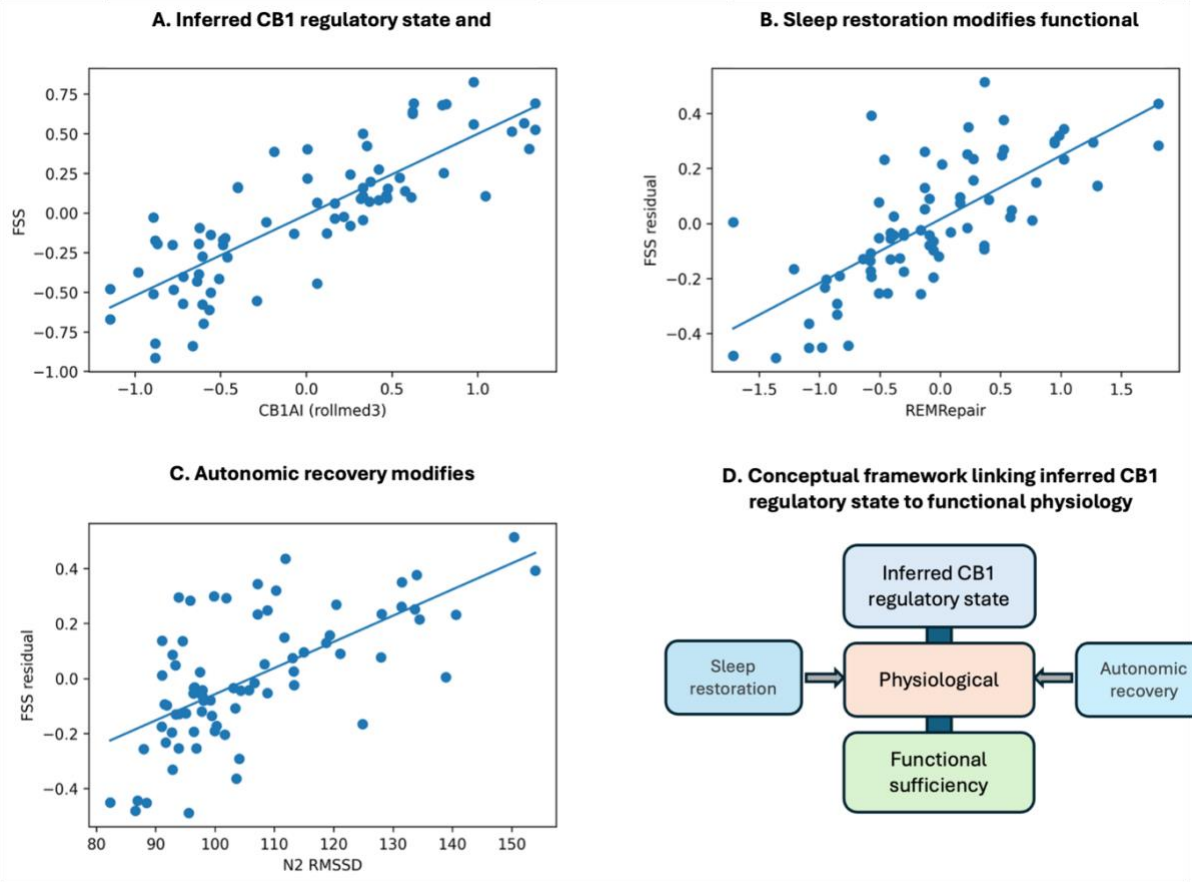


Figure 3. Linking inferred CB1 regulatory state to functional physiology. (A) Relationship between CB1AI and the Functional Sufficiency Score (FSS). **(B)** REMRepair plotted against FSS residuals after accounting for CB1AI. **(C)** N2 RMSSD plotted against the same residual construct. **(D)** Conceptual framework in which sleep restoration and autonomic recovery modify the physiological expression associated with inferred CB1 state. Because FSS is constructed from CB1AI, sleep-restoration, and autonomic dimensions, these panels are consistent with internal architecture and coherence, not independent validation of CB1AI.

6.4 Can the platform resolve context-dependent regulatory trajectories?

A useful dynamic biomarker should not be expected to produce the same trajectory after every perturbation. The response should depend on the starting state and the biological context. Figure 4 therefore compares three pre-specified longitudinal windows: a low inferred regulatory state, a recovery trajectory after reduction of sustained stimulation, and a second independent perturbation context.

The three windows show qualitatively different response architectures. The low-state window shows limited upward movement; the recovery window shows a marked transition into a higher CB1AI range; and the independent perturbation window shows an upward transition followed by relative stabilization. The result is hypothesis-generating evidence that trajectory shape may contain information beyond the absolute CB1AI value.

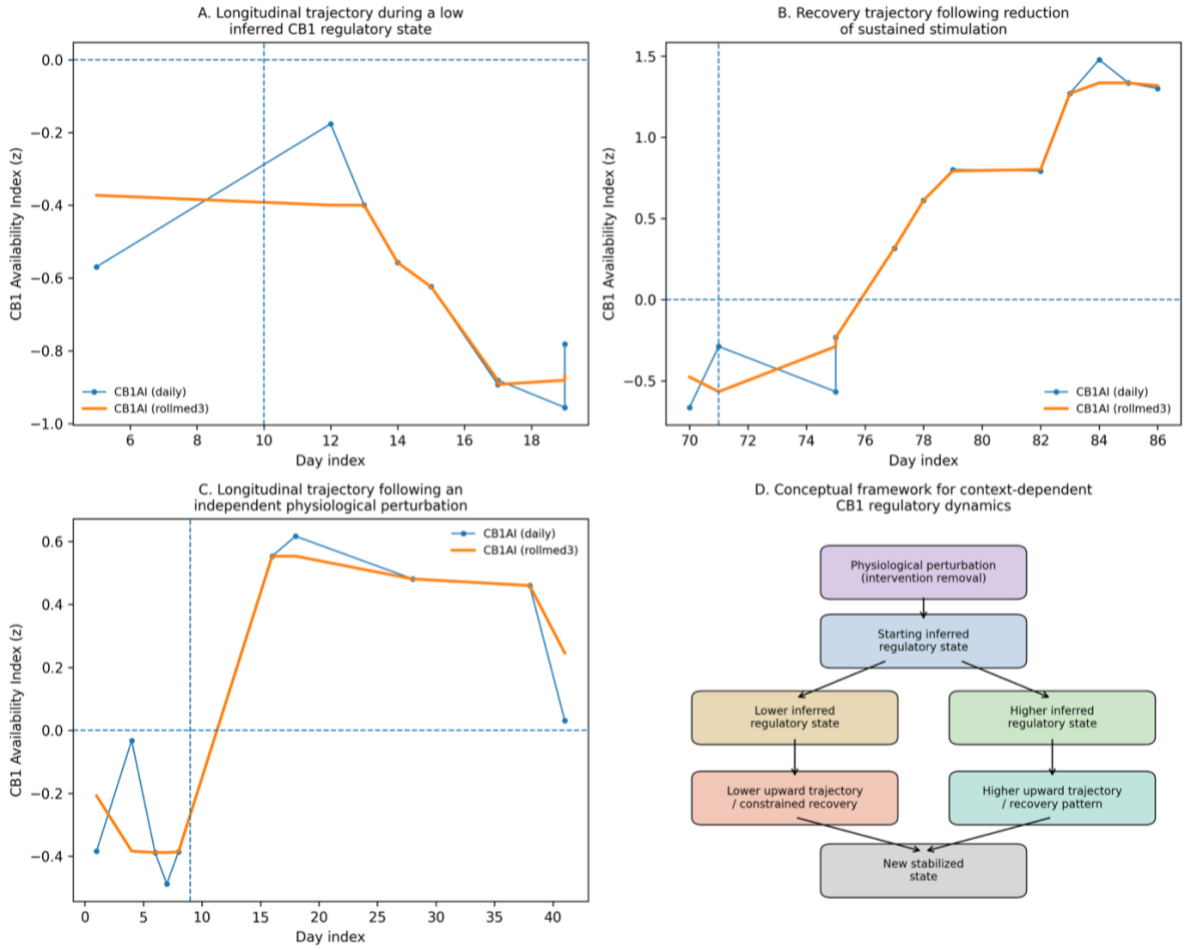


Figure 4. Context-dependent dynamics of inferred CB1 regulatory state. (A) Pre-specified window representing a low inferred CB1 regulatory state. **(B)** Recovery trajectory following reduction of sustained stimulation. **(C)** A second longitudinal physiological perturbation context, included to test whether a different starting state produces a different trajectory architecture. **(D)** Conceptual model: the response to perturbation depends on starting regulatory state and may lead to distinct recovery and stabilization patterns. The specific intervention used in panel C is not disclosed in this public white paper; the panel should therefore be interpreted as a feasibility example rather than a fully reproducible experiment.

6.5 Can regulatory dynamics be quantified?

Figure 5 converts the trajectories in Figure 4 into three descriptive features: response amplitude, transition velocity, and post-transition variability. These measures address different questions. Amplitude asks how far the inferred state moves; velocity asks how quickly it moves after perturbation removal; variability asks how consistently the new state is maintained within the observation window.

The recovery-after-reduction window showed the largest positive amplitude and the only clearly positive transition velocity, while the independent perturbation window combined a positive amplitude with relatively low post-transition variability. The low-state window showed little positive movement. These metrics are not yet a validated 'adaptive capacity score'. Their current value is that longitudinal CB1AI trajectories can be summarized as dynamic regulatory profiles rather than single static values.

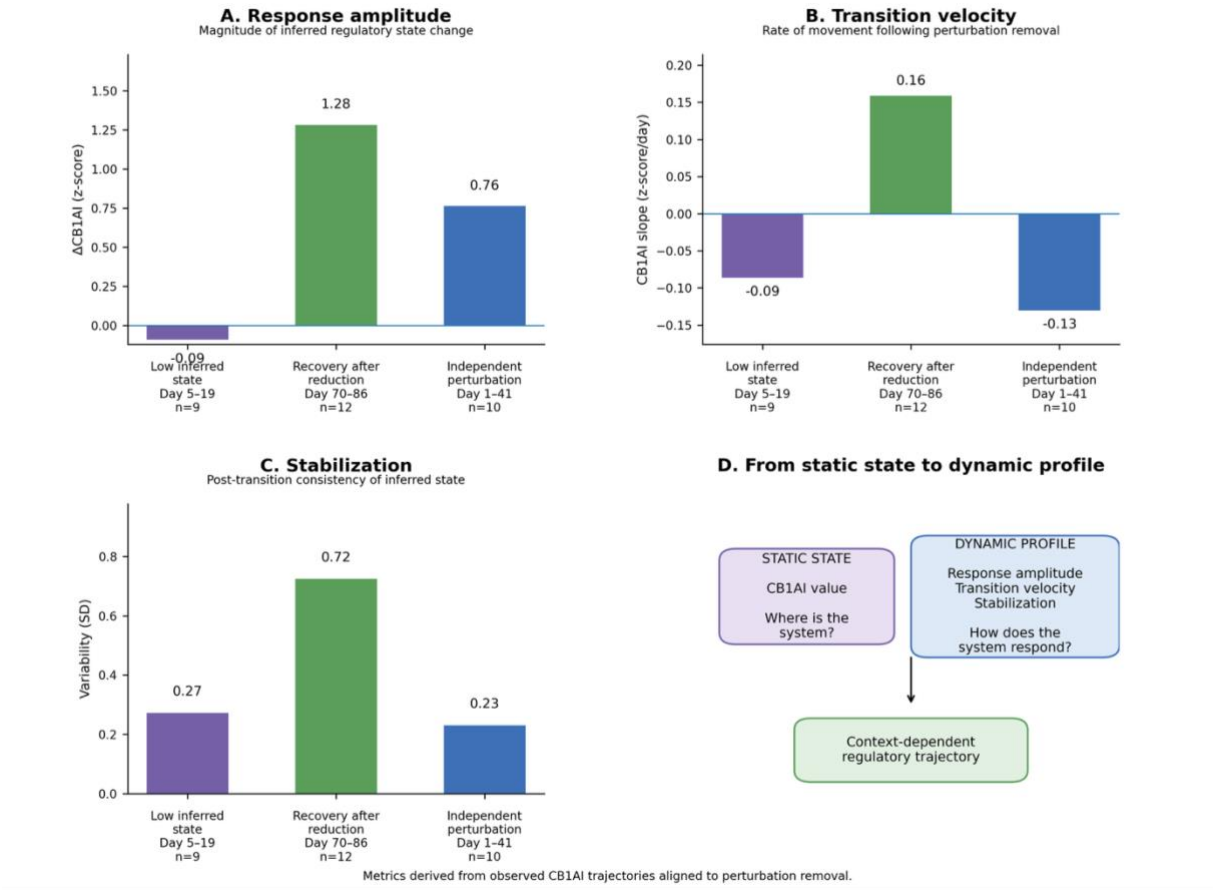


Figure 5. Quantification of inferred CB1 regulatory dynamics during perturbation and recovery. **(A)** Response amplitude summarizes the magnitude of CB1AI change across each analysis window. **(B)** Transition velocity summarizes the direction and rate of the post-removal trajectory. **(C)** Post-transition variability provides a descriptive measure of stabilization within the observed window. **(D)** Static CB1AI and dynamic trajectory features are complementary: one estimates current inferred state, while the other describes how that state responds over time. These metrics are exploratory descriptors and are not a validated regulatory-flexibility or adaptive-capacity score.

7. What the Current Evidence Establishes - and What It Does Not

The most important scientific discipline in interpreting this proof-of-concept is to separate established biology, direct observations in the dataset, and hypotheses that still require validation.

Established biology	Observed in this dataset	Hypothesis requiring validation
CB1 is a dynamically regulated GPCR; sustained agonist exposure can alter receptor responsiveness and trafficking [4-6].	CB1AI changed during a major exposure transition and reversed direction after reduced stimulation.	CB1AI quantitatively reflects receptor-level CB1 availability or signaling capacity.
Endocannabinoid/CB1 signaling contributes to sleep-wake regulation and NREM stability in experimental models [7-10].	CB1AI, spindle density, REM-related features, and autonomic variables displayed distinguishable longitudinal dynamics.	The selected sleep features are specifically driven by CB1 rather than by other neural or behavioral factors.
Sleep spindles reflect thalamocortical organization and HRV changes across sleep stages [11-14].	Different perturbation contexts produced different CB1AI trajectory shapes.	Trajectory shape measures a generalizable property of CB1-dependent adaptation across individuals.

Human PET demonstrates reversible cortical CB1 downregulation in chronic daily cannabis exposure [6].	Dynamic metrics such as amplitude, slope, and post-transition variability can be extracted from CB1AI trajectories.	These dynamic metrics predict clinical outcomes, treatment response, resilience, or future physiological adaptation.

8. Limitations

- Small, intensively sampled proof-of-concept dataset. The principal transition analyses are dominated by one individual's longitudinal trajectory, and the independent perturbation context is based on limited observations from a second individual.
- No criterion-standard receptor measurement. CB1AI has not yet been calibrated against CB1 PET imaging, ex vivo receptor measures, or another receptor-level standard.
- Potential circularity in composite analyses. FSS is constructed from CB1AI, REMRepair, and autonomic dimensions; Figure 3 therefore illustrates framework architecture rather than external validation.
- Non-randomized perturbations and potential confounding. Sleep, stress, activity, diet, medication, recording quality, circadian timing, and other exposures can influence EEG and autonomic physiology.
- Autocorrelation and smoothing. Repeated nightly observations are not statistically independent, and rollmed3 is a descriptive filter. Confirmatory models should explicitly account for within-person dependence and pre-specify smoothing choices.
- Proprietary intervention detail. The second perturbation protocol is intentionally not disclosed in this public version, limiting independent reproducibility of that specific analysis.
- No diagnostic threshold or population reference range. CB1AI is currently a within-person research index; it should not be used to classify individuals as 'healthy', 'deficient', 'downregulated', or clinically abnormal.
- Generalizability is unknown. Sex, age, fitness, cannabinoid history, sleep disorders, neuropsychiatric conditions, medications, and sensor configuration may all modify the measured relationships.

9. Future Validation Roadmap

The next phase should move from retrospective proof-of-concept to pre-specified, independently reproducible validation. A staged program reduces risk by separating analytical reliability, biological validity, and clinical utility.

Stage 1 - Analytical reliability

- Lock the CB1AI feature set and algorithm before prospective outcome analysis.
- Quantify test-retest reliability during stable periods and establish expected night-to-night measurement error.
- Define signal-quality thresholds, missing-data handling, and artifact rejection prospectively.
- Test reproducibility across sensors, nights, and analysis software.

Stage 2 - Prospective perturbation validation

- Enroll participants undergoing a defined, ethically supervised change in cannabinoid exposure or another pre-specified physiological perturbation.
- Collect dense sleep EEG and sleep-stage HRV before, during, and after the transition.
- Pre-register primary endpoints such as CB1AI slope change, response amplitude, time to stabilization, and within-person effect size.
- Use blinded or algorithm-locked analysis to prevent post hoc tuning to expected trajectories.

Stage 3 - Criterion validation against receptor-level biology

- In a subset, compare CB1AI with PET-derived CB1 receptor availability at strategically selected time points. Human PET studies provide a precedent for reversible receptor-level changes during cannabis abstinence [6].
- Assess whether CB1AI adds longitudinal information beyond exposure measures, circulating cannabinoids/endocannabinoids, sleep duration, and conventional HRV.
- Determine whether changes in CB1AI precede, coincide with, or follow receptor-level recovery.

Stage 4 - External validation and utility

- Replicate the locked model in independent cohorts and research centers.
- Establish which applications are scientifically justified: pharmacology studies, tolerance/recovery monitoring, drug-development trials, or broader adaptive-physiology research.
- Only after independent validation should clinical thresholds, treatment guidance, or individual decision support be considered.

10. Why This Platform May Be Useful for Research

The immediate value proposition is not a diagnostic test. It is a longitudinal measurement platform for studying a receptor system that is difficult to observe repeatedly. If prospectively validated, the combination of a static inferred state and a dynamic response profile could support studies in which the scientific question is not merely whether a cannabinoid exposure occurred, but how the underlying regulatory system adapted.

- Cannabinoid pharmacology: tolerance, dose reduction, recovery, and within-person response heterogeneity.
- Drug development: repeated physiological phenotyping between sparse molecular or imaging visits.
- Mechanistic sleep research: testing which EEG and autonomic features are most closely linked to CB1-regulated physiology.
- Precision research designs: N-of-1 and small-cohort studies in which each participant provides a dense longitudinal trajectory.

For collaborators, the central testable proposition is straightforward: when CB1 regulatory state changes at the receptor level, does the locked sleep-derived index change in a predictable and reproducible manner, and does its trajectory provide information that sparse receptor imaging cannot?

11. Conclusion

The proof-of-concept data support a narrow but potentially important conclusion: repeated sleep physiology contains enough structured information to generate a candidate longitudinal index that changes during biologically meaningful perturbation and recovery periods. Across the five figures, the platform progresses from detecting a state transition, to quantifying recovery, to separating regulatory state from broader physiological expression, to resolving context-dependent trajectories, and finally to describing those trajectories as regulatory dynamics.

What remains unproven is equally important. CB1AI has not yet been validated against receptor-level CB1 measurements, the current dataset is small, and several analyses are internally derived rather than independent tests. The next scientific milestone is therefore prospective validation with an algorithm-locked protocol and, ideally, a PET comparison subset.

If that validation succeeds, the opportunity is not simply to create another sleep score. It is to establish a non-invasive longitudinal window into a dynamically regulated receptor system - a tool for studying how CB1-associated physiology changes over time.

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Authorship, Intellectual Property, and Disclosure Statement

This white paper was prepared by ECS Restore to describe the scientific rationale and proof-of-concept development of a non-invasive physiological framework for inferring CB1 regulatory dynamics. The work described includes proprietary analytical concepts and intellectual property under development.

The authors disclose that ECS Restore is developing technology related to the measurement of inferred CB1 regulatory state. The framework described herein is exploratory and has not been clinically validated, approved as a diagnostic tool, or established as a direct measure of CB1 receptor abundance, occupancy, or function.

The observations presented are intended to support scientific discussion and future validation studies. Independent replication and prospective evaluation will be required before any clinical or commercial conclusions can be drawn.