# The EEG during Sleep is a Window to the Mind: Recurrence Analysis of the Sleep EEG Accurately Identifies Subjects with Mental Health Symptoms

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## Abstract

Analysis of brain recurrence (ABR) is a novel method of algorithmically quantifying the degree of non-randomness (complexity) in an EEG signal. We showed that ABR accurately identified a signature in the sleep EEG that was specific for the presence of mental health symptoms, as assessed using the MHI-5 questionnaire.

## Introduction

Our objective was to discover and alidate reliable biomarkers in the EEG for detecting the presence and severity of mental illness. We used ABR (described in earlier publications) to extract four biomarkers from each 30-second epoch of sleep-staged EEGs. A reliable biomarker function for classifying the subjects according to MHI-5 scores was identified using linear discriminant analysis.
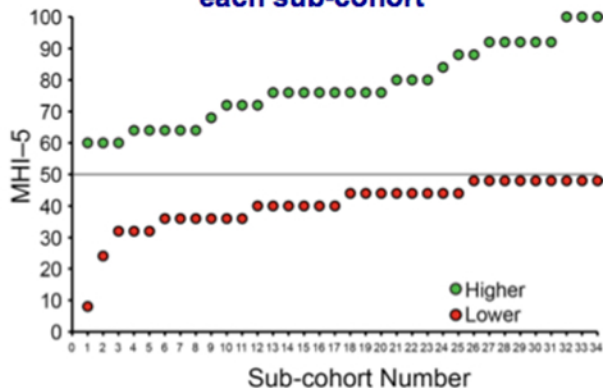
# Methods

The study sample comprised subjects drawn from the SHHS for whom mental health symptomatology had been ascertained, based on the Mental Health Index (MHI-5). MHI-5 scores were scaled to disperse values between 0 and 100, higher values indicating better mental health. From eligible subjects, we selected 34 subjects with MHI-5 scores >50, and 34 subjects matched for sex, BMI, age, and race with MHI-5 scores <50. Sleep-stage-specific ABR biomarkers were computed from the EEG (C3), and analyzed using LDA to identify combinations of the biomarkers that reliably classified individual subjects into low versus high MHI-5 scores. The classification accuracy was assessed using AUROC, with 10-fold cross-validation analysis.

## Characteristics of the study cohort

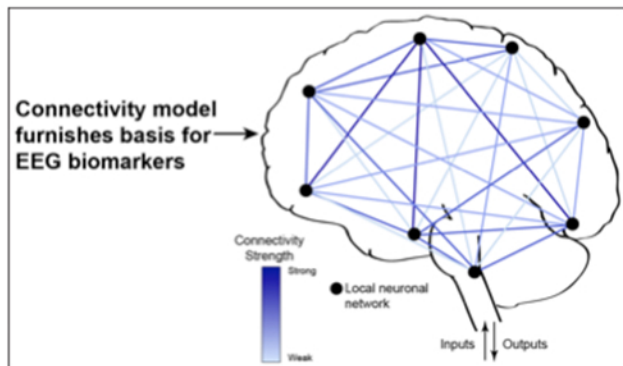|  | LOW MHI-5 (<50) | High MHI-5 (>50) |
|---|---|---|
| N | 34 | 34 |
| Race (C/non-C) | 29/5 | 29/5 |
| Age (Y) | 58.6 ± 2.3 | 58.7 ± 2.3 |
| Male/Female | 12/22 | 12/22 |
| BMI (kg/m$^2$) | 25.6 ± 0.6 | 25.9 ± 0.6 |
| RDI | 1.6 ± 0.2 | 1.3 ± 0.2 |
| MHI-5 | 40.5 ± 1.4 | 78.4 ± 2.1 |

Mean ± SE. C, Caucasian  RDI: Respiratory disturbance index

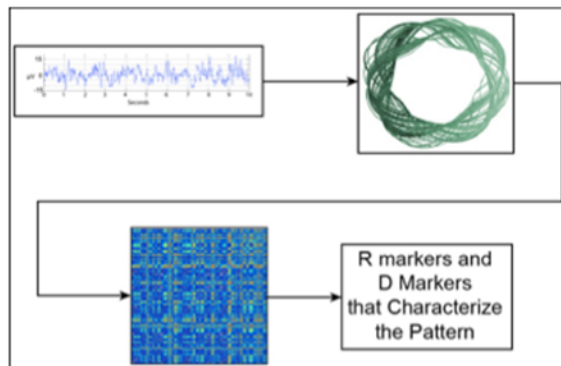## Distribution of MHI-5 scores in subjects in each sub-cohort

# Analysis of Brain Recurrence (ABR)

## Complexity model

Connectivity model furnishes basis for EEG biomarkers →

Connectivity Strength
Strong

● Local neuronal network

Weak

Inputs ↓ Outputs

## Feature extraction

R markers and D Markers that Characterize the Pattern

## Biomarkers constructed from the pattern *and* from the way it changes

R's →  R1  R2  R3  R4  R5  R6  R7  R8  R9  R10

ΔR's → R2/R1, R3/R2, R4/R3, R5/R4, R6/R5, R7/R6, R8/R7, R9/R8, R10/R9

(The same process produced the D's and ΔD's)

R   ΔR   D   ΔD

# Experimental Design

```
                    ┌─────────────────────┐
                    │    Study Cohort     │
                    │  N = 34 (MHI5 < 50) │
                    │  N = 34 (MHI5 > 50) │
                    └─────────────────────┘
                              │
                    ┌─────────────────────┐
                    │  Overnight EEG (C3)  │
                    └─────────────────────┘
                              │
                  ┌───────────────────────────┐
                  │ Analysis of Brain Recurrence │
                  └───────────────────────────┘
```

|                         |                         |                         |                         |
|-------------------------|-------------------------|-------------------------|-------------------------|
| ΔR(t)                   | R(t)                    | D(t)                    | ΔD(t)                   |
| **Fragmentation Biomarkers** WASO, N1/N2, N3, REM | **Depth Biomarkers** WASO, N1/N2, N3, REM | **Depth Biomarkers** WASO, N1/N2, N3, REM | **Fragmentation Biomarkers** WASO, N1/N2, N3, REM |

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              ┌──────────────────────────────┐
              │  Linear Discriminant Analysis  │
              │         (16 markers)          │
              └──────────────────────────────┘
                            │
              ┌──────────────────────────────┐
              │        AUROC Analysis         │
              │    for classification into    │
              │        Low MHI5 (<50)         │
              │              or               │
              │        High MHI5 (>50)        │
              │         Sub-Cohorts           │
              └──────────────────────────────┘
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The depth (R(t), D(t)) and fragmentation (ΔR(t), ΔD(t)) time series were normalized by WASO yielding 16 sleep-stage-specific biomarkers (WASO and 3 normalized stage-specific biomarkers for each time series (line 5)) that were used to create a biomarker function for discriminating between MHI-5 < 50 and MHI-5 > 50.
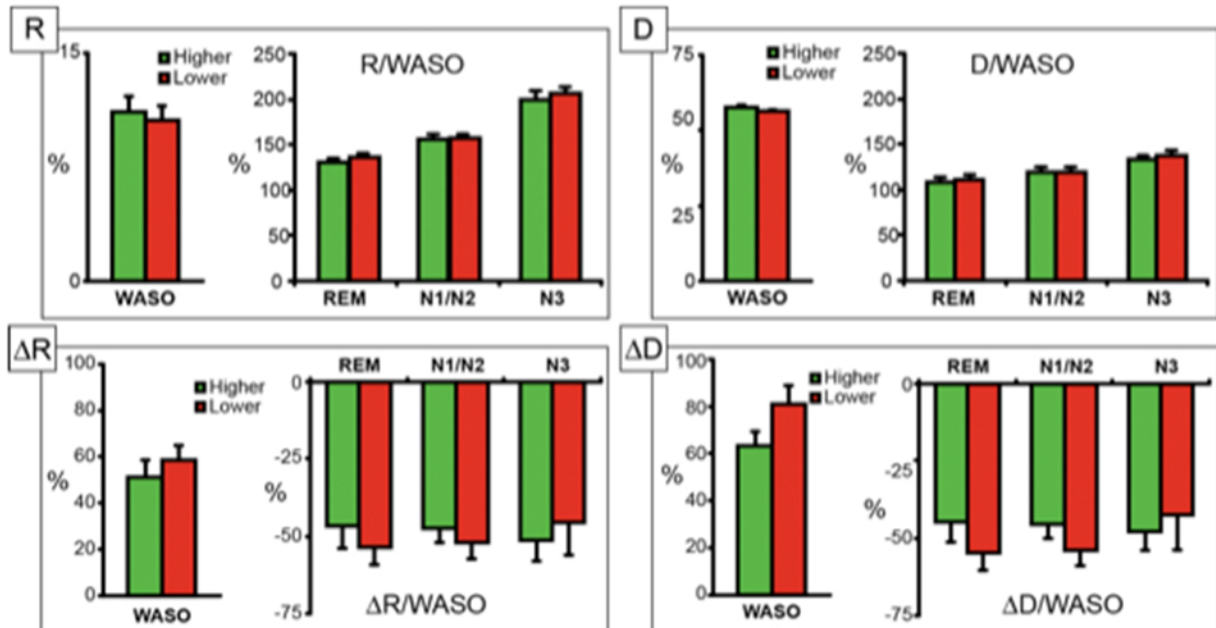
# Results

## Typical result for time-dependent change in the R depth biomarker
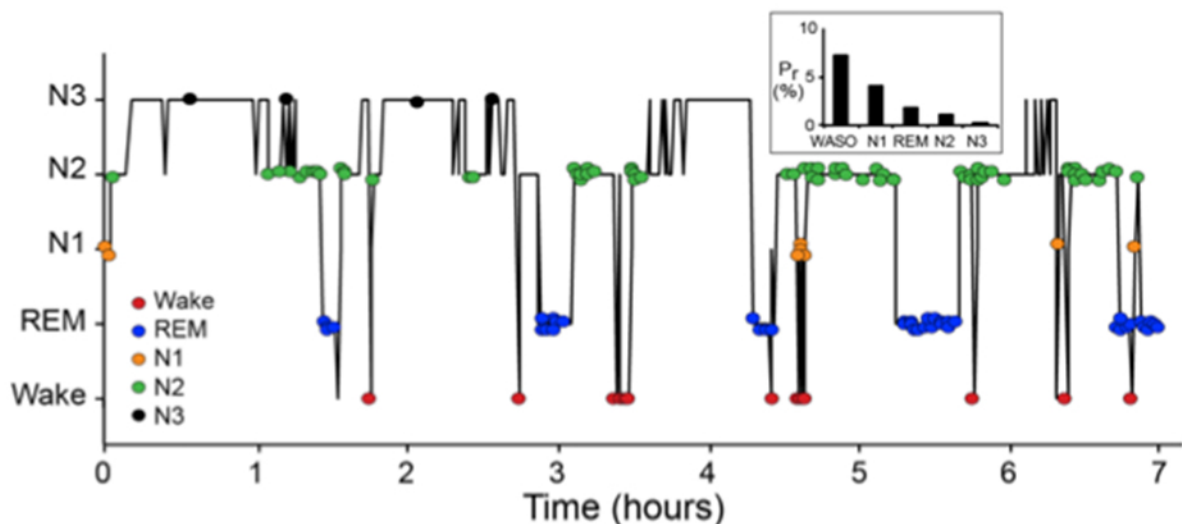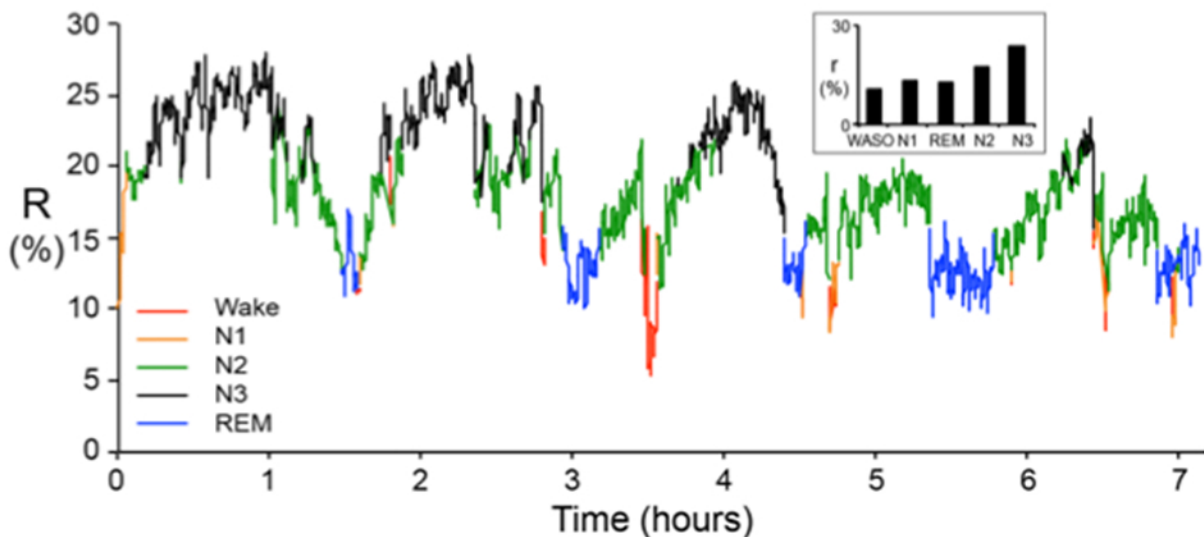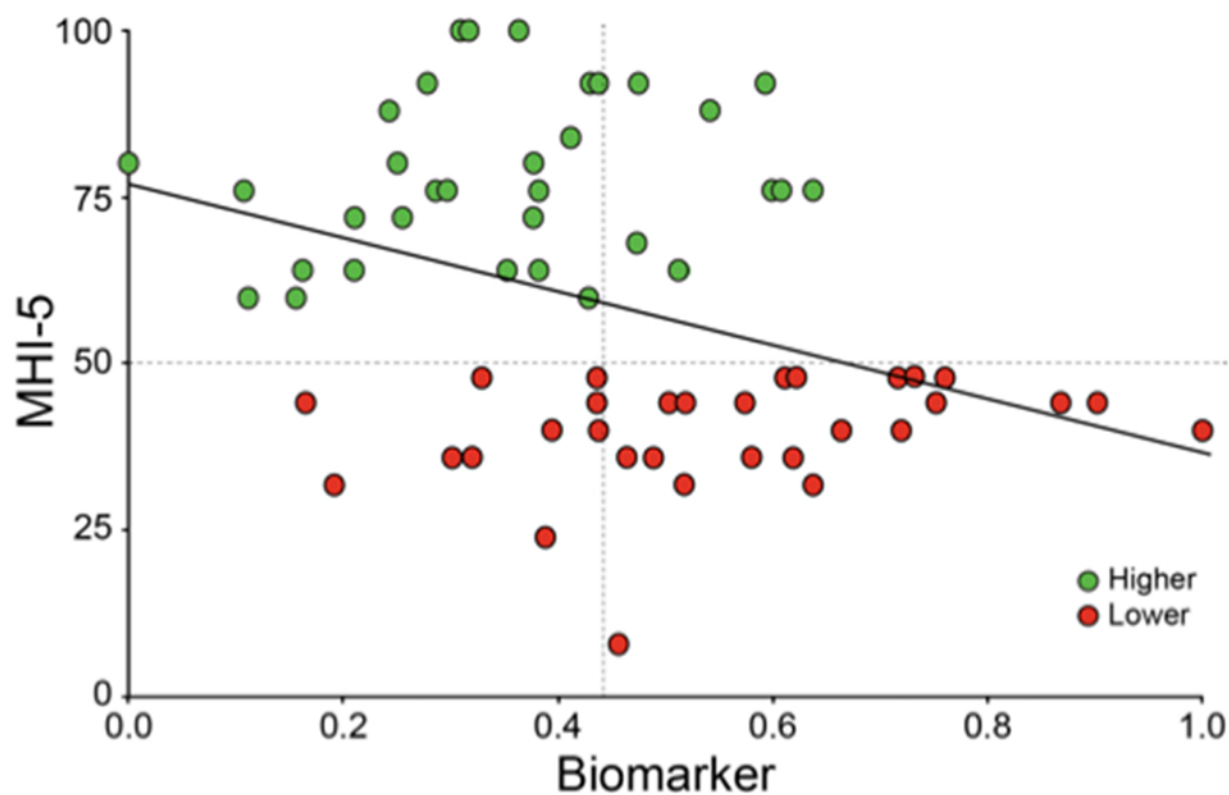


Values of R were calculated second-by-second, averaged epoch-by-epoch, and color-coded by sleep stage. Insert shows the sleep-stage-specific mean values. Distribution of generalized arousals computed from ΔR shown in lower curve. Each arousal (color-coded by sleep stage) indicated the occurrence of abrupt changes in R. Locations of arousals were jittered to facilitate graphical recognition. $P_r$, a posteriori stage-specific probability of an arousal (number of arousals in a given stage divided by the maximum possible number).

# Average results showing biomarker differences between sub-cohorts

Relation between MHI-5 scores and sleep-stage-specific changes in percent recurrence (R) and percent determinism (D), and sleep-stage-specific changes in variances (generalized arousal indices) computed from $\Delta R$ and $\Delta D$. Stage-specific results were determined, normalized by the WASO values, and averaged across 34 subjects with higher (>50) and 34 with lower (<50) MHI-5 scores (mean ± SE). A trend of average differences occurred across the individual biomarkers, but no single biomarker differed between the groups at $P < 0.05$.

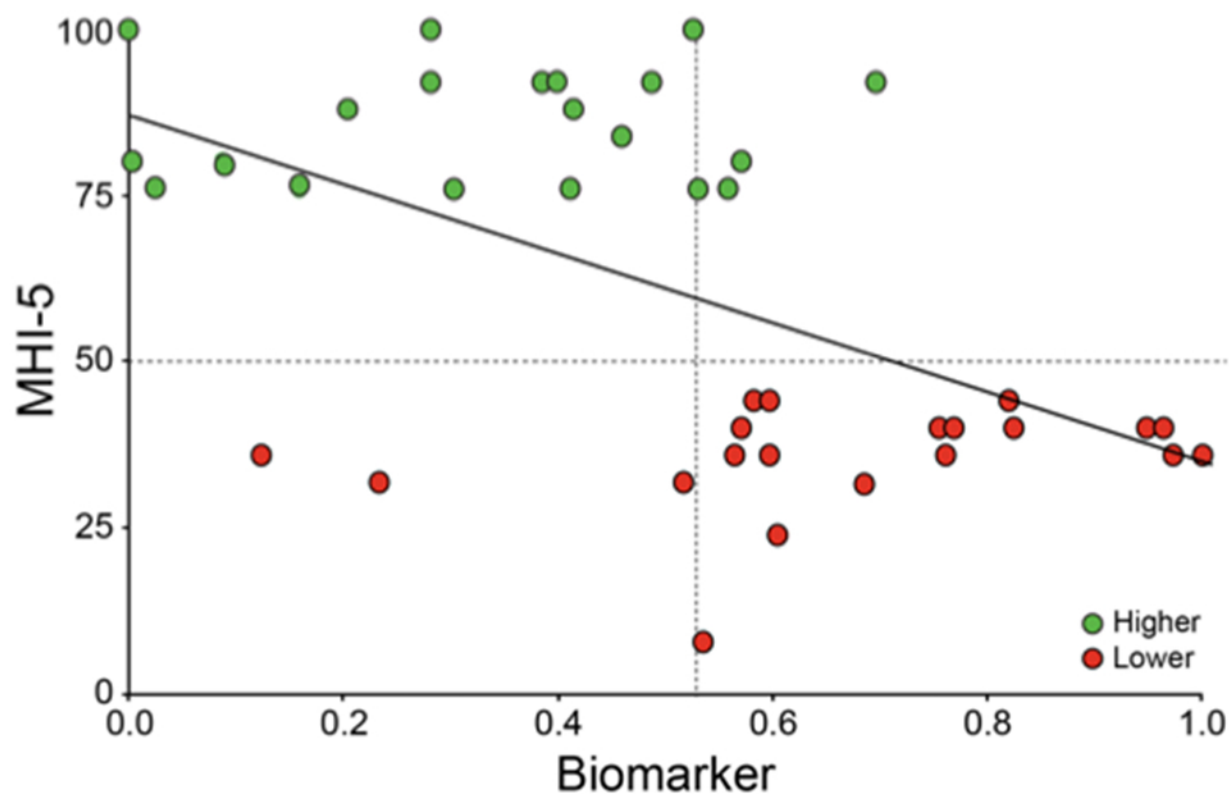# Biomarker value versus MHI-5 for full cohort and restricted cohort



N = 68          Sensitivity 79%          AUROC = 82%
r = 0.36        Specificity 77%          Cross-validation = 72%

N = 40          Sensitivity 85%          AUROC = 89%
r = 0.54        Specificity 85%          Cross-validation = 82%

Dotted line indicates thresholds for classification into higher or lower groups, 0.44 and 0.53 for the full and restricted (subjects with the 20 highest and 20 lowest MHI-5) cohorts, respectively. When the small differences in the individual biomarkers between the groups were combined using LDA, the resulting biomarker function accurately classified the subjects (AUROC 82%, 89%), and the biomarker values correlated with disorder severity (r = 0.36, 0.54).

# Discussion

ABR is a nonlinear method of algorithmically quantifying the degree of non-randomness (complexity) within a moving timeframe in an EEG signal. When applied to the staged, sleep-acquired EEG, the method yielded delocalized variables that tracked traditional stage-related concepts of sleep depth and fragmentation. We postulated that ABR-derived biomarkers could be combined statistically to accurately identify a signature specific for the presence of mental health symptoms. The assumption was tested by determining whether subjects could be reliably classified according to symptom severity as assessed using MHI-5 scores.

Using 12 ABR biomarkers, we classified 68 subjects into either low- or high-MHI-5 scores, with an AUROC of 82%. We interpret this result to mean that symptoms of psychological distress could be objetively detected in the EEG. Moreover, when subjects with mid-range MHI-5 scores were removed, subjects with intact mental health could be differentiated from those with more severe affective symptoms with even more precision (AUROC of 89%).

Diagnostic and prognostic information about numerous pathologies known to negatively affect neurobehavioral function—such as mental illness, traumatic brain injury, and chronic partial sleep deprivation—may be hiding in plain sight. More research regarding the clinical applicability of ABR is urgently needed.

# References

Carrubba S, Kim PY, McCarty DE, Chesson Jr. AL, Frilot C & Marino AA. Continuous EEG-based dynamic markers for sleep depth and phasic events. *J. Neurosci. Meth.* 208:1–9, 2012.

Frilot II C, Kim PY, Carrubba S, McCarty DE, Chesson Jr. AL & Marino AA. Analysis of brain recurrence. In Webber C & Marwan N, editors, *Applications of Recurrence Plot Analysis*. Springer, In Press.

Kim PY, McCarty DE, Wang L, Frilot II C, Chesson Jr. AL & Marino AA. Two-group classification of patients with obstructive sleep apnea based on analysis of brain recurrence. *Clin. Neurophysiol.* 2013 [Epub ahead of print.] DOI 10.1016/j.clinph.2013.11.002.

Wang L, Kim PY, McCarty DE, Frilot II C, Chesson Jr. AL, Carrubba S & Marino AA. EEG recurrence markers and sleep quality. *J. Neurol. Sci.* 331:26–30, 2013.

# Abbreviations

| | | | |
|---|---|---|---|
| ABR | Analysis of brain recurrence | LDA | Linear discriminant analysis |
| AUROC | Area under the receiver operating characteristics curve | MHI-5 | Mental Health Index-5 |
| BMI | Body mass index | RDI | Respiratory disturbance index |
| EEG | Electroencephalogram | SHHS | Sleep Heart Health Study |