EEG Entropy in REM Sleep as a Physiologic Biomarker in Early Clinical Stages of Alzheimer's Disease

By Metok Kogyal and William Bankhead

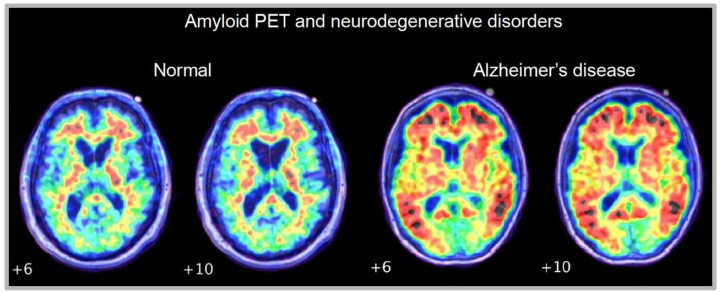
Objective:

To evaluate MFDE in awake and sleep EEGs as a potential biomarker for AD.

Background: Alzheimer's Disease (AD) Biomarkers

A biomarker is a measurement that indicates the status of cells or organisms in the body, and can signal the presence of a disease.

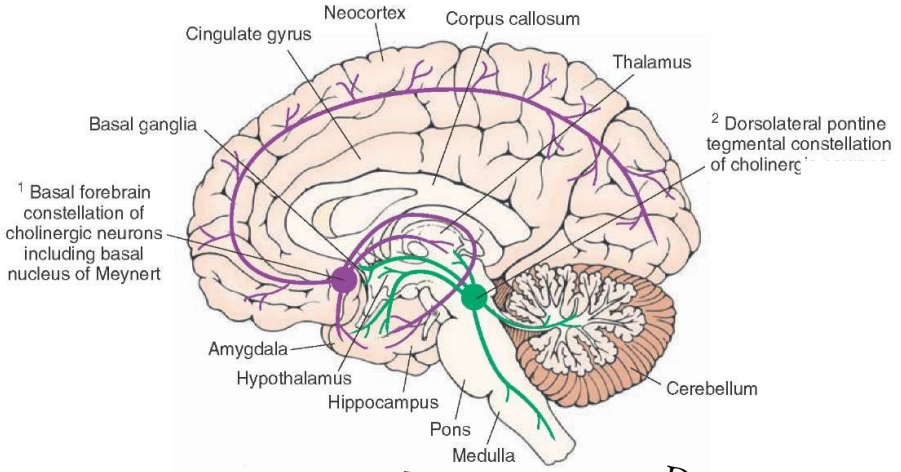
- amyloid and tau assessments w/PET imaging
- cerebrospinal fluid (CSF) analysis
- blood-based measurements in conjunction with ...
  - MRI measures of atrophy
  - CSF and blood analytes
  - fluorodeoxyglucose PET imaging
  - functional MRI
  - electroencephalography (EEG)



Background: EEG as a Biomarker for AD

- Scalp EEGs considered effective due to high temporal resolution measurements
- Many study awake-resting state EEG (rsEEG)
  - typically based on relative power spectral density (rPSD)
  - considered controversial, insufficient evidence to use as a biomarker
- Sleep EEG as an alternative
  - utilizes rapid eye movement (REM) sleep due to effect of AD on cholinergic neurons
  - even in NREM sleep that AD-like symptoms take effect
  - past study supports method of observing REM sleep for diagnosing AD
    - used measurements of slow-to-fast activity ratio of the power spectral density (SFAR-PSD)
    - slow frequencies associated with delta and theta, fast frequencies associated with alpha and beta

Background: Basal Forebrain Cholinergic Neurons (Purple)



Engages

Degenerated in early

REM Sleep ——— ——— ——— ——— ——— Alzheimer's Disease (AD)

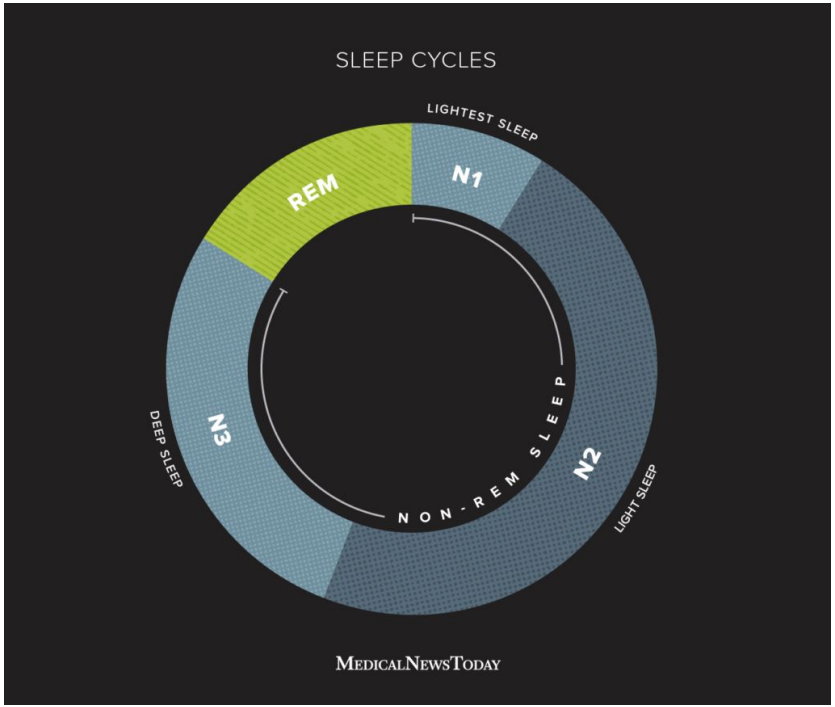
Background: EEG Entropy

Nonlinear dynamical approaches are best suited to measure constantly adapting cortical activity.

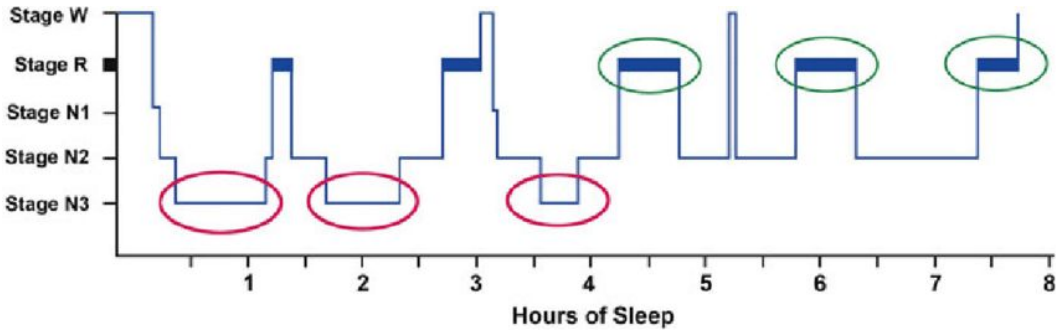
- Entropy generally used to measure nonlinear dynamics of EEG
- Still need to account for multiple-time scales
    - solution: multi scale fluctuation dispersion energy (MFDE)
    - MFDE can detect EEG fluctuation changes
    - ^ can be valuable in distinguishing AD from healthy controls

Methods

5 Stages of Sleep



Hypnogram of 8 hour sleep



Methods: EEG

Ambulatory EEG- Long-term monitoring

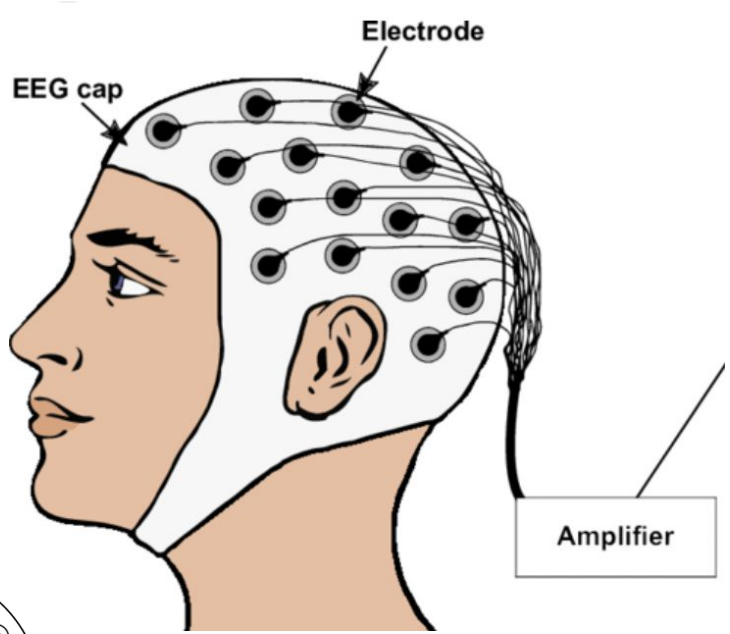
Convenient

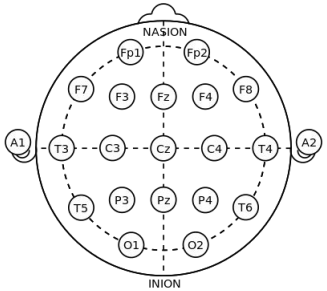
Low cost

10 - 48 hours

Scored using 5 sleep stages:

Regions: International 10-20 system





Methods: EEG Sleep Waves:

Relative alpha power = power of alpha band / total power in the frequency band

Alpha: 8-12 Hz - relaxed

Delta: 0.5-4 Hz - deep sleep

Note: REM sleep is similar to the Awake stage, therefore associated more with alpha waves compared to delta waves.

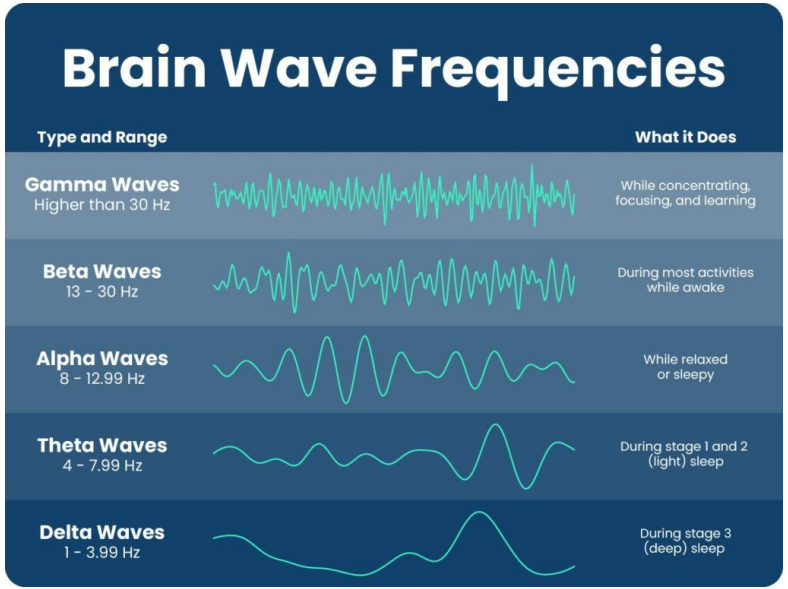


Table 1: Demographics

35 cognitively normal health controls

23 participants with mild cognitive impairment (MCI)

19 participants with mild dementia due to AD

Table 1
Study population demographics and sleep macro-architecture

	HC	MCI	DEM	ANOVA *p*
Participants (n)	35	23	19	–
Age, y (SD)	75.5 (6.9)	75 (6.9)	72.2(6)	NS
Female (# / %)	20 / 57%	15 / 65%	9 / 47%	NS
Years of Education (SD)	16.9 (2.7)	16.2 (2.3)	15.3 (3.4)	NS
Global CDR score (SD)	0 (0)	0.5 (0)	1 (0)	
Cholinesterase inhibitor use (# / %)	0 / 0%	9 / 39%	13 / 68%	p = 1e-8; HC versus MCI, p = 0.0004; HC versus DEM p = 1e-8; MCI versus DEM, p = 0.028
MoCA score (SD)	28 (1.8)	23.3 (3)	13.9 (6.4)	p = 2e-15; HC versus MCI, p = 1e-04; HC versus DEM p = 9e-10; MCI versus DEM, p = 3e-9
Sleep Macro-Architecture				
Total sleep, min (SD)	375 (88)	368 (105)	406 (99)	NS
N1 sleep, min (SD)	57 (29)	46 (24)	51 (26)	NS
N2 sleep, min (SD)	227 (72)	216 (73)	264 (92)	NS
N3 sleep, min (SD)	1 (3)	8 (21)	6 (18)	NS
REM sleep, min (SD)	89 (39)	98 (53)	85 (44)	NS
% N1 sleep	15% (7%)	13% (8%)	13% (7%)	NS
% N2 sleep	60% (10%)	59% (12%)	64% (13%)	NS
% N3 sleep	0.2% (0.8%)	2% (6%)	1.4% (4.3%)	NS
% REM sleep	24% (9%)	25% (10%)	21% (9%)	NS

SD, standard deviation.

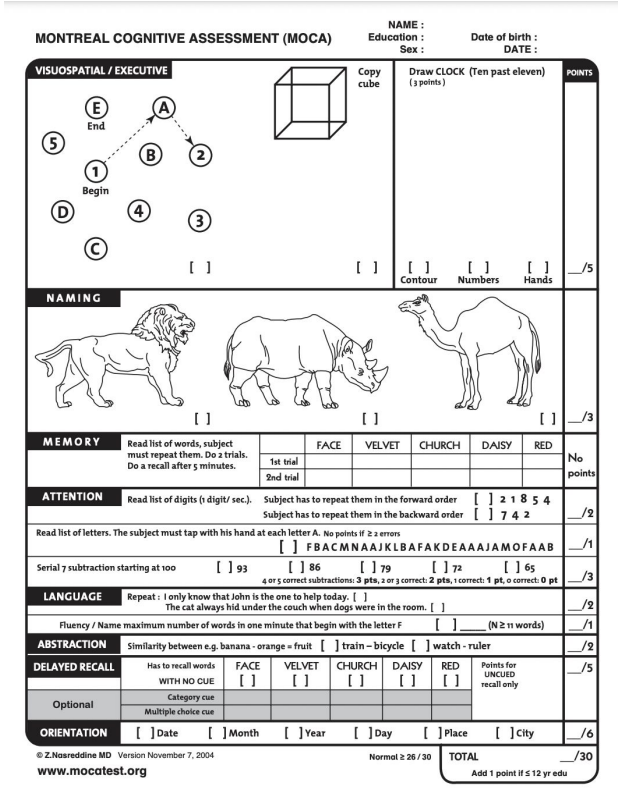
Cognitive Tests:

Montreal Cognitive Assessment (MoCA) -

Scored on 30 points and administered in approximately 10 minutes.

1. Short-term memory, Visuospatial abilities, Executive functions, Attention, concentration, and working memory, Language Orientation to time & place

2. a score of 26 or above is considered normal.



MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE — Copy cube — Draw CLOCK (Ten past eleven) (3 points) — POINTS

E End, A, B, 2, 5, 1 Begin, D, 4, 3, C — [ ] [ ] — [ ] Contour [ ] Numbers [ ] Hands — __/5

NAMING — [ ] [ ] [ ] — __/3

MEMORY — Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION — Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4. Subject has to repeat them in the backward order [ ] 7 4 2 — __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors — [ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B — __/1

Serial 7 subtraction starting at 100 — [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65 — 4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt — __/3

LANGUAGE — Repeat : I only know that John is the one to help today. [ ] The cat always hid under the couch when dogs were in the room. [ ] — __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words) — __/1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler — __/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION — [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City — __/6

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Normal ≥ 26 / 30

TOTAL __/30
Add 1 point if ≤ 12 yr edu

Results

Figure 1

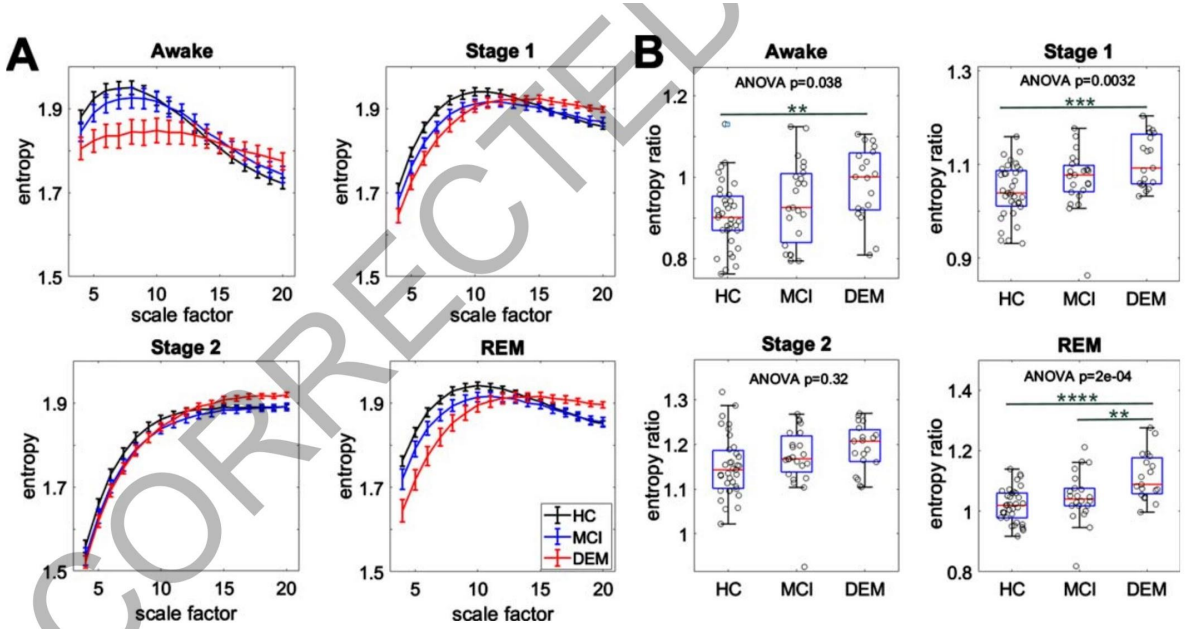
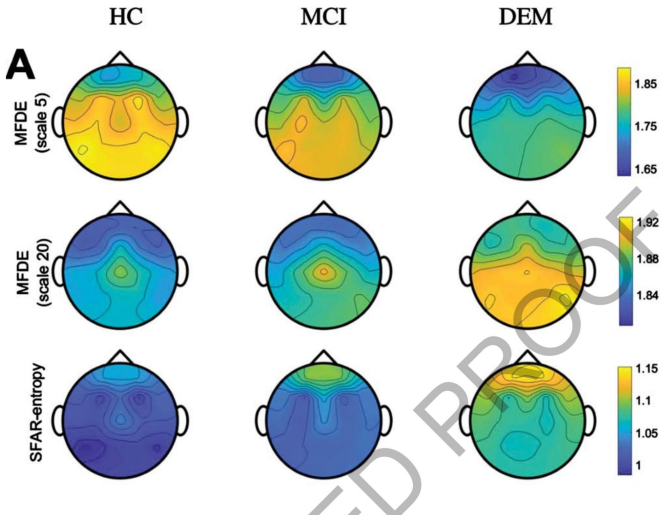


Fig. 1. Assessment of whole-brain averaged MFDE across the sleep-wake cycle in AD. A) Whole brain-averaged multiscale fluctuation dispersion entropy (MFDE) measured from EEG across awake and sleep states in 35 HC (black), 23 MCI (blue), and 19 DEM (red) participants. B) Slow-to-fast activity ratio for MFDE (SFAR-entropy) across awake and sleep states for HC, MCI, and DEM. ANOVA p-values are shown for each boxplot (Bonferroni corrected). Statistically significant *post-hoc* comparisons with p-values<0.01, 0.001, and 0.0001 are shown with **, ***, and ****, respectively.

Figure 2



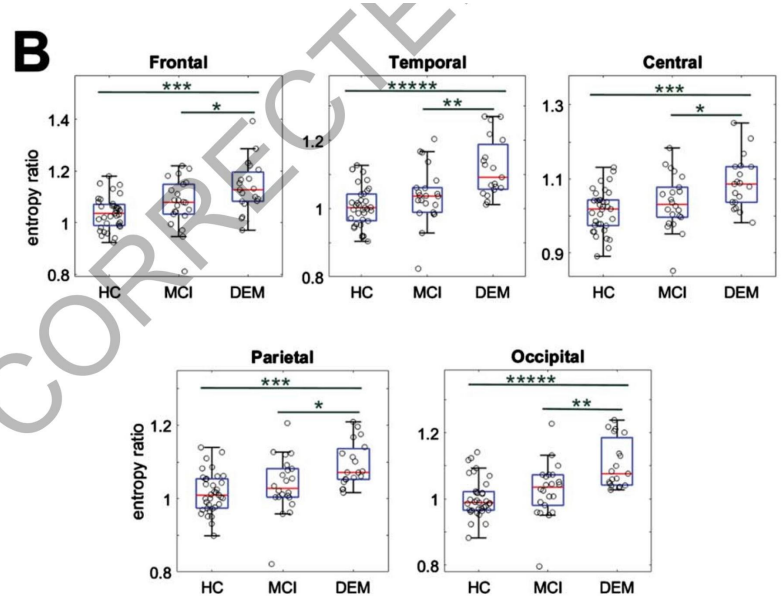


Fig. 2. Evaluation of regional REM sleep-associated MFDE changes in AD. A) Topoplots of averaged MFDE values during REM sleep at scale 5 (top row) and scale 20 (middle row), and the ratio of MFDE at scale 20 to scale 5 (SFAR-entropy, bottom row) for HC, MCI, and DEM. B) SFAR-entropy in the frontal (ANOVA, $p = 1e\text{-}03$), temporal (ANOVA, $p = 2e\text{-}05$), central (ANOVA, $p = 2e\text{-}03$) parietal (ANOVA, $p = 1e\text{-}03$), and occipital (ANOVA, $p = 3e\text{-}05$) regions for HC, MCI, and DEM. ANOVA p-values are Bonferroni corrected. Group differences with p-values<0.05, 0.01, 0.001, 0.0001, and 0.00001 are shown with *, **, ***, ****, and *****, respectively.

Figure 3

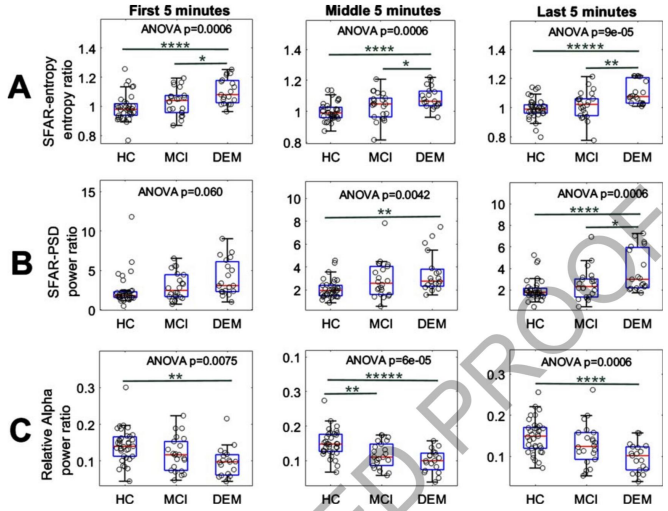


Fig. 3. Assessment of SFAR-entropy and SFAR-PSD measures across REM cycles in the night. All measures were calculated in the occipital region. A) The slow-to-fast activity ratio of MFDE (SFAR-entropy) for the first, middle, and last 5 min of REM sleep, for HC, MCI, and DEM. B) SFAR-PSD for the first, middle, and last 5 min of REM sleep, for HC, MCI, and DEM. C) Relative alpha power for the first, middle, and last 5 min of REM sleep, for HC, MCI, and DEM. The ANOVA omnibus *p*-value is listed in each boxplot (Bonferroni corrected). The Tukey *post-hoc* comparisons with *p*-values smaller than 0.05, 0.01, 0.001, 0.0001, and 0.00001 are shown with *, **, ***, ****, and *****, respectively.

Table 2
Coefficient of variation (CV) for SFAR-entropy, SFAR-PSD, and relative alpha power in HC, MCI, and DEM

	SFAR-entropy	SFAR-PSD	Relative alpha power	ANOVA *p*-value

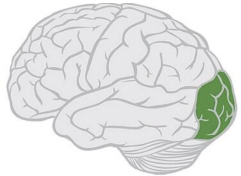
CV in HC (mean ± SD)	0.06 ± 0.02	0.45 ± 0.40	0.24 ± 0.07	p = 1e-09;
				entropy vs. PSD, p = 1e-09;
				entropy vs. alpha, p = 0.0047;
				PSD vs. alpha, p = 6e-04

CV in MCI (mean ± SD)	0.06 ± 0.03	0.40 ± 0.14	0.26 ± 0.06	p = 2e-18;
				entropy vs. PSD, p = 1e-10;
				entropy vs. alpha, p = 2e-09;
				PSD vs. alpha, p = 4e-06

CV in DEM (mean ± SD)	0.06 ± 0.02	0.32 ± 0.10	0.26 ± 0.07	p = 1e-16;
				entropy vs. PSD, p = 1e-10;
				entropy vs. alpha, p = 1e-10;
				PSD vs. alpha, p = 0.016

SD, standard deviation.

Figure 4



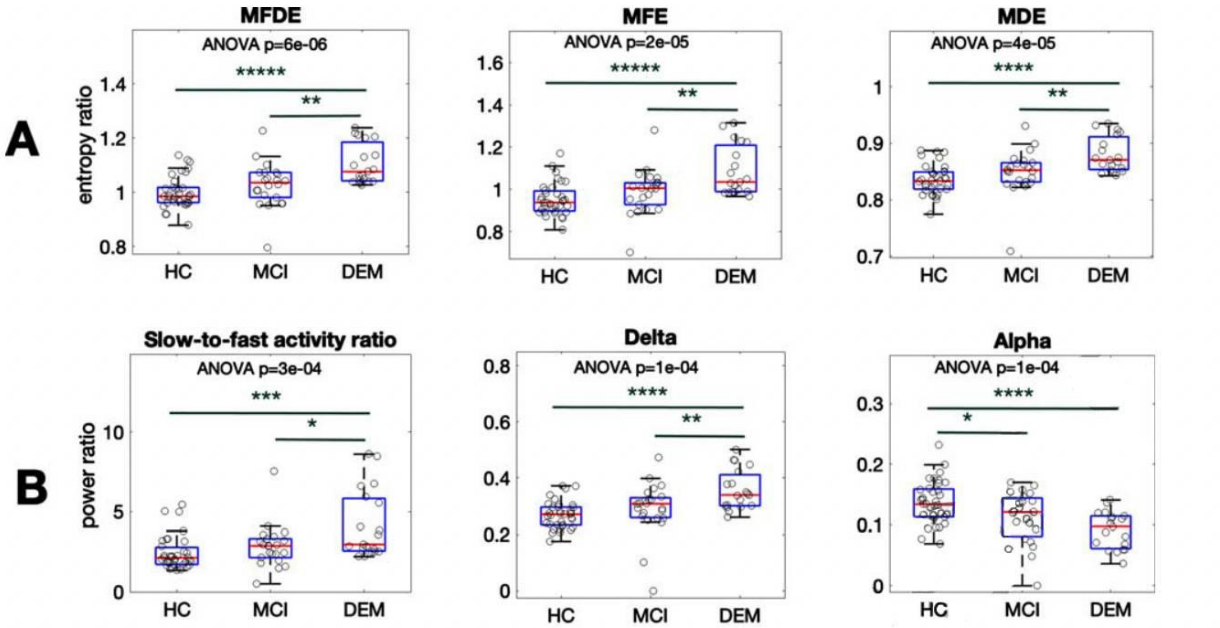

A
MFDE
ANOVA p=6e-06
*****
**
entropy ratio
1.4
1.2
1
0.8
HC
MCI
DEM
MFE
ANOVA p=2e-05
*****
**
1.6
1.4
1.2
1
0.8
HC
MCI
DEM
MDE
ANOVA p=4e-05
****
**
1
0.9
0.8
0.7
HC
MCI
DEM
B
Slow-to-fast activity ratio
ANOVA p=3e-04
***
*
power ratio
10
5
0
HC
MCI
DEM
Delta
ANOVA p=1e-04
****
**
0.8
0.6
0.4
0.2
0
HC
MCI
DEM
Alpha
ANOVA p=1e-04
****
*
0.3
0.2
0.1
0
HC
MCI
DEM

Figure 5: Global Cognitive Function

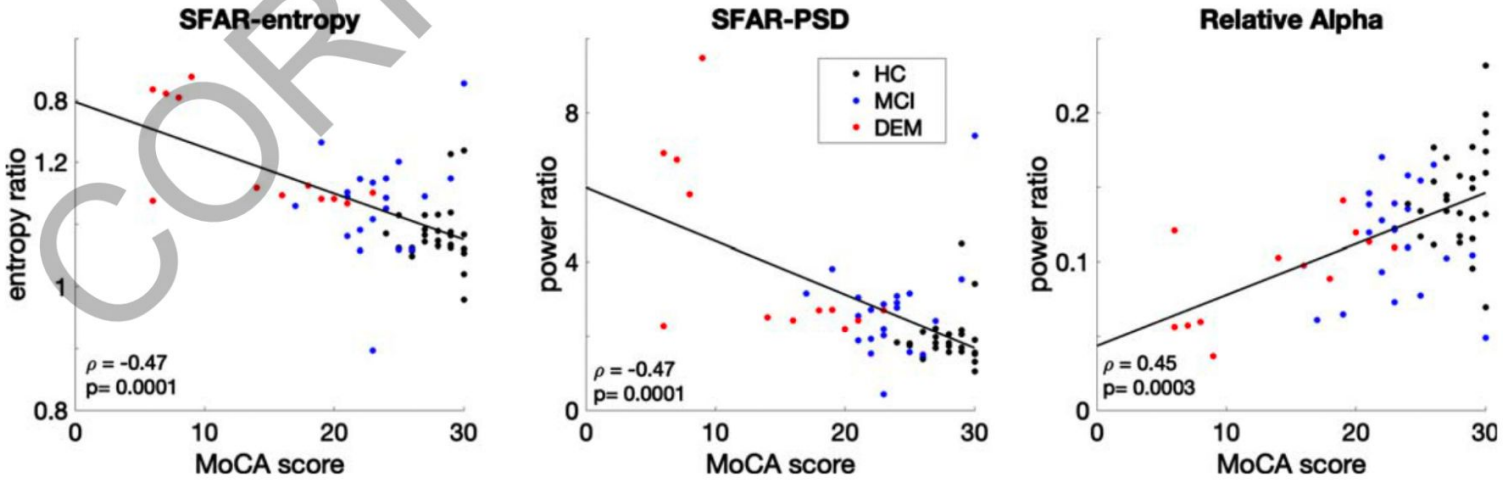


Fig. 5. Correlation between SFAR-entropy, SFAR-PSD, and relative alpha with MoCA scores. SFAR-entropy (left), SFAR-PSD (middle), and relative alpha (right) were calculated from the occipital region during REM sleep. Spearman correlations are shown.

Figure 6

Expected for random classifier.

False Positive Rate- Probability of making a false positive.

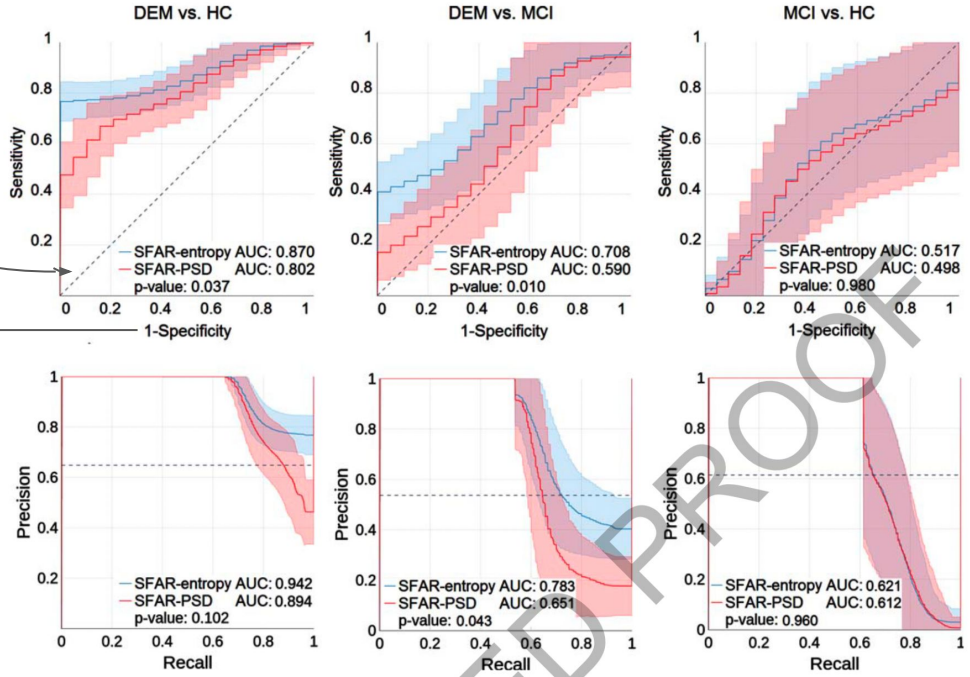


Fig. 6. Classification performance of SFAR-entropy and SFAR-PSD in REM sleep in discriminating HC, MCI, and DEM. ROC (top row) and PR (bottom row) curves for logistic regression classifiers based on SFAR-entropy (blue) and SFAR-PSD (red), for discrimination between DEM versus HC (left), DEM versus MCI (middle), and MCI versus HC (right). Both SFAR-entropy and SFAR-PSD were calculated from the occipital region during REM sleep. Shaded regions represent the 95% confidence intervals for each curve based on bootstrapping. Black dashed lines represent the expected performance for a random classifier.

Discussion: What this paper accomplishes

This paper evaluates the use of EEG entropy as a potential test and biomarker for early stages of Alzheimer's.

1. Slow-to-fast-activity MFDE ratio (SFAR-entropy) differentiated DEM from both MCI and HC in REM sleep. (Just 5 minutes of REM sleep was sufficient to differentiates)
2. Pattern of discrimination remained stable across REM cycles throughout the night.
3. Increases in SFAR-entropy and SFAR-PSD were associated with worse performance on the Montreal Cognitive Assessment.
4. On the logistic regression models, the SFAR-Entropy model significantly distinguished between DEM vs. HC and DEM vs. MCI, outperforming the SFAR-PSD model in accuracy and variability.

Discussion: Strengths & Weaknesses

This paper evaluates the use of EEG entropy as a potential test and biomarker for early stages of Alzheimer's.

1. Well-characterized clinical populations of both DEM and MCI (similar age and demographics)
2. Correlations shown across a wide range of measures (entropy and spectral measures) with similar trends.
3. Successful trials for differentiating between groups DEM vs. HC and DEM vs. MCI.

—

1. The methods in which patients were gathered: no biomarker/neuropathological evidence.
2. Need further evidence to form a conclusion on the NREM3 sleep state.

Discussion Questions:

1. What are some of the advantages of using EEG entropy as a biomarker for the early stages of Alzheimer's?

2. How might a clinician use these results in testing for Alzheimer's related dementia ?

3. What are some future areas of study that could be explored, based on the results? Consider strengths and limitations of this study.