Raw and Quantitative EEG for Identification of Ischemia

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Disclosures

- None relevant to this presentation
- Scientific Advisory Board
  - Eisai Inc.
  - Biotie, Inc.
- Research
  - UCB Pharma
  - Acorda Therapeutics
  - Epilepsy Therapy Development Project
  - Sage Pharmaceuticals
  - NeuroPace, Inc.
  - Pfizer

Detection of Ischemia

- During and after vascular neurosurgical or interventional neuroradiology procedures
- After subarachnoid hemorrhage
- In patients with hemodynamic lesions and borderline flow
- In other patients at risk for in-hospital acute ischemia

Hirsch LJ. J Clin Neurophysiol 2004;21:332-340.
Herman ST et al. J Clin Neurophysiol 2015; 32: 87-95.

Cerebral Ischemia

- EEG changes occur within 5 minutes of acute ischemia
  - Superior to current imaging techniques
  - Reversible stage

ml/100g/min	EEG change	Reversibility
35-70	Normal	No injury
25-35	Loss of beta	Reversible
18-25	Theta slowing	Reversible
12-18	Delta slowing	Reversible
< 8-10	Suppression	Irreversible

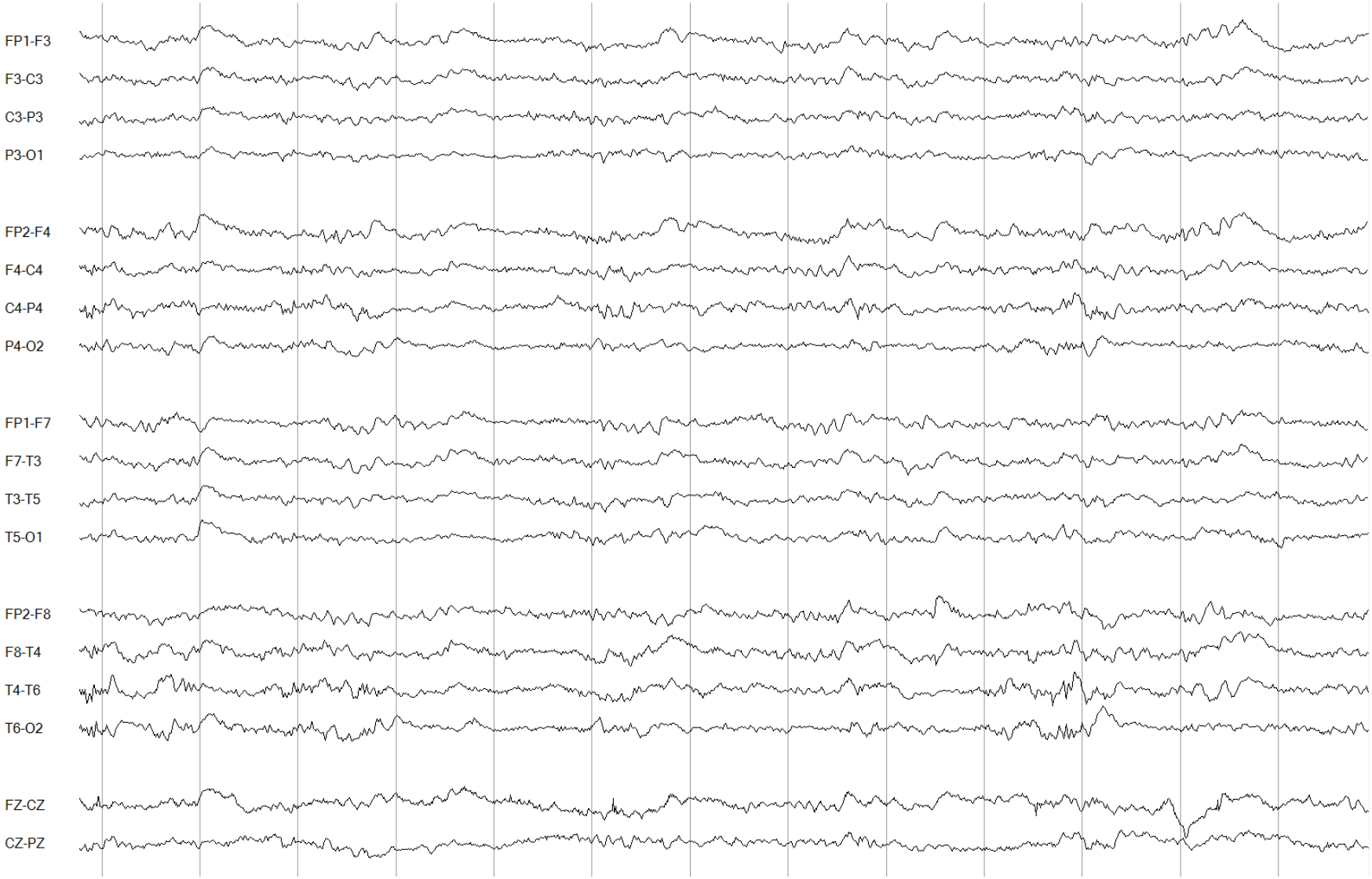
Astrup et al. Stroke 1981;12:723-725.
Jordan KG. J Clin Neurophysiol 2004;21:341-352.

EEG and Cerebral Ischemia

- Intraoperative monitoring during carotid artery occlusion
  - EEG can detect important changes in CBF
- Hemispheric EEG slowing
  - Correlates with moderate to severe reductions in CBF on stable Xenon CT
- Mean dominant EEG frequency
  - 6.5 Hz correlated with CBF 33 to 39 ml/100 g/min
  - 7.8 Hz correlated with CBF 47 ml/100 g/min

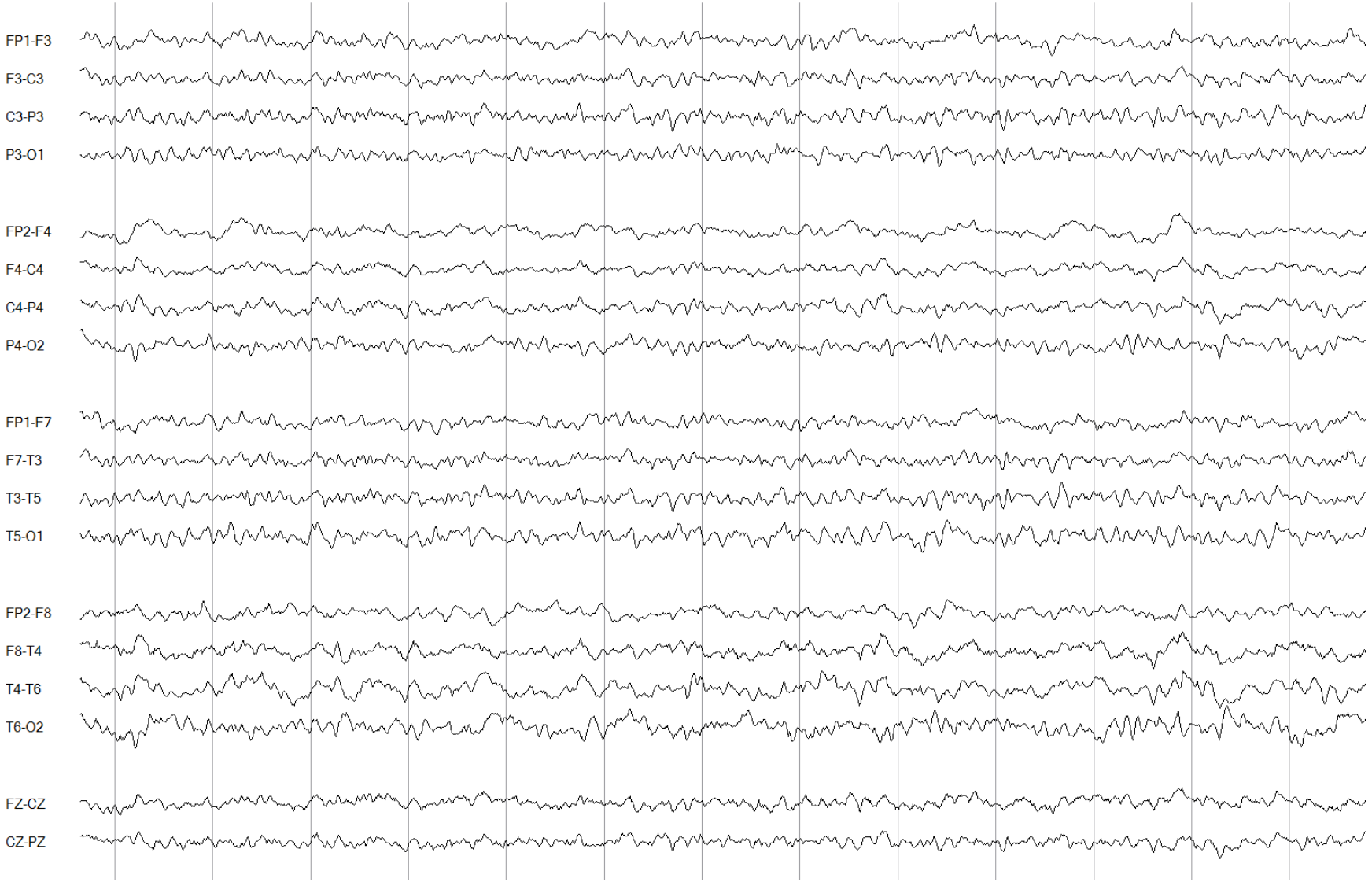
Vespa et al., EEG Clin Neurophys 1997;103:607-615
Sundt et al., Mayo Clin Proc 1981;56:533-543

Carotid Endarterectomy: Baseline

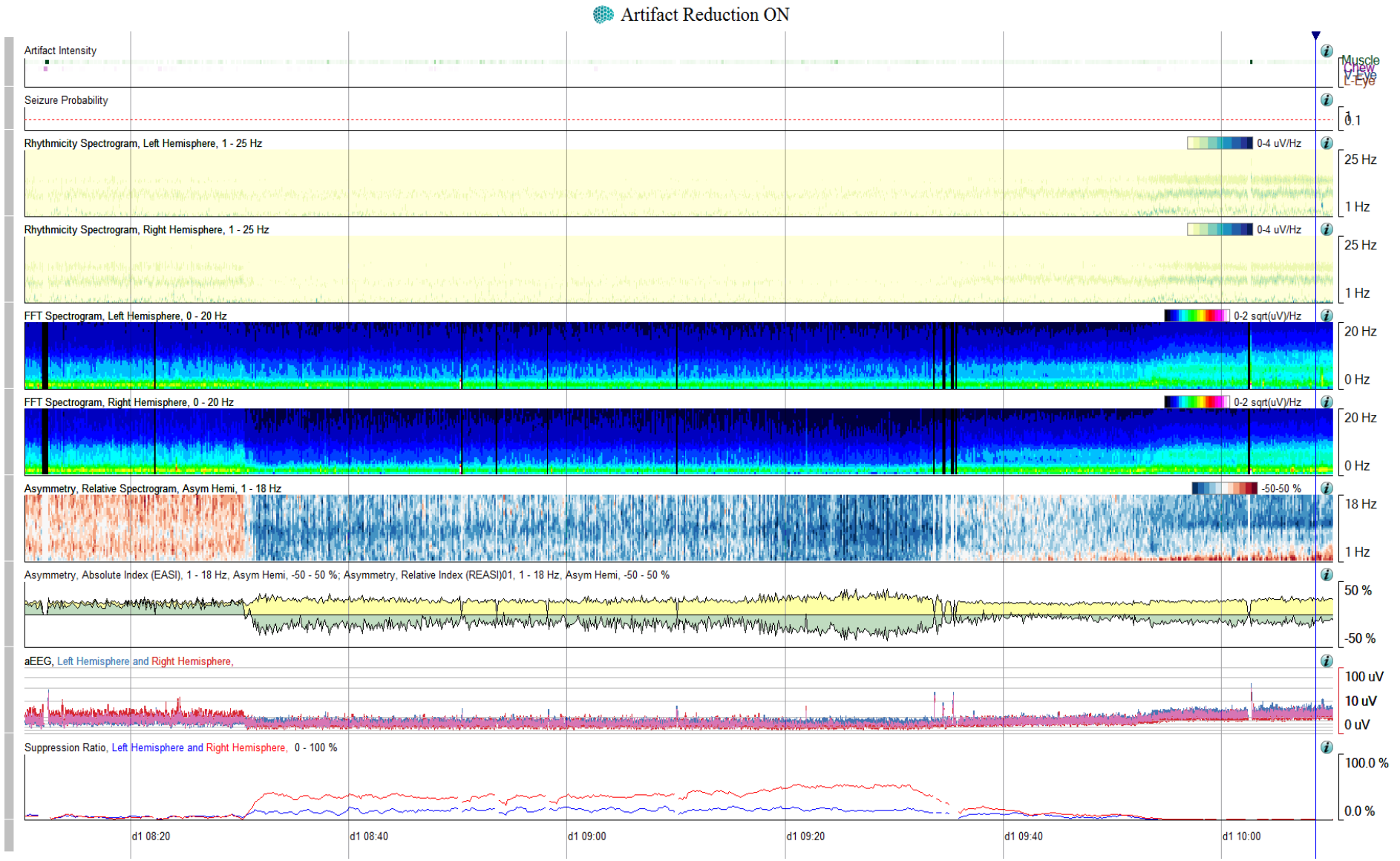


Carotid Endarterectomy: Intra-op

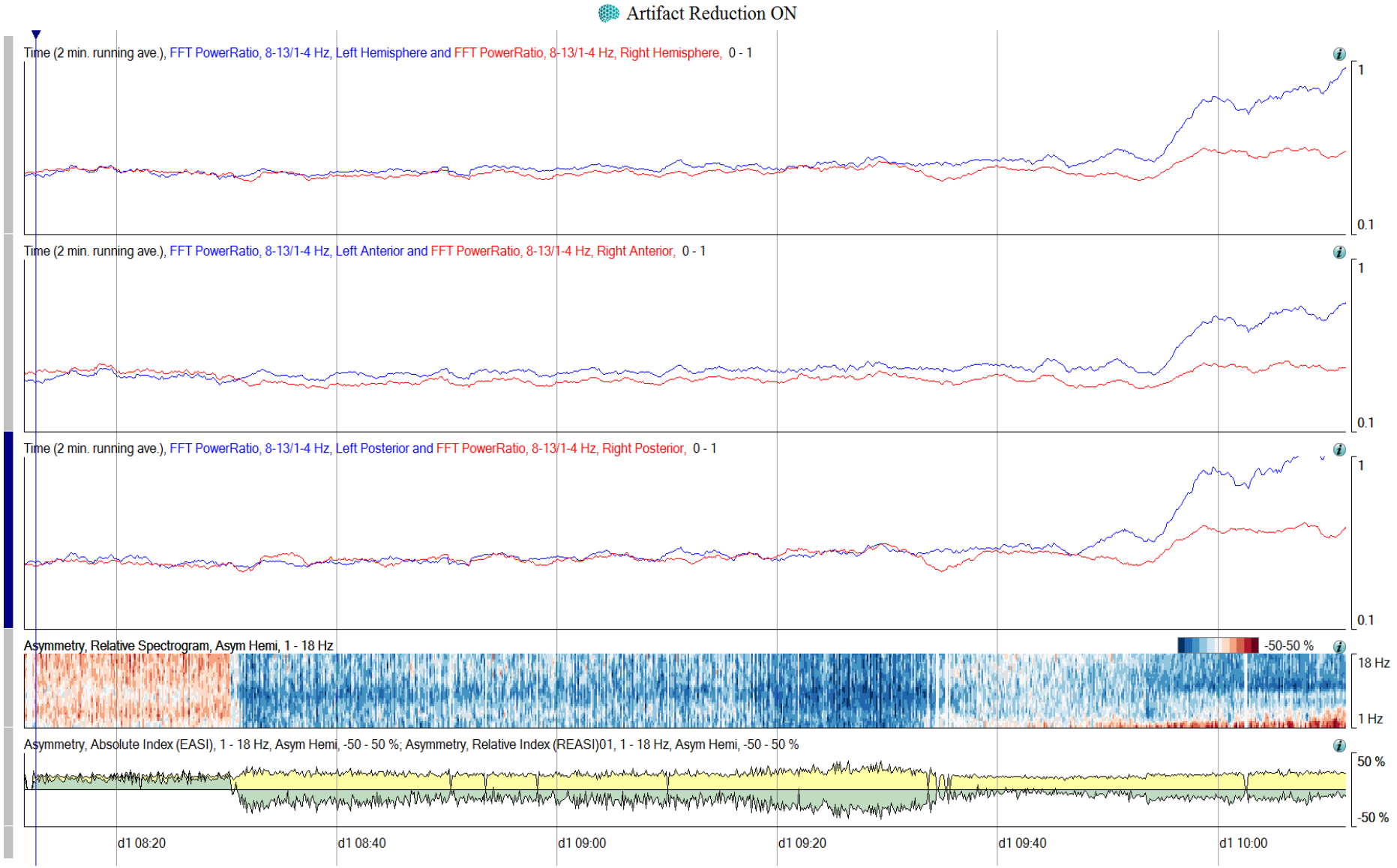
Carotid Endarterectomy: Post-CEA



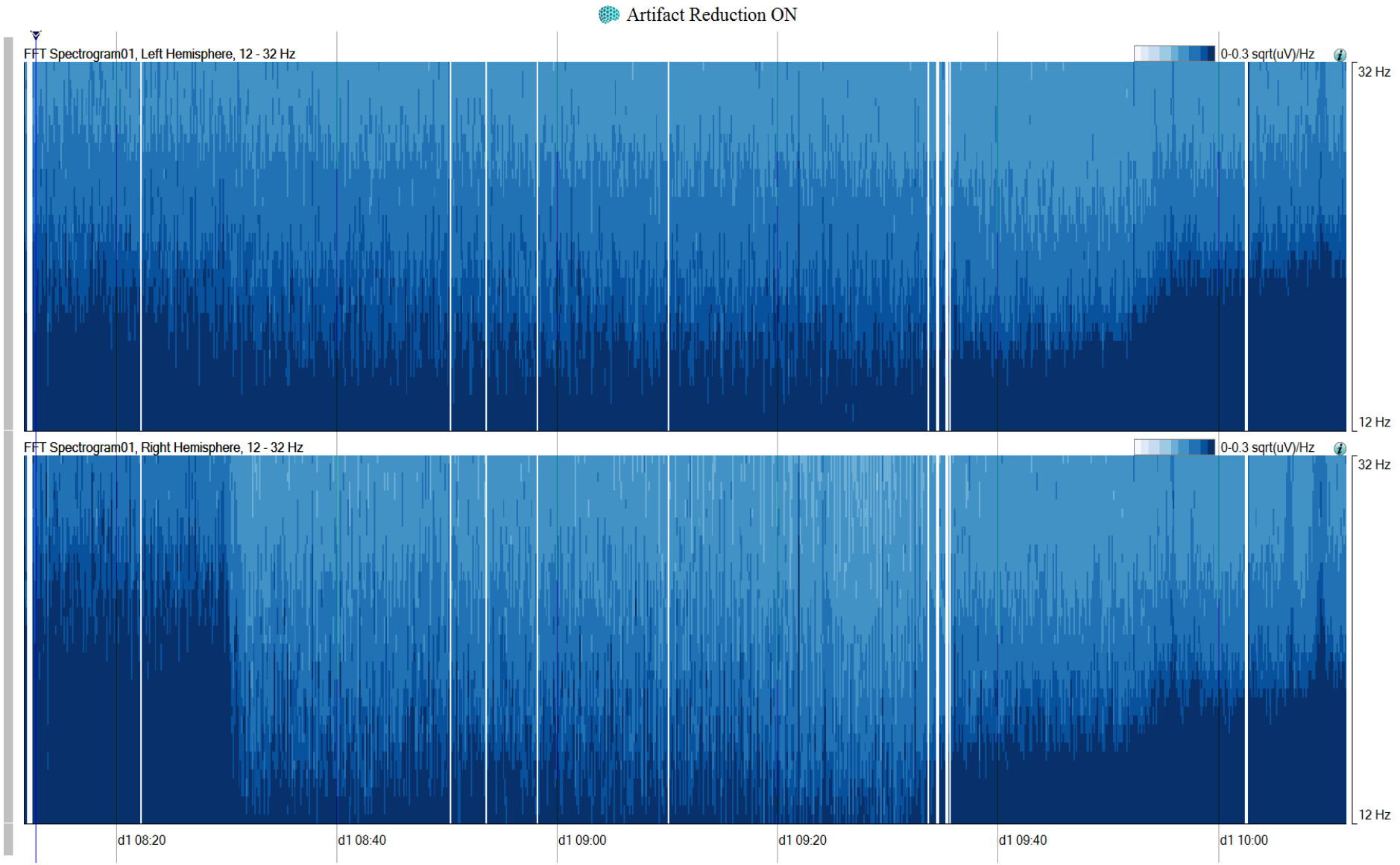
Carotid Endarterectomy: Trends



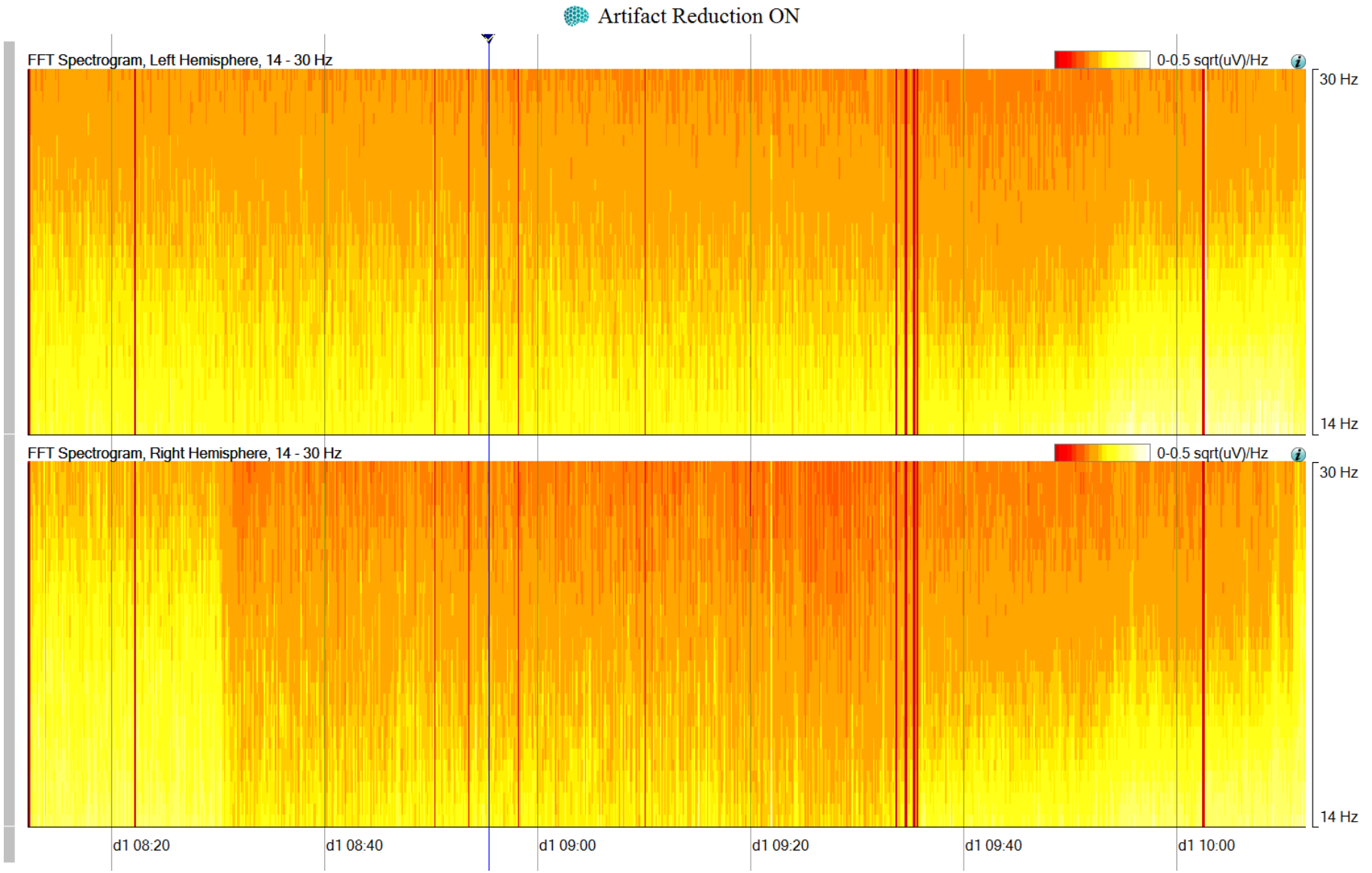
Carotid Endarterectomy: Alpha-Delta



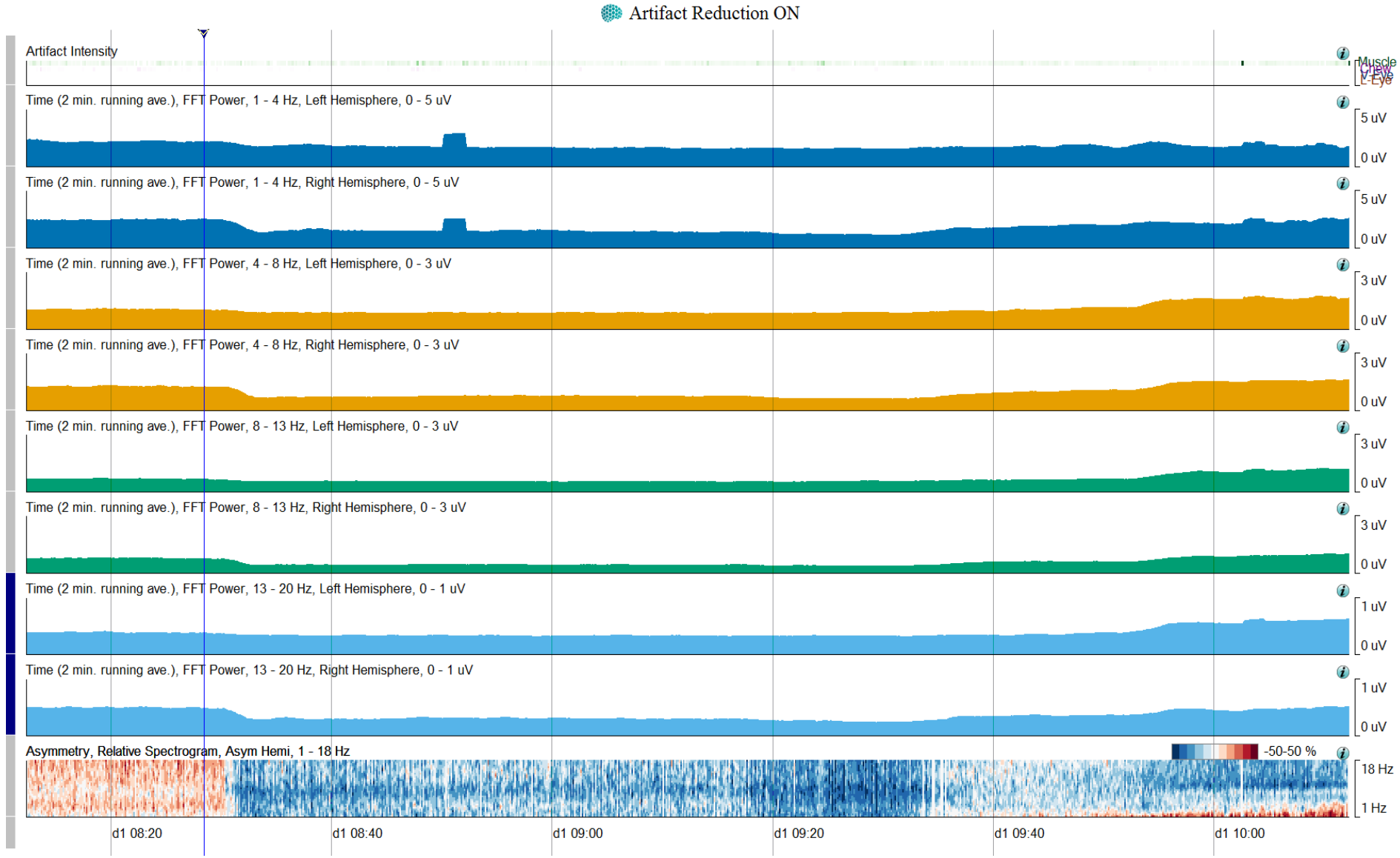
Beta Asymmetry



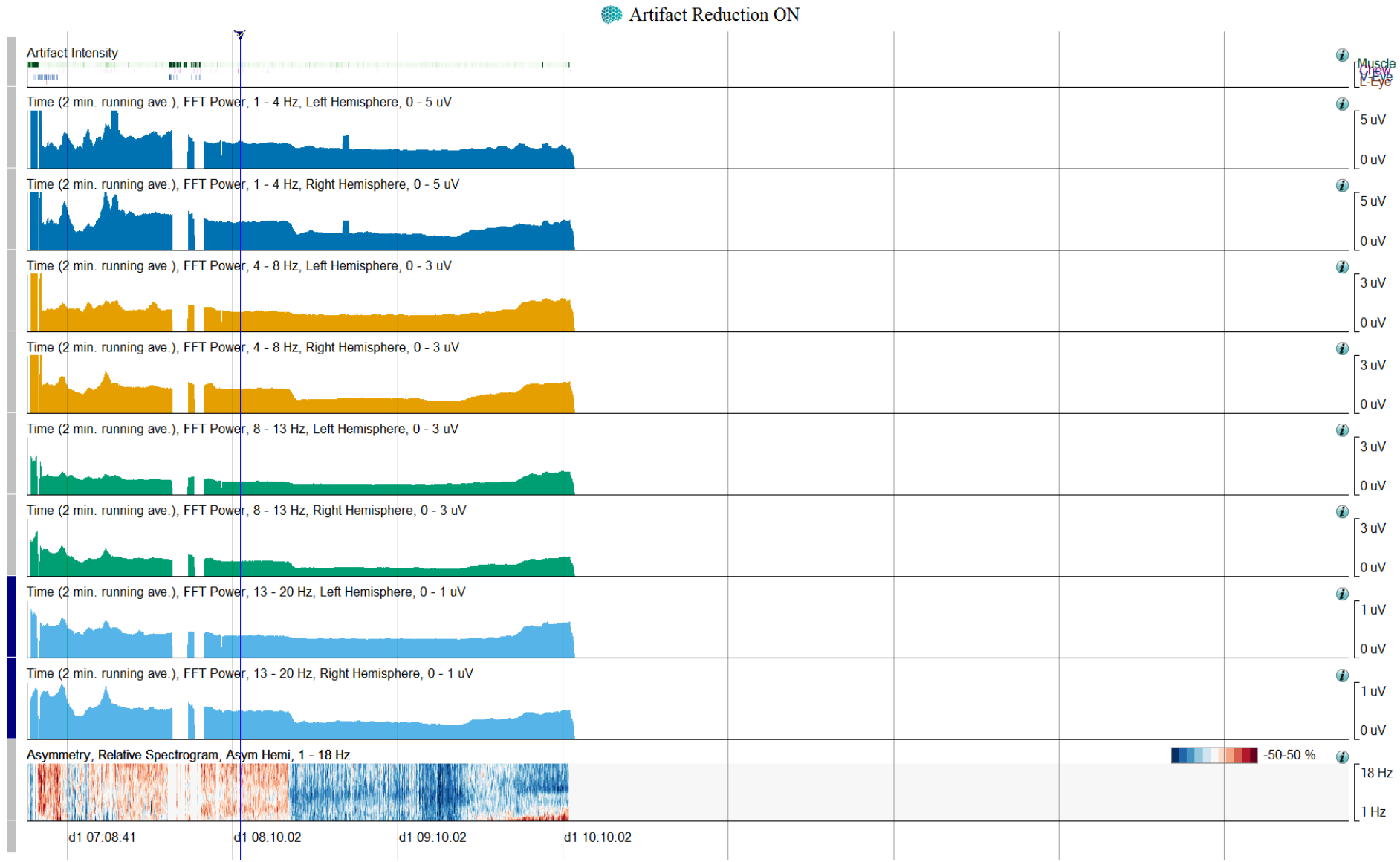
Beta Asymmetry



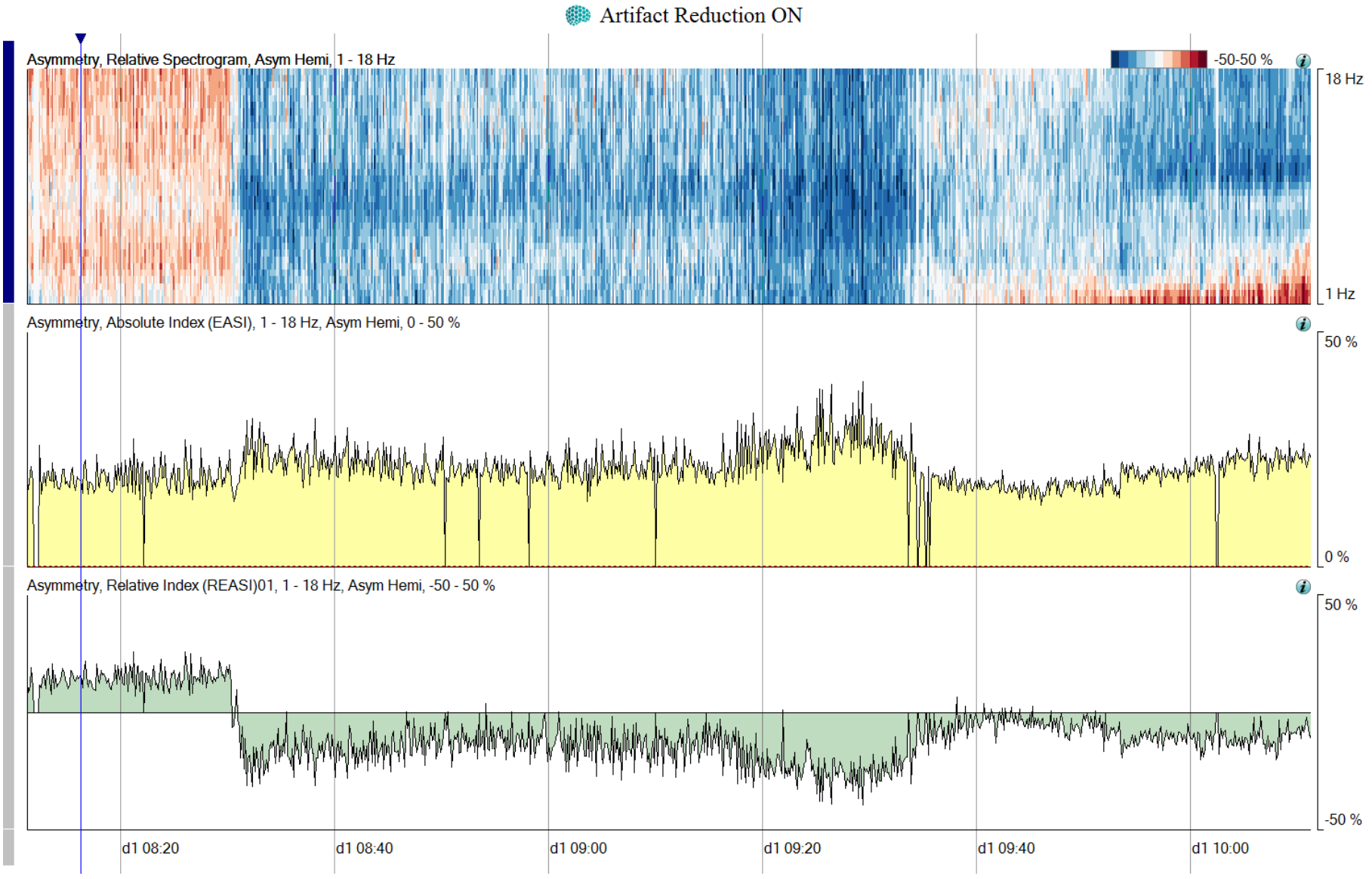
Carotid Endarterectomy: Ischemia



Carotid Endarterectomy: Ischemia



Carotid Endarterectomy, Ischemia



Delayed Cerebral Ischemia (DCI)

- New focal or global neurological deficit and/or new infarction after SAH (exclude rebleeding / hydrocephalus)
- Days 3 – 14 after SAH
- Major cause of cerebral ischemia and morbidity
- Occurs in 19-46% of patients
  - Infarct in ~ 60%
  - Subclinical in 25%, associated with poor outcome
- Risk factors
  - Poor Hunt-Hess grade
  - Large amounts of cisternal blood

1. Charpentier et al. Stroke 1999;30:1402-1408
2. Claassen et al. Stroke 2001;32:2012-2020
3. Qureshi et al. Crit Care Med 2000;28:984-990

Subarachnoid Hemorrhage

- Pathophysiology
  - Vasospasm of large vessels
  - Microembolism
  - Vasospasm of peripheral arteries and arterioles (as opposed to proximal large vessels)
  - Cortical spreading ischemia
- DCI is treatable if diagnosed during reversible phase
  - Hypertension
  - Volume expansion
  - Intraarterial nicardipine, papaverine
  - Angioplasty
- Long window for intervention (2-6 hours)

Connolly ES et al. Stroke 2012;43:1711-1737

Monitoring for Vasospasm

- Clinical examination
  - Patient often sedated, uncooperative
- Daily Transcranial Dopplers (TCDs)
  - “Snapshot” in time
  - Only monitors for vasospasm, not other causes of ischemia
  - Mediocre sensitivity and specificity
- Conventional angiography
  - Performed if above suggestive of ischemia
  - Invasive
- Brain imaging (CT, CTA, and MRI)
  - Performed if above suggestive of ischemia

Diringer MN et al. Neurocrit Care 2011;15:211-240

Labar: EEG Monitoring in SAH

- 21 patients with aneurysmal SAH
- 2 channel EEG (Cz-T3, Cz-T4)
- Automatic artifact detection methods (excess of the dynamic range of amplifiers, zero-derivative signals, and excessive 60 Hz interference)
- Compressed spectral analysis (1-30 Hz)
- Trend analysis
  - Sum of the power (total power), 1-30 Hz
  - Centroid of the frequency, 1-30 Hz
  - Power 7.5-15 Hz / power 1-7 Hz ('alpha ratio‘)
  - Power 1-3.5 Hz / power 1-30 Hz ('percent delta')

Labar DR et al., Electroencephalogr Clin Neurophysiol 1991;78:325-332

Labar: EEG Monitoring in SAH

EEG Finding	EEG Parameter	Focal CT lesions (N)	All ischemic events (N)
Change in power	Trend analysis	100% (5)	91% (11)
	Compressed spectral array	33% (6)	44% (18)
Change in frequency	Centroid	60% (5)	55% (11)
	Relative alpha	60% (5)	64% (11)
	Percent delta	80% (5)	45% (11)
	Compressed spectral array	17% (6)	39% (18)

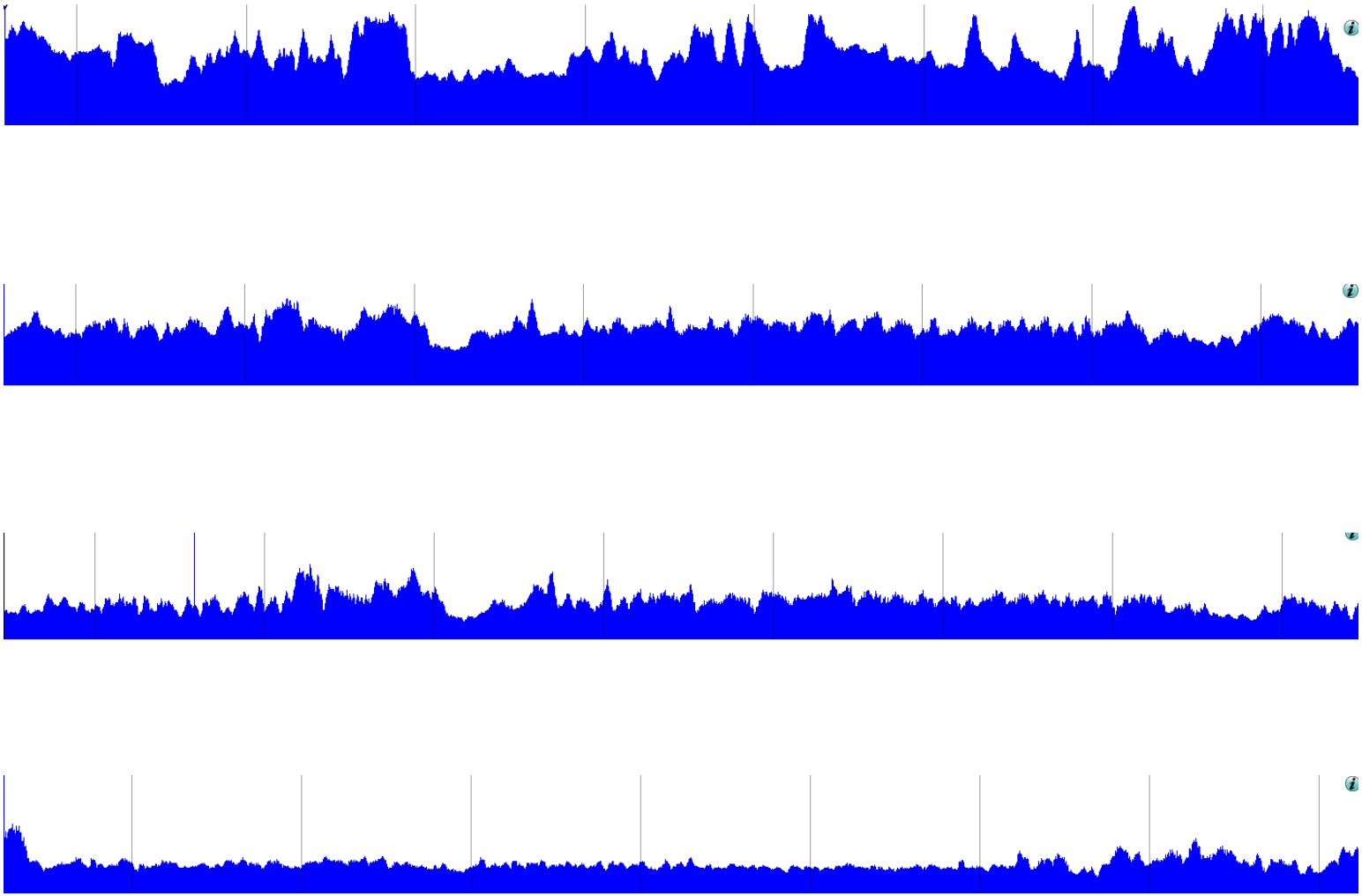
Labar DR et al., Electroencephalogr Clin Neurophysiol 1991;78:325-332

Vespa: EEG Monitoring in SAH

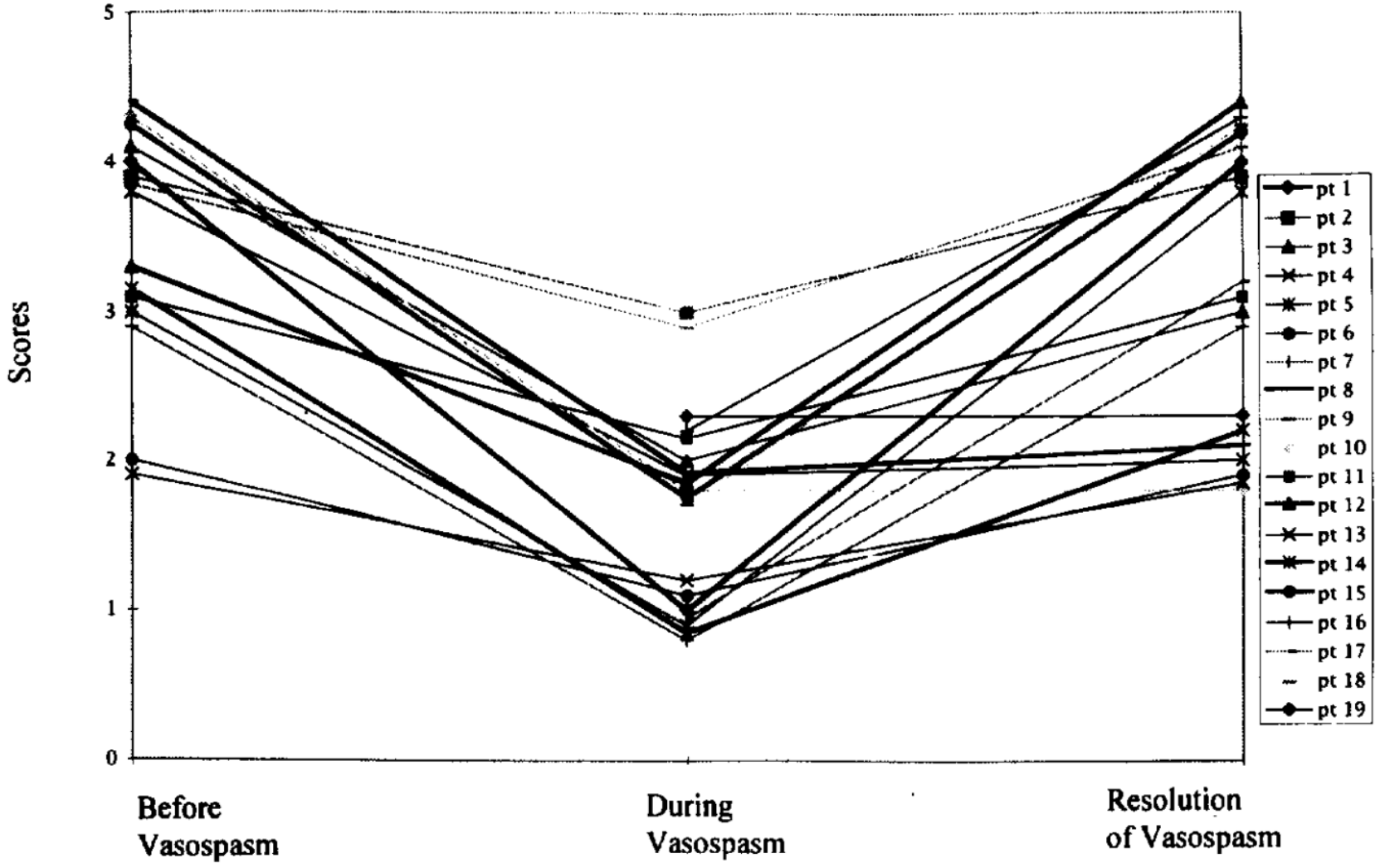
- 32 patients with aneurysmal SAH
- Reduction in variability of theta-alpha content (6-14Hz)
  - Ratio of power in 6-14Hz band relative to power in 1-20Hz band
- Sensitivity 100%
- Specificity 50% (increased ICP, recurrent hemorrhage, hydrocephalus, embolic stroke during angio)
- Preceded clinical onset of vasospasm and elevated TCD velocities in 70%
  - Mean 2.9 days

Vespa et al., EEG Clin Neurophys 1997;103:607-615

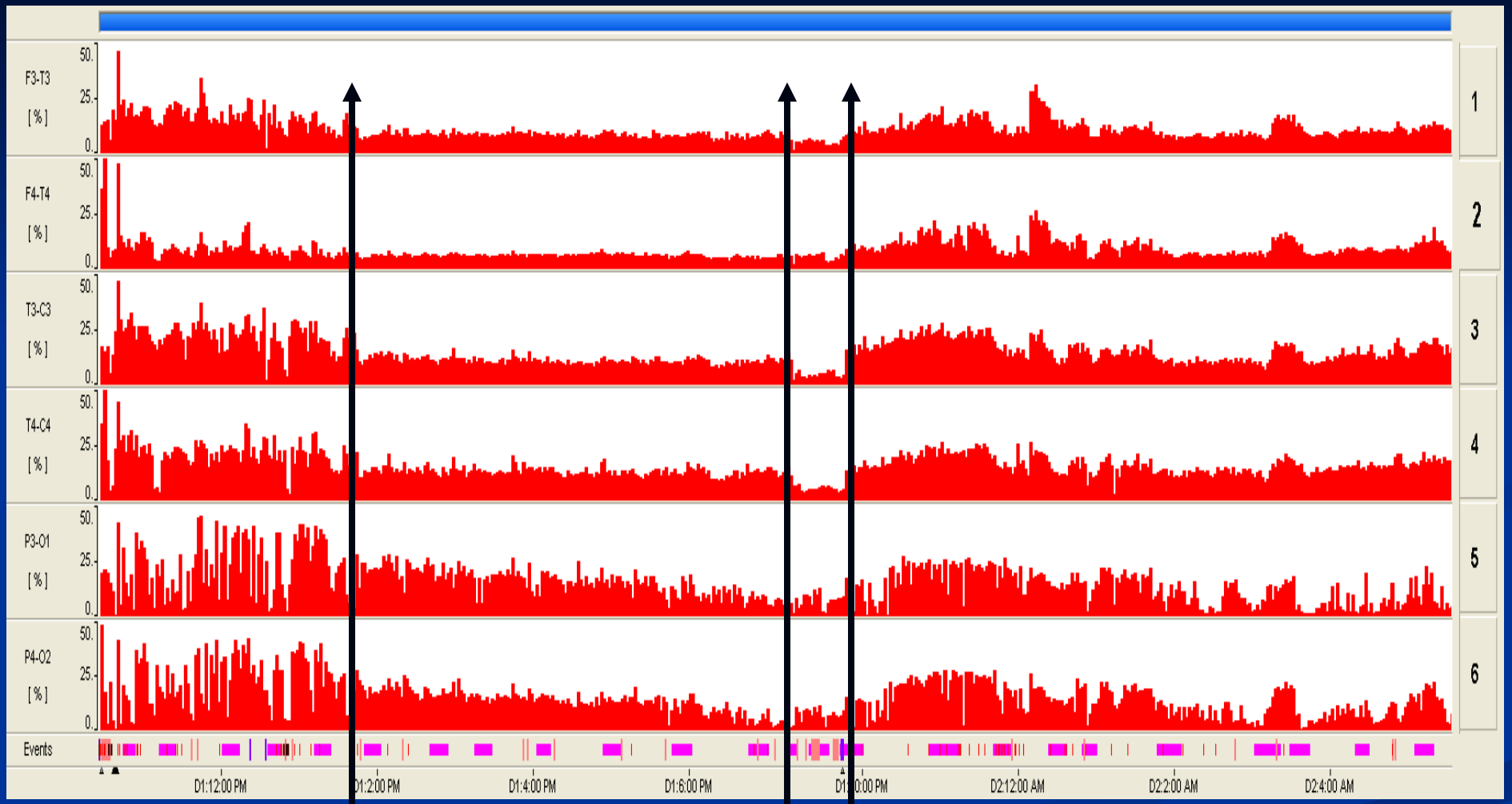
Alpha Variability



Vespa: EEG Monitoring in SAH



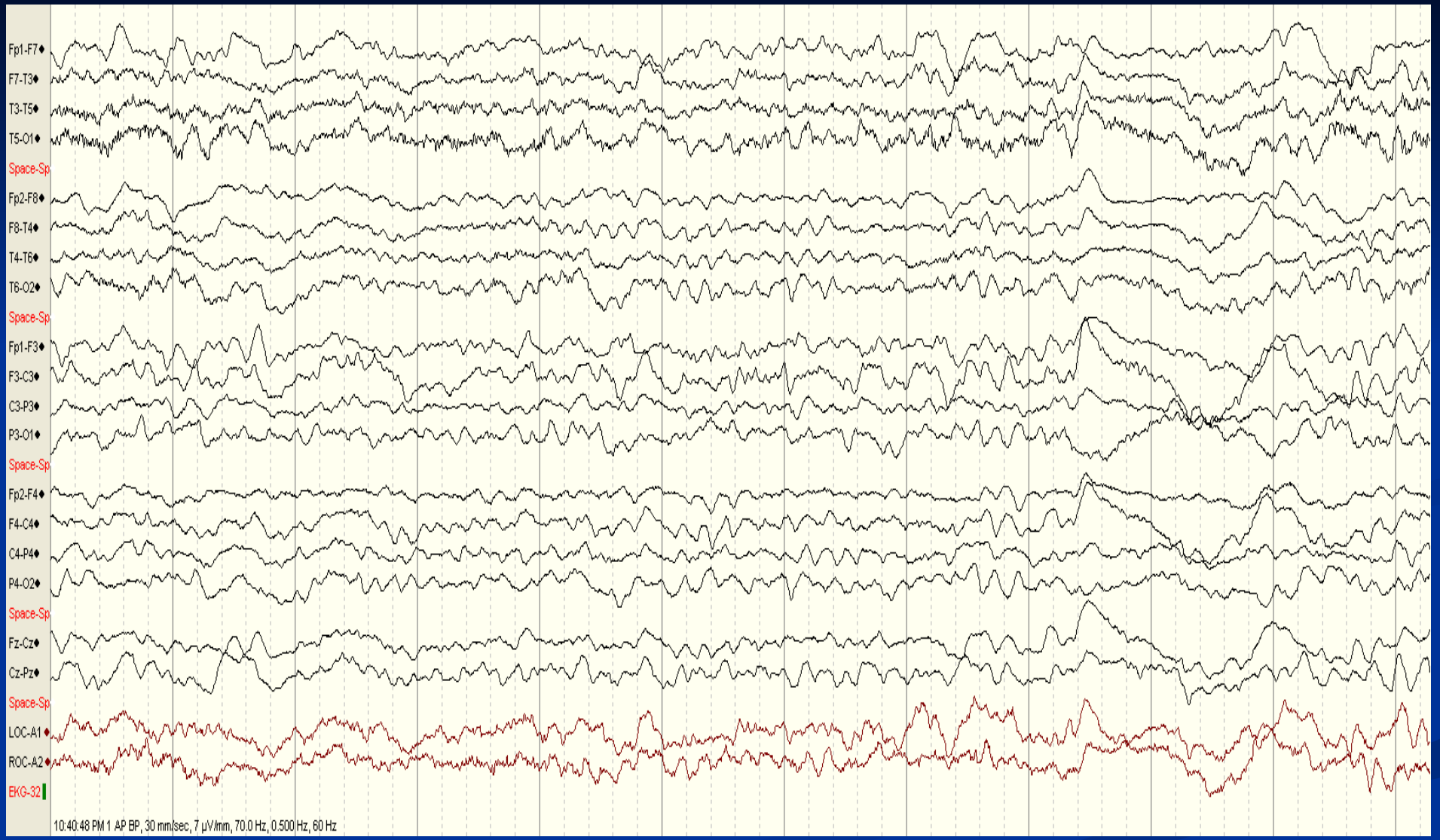
Vespa et al., EEG Clin Neurophys 1997;103:607-615

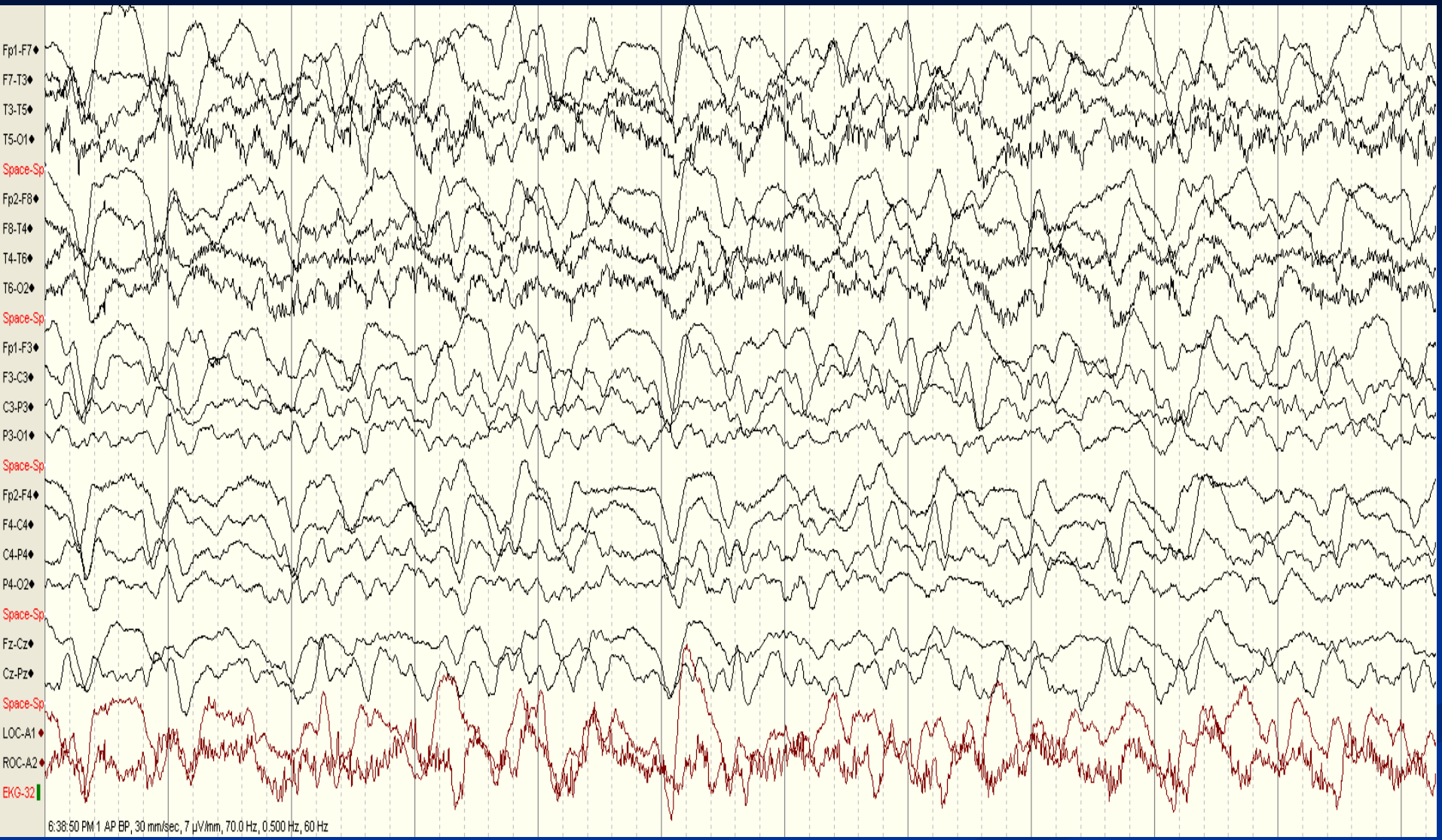


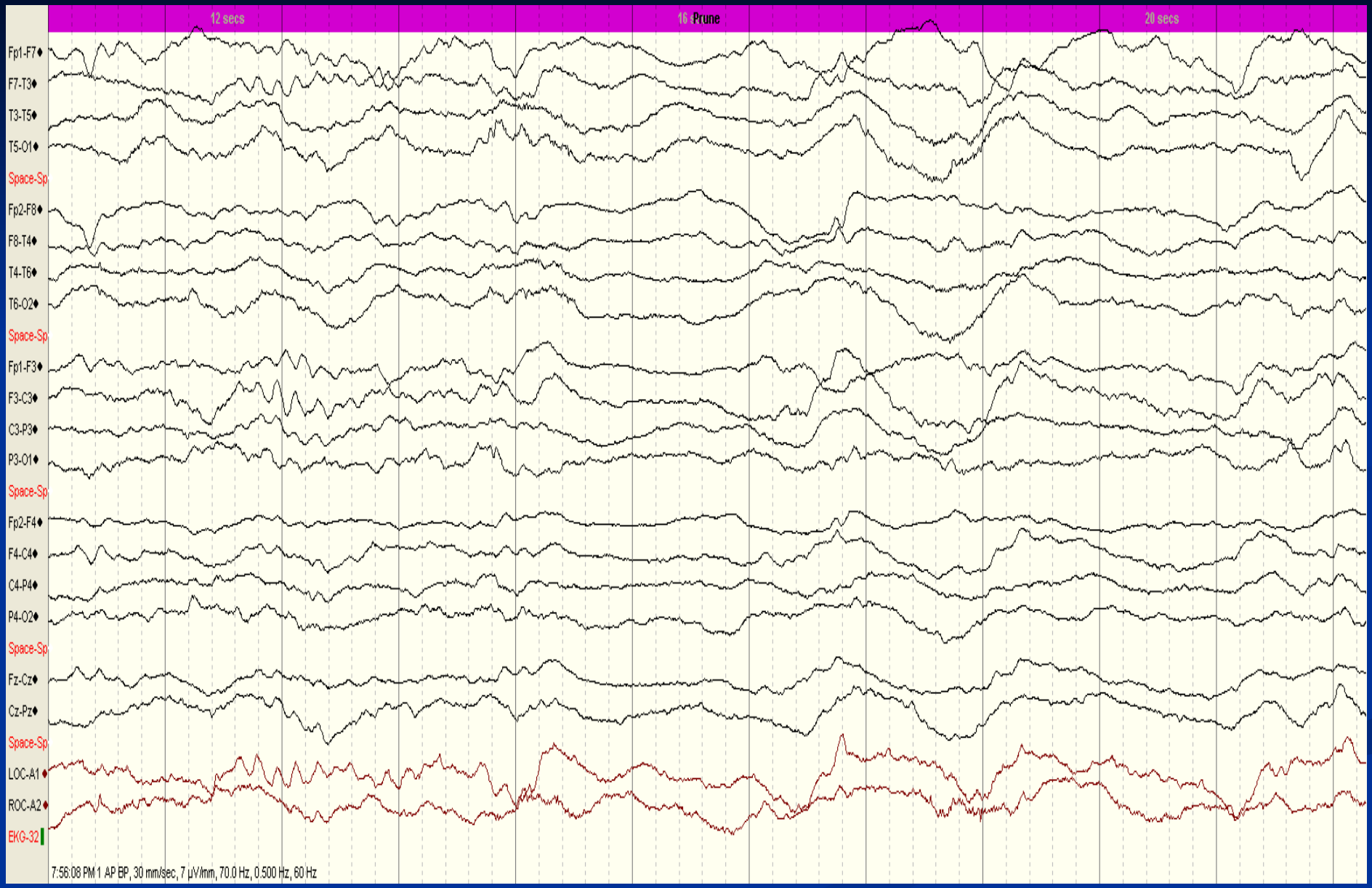
Bilateral frontal ischemia - decrease in alpha variability

Clinical deterioration sedation / intubation

Disconnected 2 hrs for angiogram: Improvement in alpha variability after angio


Fp1-F7
F7-T3
T3-T5
T5-O1
Space-Sp
Fp2-F8
F8-T4
T4-T6
T6-O2
Space-Sp
Fp1-F3
F3-C3
C3-P3
P3-O1
Space-Sp
Fp2-F4
F4-C4
C4-P4
P4-O2
Space-Sp
Fz-Cz
Cz-Pz
Space-Sp
LOC-A1
ROC-A2
EKG-32
10:40:48 PM 1 AP BP, 30 mm/sec, 7 µV/mm, 70.0 Hz, 0.500 Hz, 60 Hz


Fp1-F7♦
F7-T3♦
T3-T5♦
T5-O1♦
Space-Sp
Fp2-F8♦
F8-T4♦
T4-T6♦
T6-O2♦
Space-Sp
Fp1-F3♦
F3-C3♦
C3-P3♦
P3-O1♦
Space-Sp
Fp2-F4♦
F4-C4♦
C4-P4♦
P4-O2♦
Space-Sp
Fz-Cz♦
Cz-Pz♦
Space-Sp
LOC-A1♦
ROC-A2♦
EKG-32
6:38:50 PM 1 AP BP, 30 mm/sec, 7 µV/mm, 70.0 Hz, 0.500 Hz, 60 Hz


12 secs
16 Prune
20 secs
Fp1-F7♦
F7-T3♦
T3-T5♦
T5-O1♦
Space-Sp
Fp2-F8♦
F8-T4♦
T4-T6♦
T6-O2♦
Space-Sp
Fp1-F3♦
F3-C3♦
C3-P3♦
P3-O1♦
Space-Sp
Fp2-F4♦
F4-C4♦
C4-P4♦
P4-O2♦
Space-Sp
Fz-Cz♦
Cz-Pz♦
Space-Sp
LOC-A1♦
ROC-A2♦
EKG-32
7:56:08 PM 1 AP BP, 30 mm/sec, 7 µV/mm, 70.0 Hz, 0.500 Hz, 60 Hz

Claassen: EEG Monitoring in SAH

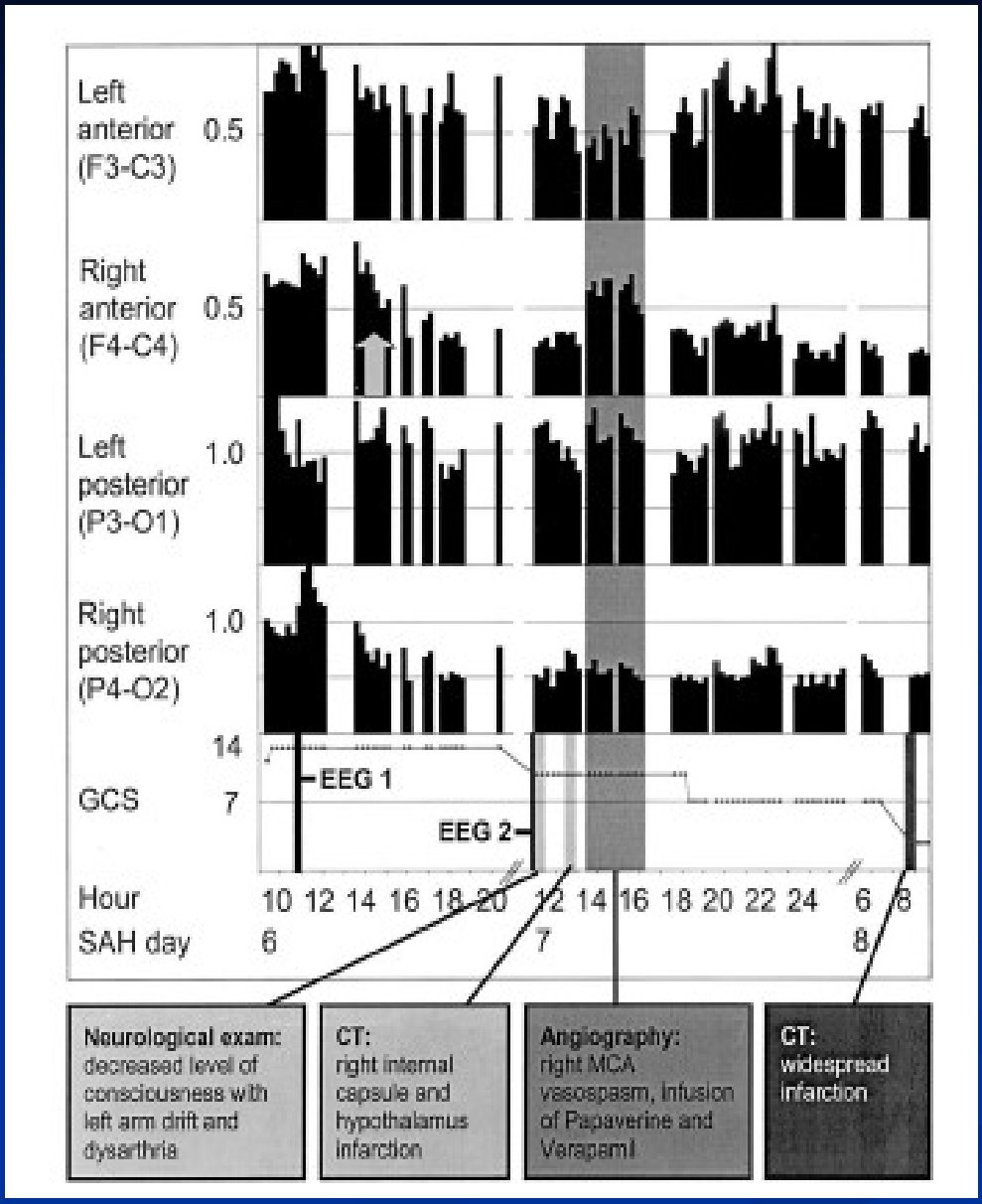
- 34 of 78 consecutive Hunt-Hess grade 4 or 5 SAH patients
- Continuous EEG post-op day 2 to post-SAH day 14
- 20 artifact-free, 1 min EEG-clips after alerting stimulus
  - 10 clips on monitoring day 1 (baseline)
  - 10 clips on days 4-6 (follow-up)
    - In DCI patients, follow-up clips after the onset of deterioration and before infarction

Claassen J et al., Clin Neurophysiol 2004;115:2699-2710

Claassen: EEG Monitoring in SAH

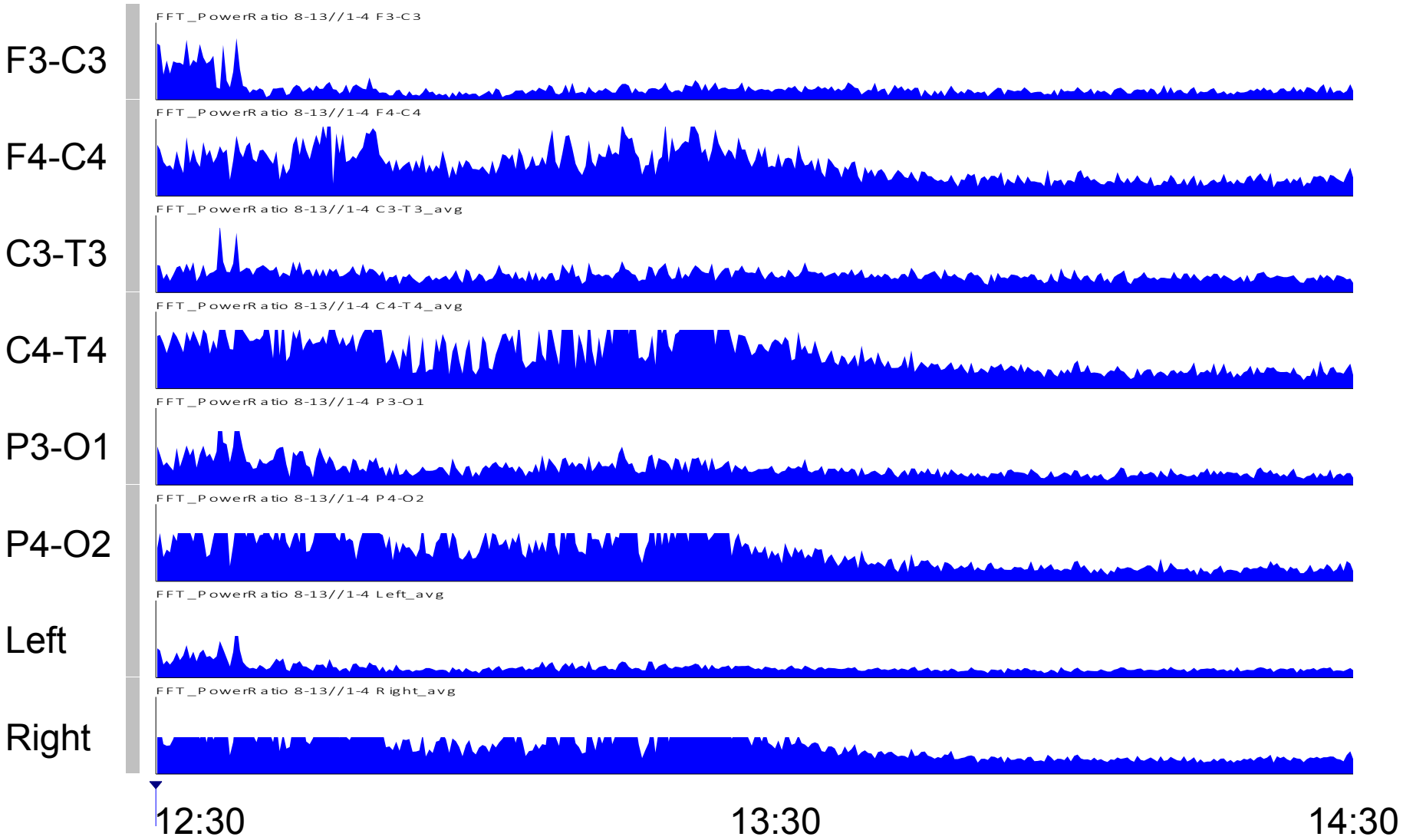
- Nine of 34 patients (26%) developed DCI
- Alpha/delta ratio (alpha power/delta power; ADR) demonstrated the strongest association with DCI
  - Median decrease of ADR in DCI was 24%
  - Median increase of 3% without DCI ($p<0.0001$)
- Clinically useful cut-offs
  - 6 consecutive recordings with >10% decrease in ADR from baseline (sensitivity 100%, specificity 76%)
  - Any single measurement with a >50% decrease (sensitivity 89%, specificity 84%)

Claassen J et al., Clin Neurophysiol 2004;115:2699-2710

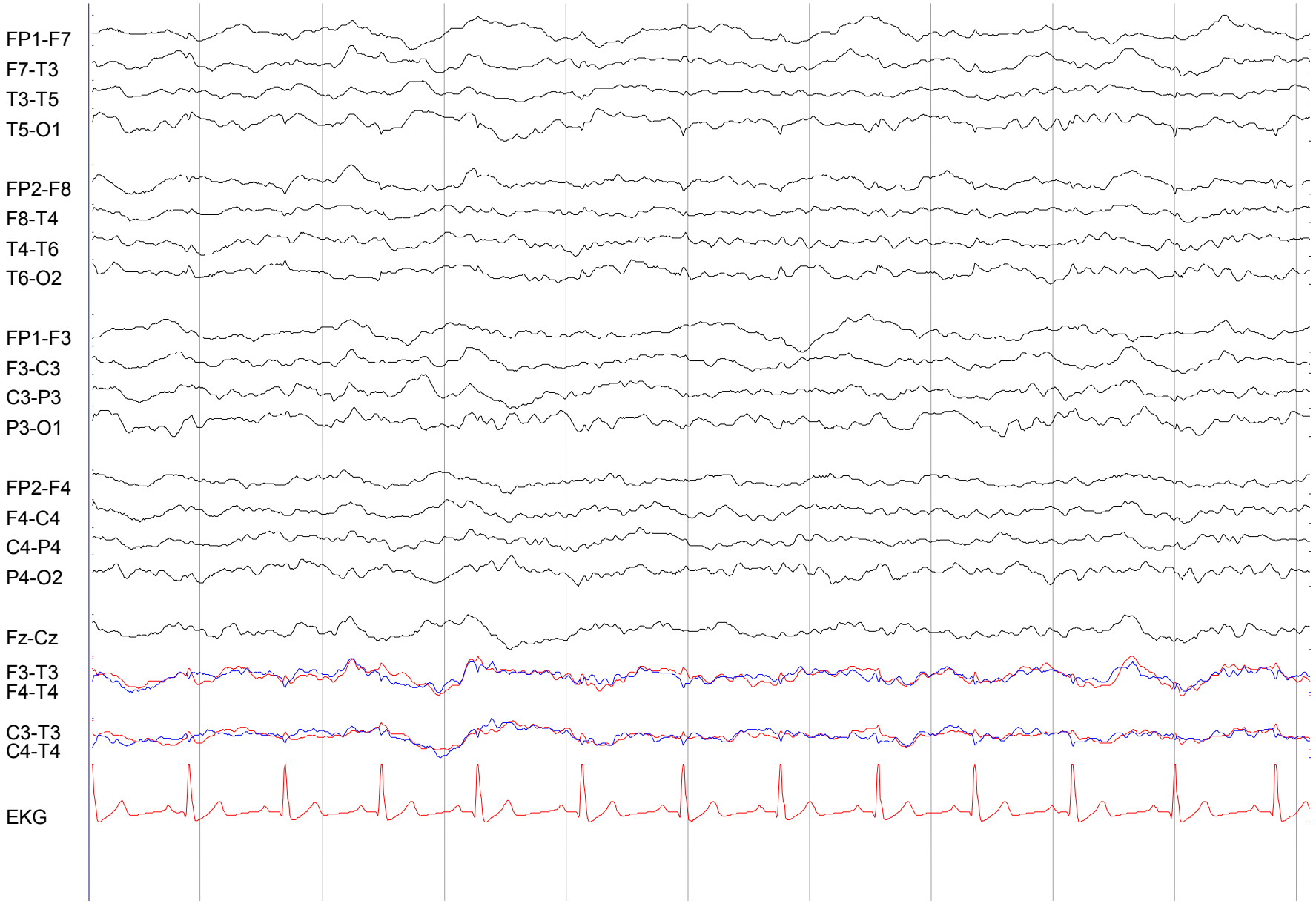


Claassen et al., J Clin Neurophys 2005;22:92-98

SAH: Alpha-Delta Ratio




FP1-F7
F7-T3
T3-T5
T5-O1
FP2-F8
F8-T4
T4-T6
T6-O2
FP1-F3
F3-C3
C3-P3
P3-O1
FP2-F4
F4-C4
C4-P4
P4-O2
Fz-Cz
F3-T3
F4-T4
C3-T3
C4-T4
EKG


FP1-F7
F7-T3
T3-T5
T5-O1
FP2-F8
F8-T4
T4-T6
T6-O2
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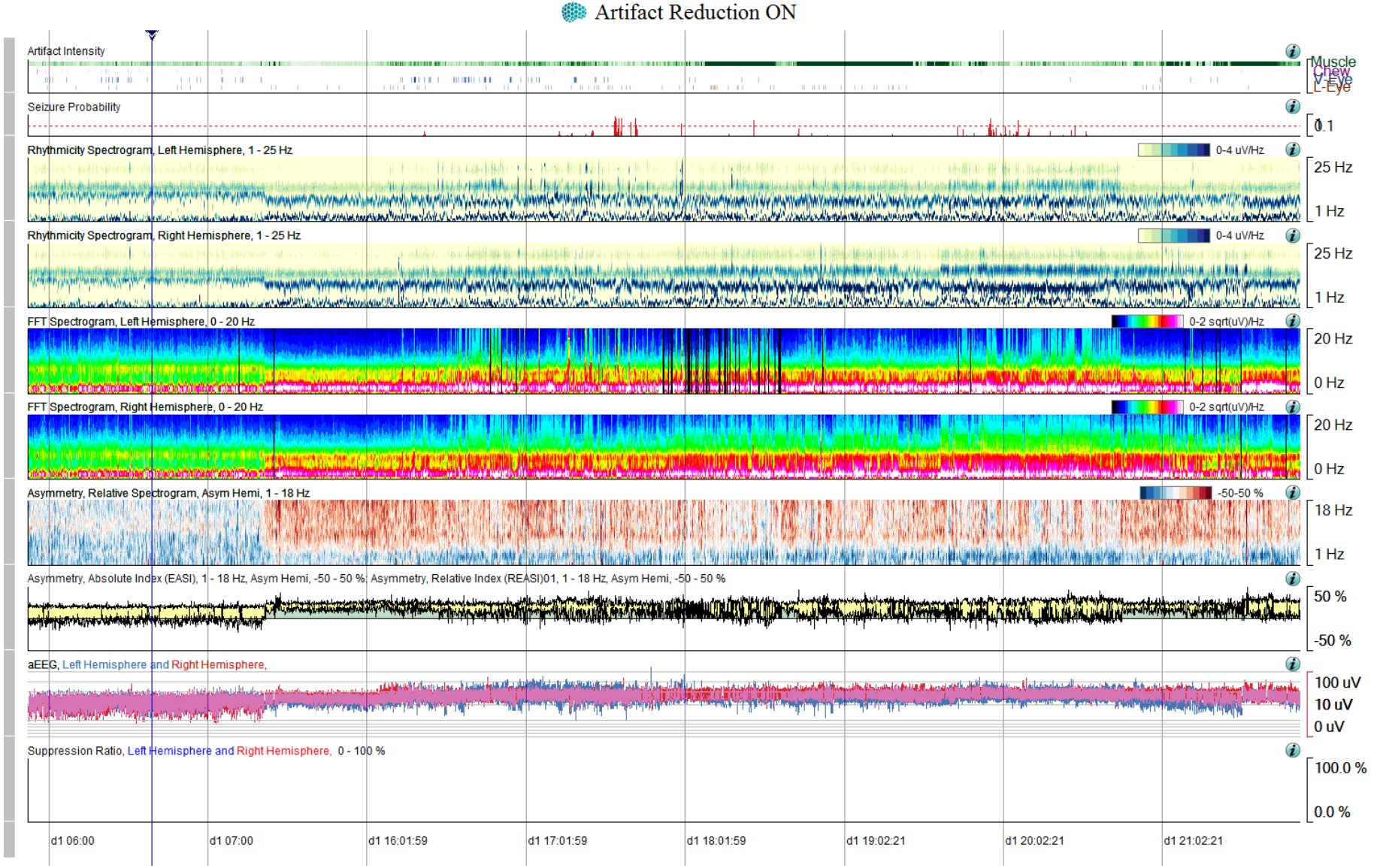
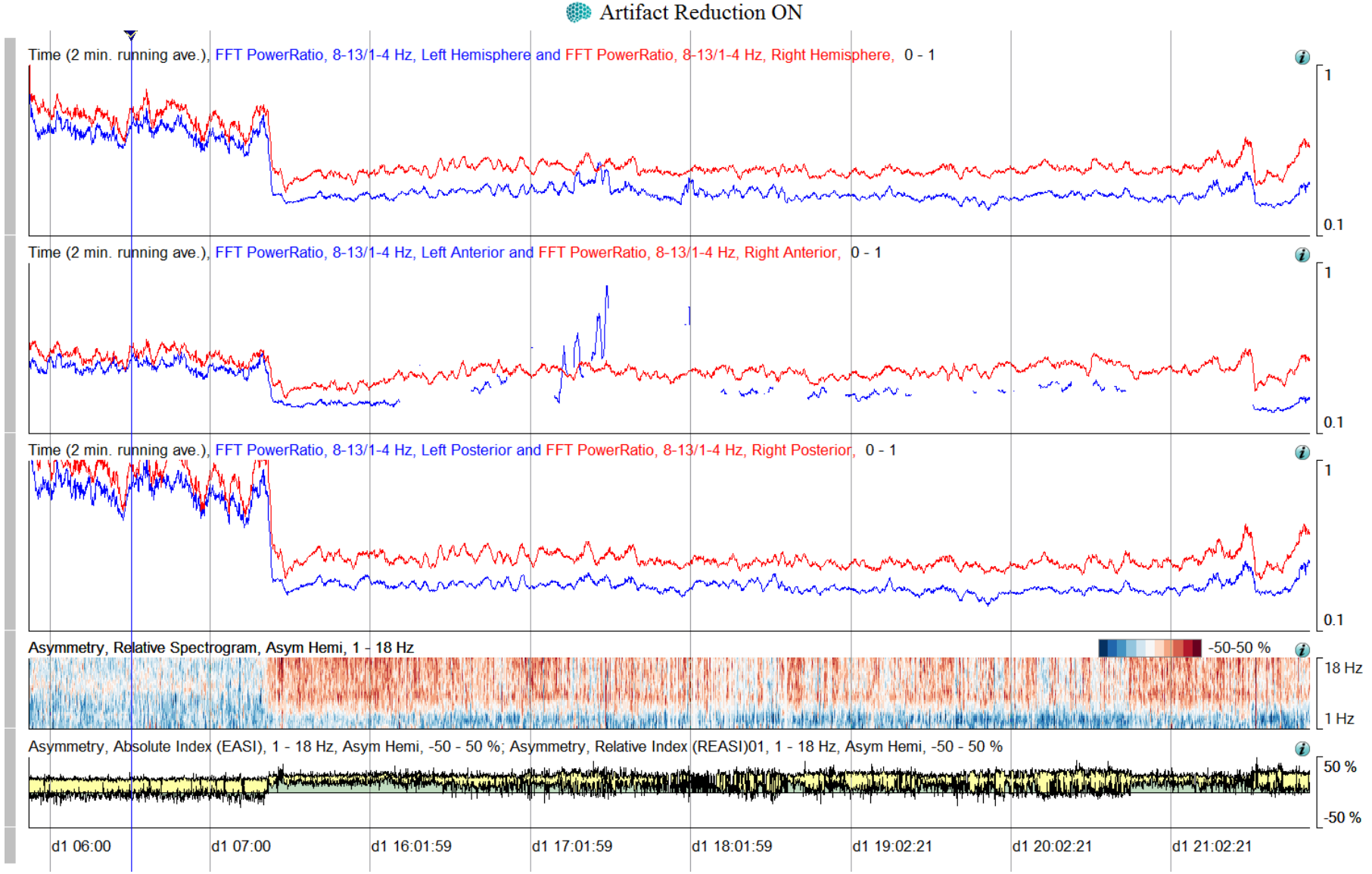
F3-C3
C3-P3
P3-O1
FP2-F4
F4-C4
C4-P4
P4-O2
Fz-Cz
F3-T3
F4-T4
C3-T3
C4-T4
EKG

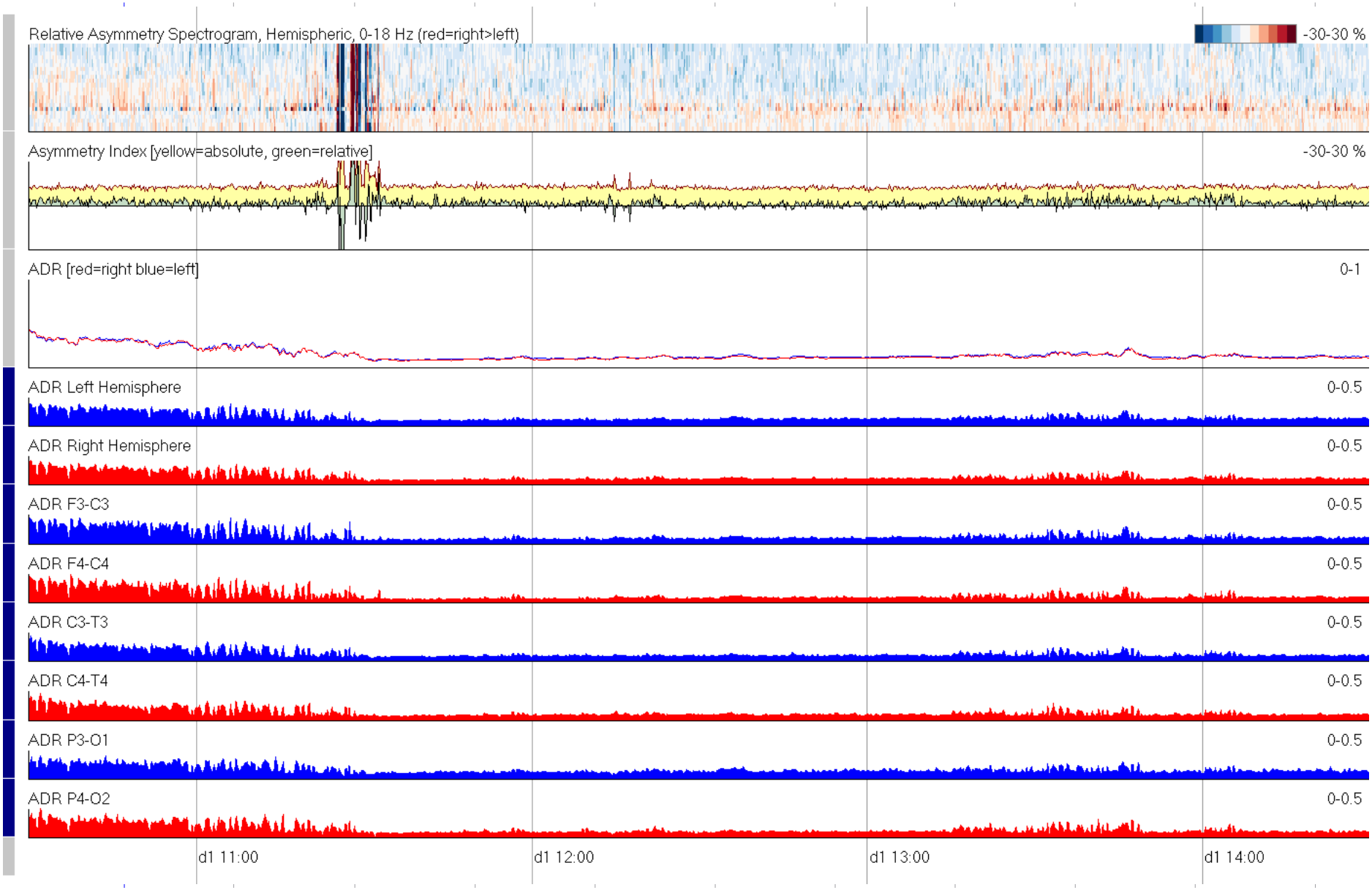
Comprehensive Panel

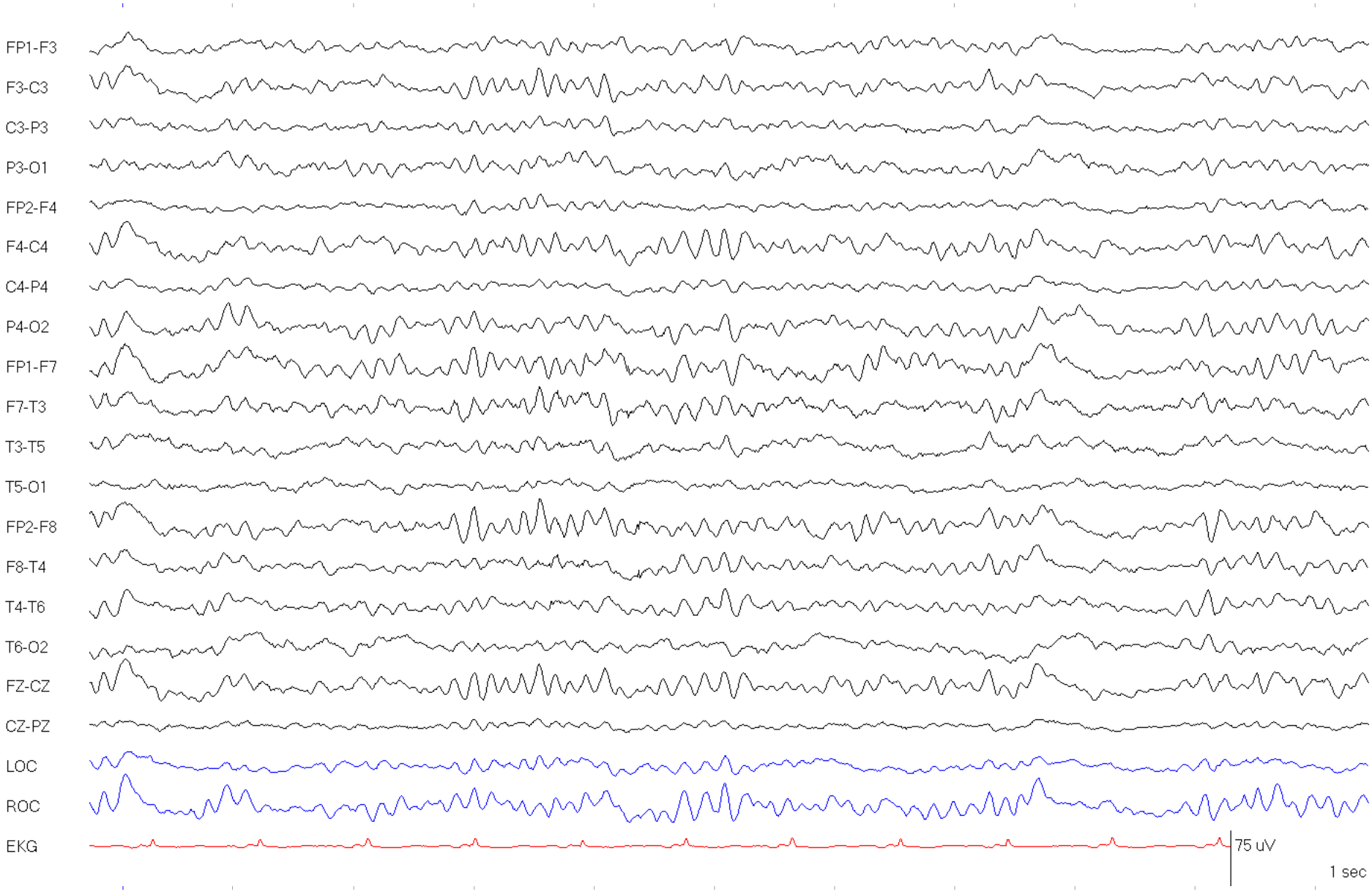


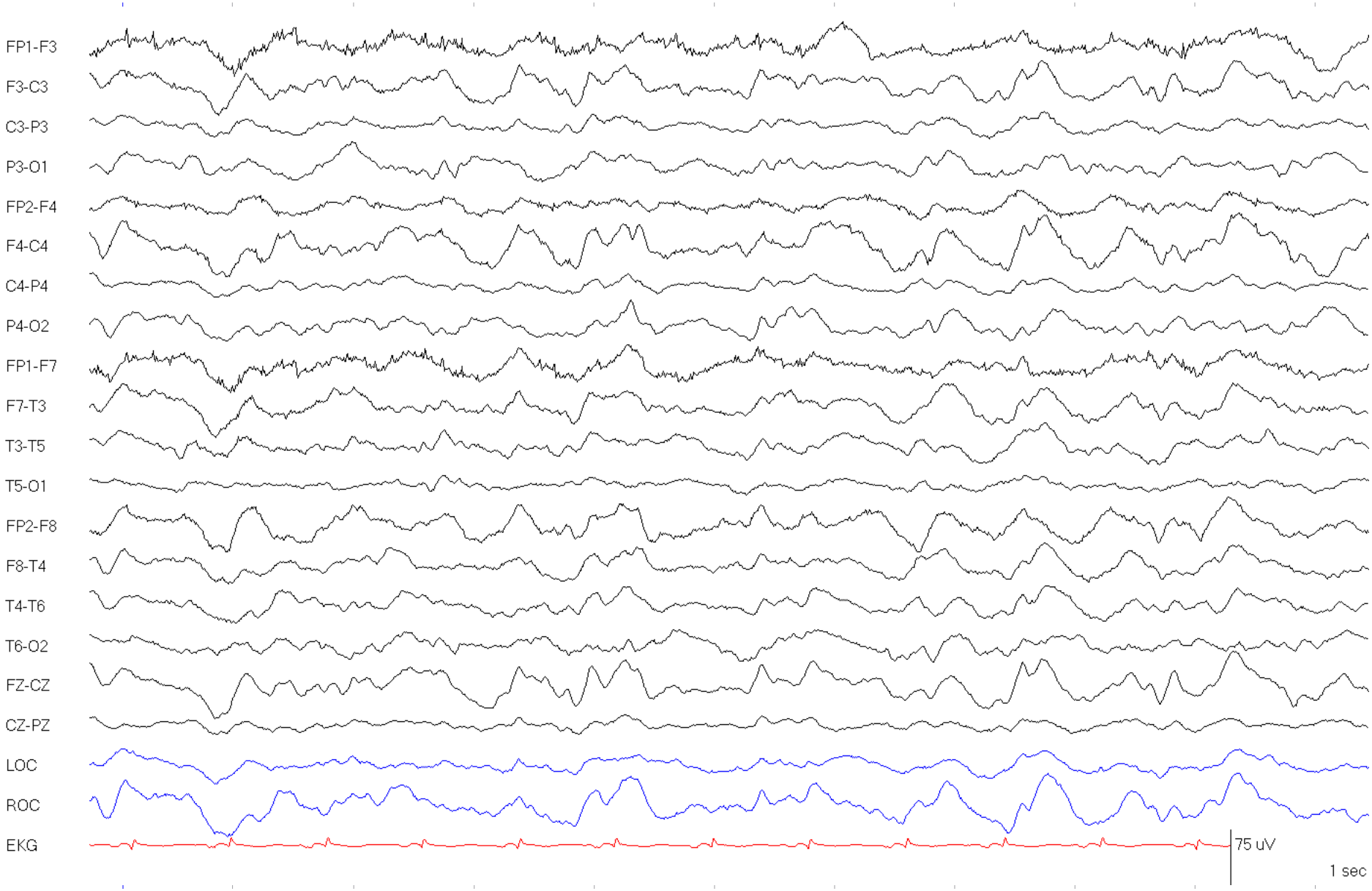
Alpha-Delta Ratio



Alpha Variability


Relative Asymmetry Spectrogram, Hemispheric, 0-18 Hz (red=right>left)
-30-30 %
Asymmetry Index [yellow=absolute, green=relative]
-30-30 %
ADR [red=right blue=left]
0-1
ADR Left Hemisphere
0-0.5
ADR Right Hemisphere
0-0.5
ADR F3-C3
0-0.5
ADR F4-C4
0-0.5
ADR C3-T3
0-0.5
ADR C4-T4
0-0.5
ADR P3-O1
0-0.5
ADR P4-O2
0-0.5
d1 11:00
d1 12:00
d1 13:00
d1 14:00

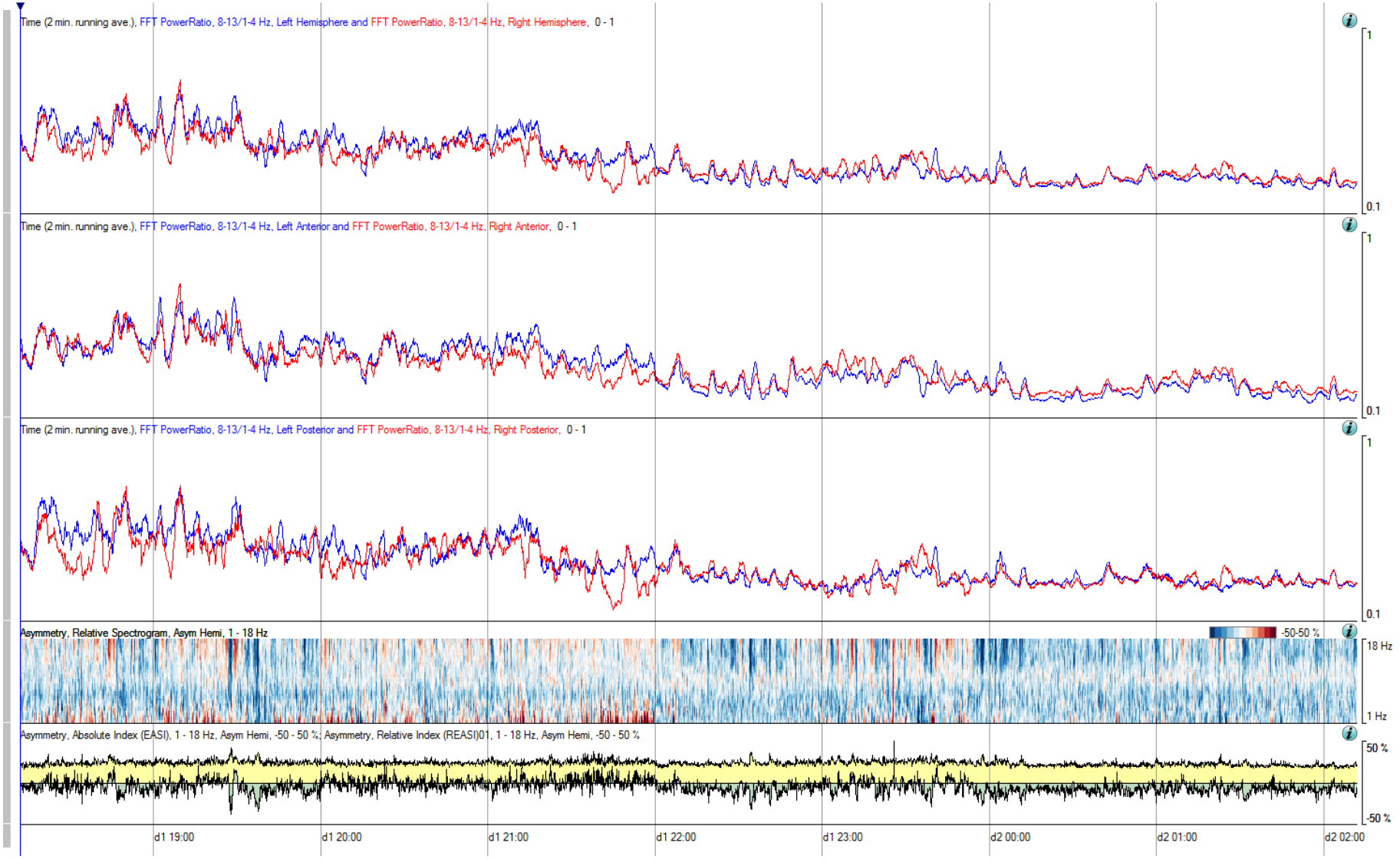

FP1-F3
F3-C3
C3-P3
P3-O1
FP2-F4
F4-C4
C4-P4
P4-O2
FP1-F7
F7-T3
T3-T5
T5-O1
FP2-F8
F8-T4
T4-T6
T6-O2
FZ-CZ
CZ-PZ
LOC
ROC
EKG
75 uV
1 sec


FP1-F3
F3-C3
C3-P3
P3-O1
FP2-F4
F4-C4
C4-P4
P4-O2
FP1-F7
F7-T3
T3-T5
T5-O1
FP2-F8
F8-T4
T4-T6
T6-O2
FZ-CZ
CZ-PZ
LOC
ROC
EKG
75 uV
1 sec

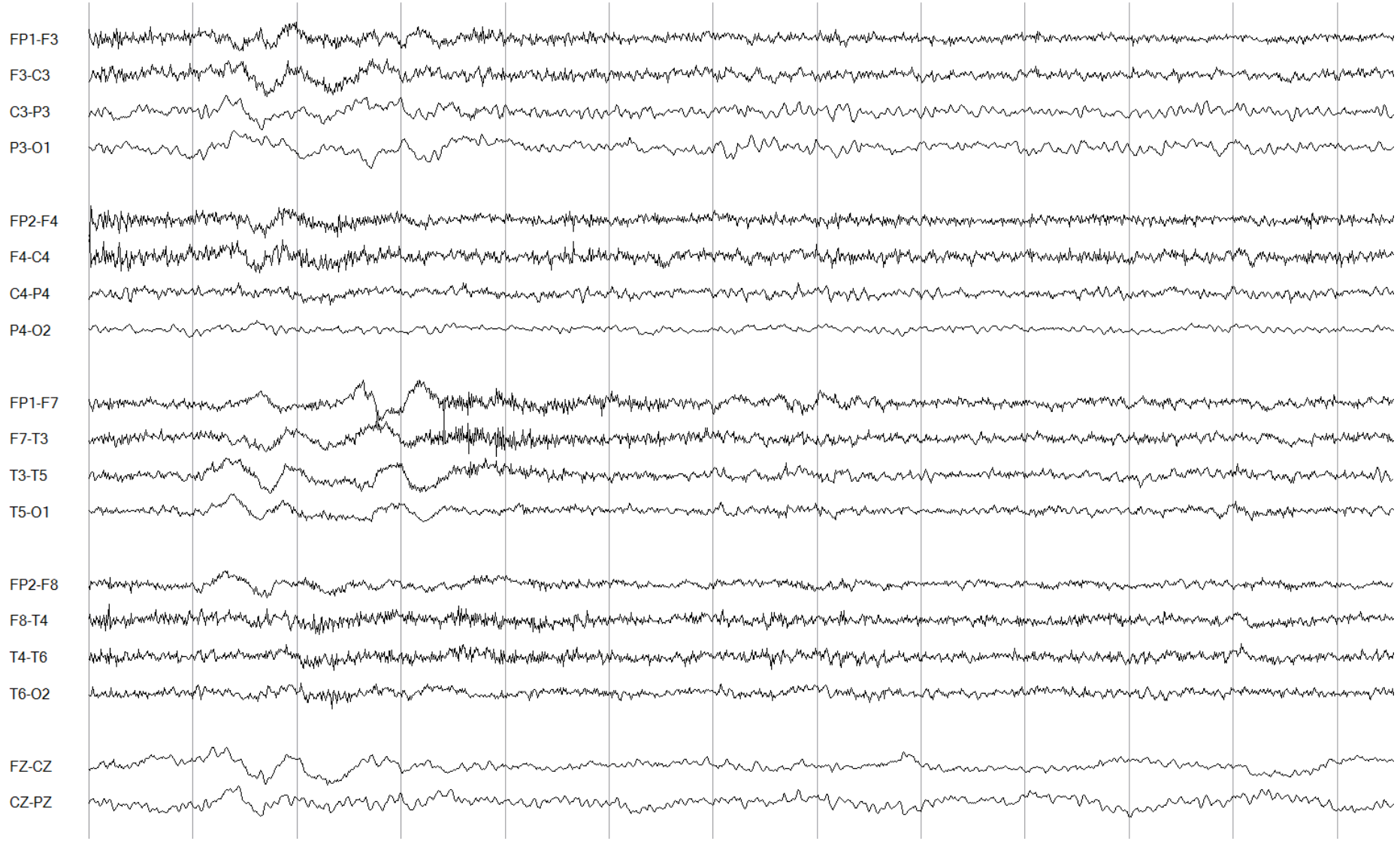
Case 1

- 56 year old man with SAH
  - Hunt-Hess grade 3
  - Fisher grade 3
  - GCS 10
- Angiography revealed a 7 mm left AComm aneurysm
- Aneurysm was clipped uneventfully

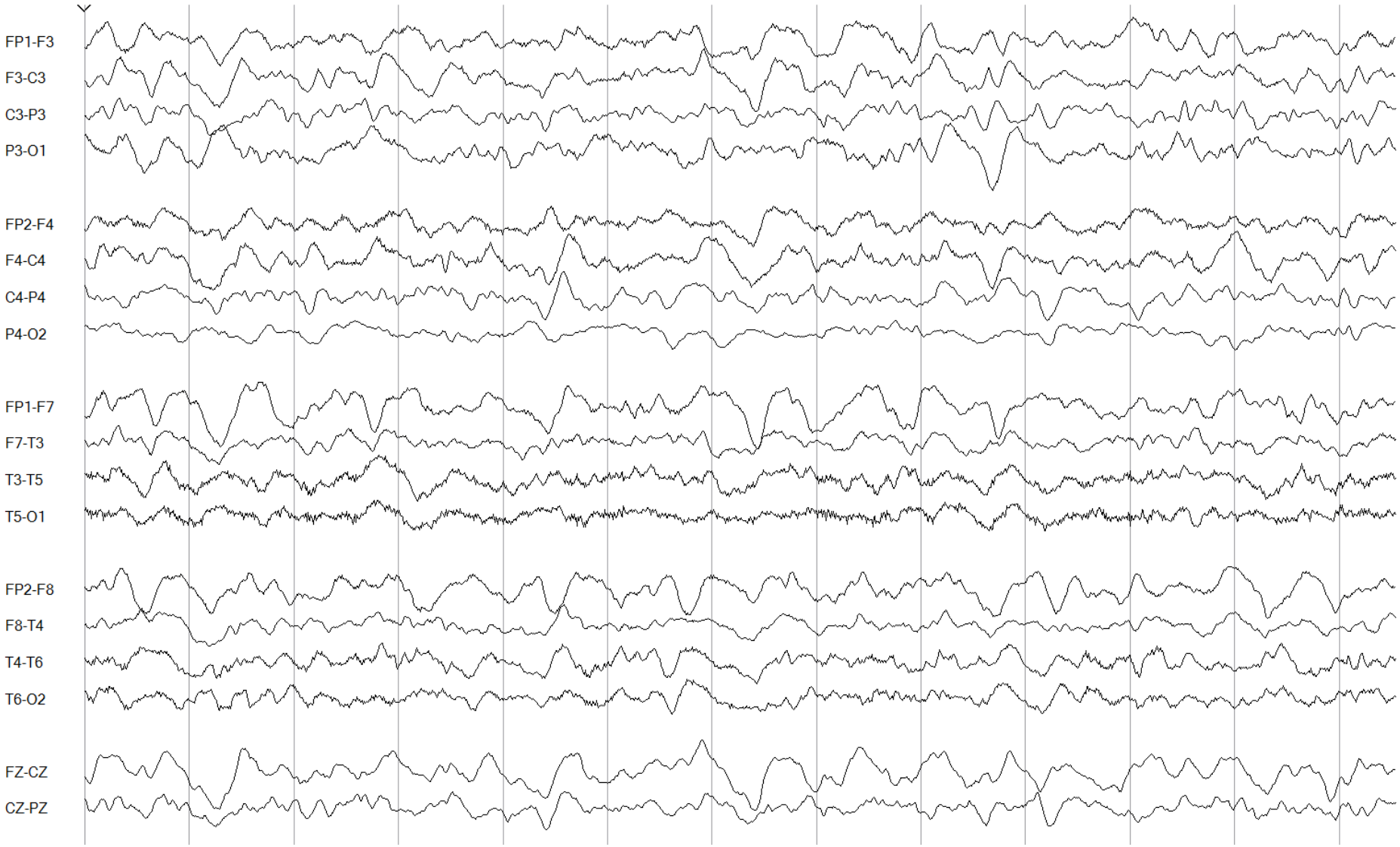
Alpha-Delta: 8 hours



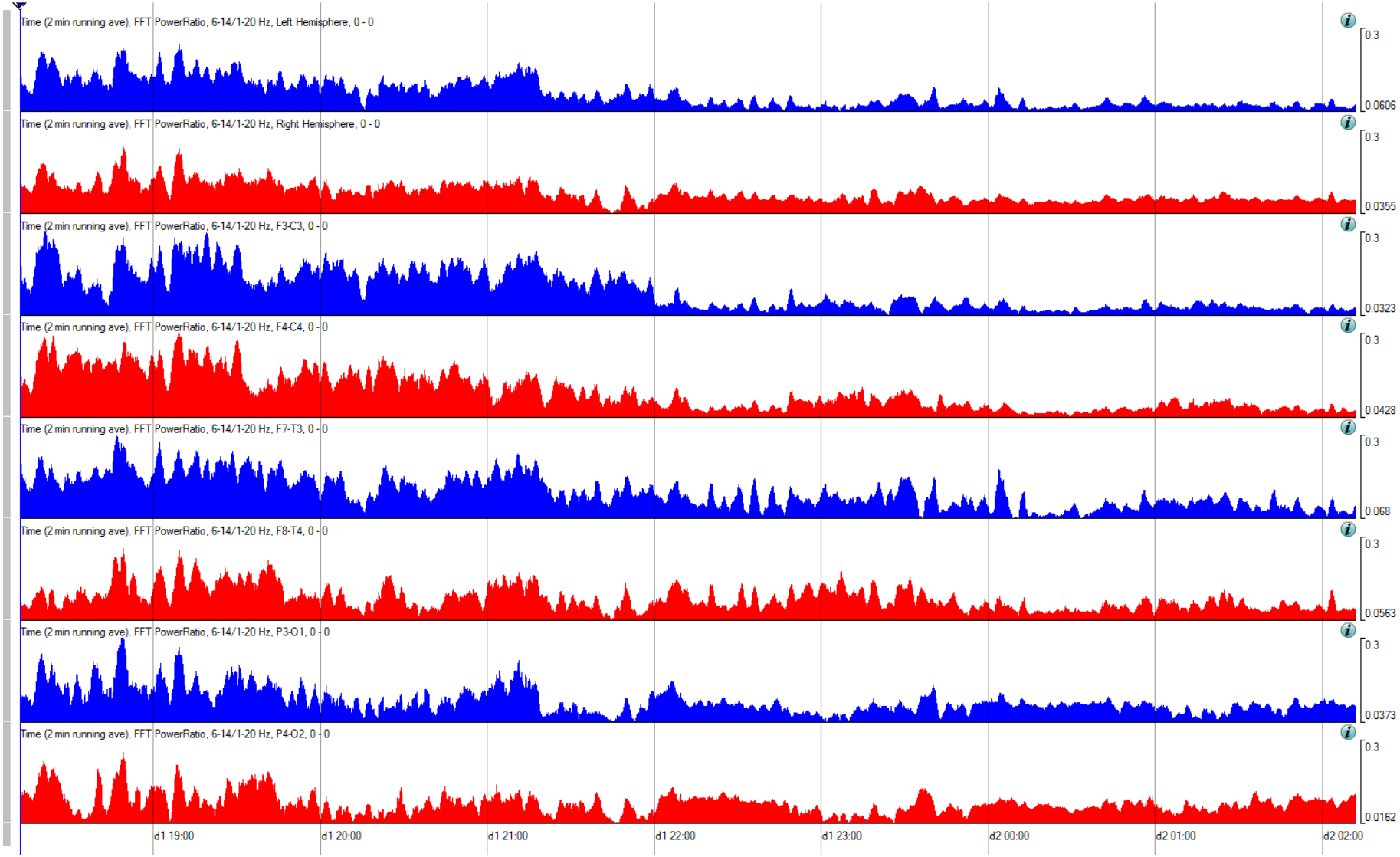
Raw EEG: 30 minutes



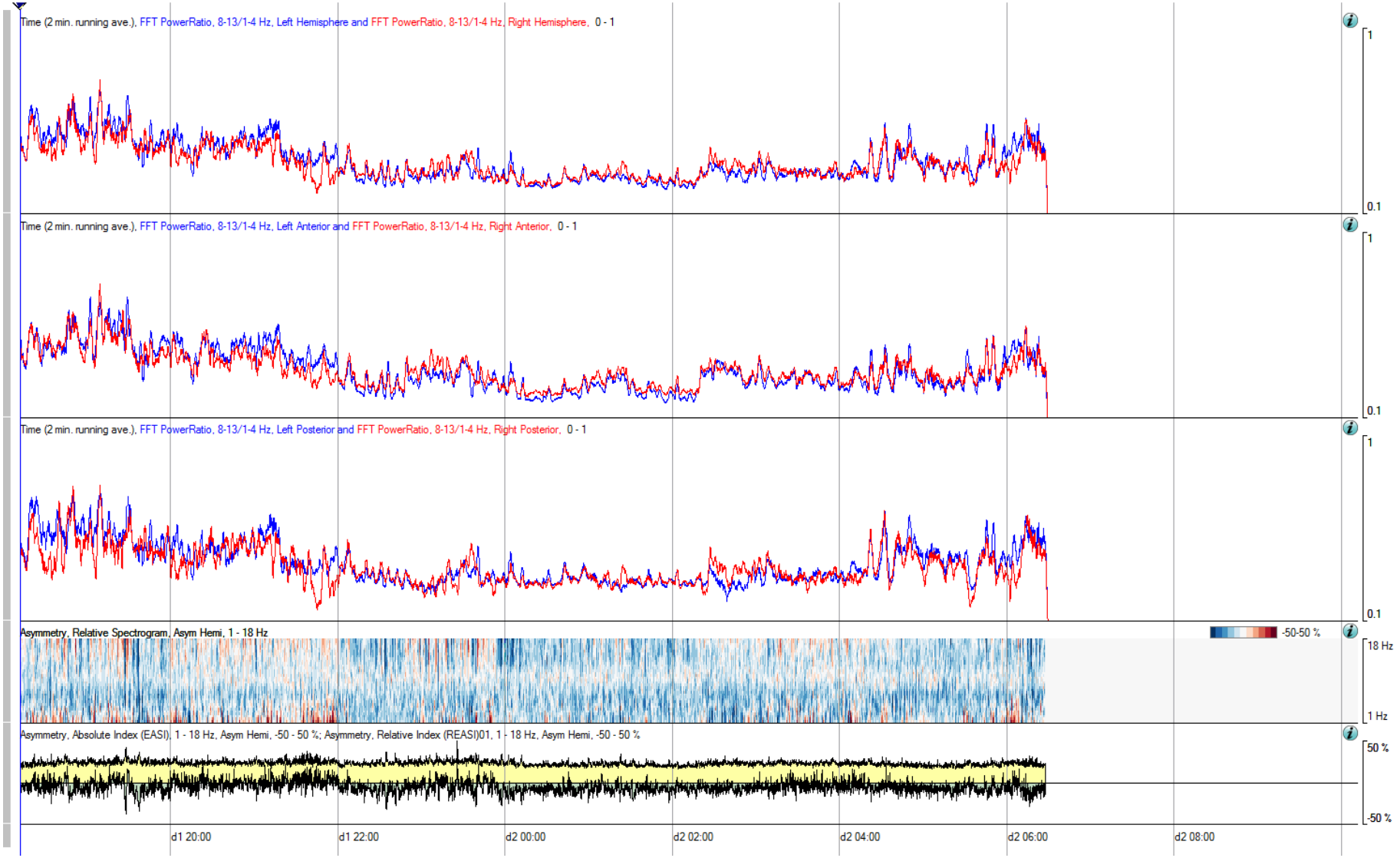
Raw EEG: 6 hours



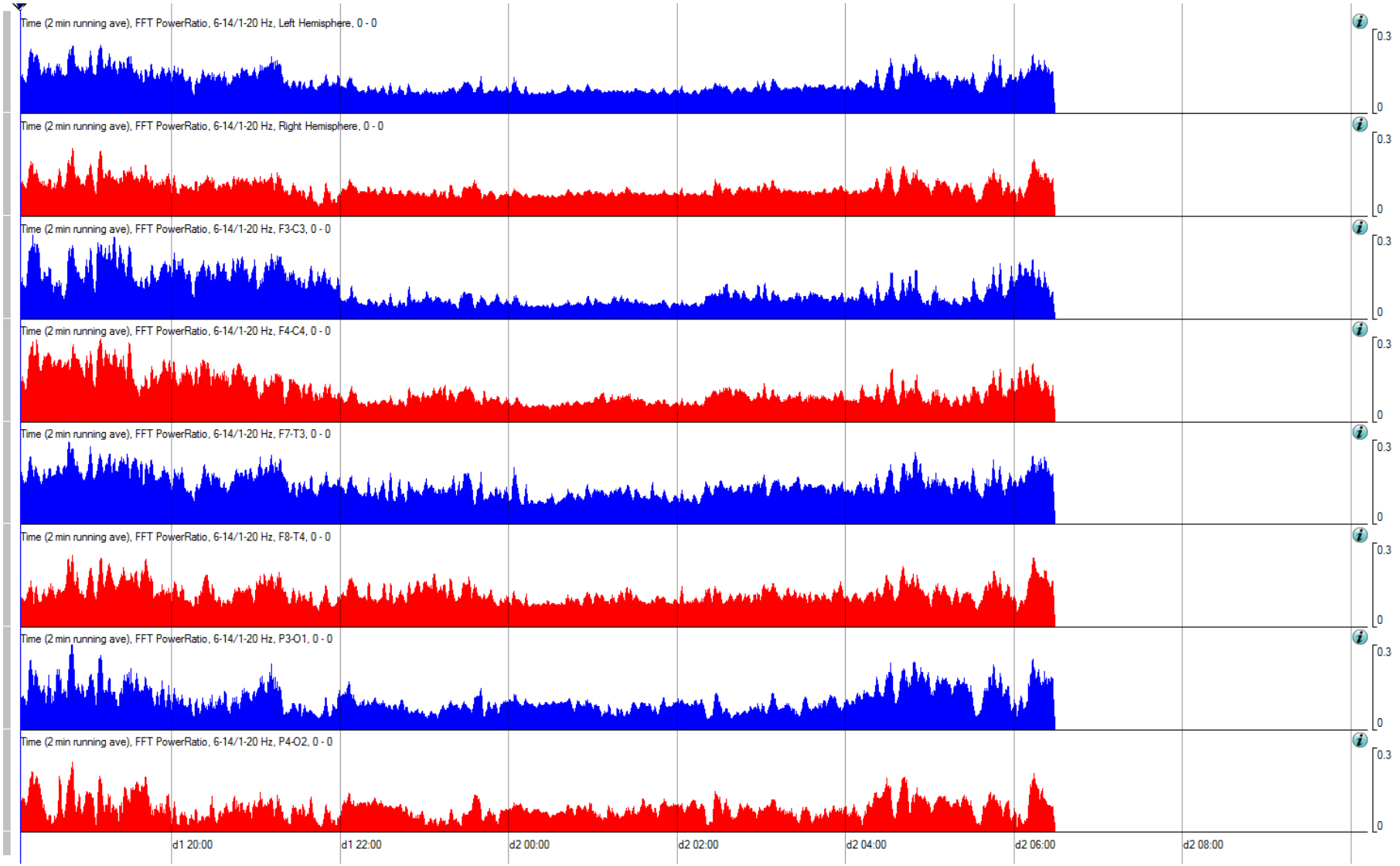
Alpha Variability: 8 hours



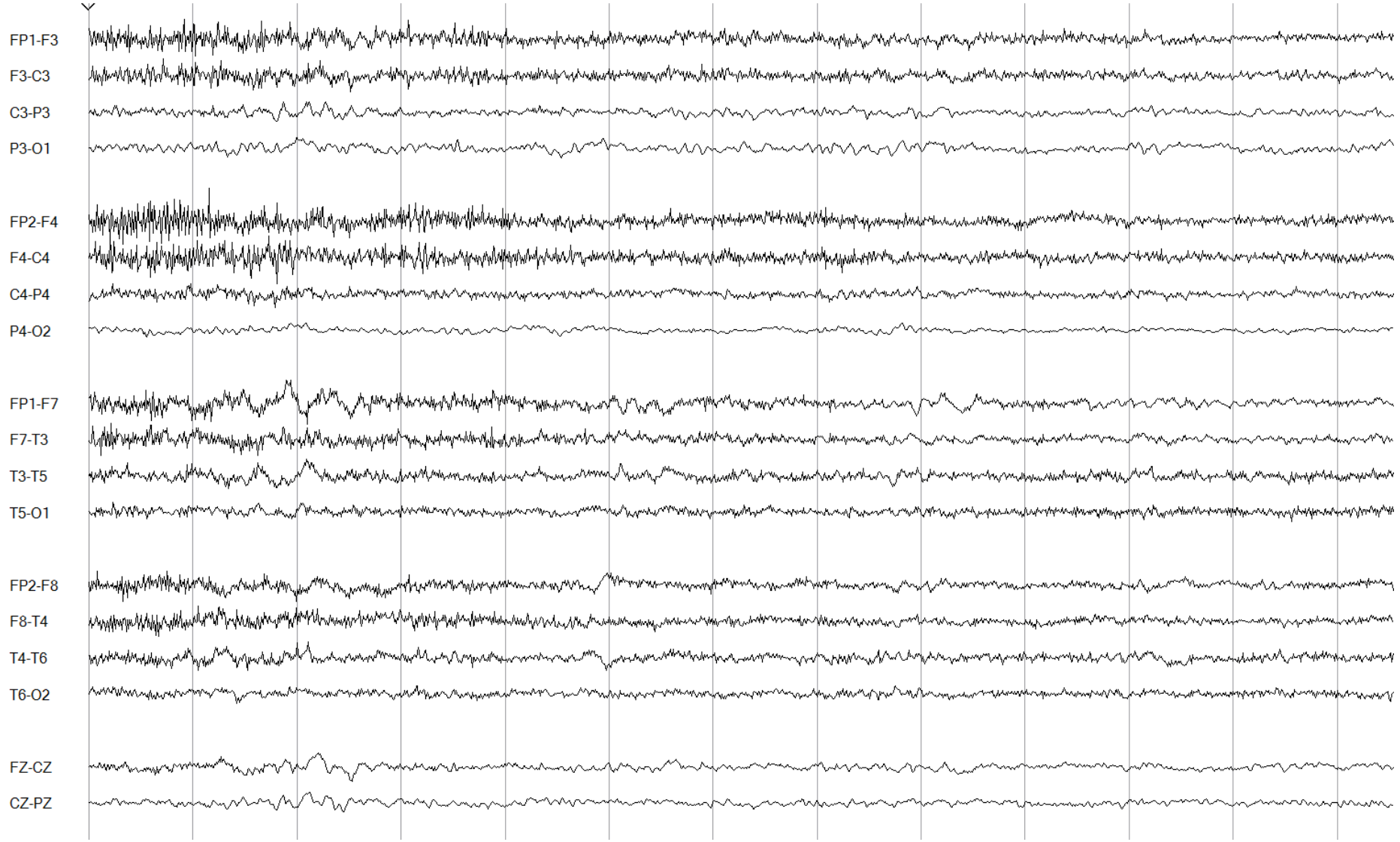
Alpha-Delta: 16 hours



Alpha Variability: 16 hours



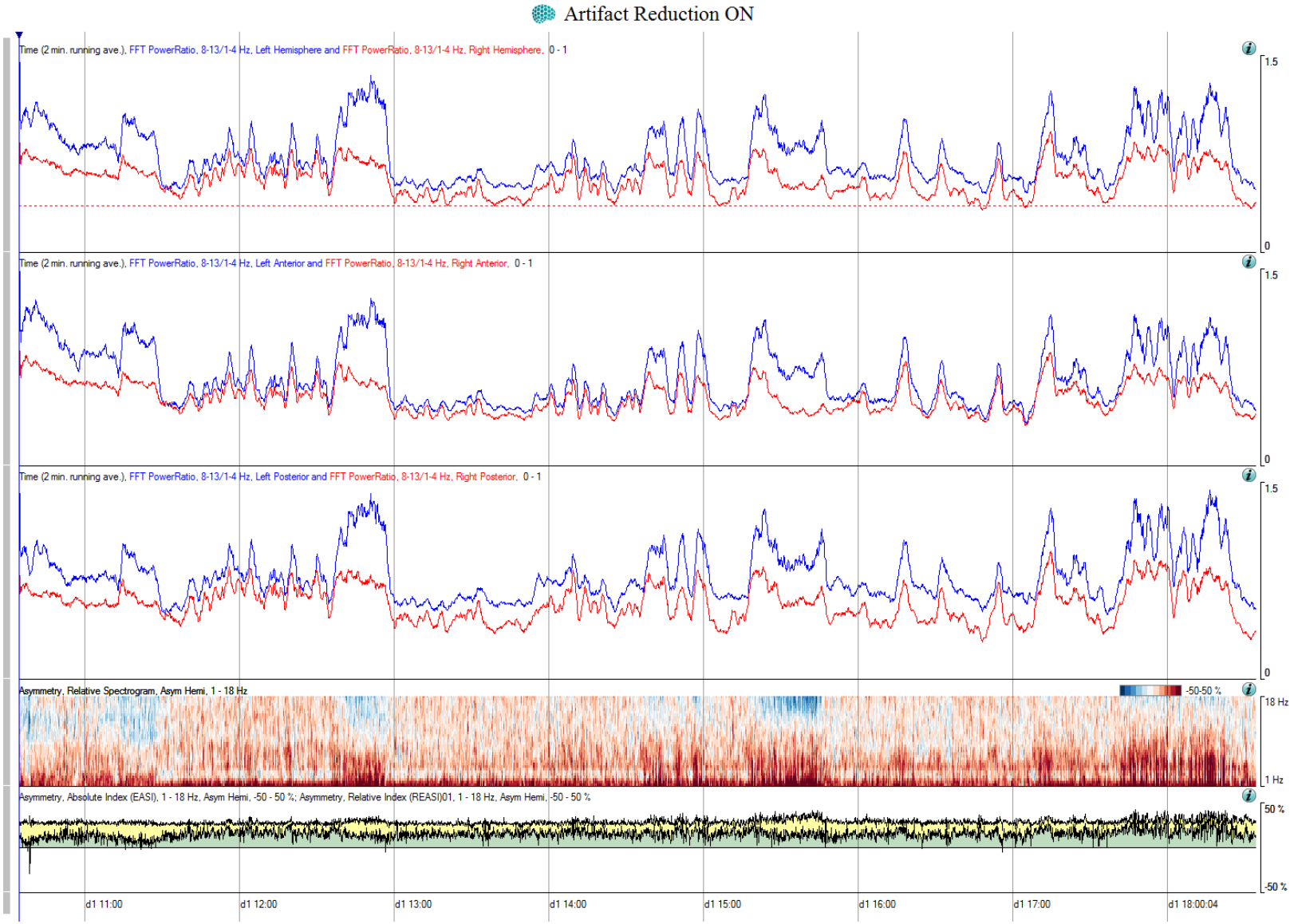
Raw EEG: 12 hours



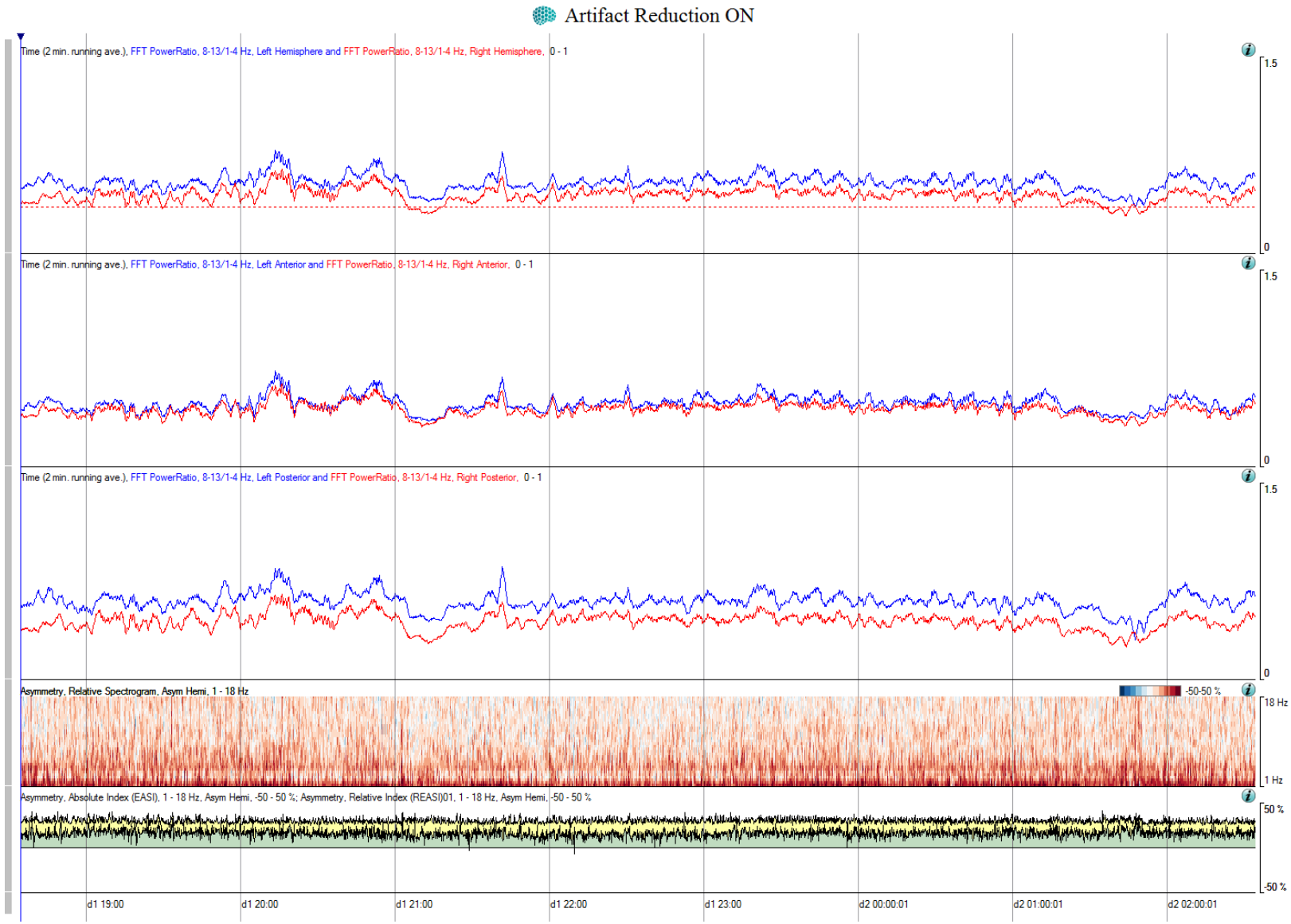
Case 2

- 62-year-old woman with SAH
  - Hunt-Hess grade 2
  - Fisher grade 3
  - GCS 14
- Angiography revealed a 8 mm right internal carotid supraclinoid aneurysm and a 4 mm left anterior communicating artery/anterior cerebral artery junction aneurysm
- Both aneurysms were clipped uneventfully

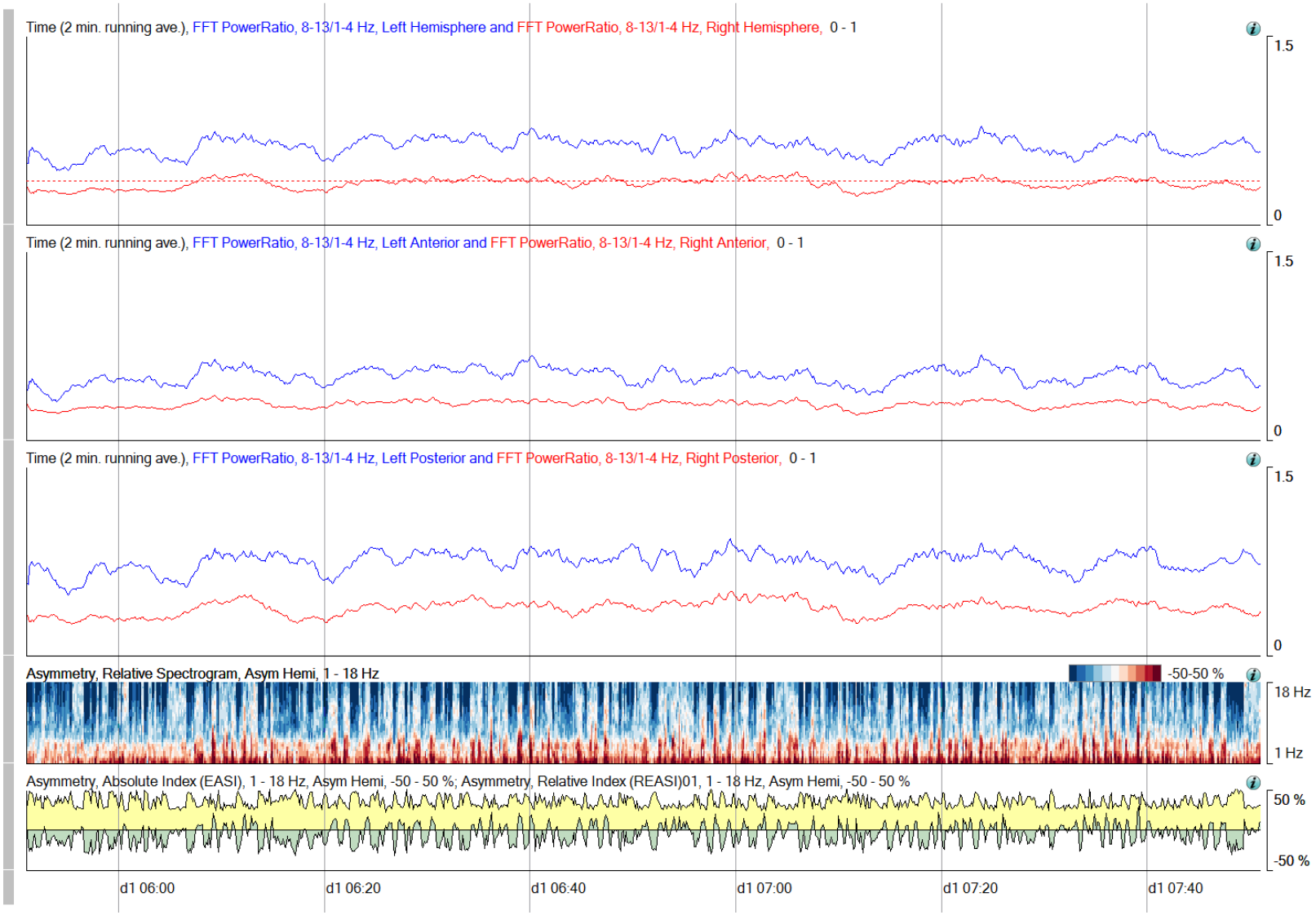
Alpha-Delta: 8 hours



Alpha-Delta: 8 hours



Alpha Delta: 8 hours, day 4



QEEG: Intracortical EEG

- Improved signal: noise and reduced artifact
- 5 patients with poor grade SAH (Hunt-Hess grade 4 or 5)
- 8 contact depth electrode (2.2 mm spacing)
- QEEG: average over 4-6 hrs baseline vs. prior to angio
  - Alpha/delta ratio (ADR, 8–13 Hz/1–4 Hz)
  - Mean amplitude
  - Suppression percent (percent below 5 uV)
  - Total power (TP, 0–23 Hz)
  - Superior to alpha-delta ratio of scalp EEG

Stuart RM et al. Neurocrit Care 2010;13:355-358

QEEG: Intracortical EEG

- 3/5 SAH patients had vasospasm on follow-up angio
- Mean ICE ADRs prior to angiography
  - Decreased by 42% for those with vasospasm
  - Decreased by 17% for those without vasospasm
  - Dropped by at least 25% for >4 h in all patients with vasospasm 1–3 days before angiographic confirmation of vasospasm
  - No false negatives
- Surface EEG was limited by significant artifact and poor signal quality, despite application of automated artifact rejection

Stuart RM et al. Neurocrit Care 2010;13:355-358

Systematic Review

- 8 publications included from 760 citations
  - All single-center case series, half retrospective
  - All affected by high risk of bias related to patient selection
  - 50% high risk of bias for EEG methodology

Kondziella D et al. Neurocrit Care 2015; 22: 450-461.

Systematic Review

- Reference standard: CT, DSA, and TCD (120 to 140 cm/min) in most but not all studies
  - 4 studies: DCI based on clinical diagnosis, presence of radiological vasospasm or increased TCD flow velocities was supportive but not mandatory
- Conclusion
  - CEEG monitoring after SAH may predict clinically symptomatic episodes of DCI many hours in advance
  - Unknown if more aggressive treatment alters outcome

Kondziella D et al. Neurocrit Care 2015; 22: 450-461.

QEEG for DCI: Confounders

- Sedation and other medications
- Increased intracranial pressure
- Reduced global cerebral perfusion pressure
- Metabolic changes
- Hydrocephalus
- Rebleeding
- Focal edema
- Artifacts
- Large variety of DCI definitions
  - New definition: infarct and functional outcome

Summary: CEEG after SAH

- EEG and QEEG trends on cEEG (performed on days 2–10) correlate with delayed cerebral ischemia
- QEEG trends designed to detect increased slow and loss of fast frequencies
- May detect ischemia prior to neurological exam and other diagnostic tests
- Sensitivity up to 90%
- Specificity 75%
- Optimal duration not defined
- Most studies examined poor grade patients
- No interventional trials using EEG as detection method

Claassen et al. Intensive Care Med 2013;39:1337-1351

Ischemic Stroke

- 91 patients with acute ischemic stroke
  - 33 (36%) initially had normal CT scans
    - 16 (48%) showed lateralized EEG abnormalities
    - All 16 showed cortical infarctions on follow-up CT scans corresponding to the EEG findings
  - 58 cortical infarctions
    - Lateralized EEG abnormalities
      - 80% of MCA
      - 86% of watershed
  - 12 lacunar infarctions with negative initial CT scans had normal acute EEGs

Macdonell RA et al., Arch Neurol 1988;45:520-524

Prediction of Malignant Course

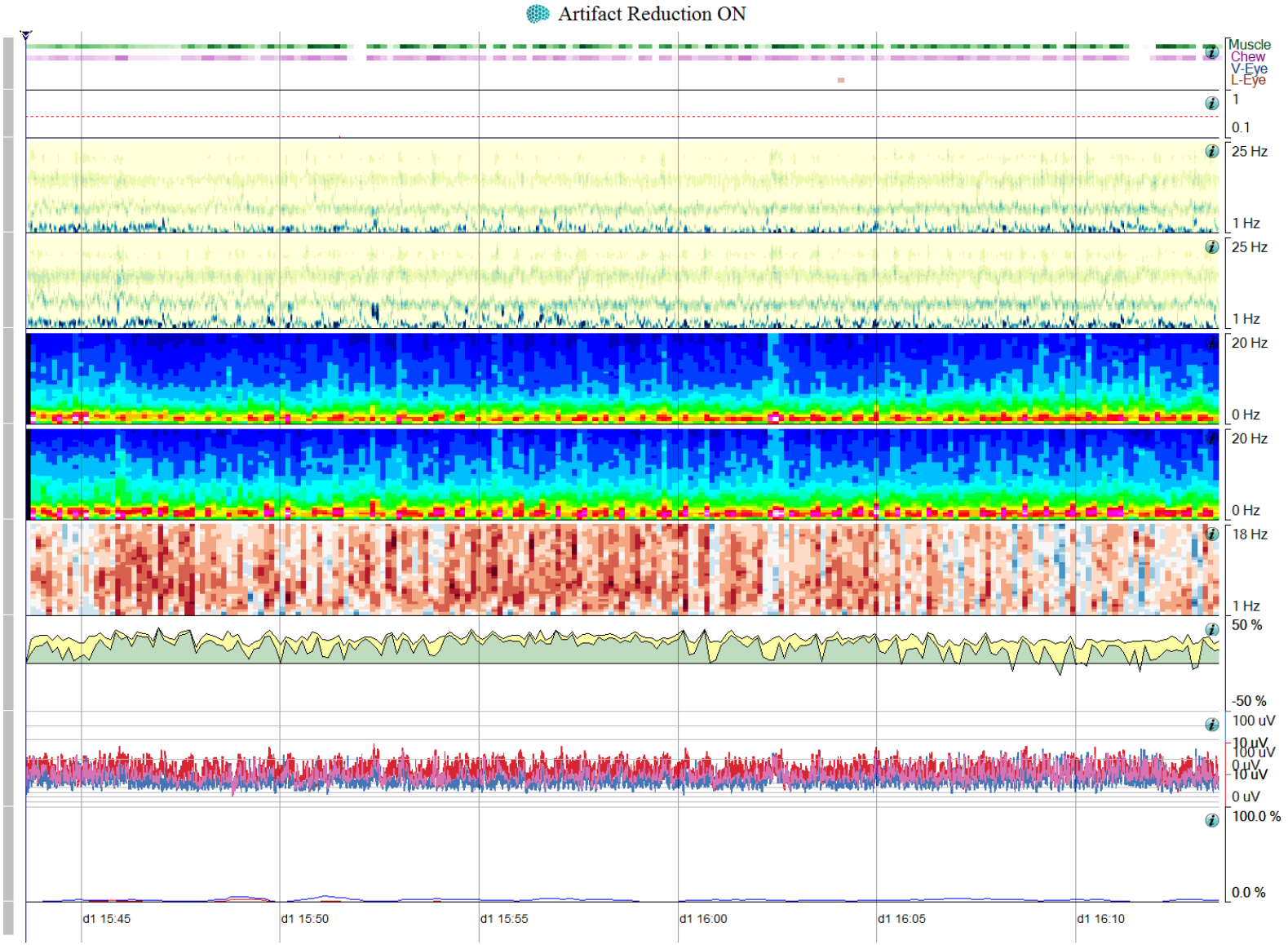
- RAWOD
  - Regional Attenuation WithOut Delta
  - Patients with large acute ischemic stroke
  - Less likely to benefit from thrombolysis
  - Likely to develop cerebral edema

Schneider & Jordan. Am J Electroneurodiagnostic Technol 2005;45:102-117

RAWOD


FP1-F3
F3-C3
C3-P3
P3-O1
FP2-F4
F4-C4
C4-P4
P4-O2
FP1-F7
F7-T3
T3-T5
T5-O1
FP2-F8
F8-T4
T4-T6
T6-O2
FZ-CZ
CZ-PZ
EKG

RAWOD: QEEG


Artifact Reduction ON
Muscle
Chew
V-Eye
L-Eye
1
0.1
25 Hz
1 Hz
25 Hz
1 Hz
20 Hz
0 Hz
20 Hz
0 Hz
18 Hz
1 Hz
50 %
-50 %
100 uV
10 uV
100 uV
0 uV
10 uV
0 uV
100.0 %
0.0 %
d1 15:45
d1 15:50
d1 15:55
d1 16:00
d1 16:05
d1 16:10

Prediction of Malignant Course

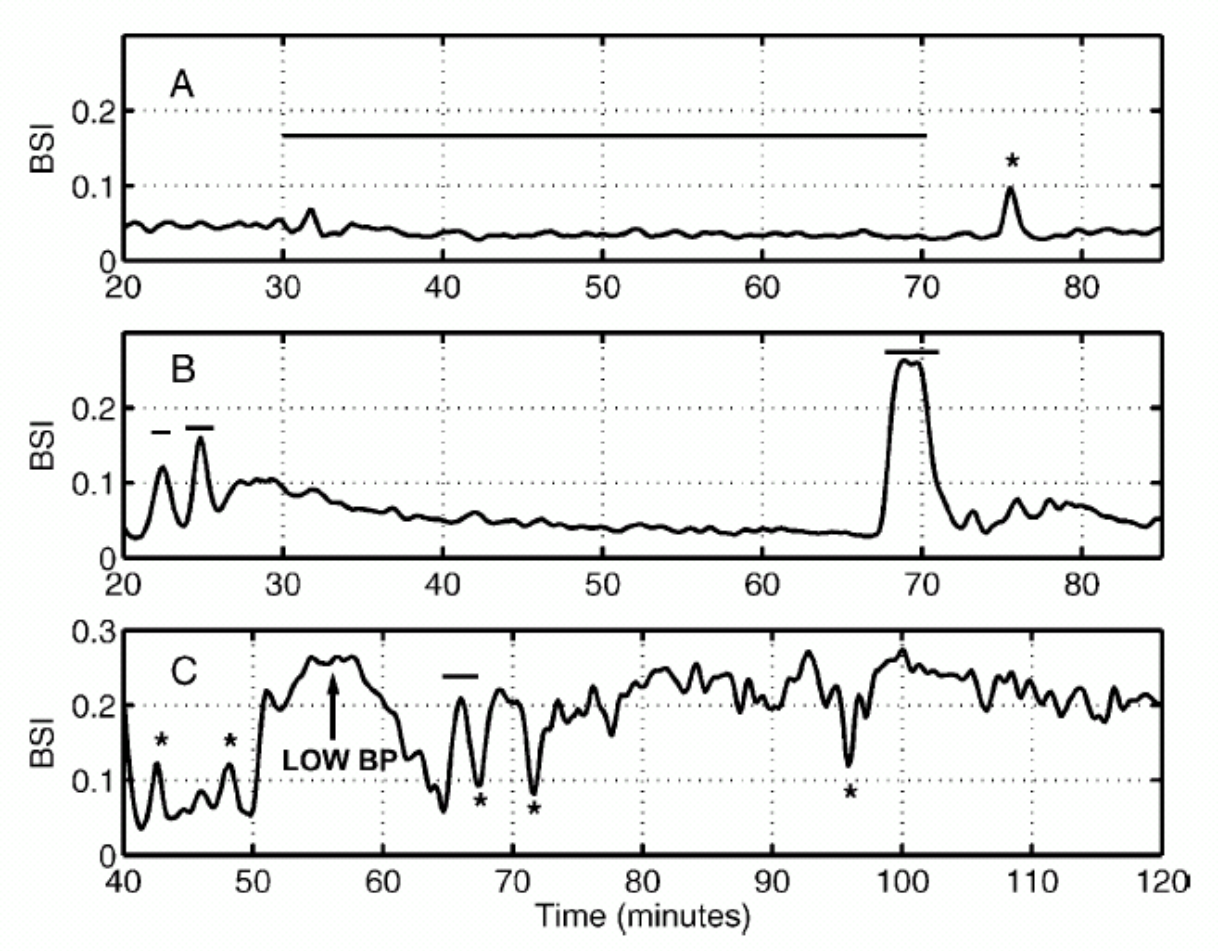
- 25 patients with large (>50%) middle cerebral artery (MCA) infarction
  - 12 malignant, 13 benign course
- EEG within 24 hours, visual analysis
- Predictors
  - Benign course: absence of delta activity, presence of theta and fast beta frequencies
  - Malignant course: diffuse slowing (< 8 Hz), slow delta activity (< 1 Hz), loss of fast beta in the ischemic hemisphere

Burghaus et al. Clin Neurol Neurosurg 2007;109:45-49

Asymmetry Indices

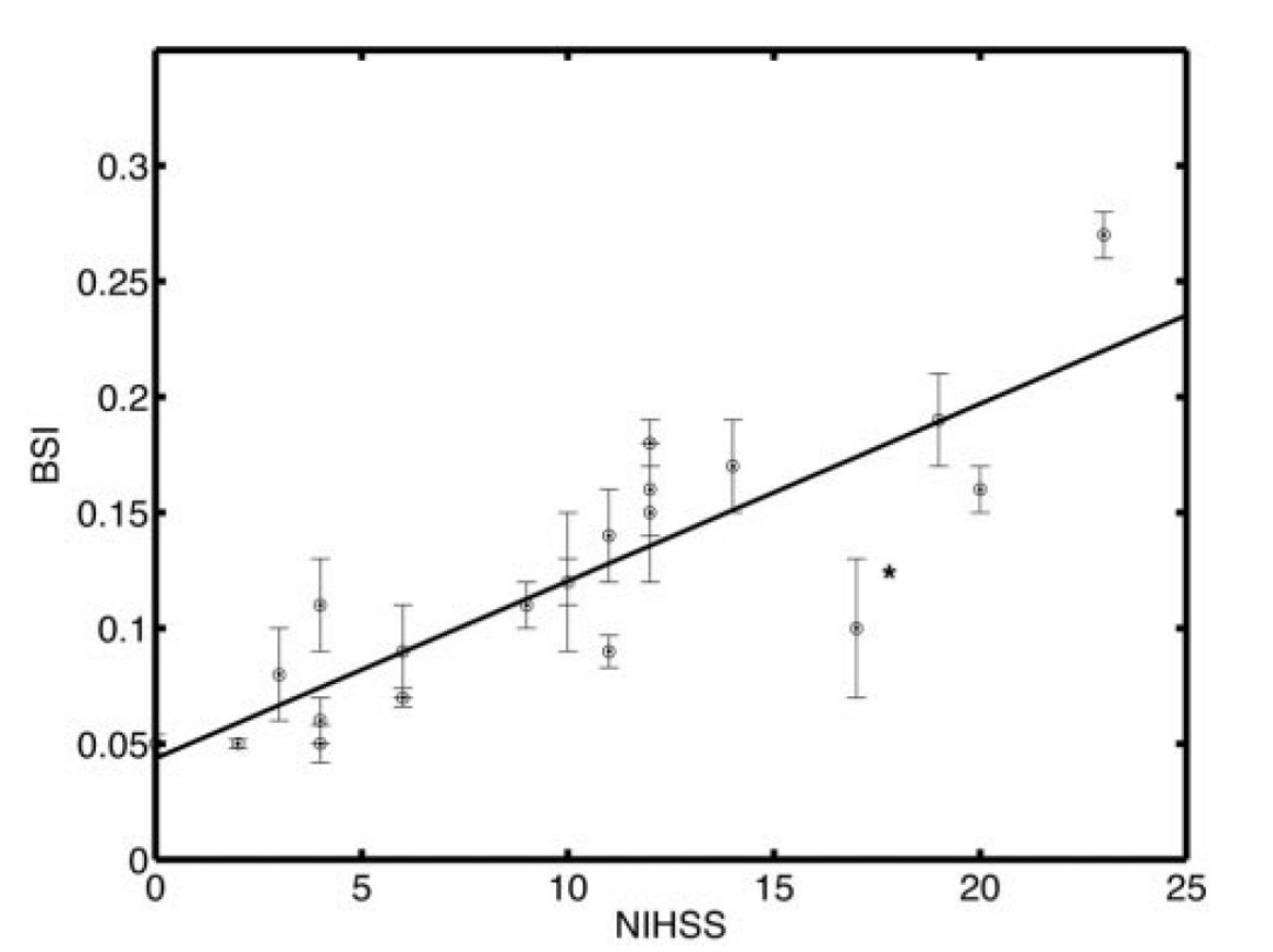
- Brain Symmetry Index (BSI)
  - Single numerical value: sums absolute values of the differences at each homologous electrode pair for all frequencies
    - 0: perfect symmetry
    - 1: maximal aymmetry
  - Correlates with clinical stroke scales
  - Has been used to follow effect of tPA

BSI for Carotid Endarterectomy



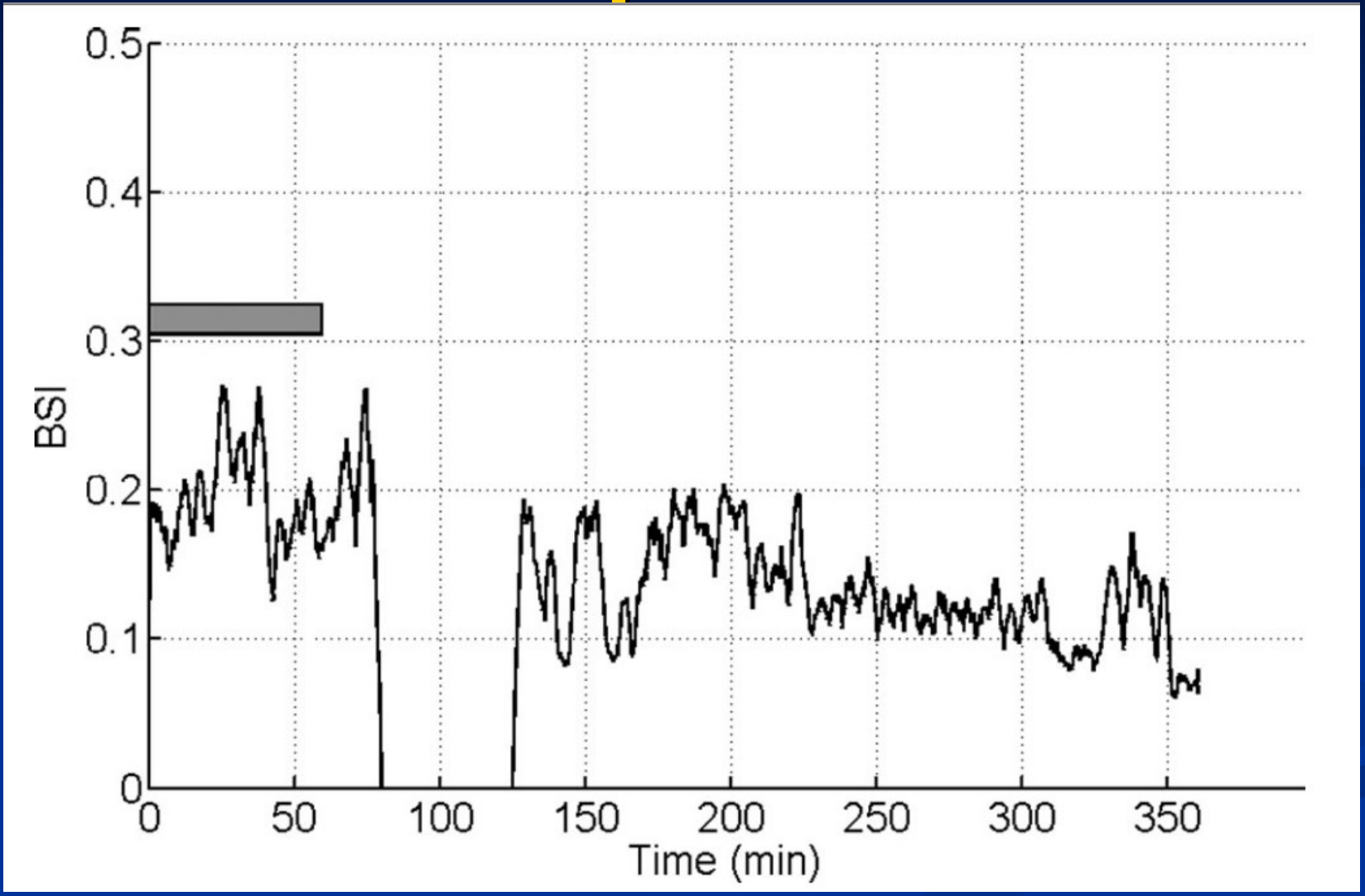
van Putten MJ, et al. Clin Neurophysiol 2004;115:1189

BSI and NIH Stroke Scale



van Putten MJ, et al. Stroke 2004;35:2489-2492

BSI: Response to tPA



de Vos CC et al. J Clin Neurophysiol 2008;25:77-82

Ischemic Stroke: Confounders

- Spontaneous or provoked state changes
- Variations in physiological parameters (BP, ICP, cerebral perfusion pressure)
- Sedative medications
- Artifacts (EMG, electrode)

Ischemic Stroke: Caveats

- Differential diagnosis of lateralized slowing / loss fast
  - Focal postictal states
  - Hemiplegic migraine
- Cortical infarctions < 3 cm may not show EEG changes
- Lacunar infarcts often show normal EEG
- Medial lesions may produce bilateral rather than focal EEG changes
- Almost no data on continuous EEG monitoring to detect worsening ischemia in real time

Conclusions

- EEG is a useful monitoring tool for cerebral ischemia
  - Large vessel territorial ischemia
  - Good sensitivity, moderate specificity
- Retrospective studies have demonstrated helpful QEEG methods in CEA, SAH
  - Limited by
    - Lack of specificity (hydrocephalus, sedatives, etc)
    - Artifacts
- No prospective real-time analysis
- Need prospective randomized blinded trials