Supplemental Digital Content

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eTable 1: Expanded information on questionnaire devised by the research team

Domain	**Evaluator questions** [a] (based on pt. response); [b] (based on pt. response and RN input / chart review)	
Acute change / Fluctuating course	▪ Acute onset / fluctuating course (0=N, 1=Y)	[a] Also had: ▪ Felt confused in past day? (0=N, 1=Y) ▪ Disoriented to place in past day? (0=N, 1=Y) ▪ Observation (during eval.) (Each: 0=N, 1=Y): ○ Fluct. LOC / Attention / Speech or thinking? ▪ Acute change in memory/thinking? (<24h) / off baseline?
Attention	▪ "SAVEAHAART" (Squeeze or tap on "A") [a] (Total errors (0-10), Missed A's (0-4), Non-A taps (0-6)) [b] (Total errors: 0/1x, 2x, >2x) ▪ DOW backwards? [a] (0 =correct, 1= incorrect) [b] (Total errors: 0x, 1x, >1x)	[a] Also had: ▪ MOY backwards (0 =correct, 1= incorrect) ▪ Digits backwards (3- , 4-digits) (each: 0=correct, 1=incorrect) ▪ Observation (during eval.) (Each: 0=N, 1=Y): ○ Trouble keeping track of things said? ○ Inappropriately distracted by environmental stimuli?
Level of conscious -ness (LOC)	▪ RASS (-5 to +4)	[a] Also had: ▪ Observation (during eval.) (Each: 0=N, 1=Y): ○ Sleepy? ○ Stupor or coma? ○ Hypervigilance?
Thinking	▪ 4 logic q's (each: 0=correct, 1=incorrect): 1) Will a stone float on water? 2) Are there fish in the sea? 3) Does 1lb weigh > 2lbs? 4) Can you use hammer to hit nail?	[a] Also had: ▪ Observation (during eval.) (Each: 0=N, 1=Y): ○ Flow of ideas unclear / illogical? ○ Conversation rambling / inappropriately verbose / tangential? ○ Speech limited / sparse?
Orientation	▪ Name? (0=correct, 1=incorrect) ▪ Month? (0=correct, 1=incorrect) ▪ Year ? (0=correct, 1=incorrect)	[a] Also had: ▪ Day? (0=correct, 1=incorrect) [b] Also had: ▪ City? (0=correct, 1=incorrect) ▪ Hosp. (MGH)? (0=correct, 1=incorrect)
Memory	▪ Memory recall (3-words) [a] 0, 2, 5 min (each: 0=no errors, 1=any errors) [b] 0, ~2 min (registration: 0 =correct, 1= incorrect; recall: # correct out of 3)	
Perceptual	▪ Visual hallucinations in past day? [a] (0=N, 1=Y) [b] (UTA, 0=N, 1=Y)	[b] Also had: ▪ Auditory hallucinations in past day? (UTA, 0=N, 1=Y) Feel unsafe / think someone is trying to harm you in past day? (UTA; 0=N, 1=Y)
Psychomotor	Observation (during eval.): ▪ Psychomotor agitation? (None, mild, major) ▪ Psychomotor retardation? (None, mild, major)	
Sleep	▪ Sleep quality in past day? [a] (0=well, 1=not well) [b] (UTA, none, mild or major problems)	

[a] Collected for Subjects 001 – 208 (Aug 2015 – Dec 2016)
[b] Collected for Subjects 209 – 407 (Oct 2018 – Dec 2019)

eTable 2: Expanded information on the rules used for scoring the severity of CAM-S domains

CAM-S Domain	Severity scoring	
1) Acute change / Fluct. course, 0-1	**0**	**0 = not present ; 1 = present**
	1	[a] Y to any of the following observation q's: 'Fluct. LOC/Attention/Speech or thinking at eval.?', or 'Acute change in memory/thinking (<24h) / off baseline' [b] Y to 'Acute onset or fluct. course' (via eval. / RN input / Chart review)
2) Inattention, 0-2	**0**	**0 = not present ; 1 = present (mild) ; 2 = present (marked)**
	1	[a] If the following subject q's incorrect: 'DOW backwards', 'SAVEAHAART' (2 errors); or if Y to any of the following observation q's: 'Trouble keeping track of things said', 'Inappropriately distracted by environmental stimuli' [b] If the following subject q's incorrect: 'DOW backwards'(1 error); 'SAVEAHAART' (2 errors)
	2	[a] If the following subject q's incorrect: 'SAVEAHAART' (3+ errors) [b] If the following subject q's incorrect: 'DOW backwards'(2+ errors); 'SAVEAHAART'(3+ errors)
3) Altered level of consciousness (LOC), 0-2	**0**	**0 = not present ; 1 = present (mild) ; 2 = present (marked)**
	1	[ab] RASS ± 1 / 2
	2	[ab] RASS ≤ -3 or ≥ +3
4) Disorganized thinking, 0-2	**0**	**0 = not present ; 1 = present (mild) ; 2 = present (marked)**
	1	[a] Combined # of errors (among 4 logic q's) = 1 ; or if Y to any of the following observation q's: 'Flow of ideas unclear / illogical', 'Conversation rambling / inappropriately verbose / tangential', 'Speech limited/sparse' [b] Combined # of errors (among 4 logic q's) = 1
	2	[ab] Combined # of errors (among 4 logic q's) = 2+
5) Disorientation, 0-2	**0**	**0 = not present ; 1 = present (mild) ; 2 = present (marked)**
	1	[a] 1 incorrect orientation domain (person/place/time): 'Name' (person) or 'Month / Year' (time) [b] 1 incorrect orientation domain (person/place/time): 'Name' (person) or 'City / Hosp.' (place) or 'Month / Year' (time)
	2	[a] 2 incorrect orientation domains (person/place/time): 'Name' (person) & 'Month / Year' (time) [b] 2-3 incorrect orientation domains (person/place/time): 'Name' (person), 'City / Hosp.' (place), 'Month / Year' (time)
6) Memory impairment, 0-2	**0**	**0 = not present ; 1 = present (mild) ; 2 = present (marked)**
	1	[a] If 'Memory registration (0-min)' correct + 'Memory recall (2-min and 5-min)' incorrect [b] If 'Memory registration (0-min)' correct + 'Memory recall (~2min)' incorrect (2/3 words missed)
	2	[a] If 'Memory registration (0-min)' incorrect + 'Memory recall (2-min and 5-min)' incorrect [b] If 'Memory registration (0-min)' in/correct + 'Mem. recall (~2min)' incorrect (3/3 words missed)
7) Perceptual disturbances, 0-2	**0**	**0 = not present ; 1 = present (mild) ; 2 = present (marked)**
	1	[a] Y to the following subject q.: 'In past day, see things not there? (visual hallucination) (mild) [b] Y to 1 of the following subject q.'s: 'In past day, 'see' / 'hear' things not there?', 'In past day, feel unsafe / someone trying to harm you (paranoia)?' [or indicated via RN input/chart review]
	2	[a] Y to the following subject q.: 'In past day, see things not there? (visual hallucination) (major) [b] Y to 2+ of the following subject q.'s: 'In past day, 'see' / 'hear' things not there?', 'In past day, feel unsafe / someone trying to harm you (paranoia)?' [or indicated via RN input/chart review] (If only 1 of the above, may also count if found to be more severe / dramatic)
8) Psychomotor agitation, 0-2	**0**	**0 = not present ; 1 = present (mild) ; 2 = present (marked)**
	1	[ab] Observational (mild) or if RASS +1
	2	[ab] Observational (major) or if RASS ≥ +2
9) Psychomotor retardation, 0-2	**0**	**0 = not present ; 1 = present (mild) ; 2 = present (marked)**
	1	[ab] Observational (mild) or if RASS -2/-3
	2	[ab] Observational (major) or if RASS -4/-5
10) Altered sleep-wake cycle, 0-2	**0**	**0 = not present ; 1 = present (mild) ; 2 = present (marked)**
	1	[a] If the following subject q. 'Sleep quality in past day?' = not well (mild) [b] If the following subject q. 'Sleep quality in past day?' = problematic, mild (e.g. falling/waking/ excessive daytime sleepiness w. insomnia at night, nightmares) [or indicated via RN/ chart]
	2	[a] If the following subject q. 'Sleep quality last night?' = not well (major); if RASS -4/-5 [b] If the following subject q. 'Sleep quality in past day?' = problematic, major (e.g falling/waking/ excessive daytime sleepiness w. insomnia at night, nightmares) [or indicated via RN/chart]; RASS -4/-5; or sedated overnight/at eval.
		[b] If pt. rated sleep good and per RN/Chart disturbances were present – points assigned; if pt. endorsed poor sleep but undisturbed per RN – points retained.

[a] Collected for Subjects 001 – 208 (Aug 2015 – Dec 2016)

[b] Collected for Subjects 209 – 407 (Oct 2018 – Dec 2019)

eTable 3: Visual EEG features and model constraints

Type	Feature [c]	Model Sign Constraint
Background / Rhythm Abnormalities	Absent sleep transients (Spindles, K-complexes, Vertex waves)	+ or 0
	Asymmetry	+ or 0
	Lateralized Rhythmic Delta Activity (LRDA)	+ or 0
	Generalized Rhythmic Delta Activity (GRDA)	+ or 0
	Generalized (G) / Diffuse Delta Slowing	+ or 0 [a]
	Generalized (G) / Diffuse Theta Slowing	+ or 0 [a]
	Intermittent brief attenuation (IBA)	+ or 0
	Low voltage: Moderate (MLV; <20μV)	+ or 0
	Low voltage: Extreme (ELV) / Electrocerebral Silence (ECS)	W [b]
	Extreme Delta Brush (EDB)	W [b]
	Burst Suppression (BS) with epileptiform activity	W [b]
	Burst Suppression without epileptiform activity	W [b]
	Unreactive EEG	W [b]
Seizure Activity	Generalized Nonconvulsive Status Epilepticus (G-NCSE)	W [b]
Periodic Discharges	Generalized Periodic Discharges (GPDs, with or without triphasic morphology), or Triphasic Waves (TWs), or Bilateral Independent Periodic Discharges (BIPDs)	+
	Lateralized Periodic Discharges (LPDs)	+ or 0

[a] EEG slowing was scored based on a patient's best awake background

[b] Always predict worst delirium severity

[c] Features coded but not included in the model: Absence of a normal Posterior Dominant Rhythm (PDR); Excess / Diffuse Alpha; Excess / Diffuse Beta; Sporadic discharges (focal or generalized); Brief Potentially Ictal Rhythmic Discharges (BIRDs); Discrete Seizures (focal (F) or generalized (G)), Focal Nonconvulsive Status Epilepticus (F NCSE)

eTable 4: Look-up table that converts VE-CAM-S score to CAM-S LF score

VE-CAM-S (0-20)	CAM-S LF (0-19)	GOS≤3 at discharge (%)	In-hospital Mortality (%)	3-month Mortality (%)
0	0	47	7	12
1	1	52	8	14
2	2,3	56	9	16
3	4,5,6	61	11	18
4	7,8,9	65	12	21
5	10,11	69	14	23
6	12,13	73	16	26
7	14,15	76	18	29
8	15+	80	21	33
9	15+	83	24	36
10	15+	85	27	39
11	15+	88	30	43
12	15+	90	34	46
13	15+	91	37	49
14	15+	93	41	53
15	15+	94	45	56
16	15+	95	49	59
17	15+	96	53	62
18	15+	96	57	65
19	15+	97	61	67
20	15+	97	65	70

eTable 5: VE-CAM-S performance on subsets

Subset	N	Spearman's correlation R	AUC (≤4 vs. ≥5)	Calibration slope (≤4 vs. ≥5)
Young (<40y)	65	0.79 (0.68 – 0.86)	0.92 (0.84 – 0.98)	1.34 (0.99 – 1.60)
Middle-aged (40 – 59y)	118	0.78 (0.70 – 0.84)	0.87 (0.80 – 0.93)	0.90 (0.71 – 1.30)
Old (≥60y)	224	0.52 (0.41 – 0.62)	0.80 (0.73 – 0.87)	0.84 (0.55 – 1.10)
Male	235	0.68 (0.59 – 0.75)	0.89 (0.84 – 0.94)	1.11 (0.93 – 1.33)
Female	172	0.67 (0.58 – 0.75)	0.82 (0.76 – 0.89)	0.90 (0.63 – 1.15)
White	321	0.66 (0.59 – 0.73)	0.85 (0.80 – 0.89)	0.97 (0.80 – 1.17)
Black	36	0.67 (0.40 – 0.86)	0.89 (0.74 – 0.99)	1.32 (0.71 – 1.71)
ICU patients	175	0.51 (0.39 – 0.61)	0.87 (0.76 – 0.94)	0.69 (0.29 – 1.04)
Non-ICU patients	232	0.55 (0.45 – 0.63)	0.81 (0.75 – 0.86)	0.99 (0.79 – 1.24)
Non-comatose	277	0.53 (0.43 – 0.61)	0.79 (0.74 – 0.84)	0.99 (0.78 – 1.18)

eTable 6: Adjusted odds ratios and p values of CAM-S LF & VE-CAM-S for predicting outcomes

Outcome	Score	Odds ratio when score increases by 1	p
GOS≤3 at discharge	CAM-S LF	1.22 (1.18 – 1.27)	<0.001
	VE-CAM-S	1.19 (1.12 – 1.36)	<0.001
In-hospital mortality	CAM-S LF	1.41 (1.26 – 1.82)	<0.001
	VE-CAM-S	1.20 (1.15 – 1.27)	<0.001
3-month mortality	CAM-S LF	1.20 (1.15 – 1.26)	<0.001
	VE-CAM-S	1.14 (1.10 – 1.19)	<0.001

eTable 7: Comparison of studies with EEG classification systems and their prognostic value

Article [a]	Study Type	Study Population	Scale Type	Sample Size	Outcomes Evaluated	Association with Outcome
Bickford (1955) [1]	Prospective	Hepatic coma; pts. w. cirrhosis w/o mental change	Nominal	21 patients	Mortality, Cognitive	*Qualitative*
Parsons-Smith (1957) [2]	Prospective	Liver dz & varying degrees of neuropsych disturbance	Grading scale (Parsons-Smith), Ordinal	66 patients (157 EEGs)	Cognitive (neuropsychiatric state)	*Qualitative*
Silverman (1962) [3]	Retrospective	Impending or actual hepatic coma	Nominal	53 patients (123 EEGs)	Consciousness, clinical status	*Qualitative*
Hockaday (1965) [4]	Retrospective, cohort study	Coma w. acute cardiac arrest or total apnea	Grading scale (Hockaday), Ordinal	39 patients	Mortality	*Qualitative*
Bergamasco (1968) [5]	Prospective	Post-traumatic coma	Nominal	18 patients	Mortality / coma recovery	*Qualitative*
Binnie (1970) [6]	Retrospective	Anoxic injury after CPR post-cardiac arrest	Grading scale (Binnie), Ordinal	41 patients (93 EEGs)	Mortality	*Qualitative*
Hughes (1976) [7]	Prospective	Anoxic, traumatic (cerebrally unresp., coma)	Grading scale (Hughes), Ordinal	63 patients (345 EEGs)	Neuro status	*P-value* (btw EEG index and Neuro index, $p<0.0001$)
Karnaze (1984) [8]	Cohort (retrospective, prospective)	EEG showing TWs	Nominal	50 patients	Mortality, consciousness	*Qualitative*
Sundaram (1987) [9]	Retrospective	Encephalopathy & TWs	Nominal	63 patients (66 EEGs)	Mortality	*Qualitative*
Scollo-Lavizzari (1987) [10]	Retrospective	Post-anoxic coma after cardiac arrest	Grading scale (SL-Basetti), Ordinal	26 patients	Mortality	*Qualitative*
Synek (1988) [11]	N/A	Adults w. traumatic & anoxic coma	Grading scale (Synek), Ordinal	N/A	Mortality	*Qualitative*
Bahamon-Dussan (1989) [12]	Retrospective	EEGs in which TWs were prominent pattern occupying ≥35%	Nominal	30 patients	Mortality, Neurological	*Qualitative*
Rae-Grant (1991) [13]	Retrospective	Posttraumatic pts, coma	Grading scale (Rae-Grant), Interval	57 patients	Neurological / Functional (GOS) [d/c]	*Pearson's* (correlation = 0.516, $p=0.0001$ for dichotomous EEG score w. GOS)
Young (1992) [14]	Prospective	Septic encephalopathy (positive blood cultures), Age >16	Grading scale, Ordinal	62 patients	Mortality	*P-value* (mortality varied w. encephalopathic category, $p<0.001$; EEG classifications across grps, $p<0.0001$)
Yamashita (1995) [15]	Retrospective	ICU pts w. anoxic encephalopathy post-CPR	Grading scale (Hockaday - modified), Ordinal	79 patients	Mortality, Neurological	*Qualitative*
Young (1996) [16]	Retrospective	NICU pts w. NCS undergoing cEEG	Nominal	49 patients	Mortality / disabled / d.c home	*OR* (Sz duration assoc. w. incr. mortality, $p=.0057$; OR=1.131/h

Article [a]	Study Type	Study Population	Scale Type	Sample Size	Outcomes Evaluated	Association with Outcome
Young (1997) [17]	Retrospective	Coma in general ICU; Age >16; coma onset 24-72h prior to EEG	Grading scale (Young), Ordinal	92 patients (100 EEGs)	Inter-observer reliability w. Synek scale	*Kappa score* (K=0.90 for our system and 0.75 for Synek)
Litt (1998) [18]	Prospective	ICU pts w. NCSE on EEG; Age ≥ 65	Nominal	24 patients	Mortality	*P-value* (death assoc. w. generalized NCSE, p = 0.017)
Young (1999) [19]	Retrospective	Comatose pts in general ICU	Grading scale (Young), Ordinal	N/A	Mortality	*OR, PPV* (Suppression, no reactivity strongly related to mortality; PPV >0.80, OR >2.0; focal epil. act., regional delta, reactivity favored survival)
Amodio (1999) [20]	Prospective	Cirrhotic pts. w/o overt encephalopathy or grade1	Grading scale (Parsons-Smith modified), Ordinal	32 patients (43 EEGs)	Cognitive (psychometric)	*Spearman's (*R = 0.57 P=0.004 and R=0.42 P=0.4, grader A & B, respectively).
Claassen (2006) [21]	Prospective	Critically ill, w. SAH undergoing cEEG in ICU	Nominal	116 patients	Neurological / Functional (mRS) [3mo-post SAH]	*OR, PPV, NPV* (poor outcome assoc. w. absence of sleep architecture, OR=4.3, 95%-CI 1.1-17.2, & presence of PLEDs, OR=18.8, 95%-CI 1.6-214.6)
Claassen (2007) [22]	Retrospective	Nontraumatic spont. ICH undergoing cEEG	Nominal	102 patients	Mortality, Neurological/ Functional (GOS) [d/c]	*OR* (PEDs were indep. assoc. w. poor outcome, OR 7.6, 95% CI 2.1 to 27.3)
Watson (2008) [23]	Post-hoc: prospective, observ. cohort	Critically ill, mechanically ventilated in MICU, Age ≥ 18	Nominal	125 patients	Mortality [ICU, hosp., 6mo], LOS [ICU, 1st vent, hosp., post-ICU]	*HR* (pts w. burst suppression had stat. sig. higher 6-mo. mortality, HR = 2.04, p = 0.02)
Oddo (2009) [24]	Retrospective	MICU pts undergoing cEEG; no acute neurological injuries	Nominal	201 patients	Mortality, Neurological / Functional (GOS) [d/c]	*OR* (ESZs or PEDs was assoc. w. death or severe disability at hosp. d/c, OR 19.1, *p* < 0.001)
Roest (2009) [25]	Retrospective, cohort study	Adult ICU pts w. post-anoxic coma	Grading scale (Synek, Young; Revised), Ordinal	115 patients (174 EEGs)	Mortality, Neurological/ Functional (GOS) [30,180d]	*HR* (Rev. Young classification, derived from EEG at d1–5, was most predictive, HR=2.06; P=0.006; 95% CI=1.52–3.52)
Bagnato (2010) [26]	Prospective	Impaired consciousness post-coma, LCF ≤4; no anoxic encephalopathies	Grading scale (Synek), Ordinal	46 patients	Cognitive (LCF)	*Spearman's* (sig. correl. btw Synek scores & LCF scores, at admission, & LCF variation in pts w. TBIs, r = -0.53; p < 0.01)
Boccagni (2011) [27]	Prospective	Impaired consciousness post-anoxic coma	Grading scale (Synek), Ordinal	15 patients	Cognitive (LCF)	*Spearman's* (Synek score sig, correl. w. LCF at admit (r= -0.69; p=0.004); Synek score sig. correl. w. changes in LCF at 3mo, r = -0.86; p<0.001)
Logi (2011) [28]	Retrospective	Unconscious pts w. TBI / CVD / anoxia; GCS ≤8, LCF ≤2	Grading scale (Synek), Ordinal	50 patients	Mortality, Cognitive (LCF)	*OR* (Synek malignant vs uncertain: OR 0.13; EEG-R = good (+) factor for prognosis of recovery of consciousness)

Article [a]	Study Type	Study Population	Scale Type	Sample Size	Outcomes Evaluated	Association with Outcome
Foreman (2012) [29]	Retrospective, case-control	Pts w. GPDs, Age > 18	Nominal	200 patients	Mortality, LOS, Neurological/ Functional (GOS)	*P-value* (GPDs assoc. w. incr. mortality on univariate analysis, p=0.049, but not multivariate)
Kamel (2013) [30]	Retrospective, cohort study	No acute brain injury w. cEEG in MICU/SICU	Nominal	105 patients	LOS, Neurological / Functional (GOS) [d/c]	*OR* (ESz assoc. w. lower odds of good outcomes on GOS at d/c, OR 0.3, 95 % CI 0.1–0.8)
Polito (2013) [31]	Prospective, observational	Septic shock w. acute brain dysfunction in MICU / SICU, Age<80	Grading scale (Synek), Ordinal	71 patients (47 with EEG)	Mortality, LOS [ICU, hosp.], Neurological/ Functional (GOS) [6mo]	*P-value* (Grade 3 was significantly more frequent in pts who died, p=0.001)
Kurtz (2014) [32]	Retrospective	SICU pts w. unexplained AMS undergoing cEEG	Nominal	154 patients	Mortality, Neurological / Functional (GOS) [d/c]	*OR* (NCSz were indep. assoc. w. poor outcome; OR 10.4, 95%-CI 1.0-53.7; p=0.039)
Rossi Sebastiano (2015) [33]	Prospective	Chronic disorders of consciousness; adult	Grading scale (Synek; arbitrary - sleep), Ordinal	142 patients	Coma Recovery Scale-Revised (CRS-R)	*P-value, Cluster analysis*
Alvarez (2015) [34]	Prospective, observational cohort study	Status epilepticus undergoing cEEG, Age > 16	Nominal	120 patients	Mortality, complete clinical recovery [d/c]	*AUC, OR* (No PDR, OR 9.8; p = 0.033, w. mortality; changes in SII sleep, OR 2.59; p = 0.002, for complete recovery; AUC using PDR & STESS to predict mortality = 0.79)
Gilmore (2015) [35]	Prospective, observational	MICU pts w. severe sepsis and multi-organ dysfunction	Nominal	98 patients	Mortality, Neurological / Functional (mRS), Cognitive (TICS) [d/c, 6mo, 1yr]	*P-value* (No reactivity assoc. w. higher 1y mortality, p=0.002; No reactivity, NCS or PD not assoc. w. functional outcome; no assoc. btw NCSE, NCS, PD, or no reactivity & cog. outcome)
Azabou (2015) [36]	Prospective, observational	ICU pts w. sepsis, Age ≥ 18	Grading scale (Synek; Young), Ordinal	110 patients	Mortality [ICU, hosp.]; Severity of sepsis / sedation / neuro status	*OR* (No reactivity, delta-predominant background, PDs, Synek≥3 and Young >1 were indep. predictors of ICU mortality: OR= 4.44, 3.36, 3.24, 5.35, 3.44; & were assoc. w. occurrence of delirium)
Azabou (2016) [37]	Prospective, cohort study	Post-anoxic coma pts in the ICU; >24hrs unconscious after CPR	Nominal; Grading scale (Synek) - Ordinal	61 patients	Mortality, Neurological / Functional (mGOS) [1y post-coma onset]	*AUC, PPV, NPV* ('Isoelectric, discontinuous, delta dominant, paroxysms, nonreactive' for predicting an unfavorable outcome w. AUC 0.53, 0.59, 0.63, 0.51, 0.82 respectively; Synek score >3 = 0.81)
Sutter (2016) [38]	Retrospective, observational, cohort study	Acute non-hypoxic encephalopathy; neuro /med/surg ICUs; Age≥18	Nominal	262 patients	Mortality [in-hospital]	*RR, HR* (Nonreactive, P<.0001, was indep. assoc. w. death & strongest predictor, RR 3.74)

Article [a]	Study Type	Study Population	Scale Type	Sample Size	Outcomes Evaluated	Association with Outcome
Knauert (2018) [39]	Retrospective, observational cohort study	MICU pts undergoing cEEG; no primary acute brain injury	Grading scale(Synek), Ordinal	93 patients	Mortality [hosp.], LOS [ICU, hosp.], Neurological / Functional (mRS) [d/c]	*OR* (w/o K-complexes, OR 18.8 (p=0.046); or w/o sleep spindles, OR 6.3 (p=0.036) incr. odds of death); Longer LOS (ICU): no K-complexes (p=.01), no sleep spindles, p=0.02)
Nielsen (2020) [40]	Prospective, observational	MICU pts w/o acute primary CNS dz and w. sepsis / septic shock / mono- or multi-organ failure; Age >18	Nominal	102 patients	Mortality [ICU, hosp., post-d/c], Cognitive (delirium)	*HR* (Preserved cEEG reactivity during all instances of arousal was only stat. significant marker for reduced mortality, HR 0.4; 95% CI 0.2–0.9; P<0.05, and preservation of cognitive fxn)
Kaplan (2004) [41]	Review	Metabolic encephalopathy & coma	N/A	N/A	N/A	N/A
Hosokawa (2014) [42]	Systematic Review	Sepsis-associated encephalopathy; Age≥18	N/A	N/A	N/A	N/A
Herman (2015) [43]	Consensus Statement	Critically ill adults/child w. encephalopathy on EEG	N/A	N/A	N/A	N/A
Sutter (2015) [44]	Review	ICU pts w. acute non-hypoxic encephalopathy; Age ≥ 18	N/A	N/A	N/A	N/A
Palanca (2017) [45]	Review	Post-op delirium	N/A	N/A	N/A	N/A
Gillinder (2019) [46]	Systematic Review	Pts w. anti-NMDA receptor encephalitis	N/A	N/A	N/A	N/A

[a] **Search strategy and selection criteria:** We conducted a literature search in PubMed including articles published from 1 January 1955 to 1 April 2019. The following search syntax was used: *(((Electroencephalogram OR Electroencephalography OR EEG)) AND (Encephalopathy OR Delirium OR Coma)) AND (Outcome OR Prognosis OR Mortality OR Morbidity OR Disability)*. Results were restricted to human studies with full text available. The reference lists of review articles were also checked for relevant studies. The results were screened based on clinical relevance, with a focus on papers which reported clinical outcomes in patients with a form of (acute) encephalopathy undergoing EEG. We excluded studies on pediatric patients, studies that recorded EEG exclusively intraoperatively, and studies with 10 or fewer subjects. The studies are separated by type (Primary vs Review) and sorted by year of publication.

Evidence before this study:

We conducted a literature search in PubMed including articles published from 1 January 1955 to 1 April 2019. The following search syntax was used: (((Electroencephalogram OR Electroencephalography OR EEG)) AND (Encephalopathy OR Delirium OR Coma)) AND (Outcome OR Prognosis OR Mortality OR Morbidity OR Disability). Results were restricted to human studies with full text available. The reference lists of review articles were also checked for relevant studies. The results were screened based on clinical relevance, with a focus on papers which reported clinical outcomes in patients with a form of (acute) encephalopathy undergoing EEG. We excluded studies on pediatric patients, studies that recorded EEG exclusively intraoperatively, and studies with 10 or fewer subjects.

We identified 6 reviews or consensus statements and 40 primary articles. Primary articles studied a mean of 82.3 patients (range 15-262, standard deviation 55.5). 19 studies explicitly studied ICU patients, 14 studied patients with coma, 10 studied patients post-cardiac arrest or anoxia, 5 studied patients with sepsis, 5 studied patients with hepatic failure, and 5 studied patients with trauma. Nominal scales, characterizing primarily the presence or absence of features, were used in 19 primary articles. Ordinal grading scales were used in 20 primary articles, with the most common being those based on prior work by Synek and Young. Only 1 primary article by Rae-Grant et al. described an interval scale, to characterize the severity of head injury in 57 patients using dichotomous variables of EEG features, which correlated with the Glasgow Outcome Score. Therefore, most past studies have been based on fewer than 100 patients and there is a marked paucity of interval-based EEG grading systems to predict multiple clinical outcomes.

Added value of this study:

Our study is the largest to date to develop a grading scale using visually assessed EEG findings. We used machine learning on a comprehensive set of visually assessable EEG features in a large and heterogeneous clinical cohort to develop the Visual EEG CAM-S (VE-CAM-S), a physiologic grading scale. VE-CAM-S is a physiological delirium grading scale for delirium and underlying encephalopathy. VE-CAM-S was validated in terms of its association with clinical outcomes, even after adjusting for age and sex, and with similar predictive value as the clinical CAM-S, age, and sex.

Implications of all the available evidence:

Collectively, the evidence suggests that even routine EEG findings can quantify delirium severity in a prospective, heterogeneous cohort with a wide spectrum of clinical disease, and provide additional information regarding important clinical outcomes. While there is an important role for quantitative analysis of EEG data, routine EEG can already serve as a valuable biomarker for delirium severity and may improve assessment across multiple clinical contexts. The consistency of identified EEG findings across multiple studies and contexts also suggests that further research is needed to identify the fundamental brain circuits giving rise to these prognostically important findings in order to develop new targeted therapies for neurocognitive vulnerability.

eTable 8: Comparison of selected EEG features and their prognostic value

EEG Feature	Clinical outcomes	Associated literature
Absent sleep transients (Spindles, K-complexes, Vertex waves)	• Unfavorable: Poor outcome [21, 47] Decr. likelihood of a complete recovery [34] Higher odds of death, longer LOS [39]	• Absence of sleep architecture, both within 24h of cEEG hookup and at any time (any time: OR=4.3, 95%-CI 1.1-17.2); sensitive but not specific for poor outcome [21]; [47] • Changes in SII sleep assoc. w. outcome (OR 2.59, p=.002) for complete recovery [34] • Loss of stage N2 is assoc. w. more severe encephalopathy, higher odds of death (w/o K-complexes, OR = 18.8 (p=.046); w/o spindles, OR=6.3 (p=.036)); longer LOS [39]
Generalized / Diffuse Theta Slowing	• Benign (if persistent) [11a] • Unfavorable: Malignant (if persistent) [11b] Poor prognosis [41, 48]	• a) Dominant diffuse theta (moderate amplitude, reactive); b) Theta pattern coma [11] • Mixed pattern (diffuse theta patterns mixed w. other frequencies like delta or alpha), ≤12% survival rate [41] • Theta/delta and delta assoc. w. more severe alteration of consciousness; Theta/delta assoc. w. poor outcome (OR=2.5, P=0.03) [48]
GRDA (Generalized Rhythmic Delta Activity)	• Benign (if persistent) [11] Better / favorable outcome [48, 49]	• FRDA (reactive/non-reactive) [11] • Theta/delta and delta assoc. w. more severe alteration of consciousness; FIRDA assoc. w. good outcome (OR=4.8, p=0.004) [48]; FIRDA assoc. w. better outcome [49]
LRDA (Lateralized Rhythmic Delta Activity)	• No diff. in mortality odds; higher odds of good functional outcome [50] • Unfavorable: Incr. risk of acute electrographic Sz [50, 51]	• No diff. in mortality odds btw LRDA-only and control grps; LRDA-only had higher adj. odds of good functional outcome at clinic follow-up (OR 3.8, CI 1.0-13.2, p=0.04) compared to control grp; incr. risk of acute electrographic Sz [50] • LRDA in critically ill pts had a similar clinical significance as LPDs, LRDA was an indep. predictor of acute seizures [51]
LPDs (Lateralized Periodic Discharges)	• Unfavorable: Malignant (if persistent) [32] Poor functional outcome [21, 22] Incr. mortality or severe disability at d/c [24]	• PLEDs assoc. w. poor outcome (mRS 4-6); (OR=11.9; CI 2.9-49.2) [21, 22] • ESz or PEDs assoc. w. mortality or severe disability at d/c (adj.OR=19.1, P= 0.001) [24] • PEDs (including GPDs, PLEDs, BIPLEDs) persisting for >24h assoc. w. poor outcome (OR=2.9, P=0.01) [32]
Low voltage: Moderate (<20µV)	• Unfavorable: Fatal (unless drug/hypothermia induced) [11] Poor prognosis [17, 19, 27, 52]	• Low output EEG, < 20µV [11] • Generalized suppression; less marked [17, 19, 52] • Generalized suppression, <20µV [27]
Generalized / Diffuse Delta Slowing	• Uncertain [11a] • Unfavorable: Malignant (if persistent) [11b] Incr. mortality [14, 42] ICU admit, incomplete recovery [46] Poor outcome [48]	• a) Diffuse delta (reactive/non-react.); b) Low amplitude delta [11] • Slowing: Delta (OR = 2.4), suppression (OR = 4.5) assoc. w. incr. mortality [14, 42] • Gen delta slowing, including EDB, correlated w. ICU admit (OR=1.92, 95%-CI 1.20, 3.07; p=0.007) and incomplete recovery (OR=2.23, 95%-CI 1.09, 4.56; p=0.03) [46] • Theta/delta and delta assoc. w. more severe alteration of consciousness; Theta/delta assoc. w. poor outcome (OR=2.5, P=0.03) [48]
GPDs (Generalized Periodic Discharges) with or without triphasic morphology, or Triphasic Waves (TWs), or BIPDs (Bilateral Independent Periodic Discharges)	• No indep. assoc. w. worse outcomes [48] • Unfavorable: Poor prognosis [12, 29, 32] Incr. mortality risk [14, 24, 48] Incr. mortality / severe disability at d/c [24, 53] Incr. LOS (ICU) [29]	• PEDs assoc. w. poor outcome (OR=7.6; CI 2.1-27.3) [22]; ESz or PEDs assoc. w. mortality or severe disability at d/c (adj. OR=19.1, P=0.001) [24]; PEDs (including GPDs, PLEDs, BIPLEDs) persisting for >24h assoc. w. poor outcome (OR=2.9, P= 0.01) [32]; GPDs not indep. assoc. w. worse outcome (incr. mortality on univariate analysis, p=0.049, but not on multivariate), assoc. w. longer ICU stay (P = 0.002) [29] • TWs [12], TWs assoc. w. mortality (OR=1.5) [14]; TWs assoc. w. more severe alteration of consciousness and w. higher mortality (OR = 4.5, P = 0.005) [48] • In multivariate analyses, BIPDs remained assoc. w. mortality (OR: 3.0 [1.4– 6.4]) & poor outcome (OR: 2.9 [1.4–6.2]) [53]
Intermittent brief attenuation	• Unfavorable: Malignant [11]	• Short, <1s, episodes of bilateral suppression (w. low amp. diffuse irregular delta), intervals of bilateral suppression lasting several secs (w. theta pattern coma) [11]

EEG Feature	Clinical outcomes	Associated literature
EDB (Extreme Delta Brush)	• Unfavorable: Higher likelihood of ICU admit or poorer outcome [46] , prolonged hospitalization [54]	• Gen delta slowing, including EDB, correl. w. ICU admission (OR = 1.92, 95%-CI 1.20, 3.07; p=0.007) and incomplete recovery (OR=2.23, 95%-CI 1.09, 4.56; p=0.03) [46] • EDB assoc. w. more prolonged hospitalization (*p*=.008) [54]
NCSE (Nonconvulsive Status Epilepticus): Generalized	• No assoc. w. survival, disability at d/c [35] • Unfavorable: Poor outcome [16, 18, 29, 32, 43] Incr. mortality[18] or severe disability at d/c [16, 32, 43]	• NCSE assoc. w. incr. mortality, risk for poor neurologic outcome [16, 43] • Gen. patterns of NCSE is assoc. w. death (p=0.017) [18] • NCSE indep. assoc. w. worse outcome [29] • NCSz (including NCSE) assoc. w. poor outcome: death & severe disability at d/c (OR = 10.4, P = 0.039) [32] • NCS wasn't assoc. w. outcome (survival/disability) at hosp. d/c or 1yr [35]
Low voltage: Extreme / ECS (Electrocerebral Silence)	• Unfavorable: Poor prognosis, Fatal (unless drug / hypothermia induced) [11, 37, 55]	• Low output EEG, Isoelectric (or near isoelectric) [11] • Isoelectric [37, 55]
Burst suppression (with or without epileptiform activity)	• Unfavorable: Malignant (if persistent) [11] Poor prognosis [10, 17, 23, 52] Incr. LOS (post-ICU hosp., total hosp.), Higher 6-mo mortality [23]	• Burst suppression [10, 11, 17, 52] • Longer post-ICU (HR=1.84, p=0.03), longer total LOS (HR=1.70, p=0.06); higher 6-mo mortality (HR=2.04, P=0.02) [23] • Burst suppression w. generalized epileptiform act. [27]
Unreactive EEG	• Uncertain [11, 28] • Unfavorable: Poor outcome [28, 32, 36, 37] Incr. mortality [35, 36, 37, 38, 48, 56]	• Non-reactive [11] • Absence of reactivity is not invariably assoc. w. a poor prognosis [28] • No reactivity tended to be assoc. w. poor outcome (OR=2.8, P=0.13) but wasn't sig. [32] • Absence of reactivity assoc. w. mortality up to 1-yr post-d/c (p=0.002) [35] • Absence of reactivity assoc. w. unfavorable outcome; ICU mortality indep. assoc. (OR=4.44) [36, 37] • Absence of background reactivity is assoc. w. incr. mortality (p<0.0001) [38] • Absent reactivity was indep. assoc. w. death (OR 3.73, 95%CI 1.08-12.80, p=0.037)[48] • Unreactive background was incompatible w. good long-term neuro recovery (CPC 1-2), strongly assoc. w. in-hosp. mortality (adj. OR for death, 15.4; 95%-CI, 3.3-71.9) [56]

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eFigure 1: Flow diagram of subject enrollment

Timeframe: Aug 2015 – Dec 2016, Oct 2018 – Dec 2019 [a]

Screening: only maintained strict records of subjects evaluated in-person

Assessed: 406 individual subjects [b]

↓

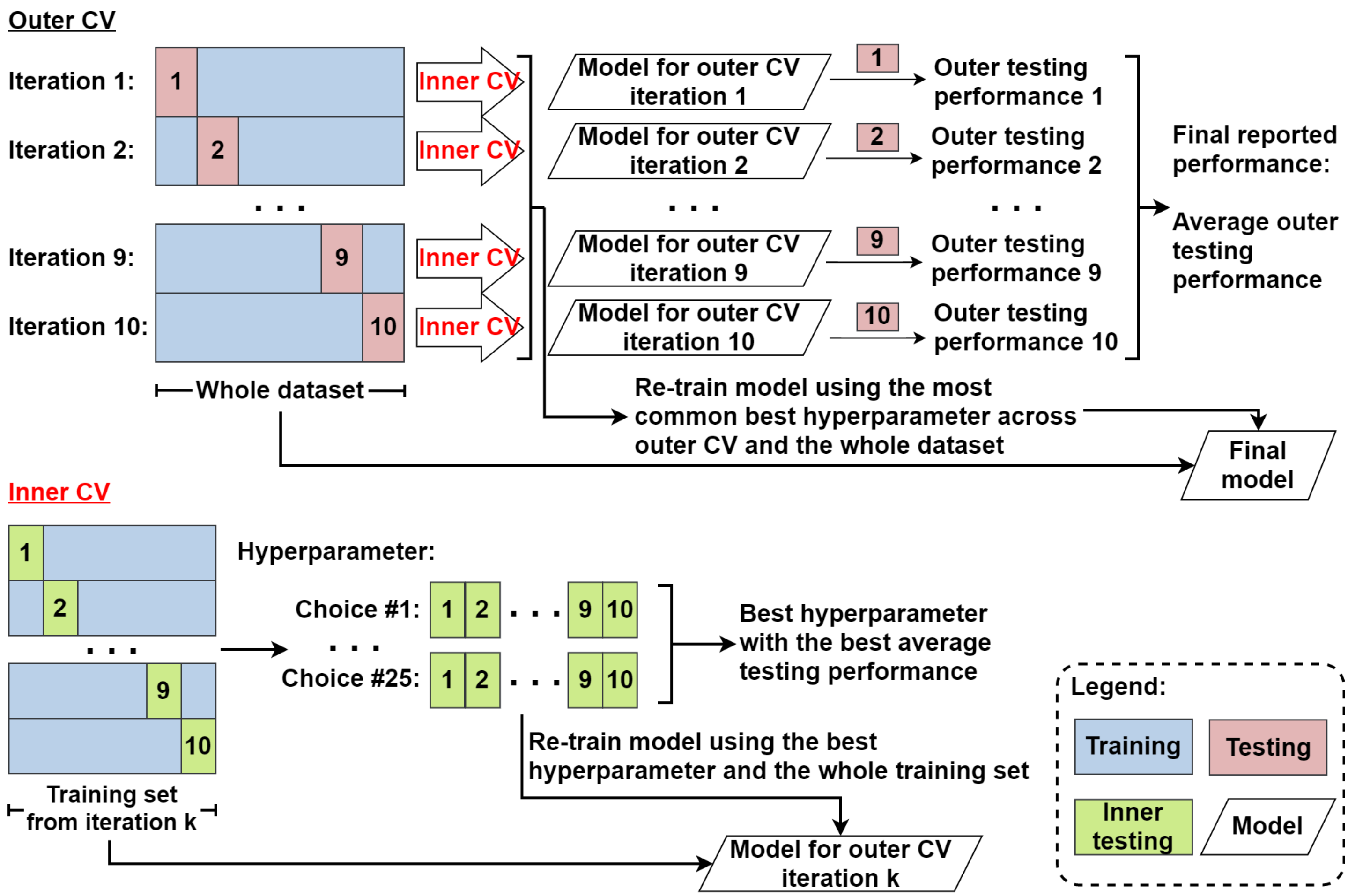
Excluded: 2 (due to technical difficulties with EEG)

↓

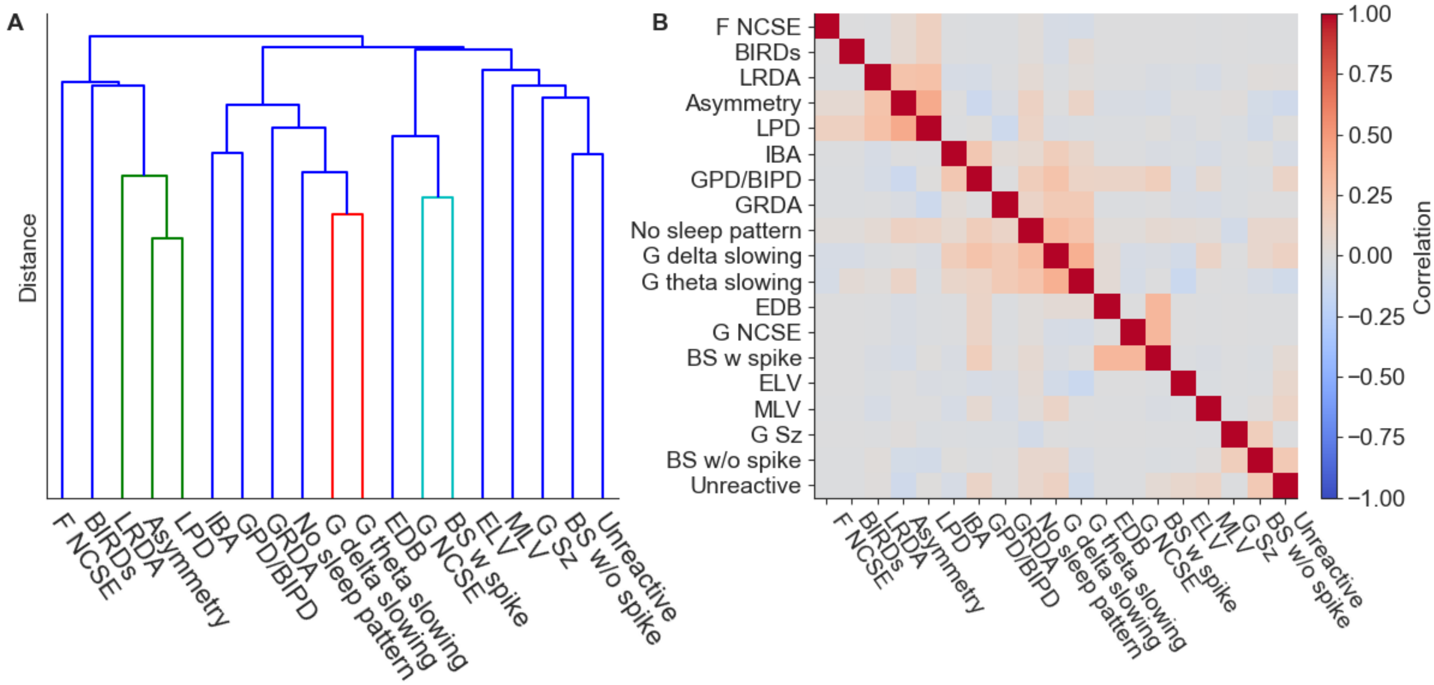
Analyzed: 404 total subjects [b]

[a] *Study recruitment was temporarily paused from Jan 2017 – Sept 2018 due to availability of research personal*
[b] *3 subjects were evaluated >1 (for a total of 407 timepoints of paired EEG and delirium assessments)*

eFigure 2: Machine learning steps for model development



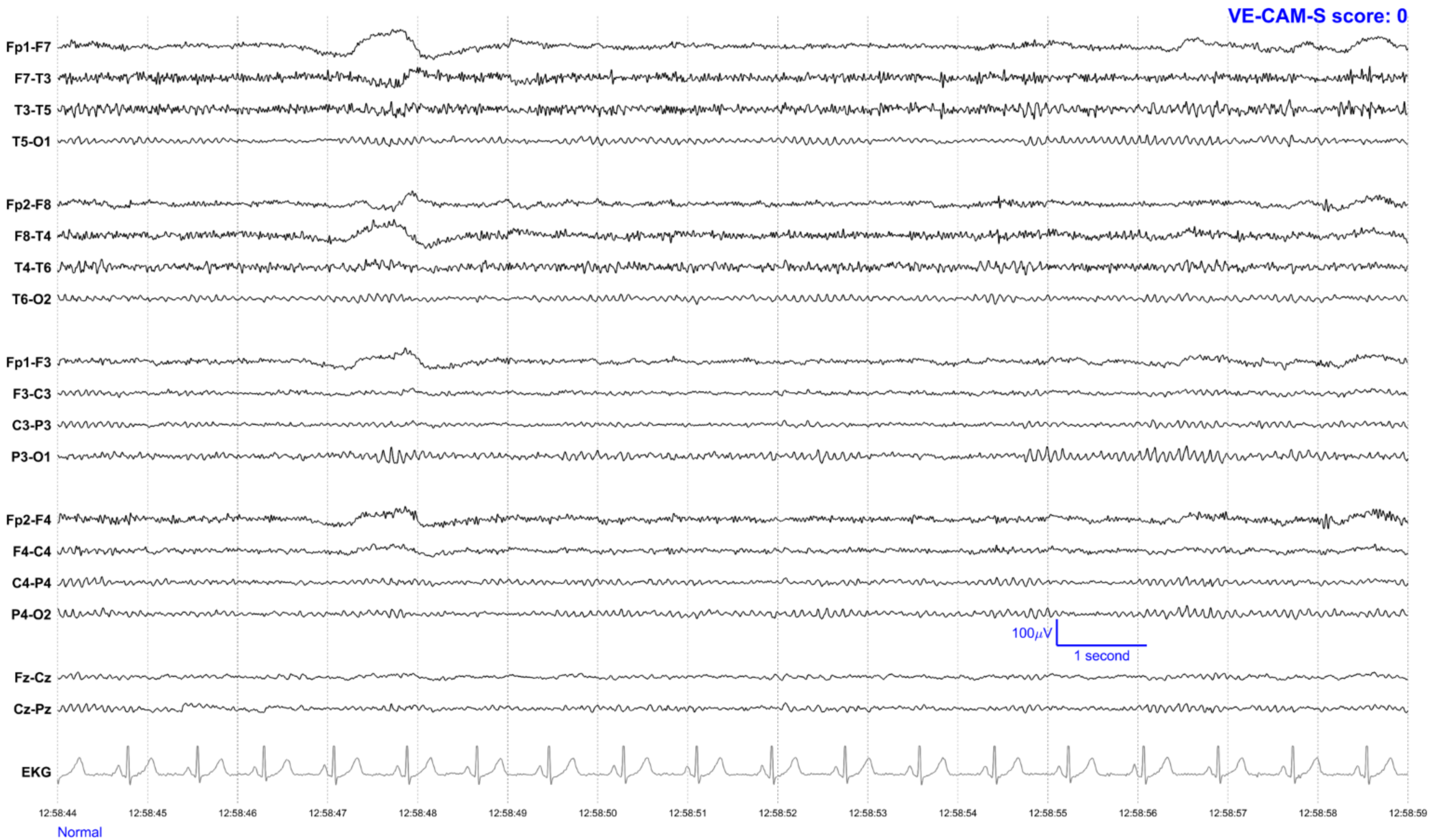
eFigure 3: Correlation among the EEG features



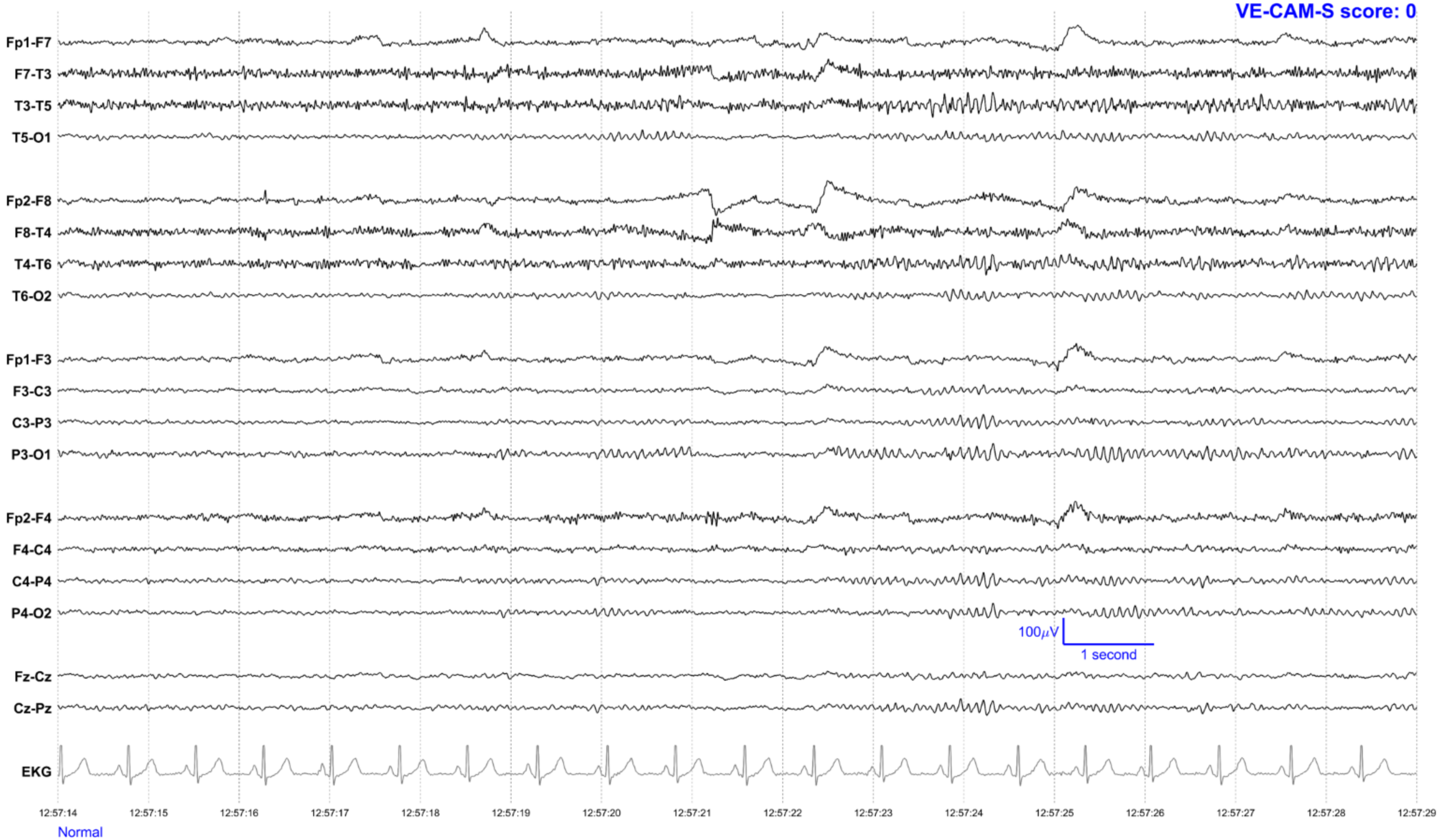
(A) The hierarchical clustering of features based on the correlation of each pair of features. We show the features used to fit the model, which include those that enter the final model in addition to a few held out for being too infrequent in the dataset. Correlation between binary features is defined according to the "Correlation" method in Table 1 of Zhang et al.[57] Lower distances represent higher correlation. (B) The correlation matrix among EEG features. High correlation (red) means more similar binary patterns; and vice versa (blue).

eFigures 4 – 58: EEG examples of normal, low, mid, high, and worst VE-CAM-S scores

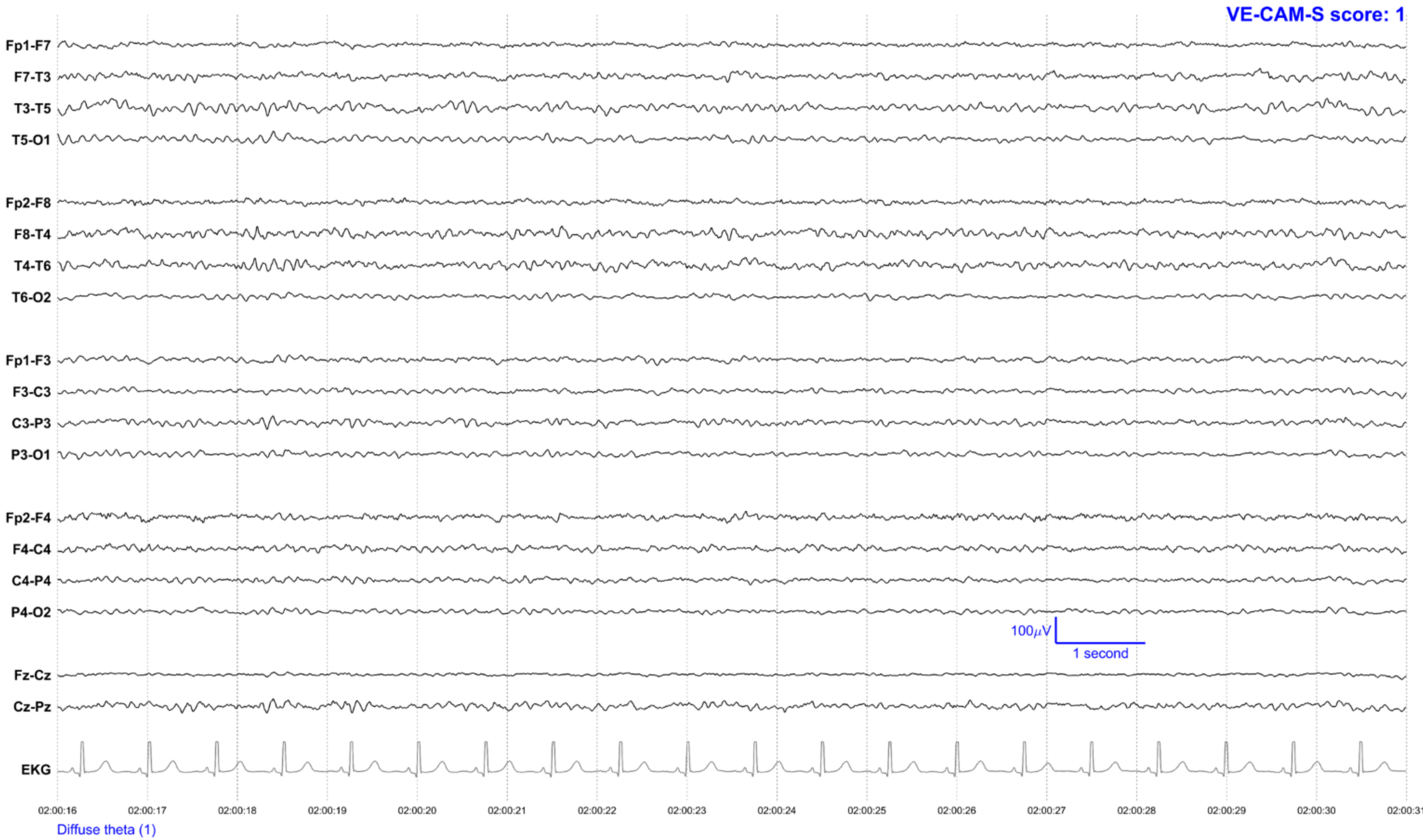
eFigure 4: Example EEG signal for 'Normal case'



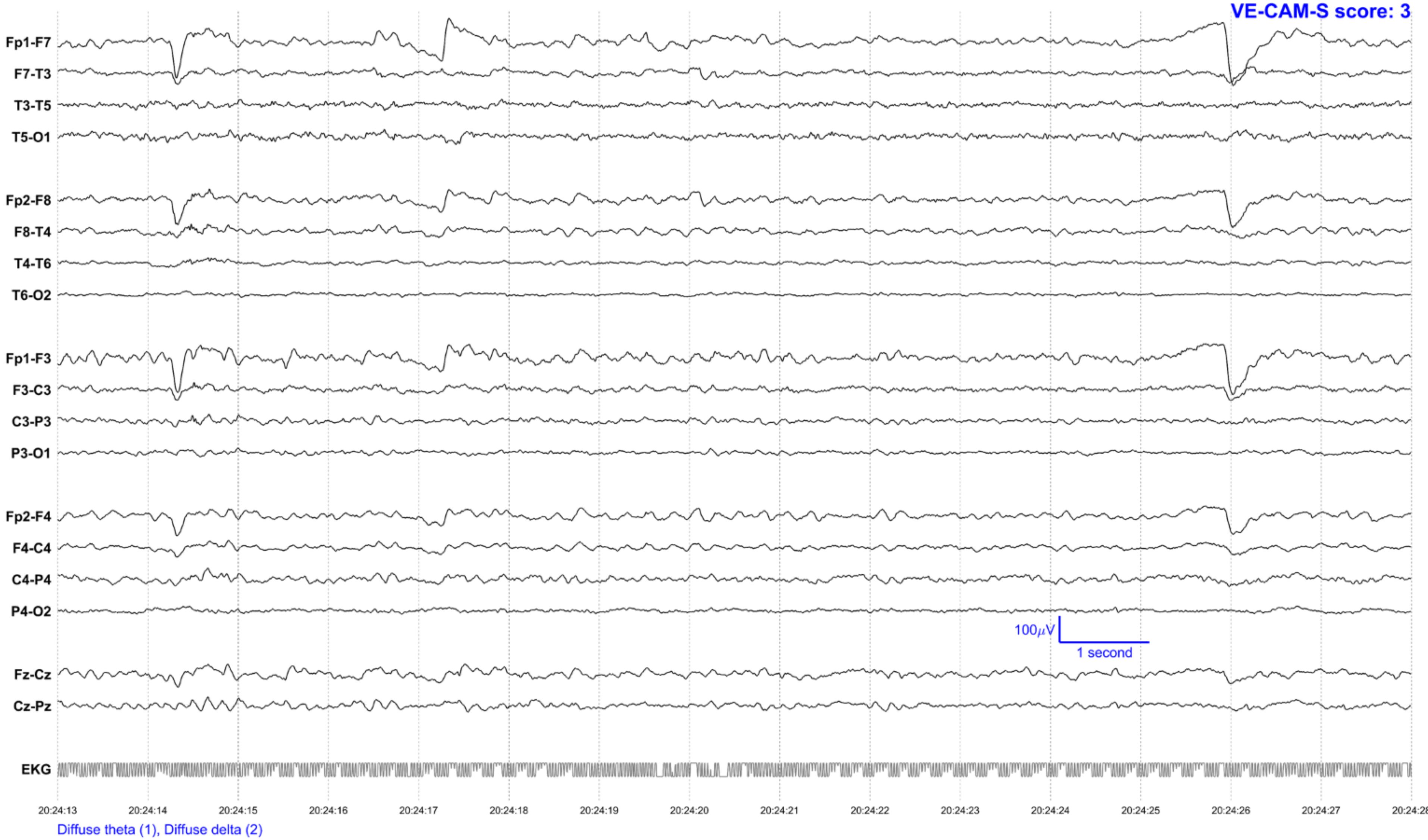
eFigure 5: Example EEG signal for 'Normal case'



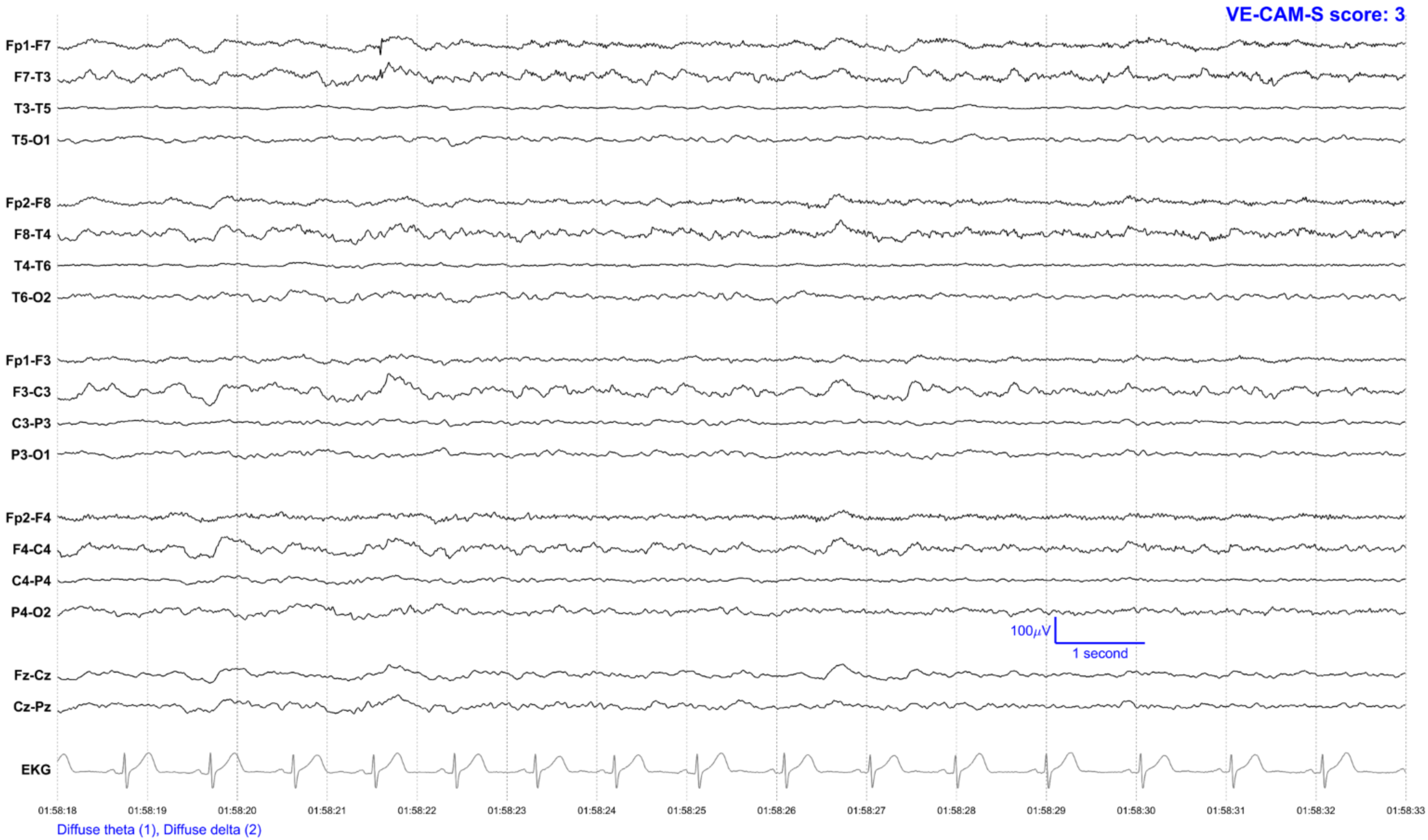
eFigure 6: Example EEG signal for 'Low delirium severity'



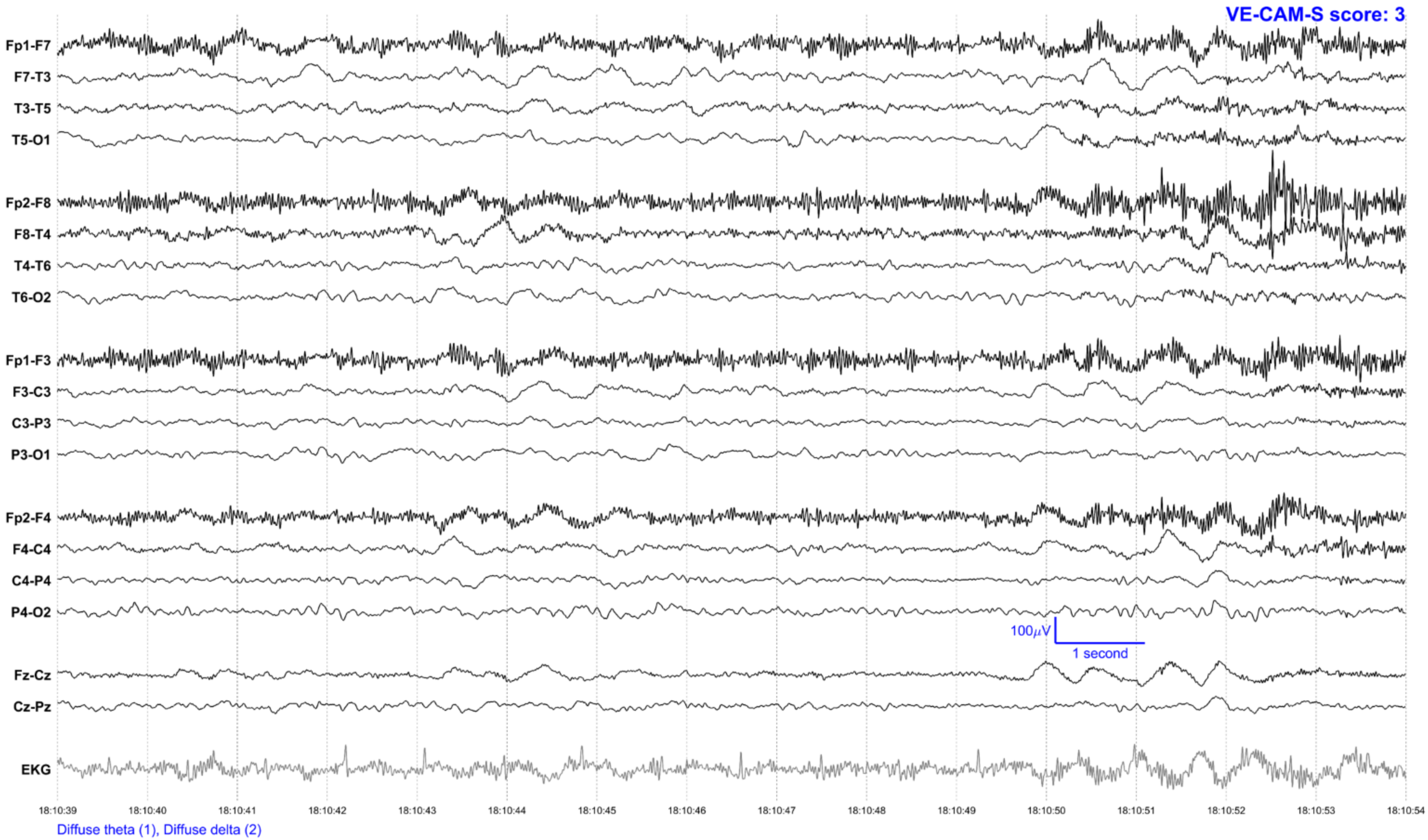
eFigure 7: Example EEG signal for 'Low delirium severity'



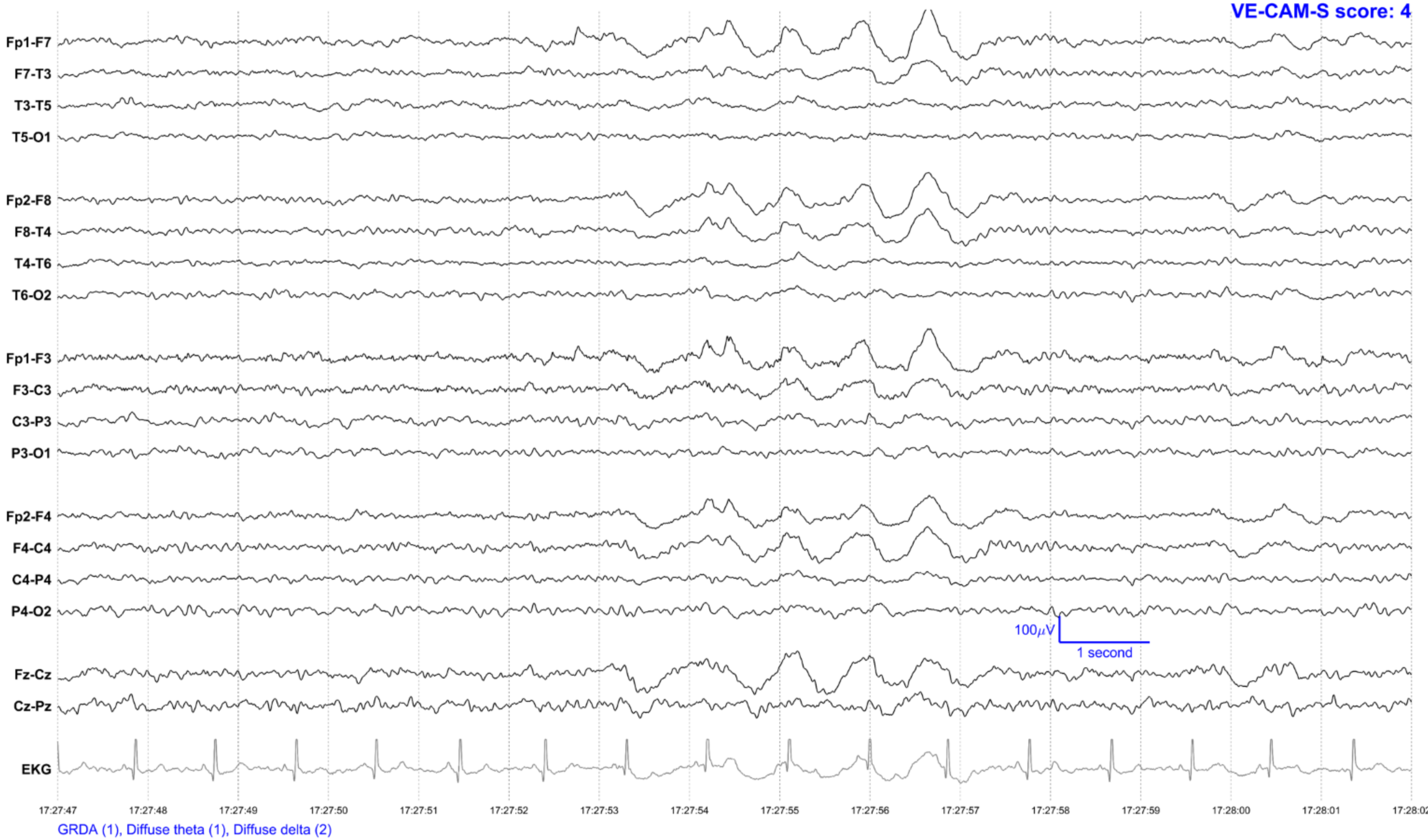
eFigure 8: Example EEG signal for 'Low delirium severity'



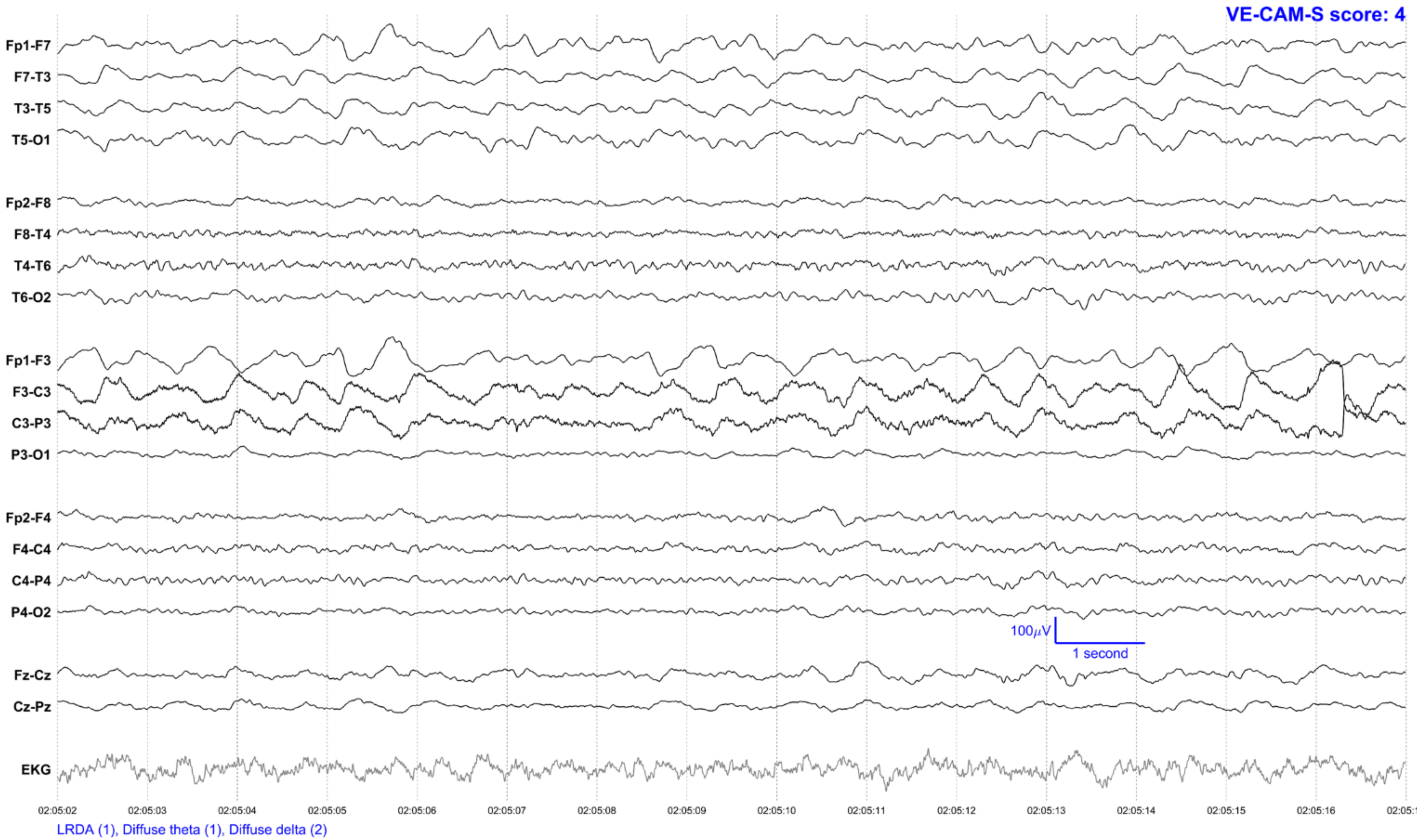
eFigure 9: Example EEG signal for 'Low delirium severity'



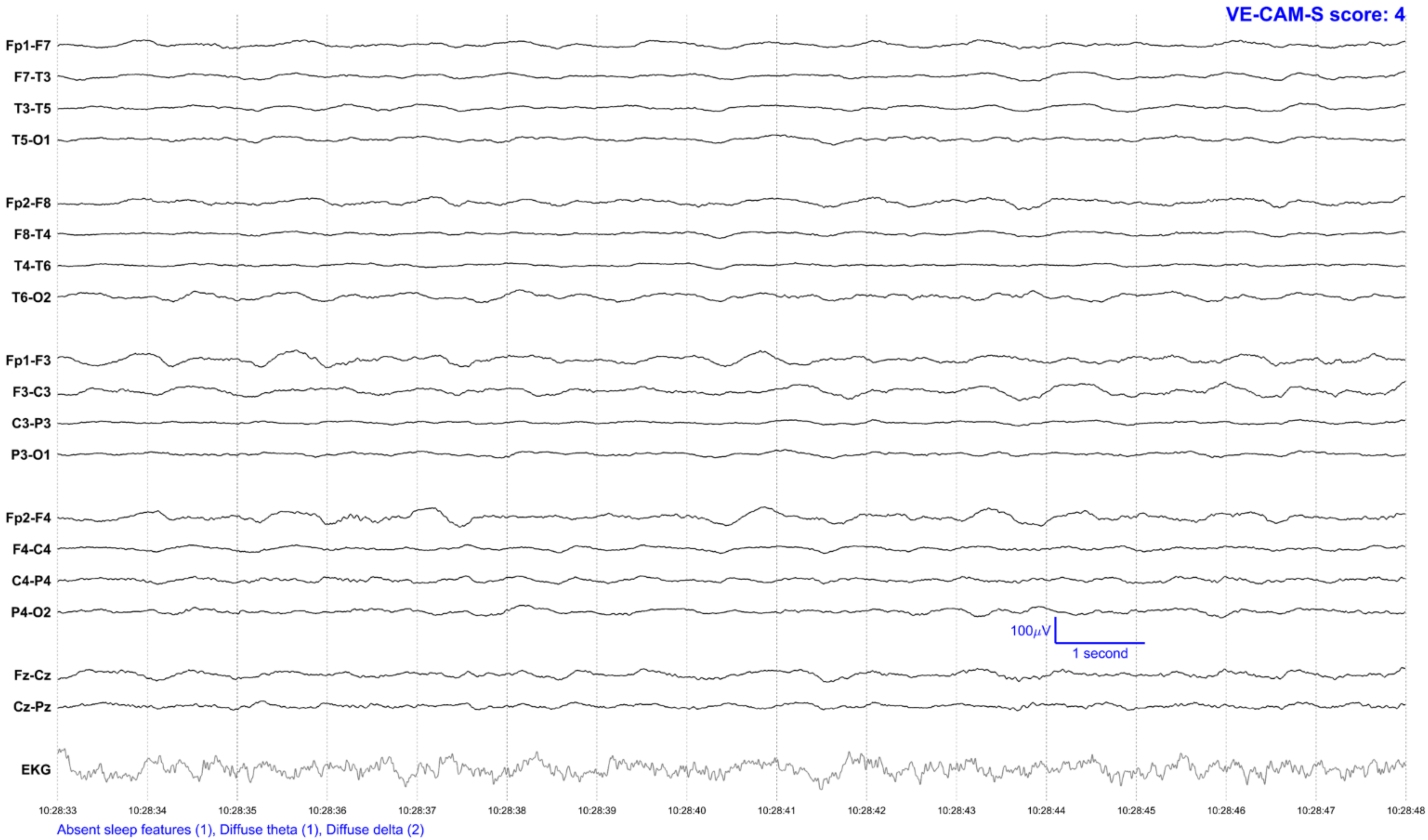
eFigure 10: Example EEG signal for 'Moderate delirium severity'



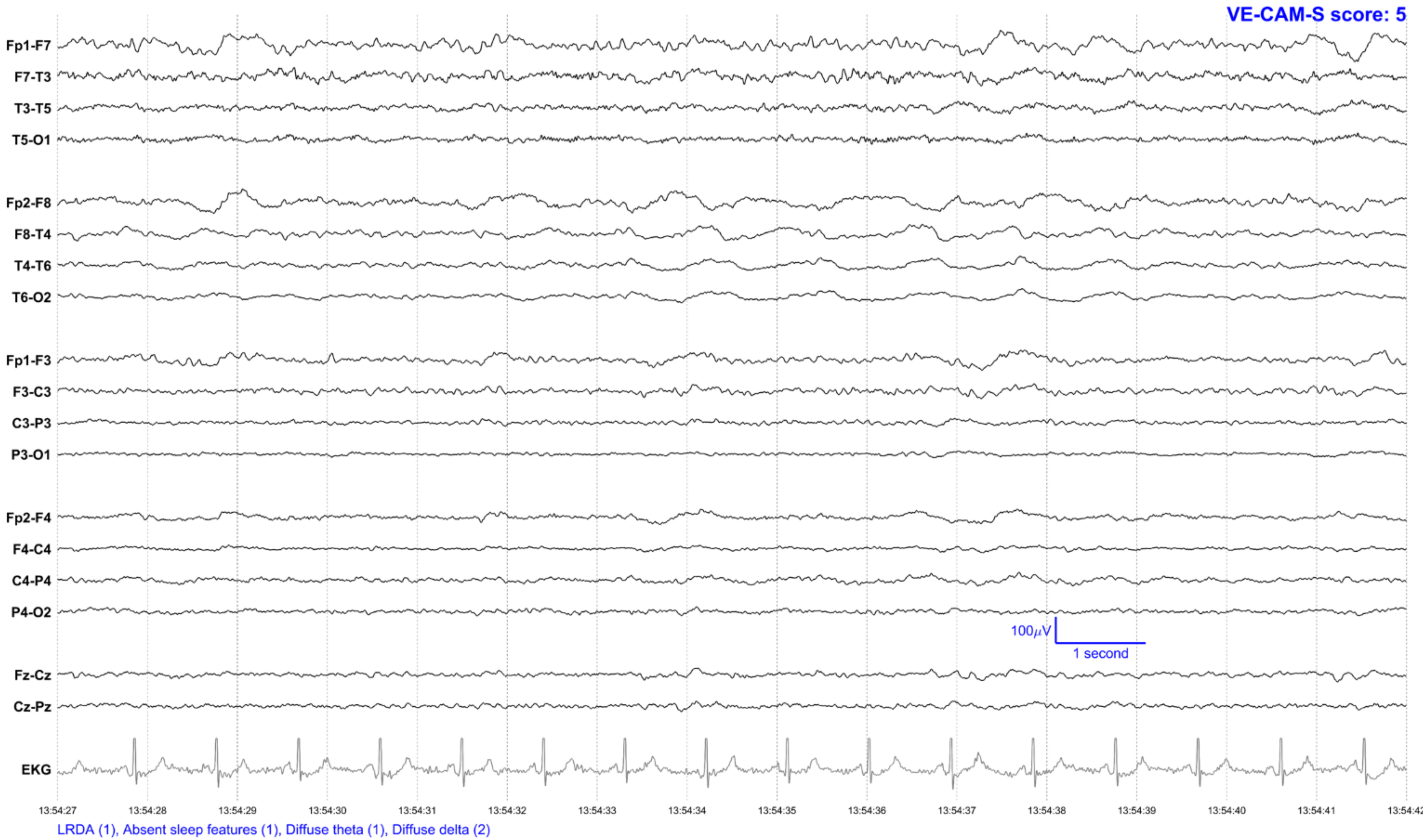
eFigure 11: Example EEG signal for ‘Moderate delirium severity’



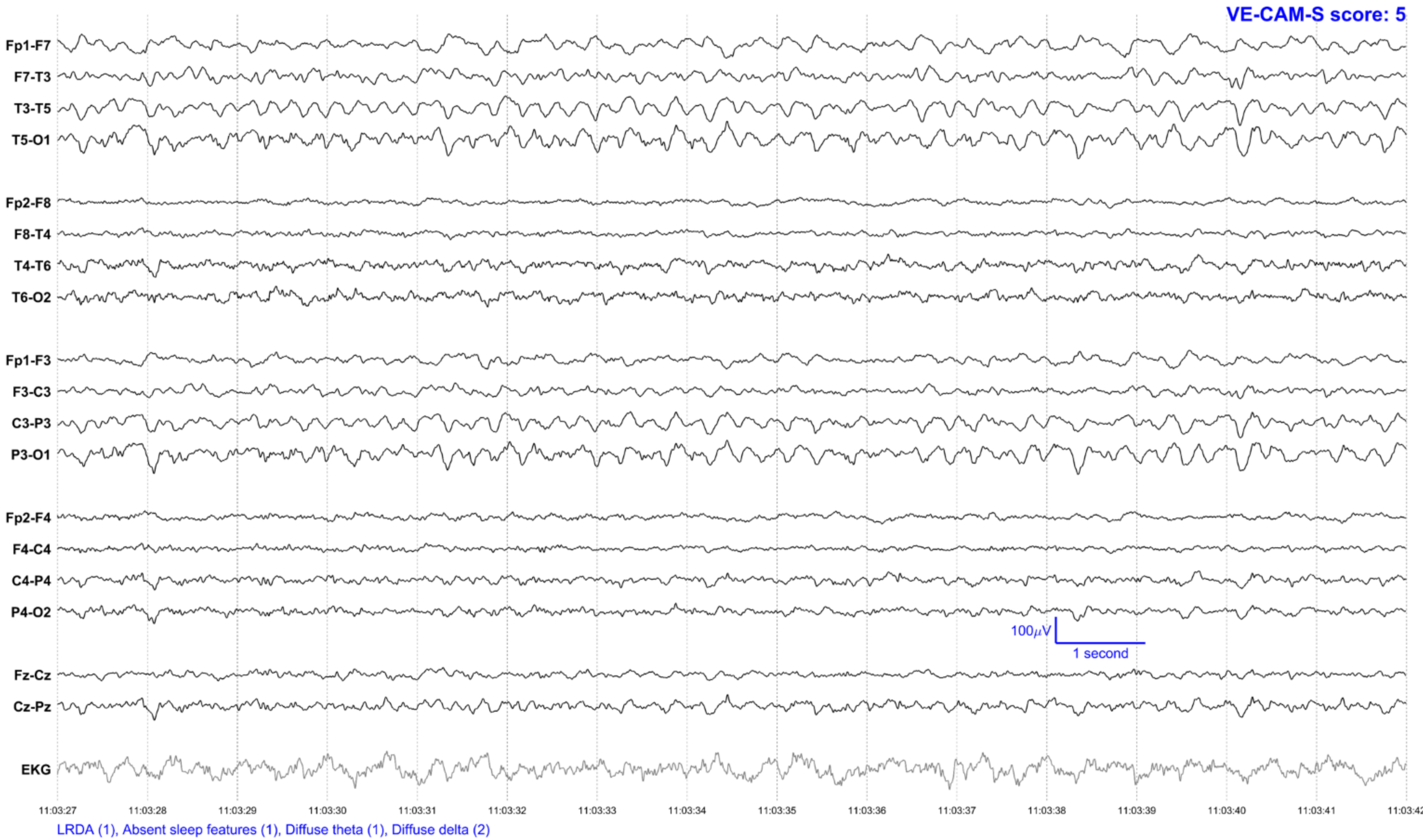
eFigure 12: Example EEG signal for 'Moderate delirium severity'



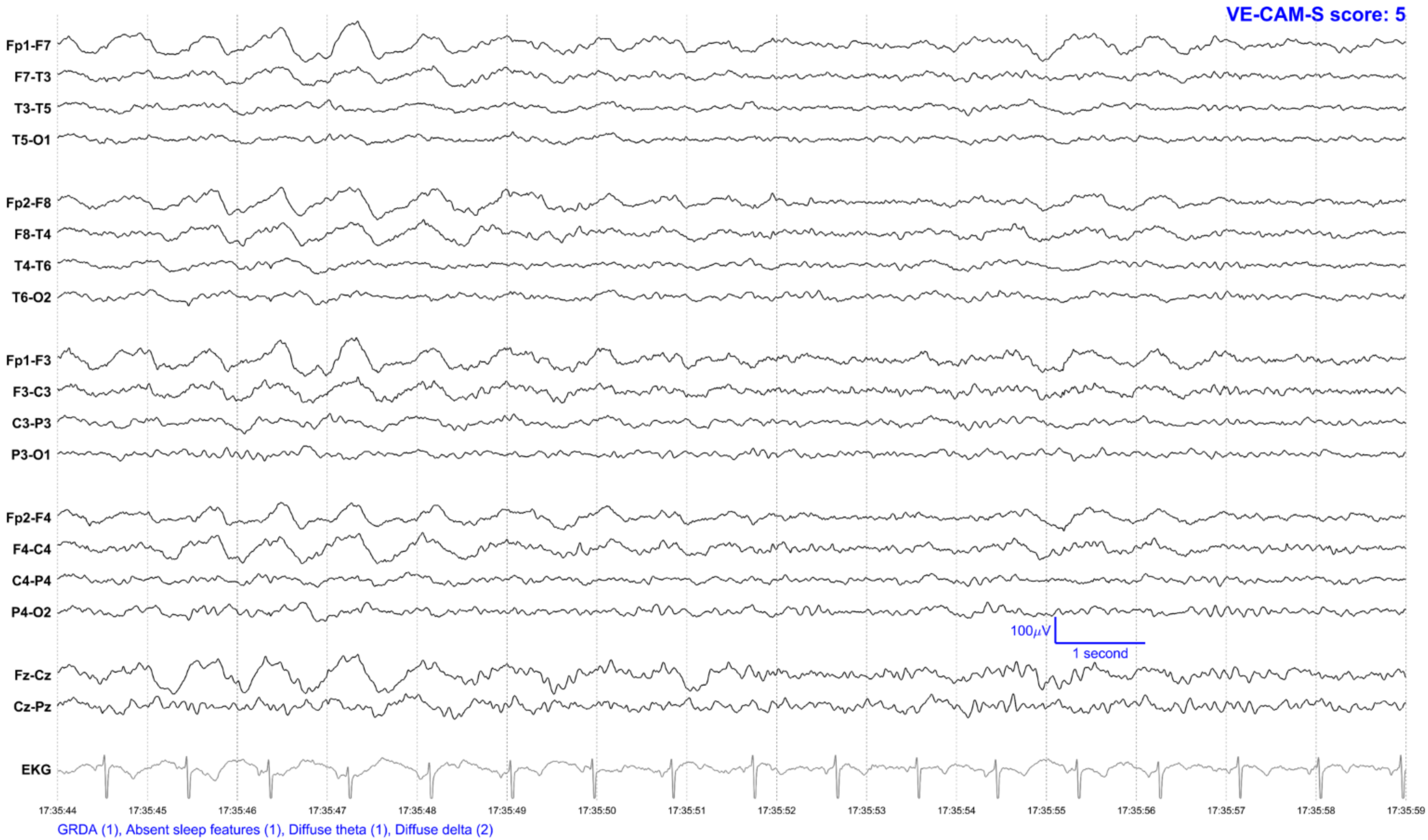
eFigure 13: Example EEG signal for 'Moderate delirium severity'



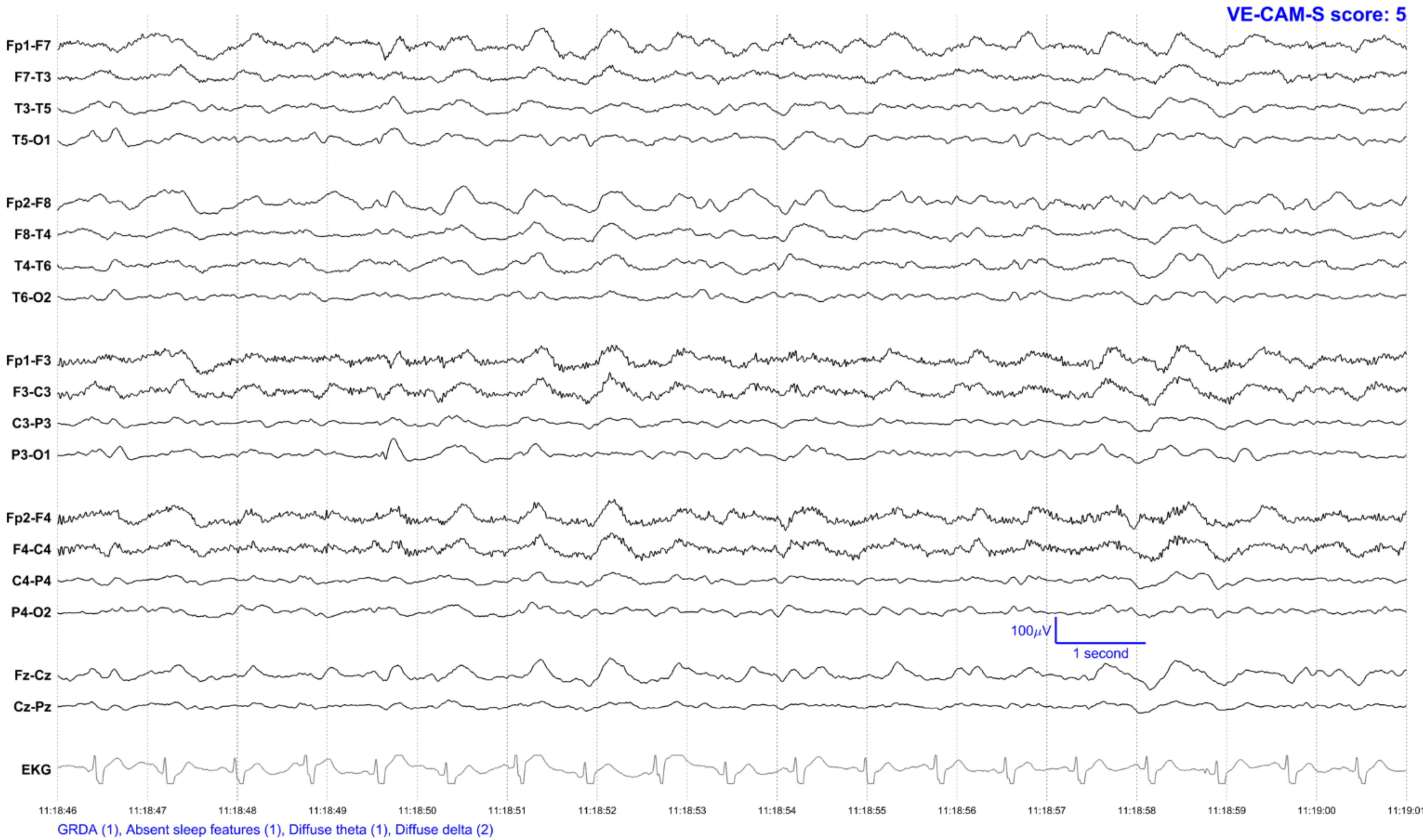
eFigure 14: Example EEG signal for ‘Moderate delirium severity’



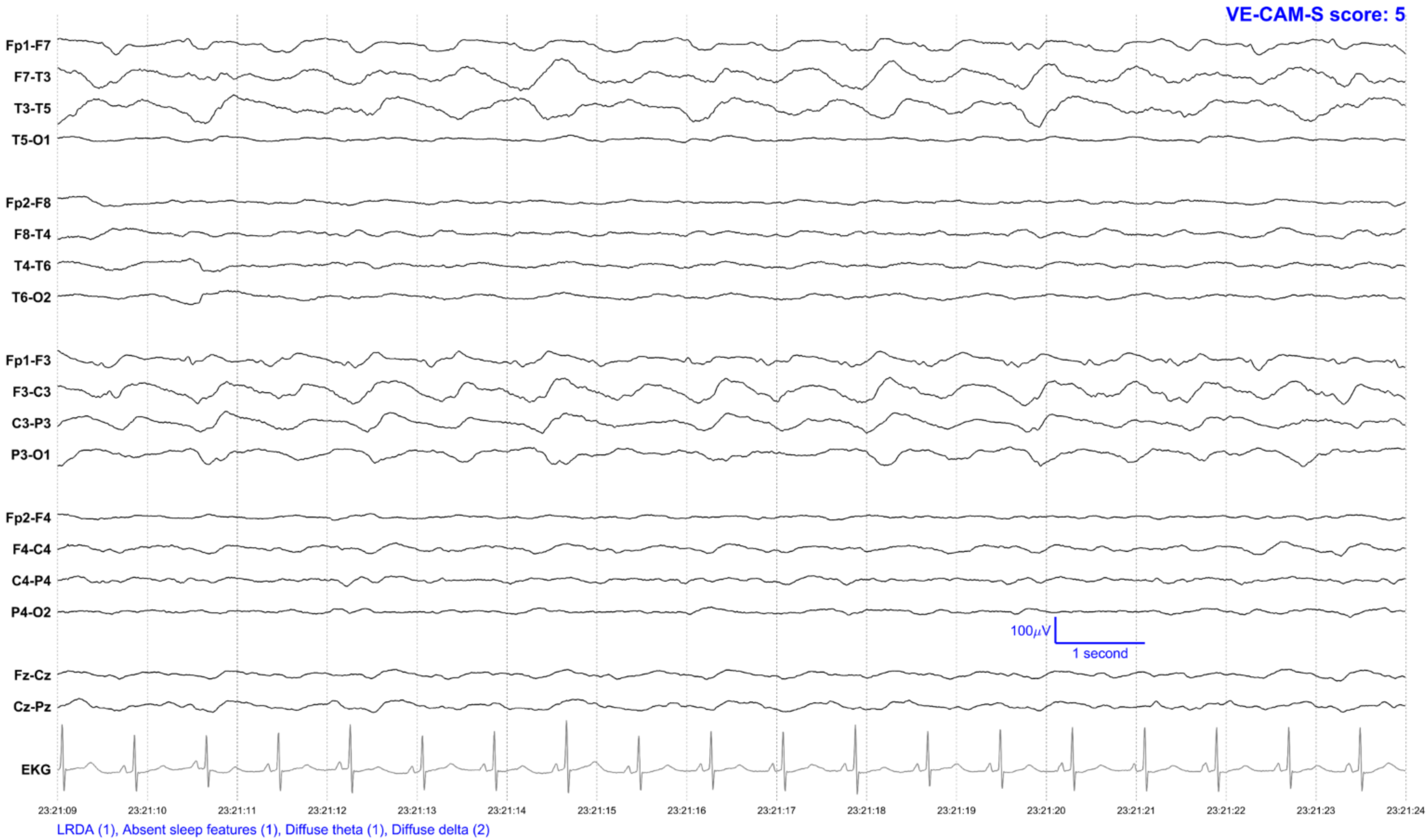
eFigure 15: Example EEG signal for 'Moderate delirium severity'



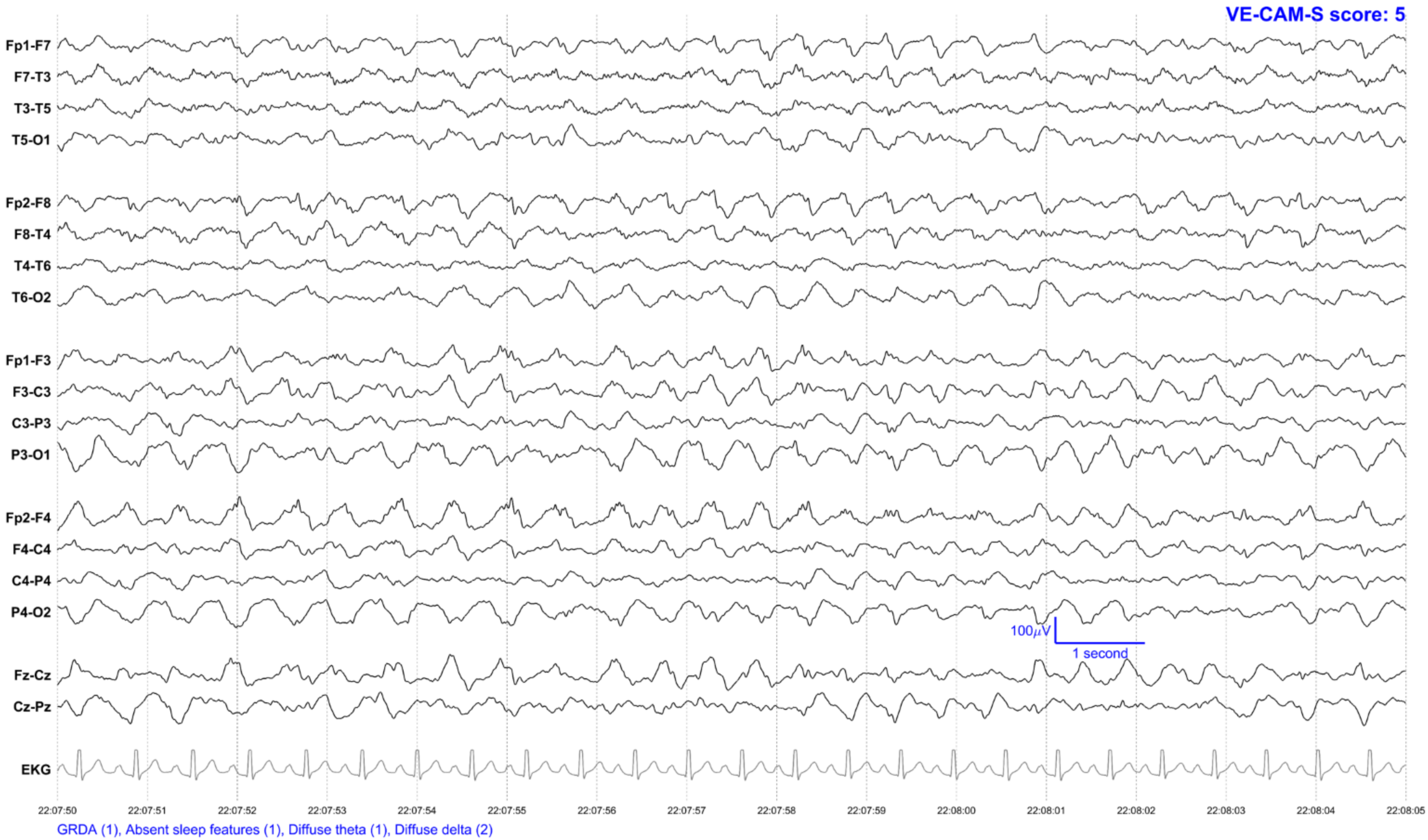
eFigure 16: Example EEG signal for 'Moderate delirium severity'



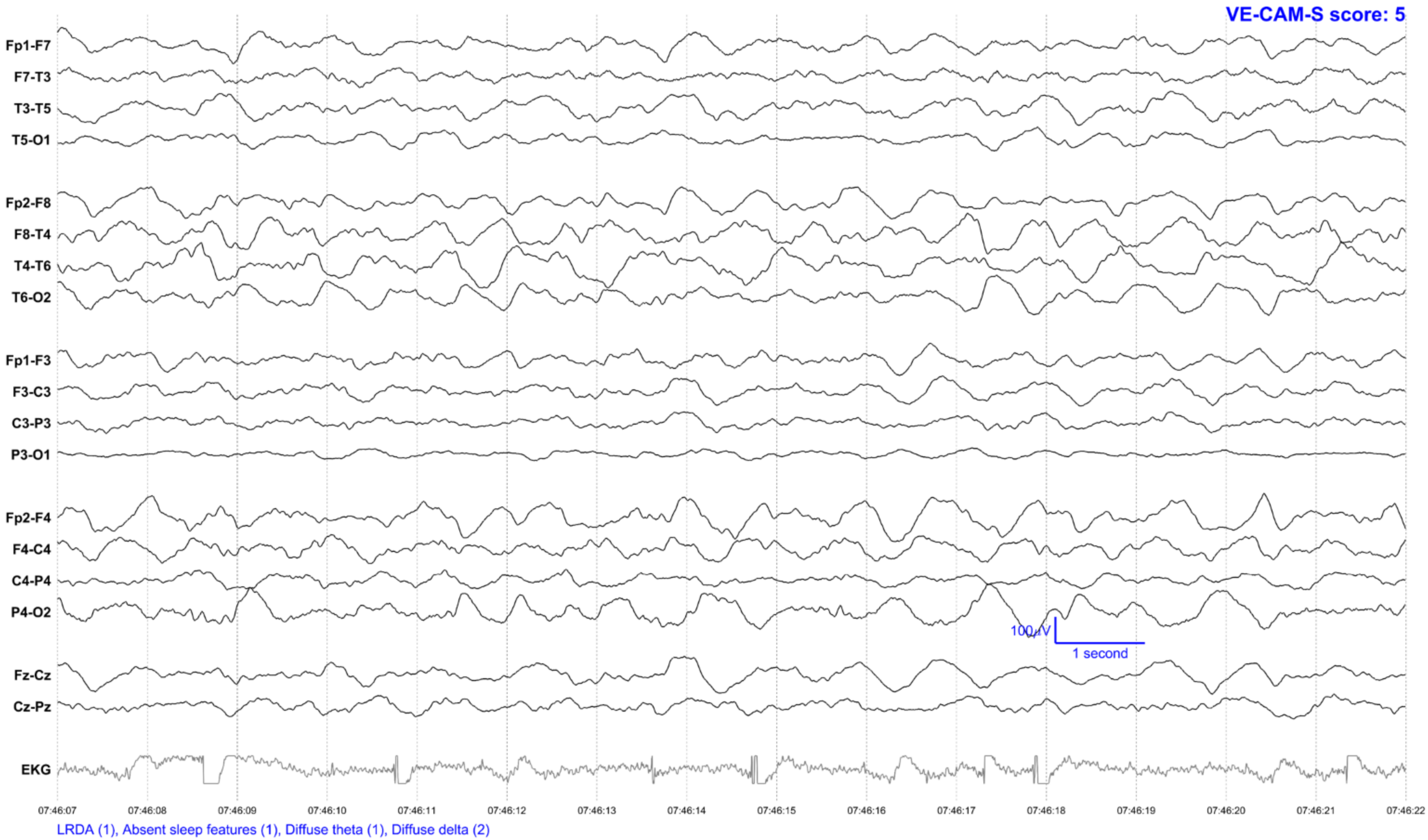
eFigure 17: Example EEG signal for ‘Moderate delirium severity’



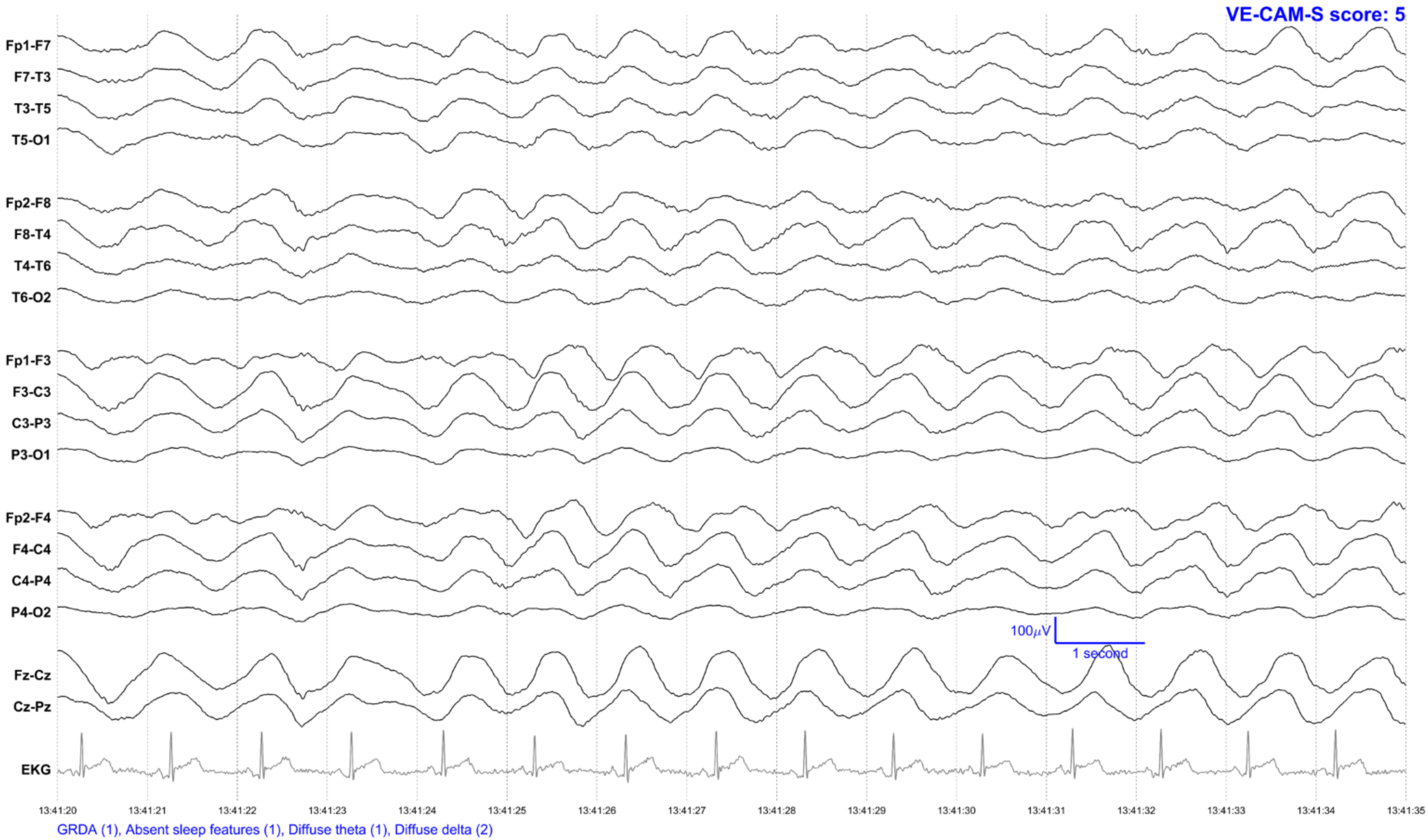
eFigure 18: Example EEG signal for 'Moderate delirium severity'



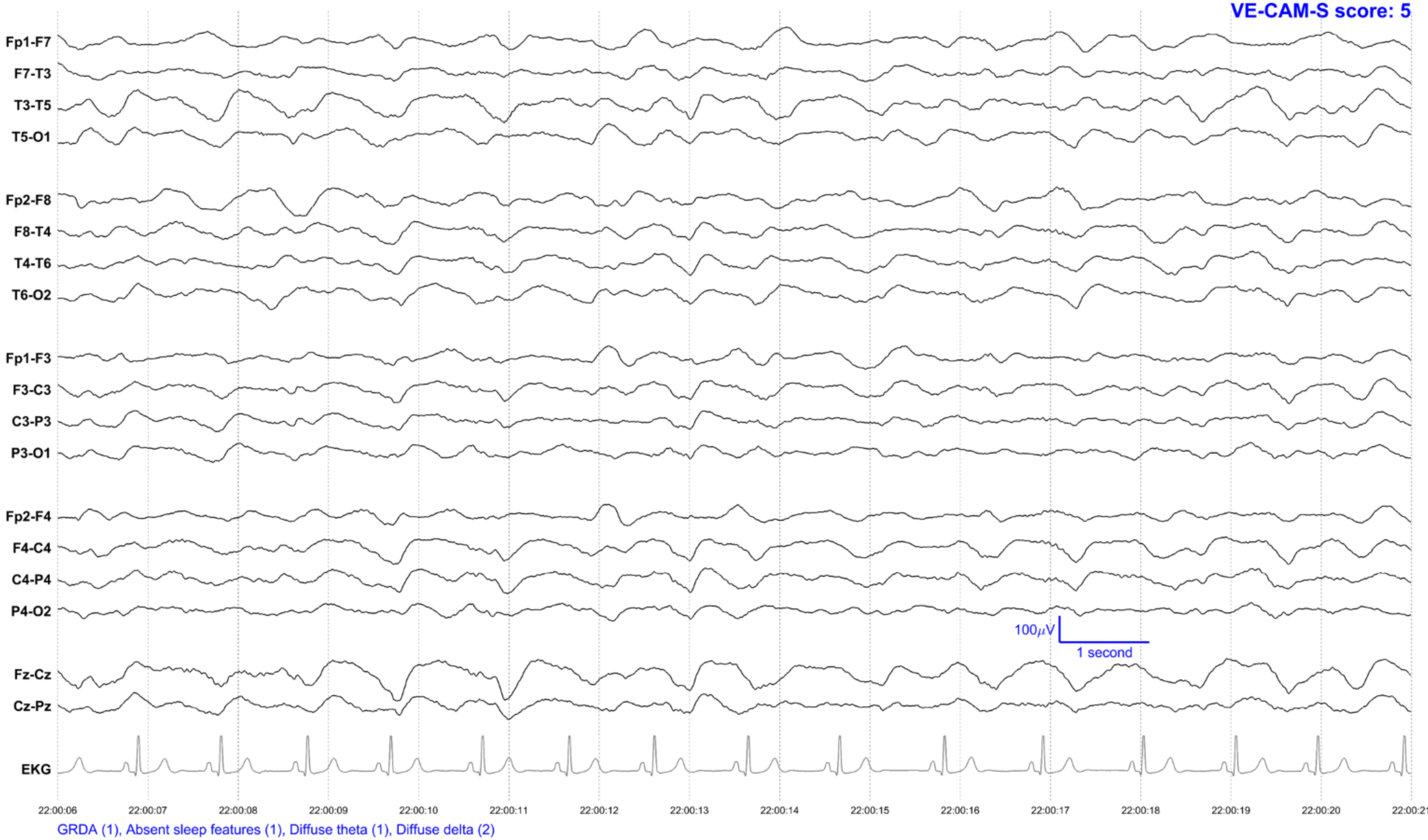
eFigure 19: Example EEG signal for ‘Moderate delirium severity’



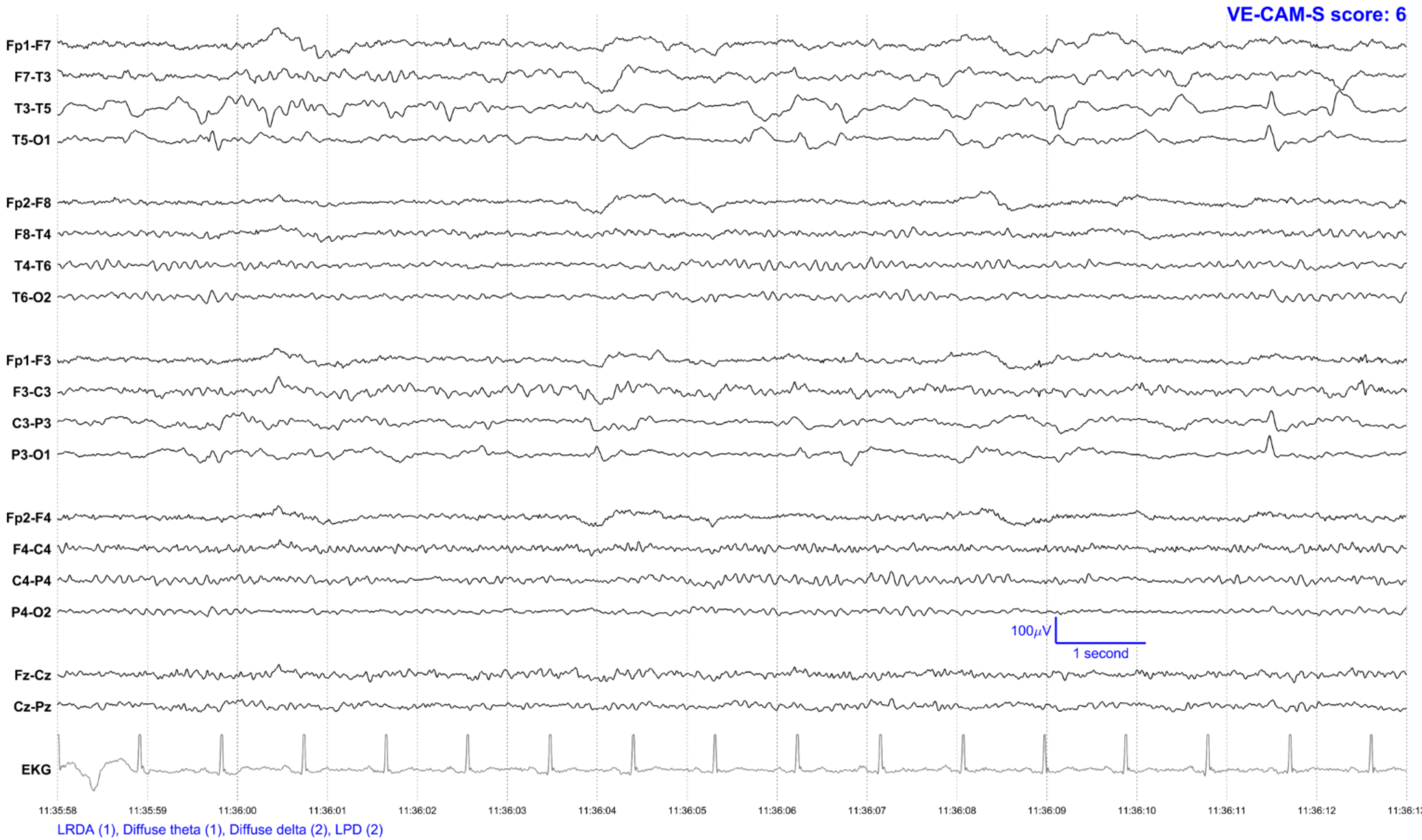
eFigure 20: Example EEG signal for 'Moderate delirium severity'



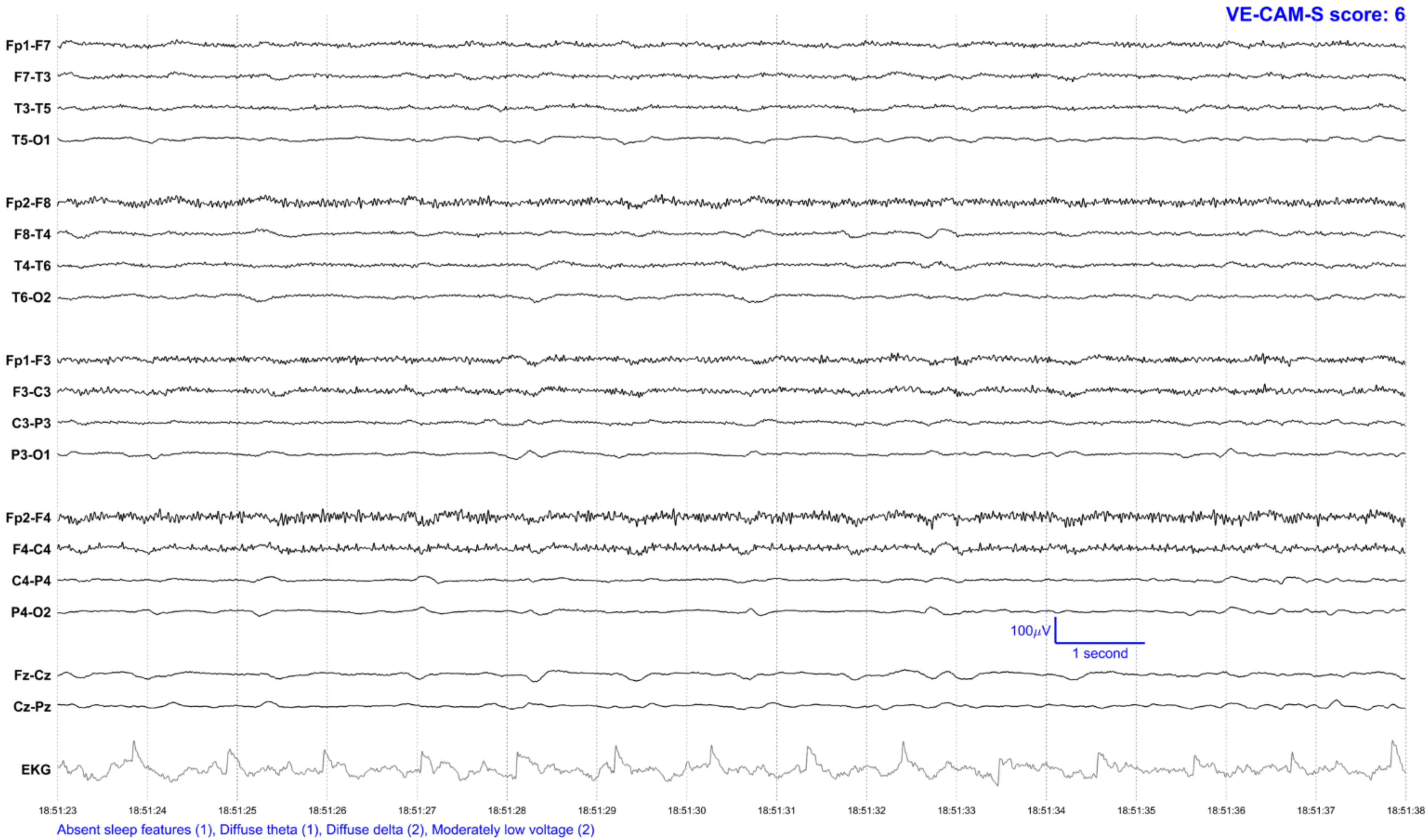
eFigure 21: Example EEG signal for 'Moderate delirium severity'



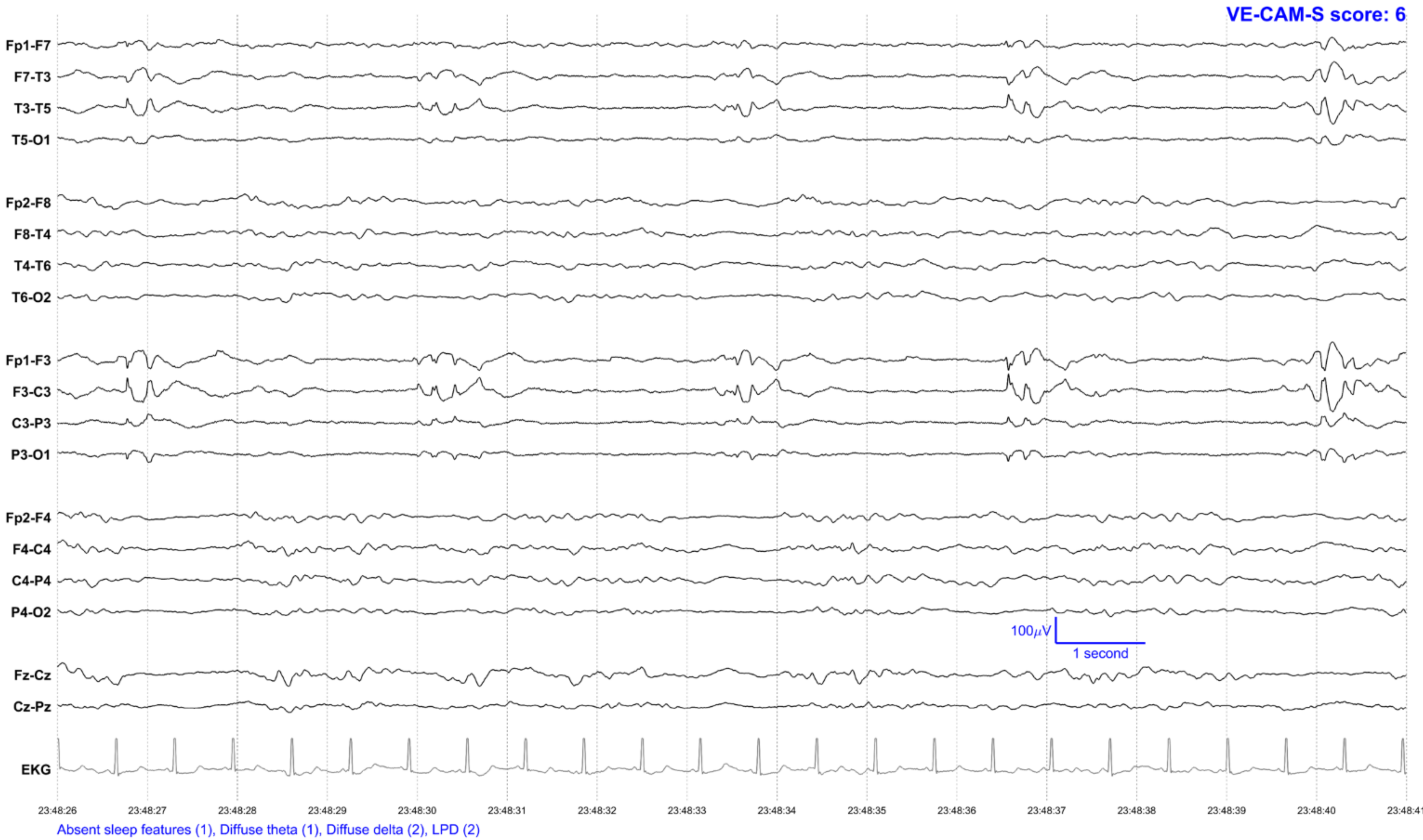
eFigure 22: Example EEG signal for 'Moderate delirium severity'



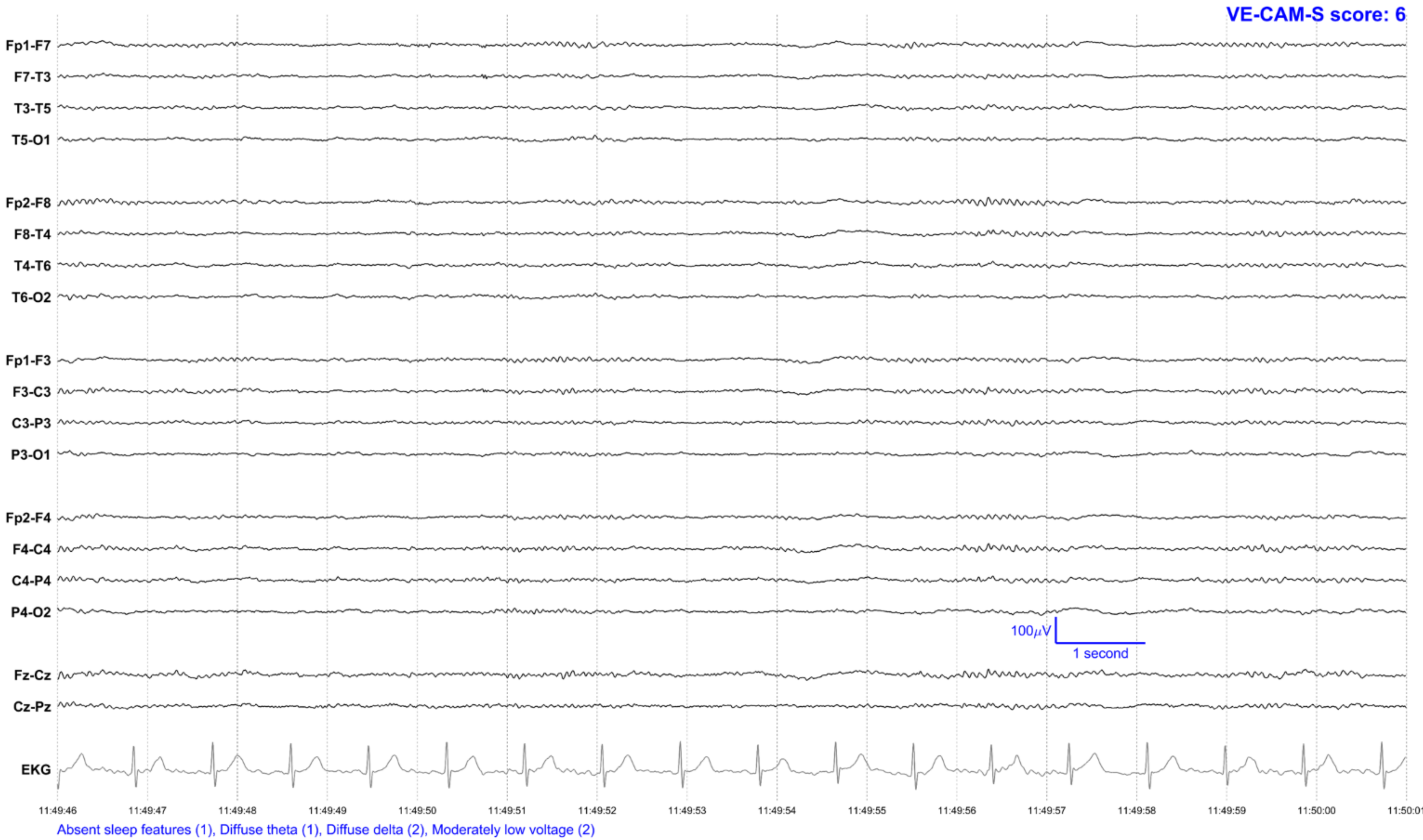
eFigure 23: Example EEG signal for 'Moderate delirium severity'



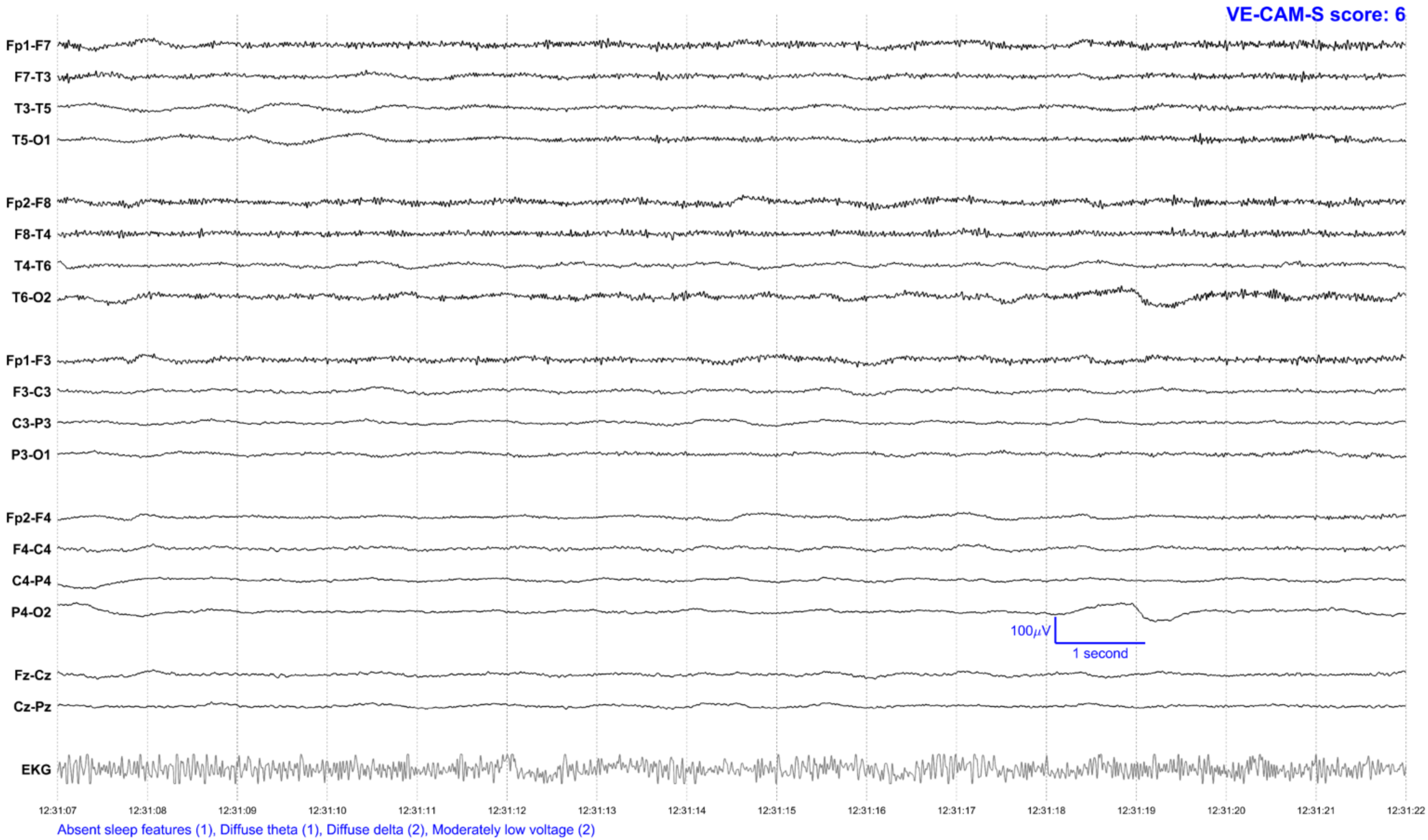
eFigure 24: Example EEG signal for 'Moderate delirium severity'



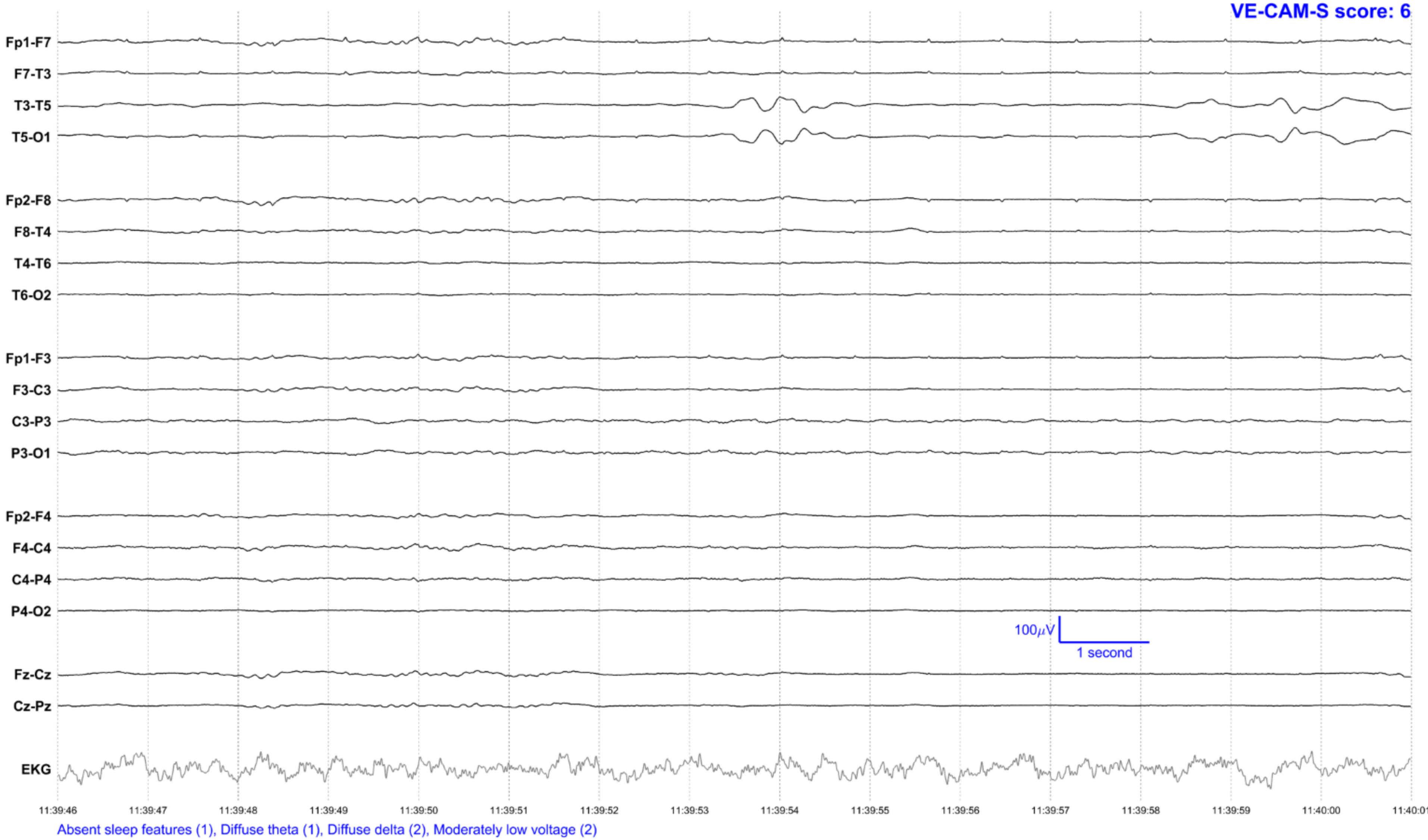
eFigure 25: Example EEG signal for 'Moderate delirium severity'



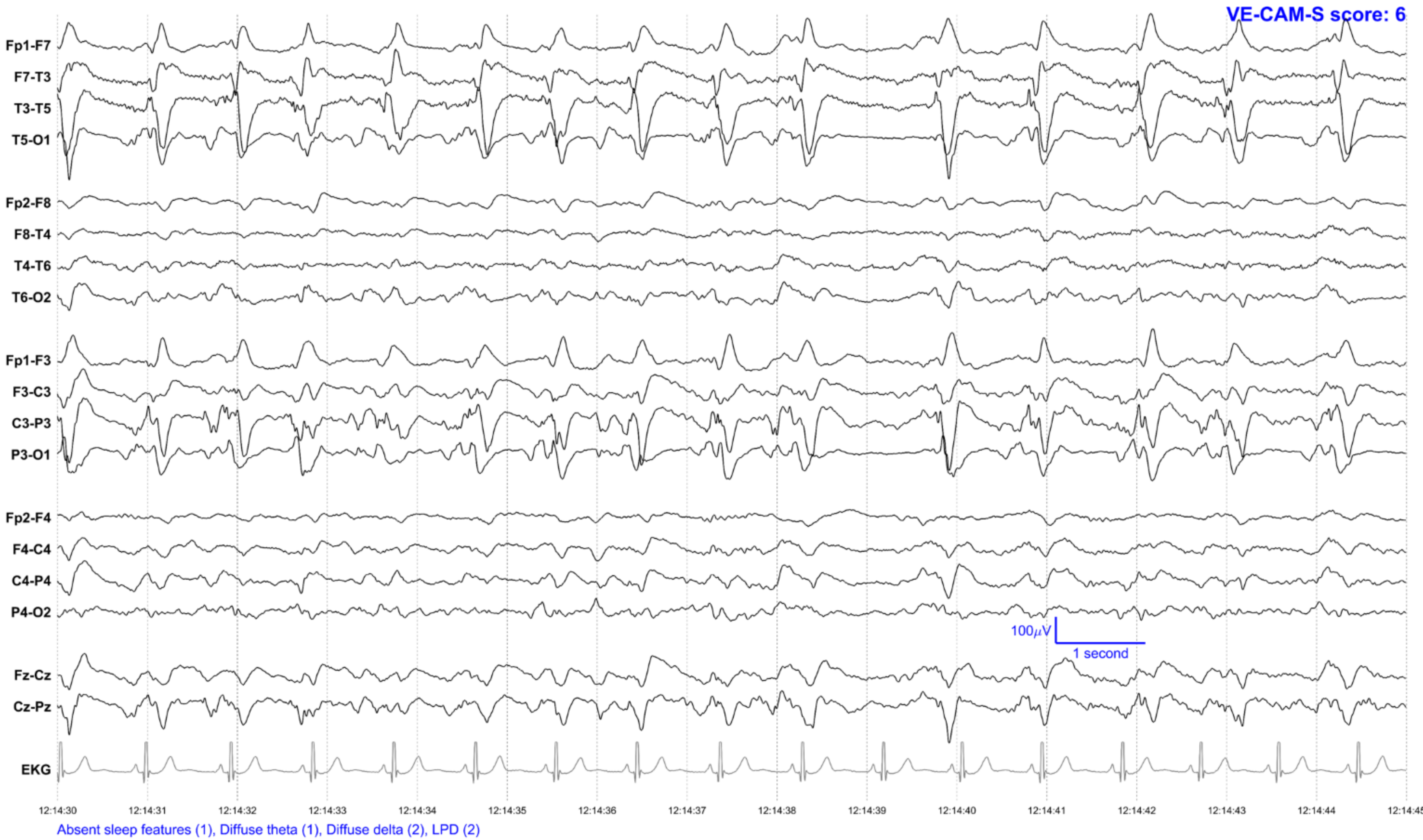
eFigure 26: Example EEG signal for 'Moderate delirium severity'



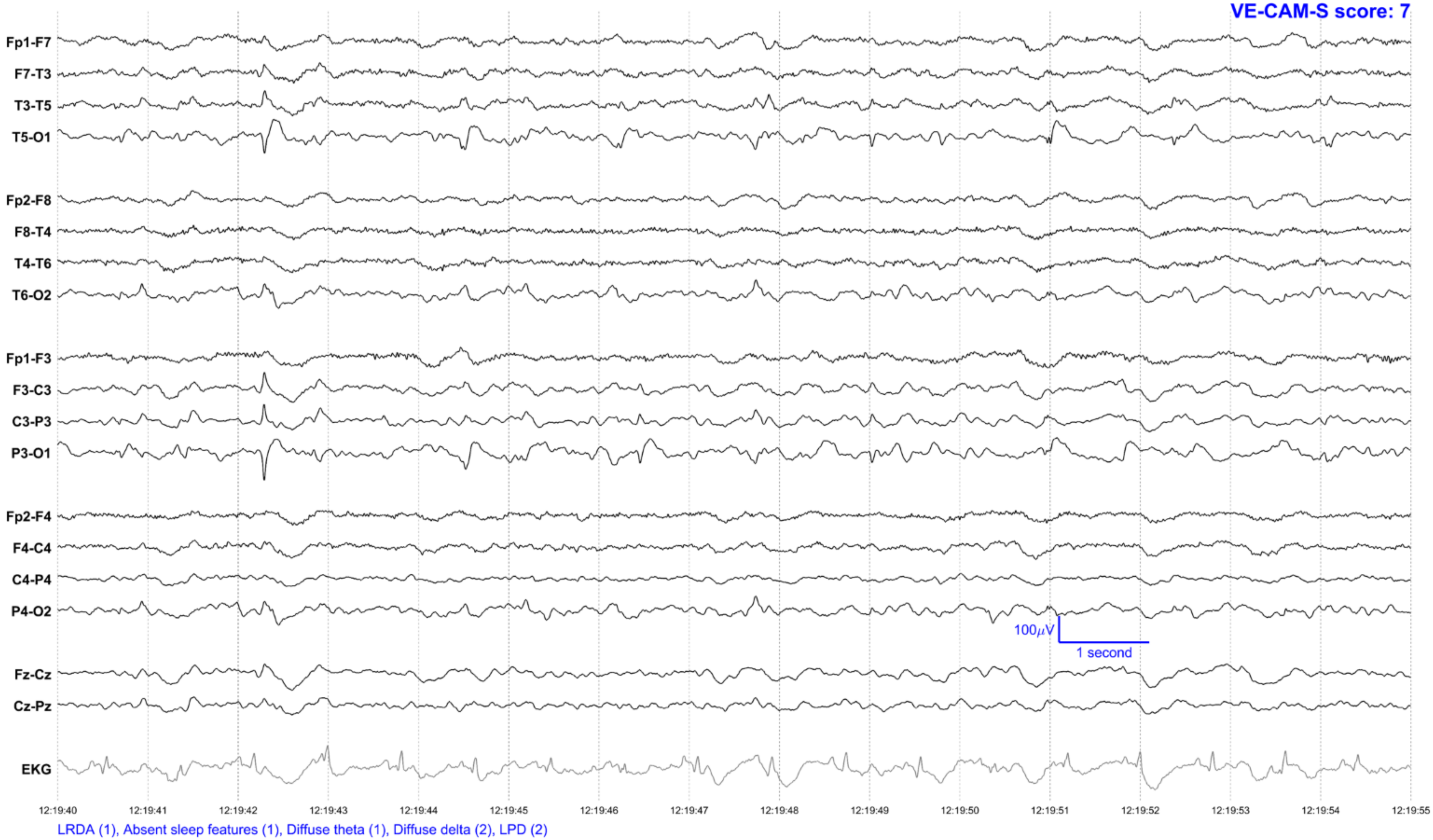
eFigure 27: Example EEG signal for 'Moderate delirium severity'



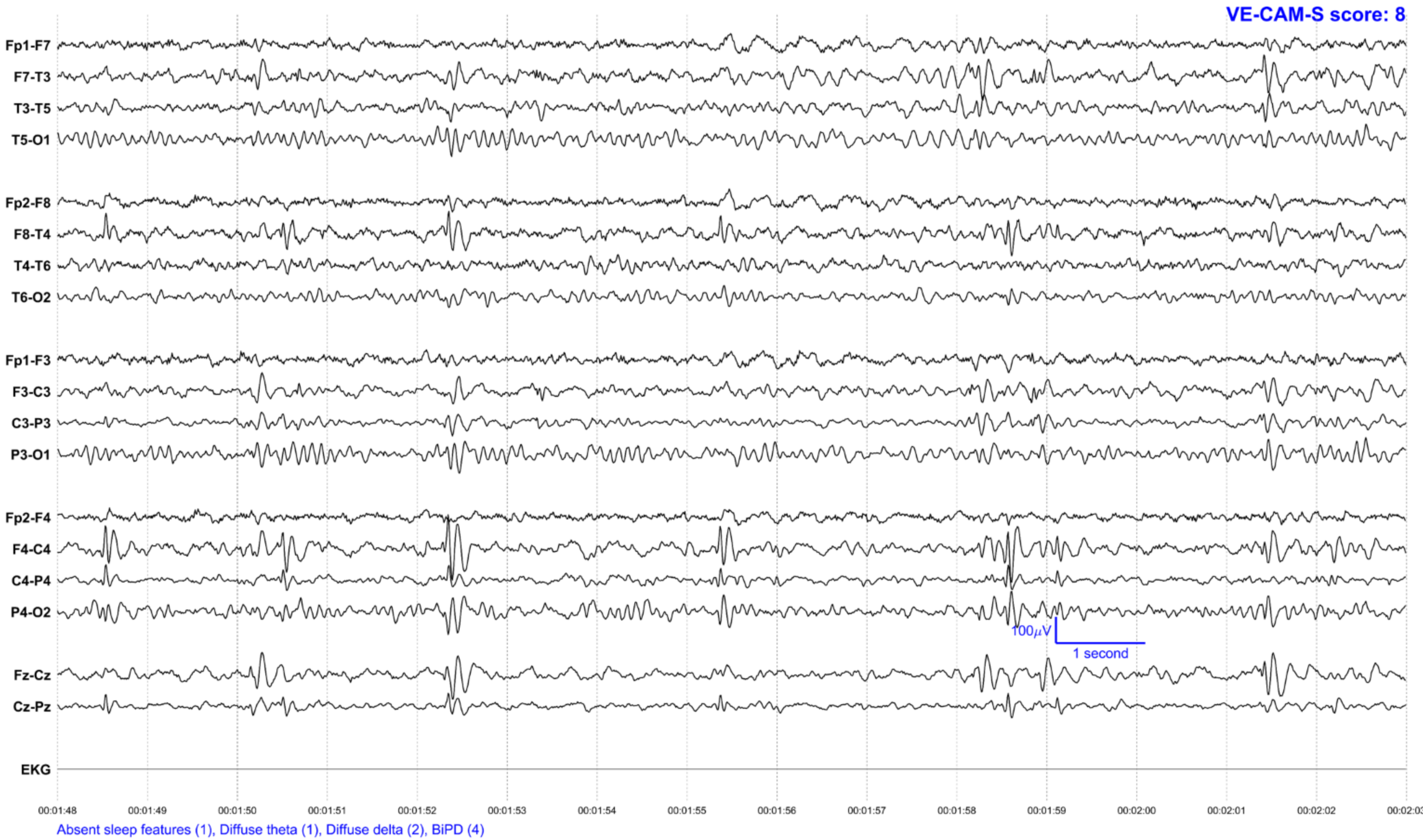
eFigure 28: Example EEG signal for 'Moderate delirium severity'



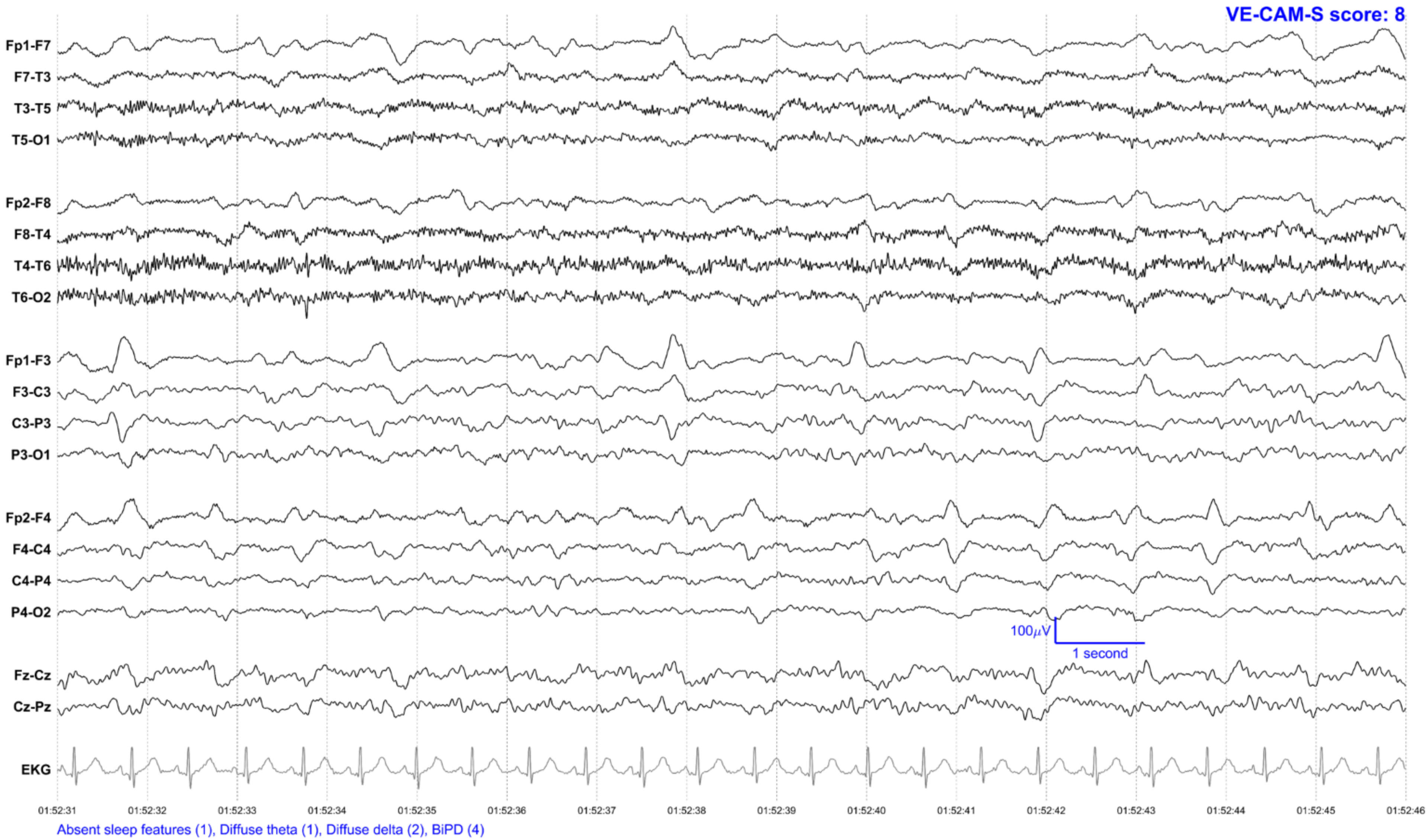
eFigure 29: Example EEG signal for 'Moderate delirium severity'



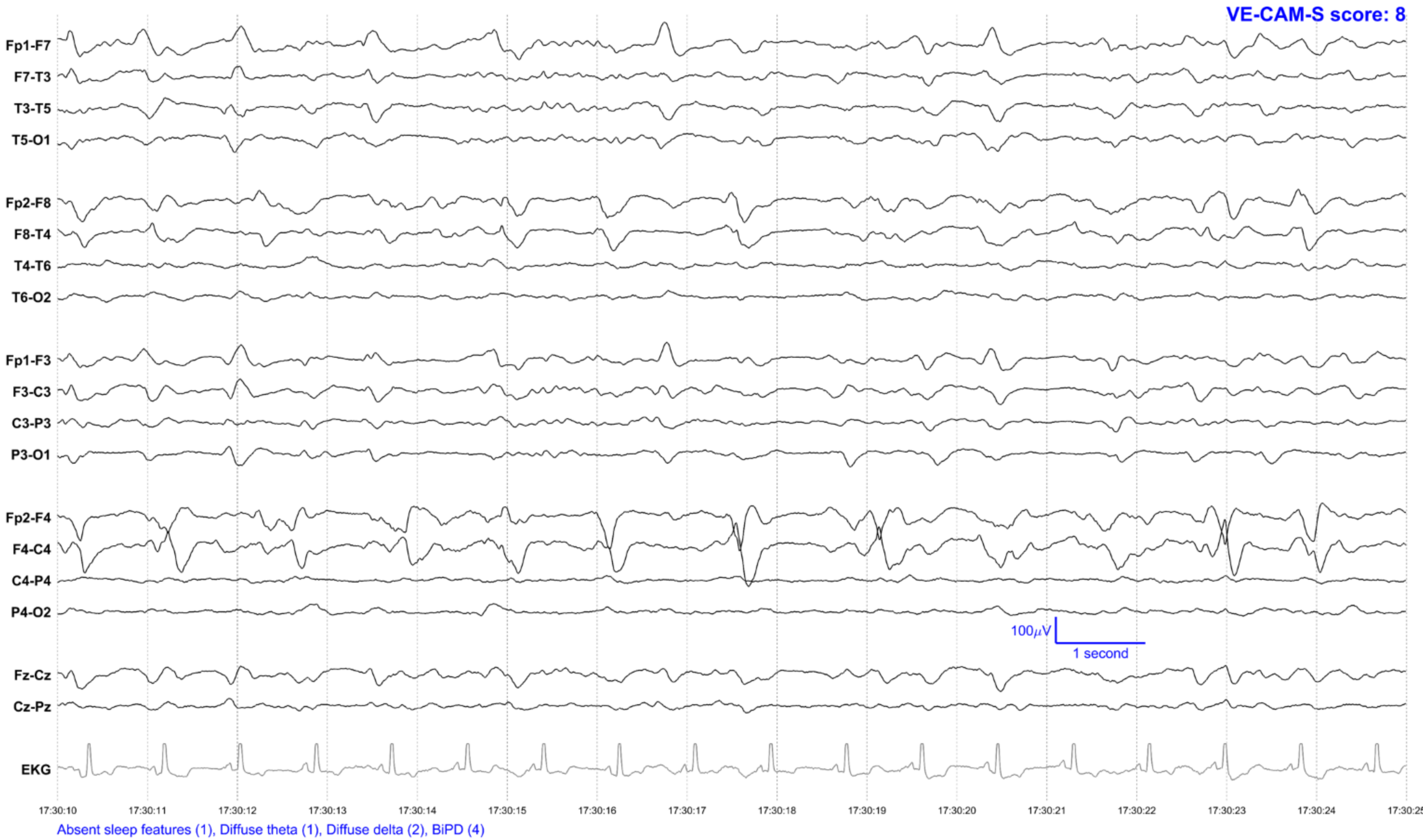
eFigure 30: Example EEG signal for 'High delirium severity'



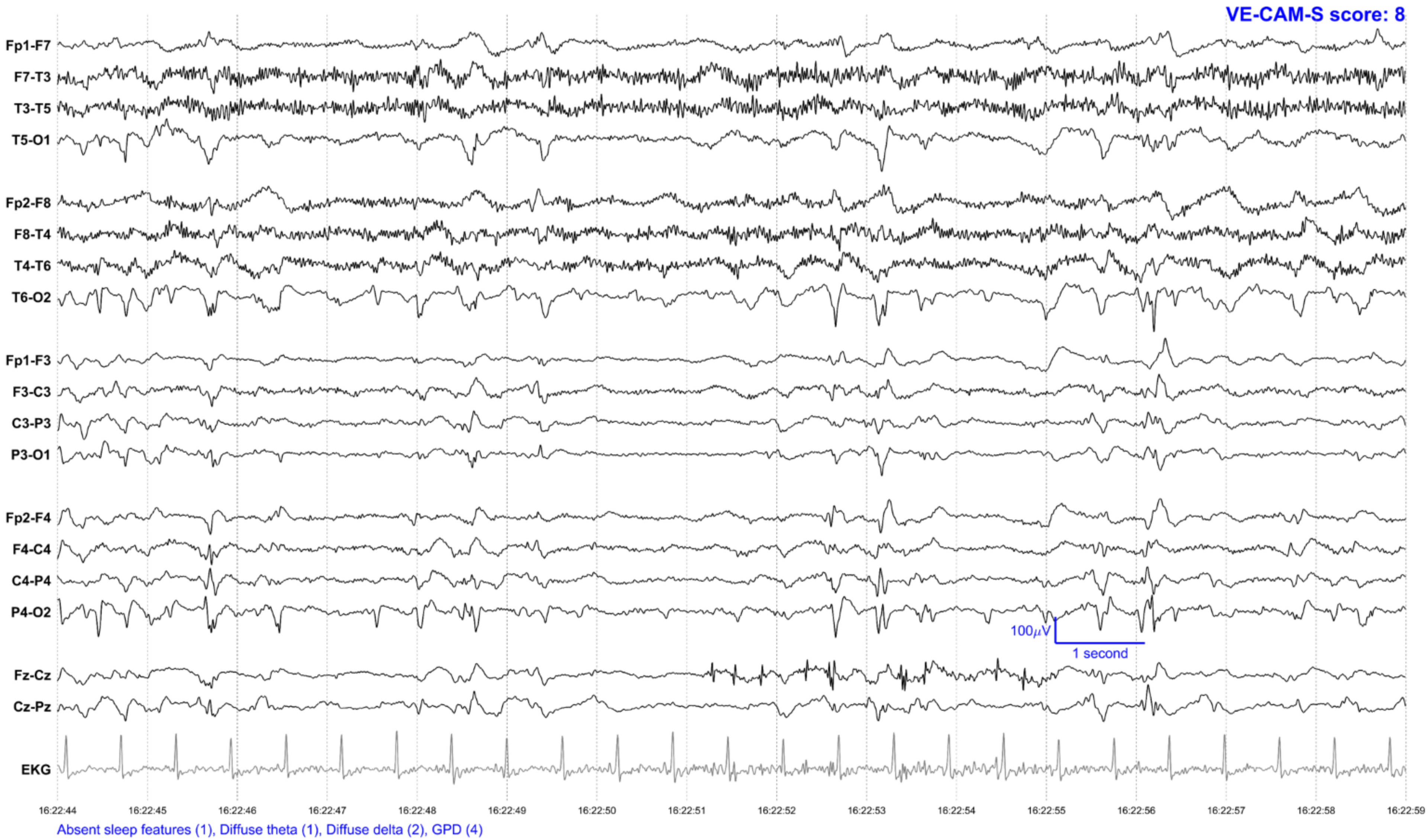
eFigure 31: Example EEG signal for 'High delirium severity'



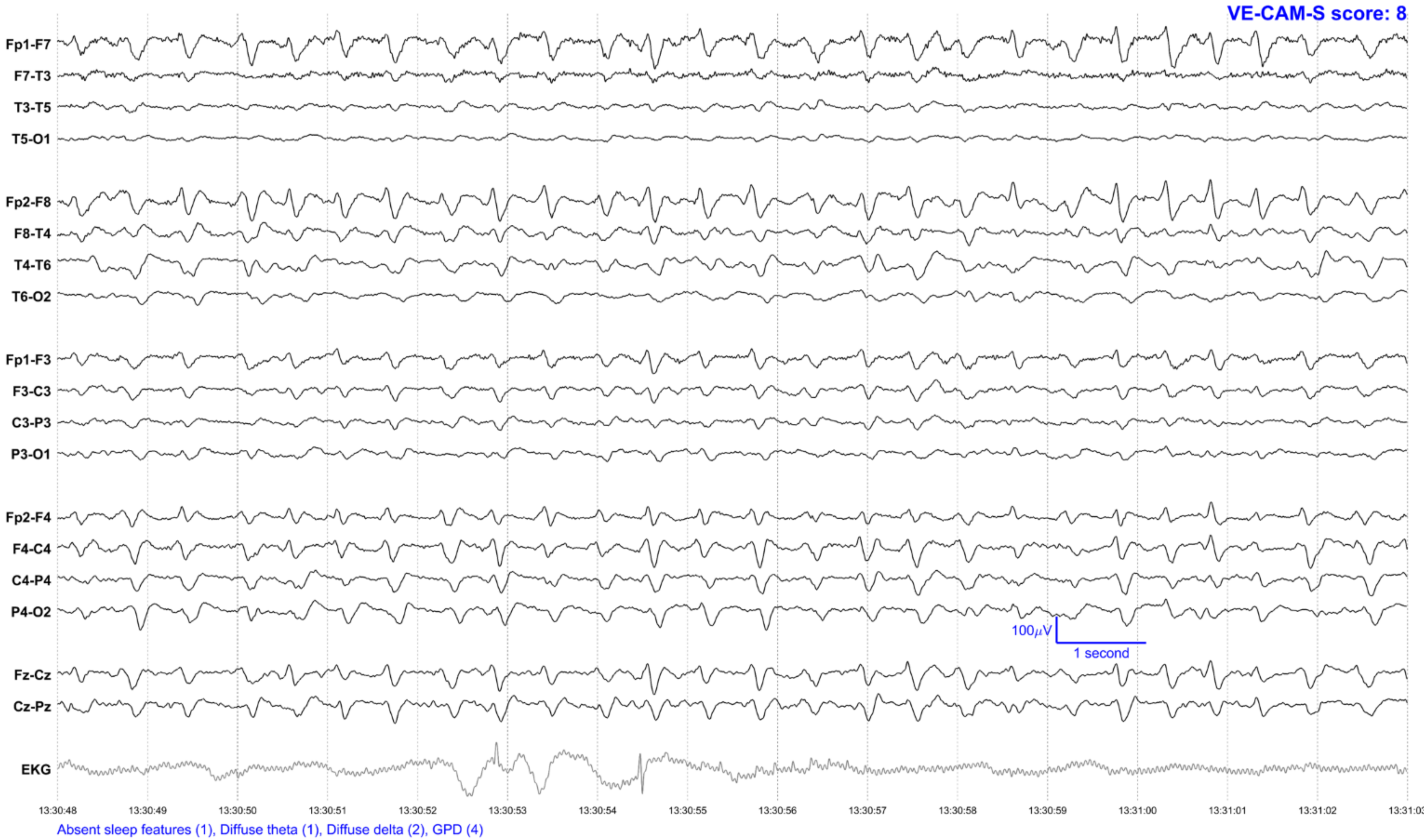
eFigure 32: Example EEG signal for 'High delirium severity'



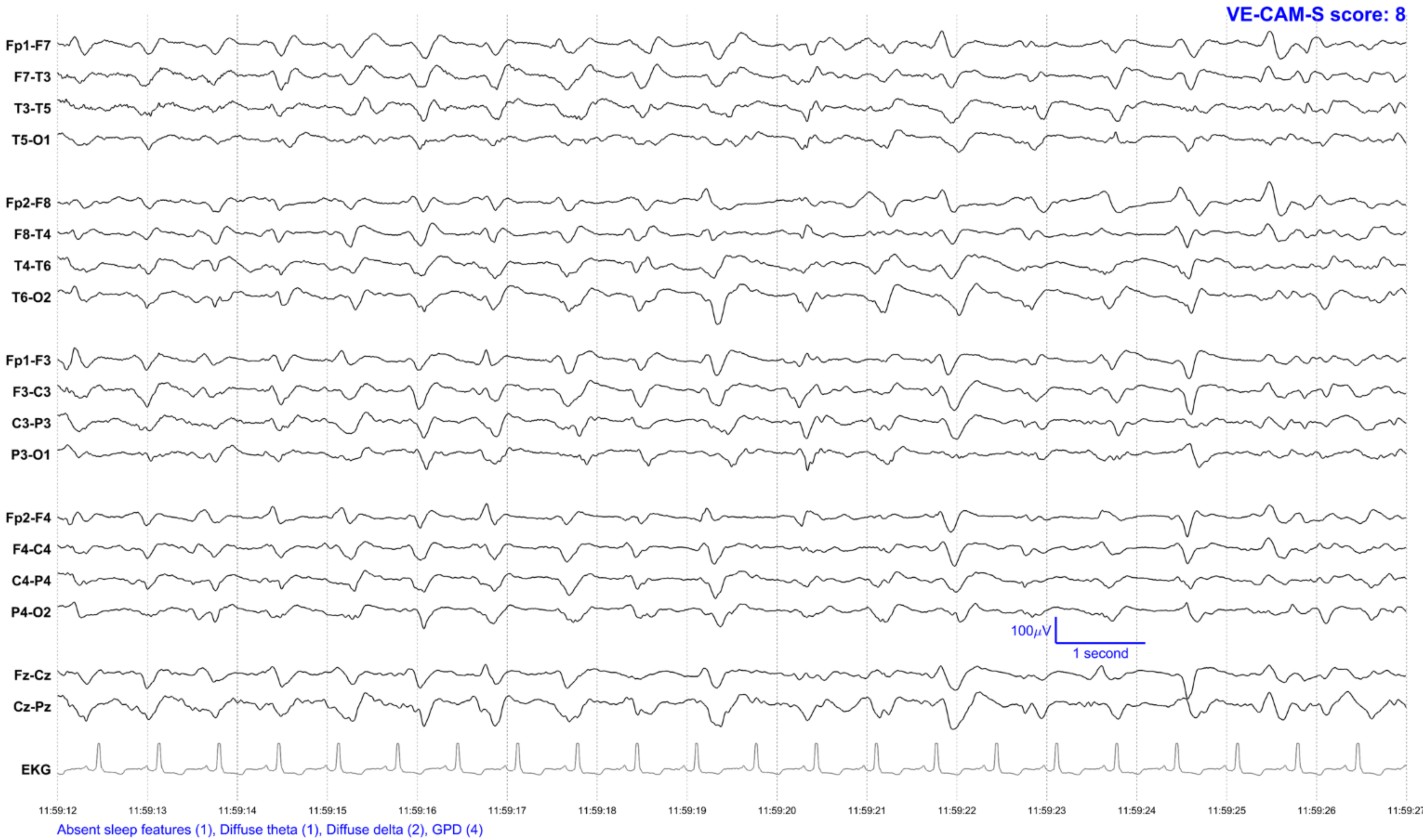
eFigure 33: Example EEG signal for 'High delirium severity'



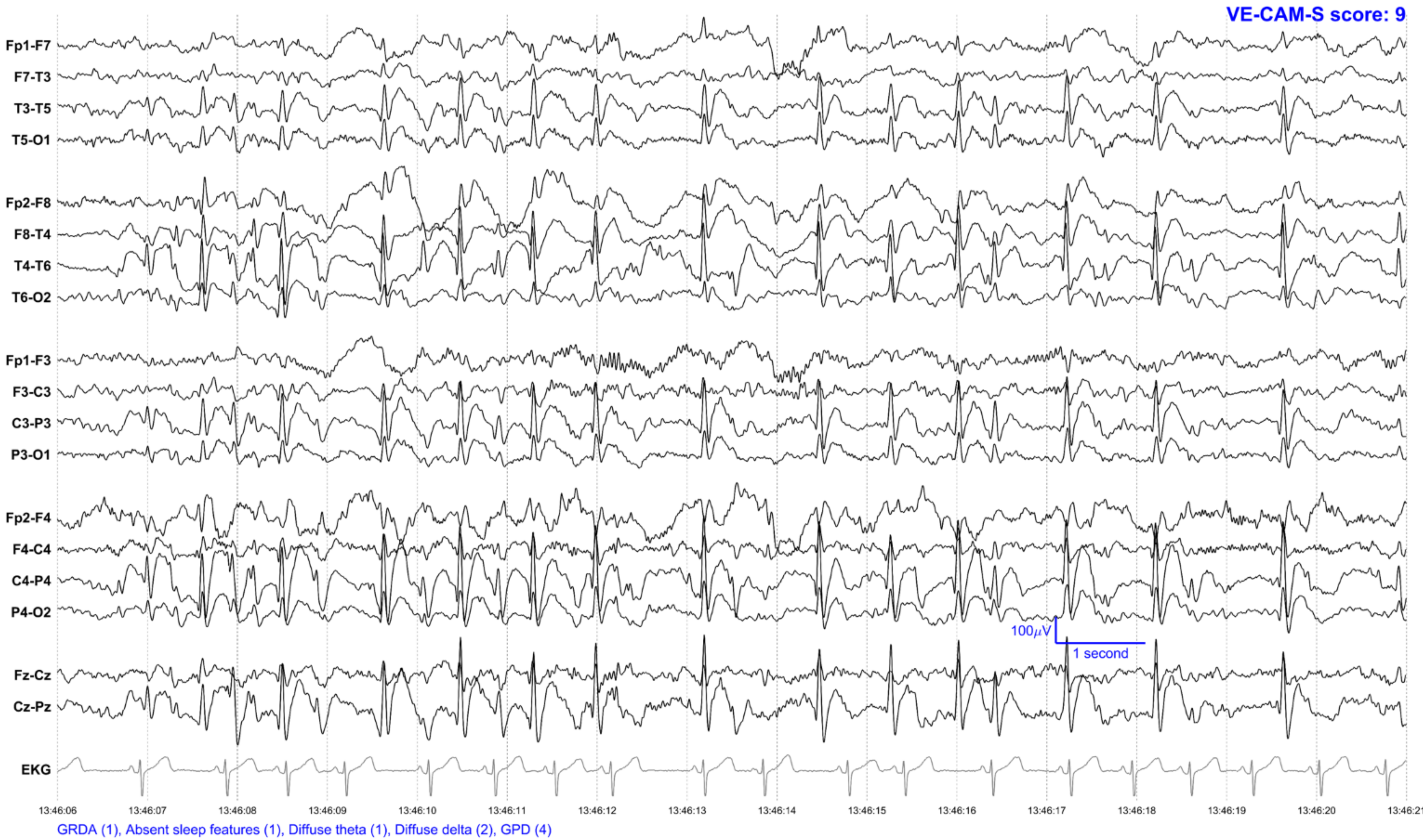
eFigure 34: Example EEG signal for 'High delirium severity'



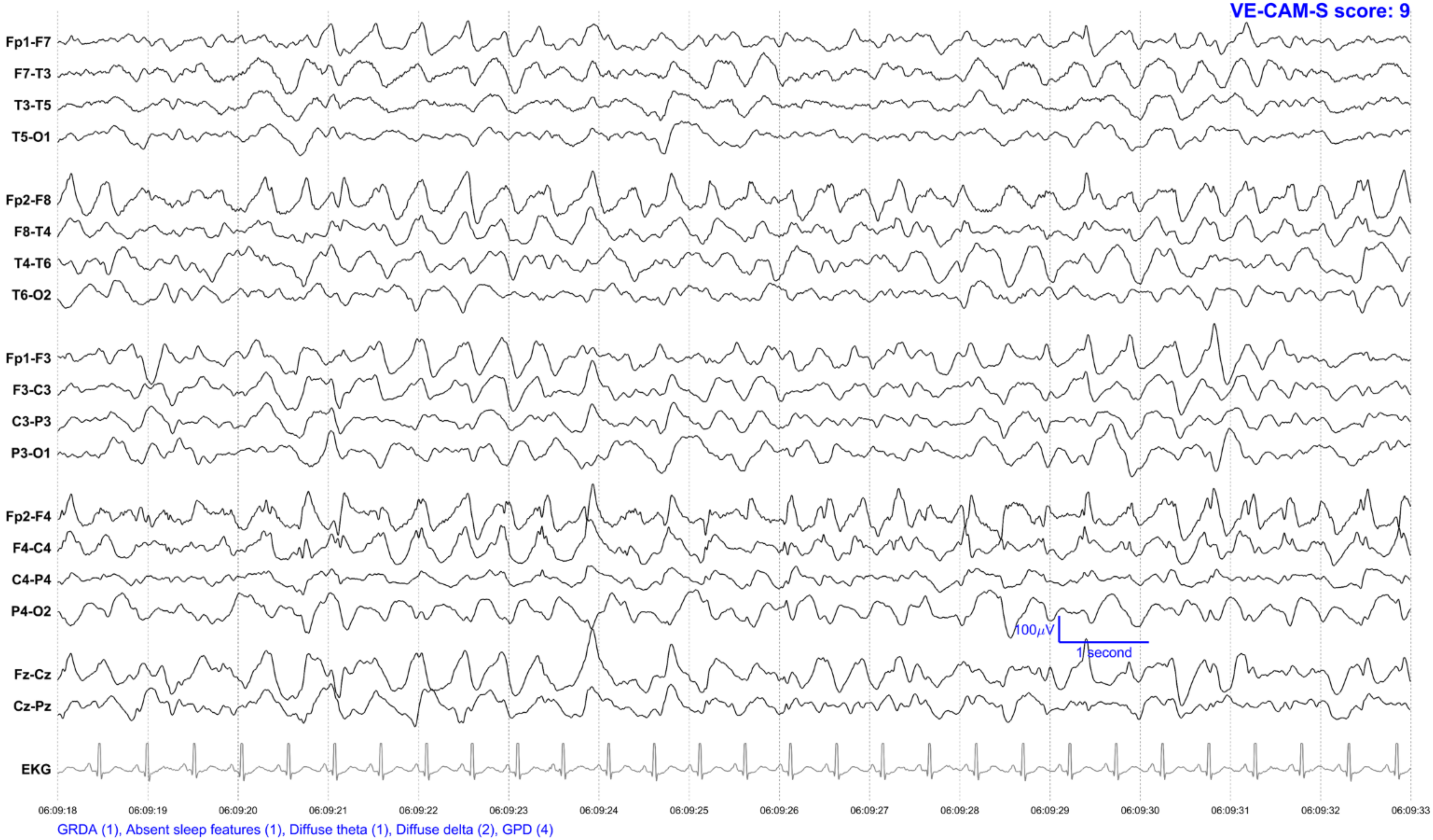
eFigure 35: Example EEG signal for 'High delirium severity'



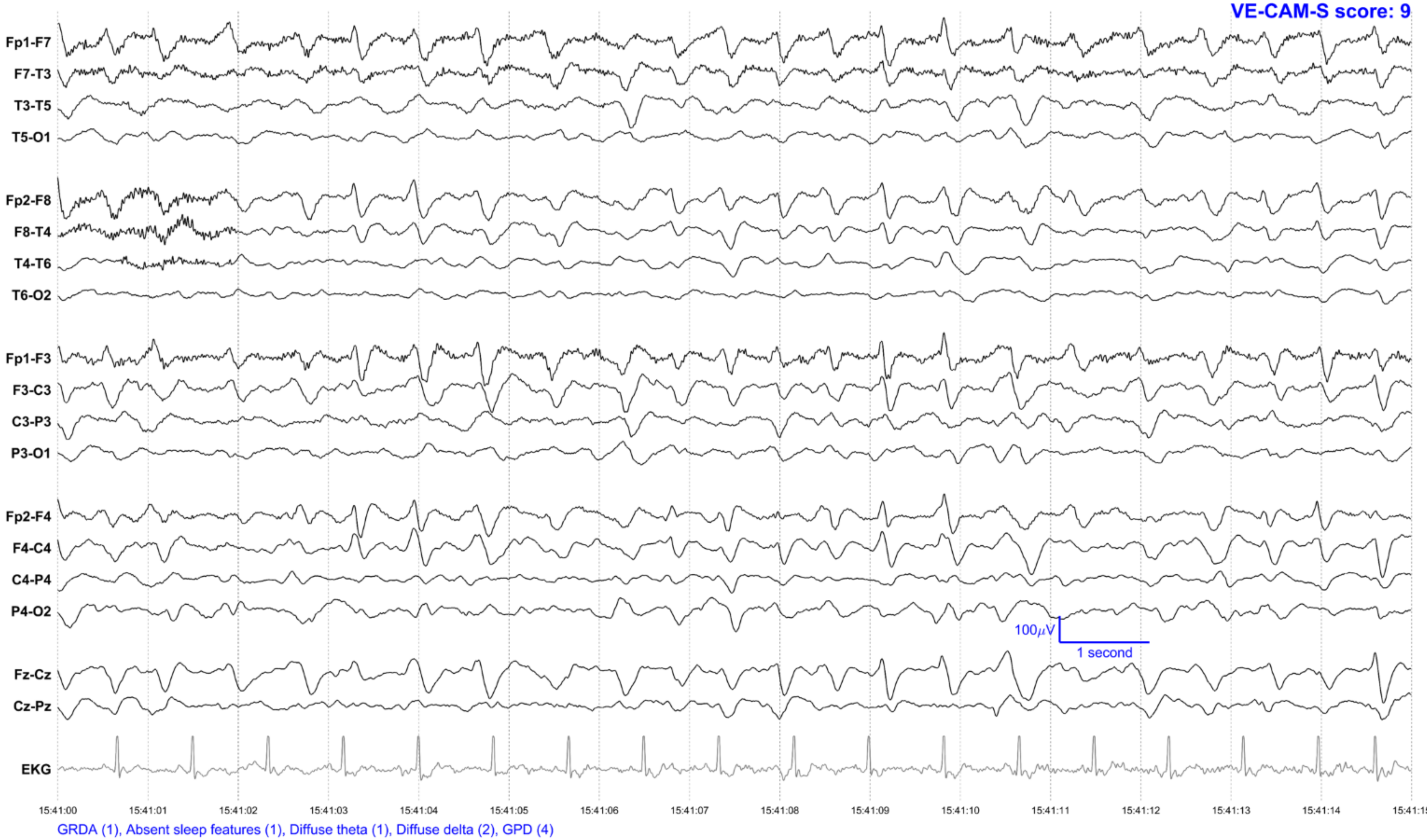
eFigure 36: Example EEG signal for 'High delirium severity'



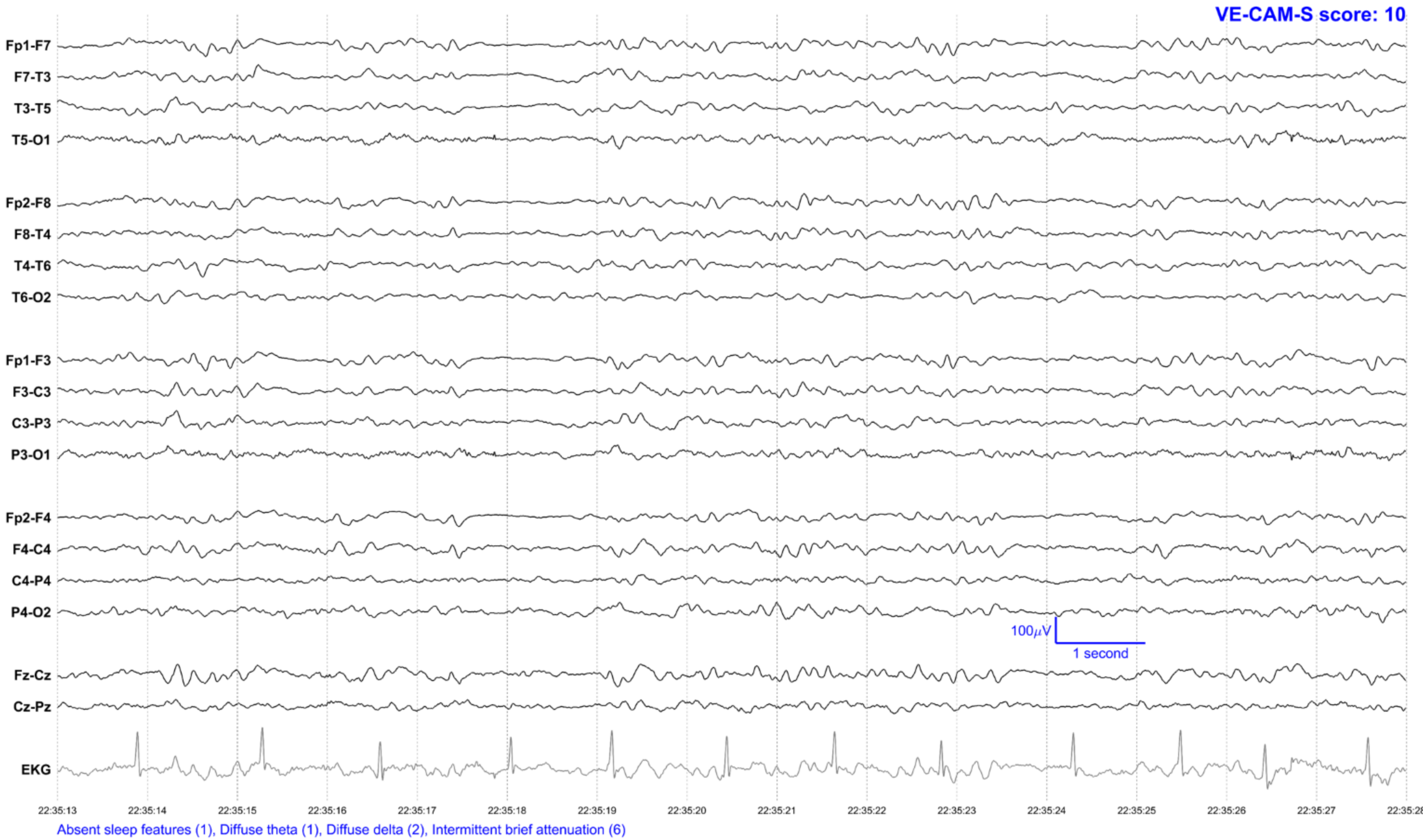
eFigure 37: Example EEG signal for 'High delirium severity'



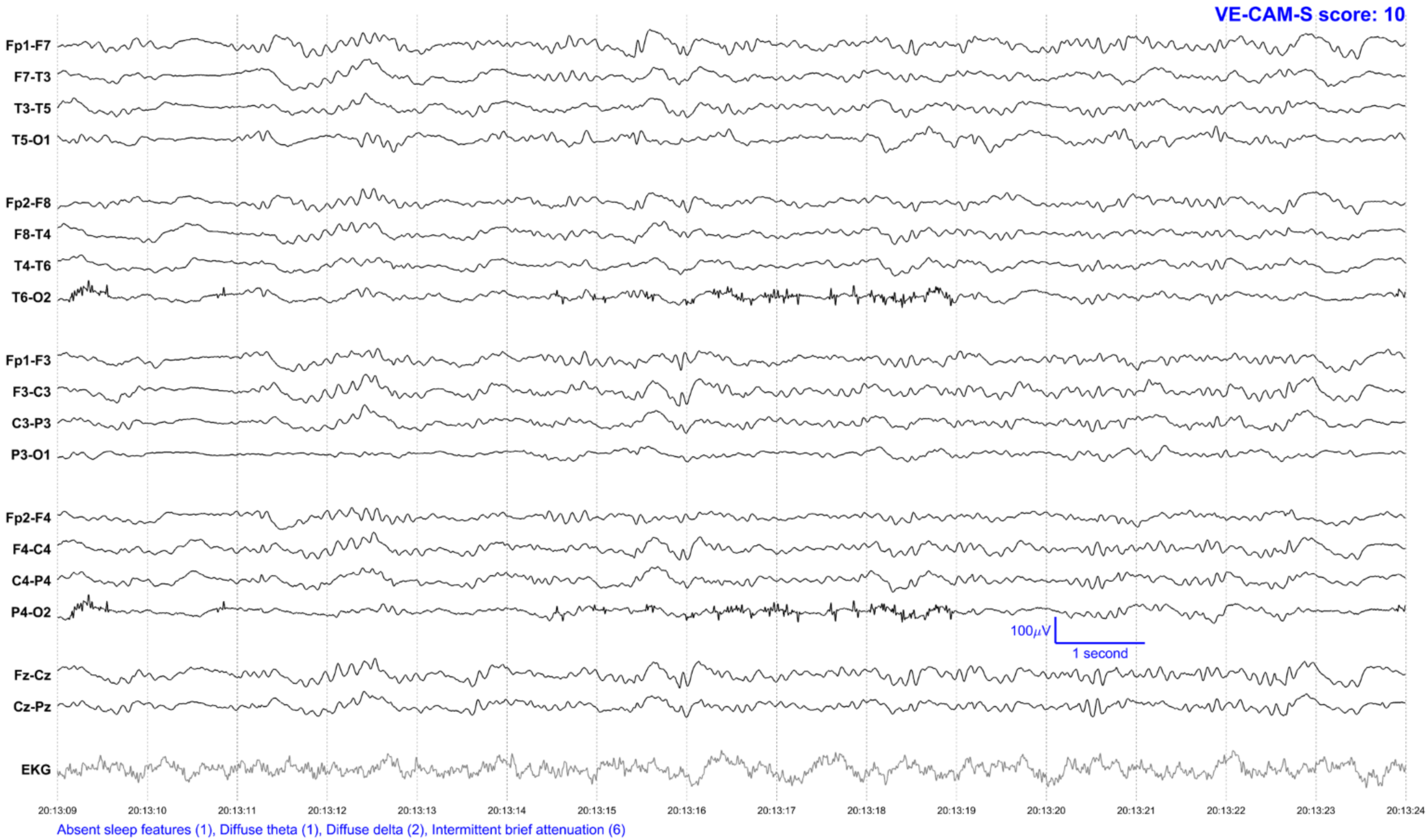
eFigure 38: Example EEG signal for ‘High delirium severity’



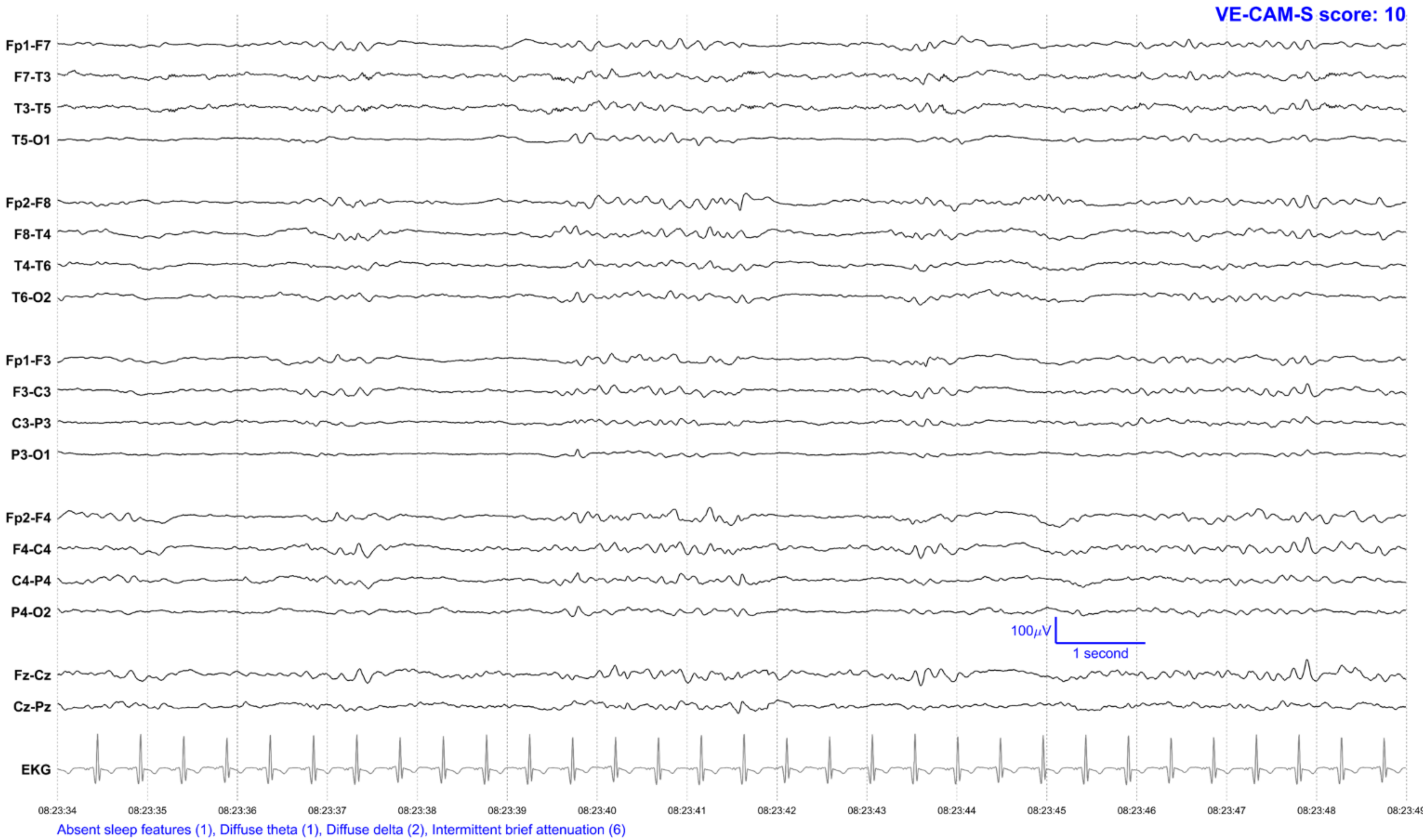
eFigure 39: Example EEG signal for ‘High delirium severity’



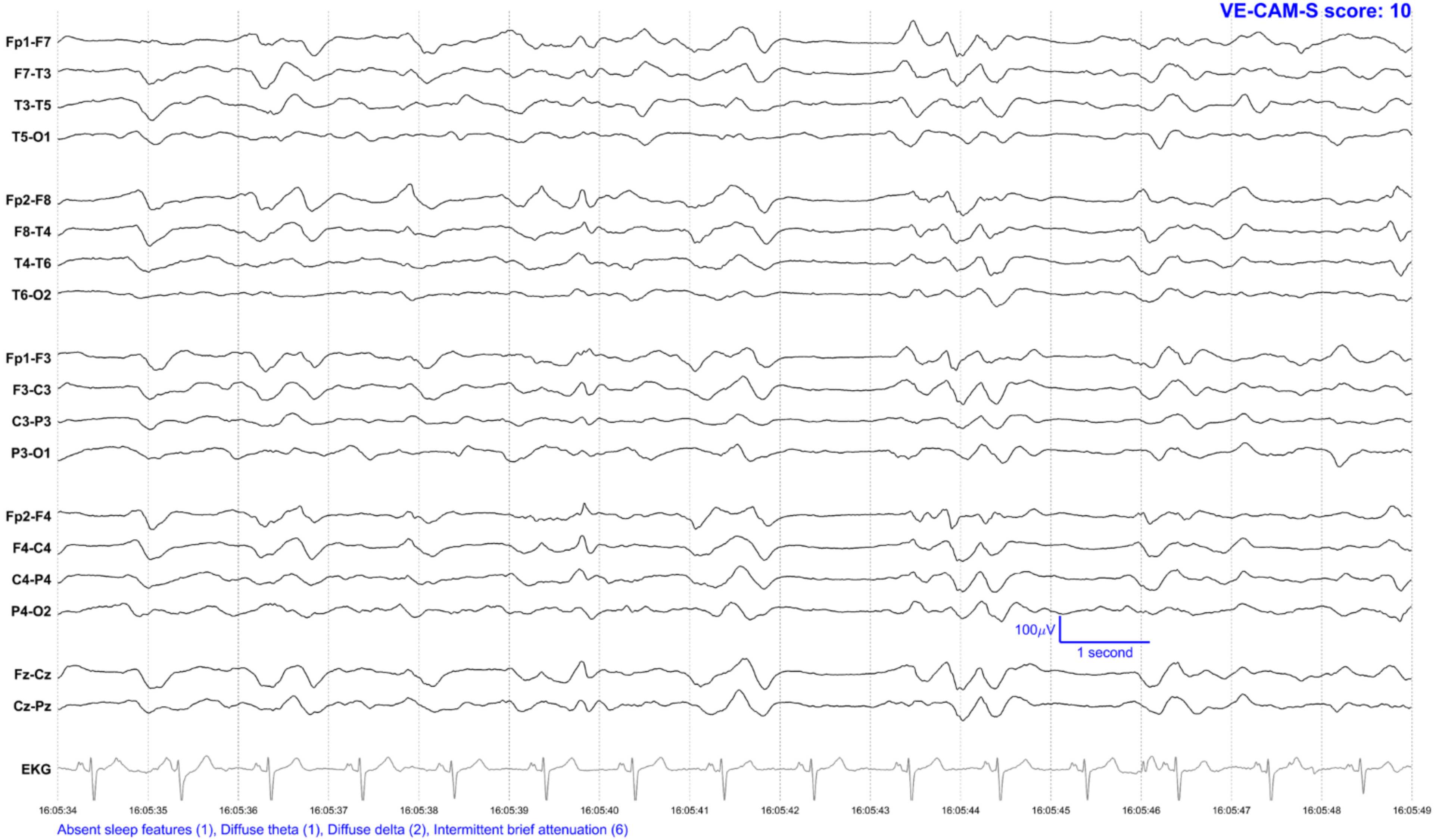
eFigure 40: Example EEG signal for 'High delirium severity'



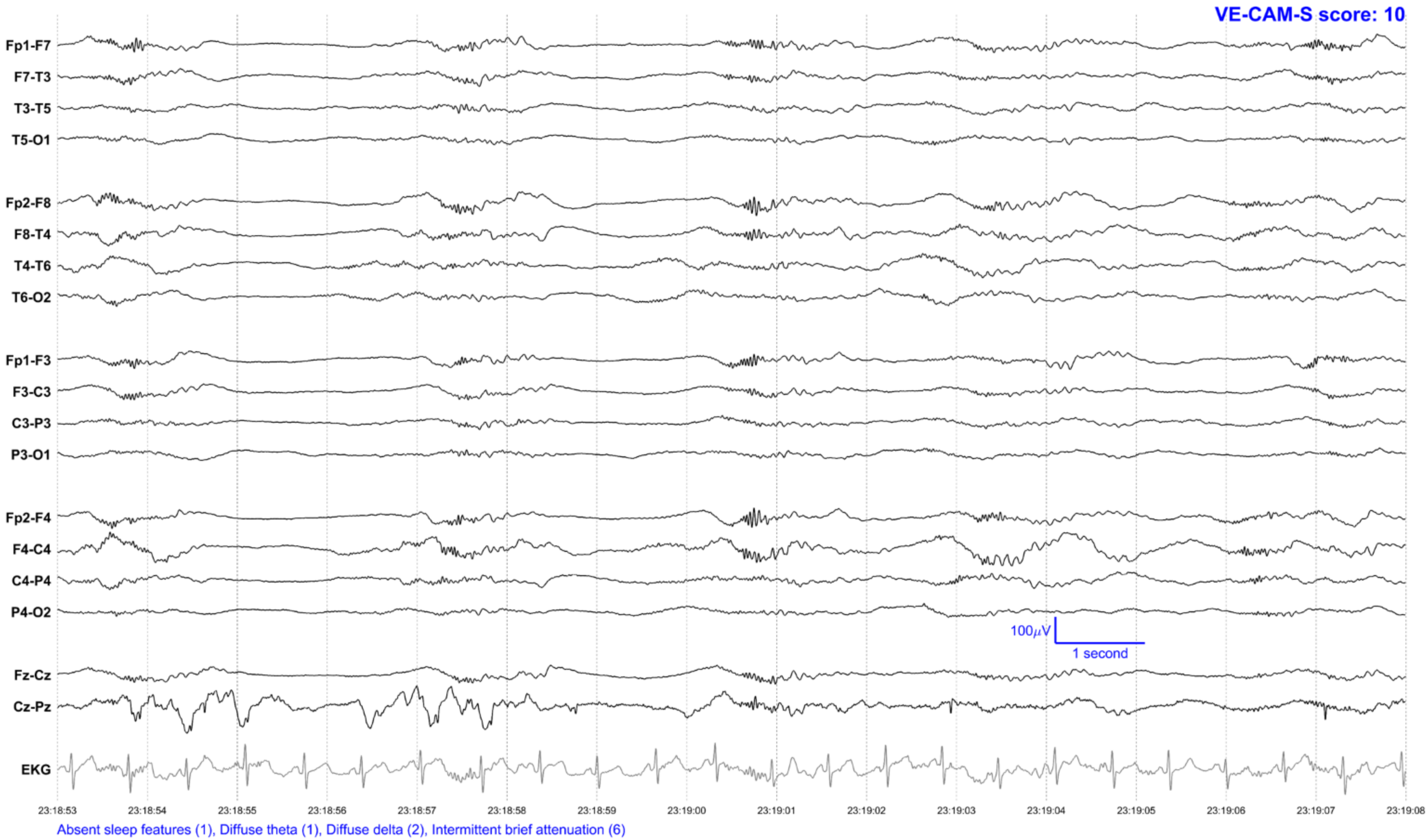
eFigure 41: Example EEG signal for 'High delirium severity'



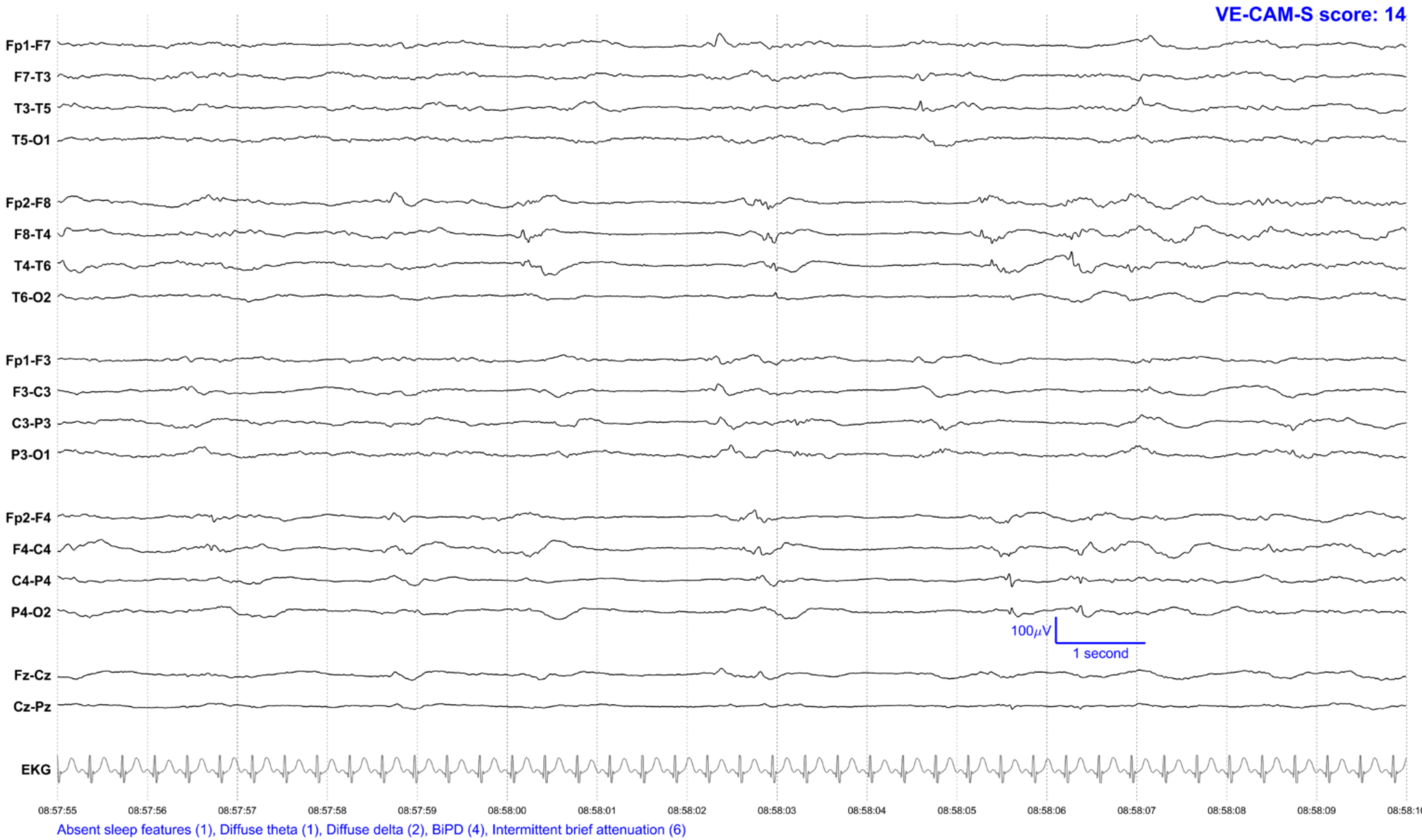
eFigure 42: Example EEG signal for ‘High delirium severity’



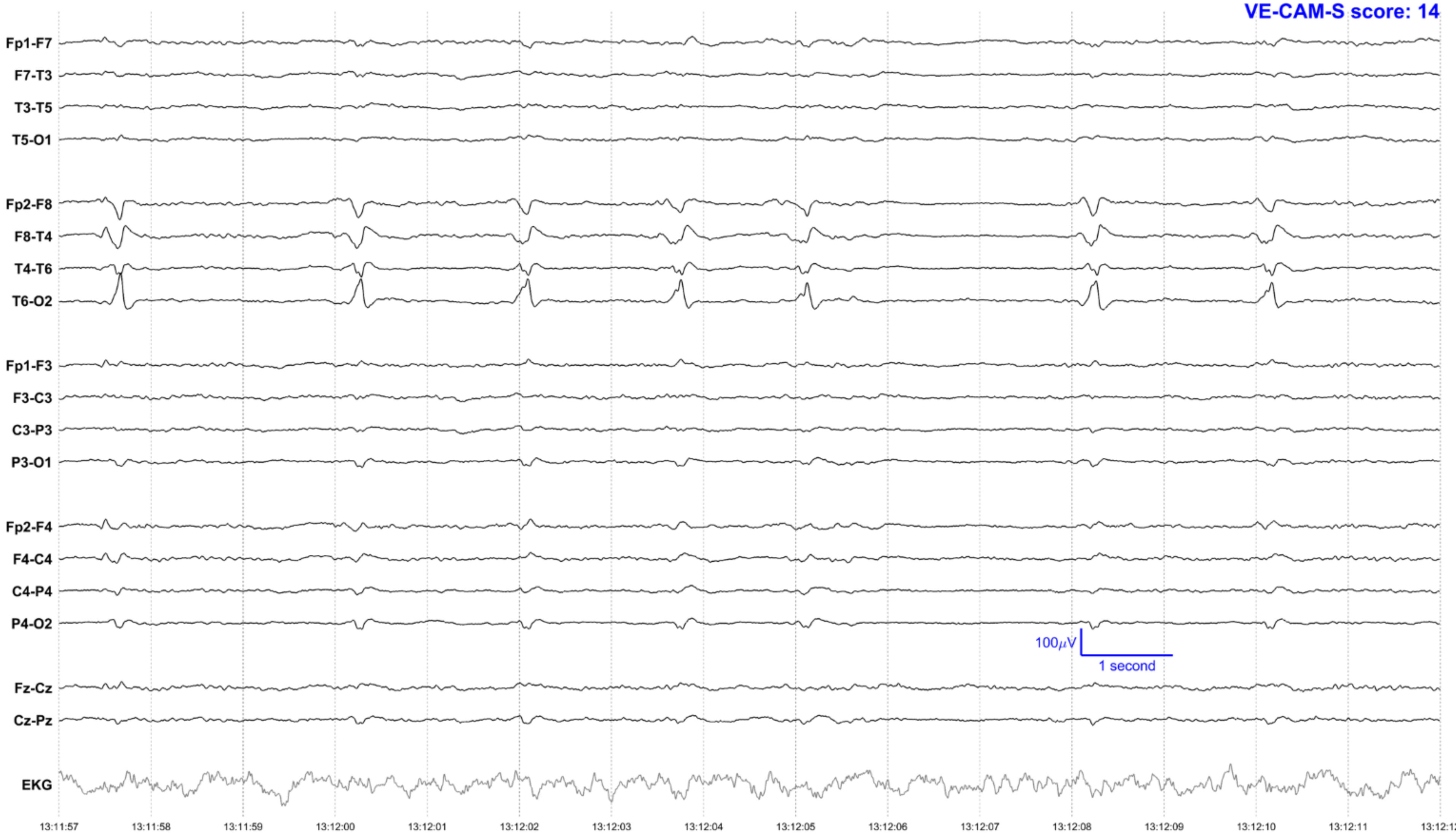
eFigure 43: Example EEG signal for ‘High delirium severity’



eFigure 44: Example EEG signal for 'High delirium severity'

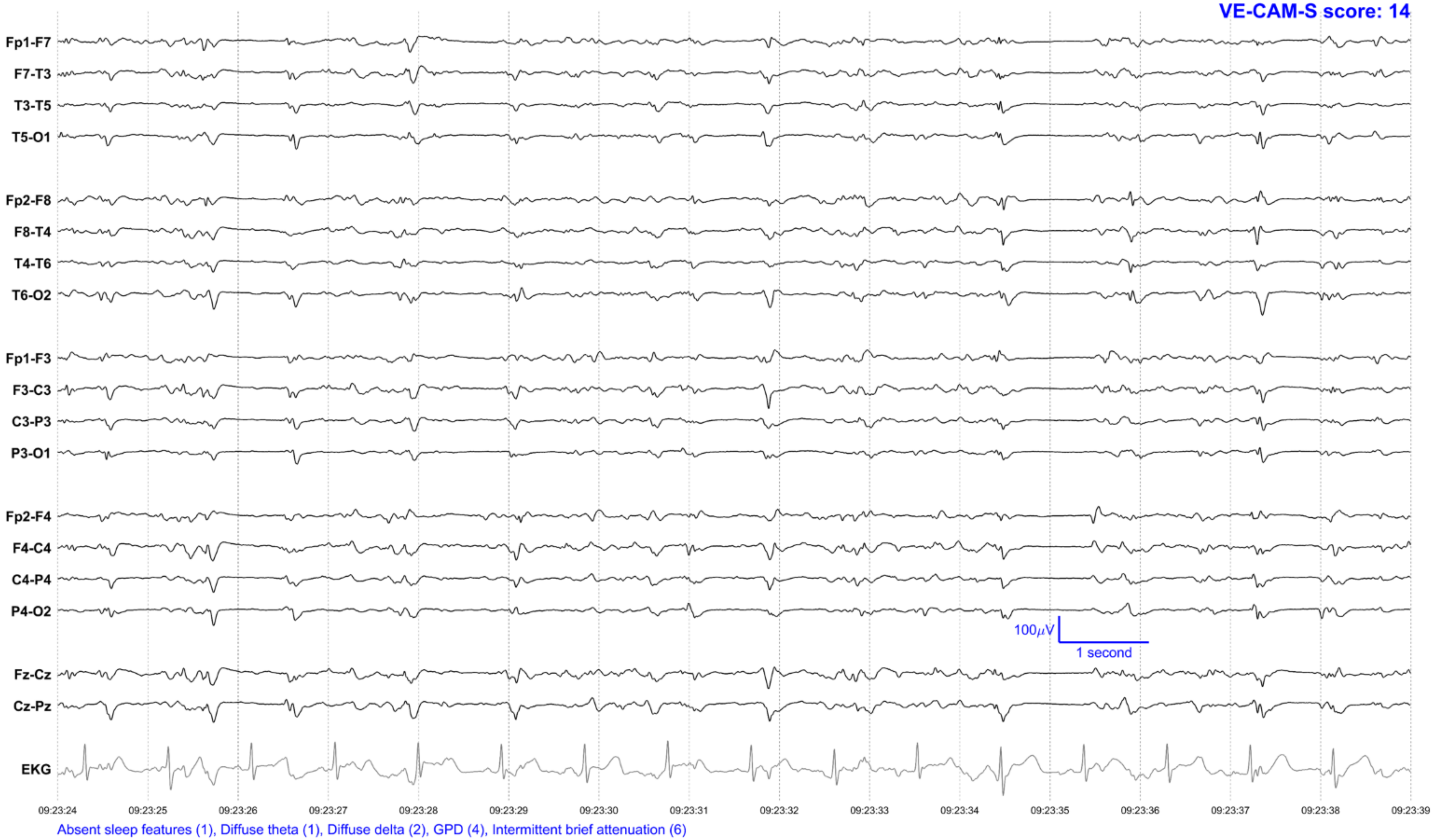


eFigure 45: Example EEG signal for ‘High delirium severity’

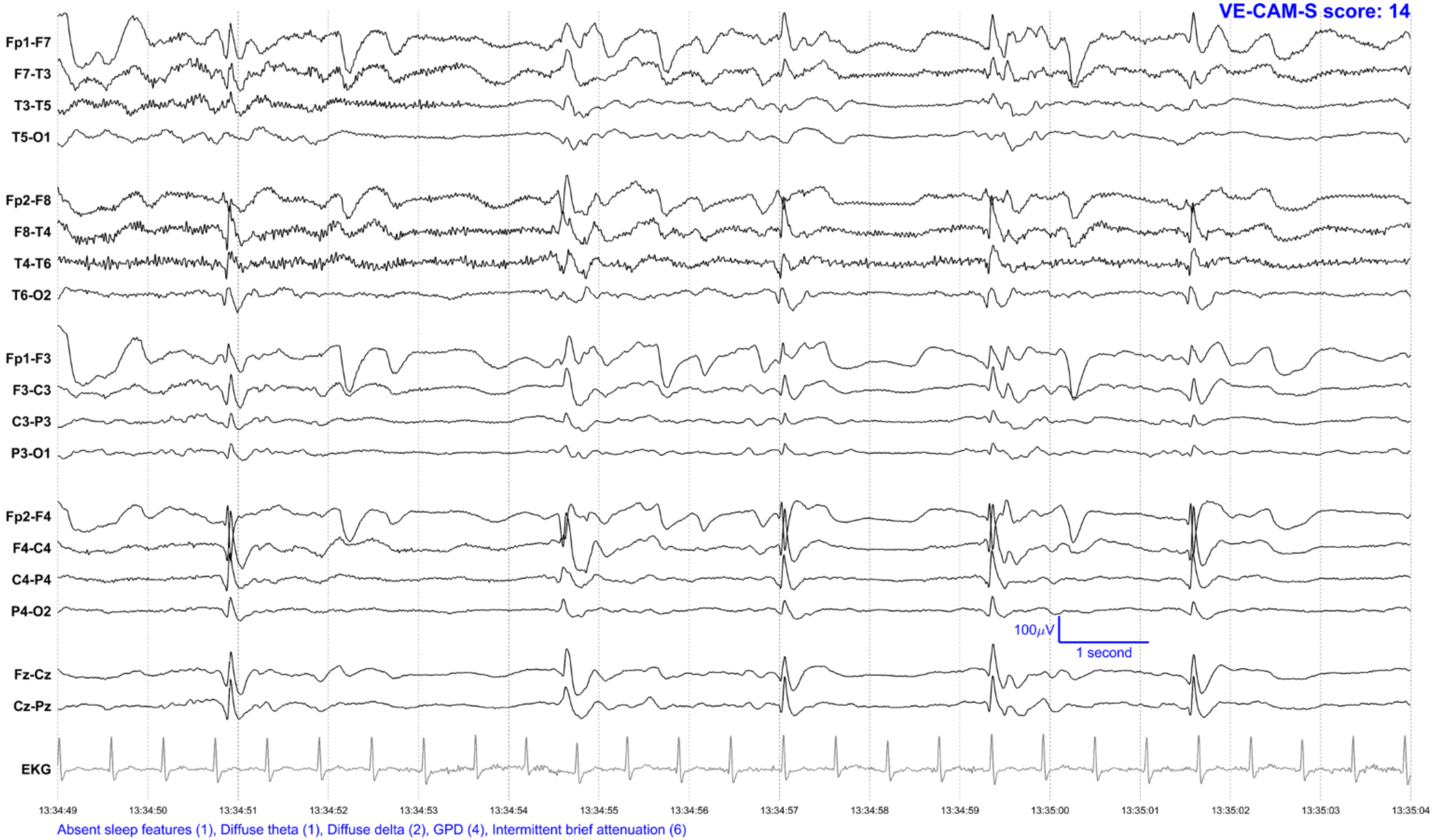


Absent sleep features (1), Diffuse theta (1), Diffuse delta (2), Moderately low voltage (2), LPD (2), Intermittent brief attenuation (6)

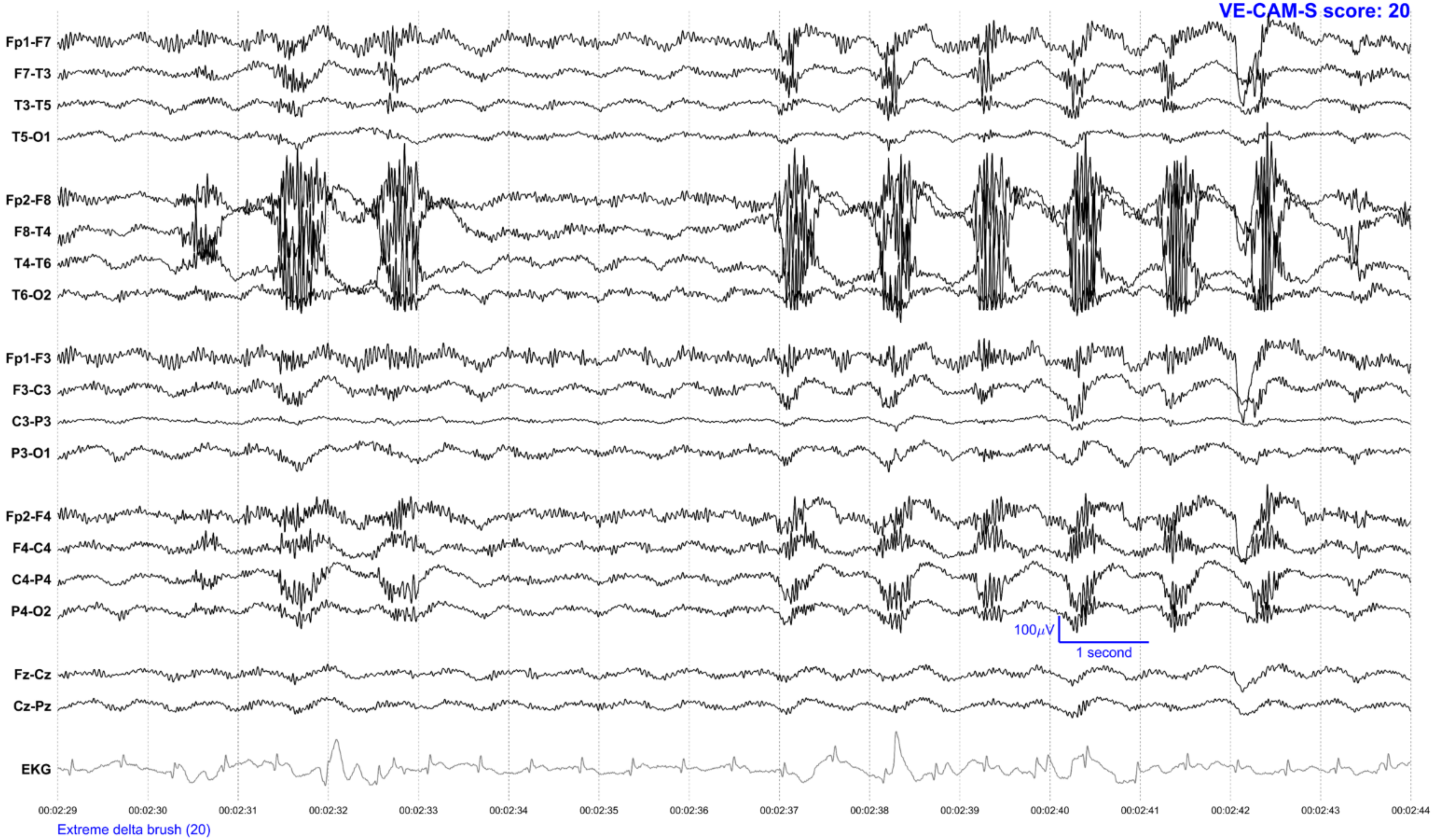
eFigure 46: Example EEG signal for 'High delirium severity'



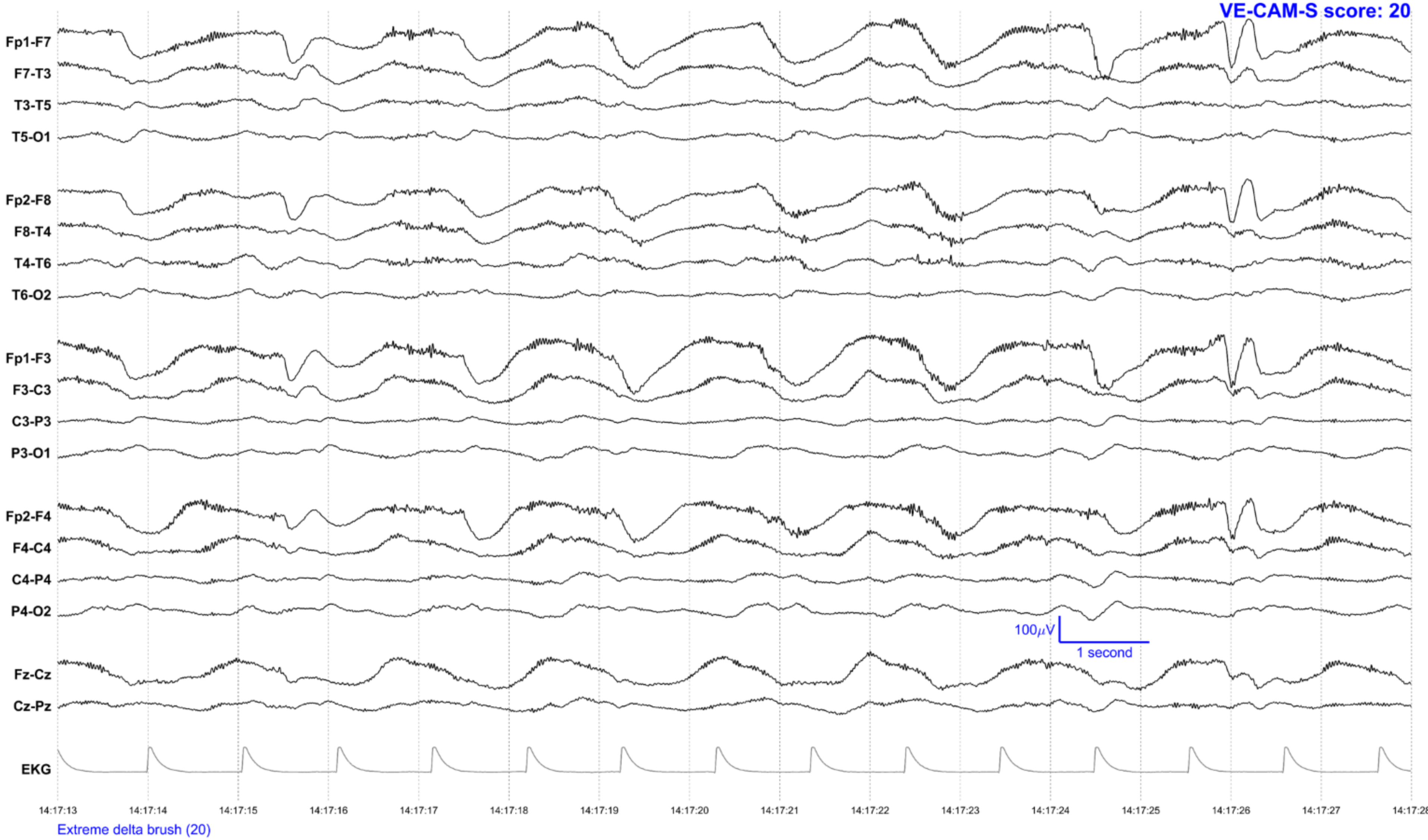
eFigure 47: Example EEG signal for ‘High delirium severity’



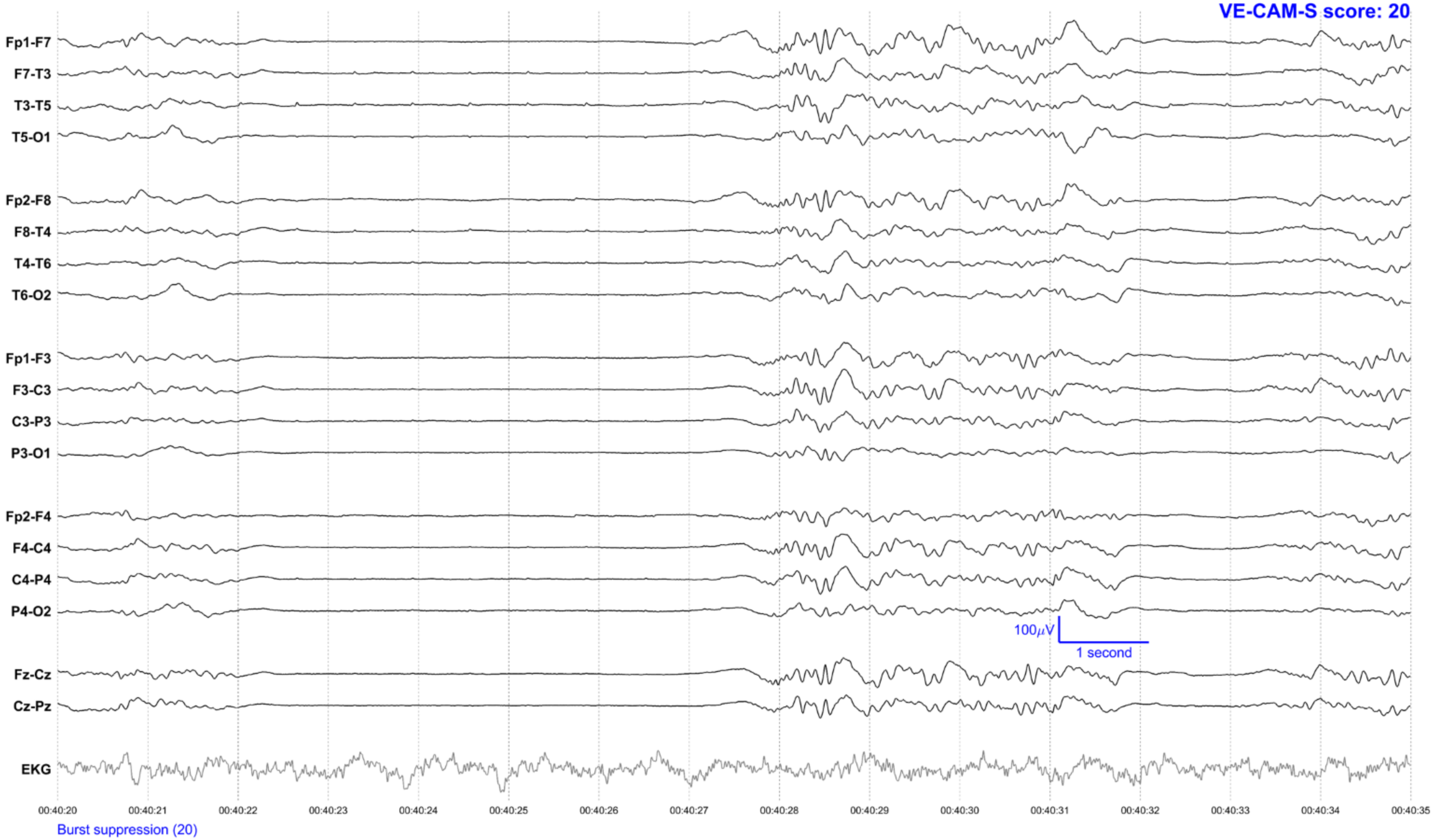
eFigure 48: Example EEG signal for 'Worst delirium severity'



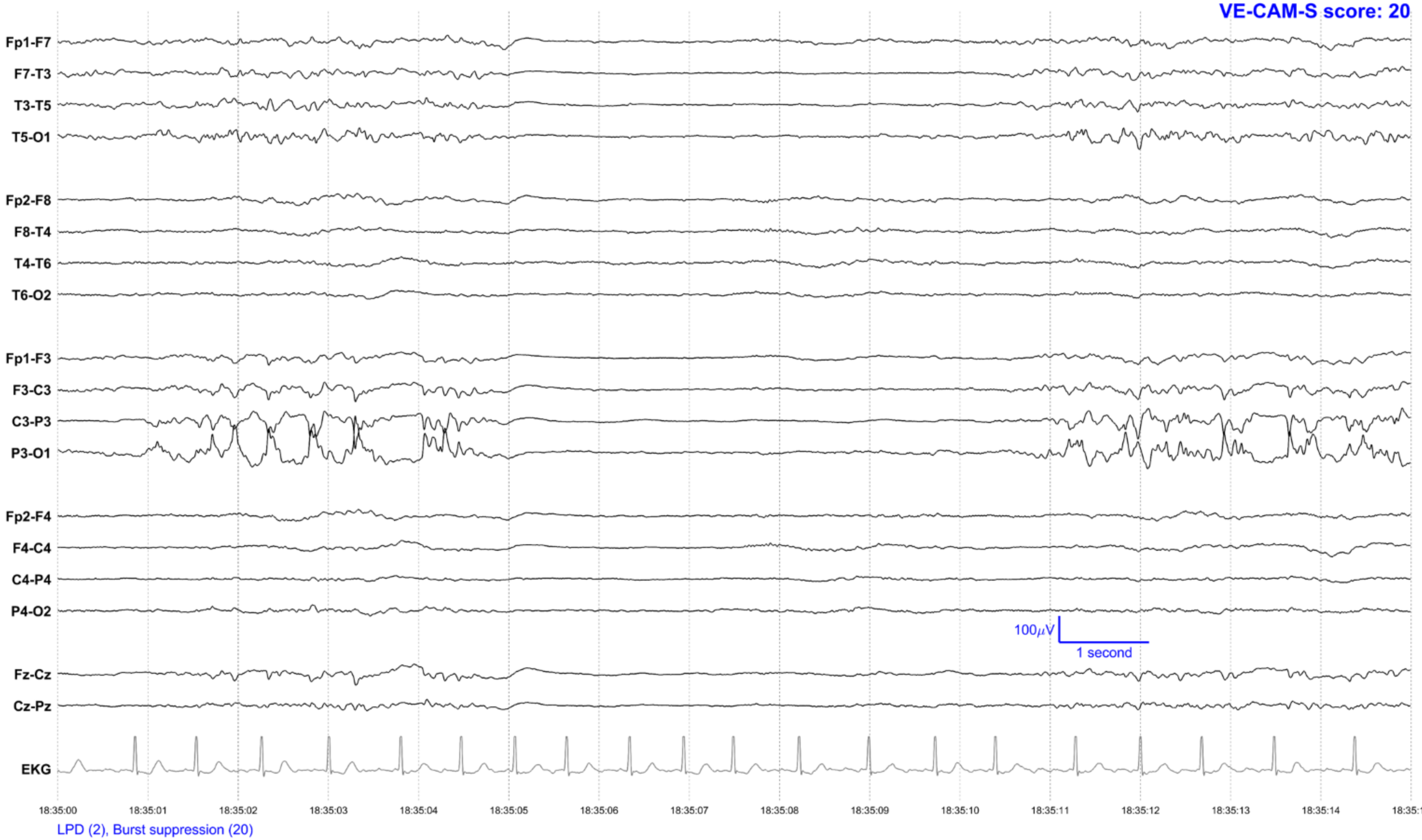
eFigure 49: Example EEG signal for 'Worst delirium severity'



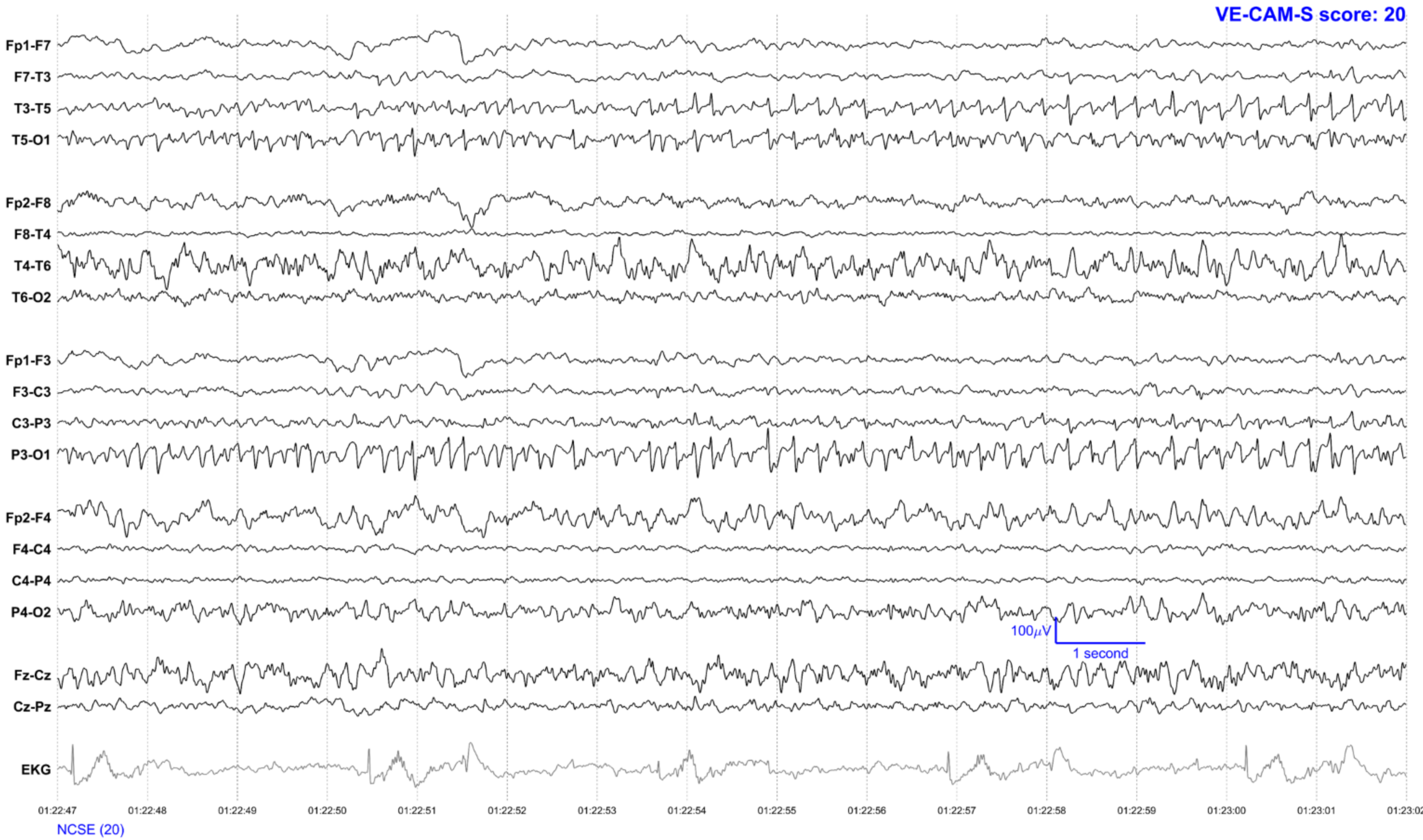
eFigure 50: Example EEG signal for 'Worst delirium severity'



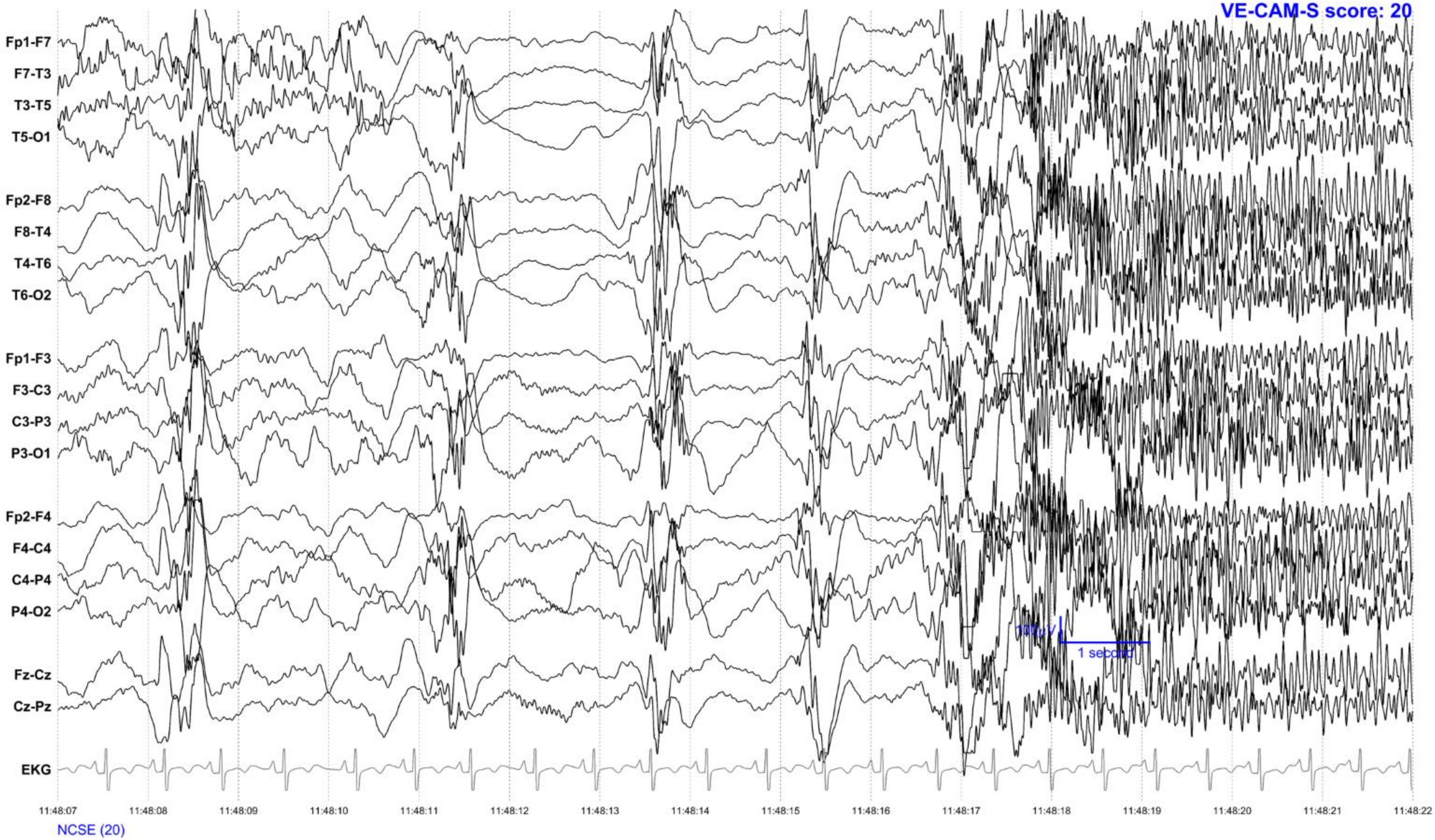
eFigure 51: Example EEG signal for 'Worst delirium severity'



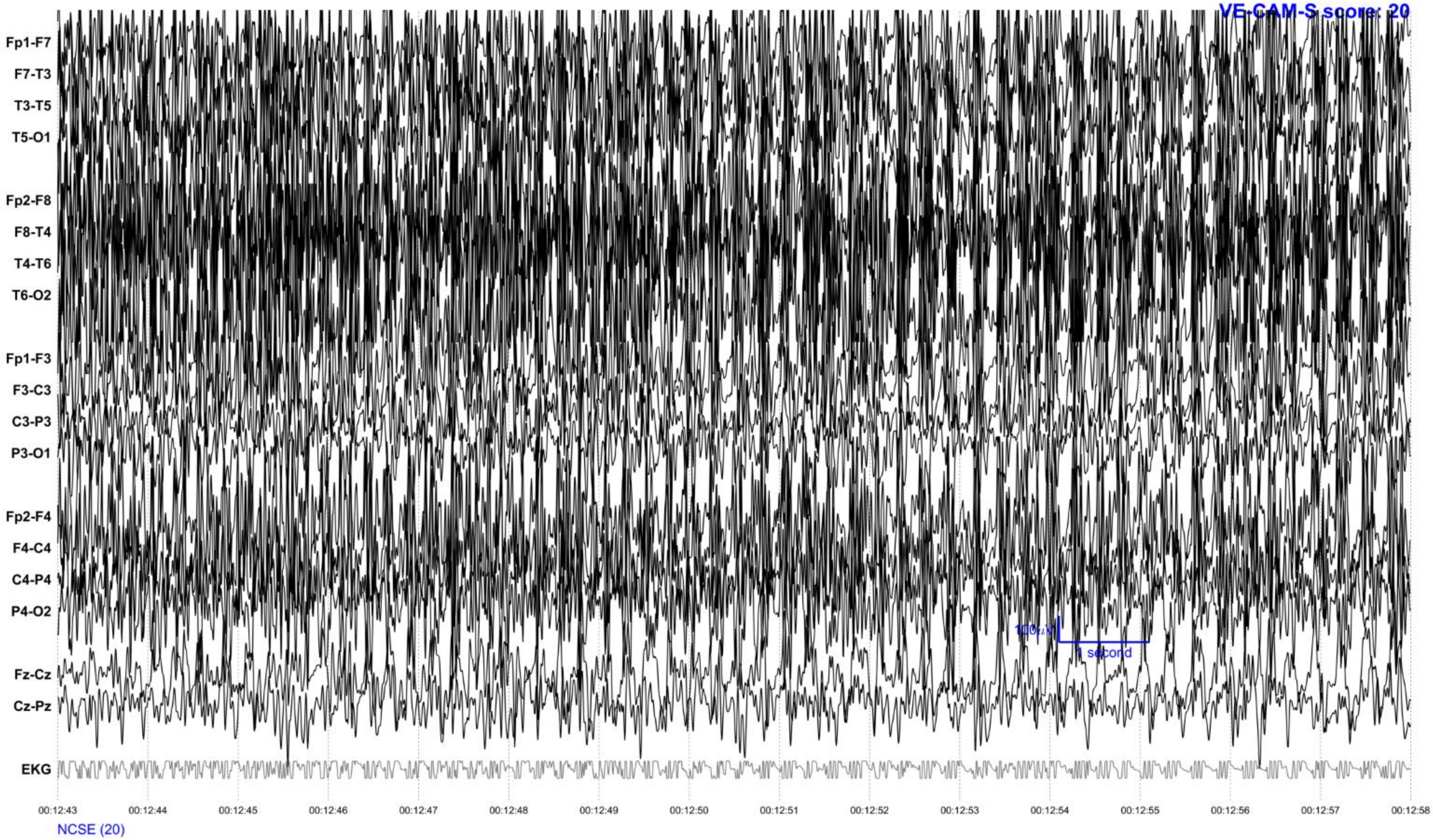
eFigure 52: Example EEG signal for 'Worst delirium severity'



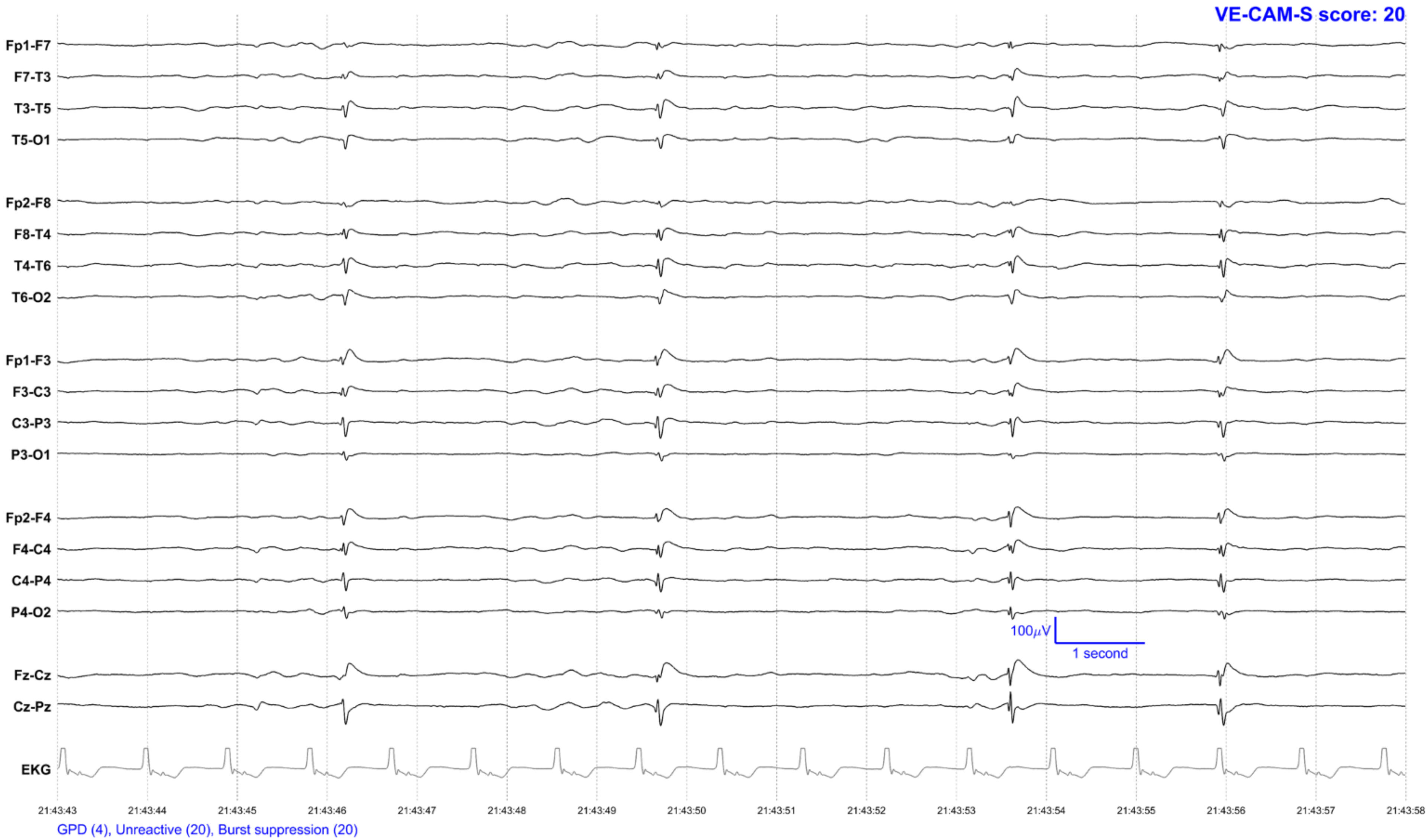
eFigure 53: Example EEG signal for ‘Worst delirium severity’



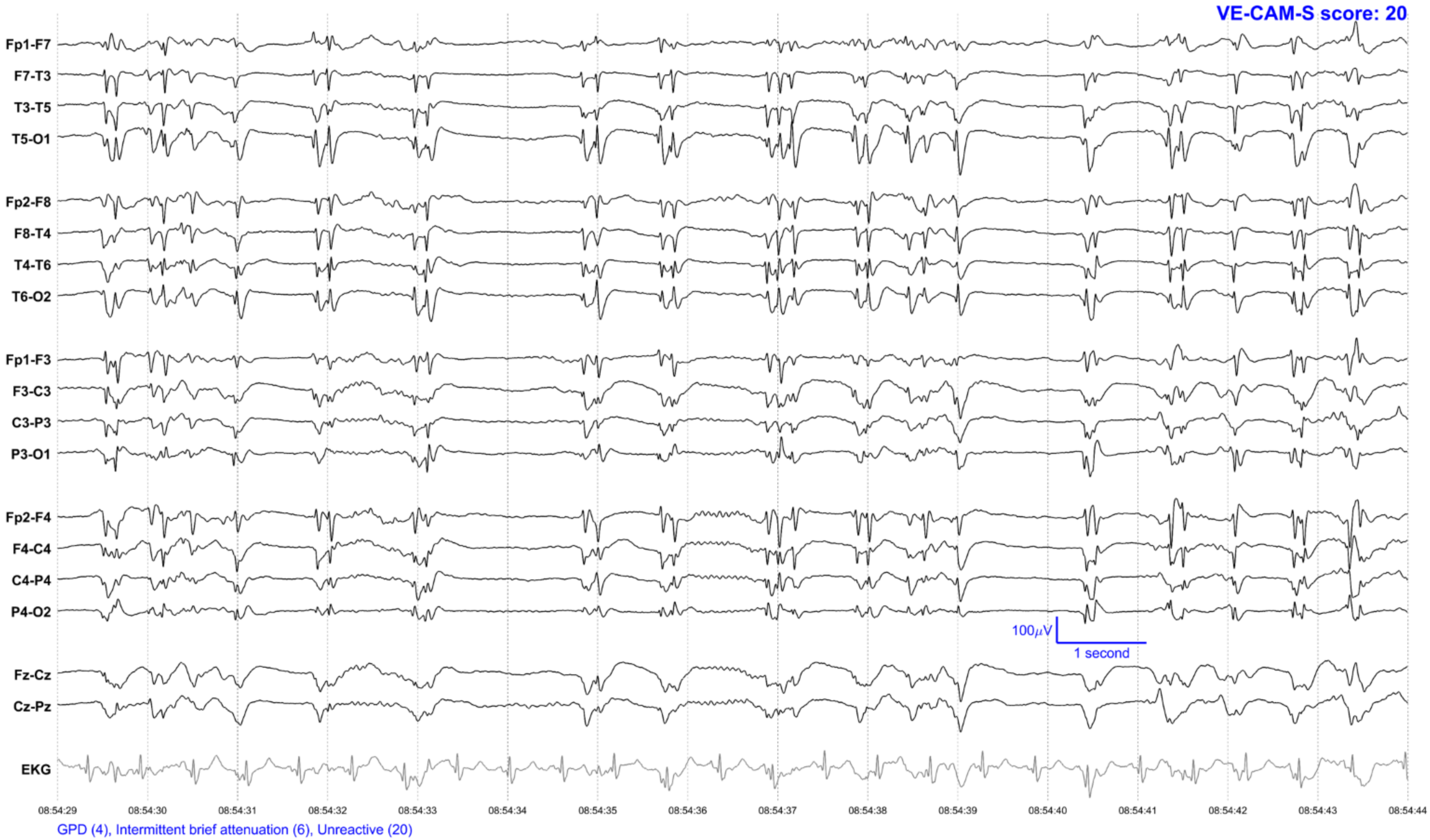
eFigure 54: Example EEG signal for 'Worst delirium severity'



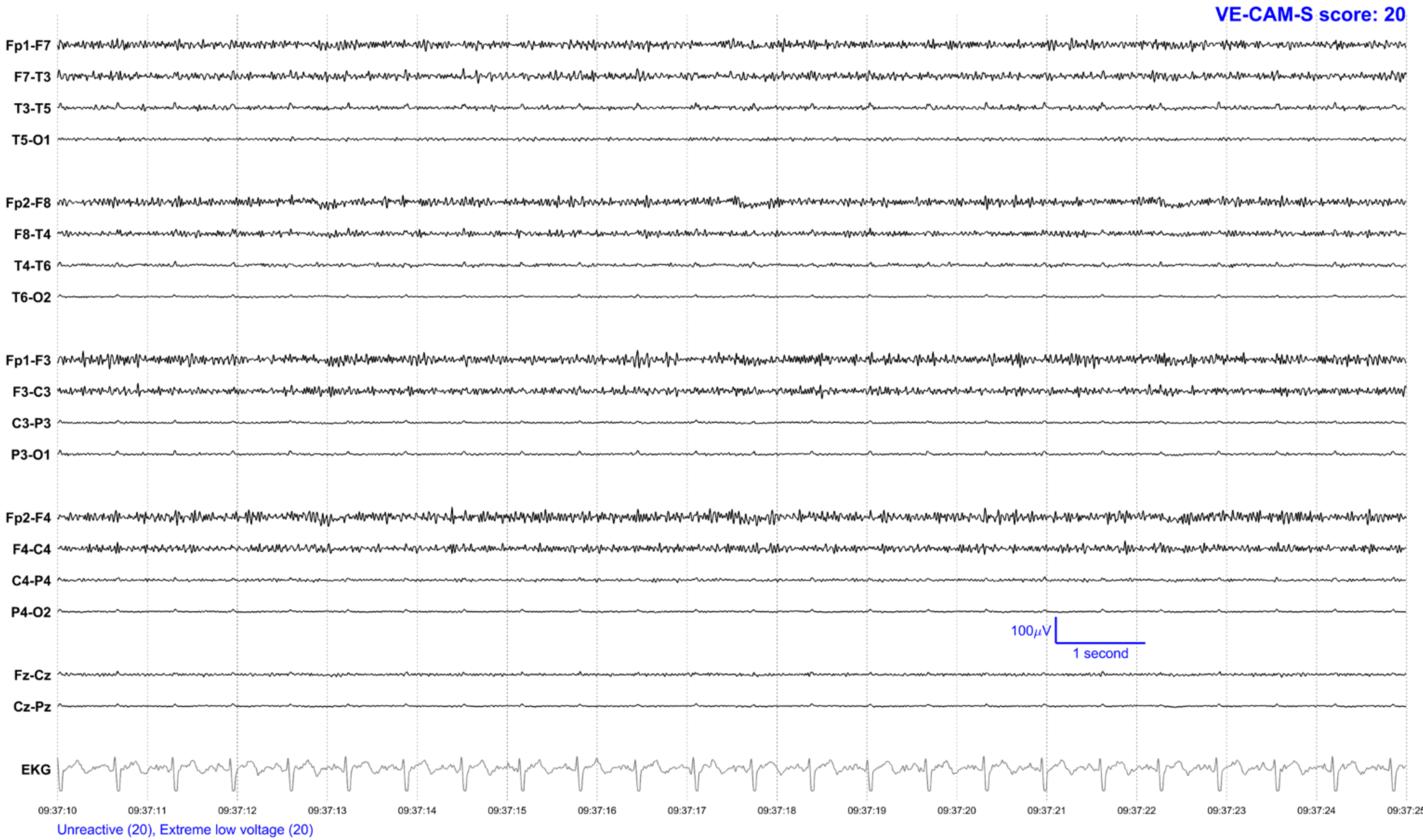
eFigure 55: Example EEG signal for 'Worst delirium severity'



eFigure 56: Example EEG signal for 'Worst delirium severity'



eFigure 57: Example EEG signal for 'Worst delirium severity'



eFigure 58: Example EEG signal for 'Worst delirium severity'