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著者 Author(s)	Yamada, Hiroyuki; Tamasaki, Akiko; Oguri, Masayoshi; Hori, Ikumi; Saitoh, Shinji; Maegaki, Yoshihiro
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## **Frequent epileptic apnoea in a patient with Pitt–Hopkins Syndrome**

Running title: Frequent epileptic apnoea and PTHS

Hiroyuki Yamada<sup>1</sup>, Akiko Tamasaki<sup>1,2</sup>, Masayoshi Oguri<sup>1,3</sup>,

Ikumi Hori<sup>4</sup>, Shinji Saitoh<sup>4</sup>, Yoshihiro Maegaki<sup>1</sup>

<sup>1</sup> Division of Child Neurology, Department of Brain and Neurosciences, Faculty of Medicine, Tottori University, Yonago, Japan

<sup>2</sup> Hakuai Child Development, Home Care Support Clinic, Yonago, Japan

<sup>3</sup> Clinical Examination Department, Faculty of Health Sciences, Kagawa Prefectural University of Health Sciences, Takamatsu, Japan

<sup>4</sup> Department of Pediatrics and Neonatology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

Corresponding author: Hiroyuki Yamada

Division of Child Neurology, Department of Brain and Neurosciences, Faculty of Medicine, Tottori University, Yonago, Japan

36-1 Nishi-cho, Yonago, 683-8504, Japan

Fax: +81-859-38-6779

E-mail address: [jms433b@hotmail.com](mailto:jms433b@hotmail.com)

**Keywords**

Pitt–Hopkins Syndrome, epileptic apnoea, breathing abnormality, EEG,

polysomnography

## **Abstract**

Pitt–Hopkins syndrome is a rare genetic disease characterised by severe intellectual disability, distinctive dysmorphic features, epilepsy and distinctive breathing abnormalities during wakefulness. Here we describe the case of a 22-year-old woman with Pitt–Hopkins syndrome who presented with intractable generalised tonic seizures from the age of 11 years, which increased in frequency with age and the onset of menstruation despite the use of some anticonvulsant drugs. From the age of 16 years, polysomnography and video-EEG detected frequent epileptic apnoea during sleep. Although the frequency of generalised tonic seizure clusters was reduced using phenobarbital and potassium bromide, epileptic apnoea persisted. Furthermore, the frequent epileptic apnoea observed in our patient was regarded as a factor involved in the aspiration and deterioration of respiratory function. This study shows that patients with Pitt–Hopkins syndrome require close monitoring of epileptic apnoea. Moreover, long-term EEG and respiratory monitoring are necessary to distinguish epileptic apnoea from other respiratory disorders in these patients.

## 1. Introduction

Patients with Pitt–Hopkins syndrome (PTHS) present with characteristic non-epileptic breathing abnormalities during wakefulness. The most common breathing abnormality is paroxysm of hyperventilation, followed by cyanotic breath-holding spells while awake. Apnoea and hyperventilation may occur independently from each other. In previous studies, nearly half of the patients with PTHS presented with these respiratory disturbances (Peippo *et al.*, 2006; Whalen *et al.*, 2012). However, there have been few reports regarding breathing abnormalities during sleep (Giurgea *et al.*, 2008; de Winter *et al.*, 2016; Motojima *et al.*, 2018). Moreover, almost half of the patients with PTHS develop epilepsy, although this can be appropriately controlled using antiepileptic drugs (Zollino *et al.*, 2019). Here we describe a case of PTHS with frequent epileptic apnoea during sleep and intractable generalised tonic seizures. Our experience indicates that EEG monitoring and polysomnography (PSG) are useful for detecting and managing epileptic apnoea during sleep and intractable seizures in patients with PTHS.

## 2. Case study

A 22-year-old Japanese woman presented to our hospital for the assessment of epilepsy potentially related to PTHS. She had been born after a full-term pregnancy and had no history of problems during the perinatal or neonatal period. She exhibited developmental delay and muscular hypotonia throughout her infancy and childhood. She developed slowly and required guidance while learning to walk. She was able to speak a few words by the age of 6 years. At the age of 11 years, she began to experience frequent generalised tonic seizures. The frequency of seizures increased with age and was aggravated at the onset of menstruation. Motor and mental abilities deteriorated with increasing frequency of seizures. At approximately 16 years of age, she exhibited frequent apnoea during sleep, as detected by PSG, when deterioration of generalised tonic seizure clusters was observed for more than half of a 1-month period (*Figure 1*). She was referred to our hospital at the age of 18 years for seizure control and examination of underlying disease. Cerebral MRI revealed mild atrophy of the bilateral anterior, parietal and left temporal lobes, indicating decreased white matter volume. At approximately 20 years of age, she required frequent hospitalisation owing to the occurrence of seizure clusters and onset of aspiration pneumonia. Interictal EEG at 20 years of age revealed periodic diffuse slow spikes and waves of 1–2 Hz, which lasted

for a few seconds (*Figure 2A*). These characteristic abnormal waves were observed in both awake and sleep states. Furthermore, ictal EEG revealed diffuse 13–15-Hz fast waves predominantly in the bilateral central–parietal–occipital region, followed by rhythmic  $\alpha$ - and  $\beta$ -waves, corresponding to the arrest of thoracic movement (*Figure 2B*). Another ictal EEG of apnoea revealed the sudden onset of diffuse rhythmic 12–14 Hz  $\alpha$ - and  $\beta$ -waves, lasting for 5–40 s, accompanied by the arrest of thoracic movement (*Figure 2C*). The patient exhibited breath-holding followed by deep expiration while awake, although this was not accompanied by epileptic discharges, as observed on EEG. After experiencing involuntary arm movement for a few seconds, the patient also presented with generalised tonic seizures with neck flexion. Ictal EEG revealed generalised  $\alpha$ - and  $\beta$ -waves with a gradual increase in amplitude, preceded by generalised spike and shift to slow spike and wave activities (*Supplementary Figure 1*). The frequency of generalised tonic seizure clusters decreased following phenobarbital (PB) and potassium bromide (KBr) administration. However, epileptic apnoea during sleep followed by video-EEG monitoring was resistant to any antiepileptic drugs. When the patient was 21 years old, PTHS was suspected owing to her dysmorphic features, upslanting palpebral fissures, deep-set eyes, wide mouth with thick lips, long and slender fingers and toes, microcephaly, severe mental retardation, lack of speech,

breath-holding, followed by deep expiration while awake and sudden-onset smile. The patient became wheelchair-bound and could not sit without support; at 21 years of age. Gastrostomy tube feeding was initiated owing to dysphagia and repeated aspiration pneumonia. Although generalised tonic seizure clusters were controlled relatively well, regular EEG monitoring demonstrated that epileptic apnoea persisted.

After obtaining written informed consent from all participants, genomic DNA extracted from peripheral blood samples from the proband was analysed using multiplex targeted sequencing. The amplicon libraries of the target exons from seven genes with phenotypes overlapping with Angelman syndrome (*UBE3A*, *SLC9A6*, *TCF4*, *MBD5*, *CDKL5*, *MECP2* and *FOXG1*) were prepared using the Ion AmpliSeq Custom Panel (Thermo Fisher Scientific, Waltham, MA, USA). Data processing was performed as described previously (Negishi *et al.* 2017). In the *TCF4* gene (NM\_001083962.1), we identified a heterozygous single nucleotide substitution (c.1732C>T; p.Arg578Cys), which was previously reported as the cause of PTHS (Marangi G *et al.* 2012). The presence of this variant was validated using Sanger sequencing. The institutional review board of the Graduate School of Medical Sciences of Nagoya City University approved the genetic analyses performed in this study.



### 3. Discussion

The disease course of this patient highlighted two important clinical issues.

First, overnight EEG monitoring and PSG revealed frequent epileptic apnoea during sleep. Second, the patient developed intractable generalised tonic seizures, which were well controlled with PB and KBr.

Few reports have described breathing abnormalities during sleep in patients with PTHS; however, only obstructive sleep apnoea, catathrenia and nocturnal irregular breathing have been documented (Giurgea *et al.*, 2008; de Winter *et al.*, 2016; Motojima *et al.*, 2018). Furthermore, to our knowledge, there are no descriptions of using overnight EEG monitoring or PSG to evaluate sleep disorders in patients with PTHS. Presumably, typical characteristic breathing abnormalities of PTHS during wakefulness (i.e. hyperventilation followed by breath-holding) do not accompany paroxysmal EEG abnormalities (Amiel *et al.*, 2007; Takano *et al.*, 2010; de Winter *et al.*, 2016). PTHS is caused by the haploinsufficiency of *TCF4*, which encodes for the basic helix-loop-helix (bHLH) transcription factor (Amiel *et al.*, 2007; Zweier *et al.*, 2007). *TCF4* forms a heterodimer with Achaete-scute homolog 1 (ASCL1), which is another bHLH transcription factor and activates the ASCL1-PHOX-RET pathway, which is responsible noradrenergic neuron development in the brainstem (de Pontual *et*

*al.*, 2003, Zweier *et al.*, 2007). Therefore, TCF4 gene mutations cause impaired neuronal development in the brainstem and breathing abnormalities while awake. Moreover, these breathing abnormalities during wakefulness are likely to be a congenital brainstem dysfunction, not an epileptic characteristic. Breath-holding followed by deep expiration while awake, as observed in this patient, is presumed to be a characteristic breathing abnormality in patients with PTHS. Meanwhile, regarding nocturnal breathing abnormalities, Maini *et al.* reported a single case with PTHS presenting with a physiologically normal sleep structure confirmed via PSG (Maini *et al.*, 2012). Whalen *et al.* described nocturnal apnoea without preceding hyperventilation, which was observed in three patients with PTHS, as a characteristic breathing abnormality. In those patients, the possibility of epileptic apnoea cannot be denied because EEG and PSG were not performed (Whalen *et al.*, 2012). Whether apnoea is accompanied by deep expiration or hyperventilation might be important for distinguishing epileptic and non-epileptic breathing abnormalities. Notably, breathing abnormalities, particularly apnoea without accompanying hyperventilation, during sleep might be an epileptic condition and have different mechanisms from characteristic breathing abnormalities during wakefulness. Furthermore, epileptic apnoea observed in the present patient must be differentiated from the arrest of thoracic movement

secondarily caused by generalised tonic seizures because ictal EEG corresponding to the arrest of thoracic movement in *Figure 2C* and that of the onset of generalised tonic seizure in *Supplementary Figure 1* were similar. Although no clinical seizure was observed upon video monitoring, it was unclear whether apnoea was associated with generalised tonic seizures due to the absence of simultaneous recording of electromyography with ictal EEG. In summary, in patients with nocturnal breathing disturbance, epileptic apnoea should be more closely examined, and overnight EEG monitoring with electromyography and recording of thoracic movement should be performed to detect and manage epileptic seizures, in addition to PSG, as recommended in the most recent international consensus statement for PTHS (Zollino *et al.*, 2019).

Our patient developed intractable generalised tonic seizures at 11 years of age. Generalised tonic seizure clusters were aggravated with the onset of menstruation; these seizures were refractory to various antiepileptic drugs during early treatment. The patient was frequently admitted to the hospital due to recurring aspiration pneumonia associated with generalised tonic seizure clusters. We assumed that this patient had recurrent aspiration pneumonia related to dysphagia caused by brainstem dysfunction associated with PTHS, resulting in deteriorating respiratory function. However, few reports have described the detailed clinical courses of epilepsy in patients with PTHS.

According to previous reports, epilepsy in patients with PTHS can be controlled relatively well with one or two standard antiepileptic drugs (Whalen *et al.*, 2012; Marangi and Zollino, 2015; de Winter *et al.*, 2016), although few patients may develop intractable epilepsy, such as infantile spasms and Lennox–Gastaut Syndrome (Peippo *et al.*, 2006; de Pontual *et al.*, 2009). However, the most effective AED is unclear owing to limited reports (de Winter *et al.*, 2016). Because PB and KBr were effective in reducing the frequency of generalised tonic seizure clusters in our patient, they might be useful for suppressing seizure clusters in patients with PTHS.

In conclusion, patients with PTHS can present with frequent epileptic apnoea during sleep and intractable generalised tonic seizures. EEG monitoring and PSG should therefore be performed for patients with PTHS. Further investigations of epilepsy, EEG and PSG findings and detailed examinations of sleep disturbances are warranted to determine whether epileptic apnoea and intractable seizures occur more frequently in patients with PTHS and to determine which AEDs are most effective in these patients.

## **Disclosure**

The authors declare no potential conflicts of interest with respect to the research, authorship and publication of this article.

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**List of abbreviations:**

KBr: potassium bromide

PTHS: Pitt–Hopkins syndrome

PSG: polysomnography

## Figure legends

**Fig 1.** Clinical course of epilepsy: The line graph shows the number of days per month that the patient experienced tonic seizure clusters. Abbreviations indicate antiepileptic drugs prescribed.

(\*) No specific records were collected during this period.

Abbreviations: VPA: valproic acid, ZNS: zonisamide, LTG: lamotrigine, CLB: clobazam, PHT: phenytoin, NZP: nitrazepam, TPM: topiramate, LEV: levetiracetam, PB: phenobarbital, CZP: clonazepam, RFN: rufinamide, KBr: potassium bromide

**Fig 2.** Interictal and ictal EEG findings:

**(A)** Interictal EEG findings during sleep at 20 years of age revealed diffuse periodic 1–2-Hz diffuse slow spikes and waves lasting for a few seconds.

**(B)** Ictal EEG findings during apnoea at 20 years of age. Diffuse 200–300- $\mu$ V high amplitude and diffuse 13–15-Hz fast waves (Black bar) followed by rhythmic  $\alpha$  and  $\beta$  activities corresponding to the arrest of thoracic movements were observed.

**(C)** Ictal EEG findings of consecutive epileptic apnoea. Diffuse rhythmic 12–14-Hz  $\alpha$ - and  $\beta$ -waves were preceded by arrest of thoracic movement lasting for 30 s. Arrowhead indicates the onset and cessation of apnoea. The EEG description for approximately 10 s in the middle of apnoea was omitted.

**Supplementary Figure 1:** Ictal EEG findings of generalised tonic seizures. These two figures are ictal EEG of the same consecutive generalised tonic seizure. Each figure indicates the (A) onset and (B) cessation of the seizure. A generalised spike, followed by  $\alpha$ - and  $\beta$ -waves with a gradual increase in amplitude, was observed at the onset of seizure; it shifted to slow spike and wave activities according to the cessation of seizure lasting for 25 s. The white arrowhead indicates the onset of involuntary arm movement, and the black arrowhead indicates (A) the onset and (B) cessation of the generalised tonic seizure with neck flexion.

**Questions (Test Yourself)**

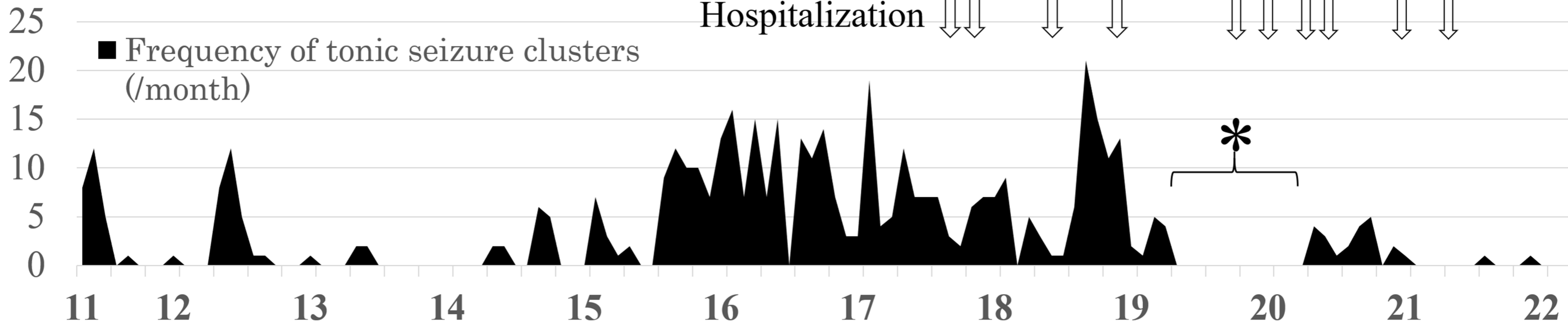
- 1) What types of sleep disturbances have been reported in patients with PTHS?
- 2) What percentage of patients with PTHS experience epilepsy and what is the optimal treatment for epilepsy?
- 3) What examinations were useful for distinguishing nocturnal breathing abnormalities in this patient?

**Answers**

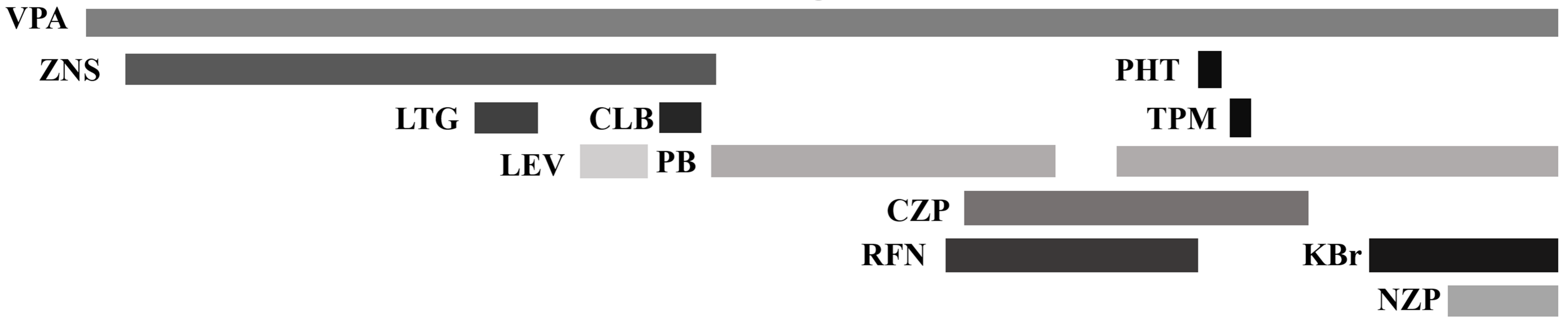
- 1) Obstructive sleep apnoea, catathrenia and nocturnal irregular breathing have been reported as breathing abnormalities during sleep, although these sleep disturbances have rarely been evaluated using PSG. The present report describes a patient with nocturnal epileptic apnoea detected via overnight EEG monitoring.
- 2) Almost half of the patients with PTHS experience epilepsy, although this can be controlled relatively well with antiepileptic drugs. Some patients may develop intractable epilepsy, such as infantile spasms and Lennox–Gastaut Syndrome. The most effective AED is unclear owing to limited number of reports.

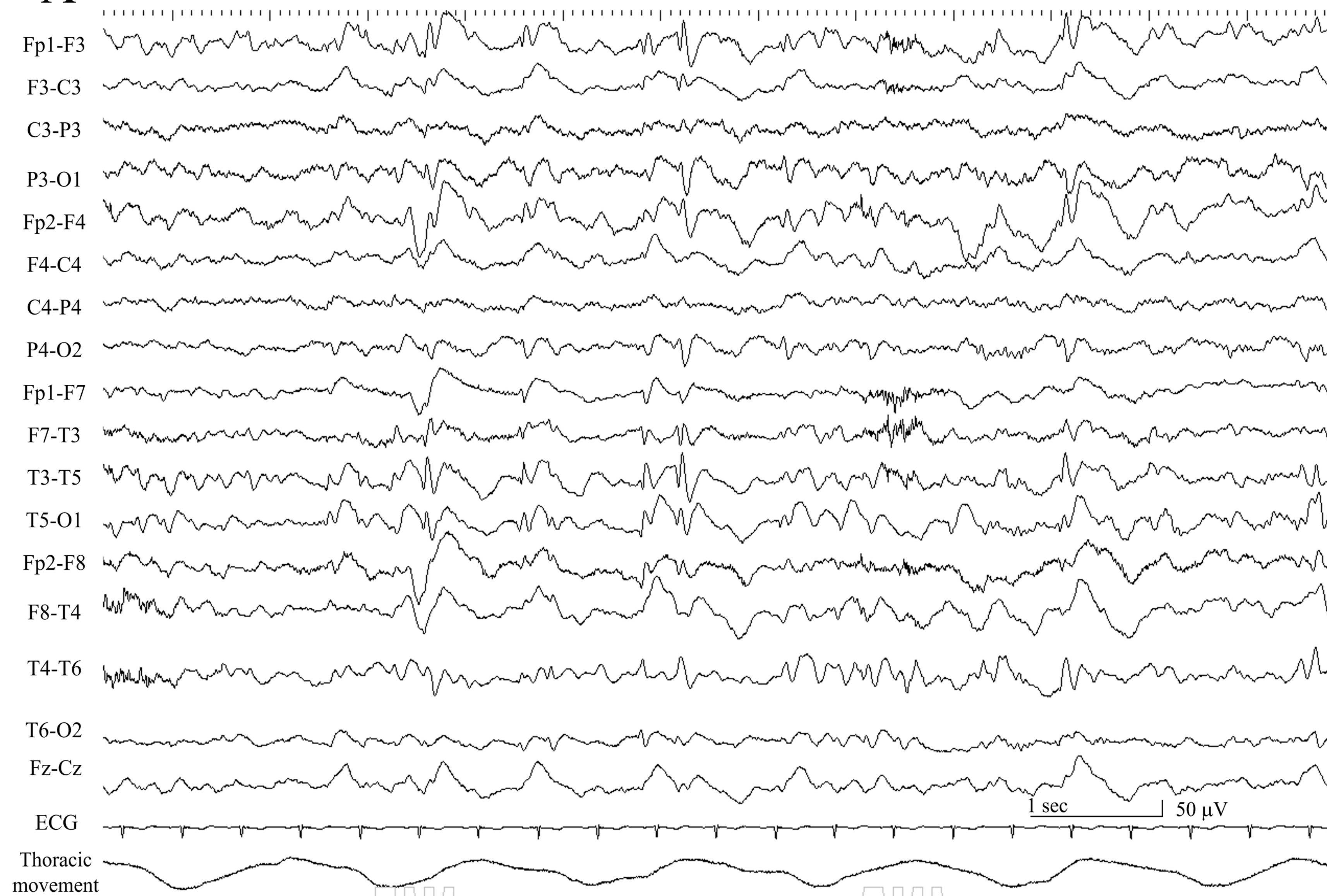
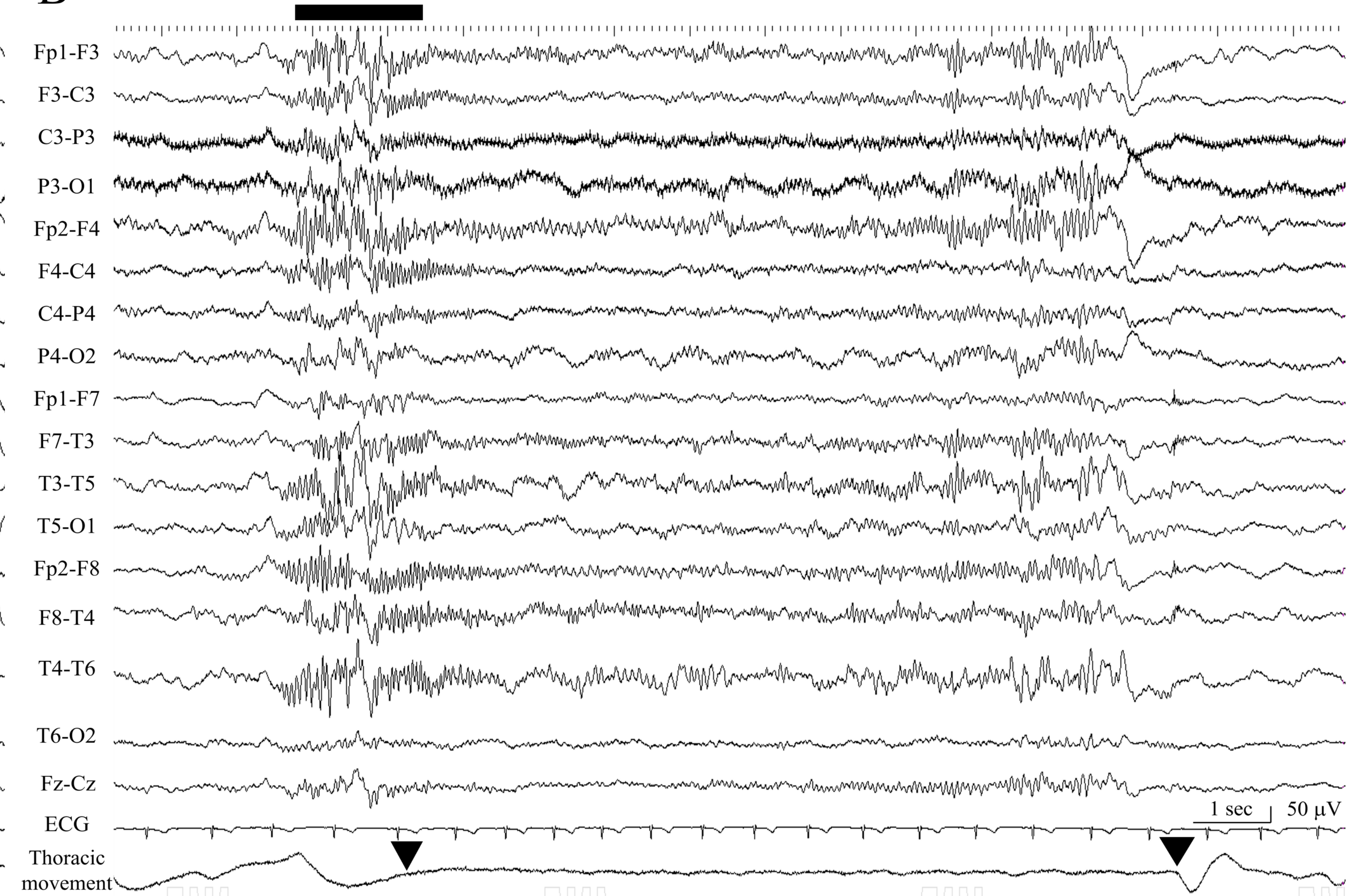
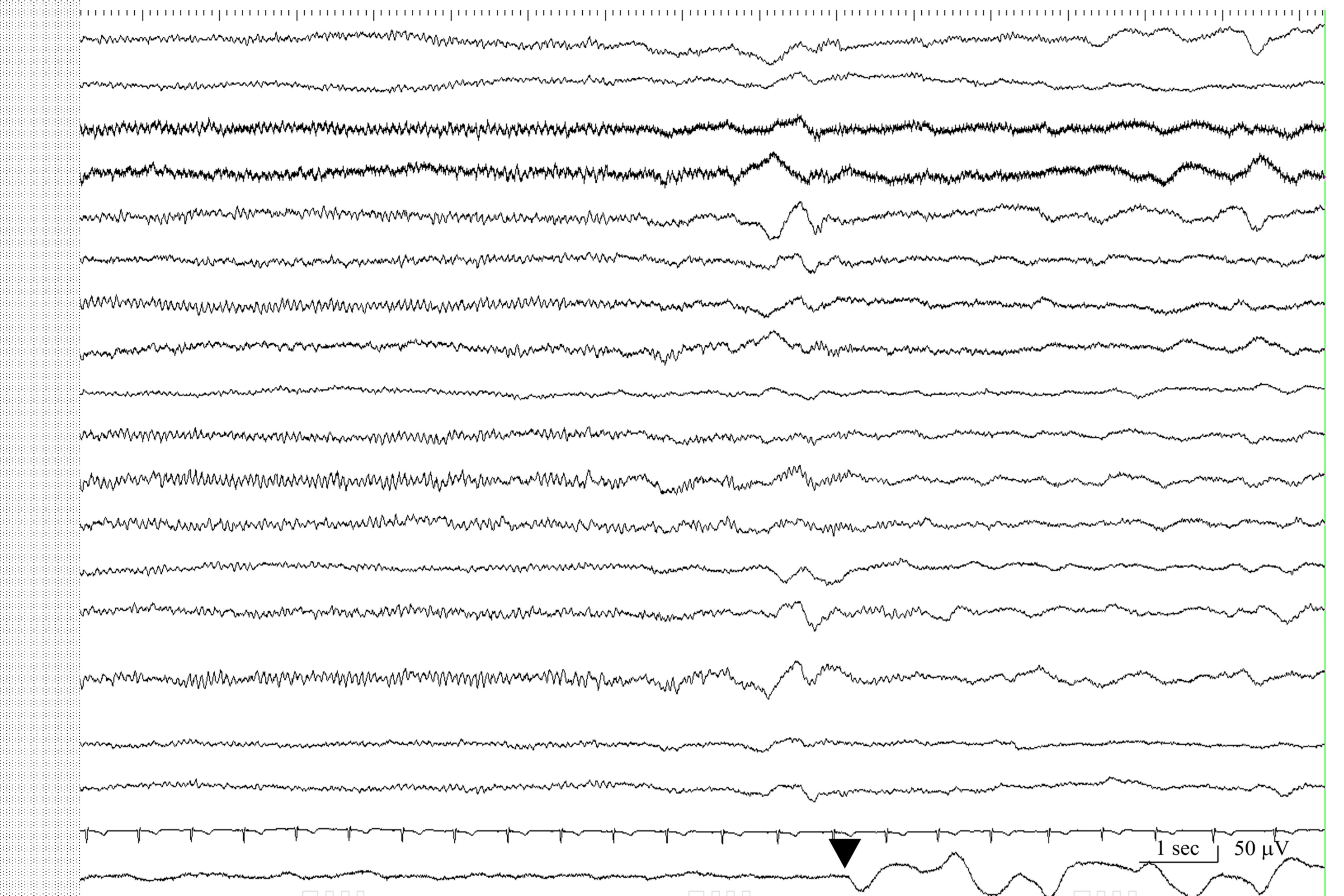
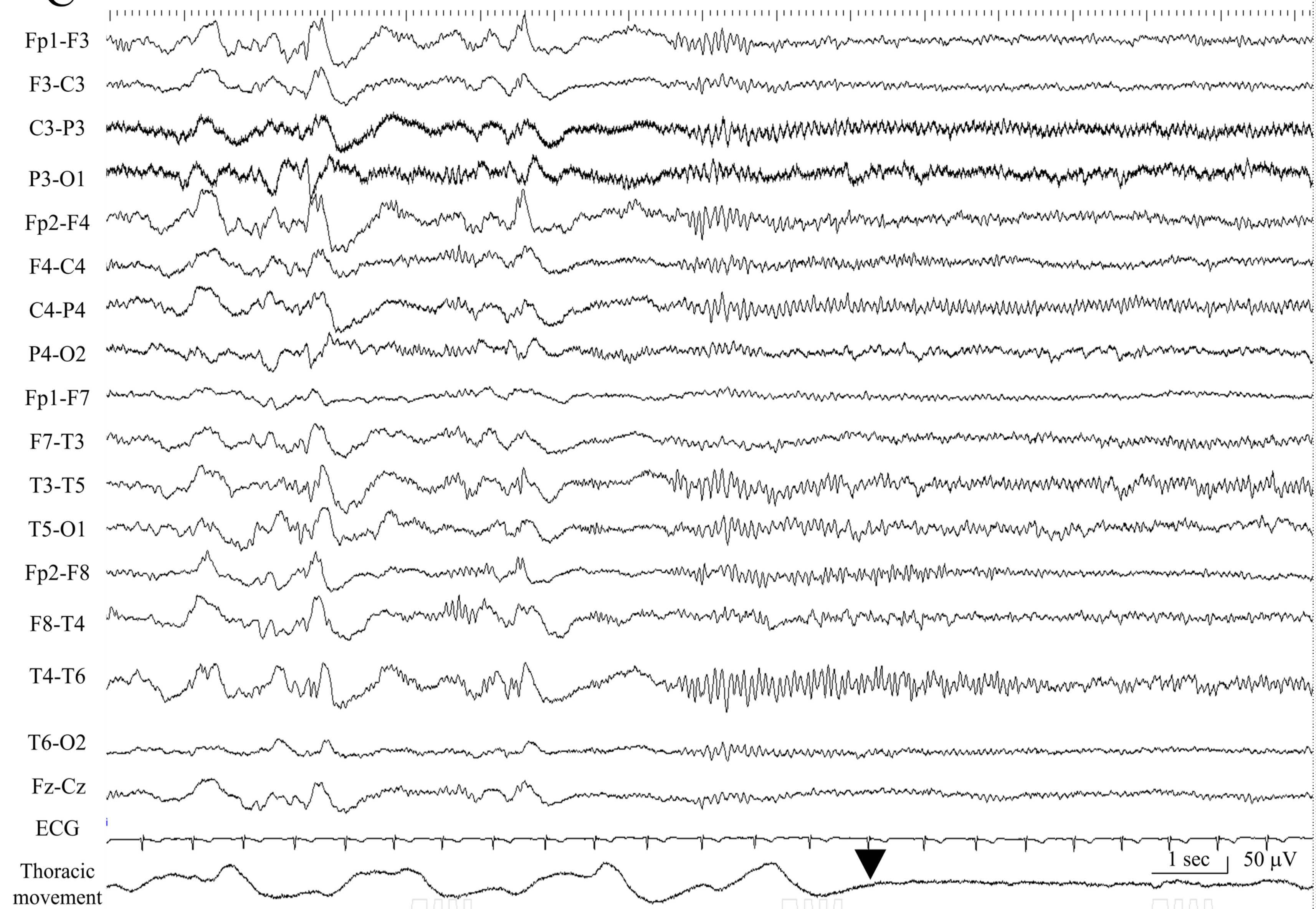
3) Overnight video-EEG monitoring was useful for detecting and managing epileptic apnoea, in combination with polysomnography, as recommended in the most recent international consensus statement for PTHS.

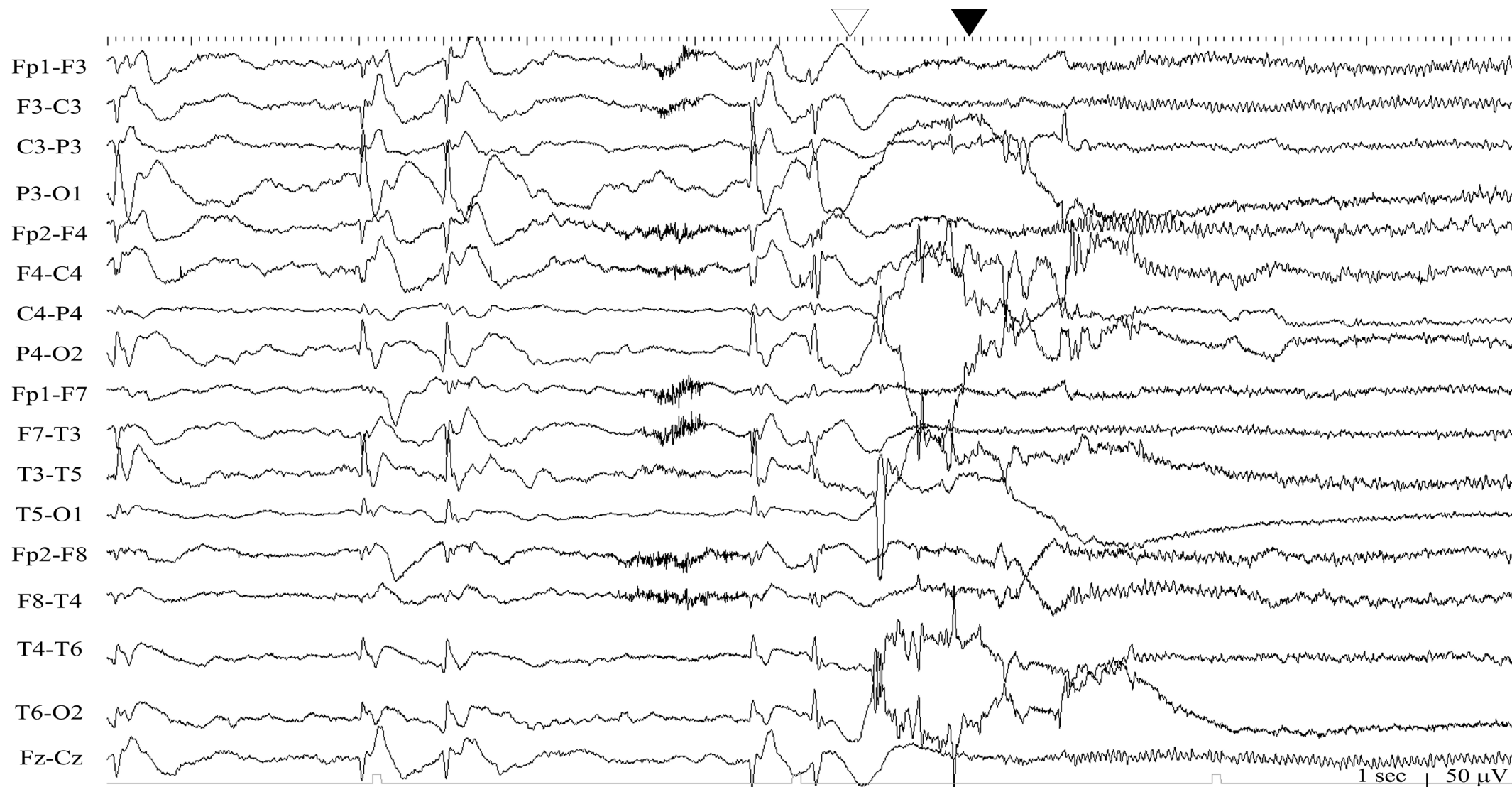
(days/month)



Age



**A****B****C**

**A****B**