

Supplementary Material S1

S1.1 Linear Mixed Effect Model

To explore the relationship between seizure durations and the associated hemodynamic response, we employed a linear mix-effect model regression model modeling event duration with fixed effect for response normalized area-under-the-curve (AUC, assessing response intensity) or response full-width-at-half-maximum (FWHM, assessing response duration) and uncorrelated random effect for intercept (grouped by patients) and residual, i.e.,

$$\mathbf{y} = \beta_0 + \beta_1 \times \mathbf{d} + \mathbf{z} \times \mathbf{u} + \epsilon$$

where $\mathbf{y}$ is the AUC or FWHM extracted from bin representative HRFs across all M patients; $\mathbf{d}$ is an N by 1 vector of the maximum event duration of the bins, $\mathbf{z}$ is an N by M random effect design matrix where

$$z_{n,m} = \begin{cases} 1, & \text{if } y_n \text{ is from patient } m \\ 0, & \text{otherwise} \end{cases}$$

$\mathbf{u}$ is the corresponding M by 1 random effect variable vector, and ϵ is the uncorrelated N by 1 model residual vector.

This structure allows the model to capture the fixed effect of seizure duration on the brain response, while accounting for patient-specific random effects due to the correlation of seizures within the same patient. Although the model is relatively simple, it effectively accounts for the intra-patient variability by modeling seizures recorded from the same patient as correlated observations, as shown in our previous study¹⁶.

S1.2 Time-To-Event Analysis

We employed a time-to-event analysis to model the time until the brain regions exhibit an unexpected second phase of hemodynamic response (a potential hypoxic state characterized by an HbO decrease and HbR increase) as a function of seizure duration. Specifically, we estimated the survival functions of the HbO and HbR responses using the nonparametric Kaplan-Meier estimator. This estimator provides an empirical survival function, $\hat{S}$, defined as:

$$\hat{S}(t) = \prod_{t_i < t} \left(1 - \frac{d_i}{n_i}\right)$$

where d_i is the number of events (e.g., potential hypoxia) occurring at seizure bin duration t_i , and n_i is the number of subjects at risk just prior to seizure bin duration t_i . The Kaplan-Meier estimator is commonly used in survival analysis as it does not assume any underlying parametric distribution and can handle censored data effectively (e.g. in patients with only uniphasic seizure response, i.e. no HbO decrease observed in all seizure bins)⁵¹.

The estimated survival curves were further fitted with the parametric Weibull distribution, which is frequently used in survival analyses due to its flexibility in modeling hazard rates. The Weibull survival function S is given by:

$$S(t) = e^{-\left(\frac{t}{\lambda}\right)^k}$$

where $\lambda > 0$ is the scale parameter and $k > 0$ is the shape parameter, controlling the rate of failure (e.g., seizure duration to hypoxia) over time. This approach allows us to estimate how the likelihood of entering a potentially hypoxic state over time as a function of seizure duration.

Supplementary Material S2

S2.1 Case study 1 – Patient P01

A 63-year-old male patient with a long-term history of hypertension and severe cirrhosis was admitted to our institution for a scheduled surgery (i.e., liver transplant). Following the transplant, the patient developed a graft-versus-host syndrome associated with refractory seizures. He was diagnosed with new-onset refractory ECSE evolving into ESE with a STESS of 3. In the ICU, the patient remained on three antiseizure medications, two anesthetics, and mechanical ventilation (**Supplementary Figure 2A**). Despite all clinical efforts, his overall medical condition deteriorated and he died 52 days later.

A total of 21 vEEG-fNIRS sessions were performed for over weeks (total duration ~144h). During the first session (duration ~4h), we were able to record 181 seizures with an average duration of 85.2s [34.1s – 136.3s] and an average interictal interval of 60.4s [17.1s – 103.7s]. Seizures were mainly characterized by diffuse rhythmic activity with a slight left-hemispheric predominance. Additional EEG patterns observed during the vEEG-fNIRS monitoring were periodic discharges with an average frequency of ~1.5Hz.

In the fNIRS data analysis, 104 seizures were grouped into six different bins with durations ranging from [0-10s] to [50s-60s] (**Figure 1**). However, the majority of recorded seizures were short, lasting between 10s and 30s (99 seizures, 95%). We observed a uniphasic HbO increase and an HbR decrease associated with the seizures in all the six bins. Such HbO and HbR concentration changes were consistent from the onset of the seizure until a few seconds after the seizure offset before gradually returning to baseline. Specifically, the comparison of HRFs between bins showed an increment in the FWHM of both HbO and HbR response with the increasing seizure durations ([0-10s]: 11.4s/15.2s for HbO/HbR; [10s-20s]: 18.0s/17.0s; [20s-30s]: 20.6s/21.4s; [30s-40s]: 31.4s/32.5s; [40s-50s]: 41.6s/33.2s; [50s-60s]: 57.1s/57.8s), as well as increased normalized AUC for HbO and decreased normalized AUC for HbR ([0-10s]: 0.0075 μ M/-0.0033 μ M for HbO/HbR; [10s-20s]: 0.010 μ M/-0.0055 μ M; [20s-30s]: 0.0111 μ M/-

0.0060 μ M; [30s-40s]: 0.0178 μ M/-0.0092 μ M; [40s-50s]: 0.0118 μ M/-0.0061 μ M; [50s-60s]: 0.0207 μ M/-0.0126 μ M). Similarly, as seizure duration increased, we observed an increment in the FWHM and the AUC (positive increase) for HbT and HbD (**Table 2, Supplementary Table 2**).

S2.2 Case study 2 – Patient P03

A 33-year-old man without any significant past medical history was admitted to the ICU for recurrent seizures in the context of fever, which started from a recent upper respiratory tract infection and later evolved into SRSE. On admission, GCS and STESS were both measured at 3. He later had aspiration pneumonia, which was treated with antibiotics. He was kept on mechanical ventilation, a minimum of four antiseizures medications, three anesthetics, and one vasopressor throughout his entire ICU stay (**Supplementary Figure 2B**). Despite extensive investigations, a specific cause for the seizures could not be found. The patient's global condition did not improve, and in spite of all treatments, he eventually passed away 28 days later.

Four sessions of vEEG-fNIRS were performed over ten days in the ICU (total duration ~36 h). During the first two sessions, which lasted ~ 17h, 30 seizures were recorded. Four seizures were excluded in the preprocessing step. The 26 remaining seizures had an average duration of 841.6s [57.2s – 4283.3s] and an average interictal interval of 813.7s [101.3s – 5555.0s]. Seizure distribution was mainly widespread, with an abrupt onset and offset. No pattern falling in the ictal-inter-ictal continuum was identified during the same period.

The 26 "full" seizures recorded during the session were divided into 10 categories ("bins") based on their duration, from [50s-60s] to [4000s-5000s] (**Figure 2**). The hemodynamic responses were twofold. For relatively short-duration seizures from 50s to 130s, we observed a uniphasic HbO increase along with an HbR decrease during the entire duration of the seizures. Specifically, the FWHM and the normalized

AUC seemed to increase with the increasing duration of seizures within this range (FWHM of [50s-60s]: 55.6s/52.0s for HbO/HbR; [60s-70s]: 63.6s/52.5s; [70s-80s]: 51.8s/50.5s; [90s-100s]: 87.8s/73.4s; [120s-130s]: 120.4s/127s. Normalized AUC of [50s-60s]: 0.0266 μ M/-0.0107 μ M; [60s-70s]: 0.0205 μ M/-0.0083 μ M; [70s-80s]: 0.0108 μ M/-0.0045 μ M; [90s-100s]: 0.0240 μ M/-0.0104 μ M; [120s-130s]: 0.0251 μ M/-0.0099 μ M).

On the other hand, HRFs to more prolonged seizures from 240s to 5000s of this patient showed a more complicated biphasic shape. While the first phase of HbO increase and HbR decrease could still be seen after seizure onset, these changes were followed by a second phase of response, most notably shown as a long reduction in HbO concentration and a long augmentation of HbR concentration, which persisted until the end of the seizures. Interestingly, the responses to long seizures showed an opposite trend to responses to short seizures, whose FWHM or normalized AUC seemed to decrease with the increase in seizure durations (FWHM of HbO increase/HbR decrease for [240s-250s]: 95.2s/117.9s; [1000s-2000s]: 45.1s/42.4s; [2000s-3000s]: 33.1s/93.3s; [3000s-4000s]: 59.2s/27.2s; [4000s-5000s]: 0s/85.8s. Normalized AUC of HbO/HbR response for [240s-250s]: 0.0133 μ M/-0.0060 μ M; [1000s-2000s]: -0.0218 μ M/0.0086 μ M; [2000s-3000s]: -0.0105 μ M/0.0070 μ M; [3000s-4000s]: -0.0110 μ M/0.0139 μ M; [4000s-5000s]: -0.0419 μ M/0.0123 μ M). Similarly, we observed an increment in the FWHM, and the AUC (positive increase) for HbT and HbD as seizure duration increased until 240s; after that, a decrease in both HbT and HbD was observed (**Table 2, Supplementary Table 2**).

Supplementary Material S3

S3.1 Monte-Carlo Simulation to Generate Cortical Projections of Seizure Responses

We utilized the open-source Matlab toolbox AtlasViewer³⁵ and employed a forward model along with Monte-Carlo simulations to generate a cortical fNIRS sensitivity matrix. This sensitivity matrix was used to project the mean value of the representative HRF onto the cortex, providing an estimate of the response spatial profiles. The following steps were applied in the cortical projection process: First, each of the light emitters and detectors was co-registered onto a Colin27 brain atlas using the measured 3D coordinates. Next, the propagation of ten million (10,000,000) photons inside the head from each fNIRS optode (emitters and detectors) was simulated, applying absorption and reduced scattering coefficients for each head layer (scalp, CSF, gray matter, and white matter) based on values from the literature⁵². The resulting sensitivity matrix was then used to solve the regularized inverse problem and generate voxel-wise concentration changes. Finally, caution is advised when interpreting the spatial patterns of the hemodynamic responses, as the fNIRS channel layout may be unbalanced, and detection sensitivity may be limited in certain brain regions.

S3.2 Representative HRFs to Seizures and Corresponding Spatial Profiles in Each Patient

In this section, we present the representative HRFs to seizures of each bin for all the seven patients.

Patient 01: Patient P01 exhibited mostly generalized seizures during the EEG-fNIRS recording. EEG data showed that the seizure activity was the most significant in the bilateral frontotemporal regions. This is concordant with fNIRS measurement, which showed the almost global HbO increase and HbR decrease following the generalized seizures but the highest changes in the bilateral frontal and fronto-temporo-central areas. As the seizures were mostly short in duration (< 60s), we observed uniphasic changes (HbO $\uparrow$, HbR $\downarrow$).

Patient 02: Patient P02 presented focal and generalized seizures that were more prominent in the right hemisphere than the left hemisphere on EEG. For 18 seizures analyzed (all < 80s), fNIRS revealed HbO

increases that were the most significant in the right frontal and central regions. Contralateral HbO increases were observed with lower amplitudes and less spatial extent. The HbR changes, on the other hand, were seen to be more heterogeneous.

Patient 03: For Patient P03, EEG recording indicated generalized seizures and also focal activities in the bilateral central regions. For short duration seizures (e.g. 50s to 60s), overall increases in HbO concentration as well as decreases in HbR concentrations were observed in the bilateral frontal and central areas (HbO $\uparrow$, HbR $\downarrow$). As seizure duration increased (e.g. in seizure bin of 2000-3000s), we noted HbO decreases and HbR increases first in the bilateral central regions (HbO $\downarrow$, HbR $\uparrow$), while the average HbO concentration in the frontal cortex remained elevated during the seizure. Further increases in seizure duration (e.g. in seizure bin of 4000-5000s) resulted in HbO decreases and HbR increases in both the central and frontal areas, suggesting potentially disrupted neurovascular coupling over a large portion of the brain.

Patient P04: Patient P04 showed mainly focal frontal seizures, more in the right hemisphere than the left hemisphere. From the fNIRS-measured hemodynamic response, we observed right frontal HbO increases as well as contralateral projections associated with short-duration seizures (e.g. seizures < 70 s). For the longer-duration seizure, HbO decreases and HbR increases were seen in the bilateral frontal and central regions.

Patient P05: Seizures in Patient P05 were generalized, but often seen to be stronger in the bilateral frontotemporal regions. fNIRS data showed mainly HbO increases and HbR decreases in the fronto-temporal areas of both hemispheres. However, for longer-duration seizures (> 20 s), significant HbO

decreases and HbR increases were seen in the surrounding regions, resulting in overall shapes of HbO decrease and HbR increase in the representative HRFs.

Patient P06: In patient P06, we observed generalized seizures most often stronger in the bilateral frontal and central regions on EEG. Shorter-duration seizures from 10s to 30s mostly presented HbO increases in a large frontal and temporal area. However, as the duration of the seizure increased, the bilateral frontal region and left centro-temporal regions showed significant reductions in HbO concentration, leading to overall HbO decreases.

Patient P07: Seven generalized seizures from Patient P07 were analyzed. Seizure electrical activities were seen to be stronger in the bilateral frontotemporal regions. Using fNIRS, we located significant HbO increases in the fronto-temporal areas, particularly in the right hemisphere. For the longer seizure bin from 20s to 30s, HbO decreases were noted in the medial prefrontal cortex and the pre-central regions. HbR increases were seen in bilateral frontal and temporal areas for both seizure bins,