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ORIGINAL ARTICLE

Neural correlates of rhythmic rocking in prefrontal seizures

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Abstract

Objectives. – Rhythmic body rocking movements may occur in prefrontal epileptic seizures. Here, we compare quantified time-evolving frequency of stereotyped rocking with signal analysis of intracerebral electroencephalographic data.

Methods. – In a single patient, prefrontal seizures with rhythmic anteroposterior body rocking recorded on stereoelectroencephalography (SEEG) were analyzed using fast Fourier transform, time-frequency decomposition and phase amplitude coupling, with regards to quantified video data. Comparison was made with seizures without rocking in the same patient, as well as resting state data.

Results. – Rocking movements in the delta (~ 1 Hz) range began a few seconds after SEEG onset of low voltage fast discharge. During rocking movements: (1) presence of a peak of delta band activity was visible in bipolar montage, with maximal power in epileptogenic zone and corresponding to mean rocking frequency; (2) correlation, using phase amplitude coupling, was shown between the phase of this delta activity and high-gamma power in the epileptogenic zone and the anterior cingulate region.

Conclusions. – Here, delta range rhythmic body rocking was associated with cortical delta oscillatory activity and phase-coupled high-gamma energy. These results suggest a neural signature during expression of motor semiology incorporating both temporal features associated with rhythmic movements and spatial features of seizure discharge.

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Introduction

Complex rhythmic movements seen in some epileptic seizures involve automatic motor behaviors such as chewing or pedaling movements [26]. Such behaviors may be associated not only with epileptic seizures but also with sleep disorders [15] or other neurological conditions [10], and have been conceptualized as being associated with central pattern generators [26] likely involving subcortical circuitry [3,18]. When occurring in the context of a seizure, these more complex patterns are generally not concomitant with a focal seizure discharge confined to a single brain region but rather emerge when several connected structures within associative cortex are involved by early propagation of seizure discharge [2,5,8,18]. Not only anatomical constraints but also the temporal characteristics of the seizure discharge (e.g. rhythmicity, frequency, time-lag, coherence between structures) influence clinical expression [5,8,18].

Body rocking occurs fairly rarely in prefrontal seizures [6,14,24] and is observed in various other physiological and pathological contexts including autistic spectrum disorder (ASD) [16]. However, neural correlates of rhythmic body rocking in humans are unknown.

We previously reported video quantification of antero-posterior rhythmic rocking [12] as a stereotyped expression of frontal seizure semiology [6,12,19]. Here, we investigate neural correlates during the period of rocking, in a patient recorded on SEEG. We wished to evaluate whether rhythmic neural activity could be evidenced in relation to the rhythmic body movements, and to describe the temporo-spatial relation between seizure- and body rocking-based activities.

Methods

Clinical case

A 32-year-old right-handed woman presented pharmacoresistant frontal lobe epilepsy from the age of 18 years. Seizures consisted of abrupt onset of stereotyped hyperkinetic motor behavior characterized by rhythmic antero-posterior truncal rocking movements, during which the patient was unresponsive. Neuroimaging was normal. Following non-invasive presurgical investigations, SEEG was performed, during which habitual seizures with rocking were recorded. The patient also presented some seizures without body rocking, characterized by hyperkinetic behavior mainly of lower limbs while she remained lying on the bed (considered "control seizures" for the present study). All seizures had similar pattern on seizure onset on SEEG. As previously reported, automated video analysis allowed characterization of the rhythmic body movements [12] and showed mean rocking frequency that varied between 0.48 and 1.01 Hz across all seizures for this patient

(Patient 1, Seizures 2 and 4 in the previous study [12]).

SEEG exploration in 2005 consisted of 7 orthogonally implanted electrodes, with 6 exploring right premotor and prefrontal structures (see Fig. 1) and one contralateral electrode in left prefrontal cortex. Analysis of SEEG data, including quantification of seizure onset with the Epileptogenicity Index [4] showed initial organization of seizures (epileptogenic zone, EZ) predominantly involving right dor-

solateral prefrontal cortex (see Fig. 1); however, early involvement of contralateral dorsolateral prefrontal cortex was also noted, as well as rapid spread of tonic discharge to mesial regions including anterior cingulate and pre-supplementary motor area (pre-SMA). To complement visual analysis, the Epileptogenicity Index [4] was applied to quantify seizure onset. This is a semi-automatic method of quantifying fast activity at seizure onset, incorporating measures of rapidity of discharge and earliness of appearance. This showed maximal values in lateral contacts of CR and FD (thus, predominantly right dorsolateral prefrontal cortex) (Fig. 1A). Semiology onset occurred around 2 s after discharge onset, at which time slower rhythmic activity was visible. Subsequent to SEEG exploration, cortectomy including right superior and middle frontal gyri was performed. Histopathology showed non-specific gliosis. The patient had satisfactory surgical outcome at 10 years (ILAE class 2).

SEEG signal analysis

A total of 4 seizures were analyzed from the beginning to the end of the semiology corresponding to clinical seizures (two with rocking, called "seizures 1 and 2"; two without rocking, called "control seizures (seizures 3 and 4)") as well as resting background activity without pathological neural or clinical activity (baseline period), within the same patient. Methodology consisted of several steps:

- (1) Preprocessing. Data analysis was performed with Brainstorm [25] and Matlab (The Mathworks). SEEG data associated with four seizures (two seizures associated with rhythmic body rocking, called seizure 1 and 2 here; also, two control seizures without rocking, called seizure 3 and 4), as determined by a clinician were selected. Four baseline epochs, of similar durations to the four seizures, but corresponding to a data segment from the interictal period while the patient was at rest, each obtained the same day as the corresponding seizure, were also selected. Channels that presented significant artefact during the seizures were discarded after visual inspection of the signal. We estimated the focal neural activity between two channels by applying a bipolar montage on the remaining neighboring channels. Of note, all the analyses were done on all the implanted electrodes to investigate the dynamic of the neural network suspected to be involved in the seizure.
- (2) Fast Fourier transform (FFT). A fast Fourier transform was applied to the coordinates of the head movements extracted from the quantified video [11] and to the neural data to estimate their respective power spectrum in the delta range (0.5–4 Hz).
- (3) Estimation of high-gamma power. A time-frequency decomposition of the neural signal was performed between 60 and 150 Hz in logarithmic scale, by applying a time-frequency wavelet transform, using a family of complex Morlet wavelets [central frequency of 1 Hz, time resolution (FWHM) of 3 s; hence, three cycles]. We then estimated high-gamma power in decimal logarithmic units (in dB), and applied a grand-average, across frequencies and time, to obtain a global estimate

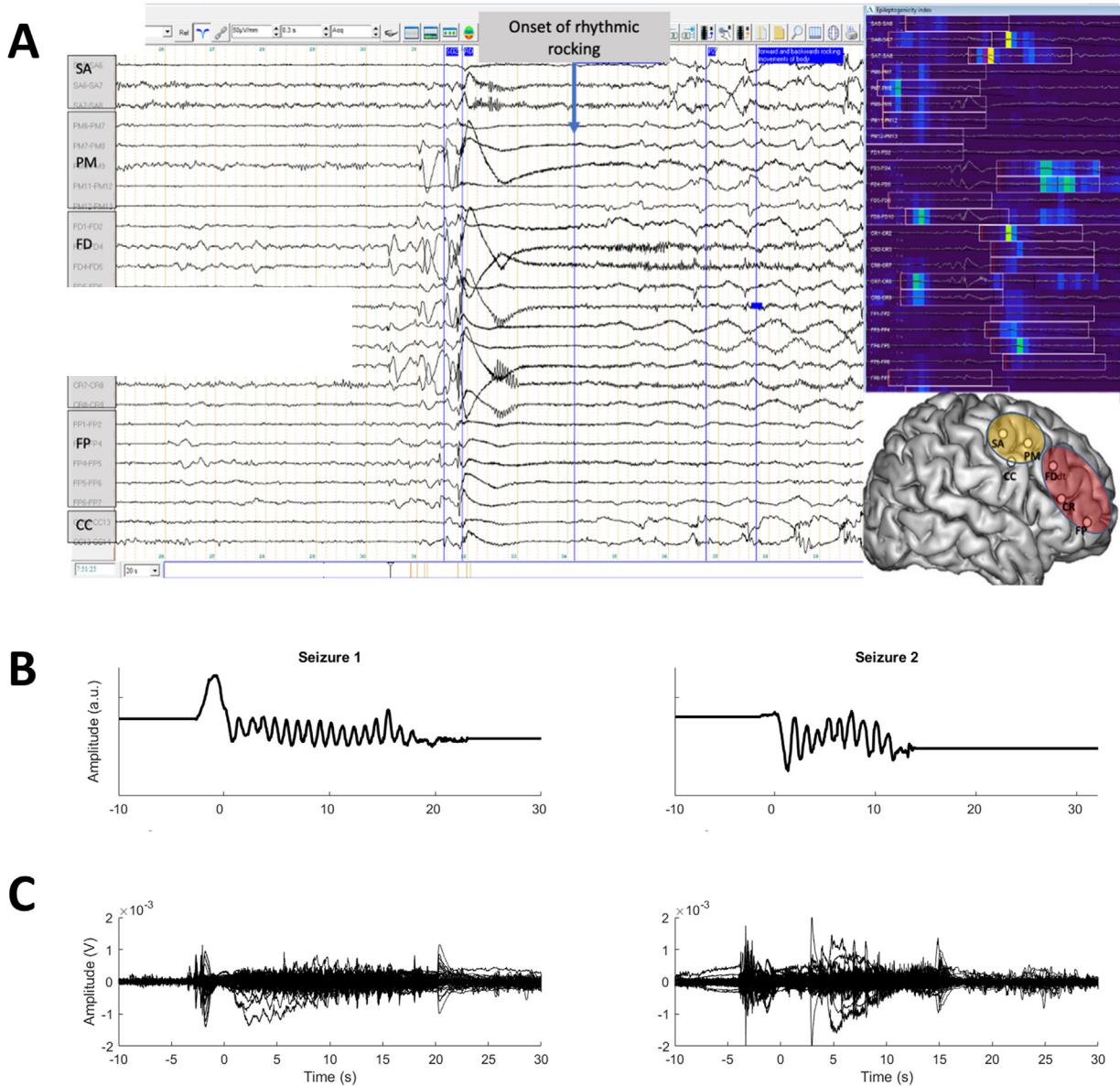


Fig. 1 A. SEEG trace of a typical seizure characterized by rocking. Semiological onset occurred 2 s after onset of low voltage fast activity (blue arrow). Lower right inset shows schematic representation of SEEG electrodes in the right hemisphere. Six orthogonal electrodes explored right frontal lobe, reaching medial structures. There is also one contralateral electrode FD', symmetric with FD (not shown in figure). The red oval represents the zone maximally involved by seizure onset (electrodes FP, CR, FD) and the yellow oval represents the zone of seizure propagation (electrodes SA, PM and CC). The top right inset shows a map of the Epileptogenicity Index [4] (see text for explanation) for this seizure, which shows maximal values at seizure onset in the external contacts of FD and CR. B, C : Selected clinical semiology and neural time courses of seizures 1 (left) and 2 (right). B. Amplitude of body rocking movement extracted from video. C. Amplitude of neural signal for bipolar montage data (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

of high-gamma activity for the seizure and baseline epochs.

- (4) Phase-amplitude coupling (Pac). In order to investigate the inter-dependence between delta and high-gamma oscillations, we estimated the phase-amplitude cross-frequency coupling between the phase of the neural signal corresponding to the body rocking movement (~1 Hz) and the high-gamma amplitude [1,22], following the method described in Özkurt and Schnitzler [22].

This estimates co-fluctuations between low and high frequency neural signals and quantifies the amount of high-gamma activity modulated in phase with the body rocking movement. The same procedure was applied to seizure and baseline epochs.

- (5) Combining the two rocking seizures. Finally, in order to obtain an overall estimate of the seizure-related activity, we first contrasted neural indexes (either, FFT, high-gamma power, or Pac) during seizure and baseline

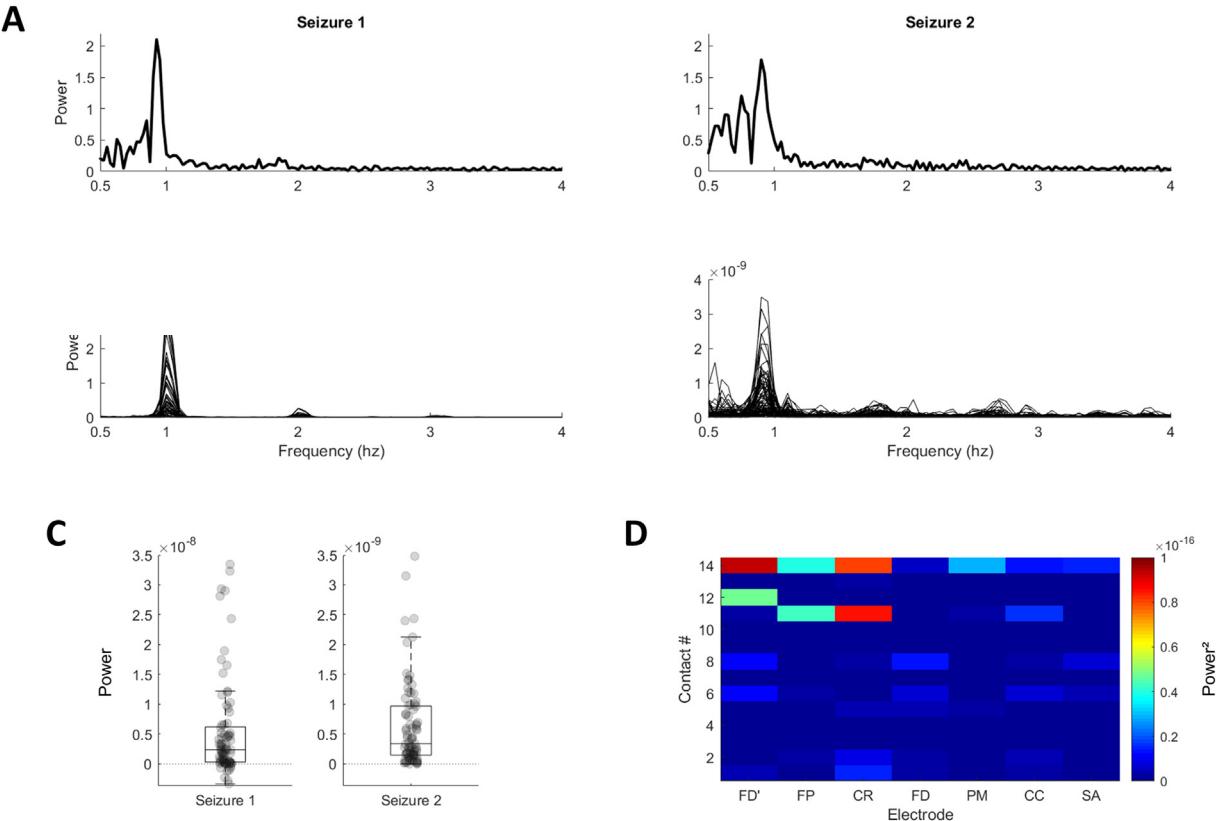


Fig. 2 Power spectra (in volts for neural signal; arbitrary units for body rocking movement) of (A) body rocking movements and (B) of neural activity from bipolar montage data for each contact, for seizures 1 (left) and 2 (right). C. Delta (~ 1 Hz) power during seizures relative to baseline, extracted from the bipolar montage data; paired t tests against zero (Bonferroni corrected with a factor 4): $t(80) = 5.83$ and $t(80) = 7.96$ for seizures 1 and 2 respectively; all $p < 0.01$. D. Spatial distribution of delta power combined across the two seizures (in volt 2). Contacts are plotted for each electrode following a medio-lateral gradient (from medial to lateral: 1-14). Each line or point corresponds to one contact.

periods. We then combined the two seizures of similar nature (i.e. associated with rhythmic body rocking or not) by multiplying their respective indexes, per channel (i.e., per contact). This allowed us to highlight the channels for which neural activity was high relative to baseline during Seizures 1 and 2. We also applied the same method to the two control (non-rocking) Seizures 3 and 4.

- (6) Statistical procedure. Paired t tests, Bonferroni corrected with a factor 4, were performed at the level of individual electrode contacts (bipolar montage) between seizure and baseline epochs.

Results

Body rocking movement and the neural signal for the two seizures present a strong similarity (Fig. 1 B,C) supported by the computation of power spectrum which revealed the modal frequency of the body rocking movement (Fig. 2 A) and neural activity in the delta range (Fig. 2 B) -1 Hz for seizure 1 and 0.9 Hz for seizure 2. Using bipolar montage, we extracted the neural power at the peak frequency and contrasted it from baseline periods (Fig. 2C). Across the

two seizures (Fig. 2D), external contacts of FP, CR and FD' electrodes (exploring right and left dorsolateral prefrontal cortex) emerged. The first two captured neural activity situated in the EZ, while FD' is situated in the early propagation zone.

We next investigated the relationship between body rhythmic movements and high-gamma neural activity (60–150 Hz), which best approximates multi-unit activity [23]. We computed the phase-amplitude coupling (PAC) between the phase of the delta (~ 1 Hz) activity and the amplitude of the high-gamma activity on the bipolar montage data contrasted to baseline periods (Fig. 3A). We show an overall increase of delta-gamma coupling during seizures (paired t tests against zero: $t(80) = 7.99$ and $t(80) = 15.9$ for seizures 1 and 2 respectively; all $p < 0.01$). Combining the coupling strength of the two seizures (relative to baseline; see Methods; Fig. 3B) we observed a maximal coupling in the dorsolateral prefrontal cortex corresponding to EZ (where a large delta activity was observed) and in the motor cingulate region (BA24; CC electrode).

Finally, we computed the overall high-gamma power relative to baseline to investigate whether the previous result was specific to a high-gamma activity locked to body rhythmic movements. We observed an overall larger high-

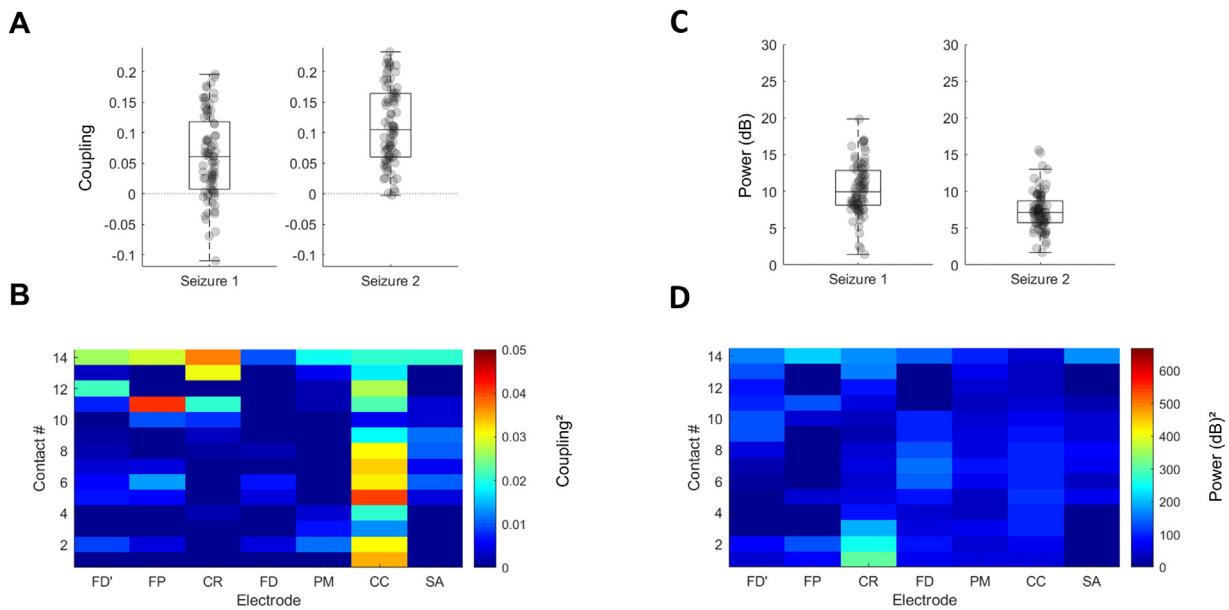


Fig. 3 A. Phase-amplitude coupling (PAC), computed between the phase of delta (~ 1 Hz) activity and high-gamma (60–150 Hz) amplitude, extracted from bipolar montage data and normalized to baseline, for seizures 1 (left) and 2 (right). B. Spatial distribution of PAC combined across the two seizures. Same convention as Fig. 2C. C. Power of high gamma activity (60–150 Hz), in decibel (dB), extracted from the bipolar montage data and normalized to baseline, for seizures 1 (left) and 2 (right). D. Spatial distribution of high-gamma power combined across the two seizures (in dB^2). Same convention as Fig. 2. Each line or point corresponds to one contact.

gamma activity during seizures (paired t tests against zero: $t(80) = 26.4$ and $t(80) = 25.3$ for seizures 1 and 2 respectively; all $p < 0.01$; Fig. 3C). Combining the profile of response of the two seizures (Fig. 3D) we observed a maximal response in the most medial contacts of electrode CR, also situated in the early propagation zone, but in anterior cingulate gyrus (BA32), a region not reported in the previous analyses. These results indicate selective coupling between delta and high gamma activity that is not merely related to non-specific global increase in gamma activity in these locations.

We applied the same analysis pipeline used for rhythmic body rocking seizures on two control seizures from the same patient (Seizures 3 and 4). They were characterized by hyperkinetic motor behavior but did not present the body rocking movement semiology of the other seizures. As expected, we did not find a selective pattern of low-frequency activity in the neural time-course (Fig. 4A) or in the power spectrum (Fig. 4B). In particular, the power spectrum of bipolar montage data at 1 Hz was not different in these control seizures than baseline activity (paired t tests against zero : $t(82) = -3.4$, $p < 0.01$ and $t(82) = -0.99$, $p > 0.05$ for seizures 3 and 4 respectively; Fig. 4C-D). No significant delta-high gamma phase-amplitude coupling was observed neither (paired t tests against zero: $t(82) = -1.21$ and $t(82) = 0.62$ for seizures 3 and 4 respectively; all $p > 0.05$; Fig. 5A-B), confirming the selectivity of the neural activity locked to the rhythmic body rocking described previously. Finally, we observed the presence of significant high-gamma activity in the two control seizures compared to baseline (paired t tests against zero: $t(82) = -11.2$ and

$t(82) = 14.5$ for seizures 3 and 4 respectively; all $p < 0.01$; Fig. 5C) in BA32 region as previously observed (Fig. 5D).

Discussion

To our knowledge, this is the first study analyzing neural correlates of rhythmic body rocking during epileptic seizures, associating quantified video and intracerebral EEG data. Here, we describe two main characteristics of cortical activity associated with rhythmic body rocking semiology, compared to seizures without rocking movements and to interictal rest periods. First, using fast Fourier transform analysis (FFT), a peak of delta band activity, maximal in EZ and early propagation zones, was observed during rhythmic body ictal rocking, corresponding to quantified rocking frequency. Secondly, using phase-amplitude coupling [1], the phase of the clear delta peak was correlated with high-gamma (60–150 Hz) activity, in EZ and propagation zones including motor cingulate regions. Thus, as well as bringing additional evidence of the tight relation between seizure onset and propagation zones in both temporal and spatial aspects [11], our data highlight a clear temporal relation between cortical activity and rhythmicity of motor clinical expression.

A limitation here, apart from the small number of data (due to rarity of SEEG recording of this clinical pattern), is the possibility of an artefactual cause for the delta activity, notably movement artefact from the rhythmic rocking being transmitted via the SEEG cable, suggested by the similarity of amplitude across electrode contacts. However,

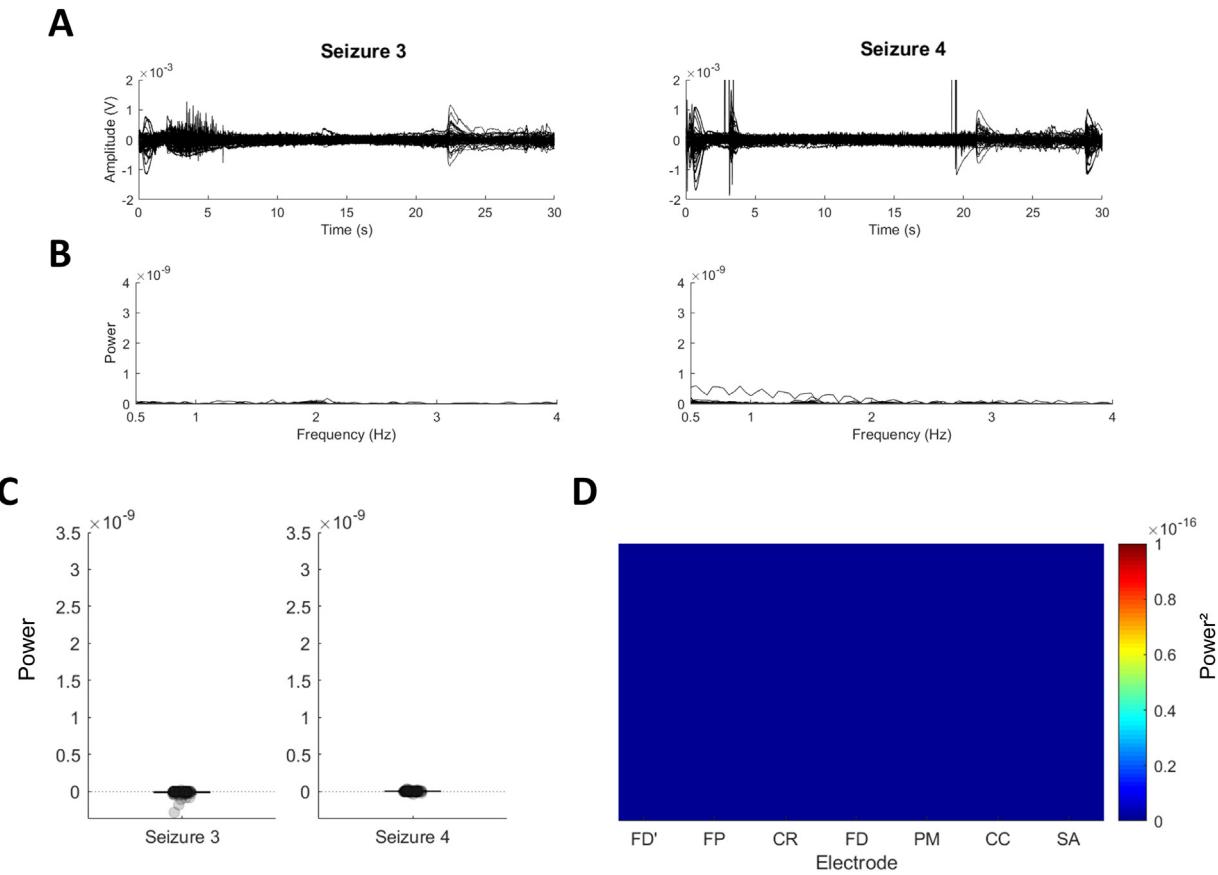


Fig. 4 A. Neural time courses of the two control seizures 3 (left) and 4 (right), without body rocking movement semiology. Amplitude of neural signals for bipolar montage data. B. Power spectra of neural activity from bipolar montage data for the two control seizures. C. Delta (~ 1 Hz) power during control seizures relative to baseline, extracted from the bipolar montage data. D. Spatial distribution of delta power combined across the two control seizures (in volt 2). Same convention as in Fig. 2. Each line or point corresponds to one contact.

we investigated this possibility by using a bipolar montage, considered to produce spatial filtering, thus minimizing artefact from a common source [7]; the same delta band peak persisted in these conditions. While head movement would be more likely to introduce artefact in contacts close to the skull [13,20] and in a widespread distribution, maximal delta activity was observed in seizure onset and propagation zones, which included deeper cerebral contacts far from electrode skull entry points; the topographical distribution of this effect thus also tends to argue against an artefactual cause. Non-rocking seizures in the same patient were characterized by hyperkinetic, non-rhythmic body and leg movements; these showed similar seizure onset pattern but were not associated with visible 1Hz activity on the SEEG trace during semiological expression.

We also investigated the dynamics of high-gamma activity, typically the predominant frequency range in neocortical seizures [5,27]. High gamma band activity closely approximates multi-unit activity [23] and cannot be induced by cable movements. In all seizures (with (Fig. 3) and without (Fig. 5C-D) body rocking semiology), high-gamma activity was maximally present in the anterior cingulate gyrus (BA32), possibly related to its important role here in seizure propagation.

We next evidenced a correlation between the phase of delta band peak and the amplitude of high-gamma oscillations selectively during the periods of rhythmic rocking. This effect was particularly marked within electrode contacts in the EZ. Additionally, strong delta-high gamma coupling was observed in the electrode exploring the BA24 section of the cingulate gyrus. This portion of the cingulate has a major role within the motor system, notably in terms of motor coordination and selection [9,21].

One possible explanation of the topographical distribution of our results could reflect the usual evolution of the seizure discharge as it spreads to cingulate motor regions. This could have a role in driving rocking behavior for example by induction of multi-unit activity by delta activity, leading to activation or disinhibition of an intrinsic neural oscillator [17], perhaps involving the striatal connections of the anterior cingulate [9].

Established models of epilepsy networks based on signal analysis from intracerebral EEG data have shown that, during seizures, connections between neural groups in different anatomical structures are abnormally selected and facilitated [5,29]. In studying these relations between neural activities, most work to date on epilepsy networks has focused on the period of seizure onset [28]; relatively few

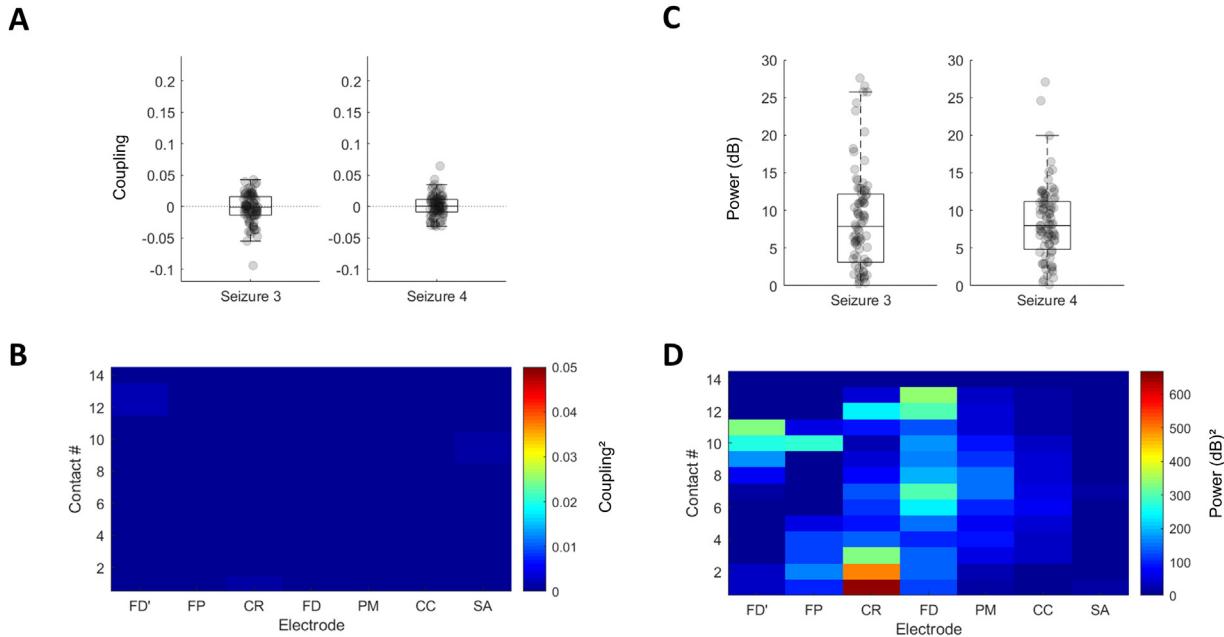


Fig. 5 A. Phase-amplitude coupling (PAC), computed between the phase of delta (~ 1 Hz) activity and high-gamma (60–150 Hz) amplitude, extracted from bipolar montage data and normalized to baseline, for the two control seizures. B. Spatial distribution of PAC combined across the two seizures. Same convention as Fig. 2C. C. Power of high gamma activity (60–150 Hz), in decibel (dB), extracted from the bipolar montage data and normalized to baseline, for the two control seizures. D. Spatial distribution of high-gamma power combined across the two control seizures (in dB^2). Same convention as Fig. 2. Each line or point corresponds to one contact.

works have investigated links to putative mechanisms of semiological production [18]. While firm conclusions cannot be drawn from the present work due to small number of data, our results suggest that correlating quantified ictal movement patterns with quantified cerebral data is feasible. Study of a larger data set could help to shed light on underlying pathophysiology of complex ictal behaviors.

Conflicts of interest

None.

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