Original article

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Averaging in time-frequency domain reveals the temporal and spatial extent of seizures recorded by scalp EEG

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ABSTRACT – *Aim.* To demonstrate the importance of averaging in time-frequency space and the added localizing value in time and space in a case of cortical myoclonus.

Methods. One hundred myoclonic jerks were averaged in time series and in spectral domain. For the latter, we chose 100 (10-second) segments from interictal background and used the unpaired t-test for the jerk-related and control spectral data to obtain the t value and corresponding *p* value at each pixel. We corrected for multiple comparisons using false discovery rate procedure. We generated maps of spectral significance per electrode. All insignificant t-values were converted to 0 for easier visual analysis.

Results. Standard back-averaging of 100 jerks disclosed a single spike preceding EMG activity by 19-27 milliseconds. No other definite ictal patterns were discernible in the time domain. Statistical analysis of the same 100 epochs in the time-frequency domain disclosed a greater temporal extent of the seizure, as well as a more detailed rendering of rhythms and frequencies involved. Valproate was added and led to substantial improvement.

Conclusions. Averaging in the spectral domain may reveal frequency-specific changes that may not be otherwise appreciated in the time domain. Future studies may elucidate the effect on the sensitivity of diagnosis of simple partial seizures and auras.

Key words: statistical spectral averaging, time, space, localization, seizure, cortical myoclonus, myoclonic jerk

Signal averaging has been widely used to facilitate visual identification of low-amplitude electrical brain activity One of the first and common clinical applications of this is the differentiation between cortical and subcortical generators of myoclonus, for example, in the diagnosis of epileptic myoclonus. Here, we present a case of frequent daily myoclonic jerks that were confirmed to be epileptic after being misdiagnosed initially as non-epileptic due to absence of ictal EEG correlate. We used a framework of statistical spectral averaging which

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involves parametric statistical comparisons between mean activity at baseline and the mean activity of epochs, time-locked to myoclonic jerks, and demonstrate the effectiveness of this framework on delineating the extent of seizures in time and space.

Case study

A 75-year-old, right-handed woman was admitted to our epilepsy monitoring unit for the characterization of episodes of body jerks. She had a remote history of generalized seizures treated for a few years with phenobarbital in adolescence. The episodes started roughly 20 years ago but became more frequent in the past 10 years. She described the jerks as spontaneous bilateral, but occasionally more pronounced over the left side of the body, with retained awareness. In addition, she also described rare episodes of "mental dullness" and an arrest of thought process, as well as episodes of losing track of time. She was not on anti-seizure medications at the time of presentation. Her neurological examination was unremarkable. Cognitive assessment disclosed a Montreal Cognitive Assessment MoCA (Nasreddine, Phillips *et al.*, 2005) of 24/30 (loss of 3 points for memory, 2 for abstractions, and 1 for executive tasks) which was consistent with the given history of mild cognitive impairment. MRI of the brain and routine CSF studies were unremarkable.

Methods

Analysis of EEG

The EEG was recorded using a digital video-EEG system (Bio-logic, Natus Medical Incorporated, San Carlos, California) with 256-Hz sampling rate and 10-20 international EEG system with EKG electrodes. Ictal and interictal digital EEG samples were analysed using different montages including referential, bipolar, and average reference with digital high-pass (1-Hz) and low-pass (70-Hz) filtering, and 60-Hz notch filtering, as needed for optimal waveform display. For signal processing, EEG data was re-referenced to the right sub-ocular contact, which is the ideal reference since it is the least likely to be contaminated by cerebral activity by the virtue of distance and solid angle theorem (Gloor, 1985). This was visually confirmed using different montages (*i.e.* bipolar, referential other electrodes and to common average).

Back-averaging was performed using an original code developed in Matlab (2012b, The Mathworks, Natick, MA). The trigger channel was an electrode placed in the masseter muscle to capture stereotyped muscle jerks, according to the patient's subjective report of seizures. The patient experienced strong jerks. It was the view at the time of recording that the facial EMG electrode was sufficiently secure in place and that EMG units were aligned to ensure reliable averaging. We identified 100 muscle jerks in the time series by screening the EMG channel and selected related 10-second EEG epochs centred on the onset of the EMG burst. These epochs were averaged in the time domain. In addition, we performed a time frequency decomposition and extracted the power spectrum of each epoch and for each EEG channel using fast Fourier transformation. Sliding Hamming windows of 156-millisecond duration and 50% overlap were used in order to construct the power spectrum for each channel. Frequency resolution was 1 Hz, and frequency range of interest was set to 1-50 Hz. The choice of window was driven by time and frequency resolutions suitable for frequencies of interest (theta to low-gamma), taking into account that some epileptic high-frequency bursts are brief/transient. The power spectra were then averaged to create an average in time-frequency space and converted to decimal logarithmic scale. Ten-second windows centred around the average muscle jerk (event)-related spectra were obtained by averaging 100 data segments for each muscle jerk.

For statistical comparisons of the power of activity in time-frequency space; 100 EEG segments of the same duration (10 seconds) were selected from the interictal background and were similarly transformed to obtain the control spectral data. The background segments were carefully reviewed and segments with artefacts were rejected. The unpaired t-test was then performed between the jerk-related and control spectral data to obtain the t-value and corresponding p value at each pixel (127-time windows representing data from 10 seconds x 50 frequency bins = 6350 pixels for each electrode). Because there was a large number of comparisons, we controlled for multiple comparisons with the Benjamini-Hochberg false discovery rate (FDR) procedure. This statistical procedure is often used in neuroimaging studies to control for false discovery rate and has also been used more recently in neurophysiology studies (Kobayashi, Oka *et al.*, 2004, Kobayashi, Jacobs *et al.*, 2009, Jacobs, Kobayashi *et al.*, 2011). The FDR is defined as the ratio of the number of false positive pixels to the number of pixels declared active. Firstly, one should select the FDR-bound q that is the maximum tolerable FDR on average (equivalent to alpha error based on standard two sample comparison). The p values obtained by the t-test above, with respect to V pixels (in this case 6,350 pixels), are ordered from smallest to largest, and indexed by j ranging from 1 to V as p(j). The pixels of significantly small values are defined based on the largest j for which $p\left(j\right) \leq \frac{j \cdot q}{c \cdot V}$ where c is $\sum_{j=1}^{V} \frac{1}{j}$. Finally, the spectrum of t-value controlled by the FDR was generated with the

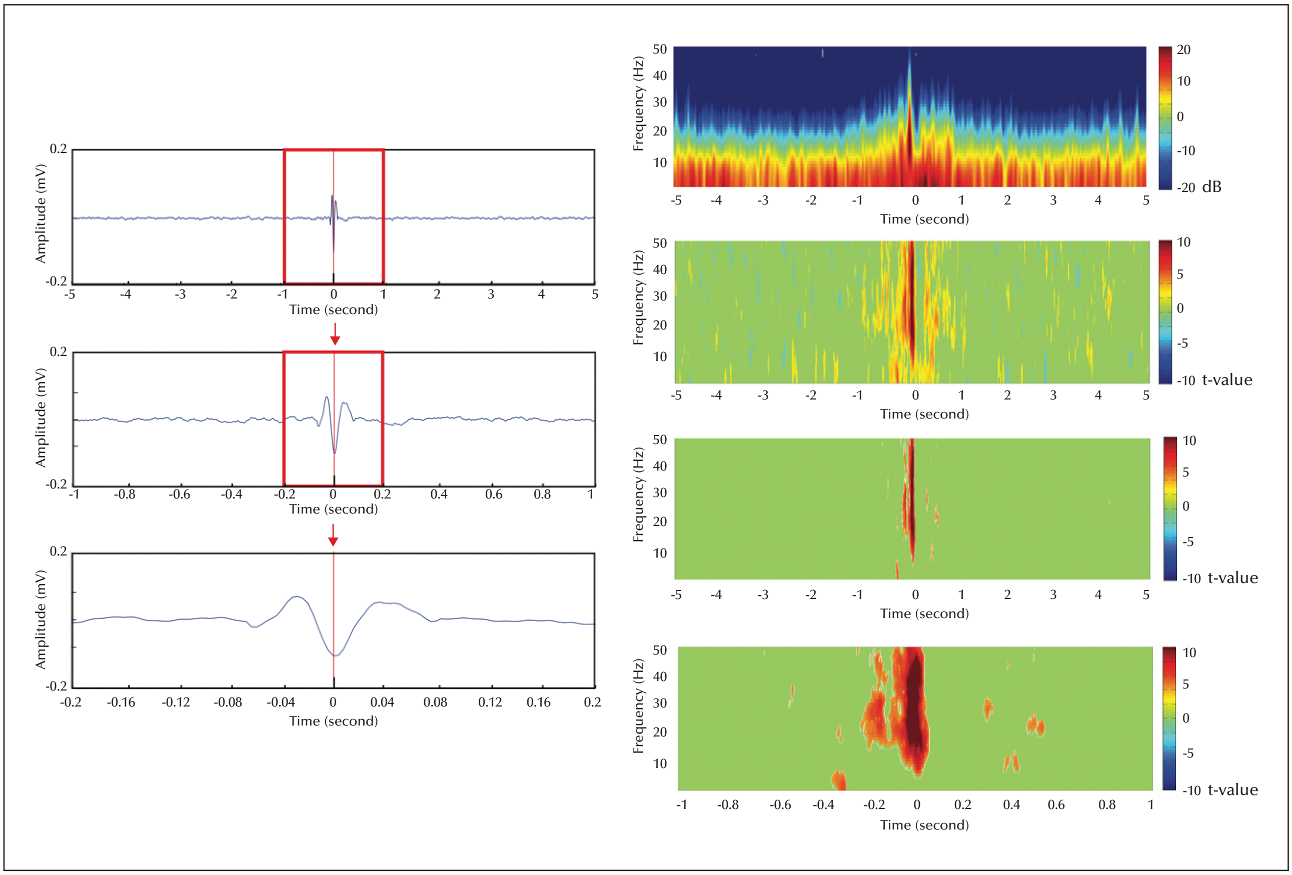

Figure 1. Steps implemented in averaging and interval outcomes: averaging of 100 jerks from Pz in the time domain (left) and time-frequency space (right).
Left: three different time bases: 10, 2, and 0.4 seconds (from upper to lower); the red line marks the time at onset of clinical myoclonic jerks; the spike preceding the muscle jerks is easily discernible.
Right: results of signal averaging in the spectral domain (upper), and then after applying statistical transformation (second from top) and correction of multiple comparisons by FDR (lower two).
We used a 10 second window (second from bottom) to illustrate the effectiveness of FDR correction on eliminating accidental detections far from seizures, due to magnification of alpha errors and multiple comparisons.

threshold corresponding to the *p* value determined above. All other insignificant *t*-values were converted to 0 for easier visual analysis (Genovese, Lazar *et al.*, 2002) (*figure 1*).

Electrophysiology

Video-EEG showed rare bilateral fronto-central spikes without clinical correlate. Frequent typical bilateral and left-sided myoclonic jerks were recorded. These jerks did not have clear ictal EEG correlate (*figure 2*). The muscle jerks occurred at no particular interval and without any discernible temporal patterns, thus they did not qualify as epilepsia partialis continua. They were characterized by rapid and brief <200-millisecond, polyphasic, and relatively stable and stereotyped, multi-unit firing in the EMG channel.

Signal averaging and time-frequency analysis

Standard back-averaging of 100 jerks disclosed a single spike preceding EMG activity by 19-27 milliseconds with a wide distribution and a maximal amplitude in the vertex and right parietal region (Fz, Cz, Pz, P4) (*figure 3*). No other definite ictal patterns were discernible in the time domain. Statistical analysis of the same 100 epochs in the time-frequency domain disclosed a greater temporal extent of the seizure, as well as a more detailed rendering of rhythms and frequencies involved: a burst of 20-40-Hz activity was observed over the parasagittal and right parietal region, at -750 to +670 milliseconds (maximum Pz-P4), in relation to the muscle jerk. Valproate was started and there was substantial reduction in the number of muscle jerks per night, from hundreds to only two jerks per night.

Figure 2. Anterior/posterior bipolar montage showing EEG activity of one of the patient's habitual events, *i.e.* muscle jerks. The arrow marks the point in time when the patient pushed the button at the start of the episode (a second after the episode actually occurred). Note that no reliable electrographic pattern is discernible on raw EEG data. The muscle jerk is not well discernible on this anterior posterior bipolar montage.

Discussion

We present a case of a woman who was referred to the epilepsy monitoring unit for evaluation of jerks that started many years ago and recently began to occur on a daily basis. Review of raw EEG data did not show clear EEG correlate to the muscle jerks (*figure 2*) and back-averaging in time-frequency space confirmed that the muscle jerks were epileptic, and in fact, revealed the extent of electrographic changes in the time and frequency domain, as well as more localized spatial involvement that was not appreciated as clearly by averaging in the time domain.

Signal averaging improves signal-to-noise ratio (SNR) by a square root number of repetitions (Schimmel, 1967) (Vaughan, 1974). The most localizing rhythms at seizure onset are known to be paroxysmal and fast, based on intracranial EEG data (Singh, Sandy *et al.*, 2015). Averaging in the time domain might be less successful for higher frequencies due to:

– lower signal-to-noise ratio as the "signal" amplitude and power decreases as a function of frequency (Kakisaka *et al.*, 2013; Petroff *et al.*, 2016);

– and short cycles per time unit, as paroxysmal fast activity is more prone to cancelation and phasing out across trials due to expected slight variations of alignment of triggers (*i.e.* muscle jerks), as well as inter-trigger variations in morphology and spatial distribution from one event to another.

There have been several applications of back-averaging in clinical epileptology and neurophysiology since the concept was pioneered by Dawson (Dawson, 1947). Expectedly, time-frequency analysis may overcome some practical limitations of standard time-domain analysis, especially for the analysis of faster frequencies, as demonstrated herein. In this case, averaging in the time series and spectral domains provided unique localizing findings that could not have been obtained otherwise. Specifically, the patient's spells were labelled as non-epileptic, hyper-vigilance, startle, panic, and anxiety-related after EEG performed elsewhere showed no reproducible ictal correlate. Averaging in time series provided evidence that the episodes correlated with spikes preceding the jerks and confirmed that the jerks were epileptic, however, localization was not specific. Averaging in the spectral domain provided another layer of localizing value both in spatial and temporal domains (*see figure 3 for a comparison of spatial extent*). This suggested that the focal jerks were originating indeed from the contralateral hemisphere at the level of the right centro-parietal region which narrowed the differential diagnosis. This relative discordance in localization brings to mind the concept of secondary bilateral synchrony with focal generators (regions generating fast paroxysmal activity in this non-lesional case with presumptive mesio-parietal onset) (Ralston, 1961). It is possible that these spells are similar to myoclonic jerks seen in

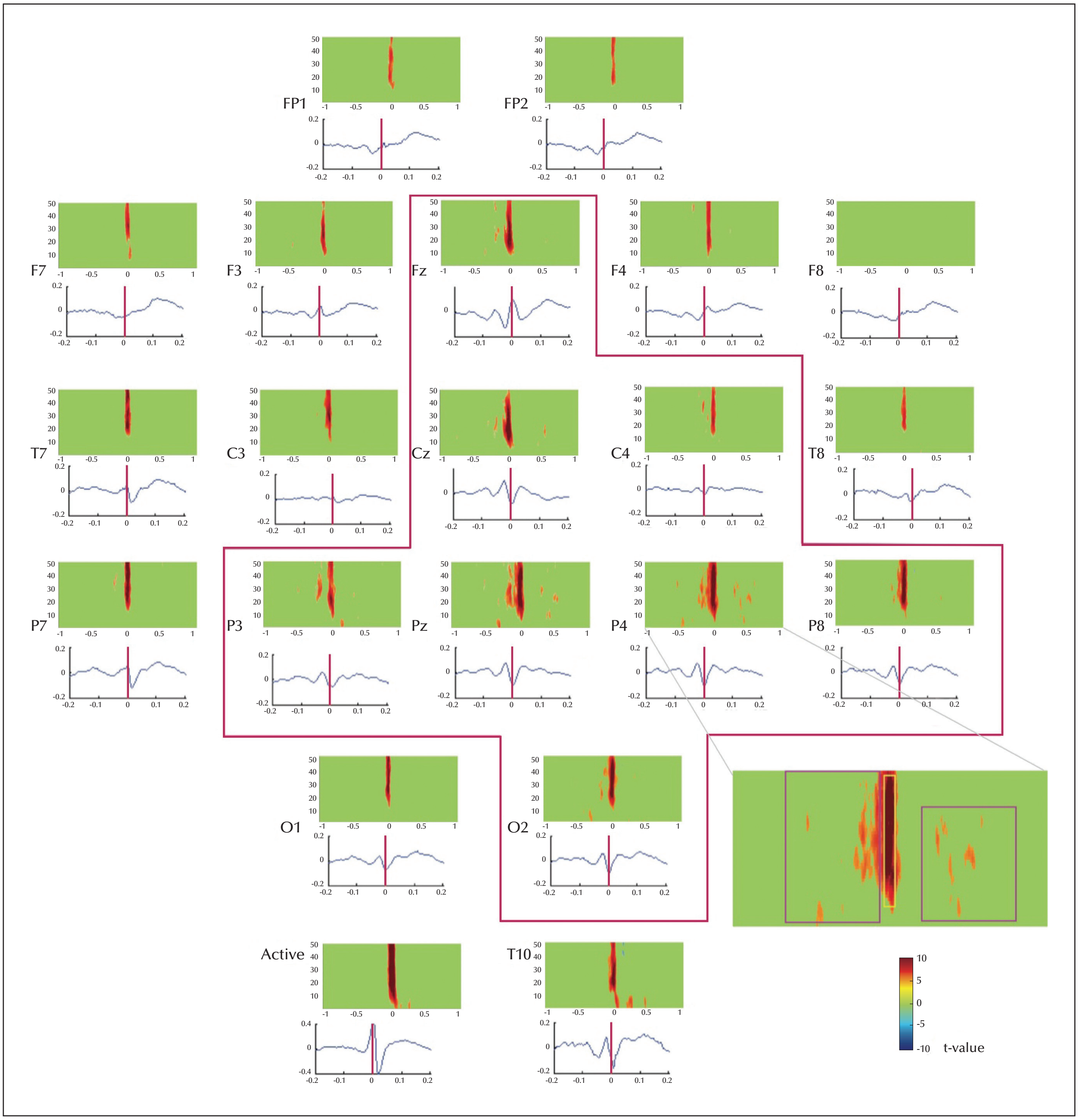

Figure 3. The spatial distribution of the spectral domain and in time-series recorded with electrodes placed according to the 10-20 international system, using all recording electrodes. Note that averaging in time-frequency space reveals more changes than in the time domain. Furthermore, there is more localized paroxysmal fast activity in the right fronto-parietal regions. Note that the widespread dense activity at time 0 corresponds to electromyographic artefact; although this is way more prominent over the left side in the time series, it appears visually equally predominant after statistical transformation (weight by statistical significance, not power). The red box highlights the spatial extent of seizures (contacts exhibiting fast paroxysmal activity); note how spatially more restricted the seizures are relative to spikes. The close-up of P4 shows EMG artefact (yellow box) and EEG seizure (purple boxes).

disorders with mild cognitive impairment or degenerative disorders in individuals with prior remote predisposition for generalized seizures. Also, conceptually, based on the differential diagnosis, the possibility of Creutzfeldt Jakob disease might be considered, however, the length of time of the course of illness does not support this hypothesis.

The spectral method may have advantages over conventional time-series averaging when:
– the alignment of clinical events is less feasible, *e.g.* for non-motor auras, or when the spikes are less prominent;
– the effect of seizures and spikes on physiological activity, remote from the pathological epileptic regions, is studied;
– the same statistical approach could be implemented for averaging high gamma activation in relation to tasks for function localization;
– and specific localizing information is provided in focal epilepsy with widespread spikes, such as those seen in secondary bilateral synchrony, similar to the case presented herein.

This is a single case report, therefore no generalizations can be drawn. Future studies should focus on evaluating the effect of the added value of sensitivity of detection compared to standard back-averaging in time domain. Finally, the statistical transformation emphasizes statistical significance, independent of power or polarity. It is possible that incorporating power, polarity, and negative statistical significance may provide clinically meaningful data. Unfortunately, despite the remarkable utility of averaging in general and averaging in time-frequency in particular, the clinical implementation, sometimes even at tertiary epilepsy centres, is still lagging. Perhaps, a collaboration with industry to enable efficient intergration with the clinical review systems would be beneficial.

Conclusions

This case indicates that averaging in the time-frequency domain may reveal frequency-specific changes that may not be otherwise appreciated in the time domain. Averaging in the spectral domain may have several clinical applications, as discussed above. Future studies may elucidate the effect on the sensitivity of diagnosis of auras using this method compared to raw EEG data and time-series averaging. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

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TEST YOURSELF

(1) Does a normal EEG rule out the possibility of an epileptic event completely?

(2) What is the rate of sensitivity of scalp EEG for detection of simple partial motor seizures or auras?

(3) How can we improve the sensitivity of scalp EEG for detection of epileptic events?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".