EEG Infraslow Activity in Absence and Partial Seizures

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Baseline Shifts Electroencephalography Glia Infraslow Topography Seizures

ABSTRACT

It is currently assumed that for recording of infraslow activity (ISA) DC-coupled amplifiers are required. This report will demonstrate that this may not be the case and presents some data about its potential clinical usefulness.

Archived EEGs of 29 seizures from 6 children with absence attacks, accompanied by 3 Hz classical spike-wave discharges (SW), were compared with 20 partial seizures from 10 adult patients. The data from the children were acquired on a Bio-logic system, those from the adults on a Grass-Telefactor instrument. In the children the original 30-minute routine EEG was used while in the adults stored videomonitored data were excerpted to provide 20-minute segments which included the preictal, ictal and postictal state. All data were analyzed with the BESA software package. The seizures were evaluated separately on conventional filter settings, full band of 0.01-to the upper limit of the instrument, and 0.01-0.1 Hz (infraslow activity, ISA).

Filter settings of 0.01-0.1 Hz provided a better assessment of ISA than when the full band was evaluated. Absence seizures showed bilateral essentially synchronous ISA with a negative positive sequence in the frontal areas and opposite polarity in the posterior head regions.

In partial seizures when seizure onset was clearly lateralizeable from conventional frequency settings ISA corresponded to that hemisphere, but the electrode position could be displaced to a neighboring one from the one which was maximally involved on conventional settings. Topographic analysis showed two types of ISA: one with focal spread only and the other where there was in addition an element of synchrony especially in the frontal areas.

It is concluded that ISA can be recovered from conventional EEG recordings and may be helpful not only in determining the area(s) of seizure onset but can also differentiate truly focal seizures from those where an additional generalized seizure tendency is present. This is likely to be important when epilepsy surgery is performed in absence of a demonstrable structural lesion

INTRODUCTION

For the surgical removal of epileptogenic tissue a precise delineation of seizure onset and its spread are imperative. Yet, this can at times be difficult to determine from scalp recordings on which the subsequent placement of intracranial electrodes depend. For this reason frequencies beyond the commonly recorded ones have aroused greater interest in the search for more accurate seizure

localization. Ultrafast activity beyond 100 Hz can be valuable¹⁴ but its applicability is limited to intracranial recordings because data obtained from the scalp can be contaminated by muscle artifact.

At the extreme slow end of the frequency spectrum negative baseline shifts have in the past been shown to accompany absence seizures⁶⁻⁷ when DC amplifiers were used. More recently Vanhatalo et al.⁸ reported that DC shifts also accompany temporal lobe seizures and provide a reliable lateralization of the process. Ictal baseline shifts have, however, also been reported from intracranial as well as scalp recordings when conventional amplifiers were used and the low frequency filter was set at 0.1 or 0.01 Hz.⁹⁻¹³ But since the shifts could be demonstrated only for some but not all seizures their localizing, as well as lateralizing, value has been questioned.¹⁴

In all of the mentioned investigations the study of infraslow activity (ISA) during seizures was limited to the demonstration of a baseline shift upon which the conventional frequencies were seen to ride. Since this methodology provides only a partial picture, because high amplitude conventional seizure frequencies may mask underlying lower amplitude slow activity, we have studied the frequencies below 1 Hz for two separate bands in the interictal and ictal state of seizure patients; subdelta (0.1-0.9 Hz) and infraslow (0.01-0.1 Hz). These findings were then compared with the delta frequency band (1-4 Hz), and it was observed that subdelta as well as ISA can present additional information which in part differed from what was seen with conventional filter settings. 15-17

Most recently Miller et al.¹⁸ have extended the previous work of Vanhatalo et al.⁸ and reported 20 seizures (temporal as well as extra temporal) from 11 patients which were recorded with DC-coupled amplifiers and stated that when the data are filtered for a frequency content of <0.5 Hz localization of seizure onset can be more precise than with that of the conventional frequency band.

This report will demonstrate: a) that ictal infraslow recordings can be of value in the further delineation of the epileptogenic zone in the presurgical workup of patients, even when conventional EEG systems, rather than those which are DC-coupled, are used; b) that this can be done retrospectively from archived data and that ISA may aid in the differentiation of purely focal seizures versus those where there exists an additional more generalized component.

MATERIALS AND METHODS

Absence seizures

Thirty minute routine recordings from six children (4 girls, 2 boys; age range 4-8 years, mean 6.3 SD 1.6 years) which included

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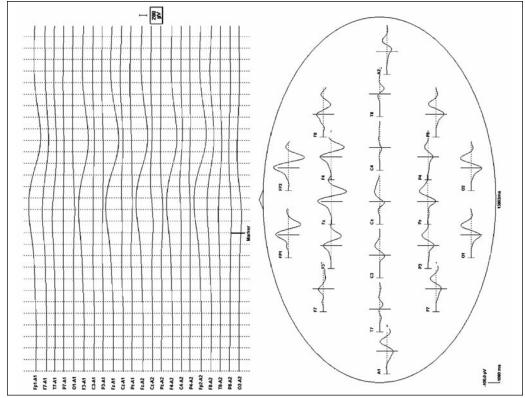


Figure 1.

Top half. Absence seizure with classic 3 Hz SW pattern. Ten second window, ipsilateral ear reference, filters 1-75

Hz. Marker at seizure onset. Bottom half: same seizure on 30 second window and filter settings 0.01-75 Hz. An additional underlying slow component becomes visible.

Top half: Same 30 second segment but filtered for 0.01-0.1 Hz. ISA becomes clearly visible. Bottom half: same data as in top half but on a topographic display. Cursor is placed on maximum negative peak. Negative-positive sequence with essentially bilateral synchrony and symmetry. Anterior head regions negative, posterior head regions positive. Average reference display.

hyperventilation (HV) and photic stimulation were studied. Twenty-nine seizures (duration: 6-26 seconds; mean 11.9, SD 6.7) were recorded, of which ten had been induced by HV while the others had occurred spontaneously. With one exception the children were unmedicated.

The EEG was recorded on a Bio-logic Ceegraph-Vision system and 21 silver/silver chloride electrodes, with impedance below 5 kOhms, were used. These data were transferred to CDs and subsequently evaluated separately, with the BESA software package, ¹⁹ for the conventional frequency band of 1-75 Hz, full band 0.01-75 Hz and infraslow 0.01 (6 db, forward) - 0.1 Hz (12 db zero-phase). The low frequency filter of 0.01 Hz was chosen because when the filter had been left open a baseline offset was apparent at times in some channels. For the demonstration of ISA a viewing window of 30 or 40 seconds was used which placed the seizure in the center of the window. For evaluation of the topographic distribution of ISA the data were reformatted to an average common reference.

Complex partial seizures

Ten patients (8 women, 2 men; age range 23-49 years; mean 32.3, SD 8.5) with longstanding, medically refractory, partial and secondarily generalized seizures were investigated. They had undergone an extensive presurgical workup which included prolonged videomonitoring for seizures as well as MRI, MEG and sometimes PET or SPECT scans. All patients were on anticonvulsant medications.

The EEG recordings were obtained on a Grass-Telefactor Millennium system. Twenty-one silver/silver chloride electrodes, affixed with collodion, were used in an augmented 10-20 montage that included infraorbital electrodes. Electrode impedances were kept below 5 kOhm. From these recordings 20 minutes of data which contained a clinical seizure were extracted in a manner that placed the seizure at the center of the epoch. These files were then exported to CDs and analyzed with the BESA program, in the same manner as the absence data, for the conventional frequency band (1-60 Hz), the full band (0.01-60 Hz) and separately for ISA (0.01 Hz 6db forward -0.1 Hz 12 db zero-phase). Inasmuch as seizures had occurred in the waking and sleeping state, eye, head and body movements which resulted from the seizures were at times significant contaminants. From 35 seizures 20 (two per patient) were selected which lasted for at least 30 seconds and were sufficiently artifact free that onset and possible ictal slow wave shifts could be evaluated. When the EEG was obscured by muscle artifact the high frequency filter was set to 15 Hz which allowed better visualization of the seizure discharges. Seizure onset was determined by consensus of two Board certified clinical neurophysiologists. For the assessment of concomitant ISA a viewing window of 30 seconds was used which placed the conventional seizure onset in the center of the window. When the first infraslow peak did not occur immediately upon seizure onset the 30 second window was expanded to 40 seconds. The data were viewed on various montages, but for topographic display an average common reference was used.

RESULTS

Absence seizures

When a full band filter setting was used it was apparent that the classic 3 Hz SW discharge was riding upon an underlying slow wave. This became much clearer when the frequency band was limited to 0.01-0.1 Hz. Under these circumstances a highly characteristic picture emerged in all patients. The frontopolar and frontal row of electrodes, including F7/8, showed an initial negative peak while the parieto-occipital, as well as temporal electrodes, showed positive polarity. The

central electrodes recorded low amplitude negativities. The negative peak in the frontal and frontopolar areas was followed by a marked positive component. The latter either returned to the baseline or was followed by another negative wave. When seizures lasted more than 15 seconds a marked additional positive swing could be observed towards the end of the SW episode which returned to the baseline after several seconds, or it could be followed by an additional negative event. When the frontal area became positive the posterior head regions and temporal areas showed corresponding negativity. Although there was no appreciable difference between spontaneous and HV induced seizures, the onset of the beginning negative baseline shift could not be ascertained with induced seizures because of HV related ISA. When seizures occurred spontaneously there were only minor latency differences between electrodes, but they were somewhat more pronounced in seizures resulting from HV.

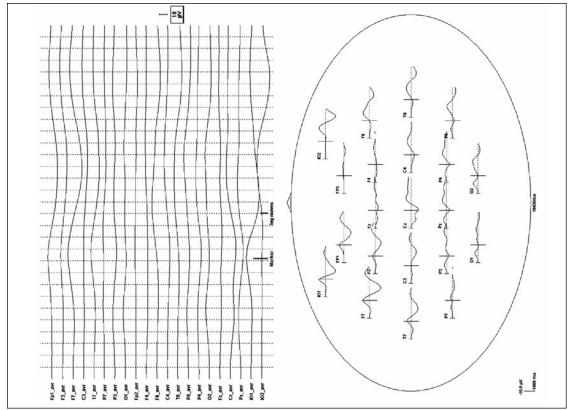
Figures 1 and 2 provide a typical example from an 8-year-old girl who suffered from frequent daily absence seizures. Otherwise she was healthy, did not take any medications, and there were no antecedents except for a positive family history of epilepsy. Five absence attacks were recorded during her routine EEG, two of which had been elicited by HV, but the figures are derived from a spontaneous seizure. The top of Figure 1 shows a 6 second 3 Hz SW absence seizure, during which the patient simply stared, without eye blinks, on filter settings of 1-75 Hz in a 10 second window on an ipsilateral ear montage. A concomitant slow component is not readily apparent. The bottom section shows the same data but on a 30 second window and filter settings of 0.01-75 Hz. Additional slow wave activity upon which the 3 Hz SW discharges ride becomes visible. ISA is better seen when the higher frequencies are removed as shown in the top half of Figure 2. It contains the same data as the bottom half of Figure 1 but with filter settings of 0.01 (6db forward) - 0.1 Hz (12db zero-phase). The bottom half demonstrates the classic ISA topography as described above.

Partial and secondarily generalized seizures

Of the 20 partial seizures 18 had remained partial while 2 continued to evolve into generalized tonic-clonic convulsions. When the low frequency filter was set to 0.01 Hz (6db forward) a baseline shift, which was sustained throughout most of the seizure, occurred only once. Most commonly there were slow waves in some channels lasting 10 to 30 seconds rather than sustained shifts. These were relatively widely distributed and could not readily be localized.

Ictal ISA was observable in all seizures but varied in its expressivity. It was mainly characterized by higher amplitude transients, lasting 30-40 seconds, which were followed by lower amplitude waves. In nine instances an additional high amplitude transient was seen at the end of the seizure. The laterality of seizure onset was the same as for conventional frequency, and when the seizure spread to the opposite hemisphere on conventional filter settings the infraslow peak shifted also to that side. The exact electrode positions of maximum discharges were, however, not necessarily identical for the conventional and the infraslow frequency bands. The infraslow maximum was frequently displaced by one electrode position to a neighboring one from that of maximum amplitude of conventional frequencies; for instance from T7 to P7 or F4 to F8.

In regard to ISA topography, at seizure onset two types of distribution were encountered: unilateral with spread to other electrodes on the same and subsequently opposite side, or an additional essentially synchronous negative peak in the frontal areas with corresponding positivity in the central and posterior head regions.



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Figure 3.

Top half. Thirty second window showing the onset of a complex partial seizure originating from the left temporal lobe. Marker is at seizure onset. First slight leg movement is also noted. Filter settings 1-15 Hz, average reference. Bottom half: same data but low filter set at 0.01 Hz. Some additional slow activity is present but masked by higher frequencies.

Top half: Same data as in Figure 3 but filter settings 0.01-0.1 Hz and increased amplification. Bottom half: same data on topographic display. Cursor is on first negative peak and shows synchrony for the negative positive sequence in the left anterior quadrant and subsequent spread to the right temporal areas.

Figure 4

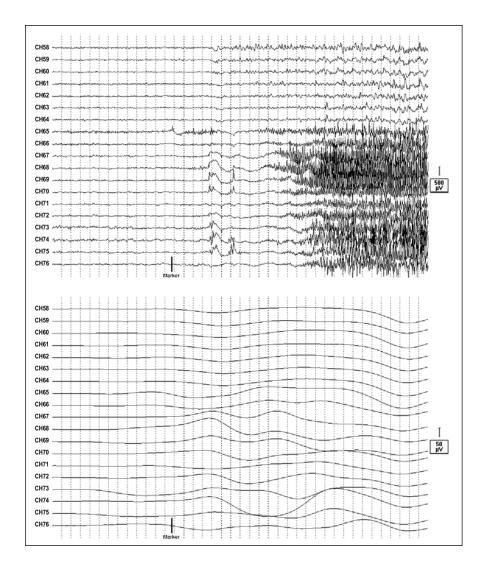


Figure 5.

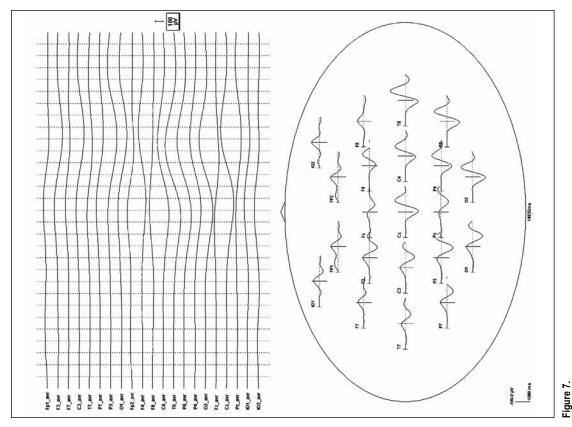
Top half: Onset of a complex partial seizure in the same patient as Figures 3, 4 but with subdural grid recording over the left temporal lobe in a 40 second window. Low filter 0.01 Hz, high filter open. Reference: a needle electrode sutured into scalp. Marker was placed on first change in the recording. Additional slow activity can be seen but is partially masked by high amplitude frequencies. Bottom half: filter settings of 0.01-0.1 Hz show ISA is initially maximal in the channels which show subsequently most marked seizure discharges and thereafter spreads to other neighboring electrodes.

Clearly focal spread was observed for both seizures in five patients while in the others one of the seizures showed in addition the mentioned synchrony in the frontal areas.

Figures 3-5 and 6-7 are examples of seizure onset for different filter settings in two patients. The first patient was a 29-year-old woman who had suffered from medically refractory partial and secondarily generalized seizures since 18 years of age. Apart from a head injury at age 20 months there were no etiologic factors. The MRI was nonspecific and a PET scan showed hypometabolism in the left temporal area. The top half of Figure 3 shows the onset of a partial seizure on an average reference montage for a 30 second window filtered between 1-15 Hz because of subsequent muscle artifact. The seizure originated in the left temporal area with a sharp transient followed by rhythmic activity. The comment "marker" allows comparison with ISA data. The patient had been asleep lying on her left side and the comment "leg moves" referred to a slight movement of the right leg. The seizure remained partial and was characterized essentially by an arrest reaction followed by a confusional state.

The bottom half of the figure shows the same data but filtered between 0.01-15 Hz and there is no evidence for a sustained baseline shift. ISA can, however, be seen when it is viewed in isolation and amplifications are increased, as demonstrated in the top half of Figure 4. The bottom half shows the ISA topography of this 30 second segment. It is apparent that negativity is highest at F7 but synchronous with IO1, Fp1 and T7. There is subsequent spread to the opposite hemisphere.

Figure 5 shows the onset of a partial seizure on intracranial recordings in the same patient. Subdural grids (Ad-Tech) had been placed over the left hemisphere to further delineate seizure onset. The reference was a needle sutured into the scalp. The top half shows a 40 second segment with a low filter setting of 0.01 Hz while the high filter was left open. For clarity's sake only the most relevant segment is shown. The marker was placed at its position because of the initial transient in channel 65 but the subsequent major discharges are in channels 67-70 and 73-75. Slow activity, which would not be visible on conventional frequency filter settings, can be seen preceding rhythmic seizure discharges and is most marked in channels 67 and 68. The bottom half of the figure shows the ISA when higher frequencies are removed. A spread from channels 67-68 to especially channels 74-75 and subsequently 76 can be seen. As such, this patient demonstrates that cortical ISA distribution is not random but follows expected pathophysiologic laws during seizures and is most pronounced in areas which are directly related to the epileptogenic zone.



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Top half. Onset of a partial complex seizure in the second patient on a 30 window. Precise moment of onset marked slow shift is now apparent in the right hemisphere which includes phase reversals in key electrodes. filter left open; average reference. Bottom half: same data but low filter at 0.01 Hz and high filter open. A is difficult to determine but rhythmic activity is most marked in the right frontal area. Low filter 1 Hz, high

Figure 6.

Top half: Same data as Figure 6 but filter settings 0.01-0.1 Hz. Amplification the same as in Figure 6. Bottom half: ISA topography reveals a complex picture. Cursor is placed on first negative peak and shows synchrony for the entire left hemisphere as well as both infraorbital, frontopolar and anterior temporal electrodes, with subsequent high amplitude activity in the right hemisphere, suggesting a generalized seizure component in addition to the focal process.

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P3 avr Ol_aw fp2_avr Figures 6 and 7 are an example from another patient and demonstrate the second type of ISA distribution. The patient was a 43-year-old man who suffered from partial and secondarily generalized seizures since 3 years of age. They were unresponsive to medications and came in clusters on a monthly basis. There was no known etiology and imaging studies were negative.

Figure 6 shows the onset of a partial seizure, which occurred while the patient was eating dinner, in a 30 second window on an average common reference montage. Clinically it was characterized by an arrest reaction without bodily movements. The top half represents the conventional filter settings of 1-60 Hz. During the first 2 seconds there is an eyeblink, subsequently some diffuse attenuation of EEG activity can be seen for 2 seconds followed by 5 seconds of ill defined slower frequencies mainly in the frontal areas, subsequent attenuation and thereafter rhythmic 4 Hz discharges which are more marked on the right than on the left. The bottom half of the figure shows the same data but with a low frequency filter setting of 0.01 Hz. The high filter was left open because there was no muscle artifact. It is apparent that there is a marked slow baseline shift which started during the phase of attenuation and is most pronounced in the channels from the right hemisphere. Furthermore, electrodes Fp2, F8, Fz and IO2 record in phase activity while there is phase reversal at electrodes F4, C4 and Cz.

The top of Figure 7 shows the same data as the bottom half of Figure 6 when only ISA is considered. A comparison with the top of Figure 6 demonstrates that ISA began at the transition to the attenuation of the conventional EEG frequencies. The bottom half of Figure 7 shows the ISA topography and reveals a rather complex picture. The cursor was placed on the first negative peak which is synchronous not only throughout the left hemisphere but also in the infraorbital and frontopolar areas as well as F8. It is subsequently followed by a high amplitude negative wave in the temporal, central and posterior head regions on the right. The picture is somewhat difficult to interpret because the left sided negativity could merely be the reflection of a process that started deep in the right hemisphere and is reflected as a positive event on the surface. The synchronous bifrontal and anterior temporal activity is, however, similar to what was seen in absence seizures and, therefore, suggests the presence of a generalized seizure tendency in addition to a more focal process.

DISCUSSION

The results of this study demonstrate that additional information about seizure onset and spread can be gained when ISA is viewed separately from other frequencies, and that this is possible from archived data obtained on conventional EEG systems. Furthermore, the fact that the topographic distribution of ISA in these selected seizures conformed to pathophysiologic expectations demonstrated that one is not merely dealing with a technical or biologic artifact.

The observation that in this sample of partial seizures two types of topographic distributions of ISA were observed is likely to be of value in the differentiation of purely partial seizures from those where they may be part of a more generalized seizure disorder. The observation that in half of the patients reported here at least one of two seizures showed at the peak of ISA synchronous topography especially in the frontal areas, with opposite polarity in anterior from posterior head regions, was unexpected. This picture was similar to what was observed in the children with absence seizures. Infraslow topography may, therefore, provide a differential diagnosis between a purely focal seizure disorder and one where an additional generalized component is present.²⁰ This differentiation is especially important when surgical

resection of brain tissue is based mainly on the results of electrographic seizure localization in absence of a radiographically demonstrable lesion.

The distribution of purely focal ISA was similar to but not necessarily identical with what was seen on conventional frequencies. As such, the epileptogenic zones overlapped and this suggests two different pathophysiologic processes. Inasmuch as one is dealing in the infraslow band with wave lengths ranging between 10 and up to 50 seconds they may reflect, at least in part, glia currents which are known to accompany seizures and have a slow time course.²¹⁻²³

While it is apparent that adding the information contained in the infraslow band to the review of video-monitored seizures is useful some limitations have to be recognized. These are biologic as well as technical. Seizures are usually accompanied by body, head as well as eye movements. The evaluation of seizure onset is, therefore, most reliable when it appears from drowsiness or sleep. Under these circumstances the data can, however, be contaminated by slow lateral eye movements which are reflected in the anterior temporal electrodes with opposite polarity in the two hemispheres. While vertical eye movements (blinks) can be adequately removed with existing software programs, this is not the case for lateral eye movements because the fields of artifact and genuine temporal lobe abnormalities overlap. For this reason seizures in which lateral eye movements preceded seizure onset were not used in this study. Although it is possible that skin currents (GSR) could contribute to ISA they were not a major contaminant. ISA distribution over the scalp was not random but corresponded to pathophysiologic expectations and ISA could also be seen in intracranial recordings as reported earlier²⁴ and again shown here.

After the manuscript was completed and sent for review it was pointed out that the forward function should also have been used for the low pass filter to avoid the occurrence of the peak earlier than might be warranted by the data. We checked this suggestion on electrode artifacts, which produced a clearly defined signal, and found that it was correct. The artifact peak appeared 2 seconds prior to the signal when it was recorded with the 0.1 Hz 12 db zero-phase filter, and at the time of the signal when the filter was set to forward. When we then applied the 0.1 Hz 12 db forward filter to the data reported here it was apparent that the ISA peaks, as shown in Figures 2, 4, 5 and 7, occurred 2 seconds later than in the figures and this needs to be taken into account when the precise time of ISA seizure onset is investigated. The forward filter could, however, introduce at times additional faster frequencies and an offset for some channels. The filter characteristics affected, however, only the time of ISA onset while the topography of the major peaks and the time course of their propagation remained unchanged regardless whether zero-phase or forward low pass filters were used.

There was, however, an unavoidable technical limitation to the data presented here because they were obtained on EEG systems which are certified for a low linear frequency of 0.1 rather than 0.01 Hz. As such amplitudes below 0.1 Hz were attenuated but not abolished. But since the attenuation affected all channels equally it did not invalidate the results. It was, therefore, gratifying to see that the recently reported findings by Miller et al., 18 which were obtained with DC-coupled amplifiers, appeared to agree with our observations. Although the authors insisted that DC-coupled amplifiers are required for the assessment of ISA it is not clear why this should be so when one deals with events which last mainly between 10-50 seconds. AC-coupling with

a low frequency limit of 0.01 Hz would seem to be sufficient for this purpose. It would, therefore, be very interesting to compare data obtained from DC-coupled amplifiers for similarities and differences with ones that were obtained on a conventional EEG system. This would be especially important because before recommending routine use of DC equipment for seizure onset localization, as was done by Miller et al.¹⁸

as well as Vanhatalo et al.,8 its clear superiority over EEG systems which are currently in wide use needs to be established empirically.

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