Summary

Digital EEG systems have a low frequency filter of at least 0.1 Hz. This allows viewing of ictal onset baseline shifts, formerly referred to as “DC shifts.” They are most pronounced with “electrodecremental” seizure onsets and have localizing value. In seizures which start with rhythmic buildup pre-existing infraslow activity (ISA; 0.01-0.1 Hz) increases in amplitude, which is at times quite wide-spread. Maximum amplitude (mV) is usually reached during the transition from partial to tonic-clonic seizures. Brief partial seizures may not be accompanied by ISA increase. But if prolonged seizures (>30 seconds) fail to show ictal onset ISA increase, it is likely that the available electrodes have not sampled the critical area(s) of ictogenesis because of ISA’s small electromagnetic field. ISA is a normal component of the EEG/MEG frequency spectrum and in long-term intracranial as well as scalp recordings intermittent interictal focal buildup from lower amplitude background activity can be seen.

The smaller electromagnetic ISA field leads to a better delineation of the epileptogenic zone(s) and also may have prognostic value. Long term postoperative follow-up studies of patients, which take ISA information into account, should be undertaken. MEG studies of ISA are currently in progress and in long-term intracranial as well as scalp recordings intermittent interictal focal buildup from lower amplitude background activity can be seen.

ISA is an important aspect of the electromagnetic spectrum and further investigations by clinicians as well as basic scientists should be undertaken.

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Key words: Epilepsy, EEG, infraslow, MEG, DC, glia

Eine Übersicht über langsamste elektromagnetische Aktivität des Grosshirns

Digitale EEG-Geräte haben einen unteren Frequenzfilter zwischen 0,016- 0,1 Hz. Dadurch kann man jetzt in archivierten EEGs das untersuchen, was als “DC shift” bei einem Anfallsbeginn bezeichnet wurde. Diese “shifts” sind bei elektrodecrementalem Anfallsbeginn bestens sichtbar und lokalisatorisch wertvoll.

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Bei rhythmischem Anfallsbeginn nimmt die normal vorhandene infralangsame Aktivität (infraslow activity [ISA], 0,01-0,1 Hz) fokal zu. Das kann manchmal vor dem Auftreten von Veränderungen im 0,5-70 Hz-Bereich gesehen werden. Die höchsten Amplituden (mV) werden bei einem Übergang von fokalen zu tonisch-klonischen Anfällen erreicht. Bei kurzen Anfällen kann die ISA-Zunahme fehlen. Wenn sie aber bei längeren fokalen Anfällen (>30 Sekunden) nicht eintritt, wurde wahrscheinlich der iktogene Hirnbereich wegen der geringeren ISA-Feldausbreitung von den vorhandenen Elektroden nicht erfasst. Bei Langzeituntersuchungen können intermittierende fokale ISA-Zunahmen sowohl im intrakraniellen als auch im Oberflächen-EEG gesehen werden.


Zusammenfassend kann festgestellt werden, dass ISA ein wichtiges Element des elektromagnetischen Spektrums darstellt, und dass weitere Untersuchungen sowohl von Klinikern als auch Grundlagenforschern vorgenommen werden sollten.

Schlüsselwörter: Epilepsie, EEG, infralangsam, MEG, DC, glia

Un aperçu de l’activité électromagnétique la plus lente du cerveau

Les EEG numériques disposent d’un filtre de basses fréquences entre 0,016 et 0,1 Hz. Ainsi, il est désormais possible d’examiner dans les EEG archivés ce que l’on appelle les « DC shifts », des déflexions de courant survenant en début de crise. Ces « shifts » sont parfaitement visibles lors d’un début de crise électrodécrémental et précieux pour la localisation. Lors d’un début de crise rythmique, l’activité lente à très basses fréquences (infraslow activity [ISA], 0,01–0,1 Hz) norma-
A Review of Cerebral Electromagnetic Infraslow Activity | E. Rodin

In the middle of the past century a great deal of experimental work was carried out utilizing DC amplifiers, but its significance in regard to current work tends not to be fully appreciated. Keeping in mind the purpose of "Epileptologie", I shall only present some key aspects of papers that have direct relevance to modern studies.

The consensus of all investigators was that the onset of induced seizures (regardless of means) was always associated with a negative shift from the previously stable baseline, which frequently preceded the appearance of electrical changes in the conventional frequency range. In most seizures, the shift subsequently became positive and the seizures terminated when the shift returned to negativity.

Most of the studies limited themselves to exploring portions of the lateral surface of the cerebrum but Vanasupa, Goldring and O'Leary, who reported on the effects of a variety of systemically administered convulsant agents in rabbits, included the cerebellum. Marked differential effects, depending on the drug that was used, were observed at the beginning of the seizure, but they subsequently tended to coalesce toward the previously mentioned sequence [1]. The importance of the paper resides in demonstrating the differential effect of drugs on cerebrum and cerebellum. The latter is currently largely omitted from the studies of ictal activity, although its marked participation in some seizures is well documented.

Apart from chemically induced seizures, Goldring and O'Leary investigated the direct and recruiting responses from thalamic stimulation and noted that with midline stimulation each recruiting spike was followed by slower positive - negative waves. This phenomenon was more pronounced in the rabbit than in the cat. A variety of drugs were then used in order to determine their effect on this phenomenon. It was observed that not all depressant agents had the same effect. They also noted that these slow changes were less pronounced when lateral relay nuclei of the thalamus were stimulated. If intense repetitive stimulation did lead to cortical paroxysms, the baseline shifted into the positive direction, while it always shifted negative with midline stimuli [2]. I am bringing this paper to attention because the thalamus is again under investigation with midline stimuli [2].

Johnson et al. expanded previous studies [1] on methionine sulfoximine seizures. Acute as well as chronic experiments were performed. In the acute situation recordings were obtained from the cerebral cortex and a depth micropipette recorded unit activity. For chronic recordings only cortical activity was studied in relation to the behavior of the rabbit. When the negative shift occurred on the surface it was mirrored by a positive one in the depth. Occasionally depth positivity preceded surface negativity. “During this phase there may be a decrease in unit discharge, but the striking change in unit behavior appears as the depth record shifts in the negative direction. Then a burst of unit activity occurs.” There was, however, some variation. The initial depth positivity was at times missing and the first shift was negative. Unit firing rate could also be increased, steady, or decreased, testifying to the complexity of the event. In the chronic preparations the shifts usually occurred after other signs of seizure activity were already
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When present, they accompanied tonic-clonic seizures rather than unilateral partial ones [5]. While the depth results are of interest in regard to current depth-electrode studies, which will be mentioned later, they failed to provide information on the approximate cortical layer they were recorded from.

A review article limited to DC changes in seizures was published by O’Leary and Goldring in 1959 [6]. It was expanded in 1964 to cover all aspects of DC changes under a variety of conditions as well as infraslow activity [7]. In regard to the latter the authors mentioned the work of Aladjhalova and co-workers, which will be reported on separately.

Caspers and Simmich, working with rats, added important information in regard to metrazol seizures [8]. The main finding was that a long-lasting negative shift developed within 30-60 seconds, passed a flat peak between the fifth and tenth minute, and then returned gradually to the baseline within half an hour. Paroxysmal spike activity was superimposed upon an additional negative shift and there was no subsequent positivity. But with repeated doses a negative positive sequence was observed. The important finding for our time was the observation that not only respiration increased but also cerebral blood flow. Although the authors did not discuss this aspect in detail, Figure 1 is instructive. The time window appears to be about 30 minutes and within seconds after drug administration one can see the beginning of the negative shift accompanied by some increase in respiration. A minor increase in blood flow can be seen after about 1 minute which lasts about 4 minutes. This is followed by another small peak of about 3 minutes duration and the major change which keeps increasing for the duration of the picture starts at about 10 minutes after the injection. If one were to extrapolate these data to the clinical situation, they suggest that since major ictal fMRI changes are likely to be delayed in relation to the electrical onset they will represent the spread of ictal activity rather than the area of onset.

While these studies dealt largely with a single electrode pair, Gumnit and co-workers concentrated on ascertaining the electrical field of local DC changes. Initially Gumnit studied the effects of sound on the DC response in cats and noted that the DC shifts were not only limited to auditory cortex but also had a very discrete electrical field. A shift observed at one point could be absent at a distance of 3 mm. The shifts arose suddenly with the onset of the stimulus and terminated equally abruptly at its end. In most experiments the electrodes were placed on the dura, but in some instances a depth electrode was inserted. On basis of the latter it was estimated that the shifts were generated within the upper or the middle third of the cortex [9].

Gumnit then expanded his studies to focal seizure generation via local penicillin application to the cortex. These revealed that sustained discharges were associated with an abrupt negative shift at the center of the field. In the periphery the onset was more gradual and became positive. The total radius was about 1 cm. The peak of the negative shift “was then observed to ‘march’ across the cortex at a speed of 5-20 mm/min”.

After the paroxysm and during electrical silence “the DC level decayed to the previous baseline over a period 3-30 seconds”. Interictal sharp waves had a similar distribution: monophasic negative at the center; briefer, polyphasic and usually predominantly positive at the periphery. Sharp wave activity appeared in the opposite hemisphere within 5-30 minutes. Once established, the center of the mirror field showed “only small negative shifts or, rarely, was isopotential”. Positive shifts were relatively more prominent in the periphery of the mirror field than in that of the primary area and could even be larger than the central negative shift [10]. This information is likely to be important in regard to currently seen ictal onset shifts which may have negative or positive polarities.

Since in the previous study a depth recording had shown no reversal of polarity within the cortex, a detailed investigation was then performed in 45 cats. The focus was again produced by penicillin and the area was explored to a depth of 4 mm below the cortical surface. There was no phase reversal and the largest shift was observed at 1 mm, which was regarded as having represented layer V. “In the periphery of the focus, where positive shifts can be recorded from the surface, the shifts reverse sign in the upper 300-500 µ of the cortex, and the maximum negativity also was located in layer V [11].”

All of these studies dealt with animals and there were only three reports on DC shifts in patients with epilepsy. They dealt with absence seizures and demonstrated negative ictal shifts [12-14]. In as much as these were not seen when AC amplifiers with a low frequency filter of 0.5 Hz were used it was felt that DC amplifiers were required to record slower frequencies. This statement, although reasonable at the time, had an unfortunate impact when digital EEG technology and improved amplifiers became available for clinical use.

Infraslow activity

As mentioned above, O’Leary and Goldring [7] had drawn attention to the work by Aladjhalova (also spelled Aladzhalova and Aladjalova in PubMed) who was probably the first to describe the phenomenon in a series of papers between 1954 and 1978. Unfortunately nearly all of the publications were in Russian and no abstracts are available for this time period. Two articles did appear, however, in English translation. Although the 1957 article was published in “Nature” it did not show up among the references in the O’Leary-Goldring review, which may well have stemmed from the prob-
lem when Cyrillic characters are made to fit the Latin alphabet. Nevertheless it appears that O’Leary and Goldring had access to the information cited in their two Russian references and since this is the first information on the phenomenon under discussion I shall quote the relevant paragraphs in their entirety.

There is a segment of spontaneous brain activity which occurs in both man and animals at the unusually slow frequency of 0.5-8/minute. Aladjhalova has also observed considerably slower potential oscillations which do not develop spontaneously but instead appear 20 to 30 minutes after intense sensory stimulation. These may persist for several hours and are called “horary swings”.

Not all brain parts yield slow waves with the dimensions of infraslow rhythmic oscillations of potential (ISOP). For example they occur in the hypothalamus and cerebral cortex but not in brain-stem reticular formation, central gray matter, or thalamus. However, such infraslow activity can be elicited in central gray by the intravenous injection of epinephrine, and acetylcholine will cause it to appear in the reticular formation. Curiously, ISOP waves are not observed throughout the thickness of the cerebral cortex, but are confined to the superficial dendritic lamina and the cortical depths where the cell bodies of the pyramidal neurons predominate.

According to Aladjhalova, ISOP waves are depressed by narcosis, metabolic aberrations, and brain trauma and exaggerated by repeated sensory stimulation and by systemic administration of certain hormones and pharmacologic substances. The exaggeration of ISOP by repetitive sensory stimulation occurs after an interval of 20 to 40 minutes, the change not being limited to the specific projection zone of the sensory receptor but appearing in other regions of cortex as well. With fluctuations in ISOP concurrent changes occur in the spontaneous rhythm of the usual electrocorticogram. For example, at the maximum infraslow wave activity the usual electrocorticogram shows higher amplitude and slower frequency. It is also important that spontaneous infraslow activity appears in neuronally isolated cortical slabs where it can be modified by stimulation of the hypothalamus and by intravenous injection of hormonal substances.

Aladjhalova views ISOP as dependent on humoral factors and not related to the immediate effects of nervous excitation. She says: “Electrical phenomena of infraslow order are defined by processes which are connected with a protracted change of excitatory properties. They do not reflect the immediate changes of excitation although inseparably related to them. The excitability of the cortical neuron depends not only upon action on it of impulses from other excited elements, but also upon non-impulse processes which are caused by humoral factors and influence the “metabolic tonus” of nervous tissue.” Her studies are intriguing and may represent an important contribution toward the understanding of brain functioning. However, appraisal of the ultimate impact must await additional investigations and confirmation by others.

In as much as the above quoted review did not contain technical details I searched PubMed for “Aladjhalova” and found one English language article, “Hypnosis in Man and Very Slow Potentials”. The paper is written in narrative style and does not contain figures, which would allow one to check the validity of the statements. The most important technical details were a) that DC amplifiers were used and the frequencies below 0.5 Hz were considered; b) that three sets of frontal, temporal and occipital electrodes were employed in bipolar connections on both hemispheres. Fifteen women patients with “neurosis” undergoing hypnotherapy were investigated during 50 sessions. Infraslow changes, called Very Slow Brain Potentials (VSBP) in this paper, were observed. In the waking state “second” potentials (quotation marks are in the original text) “with a period (T) of 7-10 seconds and an amplitude of 0.1 mV predominated all regions of the brain”, although the periods differed somewhat in the various regions. At the beginning of the session “with somnolence … homogeneous slow waves (T=30-40 sec) resembling the waves during drowsiness, spread over the hemispheres. Moreover, during somnolence, in some regions of the brain, potentials with a period of several minutes (T=2-4 min, A=0.5-0.8 mV), characteristic of changes in the level of wakefulness appeared. These phenomena were observed more frequently when a particularly deep hypnotic state was reached”[15].

The paper, which was published in “Nature” [16], did not appear in PubMed under the mentioned spelling of the author’s name but it was cited by Hughes’ et al. in their study of “Infraslow oscillations (<0.1 Hz) in thalamic nuclei”[3]. PubMed lists it under Aladjalova and is the only one that shows up with this spelling of the name. In the text Hughes et al. wrote:

“ISOs [Infraslow Oscillations] were first described in the animal brain in a study published over 50 years ago detailing gross electrophysiological recordings from the neocortex of rabbits (Aladjalova 1957). In this seminal study two main oscillations were described having periodicities of around 10 and 30-90 seconds, respectively (Figure 2A). These oscillations were present at distinct cortical sites, were not synchronized between hemispheres and, in the case of the faster rhythm, could group periods of more conventional EEG oscillations.”

Aladjalova’s paper in “Nature” also mentioned that two silver electrodes were implanted in the frontal and two in the occipital area. Differences in frequencies and amplitudes were noted not only between these brain areas when a variety of stimuli, as well as drugs, were administered but a non-polarizable microelectrode showed in a curarized animal differences between surface and the depth with slowest and highest amplitude in the superficial layers (I-IV) of the sensory cortex. During sleep, spindle bursts were seen riding on the
ascending slope and near the top of slow waves. Aladjalova concluded that, “Many other aspects of the infra-
slow rhythmical potential change also indicate that metabolic changes should be considered”. This is also
the current explanation of the phenomenon, and the phase relationship of sleep K complexes to infraslow
was confirmed in humans by Vanhatalo et al. in 2004
[17], who had been unaware of the Russian studies.

Modern studies

The modern era of ISA investigations in epilepsy pa-
tients can be dated to the seminal studies by Ikeda et
al. Initially the authors reported on 3 patients with sub-
dural implanted electrodes recorded on a Nihon Koh-
den (NK) EEG system that has a low frequency filter of
0.016 Hz [18]. Subsequently the patient series was ex-
panded to 6 intracranial recorded patients, 3 additional
ones had only scalp recordings [19]. “DC shifts” were
present in 85% of 89 seizures recorded from subdural
electrodes.

“[These] were localized to one or two electrodes at
which the conventional initial ictal EEG change was also
observed. They were closely accompanied by the elec-
trodecremental pattern in all patients except for one
in whom 1 Hz rhythmic activity was superimposed on
clear negative slow shifts. ... Scalp-recorded ictal slow
shifts were observed in 23% of all the recorded seizures
(60 seizures) among the three patients. They were, like
the subdural recorded ones, mainly surface-negative in
polarity, closely related to the electrodecremental pat-
tern and consistent in their location.”

In addition, it was noted that the shifts were mainly
observed in “clinically intense seizures, while no slow
shifts were observed in small seizures”. In the discussion
the low sensitivity of scalp recordings was explained by
the small electrical field observed in the intracranial re-
cords and that scalp-recordings require activation of at
least 6 cm² to be detectable. The authors also pointed
out that they had avoided studying patients with tem-
poral lobe seizures since these usually are characterized
by rhythmic onset of 4-7 Hz activity and ictal automa-
tisms, especially chewing motions would obscure shifts
even if they were present. Nevertheless, they felt that
reliable recordings might be obtained if movement ar-
tifact could be overcome. The authors concluded that,
“at least subdural-recorded ictal slow shifts are clini-
cally useful before epilepsy surgery to delineate more
specifically an epileptogenic area as well as to further
confirm the conventional initial ictal EEG change, and
the scalp-recorded slow shifts also have high specific-
ity although their low sensitivity is to be taken into ac-
count”.

I have discussed this paper in extenso, not only be-
cause it was the first modern study but because, with
one exception, the information has been replicated by
all subsequent authors. The term “DC shift”, which as
the authors admitted was not quite appropriate be-
cause AC amplifiers were used, has subsequently led
to some confusion and obscured the fundamental fact
that DC amplifiers are not needed to demonstrate the
phenomenon. This depends only on the low frequency
filter of a given EEG system. Since the low frequency
filter of most digital systems is at least 0.1 Hz and most
scalp-recorded shifts tend to last between 2 and 10 sec-
onds, it is obvious that they can be seen in digitally ac-
quired recordings with the simple technique of opening
the low filter to the maximum the system is certified for.
Since the filters are not sharp but show gradual de-
cay even slower activity is recorded, albeit at reduced
amplitudes and duration.

Gross et al. were the first to attempt to replicate
Ikeda’s initial intracranial observations but concluded
that “Our study failed to demonstrate any clinical ad-
vantage of intracranial telemetry recordings with a
high-pass filter of 0.01 Hz over conventional recordings
with regard to determining the timing and location of
seizure onset and propagation” [20]. The statement
was based on 47 seizures of 4 patients who had been
recorded with epidural and/or depth-electrodes made
of stainless steel. Very low frequency activity (VLFA)
was not observed in 29 seizures. It occurred with onset
of movement in one instance and in those where VLFA
was present, “the timing and location of VLFA were not
consistent with those of the conventional seizure onset
or propagation”.

A detailed study of the paper revealed that 30 of
the 47 seizures had occurred in one patient and the
electrode coverage was relatively limited. Three points,
therefore, need to be considered which may have had
a bearing on the negative conclusions. 1) The electrodes
used were of stainless steel, which has lower low fre-
cuency conductance than platinum. 2) None of the
seizures started with the electrodecremental pattern,
which tends to be most commonly associated with a
sudden baseline shift. 3) The problem of defining the
precise moment of seizure onset. This is demonstrated
by a study of Figures 1 and 3. Figure 1 shows that rhyth-
mic activity at seizure onset is distributed to varying
extent over at least 8 electrodes, while the slow shift is
limited to 3. Electrode contact 4 which appears to have the
highest amplitude rhythmic activity also had the
highest amplitude slow wave. But the authors consid-
ered, apparently based on DC literature, only the nega-
tive portion of the slow wave and neglected to men-
tion an earlier positive component which preceded the
rhythmic discharges. This problem is also highlighted
in Figure 3 B. Since, as will be shown later, ictal base-
line shifts frequently do not arise de novo, but can be
an increase of preexisting interictal and preictal infra-
slow activity, the precise onset of ictal ISA can at times
be difficult to ascertain. This is exemplified in Figure 3
B where preictal slow activity is clearly present in some
electrodes, including phase reversals. The practical im-
portance of this observation is that one needs at times
at least a 5 or 10 minute preictal segment to ascertain ictal baseline shifts rather than the commonly shown seconds.

Since the work had been carried out a prestigious site and the authors had referred to previous DC work, dealing with ictal shifts, it was subsequently tacitly assumed that AC amplifiers cannot be used for exploration of ISA, especially since Ikeda's 1999 publication overlapped that of Gross et al. and, therefore, was not referenced in their paper.

The need for DC amplifiers to demonstrate ictal onset baseline shifts was subsequently again emphasized by Vanhatalo et al. [21]. The introduction stated, “They [ictal baseline shifts] are, however, not detected by conventional clinical EEG techniques owing to high-pass (i.e. low-cut) filtering. Recording of these low frequencies requires a genuine DC-EEG amplifier and non-polarizable (i.e. Ag/AgCl) electrodes”. Seven patients with scalp recorded temporal lobe seizures were presented and “DC shifts were defined as a clear baseline deviation with a duration of longer than five seconds, and in close temporal proximity to ictal electrographic discharge”. Thirty-five seizures were recorded all of which were at some point associated with DC shifts, which allowed definitive lateralization even when the conventional EEG frequencies showed bilaterality. “Polarity was either positive or negative (referred to vertex) at the beginning but always negative during later bilateral seizure activity. ... it commenced a few seconds after the beginning of the high voltage spiking.” The amplitude ranged between 30 and 150 µV. The authors concluded that, “scalp-recorded DC-EEG might provide an invaluable tool in noninvasive determination of the site of seizure origin in these [mesial temporal lobe] patients”. They also recommended further prospective studies.

The latter was echoed in an editorial by Lagerlund and Gross, which accompanied the paper [22]. The headline raised the question: “DC-EEG recording – A paradigm shift in seizure localization?” The authors emphasized the importance of the paper but agreed that further studies are needed to “assess its reliability in more patients and to demonstrate how frequently it provides additional independent information in temporal lobe seizure patients whose scalp recorded ictal EEG gives unclear lateralization”. But since DC amplifiers are still not used in routine clinical long-term monitoring sessions, the suggestion could not be followed except for two studies from one institution [23, 24]. But before considering those, the emphasis on DC amplifiers for demonstrating infraslow may well have had a retarding influence on investigations of the frequency band between 0.016 and 0.5 Hz. It is especially regrettable that it is even contained in the most recent edition of “Niedermeyer’s Electroencephalography” [25]. This is curious because, although for instance, a DC system was used for data generation, the data were then high-pass filtered at 0.02 Hz [17]. Figure 3 of the review paper by Vanhatalo et al. on “Full-band EEG” [26], which is also reproduced in the textbook chapter, provides a typical example. It is essentially indistinguishable from our results as will be shown later.

In contrast to the negative observations by Gross et al. several authors have thereafter confirmed Ikeda's findings in patients implanted with subdural grid/strip and/or depth-electrodes. Bragin et al. noted that 75 seizures onsets in 19 patients with temporal lobe epilepsy when recorded with depth electrodes, had a low voltage fast activity onset, Ikeda's electrodecremental pattern. It was associated with an ictal onset slow wave in 89 per cent. An EEG system with a low frequency cutoff of 0.1 Hz was used and the wave lasted between 0.5 and 6 seconds (mean 2.3). The authors commented that with a low filter setting of 0.5 Hz the mentioned slow wave had previously been seen, but was disregarded as a delta wave. Hypersynchronous onset failed to show the initial slow shift and it was postulated that different generators are at work. Furthermore, since depth electrodes did not show phase reversals and maximum amplitude was in white matter or at the border of a deep temporal structure a possible non-neuronal mechanism was suggested [27].

Mader et al. reported on five patients with depth and grid/strip electrodes. The former were inserted stereotactically bilaterally from a burr hole in the occipital area and its most anterior contact reached the anterior inferior amygdala. The electrodes were lateral to the hippocampus and slightly inferior to its plane. The EEG system also had a 0.1 Hz lower frequency limit. An ictal shift was regarded as >1.5 seconds in duration and an amplitude of >100 µV. It was present in 84% of all seizures and the polarity was positive at its maximum. Since the slow wave was more discretely localized than the conventional EEG frequencies, although at times at neighboring electrodes rather than at the maximum as seen on conventional frequencies, the authors regarded it as a useful aid in determining seizure onset [28].

This study can be compared with that of Shih et al. who had likewise used the occipital approach for bilateral hippocampal depth-electrode insertion [29]. But radiographs showed that the left electrode, the side of ictal onset, had ended up in ventricular fluid rather than brain parenchyma. The anterior three contacts were located in the atrium of the inferior horn adjacent to white matter, while the subsequent five were in contact with the hippocampal formation. This allowed a determination of the extent infraslow ictal baseline shifts can be recorded under these circumstances. Although the data showed attenuation of the signal in all left sided contacts compared with the right, even in the interictal state, left sided seizure onset, accompanied by negative baseline shifts, was clearly present. The maximum amplitude of the left sided shift on a Pz referential montage was 1.9 mV at electrode contact 4. This contact also showed phase reversal on a bipolar montage and was located adjacent to the alveus of
Apart from Ikeda et al.’s original work and our studies there seem to be only two publications which deal with infraslow scalp recordings. Hughes et al. demonstrated the “initial ictal slow shift” in two patients with subdural grid electrodes and one with scalp recordings, on an EEG system with a low filter setting of 0.1 Hz [35]. The scalp recorded patient suffered from absence seizures with 3 per second spike-wave (SW) episodes. The intracranial findings were in conformity with previous reports. The scalp recording of the third patient showed in two seizures a brief positive slow wave prior to the first SW and a sustained positive shift, within 1-4 seconds after onset of the ictal pattern was seen in all. It was maximal in Fp1/2 and reached to F3/4. An asymmetry between the hemispheres also was observed. While occasionally a brief negative shift appeared, the end of the ictal pattern was always associated with a marked positive swing in the prefrontal/frontal areas lasting for up to five seconds. The authors commented that the differences from previous DC studies were that those had shown a negative displacement from the baseline and there were no preictal as well as postictal changes.

The other report by Miller et al. dealt with scalp recordings obtained on a DC system [24]. Twenty seizures from 11 patients were analyzed and the BESA software package which allows for “source montages” was used [36, 37]. Their benefit will be discussed in relation to our studies. A comparison of activity for <0.5 Hz, 0.5-2 Hz and >2 Hz was then carried out and an ictal onset shift was defined as lasting a minimum of 2 seconds. Infraslow signals occurred with all seizures and were frequently substantially higher than the conventional frequencies. In 5 of 8 patients who came to surgery infraslow activity correctly localized the ictal onset, while this was the case in only 3 of the 5 for conventional frequencies. All 5 patients had substantial improvement of seizures after surgery. Source montages combined with infraslow recordings were recommended because better localization can readily be achieved.

**Personal publications**

During the period of the late 1960s through the 1970s our experimental scientific work dealt with the problem of the relationship between the brain’s electrical activity and the behavior of cats when seizures were induced by chemical means. I am mentioning these studies because of their relevance to the plethora of high frequencies investigations which are currently being carried out. It was immediately apparent that no moment-moment correlation with behavior existed in the conventional frequency band for metrazol induced seizures. But since Buchwald et al. [38, 39] had shown that extreme high frequencies could be recorded from cerebral structures we decided to study in detail activity above 100 Hz. Through the courtesy of Mr. Albert
Grass, a 16 channel model 78 instrument was provided to us, which had a frequency range of 0.1-10,000 Hz, in addition to a DC channel. Since DC was being actively investigated by others at the time, and the amplifier required frequent resetting of the baseline, we stopped using it after a few trials. For the AC channels we compared the frequency range of 0.1-100 Hz and 30-3,000 Hz (filter settings were fixed by the system). A computer generated time code allowed comparison with the clinical behavior of the cat, which was recorded on film. A variety of cortical and deep structures were sampled with stereotactically implanted semi-micro depth-electrodes and several main findings emerged. Pre-ictal myoclonic jerks were accompanied by bursts of high frequency activity in the low brainstem and when these bursts fused into a continuum the tonic-clonic seizure ensued. This relationship was highly reproducible and unequivocal. It corresponded to the attenuation of the conventional frequencies which preceded rhythmic ictal activity and was similar to an “arousal response” resulting from reticular formation stimulation experiments. It was also shown that the high frequency discharges (frequencies varied between brain structures; in the thousands of Hz in the low brainstem, in the hundreds in cortex) were extremely localized. When the two contacts of the semi-microelectrode (spaced 0.5 mm apart) where led separately to a screw in the frontal bone of the cat, different wave forms could at times be seen. In addition, slow shifts were observed at times in close association with the high frequency discharges in the low brainstem at seizure onset, but we ignored them at the time as artifact from cable movement. In retrospect it is, however, clear that they were genuine and Figure 1 of a recent summary of the findings shows the phenomenon [40]. An earlier summary, but without reference to infraslow, was published in the German literature [41]. Since the methodology was cumbersome the study of extreme high frequency activity was not widely taken up by other laboratories, but digital technology led to a resurgence of interest. In a one minute window out of pre-existing infraslow activity a higher amplitude rhythm of slightly shorter than 0.1 Hz appeared approximately seven seconds prior to HV and persisted during it. The record was not contaminated by movement artifact and corresponded to the time when HV was considered to be performed. The phenomenon is shown in Figure 3 of the publication on “Subdelta Activity” [47]. For technical reasons we were unable to repeat the experiment on a subsequent occasion and prominent colleagues with whom I discussed the phenomenon regarded it as artifact because the readiness potential and EEG event synchronization/desynchronization, do not extend over such a relatively long time period. To the best of my knowledge the question of artifact versus genuine phenomenon has so far not been investigated by other laboratories. Yet an indirect potential validation of the observation appeared in a 2008 publication based on fMRI. Changes in prefrontal and parietal cortex were noted up to ten seconds prior to a voluntary motor act [48]. The authors were unaware of our publication and did not refer to it. Since the finding is potentially of considerable psychophysiological interest, I have referred to it here in the hope that other investigators may pursue this subject with the 10-20 system of electrode placement including the cerebellar locations.

Having established that the existence of subdelta (0.1-0.9 Hz) and even slower frequencies can be seen by commercial EEG/MEG systems without DC amplifiers, we subsequently investigated archived routine EEG data from 5 different laboratories. Scalp as well as intracranial recordings were studied and infraslow activity was present in all instances. With Dr. Wong’s intracranial recordings we could also establish the relationship of high frequency gamma activity to ictal infraslow changes. The overall purpose of this publication was to acquaint the clinical EEG community with the vast amount of information which can be obtained from archived recordings when optimally evaluated [49].
The study was then extended to a comparison of absence and partial seizures [50]. The absence findings largely agreed with those of Hughes et al.’s patient but the partial seizure patients showed a potential clinically important phenomenon. While in some instances ISA was restricted to one temporal lobe with only reduced amplitude in the contralateral one, in others an additional more wide-spread, especially bi-frontal, element was seen similar to that of absence seizures. It was suggested that in some patients with partial seizures a more generalized seizure tendency may, in addition, be present.

These investigations had also pointed to the problem of precise assessment of seizure onset, which led to a subsequent publication [51]. It was apparent that depending on filter settings different results were obtained. The most reliable determination appeared to be when infraslow shifts coincided with high frequency activity and ictal changes in the conventional frequency band. In scalp recordings high frequency activity is, however, not necessarily trustworthy because of inevitable admixture of muscle activity. Since infraslow and high frequency activity have a very restricted electrical field they are likely to be useful in distinguishing locally generated from conducted events even in the interictal state.

For most of these studies EEG systems with a low frequency filter of 0.1 Hz had been available, except for Dr. McIntyre’s routine scalp recordings which were obtained on XLTEK system. But Dr. Modur’s data, obtained on a NK system, subsequently allowed us to duplicate Ikeda et al.’s original findings on intracranial recorded seizures [52]. In as much as longer preictal data were at times available, we noted that the ictal baseline shifts usually did not arise suddenly but consisted of a gradual buildup of pre-existing infraslow activity, albeit not necessarily in the electrodes that had shown major ictal onset activity in the conventional frequency band. The most dramatic amplitude increase occurred at the transition from partial to tonic-clonic seizures when negative wave forms of several mV were reached. In addition, it was noted that in these instances ISA persisted unabated through the postictal EEG attenuation phase and beyond, for about 2 minutes. It could then be followed in some channels by the 0.1 Hz rhythm which was mentioned in the discussion of the hippocampal seizures, although only neocortical seizures were involved in these patients. Subsequent investigations showed that this rhythm could occur in any cortical area. It could last up to one half hour in the interictal state and was also seen in the scalp recording of a normal control person.

In 2012 the American Clinical Neurophysiology Society held a symposium on cerebral electromagnetic activity [53]. Rampp and Stefan presented intracranial data obtained from an EEG system with a LF of 0.1 Hz and emphasized that even this limited frequency range validated Ikeda et al.’s conclusions [54]. Constantino and Rodin provided a preliminary report on interictal scalp and intracranial data from continuous 24 hour recordings on 5 patients. Epochs of several minutes, up to one and a half hours, of spontaneous marked interictal increase in ISA, at times reaching ictal amplitudes, were noted although not necessarily in the area of ictal onset. Shorter epochs could also be detected in scalp recordings, but the latter showed considerably more movement artifact, which made interpretation difficult [55]. Modur et al. then presented the above discussed information on the relationship of high frequency activity to ictal baseline shifts [32]. Ictal MEG data were presented by Bowyer et al. from 12 patients who were recorded on a DC system. It was noted that in the minutes preceding the seizure “large ISA waveforms were detected, signaling the onset of the seizure” [56]. When the Constantino-Rodin data were prepared for publication it was noted that 2 of the 5 patients had marked diminution of amplitudes and somewhat faster ISA than the other 3. Since we did not know the cause at the time, we simply reported the fact. After further studies, we became aware that these 2 patients had not been recorded on the 128 channel XLTEK system with a low frequency filter of 0.05 Hz as was usually the case, but on a 40 channel system which had a low frequency filter of 0.1 Hz. This explained the finding.

During the following year further 24 hour data were collected from consecutive patients. The findings of 12 patients with intracranial recordings and 3 additional ones with scalp records were presented. The previously seen waxing and waning ISA interictal increase was confirmed and it should be emphasized that in contrast to Ren et al.’s observations [30] was not tied to seizure onset, but occurred in an apparently random manner especially during nocturnal sleep. The difference in ISA amplitude between the waking and sleep state, reported in the earlier publication, was also confirmed. It was increased when the patients were awake and decreased in nocturnal sleep. Although this seems counterintuitive in view of increased slow activity in the conventional frequencies during sleep, it might not be unexpected when one considers that the same phenomenon was seen in the cat experiments with high frequency recordings. In regard to scalp recordings, 2 patients showed a regular buildup of rhythmic ISA during the spindle-K complex stages of sleep, lasting 20 and 30 minutes respectively. In both instances it was terminated by a body movement [57].

Conclusions, additional unpublished observations and recommendations

From the above information it is apparent that ISA in the peri-ictal and interictal state can provide additional useful clinical information about the “epileptogenic zone.” Furthermore, there is beginning evidence for informational content in the interictal state, above
Figure 1: Relationship of interictal spikes in a routine clinical EEG to ISA. Top portion shows on topographic display 25 spikes averaged from the left midtemporal area. The inserted map shows a radial orientation. Inspection of spike latencies indicates onset in the posterior temporal area which proceeds anteriorly. The bottom portion shows 10 minutes of the drowsy/sleep state, on a temporal source montage, filtered for ISA between 0.01-0.1 Hz. The major activity, around 0.04 Hz (FFT spectrum on the right), is in the left temporal polar and frontal areas. The number 1 on top of the tracings indicates individual spikes used in the average. Their preponderance on the ascending phase and on top of the temporal polar wave is coincidental and no phase relationship existed in other samples. Vertical lines denote 10 second intervals. The first comment on the bottom is truncated for Eyes Closed.
Figure 2: Example of electrodecremental seizure onset and baseline shifts. The patient was asleep and there was no movement artifact. The top portion shows a 55 second partial seizure on filter settings 1-70 Hz. It is initiated by a relatively wide-spread 1 second discharge, which might represent momentary arousal. It is followed by attenuation of electrical activity and subsequent rhythmic frequencies. Lateralization of seizure onset cannot be reliably determined.

The bottom portion shows the same data but with the low filter changed to 0.01 Hz. Several ictal onset baseline shifts are apparent. They start after the initial discharge and continue throughout the seizure into the postictal phase, with varying polarity in different channels. The shifts involve at onset both hemispheres and a definitive lateralization is likewise not possible. Vertical lines delineate 1 second intervals.
and beyond what is seen in the conventional frequency band, but its clinical relevance requires further study.

The peri-ictal ISA investigations not only add to our information about electrophysiological processes, but since they are non-neuronal in nature, they may provide information on the metabolic processes underlying the electrical phenomena. Among those, the ones associated with glia functions are probably the most important. In this connection animal work has shown that in metrazol kindling experiments astrocytic swelling and compression of capillaries, preceded neuronal changes at a time when the animal (rat) showed only whisker twitching accompanied by the rat’s equivalent of SW discharges [58]. Early glia changes were also reported in measles infected mice prior to seizures [59]. Furthermore, it is important to point out that astrocyte oscillations have been reported for a frequency range of 0.003-0.1 Hz [3].

In as much as only patients with “partial seizures” are evaluated with intracranial recordings it has become apparent that the current distinction between “partial” and “generalized” is not as sharp as the names imply. As the published figures show, ictal onset ISA shifts are sometimes, in spite of their limited electrical field, rather wide-spread and can be seen in a regional and multi-lobar distribution, suggesting a considerably wider process than a discrete focal one. This may well have implications for the post-surgical prognosis. The other extreme, namely absence of ictal onset shifts, could also be interpreted not simply as a failure of the method [20], but that the areas sampled by the available intracranial electrodes only show conducted activity rather than what was locally generated. This is best seen when foramen ovale electrodes are added to the 10-20 system. These can not only show ictal onset, that is not seen in the conventional montage even when inferior temporal electrodes are added, but also ictal onset shifts as first reported by Wieser et al. [60] and confirmed by us [51].

Since the placement of intracranial electrodes is dependent on scalp recordings, at times supplemented by MEG, the optimal evaluation of these data is crucial. But assessment of ISA in interictal and peri-ictal recordings exists currently only in isolated case reports and systematic work-up of the data, correlated with long-term surgical results, still needs to be performed. In as much as it is well known that seizures may recur several years after surgery, 5-10 year follow-up studies, correlated with existing archived ISA data, should be performed.

Figure 2a: shows the 30 second ictal onset baseline shift prior to rhythmic activity on a topographic display. Initial negativity is most marked in the left anterior temporal and frontopolar areas. The inserted map shows the frontopolar distribution at the time of the earliest F7/Fp1 peak. In addition there is a negative event at A2, suggesting independent right sided involvement at seizure onset. Past experience suggests that patients with a complex picture of this type tend to have a poorer surgical prognosis.
The following set of figures, which have not been previously published, deals exclusively with surface recordings obtained from four different laboratories. The first two confirm that ISA can be extracted from routine recordings and show that ictal as well as interictal activity can have localizing value. **Figure 1** demonstrates the relationship between 25 averaged left mid-temporal spikes obtained during a routine clinical recording on an XLTEK system in Dr. McIntyre’s laboratory (Torrance CA). The top portion demonstrates that, in spite of the mid-temporal peak with radial orientation (map insert), the spikes appear earliest in the posterior temporal region and subsequently move anteriorly. Mirror activity with markedly diminished amplitudes is pre-

**Figure 3:** presents a co-registration of MEG with EEG for delta activity and ISA during sedated sleep. The top portion shows the MEG on a 10 minute window for delta and the bottom portion for EEG with the power spectrum inserted. In both instances maximum power is in the left temporal polar area and the data are artifact free.
Figure 3a: shows the same data for a filter setting of 0.01-0.1 Hz, with MEG again on top. Similar wave forms are seen for the two modalities. Although the left temporal area shows again maximal power it is highest in the baso-temporal, rather than temporopolar region, in the MEG, while the opposite is the case for the EEG. The phase reversals within the left temporal regions are also more marked in the MEG. The early higher amplitude transient in the EEG, which is not seen in the MEG, may represent a K-complex. Vertical lines delineate 10 second intervals. Please note that, for both frequency ranges, amplifications of the wave forms are 5 times higher for the MEG (200 nAm vs. 1μAm).

The file for Figure 2 was sent by Dr. Hasegawa (Kalamazoo MI) for a second opinion. The figure shows on top a one minute epoch of a partial seizure on a filter setting of 1-70 Hz. The tracings are artifact free and the seizure is initiated by a one second higher amplitude

sent on the right. The bottom portion shows 10 minutes ISA during drowsiness/sleep on a source montage and the corresponding power spectrum. Maximum activity is in the left frontal and temporal polar region.
Figure 4. Twenty minute ISA during a P300 discrimination task obtained on an ANT DC system on a Laplacian (CSD) montage in a normal person. In order to establish a baseline and allow slower wave forms to emerge the data are filtered between 0.0002-0.01 Hz. 128 channels were recorded. BESA coordinates were only available for the corresponding 10-10 international montage and the result is shown in the top portion. Since the picture is rather condensed, the same data are shown on an expanded 10-20 montage with some inferior temporal channels added. It is apparent that in some channels the wave forms do not return to the baseline within this 20 minute limit. While the 10-10 montage shows maximum negativity at PO7 it is maximal at P7 for the 10-20 montage. The marker, for amplitude determination, is placed at the peak of the highest slow wave. Although a somewhat complex pattern can be discerned, a statement about the clinical validity of the data requires further study. The picture is only shown to demonstrate what is seen with DC amplifiers and a relatively long time window.
discharge followed by attenuation of activity and subsequent rhythmic discharges. A determination of lateralization is difficult. In the bottom section the low filter was changed to 0.01 Hz and ictal onset shifts during the electrodecremental phase of the seizure are immediately apparent. But since they are rather widespread and of different polarities, lateralization is still difficult. Figure 2a demonstrates the 30 second shift onset on a topographic display and it seems that there are two separate distributions. One involves the left anterior quadrant, but this leaves the A2 activity unexplained. It suggests independent involvement that should probably be taken into account if intracranial electrodes were to be placed.

These figures were shown to emphasize that, especially during drowsiness and sleep, adequate scalp ISA assessment is feasible and that even partial seizures can have at onset quite complex configurations. Figure 3 demonstrates ISA relationships between MEG and EEG. In Dr. Funke’s laboratory at our University a Neuromag/Eleka system with 256 gradiometer and 128 magnetometer sensors was used; 60 EEG channels were co-registered. In view of the large number of channels the data are shown on a BESA source montage with inserts for frequency spectra. The figure shows in the top portion the MEG for a 10 minute epoch and the co-registered EEG on the bottom for delta activity. The wave forms as well as power values are shown and the data are artifact free. Figure 3a shows the corresponding ISA values in the same layout. Please note that MEG amplitudes and corresponding power values are lower for MEG in the raw data as well as the frequency spectra. Good correspondence regardless of frequencies studied can be noted. The early higher amplitude transient in the EEG, which is not seen in the MEG, may represent a K complex. The MRI was negative, and interictal spikes were seen on MEG in the area of left insular cortex as well as left inferior and middle temporal electrodes added. Both data sets are on a Laplacian (CSD) montage with filter settings of 0.0002-0.01 Hz. This is the lowest filter provided by BESA and at 0.0001 Hz the data revert to default (0.5 Hz). Removing the LF altogether led to channel offsets. The figure suggests that what we record as ISA activity may ride in part on still slower “swells,” which extend beyond 20 minutes. This would validate some of Aladjahova’s work, although technical problems such as possible amplifier drift, electrode polarization, skin potential contamination and other factors, will have to be taken into consideration in the interpretation of the results. The figure is only shown because to date no such picture seems to exist in the modern literature and to emphasize the need for ISA study also of <0.01 Hz. Theoretically MEG might lend itself well to these investigations because contamination by electrodes and skin potentials is absent. But MEG has different technical problems most of which relate to amplifier performance at extremely long wave durations and environmental noise can become a significant contaminant. Nevertheless it should not deter attempts to determine what the longest wave forms are that can be reliably recorded with current technology.

In conclusion, it is apparent that since ISA, including what is seen with DC amplifiers, is a highly promising field for the study of normal as well as pathological cerebral electromagnetic activity, it should be actively pursued with the most up to date hardware as well as signal analysis techniques.

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References:
3. Hughes SW, Lőrincz ML, Reinhalt Parri H, Crucelli V. Infraslow (<0.1Hz) oscillations in thalamic relay nuclei: basic mechanisms and significance to health and disease states. Prog Brain Res 2011; 193C: 145-162
6. O’Leary JL, Goldring S. Slow cortical potentials: their origin and contribution to seizure discharge. Epilepsia 1959; 60: 561-574
29. Shih JJ, Rodin E, Gupta V, Wharen E. Signal characteristics of intraventricular electrodes recordings in human epilepsy. CLin EEG Neurosci 2012; 43: 105-111
33. Modur PN. High frequency oscillations and infraslow activity in epilepsy. Ann Indian Acad Neurol 2014; 17(Suppl 1): S91-S106
47. Rodin E, Funke M. Cerebral electromagnetic activity in the subdelta range. J Clin Neurophysiol 2006; 23: 238-244
50. Rodin E, Constantino T, van Orman C, House P. EEG infraslow activity in
58. Rodin E, Rodin M, Lavine L. Electroclinical and ultrastructural changes associated with subconvulsant doses of pentylenetetrazol. Exp Neurol 1979; 64: 386-400

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