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Are the EEGs mainly rhythmic?

Assessment of periodicity in wide-band time series.

Test of a method

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Abbreviations: CL - confidence level; EEG - electroencephalogram, sensu latu, including intracranial and semimicroelectrode recordings; FFT - fast Fourier transform; FM - frequency modulation; LFP - local field potential; PSA - period specific average; PS - phase shuffled randomization; RS - random start randomization

Running title: Periodicity in wide-band time series

Summary To test the hypotheses that (i) electroencephalograms (EEGs) are largely made up of oscillations at many frequencies and (ii) that the peaks in the power spectra represent oscillations, we applied a new method, called the Period Specific Average (PSA) to a wide sample of EEGs. Both hypotheses can be rejected.

Although the principal peaks in the two spectra agree most of the time, quite often a peak in the power spectrum accompanies no periodicity peak and some periodicity peaks have no power spectral peak. The Fourier spectrum is not a reliable indication of rhythms. EEG samples from patients during waking, sleeping and seizure states, and volunteer healthy subjects doing cognitive tasks quite often show no significant rhythms, on an arbitrary, common sense definition. When clear rhythms are seen, they involve one or two, rarely up to four or five simultaneous non-harmonically related frequencies. Rhythms are special cases; most of the power spectrum most of the time is nonrhythmic. “Good” rhythms usually have quite narrow peaks, with frequency modulation of <5%, strengths of >2.5 up to >10 times the expectation from chance, and they often show fine structure by being quite local and brief. Most rhythms are quasisinusoidal but others are sharp-cornered recurrent events with <50% duty cycle. In the face of wide variability, we do not report any systematic differences in periodicity among EEGs from different parts of the brain or different brain states or species; it will take many more exemplars of each state, species or brain part to establish characteristic features.

The Period Specific Average method may be the best so far proposed to demonstrate and quantify periodicity in wide-band time series with noise, but it has serious limitations. Discussion leads to the conclusion that it is time for a new paradigm or metaphor for brain waves

Key words: power spectrum, theta wave, alpha wave, intracranial EEG, epilepsy, cognitive task

The most information-rich measures of the living, working brain are derivatives of its electrical activity, recorded as extracellular, wide-band local field potentials (LFP) from semi-microelectrodes at multiple sites, with millisecond and millimeter resolution. With respect to the potential information content, LFPs arguably exceed even the recordings of spikes from single units with similar numbers of electrodes.

Wide-band LFPs permit many kinds of analysis. The state of the art with recordings from both single units and compound vector sums of small populations, from many loci as close together as 0.1 mm is still advancing in respect to dynamic range of frequency and amplitude and in microstructure in

space and time. The battery of tools for extracting information from such recordings includes power, phase and coherence spectra, (simple, partial and multiple), current sources and sinks, magnetic moments, wavelets, mutual information, nonlinear higher order moments like the bispectrum and bicoherence, chaos and dimensional estimates, independent components, and each of these as a function of geographic position and of brain state, task or mood.

The field is characterized by profound differences between the features of the EEG mentioned or noticed by different authors (Buzsaki and Traub 1997, Başar 1998, Barlow 1993, Buzsaki and Vanderwolf 1985, Lopes da Silva et al. 1986, Niedermeyer and Lopes da Silva 1982). There is little agreement even on the first order description of the *ongoing* background electro-encephalogram (EEG), whether seen from the scalp or intracranially, as well as the stimulus-caused *evoked potential*, or the situation-dependent, relatively endogenous, *event-related potential* of cortical and subcortical assemblages of cells (Başar 1988b, Lopes da Silva et al. 1986, Harris et al. 2002, Makeig et al. 1999, 2002).

Classifying EEG states, episodes and responses is usually done in terms of the power spectrum (by the Fast Fourier Transform or FFT), based on the relative amplitudes of several frequency bands. Sometimes one of the other measures just listed is also used. It is the working assumption of the present study that this list is seriously incomplete and that we need new descriptors to uncover meaningful departures from stochastic temporal and spatial structure.

Current research is often aimed at characterizing the dynamics of synchronization of oscillations, explicitly or implicitly treating each peak in the power spectrum as an oscillation. In principle, Fourier components appear not only from genuinely oscillatory processes but also from transient and non-rhythmic time series, such as white noise. The power spectrum is inherently unreliable as an indication of rhythmic processes.

Working models of brain activity - the informal and unformulated mental models that determine experimental approaches - may be influenced, unrealistically, by the convenience of linear spectral analysis, like the FFT. The quite different working model and bias of the present authors are made explicit in the Discussion. The main assumption in our view is that a fraction of the electrical activity is truly random, a fraction is structured but in non-simple ways - perhaps analogous to language - and a fraction in simple ways such as rhythms. Here we address the last category and aim to assess the periodic components, of whatever form: sinusoidal or non-sinusoidal .

We have elsewhere addressed the questions how much of the wide-band activity is spatially and temporally stochastic, concluding that a significant and highly labile amount of linear coherence and of

nonlinear bicoherence bespeaks non-randomness, cooperativity and local structure in time and space (Bullock and McClune, 1989; Bullock et al. 1992, 1995a, b, 1998a, b).

We here address one seemingly simple aspect of descriptive natural history: Are rhythms prominent in the local field potential or in the scalp recorded EEG in samples not selected for waveform but in a variety of states? The aims are, first, to answer the question: how can we unambiguously detect rhythms, even relatively weak ones, of any waveform, at any frequency between arbitrarily chosen limits of one and 50 Hz, in the presence of relatively strong, wide-band, seemingly stochastic activity? We test a method probably not used before upon brain potentials. It was introduced for quantifying the periodicity in circadian data (Enright, 1965, 1990; Bullock et al., 1998a) and considered the method of choice in careful comparisons of previous ones (Schuster, 1898; Smith and Odell, 1976; Kendall, 1946; Binkley et al., 1973; Refinetti, 1993). More recent methods appear less suitable but have not been quantitatively compared with Enright's (Gilbert and Joosting, 1994; Mehta and Bergman, 1995; Başar et al. 1999). For the second aim, we report analyses on a wide variety of samples of recorded ongoing brain activity, using the proposed method.

What is a rhythm? We use oscillation, periodicity and rhythm as equivalent in our context. (For other purposes, of course, oscillation may refer to simpler, sinusoidal or quasisinusoidal series and rhythm will include syncopation and complex structure - e.g. solos on small drums.). The essence of rhythm is a reasonably regular repetition and the main components of a definition are how regular and for how long. These two depend on the context (e.g. music, business cycles, biological clocks) and are perforce arbitrary. We assume that the context of alternating swings of brain potentials is quite tolerant of fluctuations, so that the coefficient of variation ($CV = \text{standard deviation of periods} / \text{mean period}$) can, in some situations, be as much as 0.1-0.2 ($SD \pm 10$ to 20% of the mean) and we would still speak of a crude oscillation or a rough rhythm. A working definition requires a reasonable number of cycles of this moderately restricted regularity - for example, we propose, on the order of ten cycles. These are subjective values, representing our impression of currently acceptable usage. They will guide the search methods reported below.

Another difficult boundary is that between a single rhythm and a sliding or regularly modulated rhythm. A step or ramped change from one to another *maintained* frequency signifies two rhythms. A small amplitude FM or drift (tremulo or accelerando) might be thought of as one rhythm. Larger modulations, regular or episodic, such as sliding up or down the scale (glissando) are perhaps better spoken of with qualifying adjectives as something other than *an* oscillation. We have arbitrarily chosen for analysis, epochs usually of four or five seconds. This means that, if an oscillator drifts or modulates

more than $\pm 20\%$ of its mean within this epoch, it will be considered as borderline nonrhythmic, at least not *a single* rhythm. Thus fluctuations from 8 to 12 Hz within 5 s will be considered to be a rhythm. The definition in practical terms, based on the chosen measurement, is given below, under Methods.

A major underlying issue is methodological. Is the widely used power spectrum, based on the Fourier transform and its assumptions, the most appropriate way to describe a time series that may include transients which may be repeated irregularly, or rhythmic waveforms far from sinusoidal, for example with corners or highly skewed around the voltage axis or asymmetrical around the time axis? Each of these classes of waveforms is familiar in the EEG, more especially in intracranial recordings that integrate over much smaller volumes of brain tissue than scalp recordings.

The hypotheses under test in this study are two. (i) EEGs are generally and largely comprised of oscillations at many frequencies. (ii) Peaks in the FFT power spectrum represent those oscillations that are strongest. The findings we report exclude both hypotheses as general statements, based on a large sample of EEGs, including intracranial macroelectrode and scalp recordings from human subjects and macro- as well as semimicroelectrode recordings in rabbits. Sleep, wakefulness and seizure states are represented, by hospitalized epileptic patients living in the ward, and a few cognitive task states are represented by volunteer, healthy subjects. Recordings are included from the scalp and with subdural and depth electrodes from isocortex, hippocampus and transitional regions. Particularly important are the discrepancies between PSA and power spectrum peaks. The commonest of these are power peaks where there is in fact no recognizable rhythm.

EXPERIMENTAL PROCEDURES

A. Sources of data

The study is based mainly on recorded EEGs from scalp, subdural and depth electrodes from human volunteer subjects and epilepsy patients. Data from the latter group were routine hospital recordings in the course of diagnosis and preoperative examination, kindly provided, without identification, by their physicians (see Acknowledgments). Data from volunteer normal subjects were taken, with formal, informed consent, in the course of other studies and kindly provided by the Principal Investigators (see Acknowledgments), again without identification.

Intracranial EEGs of human epileptic patients represent sleep, wakefulness and seizure states. Five of these were patients of Dr. V.I. Iragui at the UCSD hospital. PSA analysis has been done on several of the ten channels available at each of eight brain regions, for up to seven 5 s epochs within the first 35 s

of our sample. Similar data from three patients of Drs. S.S. Spencer and B. Duckrow at New Haven Hospital include bilateral depth probes in temporal lobe, amygdala, hippocampus and more posterior sites. Intracranial data come also from three patients of Dr. A. von Stein of Zurich, then in Vienna. Scalp data come from two normal volunteer subjects of studies by Dr. J. Pineda in La Jolla and one subject of Dr. C.S. Herrmann in Leipzig. The only selective factor has been the suitability of the data set for our analysis.

Intracranial, epidural recordings from implanted rabbits were taken in this laboratory.

All the data were taken under protocols approved by the institutional review boards for human and for animal subjects.

Simulated EEG data were generated by a special program (“Datgen”, written by M.C.McC. and available upon request) so that the analysis program could be tested on known signals, including mixtures of various waveforms and regularity with or without “noise” of known pass-band and amplitude, with either a fixed or random seed.

B. Methods of analysis

The novelty of the study is the form of analysis, embodied in a new program based on that of Enright (1965, 1990), which was designed for accurate estimation of the period of circadian rhythms. His program was broadened in the range of periods examined from a fraction of an octave around 24 hours to nearly six octaves between periods of 20 and 1,000 ms. The new program (“Periodity”, written by M.C.McC. and available upon request) cuts the time series into segments of each possible period within this range, at a chosen resolution or spacing of the periods which is a constant proportion, usually 0.69% (100 periods per octave; thus: 1, 1.007, 1.014, ... 49.654, 50.0 Hz), giving 564 different periods. The segments at each period are averaged so that any signal of that period in the data will sum, while all other nonharmonic periods and aperiodic activity will tend to shrink. These averages are then scored by a single number for each period; we have usually used the variance (standard deviation squared). The variances are plotted as ratios of the scores based on EEG data divided by scores of stochastic control data so that an ordinate value of 1.0 means the data has the same score as the average of 200 of the randomized (“shuffled”) controls. The abscissa is the reciprocal of the periods expressed as Hertz, spaced logarithmically. This PSA or period spectrum is superimposed on the FFT “power” spectrum, usually shown as the amplitude spectrum (Fig. 1)

[Figure 1 about here]

More specifically, for each frequency, an *ensemble average* is made by summing phase-locked

epochs that are the length of the period. The *phase locking* is accomplished by starting each epoch at the data sample closest to a multiple of the period. This average is *windowed* by the selected windowing function (rectangular, Hamming, Hanning, Welsh, or tapered cosine; usually the first named) and then *scored* by the selected scoring function (standard deviation, variance, sine, or min/max; usually the variance). This score is then *normalized* to make curves comparable which differed in the recording gain or length of record or in power spectrum. This was done by making a ratio of the observed PSA to that expected in a no-rhythm control. This control is the mean of many randomized PSA measurements for each period. We do not use white noise as a control because the power spectrum has a strong effect on the PSA, especially in the low frequencies where EEG data have most of their power and short samples show widely varying power spectra. We use, instead, the original EEG time series after destroying any rhythms by either of two methods of randomizing - which prove to give almost identical results.

Random start randomization. (RS) For each frequency, an ensemble average is made by summing non-phase-locked epochs that are the length of the period. Each epoch starts at a random place in the time series.

Phase shuffled randomization. (PS) This method is the same as the calculation of the PSA, except that each epoch is phase shuffled before being added to the average. Phase shuffling entails the following operations: (a) Measure the RMS value of the epoch. (b) Pad the epoch with zeros to a power-of-two number of points. (c) Perform an FFT on the padded data. (d) Shuffle the phases of the spectrum. (e) Perform an inverse FFT. (f) Normalize the data to the measured RMS (because the points padded to zero reduced the amplitude of the phase shuffled time series). Further details are given in the Appendix, together with an evaluation of the method and its limitations.

The use of variance and linear scaling for the PSA displays, amplitude for the “power” spectra and no smoothing optimized the visual signal to noise discrimination since confidence level was not the only criterion for evaluating peaks.

This additive procedure allows the signal to have any shape or duration (within the Nyquist limits of the digitization frequency of the time series) (Fig. 2).

[Figure 2 about here]

The wide-band spectral plot permits several rhythms of different frequencies to be visualized. “Periodicity” also provides for instant inspection of the average waveforms for each period, to reveal the form of any signal that survives the averaging - which is useful to check whether the selected period shows just one cycle or two, three or more cycles of the signal and is therefore twice or more the fundamental period of the signal. Also provided is instant access to the individual segments, in sequence,

in a raster or waterfall display, which can show whether the signal appears in every second or third segment, as when the segments are one half, one third or a fraction of the fundamental (Fig. 1). We have usually used rectangular windowing in the segmentation of the data but tests with Hamming, Hanning, Welsh and Tapered Cosine windowing did not substantially change the results.

The spectral range from 1-50 Hz means that fewer segments of the longer periods are averaged and variance of a stochastic control time series increases with the length of the period.

In order to de-trend the long period up-sweep of the raw PSA curve when the ordinate is variance, we divide those values by the means of 200 phase-shuffled (or random start, see below) PSAs for each period and thus plot the ratio of raw PSA to the expectations from randomized controls. This flattens the low frequency “up-sweep” and therefore reduces the amplitude of the subharmonic peaks, which in the raw PSA all reach the same height as the fundamental. Plotting the ratio also normalizes the ordinate units so that records having different EEG amplitudes, spectra and length can be compared.

C. Confidence levels

By calculating many random-phase PSAs we get a distribution of values for each period. By sorting each of these distributions we generate the Cumulative Distribution Function for each period; actually its inverse. This allows us to determine any percentage of confidence level by reading the value at that percentage through the list. For example, to find the 95% confidence level, we read the value located 95% of the way through the list. In the textbook by Efron and Tibshirani (1993) this is called the percentage method. We have usually looked for peaks at the 99% CL, but high-lighted also the 95% points. When we have 564 points on the x-axis (periods or reciprocal frequencies), white noise with no rhythms will cross these two thresholds on average ca. 6 and 30 times, respectively, but rarely rise more than 2.5 times the control expectation in amplitude.

Additional criteria that help to make the case for a “good”, i.e. plausible rhythm are needed. Because the problem is detecting weak signals in noise (Fig. 3),

[Figure 3 about here]

we cannot usually count cycles to compare with the arbitrary duration requirement in the definition of a good rhythm. The allowable frequency wobble, drift or FM (Fig. 4)

[Figure 4 about here]

discussed above in the definition of rhythms has not turned out to present a serious problem since in our samples of EEGs, we have rarely seen a cluster of elevated points extending over more than $\pm 10\%$ of the mean period (Fig. 5).

[Figure 5 about here]

Candidates for “good” rhythms usually show two or three 99% points close together, reaching a Y-axis height >2.5 times the expectation by chance, and are most convincing when repeatable in the next short sample of data.

False negatives clearly occur when some peaks that do not reach even the 95% CL look like common-sense weak rhythms.

Another source of false negatives depends on the frequency resolution and length of data sample. The method segments the data at discrete periods; the lowest resolution and most often used in this study places these 0.7% apart (100 per octave; 564 segmenting frequencies between one and fifty Hz) and the highest we have used is 0.2% (347 per octave, 1956 points on the abscissa). Unless a periodic signal in the data happens to have a period precisely equal to one of these segmenting periods, a raster or waterfall display of every period, one above the other, will show the signal obliquely drifting across the display (Fig. 6)

[Figure 6 about here]

and the average waveform will be smaller than it would be for perfect agreement between segmenting and signal periods. The severity of this loss depends on the percentage discrepancy (rate of drift, beat frequency) and the length of the data set (amount of drift). Longer time series will at first reduce the average more and more but still longer data will then increase the average, as the drift cycles through more than one beat period. Therefore the amplitude of a peak in the PSA cannot be read as a true measure of the strength of a rhythm unless that peak is examined by the raster option to display all the segments, and found not to drift by a significant fraction of its period. Subharmonic peaks are each affected differently and can suffer less or more attenuation than the fundamental. Signals of the same strength at different frequencies will more often than not have different amplitudes because the discrepancies are different. We have compromised on the resolution and used, principally short data samples to reduce the effect. Although the method permits quantitative statements about the strength of periodicities, this complication makes comparison of strengths impractical unless carefully done with the raster control. We principally confine ourselves to the judgment call: whether a given data stream shows a “good” rhythm or not, where normalized peak height less than 2.5 times the expectation from chance is a suspect zone undeserving of the adjective “good”.

False positives must happen sometimes in the case of high amplitude events that satisfy the CL height criterion but only for a single point, with no neighbor points even half as high. The single point peak is quite unlikely to be a true rhythm because artificial data with pure tones, in our usual range of

data length (ca. 1,000 data points), show three or more points within half the height. Single point peaks are more common in some data sets. They can be of any height, reaching values far above any “good” rhythm. We do not have an explanation that surely applies to all such cases, but believe that they are at least partly due to chance - single instances of high variance in the specific period average waveform (or chance low values in the mean of shuffled controls). They usually lack any peaks at subharmonic frequencies. They can occur in samples of pure “noise” data, from computer generated random numbers, without evidence of rhythms. They are usually not repeatable in the next short epoch. We consider single point peaks in data samples of 1000 points or less very dubious as rhythms.

RESULTS

The principal result of plotting periodicity as PSAs from a diverse sample of EEGs is that a wide but bounded variety of situations can be found.

In most plots, most of the 1-50 Hz power spectrum has wide-band energy that cannot be justifiably called periodic. Those periodicity peaks that rise above the confidence levels account for a small fraction of the EEG power.

Compared to shuffled controls, many plots show no convincing periodicities at the 95 or 99% confidence levels at all (Figs. 7, 10) ; if weak rhythms are present they must

[Figure 7 about here]

be less than one half or one third of the amplitude of wide-band, apparently stochastic fluctuations or last a similar fraction of the duration of the sample.

Many EEG samples do show one or more periodicity peaks rising to >99% confidence and to heights rising well above any points in shuffled control means that reach this CL. When a single maximal point is flanked by one or more 99% points on each side, it is virtually never seen in controls and quite surely significant. Broader peaks where the maximum is defined by a cluster or mini-plateau of 99% points, are highly significant but not common in our EEGs. This says that it is unusual, in our short samples, to encounter rhythms undergoing frequency modulation, whether by drift, glissando, wobble, vibrato or cycle by cycle jitter of the period. Hence the results render moot the question of how much fluctuation of period we should allow in the arbitrary definition of the term “rhythm” or “oscillation” (see p. 00 for definition). The question how much duration or how many cycles are required to justify the term rhythm is, in contrast, quite difficult and not rendered moot by the findings, since many apparently “good” rhythms appear in one 4 second sample and not in the next - quite possibly lasting less than this time.

The results are here grouped under such features of the periodicity.

A. Power peaks with low periodicity

Whereas most peaks that rise above the general average occur in both the power and the periodicity spectra at virtually the same frequency, it is nevertheless quite common to observe power peaks that stand out without any corresponding periodicity peak (Fig. 7, 8D, H, 11B, 12, 13). The average waveform at the period of the power peak has little or no signal or variance above the expectation from chance. The power peak must be a Fourier component of some irregular event. This form of discrepancy between the two spectra is most common in the low frequencies - below ca. 10 Hz but can be seen also in the higher frequency range, 10-50 Hz, although EEG power is very low above ca. 25 Hz. It must be stipulated that the possibility can not be ruled out that one or more rhythms are present but have drifts or jumps in phase every second or two; these would cancel out in the averaging.

B. Periodicity peaks with low power

When a theta (4-7 Hz), or alpha (8-12 Hz), or beta (13-29 Hz), or gamma (30-50 Hz) wave is obvious to the eye in the raw data, its PSA peak as well as its power peak is also obvious unless the phase is jumpy. But significant peaks in the PSA can be so weak in the power spectrum as to be buried in the noise (Figs. 8B, H, 11B). PSA peaks at subharmonic frequencies of

[Figure 8 about here]

the fundamental rhythm are usually due solely to the multiple cycles at multiples of the fundamental period and do not represent oscillations or have any power at those frequencies.

C. Stability and lability of periodicity

Many of the EEG records available to us have been analyzed in 10-16 s epochs and the same data analyzed in successive 4-5 s or 8 s epochs to learn how stable or labile the periodicity peaks may be. Commonly a peak in a 4s epoch is not present in an early subsequent 4 s epoch (Fig. 8 for a few seconds, Fig. 9 for a little more

[Figure 9 about here]

than one second). It is, however, also common that a peak at the same frequency is seen in two or three or more 16 s epochs. Rhythms can be long lasting or short lasting.

D. Simultaneous non-harmonic rhythms

Whereas most EEG samples show either no good rhythm or only one, usually below 11 Hz, there may be as many as five apparently “good” oscillations, not harmonically related, in the same 4 or 5 second sample (Fig. 10A, C). We cannot tell whether some

[Figure 10 about here]

of them replaced others, i.e. whether they were all present throughout or during the same part of the 4 seconds. We cannot consider this number an upper limit, because the method makes it difficult to sort out harmonics and subharmonics of more than five fundamentals. More usual are plots with 0, 1, 2, or 3 “good” rhythms (Figs. 1, 5, 7, 8, 10, 11, 14).

Two kinds of data can complicate statements about multiple peaks. (i) One is where a cluster of single-point peaks, separated by deep valleys, is fairly tightly grouped, within ca. 10% of the same frequency. It is difficult to decide whether to recognize the multiple peaks as so many rhythms or to lump them into one (Fig. 11B). Such clusters, with

[Figure 11 about here]

deep valleys between the peaks are not the signs of a wobbly or frequency modulated oscillation, which causes a broad peak.

(ii) The other complicating factor can look the same - clustered narrow or single-point peaks with deep valleys - but is more suspect when many peaks (for example 5-10) are spaced apart over a good fraction of an octave. The suspicion is strong that at least some of these represent one-at-a-time distinct rhythms each lasting for a fraction of the epoch. This is one of the prime reasons for choosing an analysis epoch as short as 4s. With a sufficient number of samples and assumptions one could, presumably, show whether epochs of 2s or 1s, in spite of the smaller number of cycles, have on average, fewer significant peaks - which would support that suspicion. Successive short epochs can be plotted on a three dimensional plot, to show peaks that arise and subside independently (Fig. 9).

E. Width and height of peaks

We consider “good” oscillations those that rise to at least a ratio of 2.5 times the expectation from stochastic control time series. Among our data sets, peaks rose quite often to 5 or 10 times the normalized mean control (Figs. 1, 5, 7, 10, 14). Weaker oscillations may abound and be missed under our arbitrary threshold but claims of their existence are difficult to justify. The method lifts up quite weak signals if they are rhythmic and last for a good fraction of the sample, e.g. 2-4 seconds.

Good oscillations generally show two or three 99% confident points surrounding the highest point but many have four or five. Artificial data with pure tones show one or two highly confident points on each side

of the maximum, when short epochs are used, containing ca. 1000 data points. The abscissa points are ca. 0.7% apart on the period (1/frequency) axis. The surprising finding is that most oscillations in our EEG samples have quite narrow peaks, meaning that wobble or sliding frequency modulation is usually < 5%.

It is not rare to observe two good PSA peaks close together, with a significant valley between. For example, when the power spectrum shows a strong alpha peak, the PSA may show clearly distinct 8.3 and 9.2 Hz peaks, with a 6 or 7 point valley. We cannot usually tell whether this means the two rhythms are concurrent or successive, within our short (4-10s) sample.

A special category are single point peaks, mentioned already at the end of Experimental Procedures.

F. Waveform of oscillations

Most of the periodicities we have examined are quasisinusoidal. Less often they are sharp-cornered, square, triangular or very asymmetric sawtooth waves or relatively brief events, such as “spikes” or “sharp waves” - as seen by examining the average waveform at the period of a peak (Fig. 10B, 12, bottom row, 14C).

[Figure 12 about here]

If the spontaneous, wide-band background is not too high, one usually sees a PSA peak at one half the fundamental frequency and sometimes at one third and one fourth. (In noise-free artificial data subharmonics are clear out to the 10th or farther.) Only if the waveform has sharp corners, one sees peaks at twice or three times the fundamental frequency. This is common in sharp waves, seizure “spikes” and even theta waves (Fig. 5) .

G. Incidence of samples without good oscillations

Periodicity plots with no peak of 99% CL are quite common in the collection of EEGs we have examined. Their incidence depends on the epoch length. Short samples (ca. 4 s) are less likely than longer samples (10-16 s) to show no 99% CL peaks. Much of the time in both sleep and wakefulness our patients and volunteer subjects (Figs. 7A, 8G) have no rhythms, as defined.

H. Episodic oscillations

Still more of the time they have no rhythms that last over 4s. Many rhythms are present only briefly. We have not followed this dimension toward its limit, presumably so few cycles that it becomes a matter of definition whether to speak of an oscillation or an event.

I. Localization of oscillators

A feature of our data set is that we usually have many channels and in the majority of subjects intracranial, subdural electrodes with large (3 mm diameter) contacts typically 10 mm center-to-center. This permits estimation of the spatial extent of rhythms. We see the well known scalp electrode array that shows some nearly global rhythms occupying many square centimeters, at one extreme. At the other extreme we see commonly that a good rhythm in one subdural or depth probe channel can be absent in a neighboring channel ([Figs. 8, 10, 12](#)).

Rhythmicity, like coherence and bicoherence can give evidence of structure in the millimeter domain. Since we reported (Bullock et al., 1995a) some pairs of semimicro-electrodes less than 1 mm apart tangentially or radially in different cortical laminae can show very low coherence across many frequencies, it can be inferred that some oscillators are small and local.

In principle, it should be possible to compare the incidence of good rhythms in scalp recordings with that from subdural and depth electrodes. This is of interest because it cannot confidently be predicted, without a more realistic model of the genesis and spread of EEGs. The expectation is very model-dependent. The reality, in the face of high temporal and spatial variance in both sets of samples, has to be a task for the future.

J. Brain states

Our material does not provide enough exemplars of equivalent states or regions of the cortex or species to make generalizations on the periodicity that might be characteristic of a state, region or taxon.

Figures. 5, 8, 10, and 12 show several short samples of the EEG of epileptic patients during interictal, wakeful periods and during seizures. Each of these shows phases of quite different EEG character and PSA pattern.

Figure. 13 shows a few samples of slow wave sleep (stages II-III) and Figure 14 from a rabbit is

[Figures 13 & 14 about here]

probably during stage II sleep. These are mainly notable for the absence of rhythms. Most epochs and loci in the human subject during sleep stages show a virtual absence of any significant rhythms at any frequency. We cannot say, with our material that this condition is characteristic among subjects and sleeps. We can say that it is not unique to this brain state; many samples from waking states are similar. The power spectra are deceptive since their peaks do not at all signify good periodicities at these frequencies.

One or two rhythms are usual during performance of designated tasks or states in human subjects and

in rabbits (Figs. 11, 14).

The gamma rhythm associated with cognitive tasks in humans was examined in data kindly supplied by C.S. Herrmann of Bremen. The task set by Herrmann et al. (1999, Herrmann and Mecklinger, 2001) for their subjects was to notice a visual target (Kanizsa square or triangle or non-Kanizsa patterns, according to instructions). It caused gamma band (ca. 40 Hz) waves within a narrow time window 250 ms wide, starting 50 ms after presentation of the target pattern. This was detectable by their technic of averaging wavelet power spectra for this brief period. The induced rhythm is very brief and we cannot see it with our minimum epoch of two seconds.

Depth electrodes recording directly from the hippocampus (Figs. 12, 13) and its environs could be compared with subdural recordings from the surface of isocortex. Similarly the subdural, epipial recordings could be compared with scalp recordings. However, to believe that any differences we observed depended on these categories, a much larger sample of comparable data would be required than is available at present.

K. Artificial data; transients and FM

We report many tests with artificial data in the Appendix, evaluating factors and quantifying the limitations of the method.

DISCUSSION

This sample of EEGs is not sufficient to establish any features of the periodicity plots as characteristic of a brain state, brain locus or animal species. It does, however, permit some statements as the first trial of a new method of evaluating periodicity. We are not aware of any other commonly used method of distinguishing rhythms from Fourier components, for example of irregular transients, apart from autocorrelation, which is quite insensitive and unsuitable for mixtures of weak and stronger rhythms in still stronger noise. The new method, stipulating its limitations and difficulties, detailed in the Appendix, does provide a crude tool for uncovering this basic aspect of time series beyond the naked eye-visible oscillations. It works for any wave shape, albeit not with uniform sensitivity. It works for any number of concurrent rhythms (multiple simultaneous oscillations), to be sure, with increasing difficulty of reading the results when there are too many peaks or they are peaks at multiples or submultiples of the fundamental period. The method can detect imperfect rhythmicity where the periods are irregular, but loses sensitivity as the variance increases. It does not depend on general or wide-band stationarity. In its present form, the program, "Periodity," provides many convenience features, such as viewing the analysis at its several stages, to assist in interpreting ambiguous peaks, and especially viewing and scoring peaks as normalized coefficients (ratios

of observed spectra to stochastic controls based on the same data), permitting comparison of EEGs of very different amplitude and power spectra. Quantitation can be both in confidence level and in ratios, where 1.0 is the expectation due to chance in randomized data.

It would be uninteresting if the results did not disclose some variety among the EEGs sampled. Indeed, we find the gamut from many EEGs with no rhythms even at the lower of our computed confidence levels, (95%), to those with four or five distinct oscillations of different, nonharmonic, frequencies. Whereas human EEGs, both scalp and intracranial (subdural and depth probes), show mostly quasisinusoidal rhythms and not very much frequency modulation or wobble but fairly sharp peaks, the method can pick up rhythmic spikes and other events of complex shape.

It will facilitate our evaluation of the findings to disclose the frame of reference or personal view of the nature of EEGs that biases our interpretation.

1. Assumed nature of the EEG

The working model of the EEG that we have in mind (Bullock, 1945, 1989a, 1991, 1992, 1997, 1999, 2000, 2002a, 2002b; Achimowicz and Bullock, 1993; Bullock and Achimowicz, 1994; Bullock et al., 1991, 1992, 1993, 1994, 1995a, b, 1996, 1998a, b; Karamürsel and Bullock, 1994, 2000; Hofmann and Bullock, 1995; Prechtl et al., 2000; Ramón et al., 2001; Schütt et al., 1999) has the following features. A wide-band background of seemingly stochastic activity, is summed from many cellular and subcellular generators (and we believe hides significant nonrandom structures such as neuronal “coughs” or “barks”, “phonemes” or “jingles”). Superimposed on this background, various events and episodes may be transient or intermittent iterative compound fluctuations of numbers of cells, making local field potentials (LFP). In some special brain states these can include one or a few, more or less rhythmic waveforms, from sinusoids to composite spike-like discharges (e.g. strychnine or seizure spikes, hippocampal sharp waves). LFPs can be very local, changing within small fractions of one millimeter. They can also show coupling between adjacent volumes or populations. Coupling between distinct rhythms may, we believe, take any of the forms recognized by Von Holst (1936, 1939) under the name “relative coordination”.

A less obvious form of cooperativity is called quadratic phase coupling, a special, nonlinear phase relation between sets of three frequencies (any two, non-harmonic as well as harmonic, and their sum). Its measures are higher moments called the bispectrum and bicoherence. This kind of nonlinear coupling has been found to appear episodically in the EEG and to involve whole bands of frequencies with spatiotemporal structure (Bullock et al., 1998a, b). (i) *Many kinds of generators* contribute to the extracellular field, including synapses, somata, dendrites (many integrative loci or compartments in the same neuron), axons and their terminal arbors (beyond the point where the all-or-none impulse falls below a safety factor of 1.0),

pacemaker regions, neuroglia of different kinds and in some situations probably ependyma and blood vessels.

(ii) *Many kinds of fluctuating potentials* are superimposed on the standing “DC” and more or less steady, infraslow potentials: spikes, synaptic potentials (classical and nonclassical), spontaneous stochastic junctional miniature potentials, pendular and relaxation oscillator pacemaker potentials, other slow events such as hyperpolarizations of long duration, subthreshold local responses, active and passive glial potentials. Several kinds of events can influence neighboring membranes, not only spikes but subthreshold synchronization and local inhibition by hyperpolarization, for example.

(iii) The far-field signs of activity such as the scalp EEG *cannot predict the signs* seen by more local, subdural surface or depth macroelectrodes and the same is true comparing these with micro- or semimicroelectrodes in the brain tissue. Likewise, even a relatively extensive knowledge of many channels of microelectrode activity cannot in practice predict the far-field, e.g. scalp recording. For example, coherence at a given frequency can be very low between microelectrodes a few millimeters apart but high between scalp electrodes centimeters apart.

(iv) Oscillations over a wide range of frequencies, from circadian to hundreds of Hertz, *can come either from subcellular* sources intrinsic to the cell (with or without weak interactions that might synchronize a group of cells) or/and from circuits of cells where the ruling time constants are at least partly conduction time and intercellular delays.

(v) *Synchronizing mechanisms* of various kinds play a graded role or roles in some parts of the central nervous system in some species at some times. Physiological features are likely to have evolved as degrees of synchrony of various parts of the spectrum - for example of spikes and slow waves.

(vi) *Summing the field potentials* from various generators may vary from simple volume conduction in an isotropic medium to nonlinear and frequency discriminating anisotropic effects. Geometry and orientation of cellular generators may contribute to the observed great range of distances to which “far field” LFPs can spread - up to well over 10 cm for the averaged auditory brainstem response seen from hypodermic needles in dolphin skin.

This proposed model has not been formalized to permit experiments, to our knowledge. There is little basis for selecting a small set of variables to model and assuming the others can be neglected. A potentially important corollary is that the dynamic anatomy of the electrical activity of organized assemblages of cells and processes could be information-rich and highly nonrandom in ways that have escaped notice.

We believe this on the basis of the empirical finding, noted long ago (Bullock, 1945, 1989b, 1993b, Bullock and Başar, 1988) that the power spectrum of the EEG has the same general shape in all vertebrates

(glossing over differences like the pattern of sleep stages and the lower amplitude of the EEG in fishes, amphibians and reptiles.), in spite of great differences in pallial or cortical anatomy. One is compelled to presume that the power spectrum is an inadequate descriptor - as it would be for speech or music. Descriptors of many kinds are needed. According to our view, the wide-band, apparently stochastic background activity in the EEG may in part consist of structured events or sequences - as in speech or music. The difficulty of detecting and segregating such meaningful structure from truly stochastic components must depend on whether recording is done on the scalp or with macro- or semi-microelectrodes in the brain. Independent component analysis at each level, macro-, meso-, and microscopic, should be a great help in this process.

2. Types of oscillations

One expects several kinds of rhythms. Quasisinusoidal ones, such as the various forms of alpha waves, theta and others are certainly prominent when the subject is in the right state. These rhythms are usually obvious by inspection of the raw EEG. We find many examples of “good” rhythms in the 2-25 Hz range, and they are chiefly pretty sinusoidal. Much more seldom, in minutes per hour, are rhythms in the 30-50 Hz band. Sharp-cornered events such as compound spikes can, of course, be good rhythms but are not common; they seem to require unusual states, such as certain phases of seizures. Single unit rhythms do not appear in macroelectrode recordings of most vertebrate brain regions but can be conspicuous in invertebrates.

3. Incidence of rhythms: dependence on method of recording

Possibly the most surprising results are how frequently we see EEGs with no significant rhythm and how infrequently we see EEGs with three or four non-harmonically related rhythms. In the latter case, we cannot usually say with assurance whether some of the rhythms are episodes that come and go during the 4 s epoch or whether they are really simultaneous.

4. Discrepancies between power spectrum and PSA spectrum

A principal finding is that the peaks of the power spectrum computed from the Fourier transform are quite unreliable indicators of the presence or absence of periodic signals, that is to say rhythms or oscillations. Two of the classes of discrepancies may suffice for mention here.

(i) In the frequency band $>ca.30$ Hz, in most EEG recordings that we have examined, the power has fallen to relatively low values and “peaks” in the FFT that stand out from the background fluctuations are usually not evident. This includes EEG samples during mental tasks in data kindly provided by C.S.

Herrmann who did find gamma peaks in averaged power spectra when epochs of 100-150 ms at the right time after the onset of stimulation were selected for computing. We have not pushed the PSA to such brief epochs and do not see any consistent PSA peak in the gamma band in repeated epochs of two seconds duration, although we have not computed average PSA curves.

PSA peaks of high statistical confidence, however, can be episodically common. We have many records, for example during stages of electrographic seizures, in which PSA peaks rise, singly or in clusters far above randomized controls, at frequencies where the power spectrum has no elevation above the background noise or is actually in a valley. Such evidence is sufficient to establish unreliability of the power spectrum with respect to rhythms even though very often the two spectra agree, mostly in the lower frequencies. Gamma peaks have indeed been reported in the power spectrum from the human scalp under certain regimes, usually for a fraction of a second, by passband filtering or averaging a number of power spectra after adequate stimulation. It could be that phase jumps are sufficiently frequent to destroy the PSA evidence of rhythms.

(ii) In the low frequency region (1-5 Hz), where EEG power is generally high, it is quite common to observe large FFT peaks without a corresponding PSA peak in our usual four second epoch and even in 8 and 16 second epochs. Figure 15 illustrates with computer-generated random noise which should have no rhythm unless by statistical accident. A Fourier

[Figure 15 about here]

component is present due to singular or irregularly recurring transients. This can be true at any frequency but is more conspicuous in the low frequencies because each event there has so much power.

(iii) PSA spectra not infrequently show distinct peaks separated by a significant valley, i.e. two rhythms at 8.5 and 9.3 Hz (Fig. 13B, C), whereas the FFT has only one, broader peak because the sampling rate was too high for the length of the data, making the resolution too low, e.g. 1 Hz. (See also Fig. 11B).

5. Significance; Limited applications of this survey

So far, we cannot see a practical application where a new criterion for a category of clinical interest depends on the periodicity as distinct from the Fourier components. Other limitations are made explicit in the Appendix. Impractical implications of these findings may be more interesting

It may be time for another quiet revolution in our mental models and terminology of brain waves. Perhaps the frequency domain language is not the most appropriate for describing them, except for special cases of demonstrable cellular or “circuit” rhythms, pendular or relaxation oscillations. It may be that we have been bemused long enough by the convenience of the clearly inapplicable model implied by the Fourier analysis - scores of independent, stationary oscillators. To us, the time domain view is a more appropriate

way to look at events in the brain - with the stated exceptions. Elsewhere it is proposed that we have outlived the appropriateness of the mental model and terminology of “circuits”, even “local circuits” (Bullock, 1993a) and need new metaphors.

Especially for the goal of describing the levels of complexity in the evolution of brain function and activity from simpler invertebrates to mammals, concepts are called for that recognize features such as the following. We have no idea how much of the brain waves are attributable to “familiar” sources such as synaptic potentials. We have no idea how much interneuronal communication is attributable to all-or-none impulses and classical synaptic potentials. We know that graded presynaptic activity happens and causes graded transmission. Many neurons are permanently without spikes and an unknown additional number may sometimes function without spikes. We know of several mechanisms contributing to synchronization but probably not all of them. Their relative roles in different brain structures may vary widely. One example is the electrical, nonsynaptic connection that passes only slow events (Watanabe and Bullock 1960); this synchronizes cardiac ganglion activity in lobsters and may be widespread in vertebrate brains without having been noticed. If our belief is correct, much of the nonrhythmic compound field potentials we see - which means most of the activity - is not truly stochastic but has unrevealed structure and this may be the domain of evolution. We don’t know what causes EEGs of large sharks and frogs to be so much smaller than those of large dolphins and mice. We can’t explain the strong tendency for a wide range of FFT frequency components to vary in coherence together - and similarly for bicoherence. We are far from an adequate natural history of the signs of activity in organized populations of neurons in different regions, states, stages and species.

The PSA method may prove to be an insightful adjunct to the FFT power spectrum. To avoid misidentifying power peaks as rhythms and to detect rhythms missed by the FFT because they are weak or the sampling rate was too high and the resolution too low, a few extra seconds suffices to compute the PSA with 95% and 99% CL points high-lighted. It is most reliable in short samples and sometimes benefits from inspecting the segmented data in a raster plot or the average wave form. Far from the perfect tool, its limitations should be kept in mind.

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APPENDIX

A. TESTS WITH KNOWN DATA

1. Symmetrical signals: Sine, square and triangular waves, without noise Pure sine waves of a single, sustained frequency in midrange, e.g. 10 Hz, in ca. 5 s samples digitized at ca. 200 Hz (ca. 1000 points) show the characteristic PSA features (Fig.1). A narrow peak at 100 ms period has 3-5 points, (3-4% of the period in width at half height; narrower with longer data samples). Arrays of similar peaks lie at integer multiples of this period: 200, 300, 400, 500, .. ms (5, 3.3, 2.5, 2 Hz) since these periods will have the corresponding number of cycles of the signal and hence the same total variance. (In addition two smaller peaks appear between each pair of multiple and submultiple peaks (in the frequency domain at ca. 2.7, 3.0, 3.8, 4.2, 6, 7.5, 15, 25, 43 ... Hz). Since these are lost in the presence of quite modest noise, we have not noticed them in brain data and will not speak further of them.

Side lobes ca. 2% of the period in width, damping in ca. 3 cycles are clearer with longer period signals and are smaller and fewer in longer samples or with lower sampling rates. These also have played no role in brain analyses except to contribute to the “noisy” background between peaks.

In the normalized plot the baseline upsweep at long periods is flattened and the peaks of the multiple-period “subharmonics” are lower at the longer periods. For triangular or 50% duty-cycle square waves there are in addition to the “subharmonics” small peaks at the odd “harmonics” (30 and 50 Hz in the case of a 10 Hz signal = odd submultiples of the signal period). The height of the fundamental peak, without noise in the data, is ca. 40-160 times the smoothed mean shuffled control.

2. Asymmetrical signals: sawtooth, short duty cycle square waves Analysis of a noise-free 10 Hz square wave with 0.2 duty cycle (power spectra have peaks declining in amplitude at 10, 20, 30 and 40 Hz) shows PSA peaks above 10 Hz only at the integral “harmonics” = 20 and 30 Hz (but nothing at 40 or 50 Hz!), plus the “subharmonics” at 1/2, 1/3, 1/4, ... out to 1/8 the fundamental frequency, plus one small peak midway between each pair (ca. 2.8, 4, 6.6, 15, 25, 45 Hz but none at 35!). Sawtooth waves give similar peaks.

3. Tests with pulses: singles, pairs and trains Short trains or sequences of narrow pulses can give PSA peaks at the period of a regular interval, plus submultiples and multiples thereof, or a cluster of peaks if the intervals are slightly irregular, with or without the submultiples and multiples. False positive tests for periodicity can happen with a sequence of a dozen or fewer pulses of sufficient size with quite irregular intervals - not at all rhythmic. Such a sequence of transients can sometimes yield a PSA hump or a cluster of 99% CL points resembling a modulated rhythm, without all the submultiple and multiple peaks expected from single pairs or pulses. Clusters may depend on the chance concatenation of particular multiples and submultiples. The position of the cluster, suggesting the mean period of a rhythm is sensitive to the shape, especially the duration of the pulses as well as their intervals, but not to the presence or position of particular transients in the sequence.

Trains of only three or four pulses of decreasing or increasing intervals give PSAs with the “fundamental” peak at something near the mean interval and several other peaks at multiples and submultiples, sometimes out to at least the seventh. There may be no multiples. The power spectrum may not look similar. Both curves depend on the number of points in the time series analyzed and the digitization rate. Strange curves can result if the former is not at least twice the latter. If the sampling

rate is above ca.300 Hz, the power spectrum resolution is too low to show the detail of the 100 point per octave PSA.

Two brief pulses, rising sufficiently above the background noise and separated as much as a second or more can give a PSA plot with many peaks, especially at submultiples of that interval; multiples may be absent or off scale. Noise can obscure the pulses and greatly lower the PSA peaks. We have not seen a lone peak at the period of the pulse interval. Power spectrum peaks tend to correlate well with PSA peaks.

Short trains such as three successive sine waves whose periods are equivalent to 10, 15, & 23 Hz give the expected series of PSA peaks at fundamentals and subharmonics.

4. Noise in the PSA Irregular fluctuations between peaks occur even with pure tone signals, giving PSAs of sharp, narrow peaks at the fundamental and “subharmonics”. This “noise” is in part, due to the crowded, superimposed and noisy looking mixture of side lobes well seen around the base of every peak, and dependent on the length of data and sampling rate. In part it must come also from other sources - for example, in the normalized PSA plot, from the unsmoothed fluctuations of the shuffled mean control - though this source is usually minor and smoothing the mean shuffle makes little difference in the normalized ratio. “Noise” is systematically larger at the short period end of the spectrum. Its own power spectrum is wide.

Experiments with artificial data sets show that the height of the noise is constant, relative to that of the peaks, independent of the amplitude of the input signal being analyzed, if that signal is a noise-free wave of regular period. When normalized by the phase-shuffled control, so that the Y axis is a ratio, the noise is independent of the input amplitude. Therefore it comes from the input and the processing thereof, not from some “grinding” of a machine-like process independent of input. It is much less, relative to the peaks, when we plot variance instead of standard deviation. With 2048 points (ca. 10 s at our usual sampling rate), plotting variance, the spectrum is virtually noise-free between peaks.

5. Sensitivity: useful detection of rhythms in noise The value of the method depends largely on how weak a signal can be seen in the plotted PSA spectrum, relative to the ongoing background “noise” in the data plus the inherent noise referred to in the previous paragraph. The sensitivity depends, among other factors, upon the length of the data set - usually a compromise with stationarity. If this length is ca. 1000 points (ca. 5s), the just clearly detectable unmodulated 10 Hz sinusoidal, triangular, sawtooth or square wave at 50% or at 5% duty cycle, in the presence of noise in the data, has a signal to noise ratio of ca.1:4 (1 V RMS signal, 4 V RMS noise) or 1:5. Sometimes 1:6 is clearly evident, but often not. If the rhythm is frequency modulated, e.g. 10 or 35 Hz +/- 20% (8-12 Hz or 28-42 Hz), the bumpy plateau or broad hill is still clear when the S:N ratio is 1:2 or 1:3. With this level of noise, harmonic and subharmonic peaks are not clear, though knowing where they must be, a few of the largest can be seen. Smaller frequency modulation (5-10%) gives intermediate S:N ratios for clear detectability, ca. 1:3 -1:4.

6. Comparing different forms of windowing In a limited number of tests, we cannot see any consistent difference, either in noise-free signals or with band-passed noise, comparing the four kinds of windowing. We have usually used the rectangular option.

7. Data length, digitization frequency & points in FFT These interactions especially concern the power spectrum, whose resolution, in Hz is sampling frequency divided by data length in points. Therefore a common combination - 1024 points of data & 256 Hz sampling means 0.25 Hz power spectrum resolution. A higher sampling rate or a lower data length means lower resolution, and a coarser or poorer spectral plot. We use a common method - approximately half of the data length is the epoch

computed to make a spectrum, then with a large overlap, the next such epoch is computed and this is repeated to the end of the data; then these spectra are averaged. This permits calculation of the SD for comparison with that of other data sets. If frequency resolution is more important, we revert to using the whole data set as the epoch for FFT calculation.

8. *Rhythmic signals can suppress points that were "99%" confident in noise-only data.* A pure "noise" sample shows about 6 "99%" highlighted points. If we then add a pure tone, at, say 555 ms period (1.8 Hz) and 0.3 of the RMS of the noise, we thereby add a lot of variance at that period. The count of "99%" points is increased, as expected, but distributed only in the neighborhood of 555 and there they are virtually confined to the ones in the 555 ms peak. Others anywhere between 1,000 and 140 ms are "suppressed". From ca. 140 to 20 ms the same old points persist as in the pure noise PSA. In neurophysiology this would be called "lateral inhibition" (Hartline and Ratliff 1957). We have not studied the factors that control the extent of suppression - in this case from 555 to 140 ms.

To see these effects, one has to use fixed seeds both for the noise and for the shuffling - an option provided in "Periodity".

9. *Importance of shuffling seed* Using 50 or 100 shuffles, the same data re-analyzed with new random shuffling can show very small differences in the PSA plot but, sometimes, remarkably large differences at a few points, changing the count of "99%" points or the height of some points - by a factor as much as 2 or 3 or more. To avoid this, especially when looking for small effects of parameter changes, it is important to fix the seed of the shuffling which will then cause the same list of "random" numbers. Shuffling 200 or 500 times gives good, but not perfect, reproducibility. The program provides for independently fixing the seeds of the shuffling, of the noise generator and of the jitter option.

B. PSA PERFORMANCE LIMITATIONS

The additive PSA method, as modified from Schuster (1898) by Enright (1965, 1990), for measuring periodicities of any waveform, with considerable tolerance of irregularity of period, phase and waveform, has substantial limitations and *disadvantages*. It has been reported in trials of many methods (autocorrelation, power spectra, etc; Kendall 1946, Whittaker and Robinson 1924, Binkley et al. 1973, Smith and Odell 1976, Enright 1990, Refinetti 1993) to be the method of choice for circadian rhythm research. But, especially when used for a wide span of periods (here nearly 6 octaves) or for short time series (here, generally, ca. 1000 points or 10 cycles of the slowest rhythm), the following limitations should be kept in mind. Also constantly in the forefront is comparison with the Fourier analysis and the common power spectrum. This latter is so well established, powerful and convenient that it has become the standard way of estimating what oscillations or rhythms (here used interchangeably) are present and their relative strengths; indeed it is sometimes called a periodogram. The present method, which we call, after Enright's term, the additive periodogram or, to avoid confusion, the PSA, shows peaks commonly corresponding to the power spectrum peaks. But it is especially the places and occasions where they depart that we wish to lift up for attention; these are both power spectrum peaks at a frequency where there is actually no rhythmic event and rhythms shown by PSA peaks which are buried and missed in the power spectrum.

"Noise" of at least three different kinds should be distinguished, all conforming to the dictionary meaning of unwanted interference - whether it is white or far from it and wide or narrow in band. (a) Baseline fluctuations in analyses of pure (noise-free) sine wave data that lie at other points along the x axis (period) than that of the signal, are usually scattered along the spectrum but in some permutations of signal frequency, data length and sampling rate appear as damped side lobes

around each peak. (b) Nonrhythmic fluctuation in the data itself is typically not white but equivalent to stochastic activity filtered by an odd shaped filter. It does not average out in finite data sets. Therefore the mean waveforms of each period vary greatly and weak rhythmic components can be buried. EEG data, which usually includes a nonrhythmic component that looks stochastic, is inherently likely to show inconsistent power spectral peaks in the low frequency range (up to ca. 10 Hz) in short samples, because there is so much more power in this range. (c) The resulting baseline fluctuations in the PSA plot (a single datum for each period, representing the variance of the average waveform) depend on the length of the data and cannot be smoothed without serious loss of narrow peaks.

1. Limitations that depend on the stationarity of the data set:

Our data, ongoing electrical activity of the brain, varies greatly in stationarity, not only from sample to sample, time to time, and place to place but from one frequency component to another and from one measure to another (amplitude, Fourier spectrum, phase, burstiness, episodic transients). “Stationarity” is commonly a composite, “eyeball” judgment based partly on the maintained behavioral or cognitive brain state of the subject and the purposes of the study.

The limitation of the PSA method due to stationarity demands analysis of successive short samples of the time series to show whether the properties of interest are similar or changing with time. If the samples are very short, the measure suffers in precision and sensitivity. If samples are long, the chance increases that nonstationarity obscures by failing to distinguish absence of periodicity from presence of modulated periodicity.

The procedure used will miss (overlook) a rhythm that happens to flip 180 degrees in phase in half the sample. It will show a graded degree of such failure when the phase shift or fraction of the sample is less.

2. Multiples and submultiples of the period of a rhythm:

PSAs covering several octaves can have “subharmonic” peaks (a frequency domain name = period-multiple peaks in time domain terminology) or “harmonic” peaks (at submultiples of the fundamental period especially for sharp-cornered waveforms). They can be as high in amplitude as the primary (fundamental), in the raw PSA, if there is no noise. But in normalized, detrended plots of ratios of raw PSA values to control values, they are progressively smaller away from the fundamental. They fall steeply in the presence of noise in the data and with FM or frequency spread of an imprecise rhythm and are often apparently absent in real EEG data. Sometimes, in order to distinguish them from the fundamental, it may be necessary to examine the mean waveform at the suspect period, where two or more cycles will betray a “subharmonic” or to examine the single segments, in sequence, where a “harmonic” appears in every n th segment.

A limit of usefulness can become serious if two or more rhythms coexist, each making a set of harmonic or/and subharmonic peaks some of which can coincide. Although spectral resolution is high (at least 100 periods per octave), the difficulty of choosing the fundamental without knowing whether the wave form is practically sinusoidal or has sharp corners, unless one examines the averages at each period and the single segments making up an average, become inconvenient with two or more rhythms.

An unexpected limitation is the false positive that can happen with an irregular sequence of a dozen or so distinctive events, such as pulses that stand out sufficiently, without regular intervals. Such sequences can sometimes yield a cluster of 99% CL points resembling a wobbly rhythm, without all the harmonic and subharmonic peaks expected from each pair of pulses. The position of the cluster, suggesting the mean period of a rhythm, is quite sensitive to the shape of the pulses as well as their intervals, but not to the presence or position of some one of the transients. The cluster must depend on the chance

concatenation of multiples and submultiples. This limitation can be minimized by routine inspection of the raw data for numbers of large pulsatile transients.

3. Limitations that depend on the length of the data set For our purposes, we have compromised on a sample EEG of ca.5 seconds length - so that we can have at least two successive samples which are fairly often acceptably stationary. This, with other features, helps greatly in deciding whether a candidate peak should be treated as a casual accident or a possible rhythm.

The PSA curve has rough, irregular baselines between peaks even when the signal is pure, noise-free rhythms. The rough baseline obscures the peaks from weak or widely frequency modulated rhythms. This noise is reduced to insignificance if enough data points are used (i.e. duration of data). In our parameter ranges, a set of 2000 points is reasonably satisfactory; 1000 leaves quite a lot of this species of noise.

Especially in short data sets, a PSA peak of high confidence level can come from a very few cycles if their amplitude is large. A major limitation of the present program is no requirement for automatically counting a chosen number of cycles as part of the arbitrary definition of a significant rhythm

Length of data sample also influences the power spectrum and hence the discrepancies between the FFT and the PSA. Short data samples are likely to have large power peaks in the low frequencies due to transient baseline fluctuations or short episodes of 5-15 Hz activity. If the FFT is based on epochs shorter than the whole data sample in order to average several spectra, the resolution goes down, peaks become wider and more conspicuous, although quite likely not due to real oscillation.

Figure Legends

Figure 1. Steps in generating the Period Specific Average (PSA) periodogram; “print screen” image of the program “Periodity”, showing phase jumping. *Upper left panel*: raw EEG from the scalp of a resting human subject with eyes closed. *Upper right panel* shows the normalized (random start control) periodogram (green) and the confidence levels for this data set (99% = red; 95% = blue). *Lower left panel* shows the amplitude spectrum (black) and the PSA (green) as a ratio of the computed periodogram (variance of the average at each period) to the control; 1.0 is the expectation from analysis of a random time series of the same power spectrum. Red dots are at or above the 99% confidence level; blue diamonds at the 95-99% level. As expected for a sine wave signal, only the fundamental and lower frequencies (reciprocal periods) at all the integral subharmonics show peaks; harmonics do not unless the signal has corners. This subject, under these conditions, has a single, nearly sinusoidal rhythm at 8.95 Hz, verified by the display of the mean waveform at that segmentation period (111.7 ms), *lower right*. The *upper middle* display of all the successive segments at this period permits a check for waveform and mid-sample phase shifts; here it is clear that during the four seconds of data the phase of the rhythm jumped several times. Hence, the average waveform is smaller in amplitude than it would have been if phase had not changed. See also Figures 9 and 11 for the same subject in different brain states. Scalp data from a healthy volunteer, resting with eyes closed; kindness of A. von Stein.

Figure 2. Artificial data. Effects of wave form on harmonics and subharmonics. **A.** Distorted sine waves such as addition of a 30% duty cycle square pulse to a 10 Hz sinusoid adds harmonic peaks of 20 and 40 Hz to the PSA spectrum and a small power peak at 20 Hz. The number and spacing of the peaks are sensitive to the wave form of a rhythm. **B.** Quasirhythmic, irregular repetition of similar square waves, here 25 ms pulses (10% duty cycle) of 4.2 Hz with random jitter of intervals shows even harmonics (here the second only) and other short period peaks as the duty cycle is reduced to brief pulses. Note the narrow peaks in the periodogram. PSA and FFT peaks agree in this range above the fundamental but below the fundamental (long periods) the subharmonic peaks are due to the averaging and not real rhythms. Square waves of 50% duty cycle show peaks at the odd harmonics (not illustrated), both in the FFT and the PSA spectra, tapering off in height, the higher the harmonic. The power peak at 4 Hz is very broad, at least in part because the resolution for short data sets is only 0.5 Hz.

Figure 3. Artificial data. Rhythms in noise, band-limited (0.5-100 Hz) at a S:N ratio of 1:4 in RMS voltage added to two pure sine waves at 10 and 35 Hz. Note almost all 99% points are due to the signals and their subharmonics although the signals are very weak. Some of the peaks are labelled with respect to the order of the subharmonic and the fundamental frequency. This data was used to compare phase shuffle (PS) and random start (RS) methods of computing CLs; the finding was that they are equivalent; only a few points change color or height. Depending on a number of factors, the method can detect signals $<1/5$ the amplitude of the noise.

Figure 4. Artificial data. Detectability of rhythms as a function of their frequency modulation (FM). 5s samples showing that even when the rhythm is weakened by 20% FM, it is still a clear plateau of significant confidence limits. Starting with pure 10 Hz and 35 Hz signals, the sequence shows FM at 10 and 20% of the mean frequency (8-12 Hz and 28-42 Hz). Black, broken line is the FFT amplitude spectrum, green line is the PSA spectrum with points reaching a CL of 99% in red and 95% in blue. Note the amplitude of the PSA declines with FM (ordinate scales vary) and the subharmonic peaks disappear. No noise in the

signal. Noise is introduced by the analysis, from the segmentation of the time series, the random start controls and other causes (see Appendix A4).

Figure 5. Example of PSA when a theta rhythm is prominent and has ca. 10% jitter. EEG from one of 10 depth electrode contacts along a probe through the left posterior temporal lobe of an epileptic patient. Some contacts are estimated to be in the hippocampus. A sample of 4 s starting 20 s after a seizure began. Note that the PSA peak at 3.9 Hz is >0.5 of a Herz wide whereas the FFT peak is >5 times wider, with the FFT resolution at 0.5 Hz. Because the fundamental rhythm is asymmetrical, with a sharper point upwards, there are weak 2nd and 3rd harmonic peaks at 7.6 and 11.7 Hz which would not be present if the signal were sinusoidal. Subject ME1, data kindness of V. Iragui.

Figure 6. Artificial data. The reason for using high resolution of segmentation frequency. When a rhythm is quite regular and its frequency is between two of the segmenting frequencies, the resolution and record length become crucial in quantifying the strength of the periodicity, because of pattern drift. Our usual segmenting resolution is 0.69% (100 per octave), i.e. the adjacent segmenting periods are that far apart; this gives 564 frequency values in our range of 1 to 50 Hz. Here a pure sine wave is at 10 Hz; its average wave form is displayed (*lower middle*; see explanation of Fig. 1) at close to the second subharmonic frequency in order to see two cycles. The nearest segmenting frequencies to the signal are 10.002 and 10.072 Hz. Both cause pattern drift at the beat frequency in the raster display and the peak height of the mean waveform depends on the duration of the data used. Minor PSA peaks, the subharmonics, have heights dependent on the same factors. Resolution available in the program extends from this minimum value, in 5 steps, to 0.2% = 347 segmenting frequencies per octave. One other factor that determines Y value is the mean of shuffled controls, which is divided into the measured variance at each segmenting frequency (*red in lower right panel*). It fluctuates stochastically although averaged over 200 independent shuffles (*black*). It can be smoothed to emulate the effect of a higher number of shuffles.

Figure 7. Rhythms can be brief. Two 5s samples taken from locus CZ on the scalp of healthy subject SF (c5) while viewing moving bars. Since the method grades degrees of expression of periodicity, at every possible period between 1 and 50 Hz, and we set 95% or 99% confidence as a threshold for claiming a rhythm, marginal cases can be expected. **A.** Weak and border-line rhythms; only a feeble trace of a rhythm at 11 Hz. **B.** A strong 11 Hz rhythm (and two subharmonic PSA peaks which show little or no evidence of actual rhythms). Note that large power peaks below 5 Hz do not signify rhythms. Data kindness of J. Pineda.

Figure 8. Examples of weak and strong rhythms in an epileptic patient, before and during a seizure, from two electrode sites (channels 3 & 7, vertical columns) 4 cm apart on ventrolateral parieto-occipital cortex. . Periodogram spectra (in green) and power spectra (as amplitude, in broken black lines) from four second samples of subdural EEG (bottom of each panel). The two panels, side by side, in each row are from the same 4s epoch. The electrical seizure began in channel 3 (left) during the 12th second; channel 7 (right) showed low amplitude fast activity for 12 seconds before any other channel. Ordinate scales vary. The “Periodogram divided by control” ordinate is a ratio where 1.0 is the expectation for a stochastic time series of the same power spectrum; the numerator is the amplitude of the mean variance segmented at that period and the denominator is the mean of 50 shuffles of the time of segment starts. Note examples of power spectrum peaks without periodogram peaks, especially at low frequencies, and periodogram peaks without power peaks, especially at higher frequencies (see Discussion). Subject ME1, data

kindness of V. Iragui.

Figure 9. 3D view of episodic rhythms; PSA in consecutive epochs of two seconds can be quite different. Scalp data, healthy volunteer listening to music; eyes open . Data kindness of A von Stein.

Figure 10. Seizure state. Data from an epileptic patient with subdural electrodes on parietal cortex. Three near-by channels recorded simultaneously for 5 s samples. **A.** With a mixture of delta, theta, alpha and beta rhythms. Note that the broad delta power peak is really a mixture of two rhythms. **B.** With mainly theta which is spike-like and causes a second harmonic at 8 Hz. **C.** With a partial “spike and wave” pattern and at least two rhythms plus harmonics and subharmonics. Subject file AT2; data kindness V. Iragui.

Figure 11. Dependence of rhythms upon state. **A.** Resting with eyes closed. **B.** Resting with eyes open. Scalp recording from healthy volunteer. Note the single, strong rhythm at 9 Hz in the upper panel, >12 times the expectation from chance and the dominant 16 Hz rhythm in the lower panel, with a weak 9 Hz mixed with the second subharmonic of the 16 Hz. Ordinate scales vary. Data kindness of A. von Stein.

Figure 12. Hippocampal loci; near-by electrodes as well as epochs can be quite different. Seizure state. Periodicity patterns change locally during seizures. Sample PSA periodograms and amplitude spectra before and during a seizure in a subject (AD) with depth probes having electrode contacts in the right posterior temporal lobe. Shown are three loci in a line, presumably in the hippocampus. Three vertical columns are each from a different electrode - channels 1, 3, and 5, ca. 12 mm apart, channel 1 is the most posterior. Three horizontal rows are each ten second samples recorded at the same time, epochs 380, 420, and 520 (seconds after the recording began).

The neurologist reading the EEG considered the seizure to commence at ca. the 392nd second; the top row is therefore preictal and the other two are phases of the seizure, which lasted until an abrupt end at epoch 530. Note ordinate scales for amplitude spectra vary. PSA ordinates are multiples of the expectation from a random control. In reading such graphs, where a large part of the activity is apparently stochastic and short episodes are expected by chance in which some frequency component maintains phase for a few cycles, it should be pointed out that any sample of random “noise” will have, on average, about six points with 99% confidence level plus 25 with 95% but that these points rarely exceed an ordinate value of 2.5 and much more seldom 3.0. Note several examples of periodicity peaks with high confidence where no power peak occurs. Data kindness of B.Duckrow & S.S.Spencer.

Figure 13. Slow wave sleep, stages II - III. Four samples of 10 s from an epileptic patient (AD) from three electrode contacts on two depth probes in the right and left posterior temporal lobes, probably in the posterior hippocampus, at three different times many seconds apart, each in stage II-III sleep with large delta waves. Amplitude scales vary. Data kindness of R.B.Duckrow & S.S.Spencer.

Figure 14. Rabbit in theta and non-theta states. **A.** Subject R1, epidural electrode on parietal cortex; dominant delta; possibly in stage II sleep; one rhythm at 4 Hz. **B.** Animal R2, similar recording; dominant theta according to the power spectrum but the only good rhythm is 11 Hz. **C.** Same animal and electrode during strong theta state; dominant 7 Hz plus a weaker rhythm at 14

Hz partly a harmonic due to the asymmetrical sharp waves.

Figure 15. Artificial, random time series showing non-rhythmic power peaks in short data sets. Three examples of band-limited noise, 1-50 Hz, cut off at each end at -12 db per octave. Power spectrum peaks predict periodicity peaks unreliably; especially below 5-7 Hz. This is even more true when the random time series is much stronger in low frequencies, as in the EEG.

Figure 1.

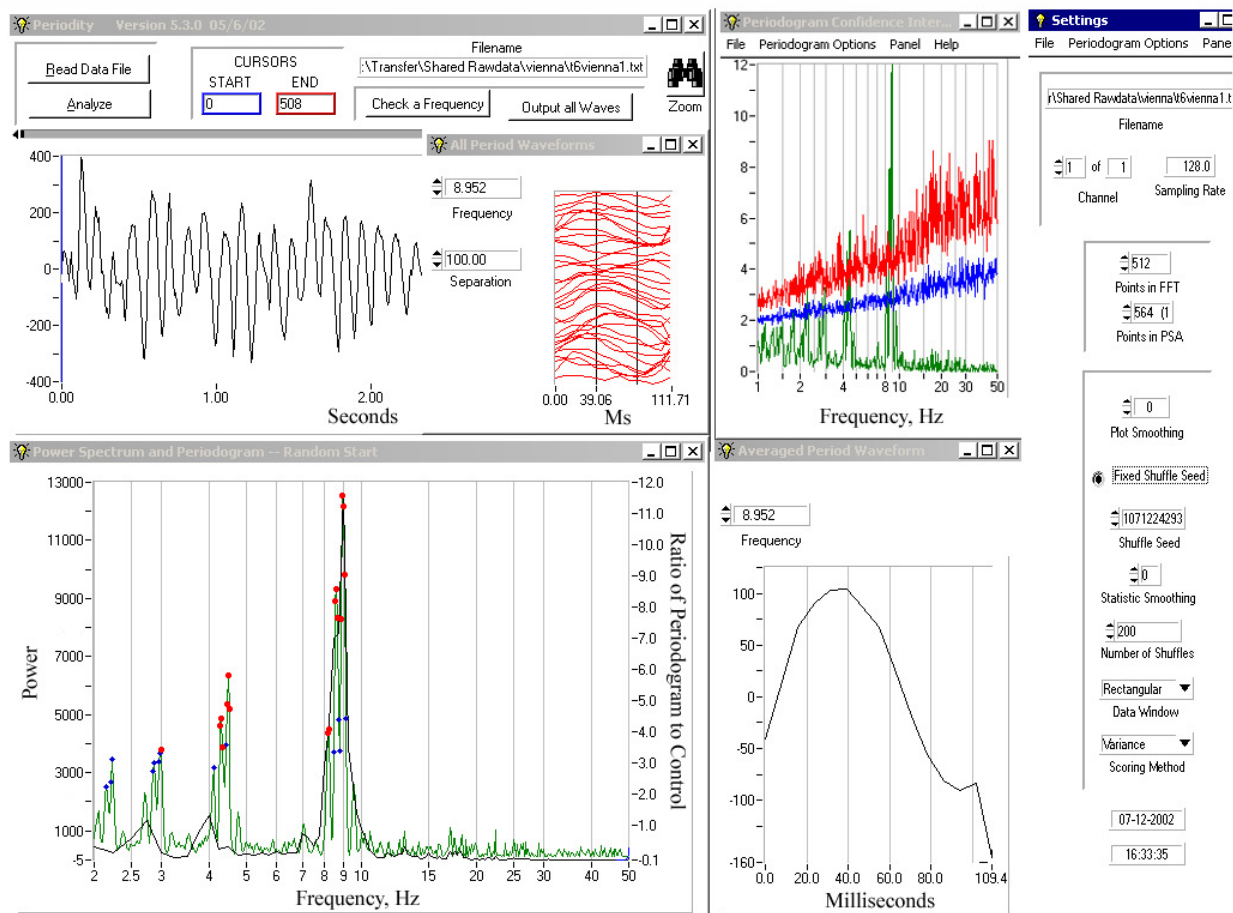


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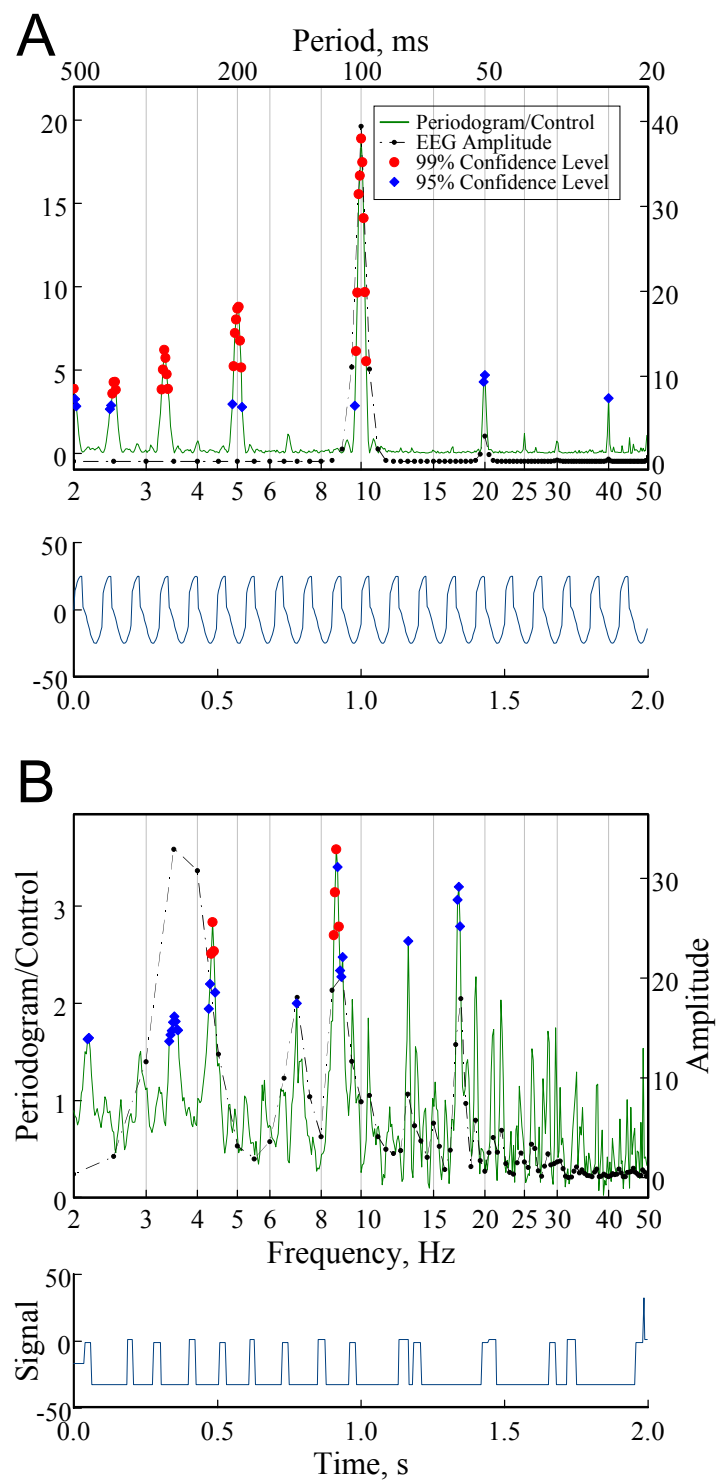


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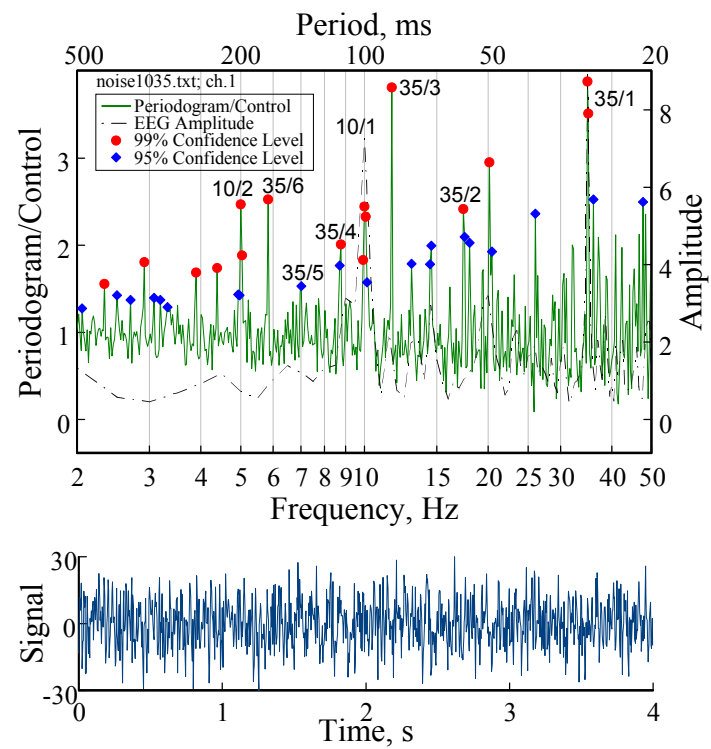


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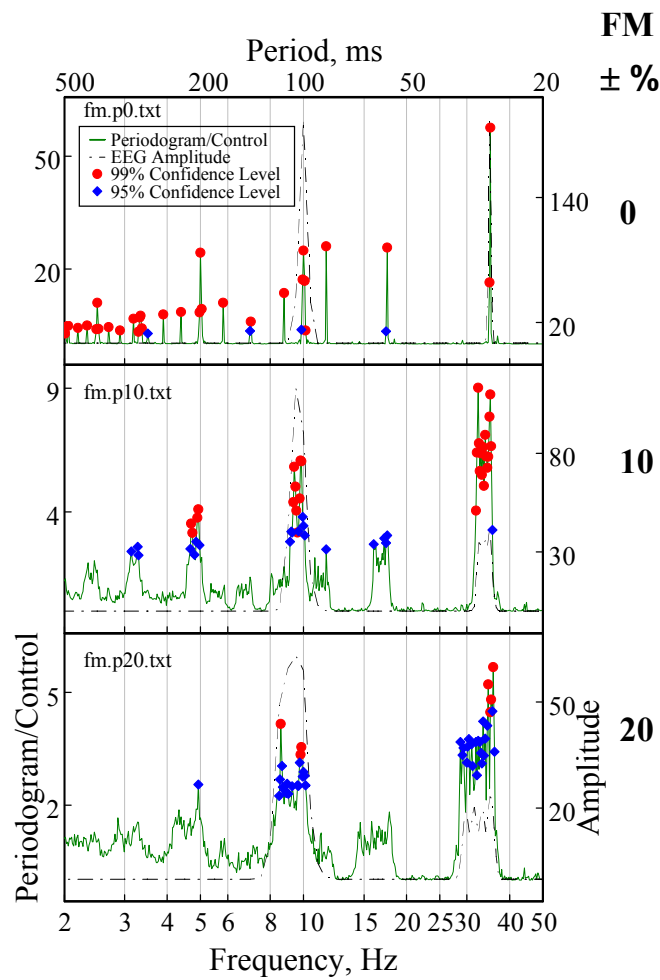


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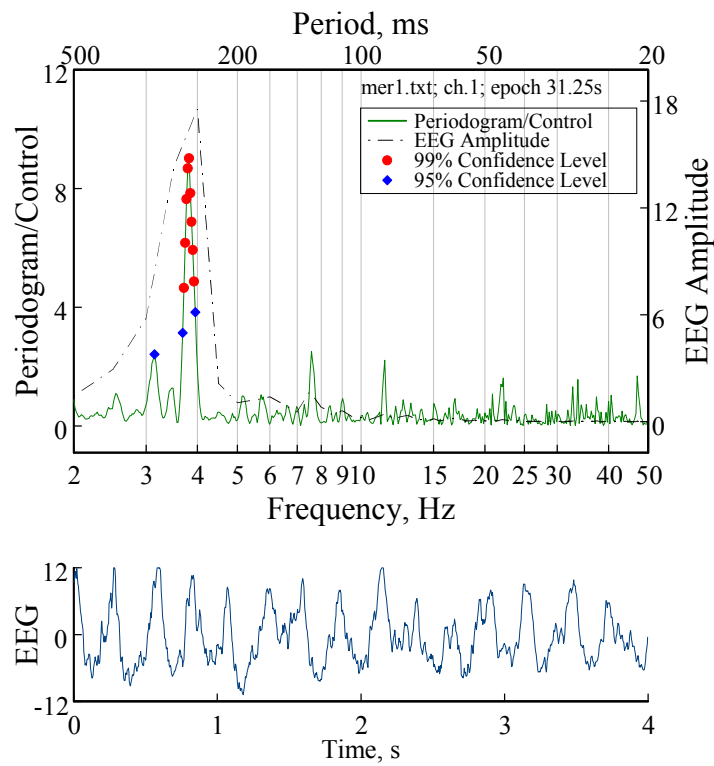


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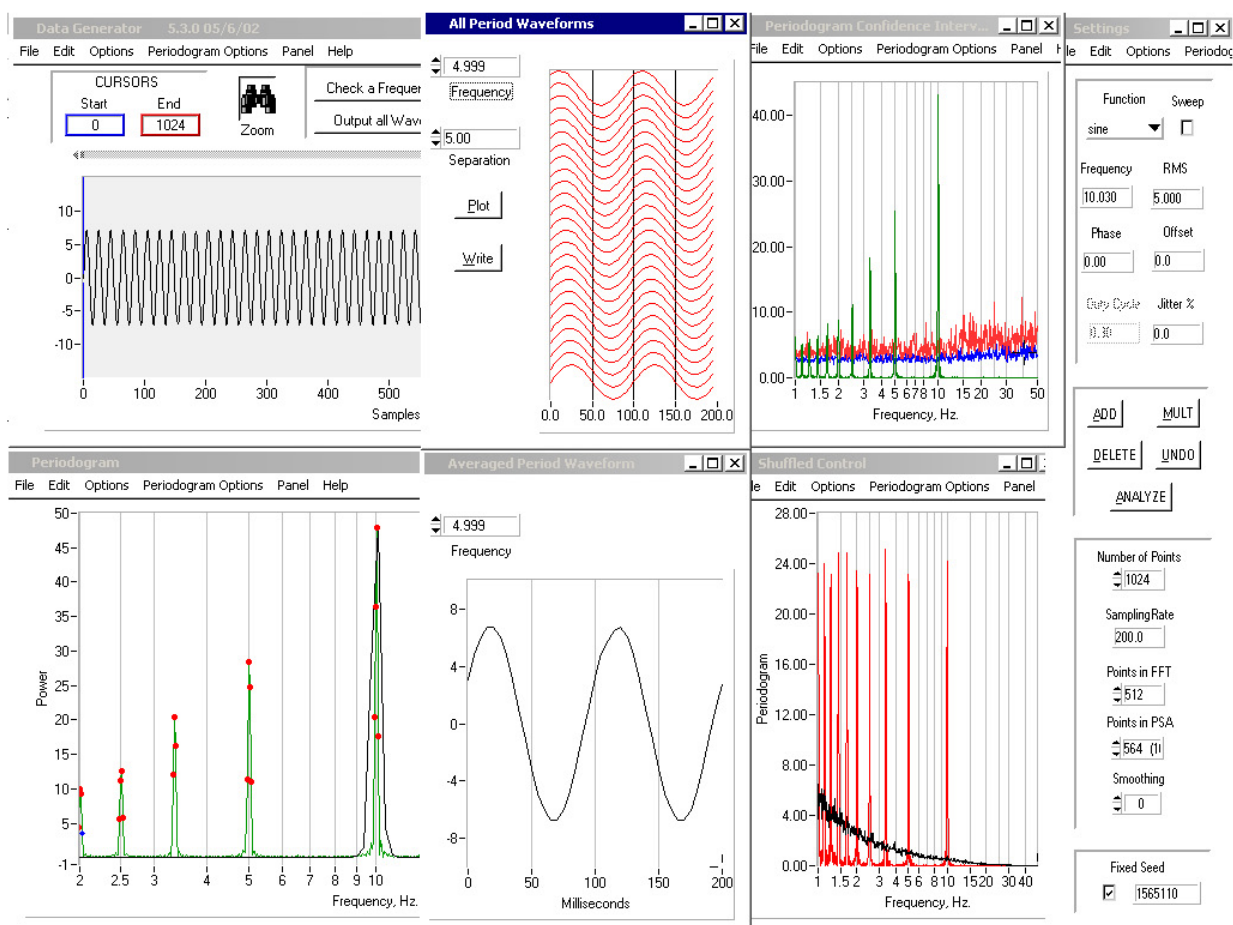


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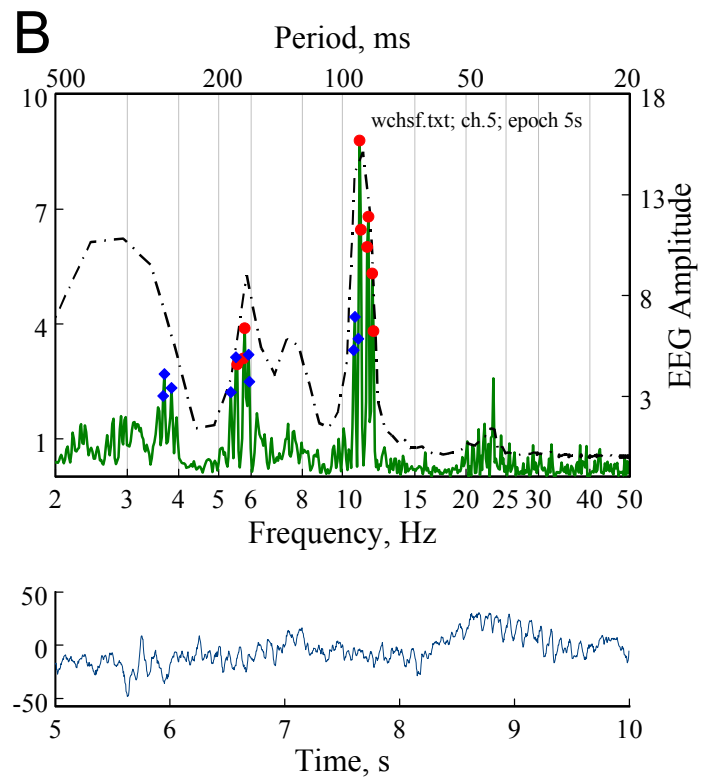
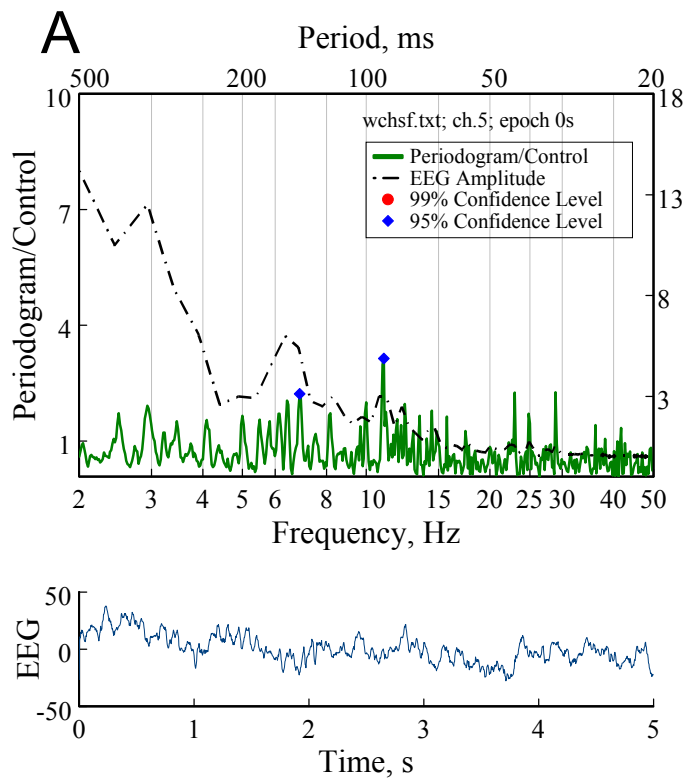


Figure 8.

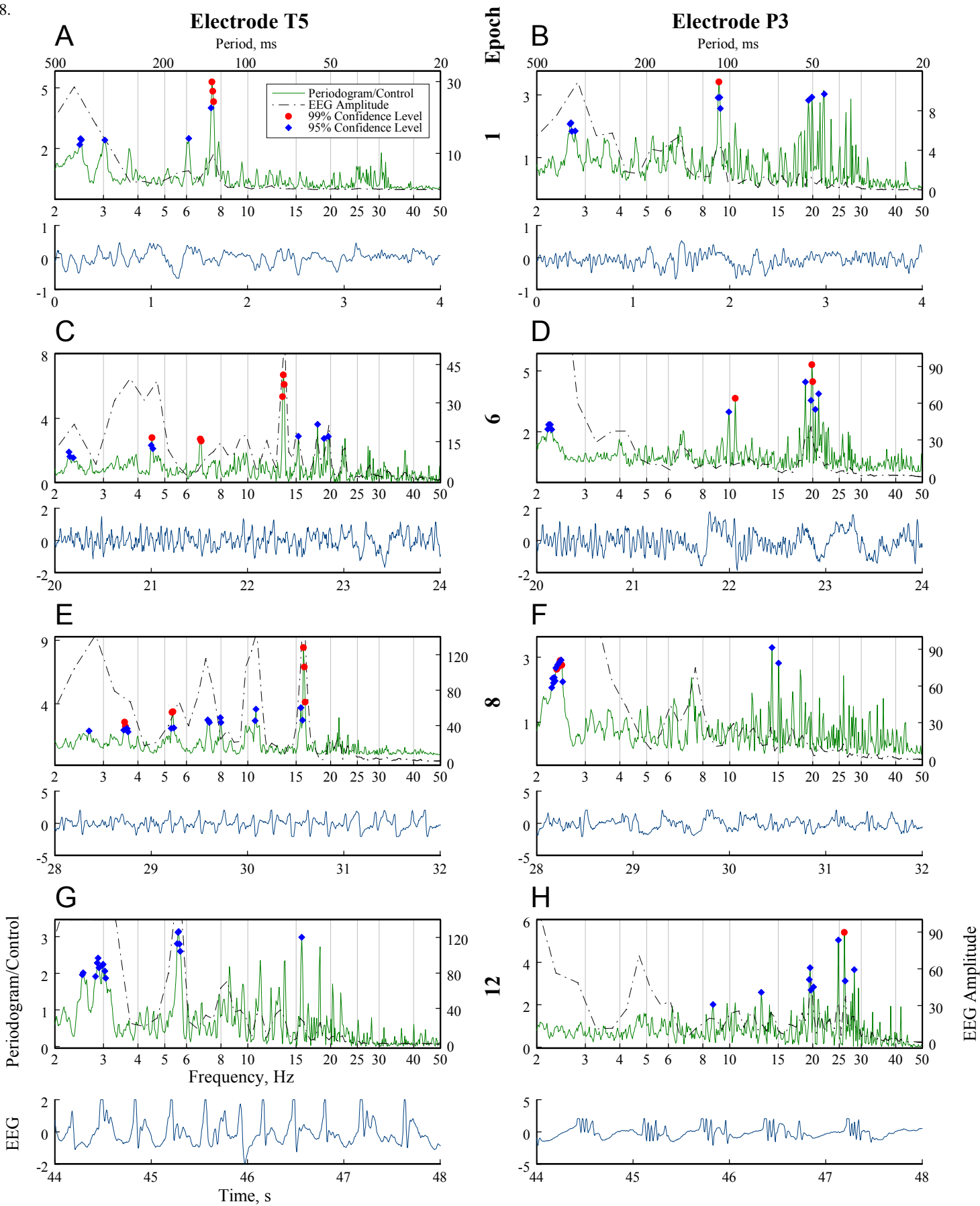


Figure 9.

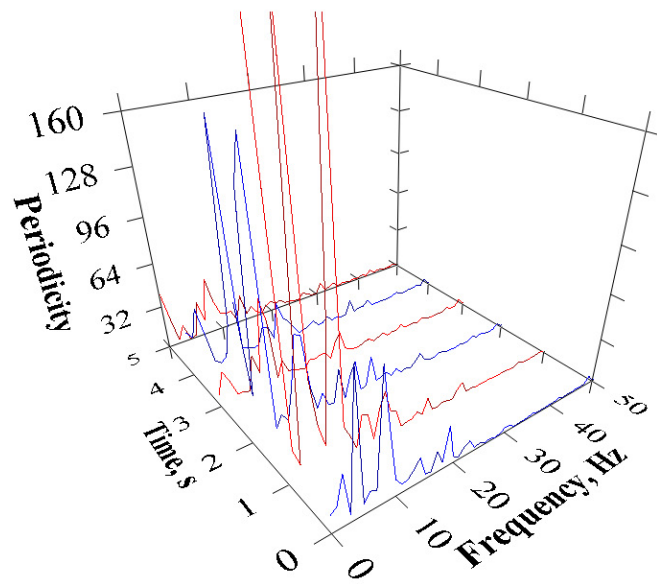


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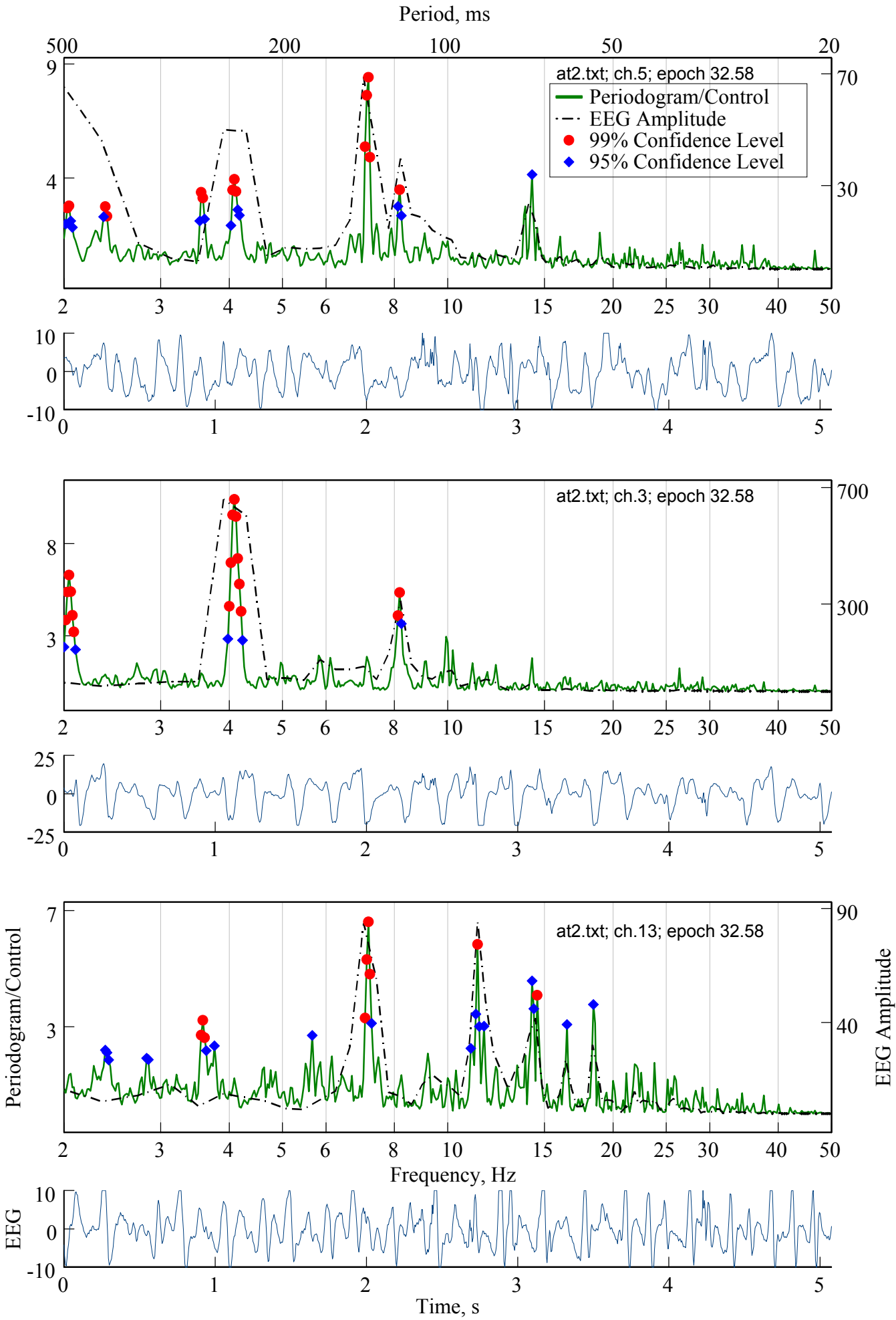


Figure 11.

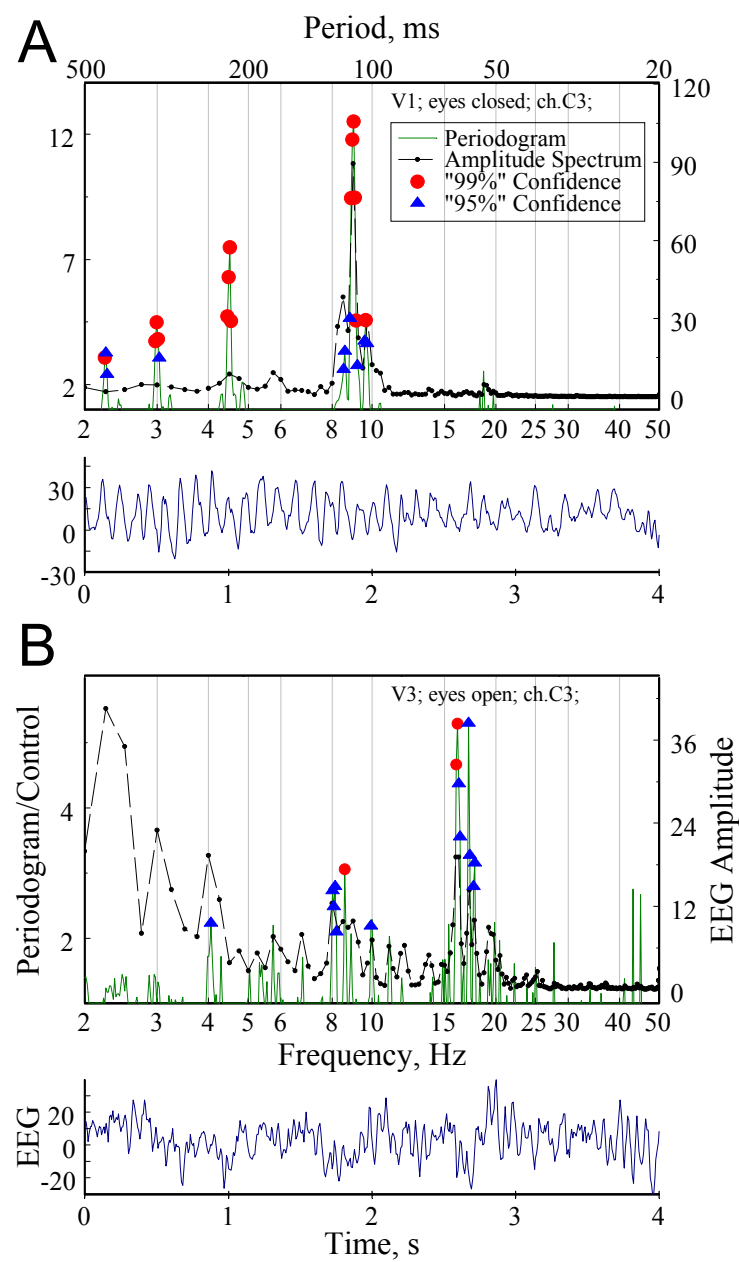


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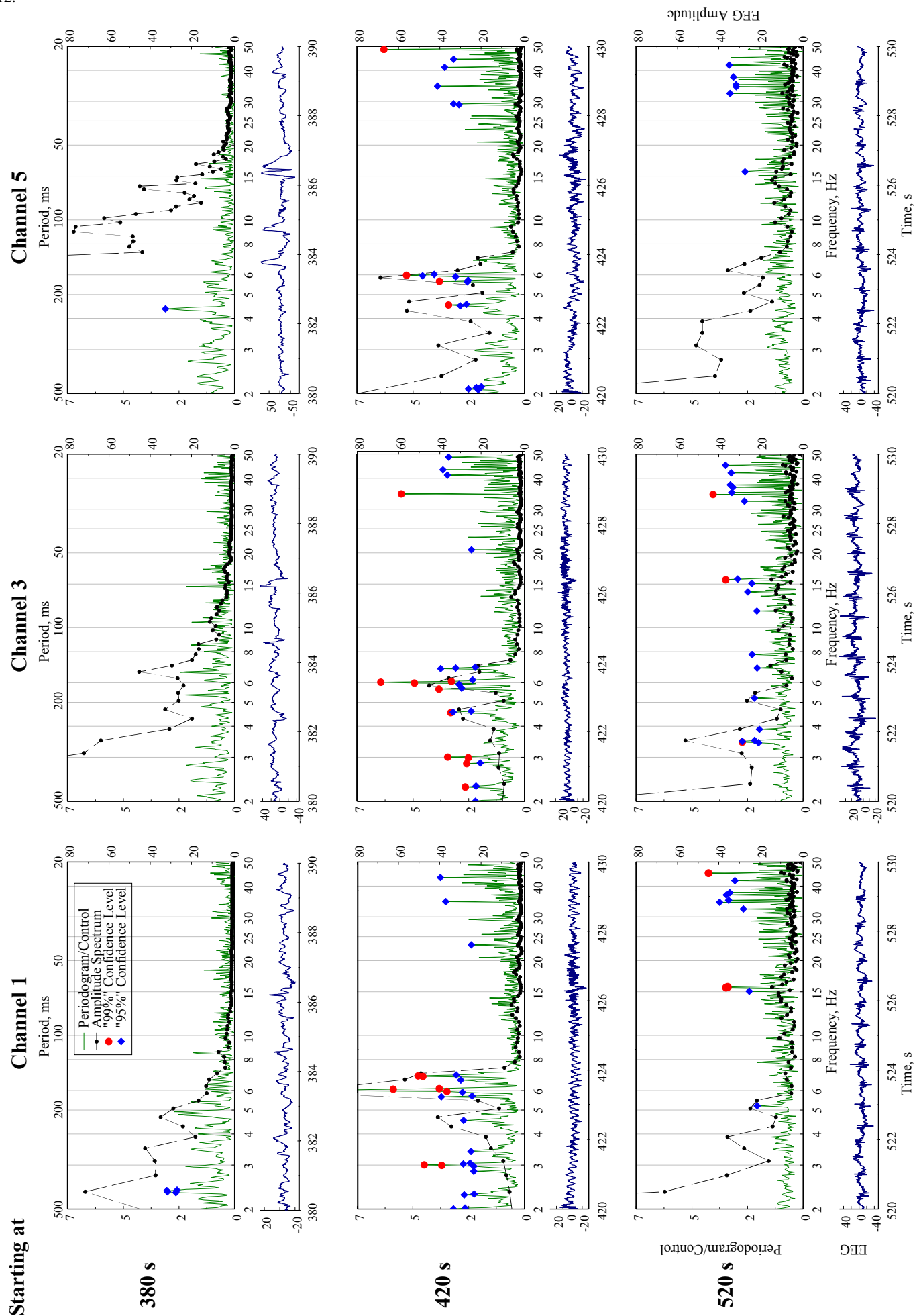


Figure 13.

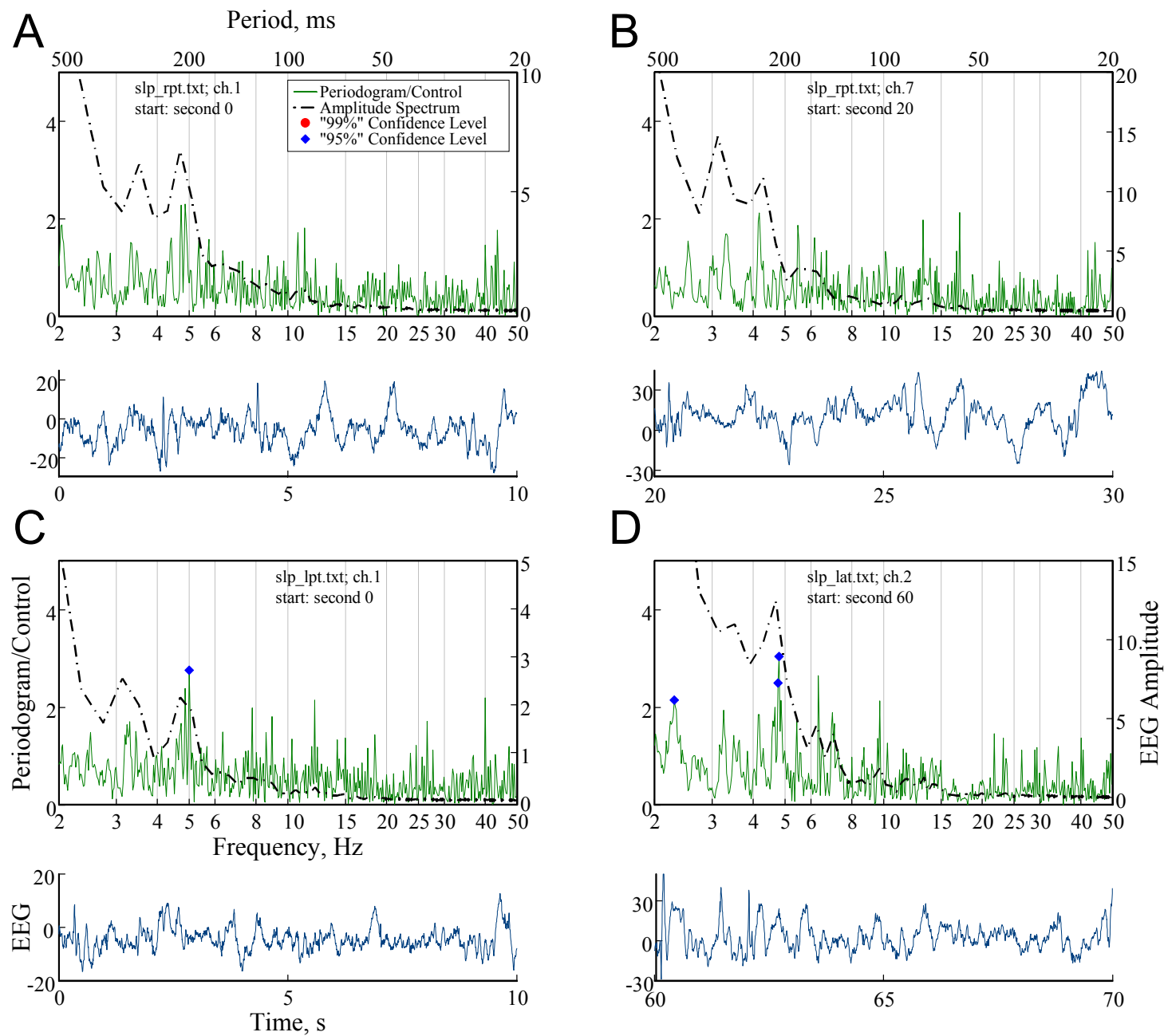


Figure 14.

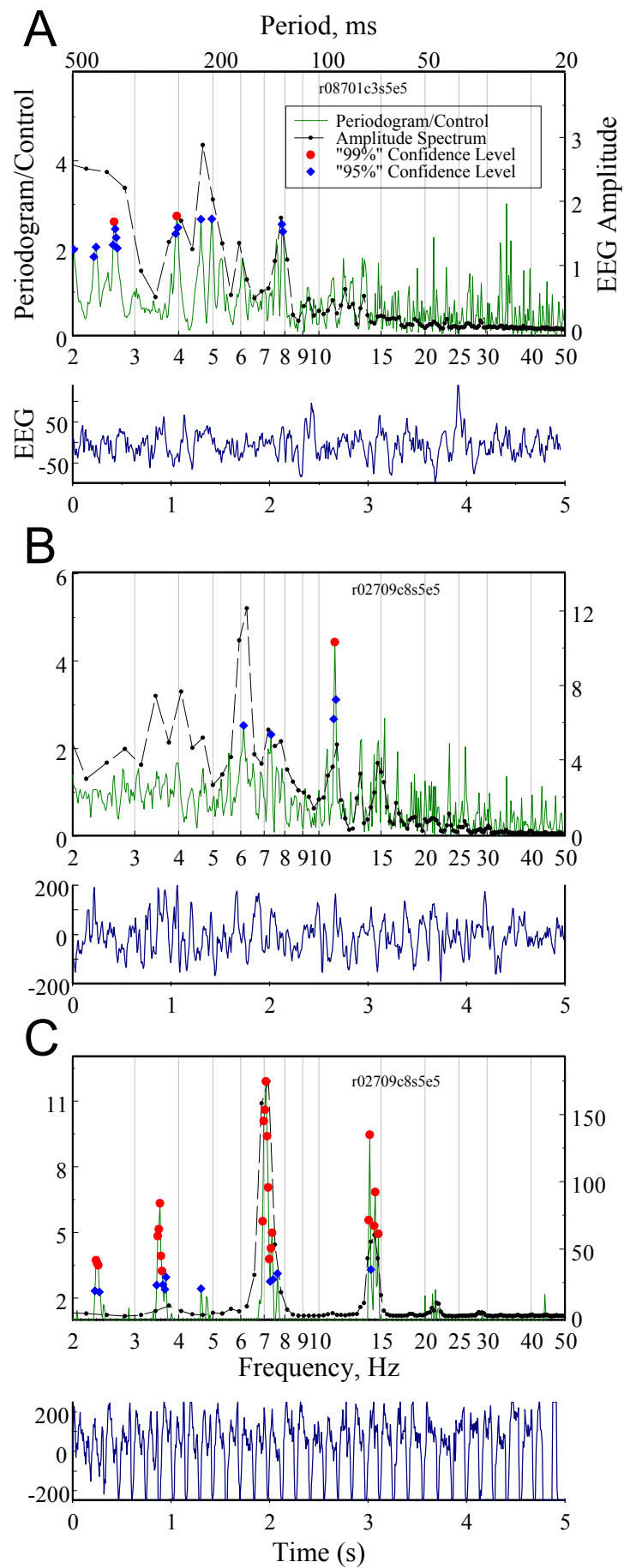


Figure 15.

