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Time-Frequency Characterization of Mismatch Negativity in Nociceptive Responses

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***Abstract*— An efficient way to investigate the neural basis of nociceptive responses is the event-related brain potentials (ERPs). One component belonging to this family of ERPs is the mismatch negativity (MMN). It reflects pre-attentive detection of changes in the incoming stimulus by comparing the new stimulus with sensory memory traces. In this work, single trials of ERP taken from EEG signal recorded under thermal and electric stimulation were analyzed with time-frequency representation (TFR). The main objective of this work was to characterize responses to frequent and infrequent stimuli with TFR functions. Variables defined on instantaneous frequency and instantaneous power presented a statistical significance (p-value<0.0001) differentiating these two kind of responses. Furthermore, differences between the averaged instantaneous power and instantaneous frequency were also analyzed. It was found that instantaneous power and instantaneous frequency were able to better isolate the MMN components from EEG noise in certain frequency bands.**

I. Introduction

EVENT related potentials (ERPs) are transient components in the electroencephalogram (EEG) generated in response to a visual, auditory or nociceptive stimulus. These potentials have been proved to be a helpful tool for the study of high order brain function such as perception, memory and attention. The mismatch negativity (MMN) is an electrical response component of the ERPs, generated as the difference between an infrequent and a frequent stimulus [1]. MMN can be recorded in response to any discriminable change in the stimulus stream. It can be explained by the existence of a memory trace of recent sensory input in which the frequently occurring standard stimulus features are represented [2]. The most recent studies have provided evidence that even complex, temporal, linguistic stimulus features and long-term learning effects are reflected in MMN responses, thus significantly broadening the theoretical scope of the MMN research. Several studies stood out the feature of MMN components for auditory stimulation ERPs [3,4]. It is currently hard to characterize with quite high accuracy this component during electric stimulation [5] and no studies have been published so far on MMN generated by thermal stimulation.

This work presents an analysis based on techniques of time-frequency representation (TFR) of EEG windows containing single trial of responses to thermal and electric stimuli. The pulse train of stimulation is made by two different kind of stimulus, one is frequent and the other infrequent. Several TFR variables were defined in order to better characterize the wave response to frequent and infrequent stimuli in order to show up the MMN component. MMN is seen usually between 150 and 300 ms after electrical stimuli. However, conduction in thermoalgesic pathways is slower and, therefore, the MMN after a thermal stimulus is expected at a latency between 400 and 600 ms.

The MMN component is frequently hidden by noise at various frequency bands generated by different neurons activities. In fact, the simple averaging of the EEG responses is not always able to distinguish those components. In order to find at what frequency band the MMN component is more detectable and separable from the EEG noise, the signals derived from the differences between the averaging of instantaneous frequency and instantaneous power of frequent and infrequent responses were calculated. These signals defined for different frequency bands were able to show and localize the MMN component in time.

II. Materials and Methodology

A. EEG Data and Preprocessing

Two types of stimuli were used. For electric stimuli, the electromyograph (KeypointNET, Alpine), set at an intensity of 8 mA (0.1 rpm), was used. The electric stimuli were applied with surface electrodes to the second and fourth finger of the right hand. For contact heat stimuli, a pair of thermofoil thermode stimulators were used, each with a surface area of 572.5 mm^2 (Pathway, Medoc Ltd, Ramat Yishai, Israel), set to reach a temperature of 53˚C at a rate of 70ºC/s. The thermodes were attached to the dorsum of the hand side by side. All ERPs were recorded from three

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EEG channels (Cz, C3 and C4) referenced to linked earlobes (A1-A2). The impedance was kept below 5 kΩ. All recordings were done with a V-Amp (BrainVision) at a sampling rate from 0.1 to 1000 Hz.

EEG was recorded from 25 healthy subjects (11 males and 14 females), aged 22 to 54 years. The actual recording was done by a technician in a warm and dimly lit room, with series of stimulus type following established recommendations. Subjects were given a book to read to divert their attention from the stimulus. The stimuli were divided in frequent (80%) and infrequent (20%). A total of 800 electrical stimuli to one finger and 200 stimuli to the other finger were applied, switching fingers at 400/100. For the test on thermoalgesic stimuli, a total of 400 stimuli through one thermode and 100 through the other were applied, switching also between thermodes at 200/50. The rate of stimulation was 0.6 Hz for thermal stimulation and 0.9 Hz for electric stimulation.

EEGs were preprocessed by filtering with a Butterworth band-pass filter of 5-th order with cut-off frequencies of 0.1-45Hz in order to reduce the influences of the EMG, EOG and the external noise. Then, they were down sampled to 125 Hz with a FIR decimation filter of 30-th order. This permitted to analyze all the EEGs with the same sample frequency. Finally, EEGs were segmented in windows taken 0.5s before and 1s after the occurrence time of each pulse of stimulation. This window length avoids the overlap between consecutive stimulations, permitting to analyze singularly each response. Channel Cz was selected for the analysis.

B. Time-Frequency Representation

Choi-Williams distribution (CWD) (1) [6] was applied on each EEG window. This is a type of TFR obtained by convoluting the Wigner distribution (WD) (2) and the Choi-Williams (CW) exponential (3),

$$TFR_x(t,f) = \iint_{-\infty}^{\infty} h(t-t', f-f')\, Wx(t',f')dt'df' \quad (1)$$

$$Wx(t,f) = \int_{-\infty}^{\infty} x(t+\tau/2)\ x^*(t-\tau/2)e^{-j2\pi f\tau}d\tau \quad (2)$$

where $x^*(t)$ is the complex conjugate of a signal $x(t)$,

$$h(t,f) = \sqrt{\frac{4\pi}{\sigma_c}}e^{-4\pi^2\frac{(tf)^2}{\sigma_c}} \quad (3)$$

Choosing an adequate parameter σ_c, the function (3) is able to reduce WD cross-terms and preserve the properties of the WD [7], such as the marginal properties and instantaneous frequency. In this work, σ_c was set to 0.005.

For a more accurate analysis, the spectrum was divided into the characteristic frequency bands of the EEGs: Delta (VLF), 0.1-4 Hz; Theta (LF), 4-8 Hz; Alfa (HF), 8-12 Hz; Beta (VHF), >12 Hz; Total frequency band (TB), 0.1-45 Hz.

Two functions were calculated on TFR: *InPow*(*t*), instantaneous power; *InFreq*(*t*), instantaneous frequency. Instantaneous power function was calculated for each window as the integral in frequency of the $TFR_x(t,f)$. In each of the considered bands, this value was normalized by the total power. Subsequently, the instantaneous frequency function was calculated [7] as the average frequency of the spectrum along the time.

C. Definition of Variables and Statistical Analysis

For each window, the following variables were calculated from TFR functions: mean, standard deviation (*std*), maximum (*max*) and minimum (*min*) value, the normalized position of the maximum (*tauMax*) and minimum (*tauMin*) value. These variables were calculated for all the window-length and from 0s to 1s and from 0.5 s to 1 s after stimulation, respectively for electrical and thermal stimulation. In this way, it was possible to deeply analyze the time instants where the responses are expected for thermal and electric stimulations. The Mann-Whitney test, a non-parametric test and therefore independent from the type of distribution, was used for the statistical analysis in order to compare data from two independent populations and to assess whether these two populations come from the same distribution. The considered populations were: windows of response to a frequent stimulation (*F*) and windows of response to an infrequent stimulation (*I*). A statistical significant level *p-value*<0.05 was considered for the present work.

D. Averaging of Time-Frequency Functions

Since instantaneous frequency and instantaneous power maintain time dependence, it was possible to make an averaging study similar to standard evoked potential processing. For each patient, the average of instantaneous frequency and instantaneous power of windows of response to *F* and *I* were calculated. The MMN components (4, 5) were obtained by subtracting the averaged function of windows of response to *F* with the averaged function of windows of response to *I*.

$$MMN(t)_{Pow} = \frac{1}{N}\sum_{i=1}^{N} InPow_{F\ i}(t) - \frac{1}{K}\sum_{i=1}^{K} InPow_{I\ i}(t) \quad (4)$$

$$MMN(t)_{freq} = \frac{1}{N}\sum_{i=1}^{N} InFreq_{F\ i}(t) - \frac{1}{K}\sum_{i=1}^{K} InFreq_{I\ i}(t) \quad (5)$$

where *N* and *K* are the amount of *F* and *I* stimulations, respectively. With this representation, it is possible to stand out the difference between the response to *F* and *I*.

III. Results and Discussion

Tables I and II show the mean value and the standard deviation for the variables with the lowest *p-value* for each stimulation type. Instantaneous frequency and instantaneous power variables were able to distinguish *F* and *I* responses with *p-value*≤ 0.0002 for thermal and electric stimulations. As it can be seen in table I, HF and LF bands are the most differentiated in thermal stimulation. Instead, in electric stimulation, the MMN components stand out also considering the total frequency band as it is shown in table II.

TABLE I
VARIABLES FOR THERMAL STIMULATION

Variable	I (m ± σ) K = 527	F (m ± σ) N = 2122	p-value
InPow_HF_max	0.6617 ± 0.2017	0.6269 ± 0.2003	0.0002
InPow_HF_max_05s	0.5870 ± 0.2362	0.5341 ± 0.2343	< 0.0001
InPow_HF_mean_05s	0.2483 ± 0.1431	0.2208 ± 0.1336	0.0001
InPow_HF_std_05s	0.1423 ± 0.0651	0.1289 ± 0.1332	< 0.0001
InFreq_LF_mean_05s	1.557 ± 0.132	1.529 ± 0.210	< 0.0001

InPow, instantaneous power; InFreq, instantaneous frequency; std = standard deviation; _05s = from 0.5s to 1s after the stimulation.

TABLE II
VARIABLES FOR ELECTRIC STIMULATION

Variable	I (m ± σ) K = 1200	F (m ± σ) N = 4846	p-value
InPow_VHF_tauMax_1s	0.4544 ± 0.3597	0.5185 ± 0.3463	< 0.0001
InPow_LF_tauMax_1s	0.3140 ± 0.3157	0.3599 ± 0.3214	< 0.0001
InPow_VLF_tauMax_1s	0.3375 ± 0.3242	0.3903 ± 0.3262	<0.0001
InPow_TB_mean	249.4 ± 298.5	234.3 ± 353.1	< 0.0001
InFreq_TB_mean	12.0 ± 2.38	12.3 ± 2.44	0.0001

InPow, instantaneous power; InFreq, instantaneous frequency; std = standard deviation; tauMax = normalized position of maximum value; _1s = from 0s to 1s after the stimulation.

In table III, variables able to distinguish the response to *F* and *I* stimulus are shown for the two types of stimulation with a statistical significant level. In instantaneous power, the peak value and the position of this peak are the best variables able to stand out MMN component.

Figures 1 to 4 show the difference of the averaging between *F* and *I* of the EEG amplitude, the instantaneous power (4) and instantaneous frequency (5) for thermal or electric stimulation.

The maximum difference (peak or valley) corresponding to MMN component was expected in time windows of 400-600 ms after the thermal stimulus and 150-300 ms after the electric stimulus. It can be noticed that the averaged EEGs (figure 1a) cannot show a real peak in the difference corresponding to MMN component.

Instead, the peak and the valley at about 500 ms stand out the MMN component respectively in instantaneous frequency (figure 1b) and in instantaneous power (figures 1c and 1d).

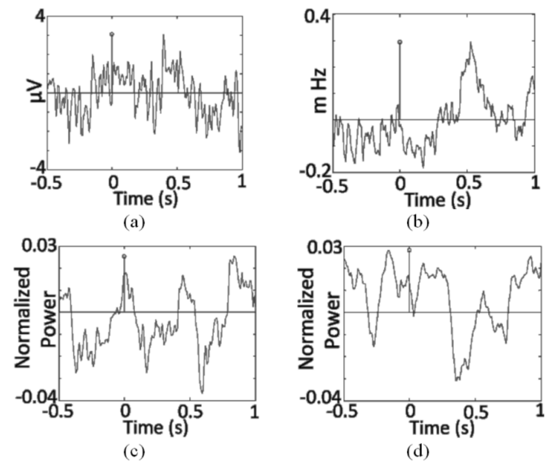

Fig. 1. Difference between F and I of averaged EEGs for thermal stimulation of a patient: (a) EEG Amplitude; (b) Instantaneous Frequency at LF; (c) Instantaneous Power at LF; (d) Instantaneous Power at HF.

Figure 2 shows that the component for electric stimulation at 200 ms is more visible both in EEGs (Figure 2a) and instantaneous power (figures 2c and 2d). In instantaneous frequency this component is less evident. The MMN component for thermal and electric stimulation stand out in the averaging of all the patients (figures 3 and 4).

IV. Conclusions

Time-frequency representation (TFR) has demonstrated to be helpful in the characterization of the MMN component. Statistical analysis reveals some significant differences in the TFR defined variables between response to frequent and infrequent stimulus. These stand out making the differences of the TFR function, instantaneous frequency and instantaneous power.

TABLE III
VARIABLES FOR ELECTRIC AND THERMAL STIMULATION

	Thermal Stimulation			Electric Stimulation		
Variables	I (m ± σ) K = 527	F (m ± σ) N = 2122	p-value	I (m ± σ) K = 1200	F (m ± σ) N = 4846	p-value
InFreq_HF_std	0.0484 ± 0.0218	0.0512 ± 0.0212	0.0143	0.0526 ± 0.021	0.0508 ± 0.0209	0.0061
InPow_HF_mean	0.2344 ± 0.1085	0.2226 ± 0.1025	0.0244	0.2104 ± 0.0989	0.219 ± 0.1033	0.0156
InPow_HF_max_05s	0.5870 ±0.2362	0.5341 ± 0.2343	<0.0001	0.5538 ± 0.2364	0.5303 ± 0.2397	0.0023
InPow_HF_std_05s	0.1423 ± 0.0651	0.1289 ± 0.0632	<0.0001	0.1381 ± 0.0662	0.1306 ± 0.0668	0.0003
InPow_HF_tauMax	0.5398 ±0.2635	0.4962 ± 0.2733	0.001	0.5060 ± 0.2475	0.4915 ± 0.2628	0.019
InPow_LF_max_05s	0.6384 ± 0.2026	0.6124 ± 0.21	0.0133	0.6061 ± 0.2243	0.5758 ±0.2262	< 0.0001
InPow_LF_std_05s	0.1443 ± 0.057	0.1354 ± 0.0571	0.0009	0.1381 ± 0.0609	0.1304 ±0.0607	< 0.0001
InPow_LF_tauMax	0.5303 ± 0.2582	0.4970 ± 0.2668	0.0084	0.5065 ± 0.2413	0.4927 ± 0.2608	0.0223
InPow_VLF_tauMax	0.5281±0.2594	0.5004 ± 0.2678	0.0274	0.5076 ± 0.2442	0.4914 ± 0.2643	0.01

In = instantaneous; Freq= frequency; Pow = power ; std = standard deviation; tauMax = normalized position of maximum value; _05s = from 0.5s to 1s after the stimulation

This study has shown that instantaneous power could better separate MMN component from noise. However, this is a preliminary study of the application of TFR on the characterization of MMN component for thermal and electric stimulus. Further analysis will be applied in order to improve the methodology, especially in the response to thermal stimulation which has not been reported before.

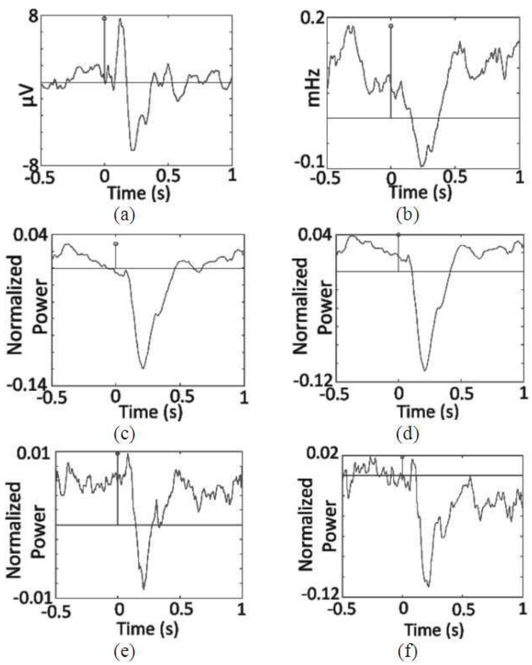

Fig. 2. Difference between F and I of averaged EEGs for electric stimulation of a patient: (a) EEG Amplitudes; (b) Instantaneous Frequency at LF; (c) Instantaneous Power at LF; (d) Instantaneous Power at HF; (e) Instantaneous Power at VHF; (f) Instantaneous Power at the TB.

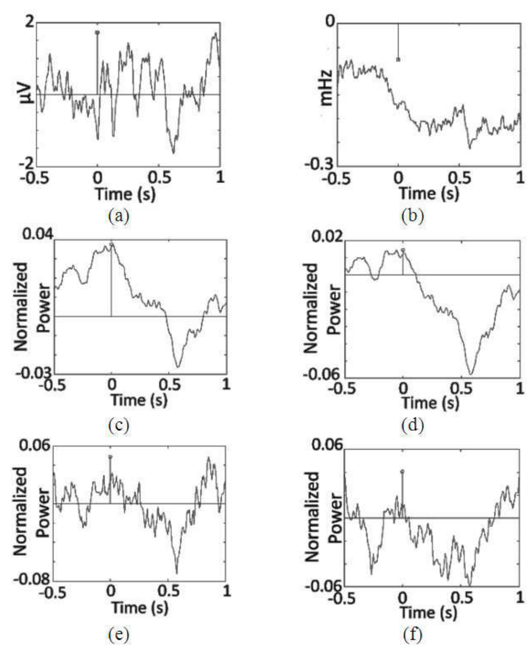

Fig. 3. Difference between F and I of averaged EEGs for thermal stimulation of all patients: (a) EEG Amplitudes; (b) Instantaneous Frequency at LF; (c) Instantaneous Power at LF; (d) Instantaneous Power at HF; (e) Instantaneous Power at VHF; (f) Instantaneous Power at the TB.

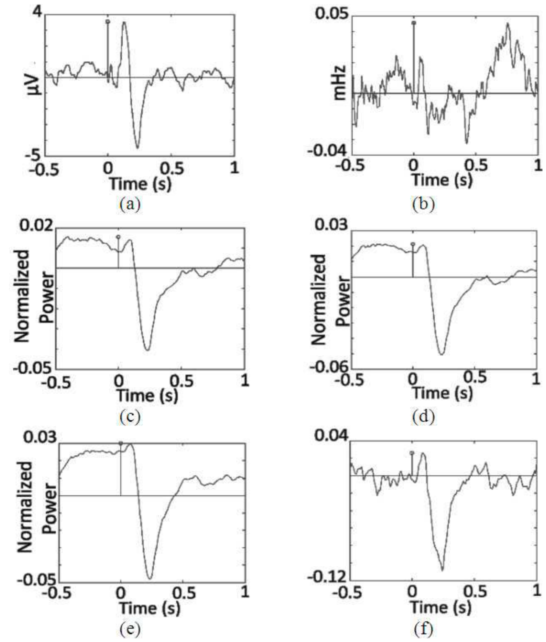

Fig. 4. Difference between F and I of averaged EEGs for electric stimulation of all patients: (a) EEG Amplitudes; (b) Instantaneous Frequency at HF; (c) Instantaneous Power at VLF; (d) Instantaneous Power at LF; (e) Instantaneous Power at HF; (f) Instantaneous Power at TB.

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