A system for the automatic analysis of brain responses evoked by musical stimuli

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1 Introduction

The system described in this technical note was implemented for two purposes: (a) to produce stimuli, significant from the musical viewpoint, according to an appropriate protocol, (b) to acquire and process the Evoked Responses Potentials (ERPs) that are elicited as responses to these stimuli.

This system was built within the scope of a research focused on the study of brain responses to musical stimuli. Recent literature about this topic has reported a number of significant results, which from the one hand have contributed to a better knowledge of the cognitive mechanisms of the human mind and, from the other, appear to suggest useful and important applications in the field of neurological clinics. Our research was carried out as a collaboration activity between researchers of the Signals and Images Laboratory of the ISTI and physicians of the Neuroscience Department of Pisa Hospital (Magrini et al., 2012; Carboncini et al., 2012; Virgillito et al, 2013a; Virgillito et al., 2013b). The system here described was devised as an integration of the BQ132S EEG amplifier (BrainQuick System, Micromed), which was used for recording electroencephalographic (EEG) signals.

The ERP signals, i.e. EEG signals obtained as responses to sensory and/or psychological stimulation, consist of components that are generally well defined with regard to their time latency, topographical distribution, and psychophysiological meaning. It is usually impossible to recognize single responses, because their amplitude is much smaller than the amplitude of the background EEG signal. However, it is possible to markedly decrease the background noise and to obtain signals with clearly recognizable components by administering a succession of stimuli and then summing the successive EEG signals starting from a precise instant in the stimulus. Among the most important components, which have been widely studied in the literature, are the Mismatch Negativity (MMN) and the P300. The MMN, which is larger in the fronto-central regions and has a latency of 150-250 ms, has been interpreted as reflecting an automatic process for the recognition of deviations of the current stimulus with respect to previous stimuli. The P300, a positive component with a latency of 250 – 500 ms or more, is characterized by a remarkable amplitude increase that occurs when the current stimulus is less probable. Among the most important components of the ERP responses to musically significant stimuli are the so-called ERAN, having latency in the 180-270 ms range, and the so-called N5, having a latency of about 550 ms. The N5 has been interpreted as corresponding to the integration of an unexpected chord within a defined harmonic context. A further significant component is the Late Positive Component (LPC), whose latency is always longer than 500 ms.

In the light of recent literature, we have preferred to apply stimuli consisting of cadences, i.e. chord successions. We have attempted to use successions of only three chords: the first and the second had the property of establishing the precise tonal context in an unambiguous way according to the rules of the so-called western tonal system, while the third chord was either in agreement or in disagreement with the tonal context determined by the two previous chords: the probabilities of agreement and disagreement could be defined arbitrarily.

The implemented system consists of the following parts:

(a) hardware – software subsystem for the production of stimuli according to pre-defined protocols (the following choices are arbitrary: time length of the chords, time intervals between two consecutive stimuli, number of stimuli to administer, respective percentages of the two kinds of stimuli, and possibility of varying the key of the tonal key in the course of the stimulation);

(b) hardware – software subsystem for recording the EEG responses with a synchronization mechanism connected with the stimulation subsystem;

(c) software subsystem for artifact removal, for computation of the average ERP responses by means of summation of an appropriate number of singles responses, and for computation of the so-called "grand average", i.e. the average calculated over the various subjects (the ERP responses, for each subjects as well as for the grand average, are calculated for each electrode site and for each of the two kinds of stimuli);

(d) software subsystem for the recognition of those time intervals that are characterized by statistical significance of the difference between the responses to the two kinds of stimuli;

(e) software subsystem for the visualization of the topographical distribution of the ERP responses over the various electrode sites.

So far, the system has been applied to the signals recorded from eight subjects.

2 Stimulation subsystem

We now describe the stimulation protocol that we introduced for our study and the HW/SW system that was implemented for the production of stimuli in agreement with this protocol.

2.1 Stimulation protocol

The purpose of the research was the computation and characterization of the ERP responses respectively elicited by the following two classes of stimuli:

a) Standard (more frequent) stimuli: successions of three major chords (sub-dominant, IV; dominant, V; and tonic, I), the key being a random note in the chromatic scale (this three-chord cadence completely identified the key);
b) Deviant stimuli: successions of two major chords (V, I) followed by a wholly dissonant third chord, consisting of a cluster of four notes at 1-semitone intervals, which was obviously in disagreement with the key defined by the previous two chords.

The time length of each chord was 350 ms; therefore, the length of the whole sequence was 1050 ms. A 950-ms pause was inserted between two consecutive chord sequences. The deviant stimuli were produced with a probability of 20%.

The recording session for each subject consisted of 500 three-chord sequences and was divided into five sub-sessions. The deviant stimuli, their percentage being 20%, were 100 out of 500.

2.2 Subsystem for sound production

An application for sound production was implemented using the C++ language. It was run on a notebook with operating system Microsoft Windows 7.

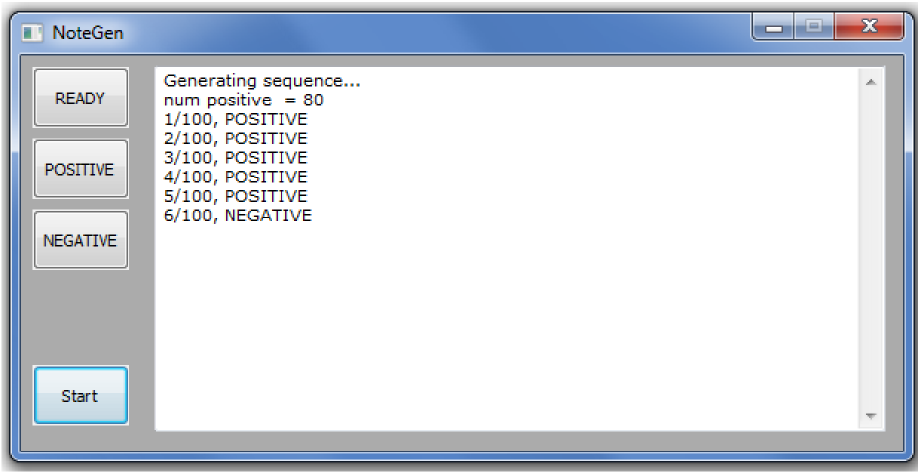

Figure 1 – GUI of the application for sound production.

The SW application for sound production used the General MIDI Synthesizer integrated in the Windows operating system. It consisted of two modules: the first allowed storing detailed information regarding the succession of stimuli determined by the protocol described in Section 2.1; the second allowed the corresponding sounds to be actually produced during the recording sessions. The General MIDI Synthesizer can produce musical notes with a variety of timbres, according to the MIDI commands that it receives. The MIDI protocol, based on a serial connection (either physical or virtual) allows a controller (a keyboard, or a procedure as well) to send commands to an executing device (e.g., a synthesizer). Typical commands are "release key X in the keyboard" or "press key X in the keyboard".

In other words, after the chord succession was established, the stimulation procedure sent the corresponding set of MIDI instructions to the Windows synthesizing module General MIDI, thus actually producing the stimulation sounds through the audio card. The MIDI protocol made it possible to select the timbre of the produced sounds among a set of available choices (their number was 127, according to the standard General MIDI). In our case, we selected the piano timbre, considering it as generally recognizable and "neutral".

3 Subsystem for the acquisition of the EEG traces

Nineteen electrodes were placed according to the standard 10-20 System: using the conventional terminology, the EEG traces were: Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, 01, O2.

The HW acquisition device received the EEG signal from the electrodes and sent it to a notebook through a fast connection (optical connection + Express Card). SW procedures running in this notebook allowed configuring the card, recording the EEG signals, and visualizing these signals.

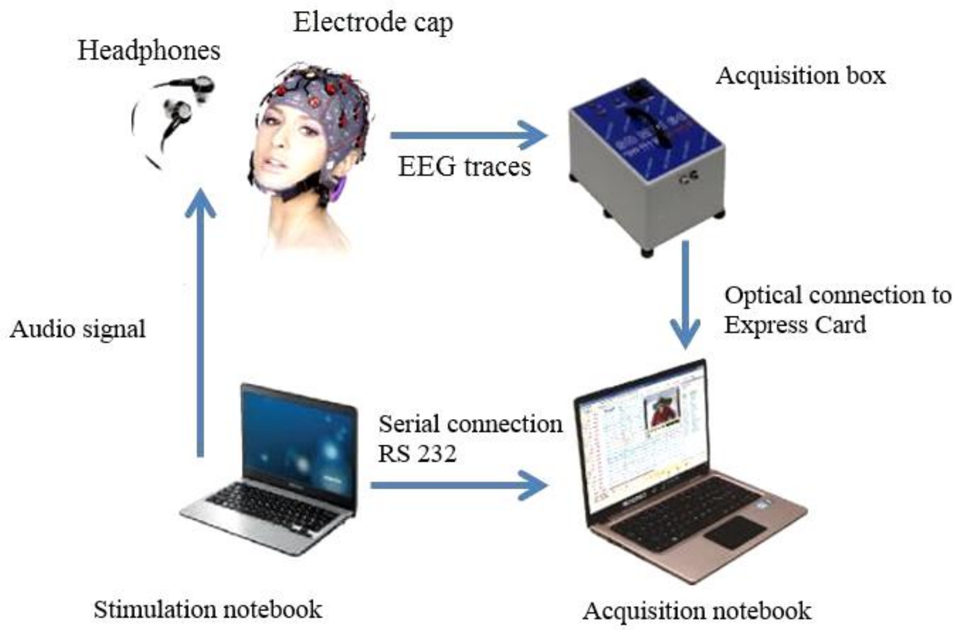

Figure 2 – Configuration of the acquisition system

3.1 Synchronization

The typical method for the acquisition of evoked potentials usually consists in recording the responses to a succession of stimuli and then averaging these responses, thus reducing noise and artifacts. In order to assure that this processing is successful, the time intervals corresponding to the various responses must be correctly identified, by means of a perfectly synchronous correspondence between EEG signals and stimuli. For this purpose, we implemented a serial synchronization mechanism: at the start time of each stimulus, a one-byte message was sent to the EEG-acquisition device through the serial port. This message contained the information regarding the class of the stimulus, either standard (more frequent) or deviant. The acquisition procedure then inserted a time marker, corresponding to the start time of the stimulus, into the signal traces: in this way, during the analysis stage, the task was facilitated of joining and/or segmenting the responses.

4 Subsystem for the calculation of the ERP responses

This subsystem was implemented in the Matlab environment, specifically using the EEG Lab toolbox, a software library for the processing of EEG signals. The responses obtained during each session were loaded into EEG Lab, filtered between 0.5 Hz and 40 Hz., and then processed.

4.1 Artifact removal through ICA

Independent Component Analysis (ICA) is a computational method that allows separating a multifold signal into its additive subcomponents. In fact, in our case, we assumed that the whole signal, consisting of the traces elicited by the various electrodes, and containing artifacts and noise in addition to the proper ERPs, could be approximately described as linear combinations of subcomponents. We applied the ICA method to remove, or at least substantially reduce, artifacts, such as those due to ocular movements.

The first stage of the ICA procedure separated n subcomponents starting from the n given linear combinations (i.e., EEG traces). Then, the EEG Lab toolbox offered a graphical representation of the subcomponents. At this point, artifacts due, for instance, to blinking were easily recognizable for their shape and periodicity. The toolbox also provided a color-coded graphical representation of the topographical distribution of the various subcomponents: for instance, the blinking subcomponents presented a clear frontal prevalence.

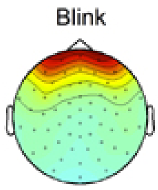

Figure 3 – Topographical distribution of artifacts due to blinking

At this point, the subcomponents due to artifacts, such as those due to blinking or to electromagnetic interference, were removed. Then, the inverse ICA procedure was applied, to obtain linear combinations that no longer contained the subcomponents due to artifacts.

4.2 Epoch selection

After the removal of artifacts, the EEG signal was segmented into "epochs", i.e. time intervals that corresponded to single stimuli. According to the stimulation protocol described in Section 2.1, the time distance between two consecutive stimuli was 2 seconds. We decided to consider epochs starting at the beginning of the third chord of each stimulus and lasting one second, assuming that the maximum latency of significant ERP components was not longer than 1 second.

The epochs were then labeled according to the two stimulus classes (standard and deviant) by taking account of the markers inserted by the stimulation subsystem (see

Section 2.2). After this stage of segmenting and labeling, we obtained 400 epochs corresponding to standard stimuli and 100 epochs corresponding to deviant stimuli. Out of the 400 epochs of the former class, 100 were randomly chosen, in order to have the same number of epochs for the two classes. This number was then reduced to 80 considering that artifacts were probably still present, in particular those to movements of the subject, and that these artifacts were expected to introduce large deviations in the average amplitudes of the signals. For this purpose, a quantitative parameter was calculated for each epoch, given by the ratio between the maximum difference from the average amplitude and the average amplitude. The 20 epochs that presented the maximum values of this parameter were then discarded.

4.3 Calculation of individual ERPs and of the grand average

For each subject, each trace, and each class of epochs, the individual ERP responses were computed by averaging the EEG traces over the 80 selected epochs. The grand average was then calculated, i.e. the average over the subjects, for both classes. The grand average offered a visually impactful representation of the various ERP components, thus providing a remarkable confirmation that the properties of the various components were common to the subjects.

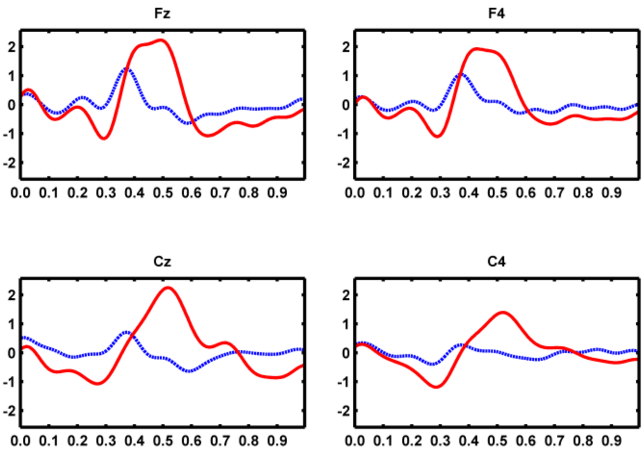

Figure 4 – Example of grand average for four traces

Figure 4 shows the grand averages for traces Fz, F4, Cz and C4, the blue line corresponding to the more frequent stimuli and the red line corresponding to the deviant stimuli.

5 Calculation of the statistical significance

A statistical procedure was implemented to measure and effectively represent the significance of the results. For each subject and each trace, this procedure was applied to the individual ERP responses. The 1-s epochs were subdivided into overlapping subintervals, each of which lasted 100 ms. For each epoch and each subinterval, two vectors, Va and Vb, were then computed, whose size was equal to the number of subjects, containing the average amplitude values of the responses over the interval: these vectors were obtained considering the responses to the standard and to the deviant stimulus, respectively. The non-parametric Wilcoxon test was then applied to check if the following hypothesis could be rejected: "the statistical distribution of the two vectors presents the same median value". The application of this test provided a quantitative measure of statistical significance, given by a probability level of error: in other words, low values of this measure confirmed the hypothesis that the median values were different: usually, significance measures smaller than 5% are considered to indicate that the difference is significant. A visual representation of the statistical results was obtained by building graphs of the statistical significance as a function of time for each trace, considering, for each instant, the 100-ms interval centered on that instant. In Figure 5, which refers to traces Fz, F4, Cz and C4, the vertical axis indicates the percentage values obtained by subtracting the statistical significance from the 100% value. Therefore, high values in the vertical axis indicate that the hypothesis of difference between the two responses had a high statistical significance.

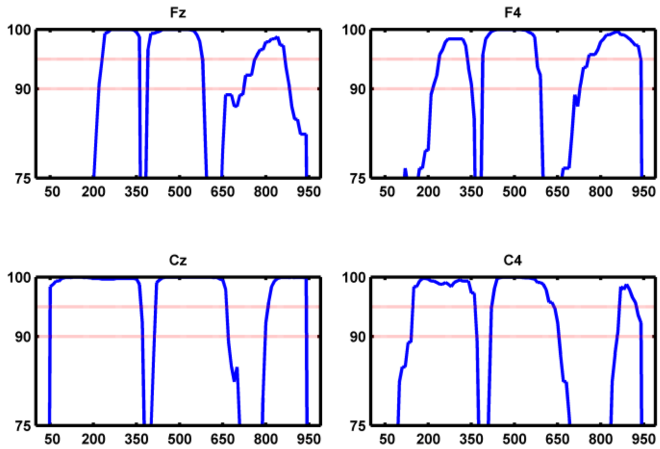

Figure 5 – Graphical representation of the statistical significance for four traces.

6 Computation of the space distribution of the ERPs

The EEG Lab toolbox was used to obtain a visually effective representation of the topographic properties of the various components at each instant by means of color-coded maps obtained by interpolation of the various EEG traces over a 2-dimensional circular view of the encephalon.

This representation allowed advancing hypotheses about the brain regions where the various components originated. This point is particularly important for future applications in neurological clinics.

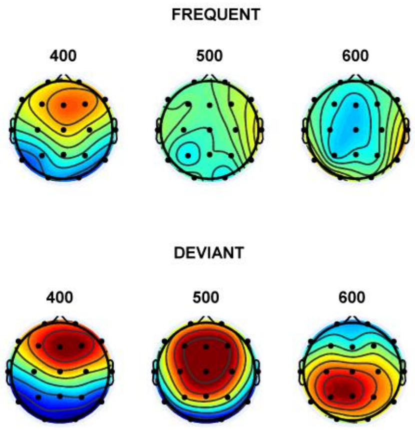

Figure 6 – Topographical representation of the responses to the standard and deviant stimuli, respectively, at 400, 500, and 600 ms.

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