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WHAT CAN WE LEARN FROM SINGLE-TRIAL EVENT-RELATED POTENTIALS?

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Abstract

We present a method for visualizing single-trial evoked potentials and show applications of the consequent single-trial analysis. The method is based on the wavelet transform, which has an excellent resolution both in the time and frequency domains. Its use provides new information that is not accessible from the conventional analysis of peak amplitudes and latencies of average evoked potentials. We review some of the applications of the single trial analysis to the study of different cognitive processes. First, we describe systematic trial-to-trial changes reflecting habituation and sensitization processes. Second, we show how an analysis of trial-to-trial latency variability gives new insights on the mechanisms eliciting a larger mismatch negativity in control subjects, in comparison to sleep deprived subjects when performing a pattern recognition learning task. Third, we show in a rhythm perception task that trained musicians had lower latency jitters than non-musicians, in spite of the fact that there were no differences in the average responses. We conclude that the single trial analysis of evoked potentials opens a wide range of new possibilities for the study of cognitive processes.

1. Introduction

It is common practice to study electroencephalographic (EEG) responses, recorded by scalp electrodes, to different types of sensory stimulation. These evoked, or more generally, event-related potentials (ERPs), are very small in comparison with the ongoing electroencephalogram (EEG) and are barely visible in the individual trials. Therefore, most ERP research relies on the identification of different waves after averaging several presentations of the same stimulus pattern. From the average responses it is possible to

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identify evoked components, whose amplitudes, latencies and topography have been successfully correlated with different sensory and cognitive functions in both the healthy and disordered brain (Regan, 1989; Quian Quiroga, 2006).

Although ensemble averaging of individual cerebral responses improves the signal-to-noise-ratio, it relies on the basic assumptions that the evoked responses constitute an invariant pattern that is perfectly locked to the stimulus (assumption 1), laying on an independent stationary and ergodic stochastic background EEG signal (assumption 2) (beim Graben et al, 2000; Frisch et al, 2004). These assumptions are in strict sense not valid. In particular, it has been shown that the spectral content of the background EEG at the time of stimulation does have a strong influence on the ERP waveform (Jongsma et al., 2000a; 2000b). And, more importantly, averaging implies a loss of information related to systematic or unsystematic variations between the single-trials. These variations might affect the reliability of the average ERP as a representation of the single trial responses and such information may be crucial to study the time course of dynamic cognitive processes, simple and complex behavioral patterns and cognitive dysfunctions in pathological conditions.

Growing evidence shows the important contributions of single-trial ERP analysis to cognitive neuroscience (see e.g. Quian Quiroga, 2006). From a physiological perspective, one might expect that neural responses are modified after several repetitions of the same stimulation pattern, or that they change during the emergence and consolidation of new brain representations, as occurs during learning processes. Single-trial analysis techniques are particularly suitable to gain insights into the time course of neural responses associated to cognitive acts. The present study is aimed at describing a denoising method that is applied to single brain responses. In the following sections, recent contributions of the subsequent single-trial analysis to cognitive processing will be showed, particularly stressing how the tracking of the single-trial responses allows the study of neural phenomena inherent to habituation, learning, and memory processes.

2. Wavelet Transform

The wavelet transform of a signal *x(t)* is defined as the inner product between the signal and the wavelet functions $\Psi_{a,b}(t)$

$$W_{\psi}x(a,b) = \left\langle x(t), \psi_{a,b}(t) \right\rangle$$

where $\Psi_{a,b}(t)$ are dilated (contracted) and shifted versions of a unique *wavelet function* $\Psi(t)$ *(usually called "mother wavelet")*

$$\psi_{a,b}(t) = |a|^{-1/2} \psi\left(\frac{t-b}{a}\right),$$

(*a,b* are the scale and translation parameters, respectively). In brief, the wavelet transform gives a time-frequency representation of a signal that has two main advantages over previous methods: a) an optimal resolution both in the time and in the frequency domains, adapted for

each frequency; b) the lack of the requirement of stationarity of the signal. These advantages are particularly suited for the analysis of ERPs, since these brain responses show multiple frequency components with different time localizations (Quian Quiroga et al, 2001). In order to avoid redundancy and to increase the efficiency of algorithm implementations, the wavelet transform is usually defined at discrete scales *a* and discrete times *b* by choosing the dyadic set of parameters $a^{j} = 2^{-j}$, $b_{j,k} = 2^{-j}k$, for integers *j* and *k*. The wavelet transform gives a decomposition of *x(t)* in different scales, tending to be maximum at those scales and time locations where the wavelet best resembles *x(t)*. Contracted versions of $\Psi_{a,b}(t)$ will match high frequency components of *x(t)* and on the other hand, dilated versions will match the low frequency ones.

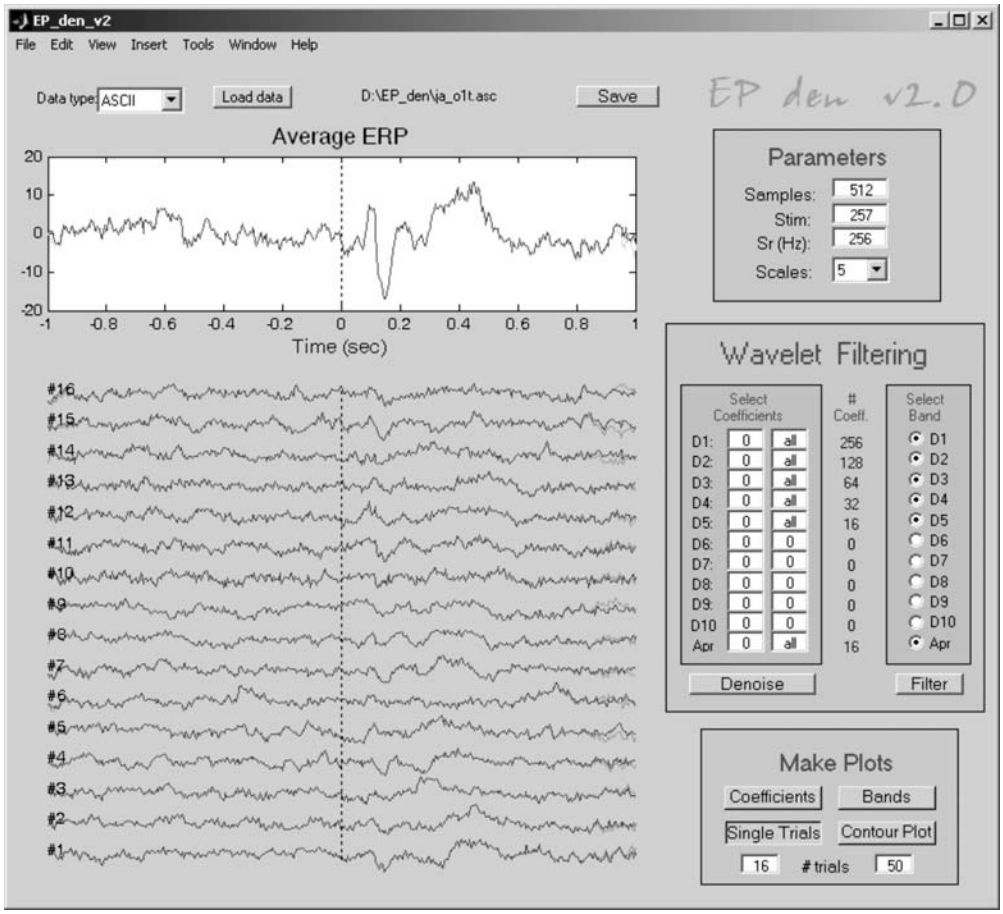

Figure 1. Single-trials (bottom) and the average ERP response (top) to pattern visual stimulation. Note that evoked responses are clear in the average signal but are hard to be seen in the single-trials.

The information provided by the wavelet transform is structured according to a hierarchical scheme called multiresolution analysis (Mallat, 1989). This method gives a decomposition of the signal in different level of 'details' (i.e. components in consecutive frequency bands) and a final approximation or 'residual' that is the difference between the original signal and the sum of all the details. One main advantage of the multiresolution

decomposition is that it can be implemented with recursive and fast algorithms (for details, see Quian Quiroga et. al, 2001 and references therein). Moreover, components corresponding to the different frequency bands can be reconstructed by applying an inverse transform.

In the present study, a five level decomposition was used, thus having five scales of details (D_1 to D_5) and a final approximation (A_5). Cubic bi-orthogonal B-Splines (Cohen et al, 1992) were chosen as the basic wavelet functions due to their similarity with the evoked neural responses (thus having a good localization of the ERPs in the wavelet domain), and due to their optimal time-frequency resolution (for more details see Cohen et al, 1992; Chui, 1992; Unser et al, 1992; Quian Quiroga et al, 2001).

3. Obtaining Single-Trial ERPs with Wavelet Denoising

Figure 1 depicts an event-related cortical response evoked by a checkerboard pattern. This figure and the following ones are the output of a software package for denoising ERPs (EP_den) available from the internet (webpage: www.vis.caltech.edu/~rodri). These waveforms were obtained from a scalp electrode located over the left occipital lobe in response to 16 target stimuli within an oddball paradigm, in which infrequent target stimuli have to be detected within a sequence of frequent (non-target) ones. Non-target stimuli were color reversals of a checkerboard pattern and target stimuli were also color reversal of the checkerboard but with a small displacement. Subjects were instructed to pay attention to the appearance of target stimuli (Quian Quiroga and Schürmann, 1999). Note in the average ERP response the presence of a first positive deflection at 100 ms (P100) followed by a negative rebound at 200 ms (N200). At 400ms we observe a large and slower positive peak, the P300, which is usually elicited by the target stimuli. These evoked responses are clearly seen in the average signal but are hard to identify in each individual trial.

Figure 2 shows the 5-scales wavelet decomposition of the average ERP of the previous figure. D1 corresponds to the highest frequency band and A5 to the lowest. Band limit values correspond approximately to: 63-125 Hz (D1), 31-62 Hz (D2), 16-30 Hz (D3), 8-15 Hz (D4), 4-7 Hz (D5) and 0.5-4 Hz (A5). Each coefficient shows the correlation of the signal with a wavelet function at different scales and times. Note that the P100-N200 response is mainly correlated with the first post-stimulus coefficient in the details D4-D5. The P300 waveform is mainly correlated with the coefficients at about 400-500 ms in A5. This correspondence is easily identified considering the following facts: 1) the coefficients appear in the same time (and frequency) range as the ERPs and 2) they are relatively larger than the rest due to phase-locking between trials (coefficients reflecting background oscillations cancel in the average). A straightforward strategy to avoid the fluctuations related with the ongoing EEG is to equal to zero those coefficients that are not correlated with the ERPs. However, the choice of these coefficients should not be exclusively based on the average ERP and should also consider the time ranges in which the single-trial ERPs are expected to occur (i.e. some neighboring coefficients should be included in order to allow for latency variations). The black coefficients are the ones used for denoising P100-N200 and P300 responses. Note that background EEG oscillations were filtered out in the final reconstruction of the average brain response. It is quite difficult to achieve this result by applying filtering approaches based on Fourier transform due to the different time and frequency localizations of the P100-N200 and P300 responses, and also due to the overlapping frequency components of these peaks and the

ongoing EEG. Summarizing, the main advantage of wavelet denoising over conventional filtering is that one can select different time windows for the different scales. Once the coefficients of interest are identified from the average ERP, this same denoising can be applied to each single brain response, thus filtering the contribution of background EEG activity.

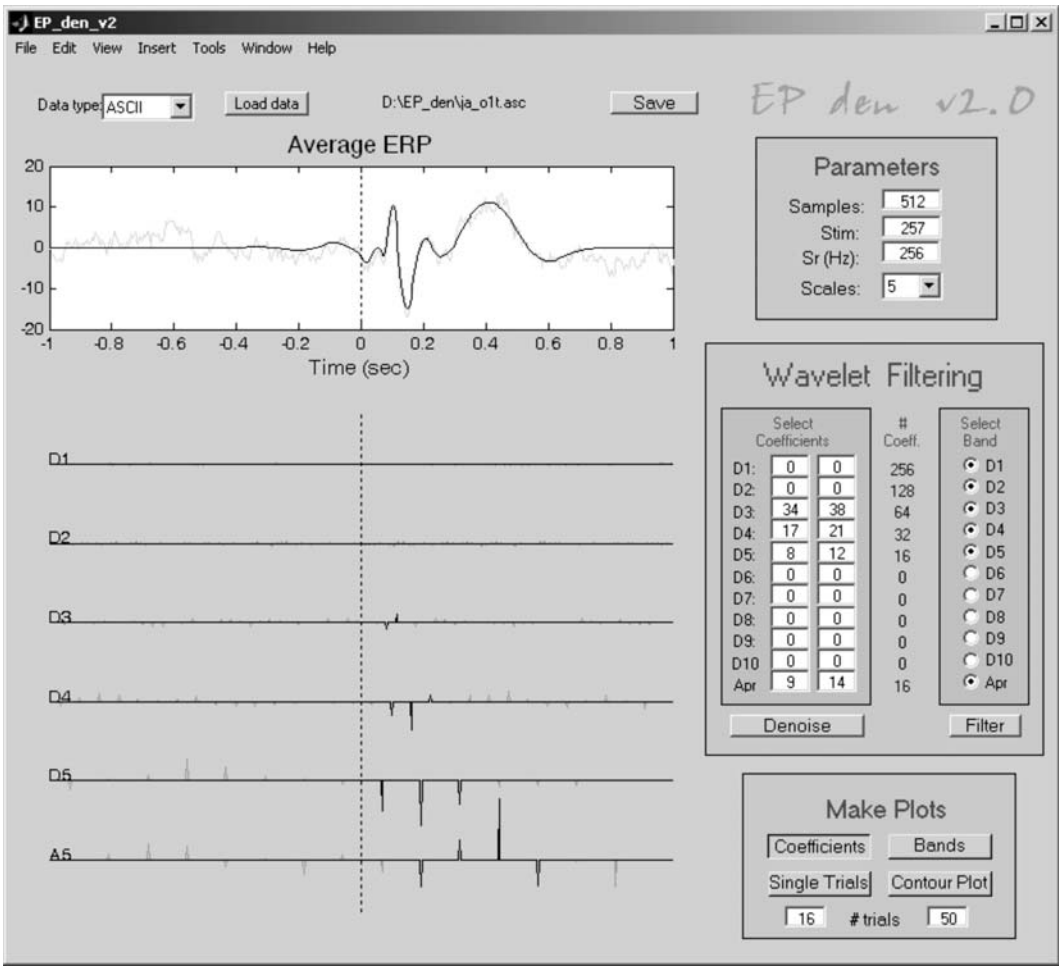

Figure 2. Wavelet decomposition of the average ERP from the previous figure. D1-D5 and A5 are the scales (i.e. frequency bands) in which the signal is decomposed (wavelet coefficients shown in grey). Note that ERPs are correlated with a few wavelet coefficients (in black), which can be used to denoise the signal. At the top, the original average ERP (grey) and the denoised reconstruction of the average ERP using only these coefficients (black) is shown.

Figure 3 displays a contour plot of the 16 single trials after wavelet denoising. We observe a white pattern followed by a black one between 100-200 ms, corresponding to the P100-N200 complex. The more variable and wider white pattern at about 400-600 ms corresponds to the P300 component. Note that with denoising we can distinguish the P100-N200 and the P300 in most of the individual trials. We remark that these responses are not easily identified in the original signal due to their low amplitude and their similarity with the

ongoing EEG (Figure 1). This issue has been recently confirmed by using simulated datasets closely resembling real ERPs, which showed that wavelet denoising significantly improves the visualization of the single trial components (and the estimation of their amplitudes and latencies) in comparison with the original data and with previous approaches, such as Wiener filtering (Quian Quiroga and Garcia, 2003).

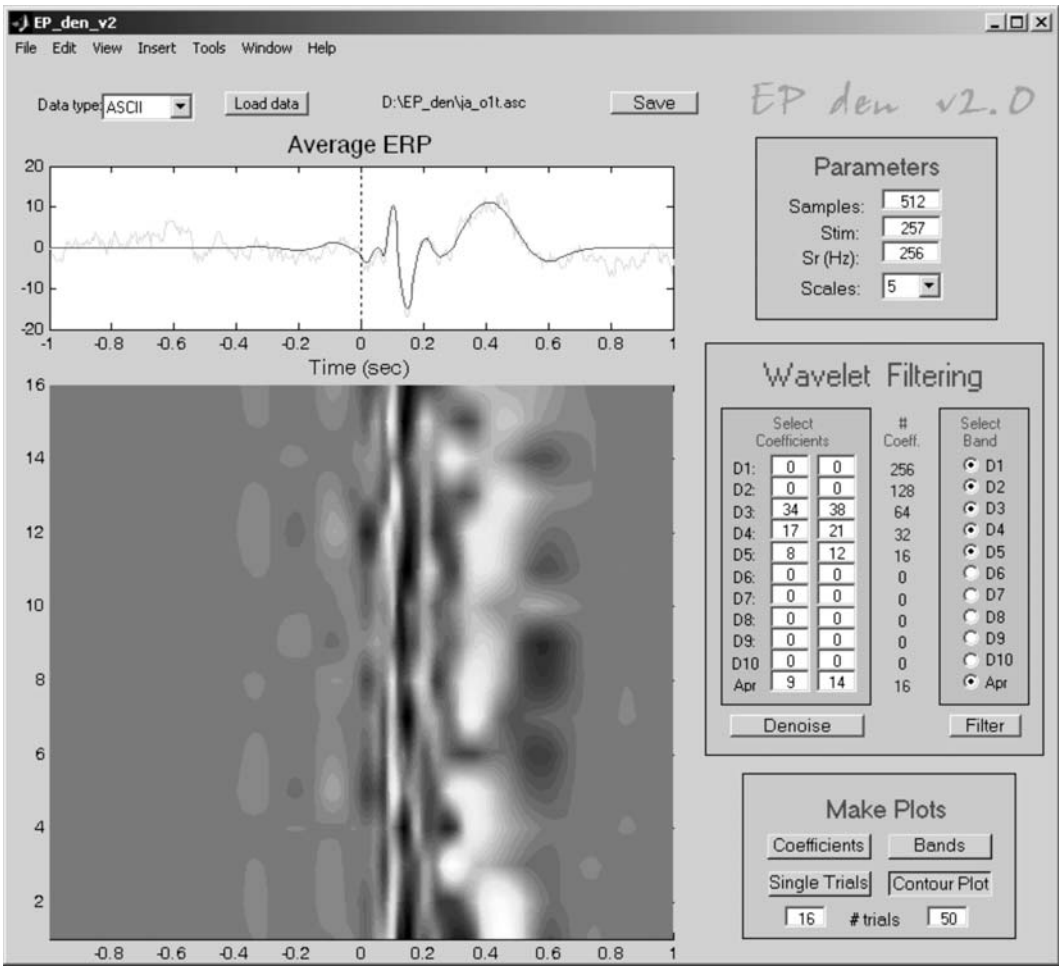

Figure 3. Single-trial denoising of the ERP shown in the previous figure. Note that all the components are now recognized in the single-trials.

4. Neurophysiological Correlates of Habituation in Rat Auditory Evoked Potentials

Auditory evoked potentials (click stimuli, 1 ms duration) were obtained from 13 adult male albino rats. For each rat, vertex EEG recordings were analyzed during 250 ms pre- and 250 ms post-stimulation in the first 100 trials (for details see Quian Quiroga and van Luijtelaar, 2002; de Bruin et al, 2001).

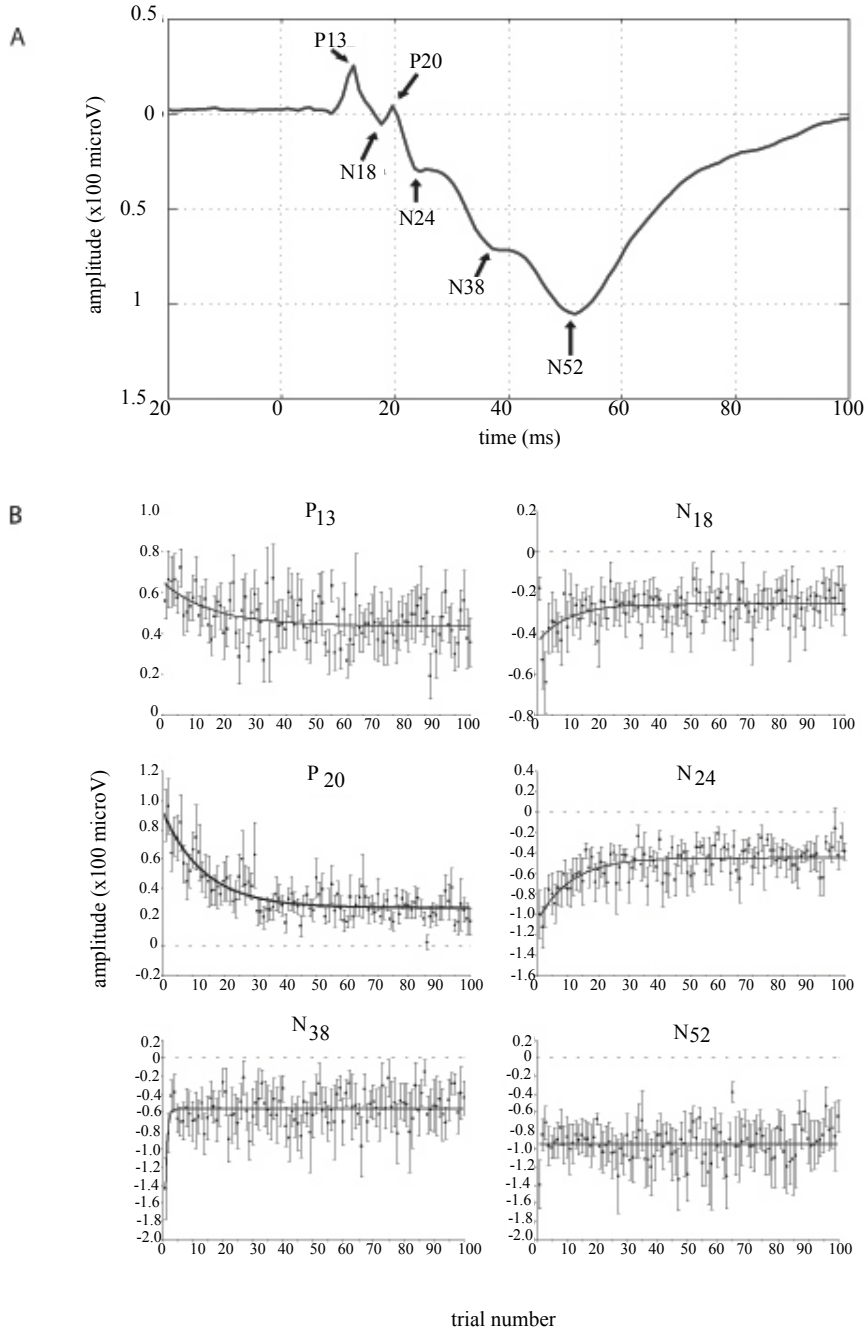

Figure 4A. Grand average auditory evoked potentials of 13 rats. B: Amplitude changes with trial repetition of the 6 components marked in A. Note the clear exponential decays in the first 4 components.

Figure 4A displays the grand average auditory evoked potentials of 13 rats. Note the presence of two positive components, at 13 and 20 ms, and 4 negative ones at 18, 24, 38 and 52 ms, respectively. For these components, amplitude and latency variations in the first 100 trials were further studied by implementing a denoising scheme, as explained above. For each

rat, we further identified the peaks of Fig. 4A in the single trials. Amplitudes and latencies of each peak were automatically defined from the maximum (minimum) value within appropriate time windows. For the P13 the time window was defined between 10-15 ms, for the P20 between 17-23 ms, for the N18 between 15-20 ms, for the N24 between 20-25 ms, for the N38 between 30-40 ms, and for the N52 between 40-60 ms (for more details see Quian Quiroga and van Luijtelaar, 2002).

Figure 4B shows the amplitude variations of the different ERP components of Figure 4A as a function of trial number. An exponential decay of the amplitude for the first 4 peaks was observed as the number of trials increased. This decrement in amplitude was completed after 30-40 trials, and it is functionally related to an habituation process. No systematic changes were determined in later trials. Moreover, the brain response to the first trial was smaller than the following ones for the P13, P20, N24, and most markedly for the N18. This is related to a sensitization process. Indeed, a one-way analysis of variance comparing the peak amplitude for the first 3 trials showed a significant increase for the N18 ($p<0.05$). Differences in the first 3 trials were non significant for the other fast components.

The two late components (N38 and N52) did not show a slow exponential decay as the previous ones. However, in this case a one-way ANOVA comparison of the amplitudes of the first 3 trials showed a significant decrease ($p<0.01$) pointing towards a fast habituation process.

5. A New Mechanism of Sleep-Induced Learning Revealed by Single-Trial Analysis

It is well known that practice helps in the acquisition of perceptual and motor skills. In the last two decades, however, growing evidence supports the notion that the waking and sleep states following a single training session also contribute to the consolidation of learned material. Indeed, improvement in performance can be seen several days after training without additional practice. We have recently shown that slow neural changes underlying consolidation of learning can also be reflected in modulations of event-related potentials elicited by complex sounds, which only became apparent 48 h after training. Interestingly, these ERP modulations failed to develop after post-training sleep deprivation (Atienza et al., 2004). In that study, the complex sounds were arranged in an oddball paradigm and subjects (N=20) were asked to respond to the infrequent sound (deviant) as accurately and quickly as possible. They required between 6 and 13 blocks of sounds to reach the learning criteria of 80% successful detections in each of two consecutive blocks, with a maximum of three false alarms per block. ERPs were obtained immediately before and after training, as well as at 48 and 72 h posttraining. During recordings, subjects were required to read a book of their own choosing in order to direct their attention elsewhere. All subjects followed the same protocol, but half of them were deprived of sleep the night after training.

Figure 5 shows the grand average difference waves obtained after subtracting ERPs recorded from a frontal derivation (Fz) in response to the repetitive sound (standard), from those elicited by the infrequent sound (deviant) immediately before and after training, as well as at 48 and 72 h post-training. Just after learning, all subjects were able to automatically detect the change in the sound sequence while they read a book, as reflected by the

appearance of the mismatch negativity component (MMN) at 425 ms from the stimulus onset (i.e., 200 ms from the introduction of the deviance within the sound pattern). This ERP component is thought to result from a comparison process between the neural representations of the repetitive and infrequent sounds (Näätänen, 1992). At the 48 and 72 h post-training sessions, the MMN amplitude not only showed an additional increase, but it was also followed by a P3a component. This enhanced MMN has been suggested to reflect the triggering of an automatic shift of attention towards the deviant sound (Näätänen, 1992), which is indexed by the subsequent P3a wave (Escera et al., 1998). These results suggest that information processing becomes more automatic after post-training sleep.

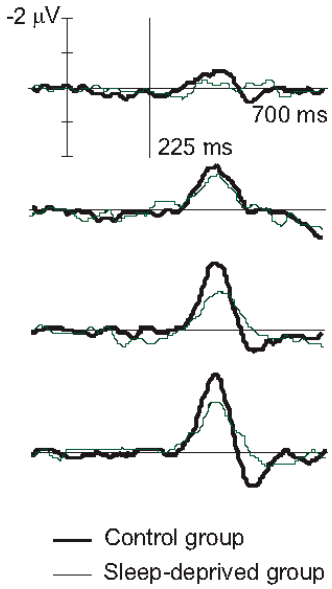

Figure 5. From top to bottom, grand averaged difference waves (N=10) recorded from Fz after subtracting ERPs to repetitive sounds from those elicited by the deviant sound just before and after training, as well as at 48 and 72 h without further training for the control group (after two and three consecutive nights of sleep, respectively) and for the sleep-deprived group (they were sleep deprived on the night following training).

The neural mechanisms underlying the experience-dependent and sleep-dependent enhancements of the MMN are unknown. These mechanisms cannot be inferred from previous findings because studies of the response characteristics and organization of neurons in primary cortex of long trained animals have provided contradictory results. In fact, changes in perceptual discriminative capacity in somatosensory, visual, and auditory modalities have been reported to occur with (Recanzone et al., 1992, 1993) and without changes in neuronal response parameters and cortical topography (e.g., Schoups et al., 2001; Brown et al., 2004). Though these neural changes might parallel changes in the MMN appearing immediately after training in both groups, the analysis of the single-trial ERPs has shown that the posttraining sleep-induced enhancement of the MMN seen in control subjects neither resulted from a change in neural recruitment nor from a change in neural synchronization. On the contrary, it stemmed from a reduction in the MMN latency jitter (Atienza et al., 2005).

Figure 6 shows the contour plots of 200 single trials after denoising for one control subject (A) and one sleep-deprived subject (B) across sessions (pretraining, posttraining, 48 and 72 h posttraining). Note that in the range of the MMN (around 200 ms), the white pattern across single trials becomes more regular at 48 and 72 h. Remarkably, changes in the regularity of the brain response are not seen after sleep deprivation.

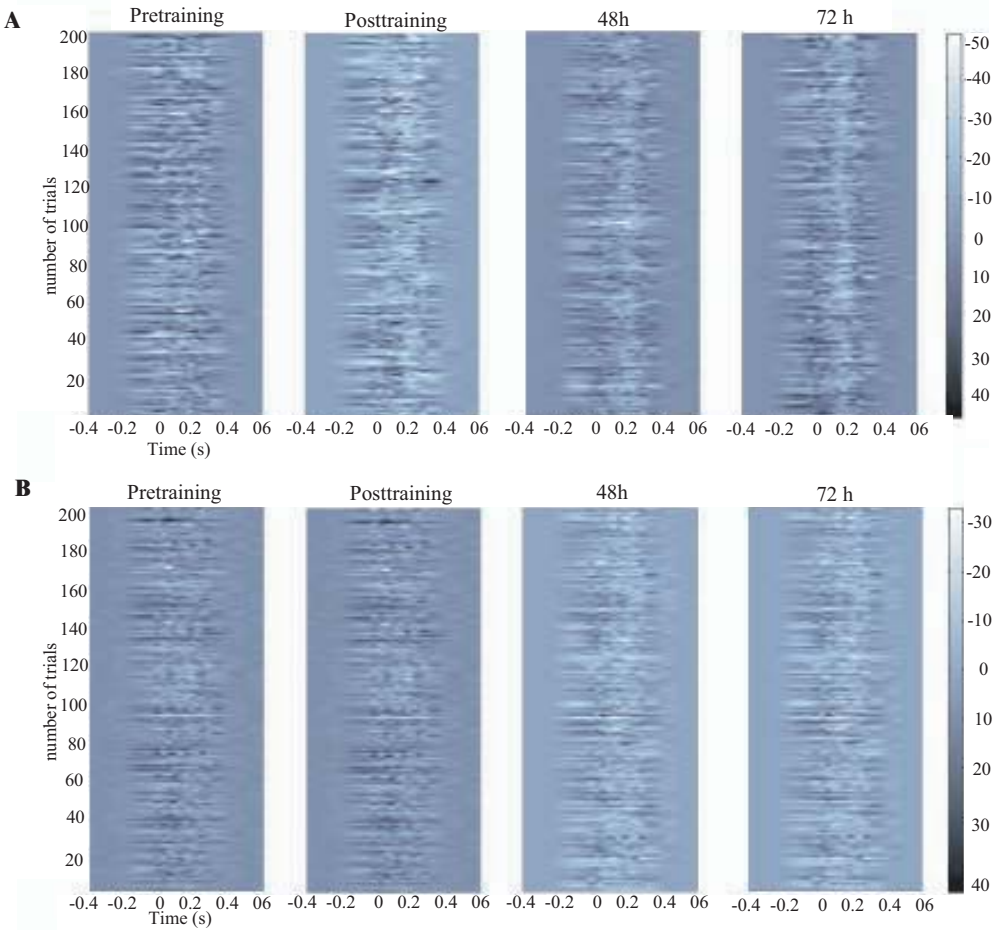

Figure 6. Contour plot of the denoised single trials obtained in response to the deviant sound at Fz from the control and sleep-deprived group immediately before and after training, as well as 48 and 72 h post-training.

Figure 7A shows the grand average difference waves obtained from Fz in the control and sleep deprived group at 48 and 72 h posttraining sessions after signal denoising. As shown in figure 7B, differences in the MMN amplitude between the two groups disappeared after correcting for latency-jitters (i.e. aligning the maximum amplitudes of single-trial components, see e.g. Quian Quiroga, 2000; beim Graben, 2001). So, we can conclude from these results that precise timing, namely, a decrease in the variability of the MMN latency, accounts for posttraining sleep-dependent enhancements of the auditory MMN.

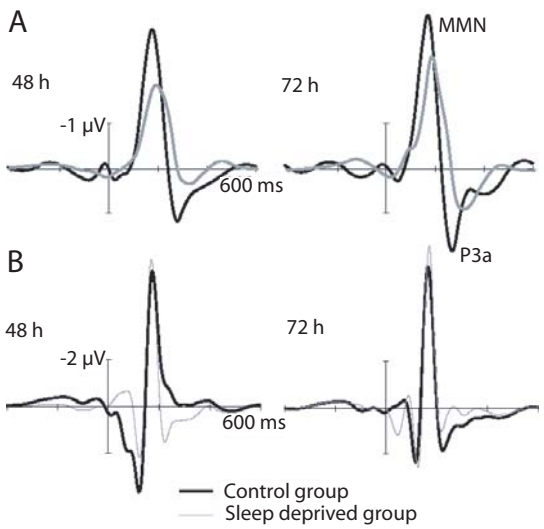

Figure 7. Grand averaged difference waves (N=10) obtained at Fz in the control and sleep-deprived group at 48 and 72 h posttraining sessions after denoising the single-trials (A) and after correcting the latency-jitter of the brain response obtained within the time interval of the MMN.

6. Omission Evoked Potentials – Effects of Stimulus Modality

Omission Evoked Potentials (OEPs) are brain responses elicited by stimulus omissions occurring within a regular sequence. The typical waveform elicited by the stimulus omission has been reported to consist of a late positive wave similar to the P3b (Jongsma et al., 2005; Bullock et al., 1994; Ruchkin et al., 1981). OEPs are supposed to reflect expectancy and are strongly influenced by attention (Jongsma et al., 2005; Besson et al., 1997; Bullock et al., 1994;). Though OEPs have been described in humans for years, they appear difficult to be measured (Alain et al., 1989; Näätänen et al., 1987).

We have recently shown that OEPs can be more easily extracted from the EEG by applying the denoising procedure described above (Jongsma et al., 2004; 2005). In order to investigate the gradual effects of expectancy on the elicitation of OEPs, we applied the following paradigm: Trials started randomly with between 3 to 7 stimuli and contained five omitted beats, presented in a regular order (i.e. with 1, 2 or 3 beats presented between stimulus omissions). Thus, the dynamic process underlying a shift from unexpectedly omitted stimuli towards expectedly omitted stimuli could be tracked. In this initial study, omitted stimuli were embedded within a train of auditory beat sounds. Twenty-four participants (12 musicians and 12 non-musicians) had to tap along with the first beat after the fifth omission, thus determining timing-accuracy and their ability to track the pattern. Clear OEPs were observed and appeared to be maximal over the parietal cortex (Pz). A main effect of expectancy was observed such that OEPs P3b amplitude diminished when a stimulus omission could be expected. Musicians performed more accurately on the behavioral tapping task and showed a large OEP N600 at the end of a trial. No effect of musical training was found with respect to the OEP P3b component amplitude.

Since OEPs have been measured in human subjects by using both auditory, (Rüsseler et al., 2001; Ruchkin et al., 1981) and visual stimuli (Bullock et al., 1994), this suggests that OEPs might be modality independent. However, to our knowledge, OEPs have not been investigated applying the same stimulation paradigm within different stimulus modalities. Therefore, in the current experiment, we determined whether OEPs are indeed modality independent, by applying the same paradigm within an auditory and a tactile session. Ten participants followed the same procedure as described in the previous study (Jongsma et al., 2005). However, instead of sound stimuli, they were presented with tactile stimuli. Both hands were placed on a soft surface that vibrated with a low intensity for ca 50 ms at the designated background stimulus times. White noise was presented via headphones.

Figure 8A shows grand averages of OEPs at Pz for the 5 consecutive stimulus omissions. On the left, grand averages obtained within the auditory session (n=24) are depicted with denoised waveforms in solid lines and raw waveforms in dotted lines. On the right the grand averages obtained in the tactile session (n=10) are depicted.

Figure 8B shows a bar graph of the OEP P3b amplitudes for the 5 consecutive stimulus omissions. P3bs are depicted for both the auditory session (on the left) and the tactile session (on the right). For both modalities, a strong effect of the expectancy of stimulus omission was found ($p<.0001$), such that OEPs elicited by the first two, the unexpected, omitted stimuli contained a high P3b that rapidly disappeared on the following, more expected, omitted stimuli. However, no effect of modality was observed, indicating that OEPs are indeed modality independent.

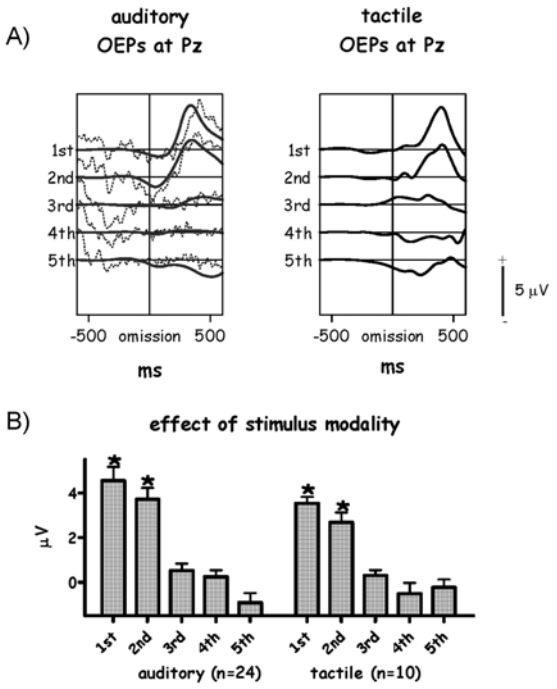

Figure 8A. Grand average OEPs (dotted lines) and denoised grand average OEPs (solid lines) obtained with an auditory (24 participants) and tactile session (10 participants). The x-axes depict time (in ms) and the y-axes depict the omission order within trials (n=90). B: OEP P3b amplitudes (average value in window 350-450 ms obtained within an auditory session and tactile session. The x-axes depict the

omission order within trials and the y-axes depict the OEP P3b amplitude (in μV). Asterixes (*) signal the level of significance (P<.05).

7. Latency Jitter of Single-Trial Omission Evoked Potentials – Effects of Rhythmic Training

The difficulty in measuring OEPs might be explained by the fact that OEPs are conventionally obtained by averaging over a large number of trials. While a component of interest may occur in individual trials, these components could become smeared in the average OEPs due to latency-jitter (Bullock et al., 1994; Besson et al., 1997; Jongsma et al., 2005). OEPs might be especially sensitive to latency-jitter since no external stimulus marks their exact onset times (Näätänen et al., 1987; Jongsma et al., 2005).

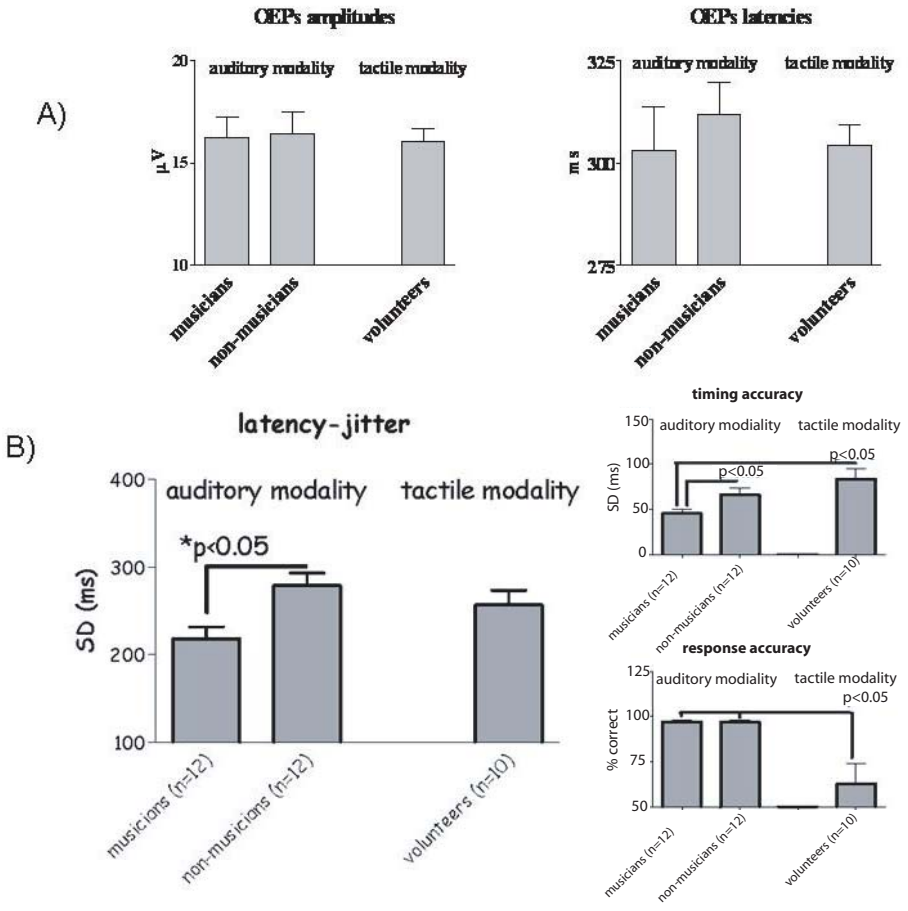

Figure 9A. Bar graphs of the averaged OEP P3b amplitudes and latencies after single-trial peak-picking. B: On the left: bar graphs of the latency jitter (SD: Standard Deviations of single-trial peak latencies) of the OEPs. On the right: bar graphs of the behavioral results, as reflected in their Standard Deviations.

In a previous study, we addressed this issue by applying single-trial ERP analyses on a subset of the above-described experiment. OEPs elicited by every first omitted stimulus from each trial (n=90) were taken into analyses. The OEPs P3b amplitudes and latencies were determined for all single trials by taking the positive maximum within the total time window of the signal (0 – 800 ms) (Jongsma et al., 2004). Data were obtained from 12 musicians and 12 non-musicians (see Jongsma et al., 2004, for details). Musicians are generally found to be both more accurate and consistent in their responses compared to non-musicians (Aschersleben, 2002). In line, we found that musicians showed less latency-jitter of both the OEPs positive wave and of behavioral responses compared with non-musicians (Jongsma et al., 2004).

In the current study - comparing OEPs elicited by omitted stimuli that were either embedded in a train of auditory stimuli (auditory session) or embedded in a train of tactile stimuli (tactile session) - we also analyzed modality effects on the latency-jitter and timing accuracy of OEPs. Again, no differences with respect to P3b amplitude or latency were observed with respect to modality. Figure 9A shows a bar graph of the OEPs P3b amplitudes for the auditory session (musicians and non-musicians), and the tactile session (volunteers). Figure 9B shows a bar graph of the OEP P3b latency jitters for the auditory session (musicians and non-musicians), and the tactile session (volunteers).

With respect to the latency jitter, a one-way ANOVA comparing 3 groups — musicians (n=12) auditory session; non-musicians (n=12) auditory session and volunteers (n=10) tactile session — showed a significant group effect ($F(2, 31) = 4.6$; $p=0.017$). Post-hoc analyses showed that the latency jitter was decreased within the group of musicians compared to the group of non-musicians ($p<0.05$). In addition, one-way ANOVA analyses showed that this decreased latency jitter was observed together with a decrease in the variability of response times ($F(2, 31) = 6.1$; $p=0.006$). Post-hoc analyses showed that the variability of response times was decreased within the group of musicians compared to both the group of non-musicians ($p<0.05$) and the group of volunteers ($p<0.05$). With respect to the percentage of correct responses, one-way ANOVA analyses showed an effect of group ($F(2, 31) = 11.0$; $p=0.0003$). Post-hoc analyses showed that the accuracy was decreased within the group volunteers (tactile session) compared to both groups from the auditory session, the musicians ($p<0.05$) and the non-musicians ($p<0.05$).

Though a decrease in latency jitter normally results in an increase in average amplitude, no group difference with respect to P3b amplitude was observed. There was, however, a non-significant tendency for non-musicians to have higher P3b amplitudes, possibly because omissions held a higher unexpectedness due to a lower familiarity with processing rhythmical patterns for this group. Thus, latency-jitter seems to broaden and diminish the P3b amplitude.

The behavioral responses from the volunteers in the tactile session showed similar timing accuracy (timing variability) compared to the non-musicians of the auditory session. Musical training increased timing accuracy. The response accuracy (i.e. percentage of correct responses) from the tactile session compared to the auditory session was much lower. Therefore, tracking omitted stimuli embedded in a train of tactile stimuli seems to be harder than tracking omitted stimuli within a train of auditory stimuli.

Although tactile presentation of a temporal pattern shows the same expectancy effects on the OEPs P3b component as in the case of auditory presentation, keeping track of such a pattern in order to give an accurate response at the end of each trial seems to be far more difficult. We propose that by applying single trial ERP analyses methods, we can now

investigate new stimulation paradigms that no longer try to avoid systematic trial-to-trial variations (to improve averaging) but instead attempt to introduce such systematic variations in order to track dynamic changes underlying cognitive processes.

8. Conclusion

The analysis of single-trial brain responses is slowly becoming an active topic of research in cognitive neuroscience. In fact, a few methods have been proposed to improve the visualization of single-trial ERPs. First attempts involve the filtering of single-trial traces by using techniques that are based on the Wiener formalism. This provides an optimal filtering in the mean square error sense (Walter, 1969; Doyle, 1975). However, these approaches assume that the signal is a stationary process and, since ERPs are compositions of transient responses with different time and frequency localizations, they are not likely to give optimal results. An obvious advantage is to implement time-varying strategies, as described in this study with the wavelet transform (Quian Quiroga, 2000; Quian Quiroga and Garcia, 2003). Other works also reported the use of wavelets for filtering average ERPs or for visualizing the ERPs in the single-trials (Bartnik et al, 1992; Bertrand et al, 1994; Thakor et al, 1993). Alternative denoising methods have been proposed using a phase space reconstruction (Effern et al, 2000), or using independent component analysis (Jung et al, 2001; Parra et al, 2002), or a Bayesian inference framework (Truccolo et al, 2003).

Changes in neural responses across single trials can be systematic or unsystematic. Examples of systematic changes are amplitude decreases of the ERPs due to habituation (Sokolov, 1960). In rats, we showed exponential amplitude decays of ERPs elicited with auditory clicks. Moreover, a different temporal profile of habituation was observed between the early and the late components suggesting that they are related to different functions. Furthermore, some of these components showed a significant amplitude increase in the first trials due to sensitization. Using wavelet denoising it was possible to obtain more information in comparison with a previous study that used sub-ensemble averaging (averaging of a few trials) with a similar dataset (de Bruin et al, 2001). More recent studies have also used denoising approaches to study habituation in human and rat ERPs (Sambeth et al, 2004a, 2004b).

Unsystematic single-trial ERP changes are reflected in amplitude and latency jitters. In the average ERPs amplitude jitters can be corrected using selective averages (Pfurtscheller and Cooper, 1975) and latency jitters using latency corrected averages (Woody 1967), as shown in Fig. 7. These procedures allow improved averages (Quian Quiroga 2000, Quian Quiroga 2003), which can have clinical relevance when studying, for example, patients with attention-deficit/hyperactivity disorders or somato-sensory ERPs that are painful to the patient.

Besides the possibility of improving the ERP averages, the analysis of latency and amplitude jitters of the single-trial responses can provide crucial insights on the mechanisms responsible for the modulation of the neural responses. In fact, we showed that the reduced MMN seen in sleep-deprived subjects, after training in an auditory discrimination task, was due to a larger latency jitter in comparison with the control subjects. Then, the neural mechanism underlying sleep-induced automatization (another aspect of learning consolidation) was neither based on recruitment of more neurons involved in the task nor

based on reinforcement of their functional connectivity, as one would in principle presume from the differences in the average MMN plots (Näätänen, 1992). On the contrary, it was rather due to a more precise timing for the subjects that were not sleep-deprived. This might result from a change in synaptic efficacy and/or neural excitability (Atienza et al., 2005).

We also showed that a long term learning of rhythm perception in professional musicians was reflected in a more accurate timing (i.e. less latency jitter) in their omission event-related potentials (OEPs) in comparison to non-musicians (Jongsma et al, 2004). This observation was additionally reflected in a more accurate timing of their behavioral tapping responses. Interestingly, similar OEPs were observed when elicited within a tactile session, thus demonstrating the modality independency of OEPs.

Changes in the pattern of single-trial responses can be also used as neurophysiological correlates of learning processes that take a few trials. In particular, it was shown in rats that the learning rate of an oddball paradigm, as quantified by several behavioral measures, was correlated with the appearance of a negative potential in the entorhinal cortex with a latency of 100ms (Talnov et al, 2003). Interestingly, this neural response in rats behaved in the same way as the human P300, when variables such as the target probability or inter-stimulus-interval were manipulated (Talnov et al, 2003). It took the rats between 200 and 300 trials to learn this task. Of course, the tracking of such learning processes in humans requires more complex paradigms. We have been developing such paradigms and recently found, using an oddball paradigm, that the switch from a pseudo-random to a fixed sequence of interleaved standard and target tones, even if not consciously noted by the subjects, was correlated with clear reduction in the P300 (Jongsma et al, 2006). This change in predictability of the targets was also correlated with the appearance of a slow negative component, called contingent negative variation, which has been traditionally related to a higher expectancy and anticipatory brain activity (Jongsma et al, 2006). The same experiment was repeated with simultaneous fMRI acquisition and single-trial covariations of the ERP amplitudes were correlated with bold activations. This allowed the localization in time (using the ERPs) and space (using the MRI scans) of the different evoked activations (Eichele et al, 2005).

ERP research has a long and successful story of more than 50 years. A countless number of studies have shown the utility of ERPs to study different states, functions and pathologies. The introduction of new methods of data analysis, such as the wavelet transform and the single-trial analysis derived from its use, allows a further ‘zoom’ into the data that may lead to new insights into various brain processes. This gives renewed strength to ERP research and opens vast new possibilities for the study of sensory and cognitive processes in the healthy and disordered brain.

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