Multiple time–frequency components account for the complex functional reactivity of P300

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Consecutive and overlapping time–frequency (TF) components of auditory event-related brain potentials (ERPs) were analyzed to examine whether multiple co-existing components may account for the complex functional reactivity of P300. Auditory ERPs of 14 adult subjects were decomposed by means of the wavelet transform (WT), and TF components within P300 were tested in a systematic manner for the effects of major P300 determinants: stimulus probability, active discrimination, and mental count task. The results demonstrated that several partly or fully simultaneous delta, theta, and alpha TF components significantly depend on the factors eliciting P300, and also manifest distinct patterns of task reactivity and scalp distribution. Thus, specific functional processes that underlie the P300 ERP can be distinguished that help to account for its responsiveness to task variables.

Key words: Cognitive processing; Event-related oscillations; Event-related potentials; P300; Time–frequency components; Wavelet analysis

INTRODUCTION

The P300 component of the event-related brain potentials (ERPs) has been consistently associated with attention and memory processes in humans [1], which makes it a promising tool for fundamental and applied cognitive brain research [2]. Typically, P300 is analyzed as a homogeneous phenomenon. However, several lines of research strongly indicate that P300 is a complex ERP component with respect to source of generation [3–5], wave shape and scalp topography [6,7], and functional reactivity [8]. To explain the relationships of P300 with various physical, cognitive, and biological factors, basic cognitive constructs such as working memory updating [1], unitary fundamental processes such as general and phasic arousal [8], or inhibition of stimulus-related cortical excitation [9], have been proposed, but no principal correlate has been established so far.

An advantageous perspective to understand the heterogeneous nature of P300 is provided by recent findings on oscillatory electroencephalographic (EEG) activity indicating that event-related oscillations (EROs or EEG frequency responses) are functionally relevant to sensory and cognitive information processing [10,11]. More specifically, it has been demonstrated that frequency-specific EROs from delta (0.1–4 Hz), theta (4–7 Hz), and alpha (7–14 Hz) EEG ranges are sensitive to the processing conditions eliciting P300, with P300 variations also being directly influenced by the EROs [10,12–14]. Thus, even though P300 often appears as a single waveform in the ERP, it may reflect multiple functionally different EEG processes as defined by specific frequency bands that may be partly or fully simultaneous and contribute differentially to P300 sensitivity to task variables.

Indeed, a time–frequency (TF) decomposition of ERPs from a simple discrimination (oddball) task has revealed that several independent TF components during a single P300 waveform differentiated rare target from frequent nontarget processing [15,16]. In the oddball condition, however, the low probability tones were also task relevant, and the effects of stimulus probability, target discrimination, and task relevance on ERPs were confounded. Hence, although the contribution of multiple overlapping components to oddball P300 is strongly implied by these results, whether and how distinct TF components within the P300 may relate to specific aspects of the oddball task processing has not been demonstrated so far. Therefore, since P300...
has been consistently found to independently vary with stimulus probability, active discrimination, and count task performance [2,6], the present study was undertaken to examine whether multiple components from the time–frequency plane account for the functional reactivity of P300 to these experimental variables. To evaluate the multicomponent structure of the ERPs a wavelet transform (WT) was used, because it performs an optimal time–frequency decomposition that permits assessment of overlapping ERP components from different frequency bands with their time localizations [16–18]. Given that WT provides additional information about both the time and frequency characteristics of the EEG response, the question was also addressed of whether the functional processes during P300 elicitation can be characterized more precisely than has been done in the time domain.

MATERIALS AND METHODS
Subjects were 14 healthy volunteers (eight female) between 18 and 35 years. EEG data were derived with Ag–AgCl disc electrodes placed at the frontal (Fp1, F3, Fz, F4, Fp2), central (C3, Cz, C4), parietal (P3, Pz, P4), temporal (T3 and T4), and occipital (O1, Oz, O2) locations (International 10/20 system), referenced to linked earlobes. Electrode impedances were < 5 kΩ. The electrooculogram (EOG) was recorded to detect both vertical and horizontal eye movements. The cut-off frequencies of EEG amplifiers were 0.16 and 70 Hz (–3 dB/octave). The amplified signals were sampled with a frequency of 256 Hz (12 bit resolution). The length of the analysis epoch was 1125 ms, with a 250 ms pre-stimulus recording.

Two types of auditory stimuli (L = 800 Hz and H = 1200 Hz) were randomly mixed in each of the four experimental sessions, the order of which was counter-balanced across subjects. In each session, a total of 200 tones (60 dB SPL, 50 ms duration, 10 ms r/f, varying interstimulus intervals 2–2.5 s) were presented. (1) In the passive condition, the probabilities of L and H were 0.2 and 0.8, respectively. The subjects were instructed to relax silently. (2) In the count-all condition, the same stimuli were delivered with the instruction to count covertly every stimulus. (3) In the oddball-low probability condition, the instruction was to count only the L tones (p = 0.2). (4) In the oddball-high probability condition, the L tones were again counted but they were presented frequently (p = 0.8), whereas the H tones were rare (p = 0.2). During recording subjects kept their eyes closed.

Data analysis: Sweeps contaminated (± 45 μV) with ocular, muscle or other non-EEG activity were excluded. Thirty artifact-free trials from each stimulus type (L and H) were selected for further analysis. In the averaged ERPs, P300 amplitude was measured at the most positive point between 240 and 450 ms relative to the pre-stimulus 250 ms baseline. P300 peak latency was also measured relative to stimulus onset.

Wavelet transform: The wavelet transform performs a multiresolution decomposition of the signal in both the time and frequency domains using families of functions that are generated from a single function by the operation of dilations and translations [17,18]. In the present study, quadratic B-spline wavelet basis functions were used in the form of multiresolution scheme [17]. A detailed description of the method is given elsewhere [15–17].

The application of a four-octave wavelet transform to the data yielded four sets of coefficients in the 32–64 Hz (gamma), 16–32 Hz (beta), 8–16 Hz (alpha) and 4–8 Hz (theta) frequency ranges, and a residue in the 0.16–4 Hz (delta) frequency band. Because the WT samples the frequency domain of the phase space logarithmically, 64 gamma, 36 beta, 18 alpha, nine theta, and nine delta coefficients were obtained for the analysis epoch of 1125 ms. In the present study, coefficients from the delta, theta, and alpha ranges within the P300 latency range were analyzed. The window size was 125 ms for the delta and theta levels, and 62.5 ms for the alpha level. The time localizations of consecutive delta and theta coefficients evaluated for the P300 latency range were 187.5–312.5 ms and 312.5–437.5 ms, with respective localizations obtained for alpha coefficients from these time epochs. The wavelet coefficients are designated with a letter corresponding to each frequency band (D for delta, T for theta, and A for alpha) together with a number representing the approximate center of the respective time window in ms: D250, D250, D370, T370, A310, A370, A430.

Individual means of wavelet coefficients obtained from the single sweep potentials were subjected to repeated measure analysis of variance (ANOVA). ANOVA was performed with 2 probability conditions (low = 0.2 vs high = 0.8) × 2 active discrimination conditions (non-discriminated = ND vs discriminated = D) × 2 presence of the mental count task (no count = NC vs count = C) × 3 electrodes (Fz, Cz, Pz). P300 amplitude and latency measures were subjected to the same analysis. Greenhouse–Geisser corrections were employed, and the original df and the probability values from the reduced df are reported in the results. Correlation analyses were performed across individuals by means of Pearson correlation coefficients to assess relationships among various time–frequency components within P300.

RESULTS
Although only measures from midline electrodes were statistically assessed, Fig. 1 presents topography maps to illustrate specific differences in scalp distribution of P300 and concurrent TF components. Figure 2 summarizes the mean value for each dependent variable for each stimulus and task condition. Table 1 presents the ANOVA results for each variable.

Time-domain P300 analysis: Figure 1 demonstrates the parietal distribution of P300 (main Electrode effect in Table 1). As shown in Fig. 2, P300 amplitude increased as stimulus probability decreased (P), and active discrimination and mental count were engaged (D,C), with these main effects being most pronounced at posterior locations as indicated by the significant interactions with the electrode factor. However, discrimination and count effects were not independent, because P300 was most enhanced for count stimuli in the discrimination condition (D × C). Also, both discrimination and count factors modulated the effects of probability on P300 (P × D, P × C), because the difference in P300 amplitude between low and high prob-
ability was larger when discrimination or count were needed.

P300 latency tended to be longer for low than for high probability tones (P, F(1/13) = 3.67, p = 0.06) and increased upon discrimination (D, F(1/13) = 37.86, p < 0.001) and count tasks (C, F(1/13) = 15.6, p < 0.001).

Wavelet analysis: Figure 1 and Fig. 2 demonstrate that D250 was positive and with a clear vertex maximum (E). D250 was larger for high than for low probability stimuli (P), with this effect being significant at frontal-central locations (PxE). The discrimination task produced a decrease in D250 mainly at anterior sites (D × E), while the count task enhanced it mostly at posterior sites (C × E), so that D250 was maximal for count stimuli in no-discrimination condition (D × C).

Because the count task suppressed T250 (C), the values of this coefficient were negative in task conditions, with
Fig. 2. Mean ± 1 s.e. of P300 ERP amplitudes and WT coefficients of TF components at three electrodes as a function of probability, discrimination and count variables.
only temporal (predominantly right) locations manifesting positive values (Fig. 1). Figure 2 shows that T250 was larger for low than for high probability tones (P), with this difference being evident only when no discrimination was required (P × D). Therefore, in the passive low probability condition, T250 was positive and with fronto-central enhancement.

Figure 1 and Fig. 2 show that D370 was maximal at the parietal locations and, depending on the eliciting conditions, negative at anterior locations (E). D370 was significantly larger for low than for high probability (P), for to be discriminated than for not to be discriminated (D), and for count than for no count stimuli (C). It is important to note that these effects were additive as no significant interactions between task variables were detected.

Figure 1 shows that T370 was maximal at anterior (central-frontal) locations (E). T370 was enhanced by both the discrimination and count tasks (D, C).

Low probability tones produced positive and significantly larger A430 relative to high probability tones (P, p < 0.05). This effect was most pronounced for stimuli that were both discriminated and counted as well as for no-task stimuli (P × D × C, F(1/13) = 4.6; p < 0.05).

Correlation analyses: For each coefficient, strong and significant inter-individual correlations (r > 0.65, p < 0.05) were obtained between measures from different leads, which indicates that a unique time–frequency component may be reflected by single coefficient measures. In addition, no correlational relationships were found between coefficients from overlapping or consecutive time windows (p > 0.1), which points to the independence of the corresponding time–frequency components.

DISCUSSION

The present study’s new findings demonstrate that several time–frequency components from the P300 latency range significantly vary with major P300 determinants (probability, discrimination, count task), and also manifest distinct patterns of task reactivity and scalp distribution. These results provide evidence for (1) the co-existence of multiple functionally heterogeneous components during P300 [6,7,15,16,19], and (2) the association of event-related oscillations from delta, theta, and alpha frequency bands with the functional mechanisms eliciting P300 [10,12,13].

Because these mechanisms can be described by the time–frequency ERP decomposition (i.e., scalp recorded time–frequency components) an important question is whether the TF signals represent independent functional components within the P300 range. In this context it is important to note that: (1) the different topography patterns of single time–frequency components, as well as the relative stability of these patterns across conditions, serve as a physiological evidence for the functional separability of the TF components. (2) Correlational analyses performed across subjects for pairs of wavelet coefficients demonstrated that no relationships existed between consecutive or overlapping TF components during P300. (3) The time–frequency components manifested specific patterns of functional reactivity to task variables. Thus, the wavelet analysis coefficients analyzed in the present study may be regarded as representing functionally independent TF components of the ERPs.

Functional significance of TF components: On the base of their frequency content, scalp distribution, time localization, and functional reactivity, the TF components helped to reveal partly or fully simultaneous processes taking place in the P300 latency range that are indistinguishable in the ERPs analyzed only in the time domain. D250 was elicited consistently and was with a clear central (vertex) maximum for all processing conditions, which implies that concurrent with P300 generation there exists an obligatory processing mechanism operating in the delta frequency channel that is functionally associated with auditory stimulus evaluation. According to the present results, D250 depended on experimental conditions such that this processing mechanism in the early P300 range

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### Table 1. Summary table from the probability (low, high) × discrimination (no discrimination, discrimination) × count (no count, count) × electrode (frontal, central, parietal) analysis of variance performed on the P300 ERP amplitude and time–frequency components.

<table>
<thead>
<tr>
<th>Source</th>
<th>df</th>
<th>P300</th>
<th>D250</th>
<th>T250</th>
<th>D370</th>
<th>T370</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability</td>
<td>1/13</td>
<td>11.93***</td>
<td>6.28*</td>
<td>5.50*</td>
<td>21.04***</td>
<td>5.81*</td>
</tr>
<tr>
<td>Discrimination</td>
<td>1/13</td>
<td>14.32***</td>
<td>–</td>
<td>–</td>
<td>25.60***</td>
<td>5.34*</td>
</tr>
<tr>
<td>Count</td>
<td>1/13</td>
<td>4.75*</td>
<td>–</td>
<td>7.77*</td>
<td>10.64**</td>
<td>5.34*</td>
</tr>
<tr>
<td>Electrode</td>
<td>2/26</td>
<td>11.87***</td>
<td>1.88*</td>
<td>2.45*</td>
<td>10.23***</td>
<td>6.12*</td>
</tr>
<tr>
<td>P × D</td>
<td>1/13</td>
<td>17.15***</td>
<td>–</td>
<td>–</td>
<td>8.04**</td>
<td>–</td>
</tr>
<tr>
<td>P × C</td>
<td>1/13</td>
<td>4.94*</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>P × E</td>
<td>2/26</td>
<td>5.67*</td>
<td>–</td>
<td>8.99***</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>D × C</td>
<td>1/13</td>
<td>10.71***</td>
<td>7.22*</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>D × E</td>
<td>2/26</td>
<td>4.10*</td>
<td>–</td>
<td>4.35*</td>
<td>–</td>
<td>–</td>
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<td>C × E</td>
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<td>–</td>
<td>5.30*</td>
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<td>P × C × E</td>
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<td>D × C × E</td>
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<td>P × D × C × E</td>
<td>2/26</td>
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</tr>
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</table>

*p < 0.05
**p < 0.01
***p < 0.001
appears to emphasize frequently repeated and relevant events [20].

An early P300 subcomponent with a central maximum, called ‘positivity in simple reactions’ (P-SR) has been previously elicited in both simple and choice reaction auditory conditions, as well as for go and no go stimuli [7,19]. In a manner similar to the time–frequency component D250, P-SR was most clearly detected in the simple reaction task where no stimulus selection was needed, because in the choice reaction task it was overlapped by a later positivity with a parietal maximum. Furthermore, P-SR was larger for go trials at parieto-occipital leads, and for no go trials at frontal-central leads [19]. Wavelet analysis is therefore likely to have extracted an early P300 subcomponent with a central maximum that can be consistently elicited in auditory processing conditions, although it may be only rarely identified or functionally detected in the averaged ERPs [7,21].

T250 occurred in parallel to D250 in the early P300 range and was pronounced at the temporal locations in each processing condition. However, low probability tones in the no-discrimination, and especially in the passive condition produced a substantial increase in T250, with frontal regions being also involved. The primary auditory (temporal) cortex has been strongly implicated in the processing of auditory stimulus deviance producing a subsequent automatic attention-switching process in the right frontal cortex [22,23]. The specific task and topography effects obtained for T250 suggest that this time–frequency component may reflect such automatic detection of deviant auditory stimuli and orienting attention switching. Additionally, the hippocampus may be strongly involved with T250 generation because the hippocampus has direct and strong reciprocal connections with the temporal/frontal lobes and the hippocampal–cortical feedback loops are known to operate in the theta frequency channel in relation to stimulus context integration [24] and unexpected stimulus detection [4]. Moreover, the hippocampus has been directly and indirectly implicated with the generation of P300 (cf. [3]). Thus, T250 may reflect a cortical–hippocampal process in the theta channel related to stimulus evaluation, which, in case of physical or context deviations, can co-activate the frontal regions for subsequent controlled processing.

T250 may correspond to a frontal aspect of the P300 component often identified as P3a because P3a is elicited most reliably by rare or novel stimuli in unattended conditions or in the absence of a response, P3a is with a frontal-central maximum and short latency [25], and P3a is believed to reflect an alerting process in the frontal cortex, or an automatic attentional switch [22,25]. It appears from the WT analysis results that T250 is consistently present at the temporal cortex after each auditory stimulus [5], but only during some conditions (i.e. passive, ignore, context deviant) can be reliably detected as P3a.

D370 is a parietally distributed time–frequency component from the late P300 range that interacted with each P300 determinant (probability, discrimination and count) in highly significant, additive and topography-unspecific ways. These results suggest that D370 may relate to a basic and less cognitive-specific process activated upon any increase in task demands referred to as processing resource allocation [8].

With respect to topography, time localization, and task effects, D370 strongly resembles the classical auditory P3b component [2,6]. Furthermore, the major power of P3b is in the delta frequency range [14–16]. Given that processing resource allocation is a construct used to explain adequately the functional significance of P3b [8], D370 appears to represent in a more refined manner the most relevant features of P3b related to attentional/arousal mechanisms.

T370 indicates the presence of an anteriorly (fronto-centrally) localized processor operating in the theta frequency channel that is activated selectively by task relevance (discrimination and count). Since both theta EEG frequency and frontal cortical regions have been consistently associated with memory functions [11,20], this frontal theta subcomponent within P300 may reflect task-induced activation of working memory and account for the relationships of P3b with memory operations [1].

A specific frontal aspect of the auditory P3b has been implied by previous results on the base of differential amplitude/latency P3b correlations [26]. Similar to the functional sensitivity of T370, an anterior P300 has been obtained with manipulating target discriminability but not with varying probability in task conditions [25]. These previous observations may have at least partly resulted from the contribution of a frontal theta component in the range of P3b, which could be reliably distinguished by time–frequency analysis employed in the present study.

CONCLUSION

The time–frequency analysis demonstrated that functionally distinct subcomponents co-exist during auditory P300 ERP component. In the early P300 time period, a central delta frequency component reflects the evaluation of frequent and relevant events, while a second mechanism in the theta frequency channel is simultaneously activated at temporal-frontal sites to detect stimulus and/or context deviations and switch orienting attention. In the late P300 time period, in parallel to a mechanism mobilizing processing resources as reflected by a parietal delta component, a frontally localized process in the theta frequency is activated presumably in relation to working memory. Thus, the time–frequency decomposition of P300 helps to isolate and describe more precisely different consecutive or overlapped functional processes during P300, provides a possibility to study these processes even in a single experimental condition, and may aid to reduce controversies about P300 functional significance.

REFERENCES