Visual event-related components in human. A diagnostic tool for early detection of metabolic brain disorder
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CHAPTER II

ISOLATION OF LATE EVENT-RELATED COMPONENTS TO CHECKERBOARD STIMULATION


Abstract
In this study we established the optimal physical parameters of visual stimuli to elicit event-related potentials (ERPs) from the brain derived from midline scalp electrodes (Fz, Cz, Pz, Oz). The character of the ERPs was investigated for different states of attention (conditions).
To elicit visual ERPs, two types of black-and-white checkerboard onset stimuli were presented. “Frequent” stimuli (40 ms presentation of 12' checks) were randomly interleaved with “infrequent” stimuli i.e., events (40 ms presentation of 200' checks). Similarly two types of auditory tone bursts were presented: “frequent” (40 ms duration of 2 kHz) and “infrequent” (40 ms duration of 8 kHz). Recordings were taken in the situation that subjects were instructed to count the “infrequent” visual or auditory stimuli. Brain mapping (32 electrodes, three subjects) and dipole localization were performed.
Sixteen subjects were tested for both modalities. In four subjects, only visual ERPs were measured. We studied the dependence of the components on check size, contrast and interstimulus time interval.
Our findings are as follows: low contrast (10%) checkerboard stimuli optimize the isolation of the long-latency components. N200 (occipital source) is related to temporal irregularity; P3a (parietal source) is related to the interstimulus time interval; P3b (central) is related to the cognitive processing of “infrequent” sensory stimuli.

Introduction
It has been proposed that several structures in the brain are involved in the generation of the long-latency components in the electrical responses and magnetic fields evoked by “infrequently”- presented or omitted sensory events (Halgren et al., 1980; Okada et al., 1983; Rogers et al., 1991, 1992, 1993; Tarkka et al., 1995; Knight et al., 1996). One of these long-latency components, the P300, was described for the first time by Sutton and colleagues (Sutton et al., 1965). Since then several long-latency components have been reported. The N200 "discrimination potential" (Ritter et al., 1979; Taghavy and Kügler, 1988) seems to be caused by counted and ignored events (mismatch negativity), and by random absence of visual and auditory events (omission N2; Klinke et al., 1968; Simson et al., 1976; Näätänen et al., 1978, Alho et al., 1994). The topography of N200 seems to be modality-specific. The
fronto-central P3a has been reported to be generated by “infrequent” auditory stimuli that are ignored by the subject (Squires et al., 1975) and also by novel stimuli (Courchesne et al., 1975). The parietal P3b has been reported to be produced by “infrequent” auditory and visual stimuli that the subject has been instructed to count (Squires et al., 1977; Israel et al., 1980; Wickens et al., 1983; Knight, 1997), and by random omission of “frequently”-presented visual and auditory stimuli that the subject has been instructed to count (Ruchkin et al., 1975; Simons et al., 1976).

It has been proposed that every event-related potential (ERP) contains both early sensory and late cognitive components which might overlap in time. To allow these late components to be studied it is necessary to isolate them, for instance, by minimizing the amplitude of the sensory part of the response so that it does not interfere with the later components. Furthermore, optimal recording positions have to be chosen on the basis of the potential distribution of the components over the head. Once the sensory and cognitive components have been isolated, a parametric study can be carried out on the two kinds of response.

The first aim of the present study was to optimize the parameters of the visual events for isolation of the late components. The technique we report here allowed us to clearly separate the various event-related components. These components were distinguished on the basis of their distribution across the scalp and on the basis of their amplitude- and latency-dependence on the following stimulus parameters: check size, contrast, and interstimulus time interval. Secondly, some experiments with 32 derivations were carried out to allow source locations of responses to be estimated. These topographical studies indicated that four recording sites are sufficient for isolation of the N200, P3a, and P3b components. The visual N200 proved to be an occipital component; the P3a component is a broadly distributed fronto-central complex; and the P3b component can be recorded from all derivations but shows a parietal maximum.

Having visual stimuli optimized for the separation of the various components, we then studied the effects of the following different states of attention: (1) passively ignoring the visual events; (2) ignoring the visual events distracted by counting auditory events; (3) ignoring the auditory events distracted by counting visual events; (4) counting the visual events; (5) ignoring and counting random omissions of the stimulus (the event is defined as an absence of a “frequent” visual or auditory stimulus) and (6) observing standard (pattern onset/offset) stimuli. We recorded a clear N200 peak in both the ignoring and counting conditions. On the other hand, P3a and P3b were best isolated in the counting condition. In this way we will establish the normative parameters of N200, P3a, and P3b. We report here how we used these component-separation techniques to examine patients suspected of experiencing cognitive impairments.

**Methods and materials**

Twenty healthy volunteers (14 males and 6 females, age of 40 to 60 years) with (corrected) visual acuity better than 1.0 took part in the study. Sixteen of them had never participated in similar experiments and the remaining four were co-authors.
The subjects were informed about the aim of the study and the general procedures of the experiments.

The electroencephalographic (EEG) activity was recorded from four midline Ag-AgCl electrodes near Fz (frontal), Cz (central), Pz (parietal), and Oz (occipital). First the distances between inion and nasion, and between the preauricular depressions were measured, and the central electrode (Cz) was positioned in the centre of those two lines. The occipital (Oz) electrode was positioned 3 cm above the inion. Pz was 9 cm above Oz (along the midline of the head), and Fz was positioned on the hairline. The right earlobe electrode was chosen as reference and the common ground electrode (G) was placed arbitrarily. The electrodes were attached with collodion to the scalp, and their impedances were reduced to below 10 kohm. The EEG was sampled every 4 ms. Since the power of the long-latency components is known to be maximal below 5 Hz (Stampfer et al., 1985; Schürmann et al., 1995), the signals were filtered on-line between 0.6-4.5 Hz with a first-order lowpass and a first-order highpass filter introducing an extra latency of about 20 ms of the peaks of the responses.

The potential distribution across the four midline electrodes (position along the vertical axis) against time (horizontal axis) was plotted in chronomaps (20 subjects) to study the distribution of the isolated activities over the scalp (Rémond, 1969). Although these chronomaps do not add extra information to the data presented, we found them useful to have them available on-line during the experiments, which was experienced to be very informative. Maps of the potential distribution based on 32 recording sites were investigated in three subjects. The positions of the electrodes on the scalp were determined with a positionmeter ("Polhemus"-Isotrack II). We carried out a source location based on a four-layer sphere model (De Munk et al., 1988) on the assumption that each of the isolated long-latency responses could be accounted for by a single equivalent dipole. For each component, a time interval of the response was selected in which this component dominated.

The electrophysiological examinations took place in a semi-darkened room (mean illuminance 10-30 lux). Subjects were sitting at a distance of 1.20 m in front of a television screen (Tetracon; mean luminance 200 cd/m²). Subjects fixated a central point (5′ x 5′ visual angle size). Two types of black-and-white checkerboard patterns with different checks were presented for 40 ms every 640 ms, with one check size stimulus occurring more frequently than the other. This check size was replaced randomly by the other stimulus (event) every 4th to 8th appearance of the first stimulus; the mean interval between the events therefore was 3.84 s. Responses were averaged on-line, usually the responses to the “frequent” stimuli about 175 and the responses to the events about 35 times. The latency and amplitude of the isolated components were measured with respect to the first 40 ms after stimulus onset. The subject was instructed to keep a mental count of the events (counting condition) and to report the total count after each series. To estimate the alertness of the subject we compared the reported number with the number of events actually presented.

Following previous studies (Taghavy and Kügler, 1988), we recorded responses to pattern onset stimuli with high contrast (80%). Figure 1 shows a typical example of a recording upon “frequent” 200′ checks and “infrequent” 12′ checks
with 80% contrast in the counting condition. Since the earlier sensory components overlapped the event-related peaks (especially obvious in the "calculated" bipolar derivation: Oz-Fz), a study of different stimulus variables such as contrast (20 subjects) and check size (four subjects) was made to establish the visual stimulus that would best isolate the various late components.

**Fig. 1** Event-related responses in a visual counting condition. The responses evoked by the events (12' checks, 80% contrast) are presented on the right. The early visual evoked potential (VEP) is large in amplitude compared to the VEP on the left side, evoked by the “frequent” stimuli (200' checks, 80% contrast). In the response to the events the sensory component is followed by the late P300 component. There are no other late components to be distinguished across all derivations. Due to the time overlap between the large early and the long-latency responses, no separate late components can be seen (especially at the bipolar Oz-Fz derivation).

In an attempt to understand the character of the different components, we studied the responses in a passively ignoring condition: the subject was instructed to fixate a black dot in the centre of the screen and to pay no attention to the randomly occurring events. We arranged for each session to be started in this way, since we expected that it would be difficult for the subjects to ignore the events, once they knew that their next task would be to count these events.

To compare the responses in these conditions with sensory evoked responses we also recorded standard pattern onset/offset VEPs to 5%, 10%, 20%, 40%, and 80 % contrast large checks (200') and to 80% contrast small (12') checks (standard condition). The whole experiment took about two and a half hours.
Because the ignoring condition was not unequivocally defined by the task given, we retested sixteen of the subjects with visual-auditory stimuli. This procedure involved simultaneous presentation of the auditory and visual stimuli. The “frequent” auditory stimulus was a tone burst of 2 kHz. The “infrequent” auditory stimulus was a tone burst of 8 kHz. The 2 kHz tone had a sound pressure level (SPL) of 64 dB and the 8 kHz tone had a SPL of 50 dB. The auditory stimuli were generated by the computer, and were presented for 40 ms every 800 ms. Thus the interstimulus interval was 800 ms versus 640 ms for the visual stimulation and the mean interval between the auditory events was 4.8 s. In this way the “frequent” visual and auditory stimuli were essentially asynchronous, while the events of both modalities were controlled in such a way that they never coincided in time. The recording program allowed for simultaneous separate recording and averaging of the responses to the four types of stimuli (“frequent” and “infrequent” visual and auditory stimuli). These stimuli were presented to the subjects in two experimental conditions:

a) Ignoring the visual events while counting the auditory distinctive events (8 kHz tones).
b) Ignoring the auditory events while counting the visual distractive events (200' checks).

Additionally the responses to randomly omitted stimuli (omission condition) were recorded (in four subjects). In this condition the event was defined by the random absence of the visual (200' checks, 10% contrast) or the auditory (8 kHz tones) stimulus.

Results

Stimulus parameters
Since the “infrequently”-presented small checks evoked large early sensory responses, while the larger checks of the “frequent” stimulus evoked small sensory responses (see Fig. 1), we interchanged the check sizes and recorded the responses in 20 subjects with the large checks (200') used as the event, and the small checks (12') as the “frequent” stimulus, and varied the contrast. Figure 2 illustrates such a series of responses to different contrasts in the counting condition.
Fig. 2 A series of event-related components evoked upon different contrast (5%, 10%, 20%, 40%, 80%) 200' events, in a visual counting condition. N200 (at Oz), P3a (at Fz) and P3b (at Cz and Pz) are best separated (spatially and in time) when the events are presented at 10% contrast. At 5% contrast the events evoked delayed and smaller amplitude components, suggesting that the 5% stimulation is near threshold. The N200 amplitude increases from the subjective threshold up to the maximum at 10% contrast and decreases with higher contrasts. The P3a component (Fz) does not change with contrast (except for the lowest contrast of 5%). In this subject the amplitude of the P3b component (Cz and Pz) diminishes above 10% contrast.

Stimulus parameters
The best isolation for the three components was obtained in the 10% contrast condition, which yielded small sensory components in the response to the “infrequent” stimuli, whereas the event-related peaks were clearly identifiable. The negative (N200) component in the response to the events had an occipital maximum and peaked around 200 ms after stimulus onset. At the frontal and central derivations a positive component (P3a) could be identified. The P300 (called P3b) was largest parietally. The amplitudes of N200 and P3b were largest at 10% contrast (in this subject), whereas the amplitude of P3a did not seem to depend much on the contrast of the “infrequent” stimuli.
To test whether using 200’ checks as event gave the optimal separation of the components, we recorded (in four subjects) a series with 12’ checks as “frequent” stimuli and 200’, 100’, 50’, and 25’ checks respectively as “infrequent” stimuli at 10% contrast. Figure 3 illustrates an example while the subject was counting the events. N200 was maximal in the occipital lead, P3a was present in the frontal and P3b in
Event-related components to counted visual events of different check sizes (200’, 100’, 50’, 25’) at 10% contrast. The responses to the “frequent” stimuli (12’ checks) are not presented on the figure. The latency of the N200 component (Oz) shortens systematically with the smaller check sizes of the events. The P3a is most outspoken at the frontal derivation (Fz) and seems not to be affected by the check size of the events. The P3b shows maximal amplitude for the 200’ events (Pz).

As can be seen the condition with 12’ for the “frequent” stimulus and 200’ checks for the events gave the optimal separation of the P300 components.

To establish whether the electrode choice of four derivations was appropriate for this optimal stimulus condition, evoked potential data were also collected from 32 electrode positions in three subjects. Figure 4 shows maps of the distribution of the potentials across the scalp of one subject at consecutive time instants (every 16 ms, starting at 48 ms until 512 ms after the stimulus onset), recorded during stimulation with 10% contrast 12’ “frequent” checks and 200’ “infrequent” checks, while counting the “infrequent” stimuli. The “frequent” stimuli evoked weak sensory responses (occipitally, in the area of the visual cortex) as a result of the low contrast influencing the extent of the primary VEPs. There are no late activities to be seen on these maps, whereas there were three distinct activities caused by the counted events (on the right): an early spatially-restricted occipital negativity at around 200 ms (N200), a broad fronto-central positivity at around 230 ms (P3a) and a broad parieto-occipital positivity at around 330 ms (P3b).
Figure 5 illustrates the averaged time signals and the results from the source modeling (of the same subject as in Fig. 4). The responses to the events (200' checks of 10% contrast) are shown on the left. The cursors were located on the main peaks: N200 at 192 ms, P3a at 232 ms and P3b at 328 ms. The distribution of the potential fields for these latencies are given in the middle of this figure and the equivalent dipoles found for the sources of N200, P3a, and P3b are plotted at the right.

The spatio-temporal characteristics of N200, P3a, and P3b suggest that they have different generators, and that P3a and P3b originate from deeper structures.

Source modeling (assuming a single dipole source for each of the three components) yielded for the N200 response in all three subjects an occipital source in the brain, close to the scalp. Its equivalent dipole can be found superficially in the mid-occipital area, or occipitally in the left or right hemisphere, pointing forward. For the P3a component the dipole was found in two subjects deep and parietally, with a direction of the current pointing forward or to the central part of the scalp. In the third subject, source modeling of P3a failed, because of overlap in time with the N200 and P3b components. The P3b source was for all three subjects located deep centrally, with a dipole pointing towards the parietal part of the scalp.

It can be concluded from the distribution of the late components that they are best recorded at the four electrode positions as indicated in Figs. 2 and 3. Therefore, in the following these four midline electrodes were used to record the late ERPs.

**Conditions**

Figure 6 presents (at the left) a recording during which the subject was passively looking at the screen (i.e., ignoring the events). Two prominent long-latency responses can be seen: the occipital N200 and the centro-frontal P3a (the left side of the figure). A small amplitude parietal P3b may be seen sometimes on the trailing flank of the P3a. To strengthen the ignoring condition, 16 subjects were retested with simultaneously-presented distractive (“infrequent”) auditory stimuli (events). The right side of Fig. 6 depicts a recording of the same subject when the subject was counting the auditory events and at the same time was observing the checkerboards. In this "distracted" condition the visual events (which were not counted) evoked N200 and P3a; the P3b was always absent or very small (except for the four co-author subjects). The recordings in Figs. 1, 2, 3, 6 and 9 were obtained from the same subject.

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**Fig. 4 Maps of the distribution of the potentials across the scalp (32 electrodes; one subject) at every 16 ms after the stimulus onset (starting from 48 ms post stimulus). The stimuli are presented at 10% contrast in the visual counting condition. The meaning of the colors is red for positive, blue for negative, yellow for zero (color scale at the bottom). The left side shows maps of the potential distribution upon the “frequent” (12' checks) stimulus. As a result of the low contrast the primary visual activity is very weak so that only a weak positivity at around 185 ms can be distinguished (occipital region). The right side shows maps upon the events (“infrequent” 200' checks). In these it can be seen that there is an early occipital negativity (maximal at around 200 ms, N200), two frontal positive activities (maximal at around 230 ms, P3a) and a parieto-occipital positivity (maximal at around 330 ms, P3b).**

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N200

N200 was present both when ignoring and counting the visual events. In both the passively-ignoring and the counting condition, the amplitude of N200 was larger than the value found in the ignoring with distraction condition. In the passively-ignoring condition the N200 amplitude was 2.9µV ± 1 (detected in 17 subjects, 18 tested) and in the counting condition it was 2.6µV ± 1 (detected in 17 subjects, 19 tested), whereas in the ignoring with distraction condition it was 2.3µV ± 1 (detected in all 16 subjects) and 1.9µV ± 1 upon standard pattern onset/offset 200' stimuli (detected in 16 subjects, 20 tested).

The latency of N200 was found to be shorter to standard 200' stimuli (180 ± 30 ms) compared to passively-ignored 200' events (200 ± 20 ms). The difference in latency of N200 to standard versus the ignored (with distraction) irregular condition was found to be significant (p<0.01). They showed a high intrasubject correlation (r=0.7, p<0.005), whereas standard to counting condition did not (r=0.38, p>0.2, for 12 subjects). There were no significant differences found in the latency of N200 upon irregular stimuli: counted versus passively ignored (t=0.7, p>0.2, for 15 subjects).

The N200 was studied as a function of contrast. The N200 amplitude increased from the subjective threshold up to a maximum at 5-10% contrast and decreased with higher contrast. The latency shortened with higher contrast (Fig. 2).

In the visual omission condition the N200 component was only detected when the mean interval between the omissions was made large. In a separate experiment it was varied from 3.84 till 26.24 s, which proved to increase the amplitude up to 9.6 s. It had an occipital maximum (at Oz) and a more than 100 ms latency variation in the same subject.

When the “frequent” 12' stimuli were “infrequently” replaced by events of different check sizes (25', 50', 100', and 200'), N200 latency shortened as the check size of the event became smaller (Fig. 3).

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**Fig. 5** The event-related responses to counted 200' events (10% contrast, 32 electrodes) are shown in the left column. The cursors are placed on the channels, where the evoked components have maximal amplitude: N200 at 192 ms, channel 28; P3a at 232 ms, channel 5; P3b at 328 ms, channel 2. The middle column depicts the potential maps for N200 (top), P3a (middle) and P3b (bottom). The corresponding equivalent dipoles, found for the sources of these components are shown at the right side. The outer sphere is the best fitting sphere through the electrode positions. The point corresponds to the position of the source and the line to the direction of the current. The error of the unexplained variance of the fit was smaller than 6%. The equivalent dipole for the source of N200 is located superficially (i.e., close to the scalp), occipitally in the right hemisphere. The dipole for the P3a is located deep parietally in the right hemisphere with the direction of the current pointing towards the central part of the scalp (Cz). The dipole for the P3b is found deep centrally, pointing towards the parietal part of the scalp (Pz). The results in Figures 4 and 5 are obtained from the same subject.
Fig. 6 A comparison between the event-related responses obtained in a passively ignoring (the 200' events, 10% contrast) condition (left panel) and in an ignoring (the 200' events) with auditory distraction condition (right panel). The N200 and P3a components are elicited upon both conditions. In the passively ignoring condition P3b component can still be detected, while in the ignoring with a distraction condition this component is no longer obvious.

**P3a**

The P3a component was evoked in both the ignoring and the counting conditions. It was recorded in 17 subjects (19 tested) upon counted visual events, in 18 subjects (20 tested) upon standard 200' pattern onset/offset stimuli, in 17 subjects (18 tested) upon passively ignored events, in 15 subjects (16 tested) upon ignored visual events with distraction, in 10 subjects (15 tested) upon counted auditory events and in 13 subjects (16 tested) upon ignored auditory events with distraction.

The latency and amplitude of the P3a components to passively ignored visual events versus the components to ignored visual events with distraction are not statistically different (amplitude: t=2.3; p<0.05; 12 subjects) and show high intrasubject correlation (latency: r=0.81; p<0.001, amplitude: r=0.77; p<0.01). These components differ both in latency and in amplitude from the P3a evoked by counted visual events and standard stimuli. There was no statistical difference between the latencies of P3a to counted visual events (262 ± 26 ms, in 17 subjects detected, 19 tested) and standard stimuli (260 ± 26 ms, in 18 subjects detected, 20 tested). The amplitude of P3a to irregular 200' stimuli (ignored or counted) was larger than the amplitude of P3a to standard 200' stimuli. Since P3a was found to be present for all stimulus parameters and in all conditions, and was smaller in the standard pattern onset/offset responses than for the irregular interstimulus intervals, we recorded a series of
standard pattern onset/offset responses with varying interstimulus interval. The amplitudes of P3a were fitted with an exponential function: \( S(1 - \exp(-l/T)) \), in which \( S \) is the asymptotic value of the amplitude; \( l \) is the interstimulus time interval. The time constant \( T \) was found to be 0.6 s.

Thus, P3a is related to the interstimulus time interval of the presented stimuli. Provided that the interstimulus time interval was the same, no difference was found in P3a evoked by irregular and regular stimuli.

We studied the behaviour of P3a as a function of contrast (above 10% contrast) for all the subjects and did not find any systematic influence on the latency or the amplitude of this component. In the "omission" condition the P3a component was clearly elicited in two of the four tested subjects. It had a centro-frontal maximum with a large intrasubject latency range (392-584 ms).

The mean latency of P3a upon standard 12' pattern onset/offset checks at 80% contrast was found to be 317 ± 14 ms (in 19 subjects recorded, 20 tested). There was no significant correlation between N200 and P3a (\( r=0.06, p>0.2 \), for 16 subjects).

**P3b**

In the visual counting condition (recorded in 18 subjects, 19 tested) and in the visual counting while presenting auditory stimuli condition (recorded in 14 subjects, 16 tested) P3b was present in all derivations with maximal amplitude parietally. For the one subject in whom P3b was not identified upon visual counting, P3b was clearly detected upon visual counting while presenting auditory stimuli and in the auditory counting while presenting visual stimuli condition (for the two subjects in whom P3b was not detected in the visual counting while presenting auditory stimuli, it was clearly found in the pure visual counting condition). When passively ignoring the visual stimuli (Fig. 6), in most of the subjects P3b was small or could not be detected at all. In six subjects we could identify a small P3b; four of them were the co-authors, i.e., the experienced subjects.

In the visual ignoring with auditory distraction condition P3b was not detectable (16 subjects tested), except for the four co-authors. The mean latency of P3b component was 380 ± 40 ms (detected in 18 subjects, 19 tested) for the visual counting condition and 390 ± 40 ms (15 subjects) for the visual counting while presenting auditory stimuli. We investigated P3b component with different contrast and check sizes of the presented events (20 subjects), and did not find any systematic influence of those parameters on the P3b component. In counting the omissions condition the P3b component was distinguished in the responses of all four subjects tested. However, its latency was much longer and more variable, and its waveshape broader than in the case of 200', 10% contrast events.

The correlation between the latencies of P3a and P3b components across the subjects (both in counting condition) was not significant (\( r=0.41, p>0.1 \), 16 subjects), also

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1 The signal-to-noise ratio of the response in such an amplitude relation is proportional to \((1- \exp(-A))/\sqrt{A}\), where \( A=l/T \). The maximal signal-to-noise ratio is reached for \( A=1.26 \), therefore, the optimal stimulus interval for P3a would have been 0.74 s. We used an interstimulus interval of 0.64 s which gave a signal-to-noise ratio close to the optimal value.
P3b and N200 (both in counting condition) showed no significant correlation ($r=0.56$, $p>0.2$, 13 subjects).

**Visual-auditory condition**

The event-related responses evoked by the auditory events (counted and distracted) were isolated and compared with those evoked by the visual events. The P3a component in the auditory ERPs was obtained in the distracted condition (Fig. 7), its mean latency was $289 \pm 38$ ms (in 12 subjects recorded, 16 tested). In eight subjects (15 tested) in the counting condition the mean latency was $285 \pm 38$ ms. In four subjects (16 tested) auditory P3a could not be detected at all, whereas P3a for those subjects was clearly evoked by the visual stimuli. Like in the visual ERPs recorded in the distracted condition of the four co-authors, the auditory P3b in the distracted condition was also only distinguished in those subjects.

Auditory P3b components were isolated in all 15 subjects tested in the counting condition. Maximal auditory P3b peaks were registered at the parietal derivation, like for the visual P3b (Fig. 8). The mean auditory P3b latency was $376 \pm 26$ ms (15 subjects).

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**Fig. 7 (up)** Event-related components of a subject to simultaneously presented visual and auditory stimuli. The left two panels represent the responses to the visual "frequent" 12' stimuli and the 200' events. The right two panels give the responses to the auditory "frequent" 2 kHz tones and the 8 kHz "infrequent" tones. When the auditory attention is distracted by counting the visual events, three distinct components are detected in the visual responses (second column): N200, P3a, and P3b. The P3a is the only component present in the auditory responses to the "infrequent" tones (fourth column).

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**Fig. 8 (down)** When the visual attention is distracted by counting the auditory events (second column), the N200 (maximum at Oz) and the P3a (maximum at Fz and Cz) can be recognized. In the auditory responses (fourth column) a clear P3b can be seen.
Statistically there was no significant latency difference between auditory and visual P3a \((t=0.53, p>0.2; 11\) subjects) and accordingly, no significant latency difference was found between auditory and visual P3b components \((t=1.30, p>0.2; 14\) subjects). The correlation between the visual and auditory P3a was low \((r=0.2, 7\) subjects), as for the P3b components \((r=0.1, 14\) subjects).

A negative component was not detected (one subject tested) when the subject counted the random absence of a tone in a "frequent" presentation of 2 kHz tones (omission condition, the stimulus was absent on average every 4.8 s). Like in the visual omission condition, N200 was detected when the time interval between the omissions was longer. N200 in this condition had a fronto-central maximum and a latency range of 112-200 ms.

Apart from N200, the counted omissions evoked a central positive P3a component (maximum at Cz), in the latency range of 296-424 ms, and a parietal positivity P3b (maximum at Pz) in the latency range of 416-664 ms.

**Chronomaps**

Chronomaps of the responses to 10% contrast standard pattern onset/offset, ignored and counted 200' checks are presented in Fig. 9. (Chronomaps are potential distributions along the line defined by the four electrodes as a function of time). The N200 activity can be seen in the three stimulus conditions; it was localized at the occipital part of the scalp (at the level of Oz, blue), which suggests that its generator was superficial, i.e., near the occipital cortex. The P3a potential can be identified upon standard stimuli and events. It showed similar broad topography for the three conditions (at the level of Cz, red), and might be concluded to be one and the same component. P3b activity only dominates in the counting condition (maximal at the level of Pz, red). In the chronomap of the counting condition the P3a activity is partially visible since it is overlapped by the P3b. Both P3a and P3b components show a widespread scalp topography, which can be seen in the responses from the four electrodes and the corresponding chronomaps.

**Fig. 9** The potential distributions (chronomaps) along the four midline electrodes (vertical scale) for a whole sweep time (horizontal scale) in three visual conditions from left to right: standard pattern onset/offset 200' checks, passively ignoring 200' events, counting 200' events at 10% contrast. The color scales of the maximal potentials (from left to right) are from -3.3 μV till 3.3 μV, from -6.9 μV till 6.9 μV, and from -14.5 μV till 14.5 μV. The chronomaps are based on the evoked responses of one subject. The early occipital negativity (N200, at the level of Oz electrode) can be seen in all three chronomaps. A centro-frontal positivity (P3a, at the level of around Cz) is most clearly seen in the first two conditions and less obvious in the third one due to the dominance of P3b.
Discussion

This study provides evidence that clear identification of the three long-latency components to rare meaningful events can be facilitated by using the onset of low contrast (10%) large checks (200') as the rare visual event in the “frequent” presentation of 12' small checks.

To record different late components (N200, P3a, P3b), four midline electrodes seem to be sufficient, as was used before (Friedman et al., 1978; Verleger et al., 1991). Separate long-latency components could not be obtained using the technique of Taghavy and Kügler (Taghavy and Kügler, 1988) who used small checks at high contrast as an event, and recorded from a calculated Oz-Fz bipolar lead. Estimated from the maximal activity in the chronomaps of the responses to counted events, the average position in the midline of the P3a peak was 19 ± 6 cm (away from the inion), and of the P3b peak 13 ± 6 cm. Therefore, the optimal electrode position for recording of the P3a would be at Cz. However, at this central electrode often a mixed P3a/P3b response is recorded, whereas the frontal one most often records a single isolated P3a (see Fig. 2). Therefore, Fz was chosen to estimate the P3a latency for the normative data, Pz for the latency of the P3b peak and Oz for the latency of N200.

In this way the dependence of the individual components on contrast and check size could be studied. If this parametric behaviour of the N200, P3a, and/or P3b would reveal a strong dependence on pattern parameters, a sensory origin of that component would be suggestive since cognitive components are supposed to have a weak dependence on stimulus parameters.

N200 component

With increasing contrast, the N200 peak latency shortens, whereas its amplitude (absolute value) increases from the subjective threshold up to a maximum at about 5 to 10% contrast and then decreases at higher contrasts (see Fig. 2). By being so strongly related to contrast, N200 seems to reflect sensory qualities. Above the subjective threshold, different check sizes of the stimulus do not influence the amplitude of N200, whereas its latency increased with check size (see Fig. 3). The latency and amplitude of N200 is influenced by the regularity of the stimuli, regular versus irregular. The N200 amplitude was smaller in the responses to the standard 200' checks than to the 200' events. This suggests that this component was associated and influenced by the novelty of a stimulus. There was a statistically significant intersubject latency difference between N200 upon standard stimuli and irregular events and these latencies were significantly correlated.

N200 was clearly detected upon the visual stimuli used in our study. In the responses upon the auditory events with the 6 kHz difference between the tones N200 was not detected. Therefore, stimuli with small frequency difference between the regular and irregular tones were tested as well (500 Hz for the “frequent” and 525 Hz for the event, 1000 Hz for the “frequent” and 1025 Hz for the event, 2000 Hz for the “frequent” and 2025 Hz for the event). A negative component with frontal maximum was detected in the responses upon these events. If the responses to the “frequent”
stimuli were subtracted from the responses to the events then for all frequencies presented a clear negative component (frontal maximum) could be found. The amplitudes of the visual negative component (occipital maximum) obtained by subtraction (the responses to standard stimuli of various check sizes were subtracted from the responses to the counted events of the same check sizes) were inversely related to the size difference between the stimuli as long as one can discriminate the event from the regular stimuli. This is in line with the subtraction results obtained for auditory stimuli, where the negative component had a fronto-central maximum. These results suggest that the N200 component obtained by subtraction is the modality-specific mismatch negativity (MMN), which has been described extensively for auditory stimuli (Naätänen, 1978, 1991; Alho et al., 1994; Töitten et al., 1997).

In the visual and auditory omission conditions the N200 component became more outspoken when the time interval between the omissions was longer. This confirms earlier findings on the "omission N2" component (Simson et al., 1977).

The topography of the visual N200 did not change with stimulus manipulation. Brain maps (three subjects) and chronomaps (20 subjects) reveal a localized occipital topography of N200. From the source analysis it can be concluded that the source of N200 is indeed superficial and varies in its exact occipital location across the subjects. It suggests N200 to originate from the visual associative cortex (Simson et al., 1977; Alho et al., 1994).

**Conclusion:** The N200 component (occipital source) reflects modality specific sensory qualities and is related to the irregularity and unexpectedness of the stimulus.

**P3a component**
Different check sizes of the stimuli (standard and events) did not influence the latency and the amplitude of P3a. The amplitude of P3a increases with contrast, and saturates at a contrast level of about 10%. The P3a component was not always detected in all subjects when evoked in a certain condition (ignoring) but was detected for those subjects in another condition (counting and/or standard). Therefore, performing tests in both ignoring and counting conditions enhances the chance to isolate a P3a response. We find that P3a activity can be evoked by both counted and ignored events. The "frontal late positivity" (Knight, 1997) evoked by "frequent" (standard) stimuli, coincides in latency and topography with the P3a component when the same stimulus is presented "infrequently" and being counted.

P3a is not influenced by the stimulus condition (standard, ignoring, counting) but its amplitude increases with longer interstimulus time intervals. Its amplitude for the standard condition becomes equal to the event-related P3a when presented with the same time interval. P3a could be clearly distinguished (two subjects) in the omission condition both when ignoring the absences (by counting the "frequent" stimuli) and when counting the omissions. Furthermore, it is equally present upon auditory stimulation. This suggests that this component reflects the detection of sensory events as a function of the interstimulus time interval, irrespective whether visual or auditory sensory inputs are used.
P3a has a broad potential distribution over the head, therefore its origin is deep or originates in a large part of the cortex. However, this last possibility seems unlikely given the large intersubject variability of the potential distribution on the scalp (20 subjects, chronomaps).

Source modeling (assuming one dipole source; two subjects) revealed a parietal source with a direction of the current pointing centrally (i.e., towards the Cz point) or frontally (towards the Fz point). These findings also suggest that the generator for the P3a component is located rather deep in the head (Halgren et al., 1980; Rogers et al., 1991; Knight et al., 1996).

**Conclusion:** P3a most probably originates from a deep source. It reflects sensory stimuli independent of their modality and increases in amplitude with the length of the interstimulus time interval between these sensory stimuli.

**P3b component**

From the literature it is known that P3b is a cognitive event-related component i.e., related to the meaning (to the subjects) of the stimulus. Although the latency and amplitude of P3b show large variation among subjects, P3b sometimes seemed to be sensitive to the contrast of the stimuli (see Fig. 2), although this was not found systematically. High contrast stimuli deteriorate the isolation of P3b as this component overlaps with the large preceding sensory components.

P3b is clearly present when counting the random omissions and has a parietal maximum. Previously it has been reported that two components: N200 and P300 are elicited after the random absence of the “frequently”-presented stimulus (Simson et al., 1976). In our experiments, we identify N200, P3a, and P3b when the time interval between the omissions was long, and P3a and P3b (or only P3b) for shorter time intervals. The latency of P3b evoked in counting the omissions condition is much longer and the waveshape broader than when the event is a different checkerboard, probably because of the absence of a trigger for the subject to detect the event which the visual stimulus obviously provides. However, sensory input is not necessary to evoke P3b since counting the random omissions of visual and auditory events also evokes P3b.

Whether the P3b component is present in the passively ignoring condition could not be unequivocally concluded, since it was not certain whether the subjects indeed really ignored the events. That was the reason for introducing distracting stimuli (auditory events), and registering the responses to visual events when the auditory events were counted and vice versa.

Although we tried to distract the attention to avoid generation of a P3b component, in the subjects who were rather familiar with the experiments a small P3b was still detected; it suggests that P3b is closely associated with recognition of already processed information in the brain.

Just like P3a, P3b shows a broad potential distribution and a large variation in position of its maximum over the head. On average (20 subjects, chronomaps), P3b shows a parietal maximum; besides at the parietal lead, high P3b peaks can be also detected at other leads (Cz and Fz). Source modeling (three subjects) revealed a centrally located generator with an equivalent dipole pointing in parietal direction.
This suggests a deep subcortical P3b generator, which is in agreement with previous studies (Okada et al., 1983; Rogers et al., 1991; Paller et al., 1992).

**Conclusion:** The P3b component reflects deep source activity which is modality independent. It is evoked only when events are presented on which the subject has to perform an event-related task.

**Visual versus auditory modality**
The visual stimuli allowed clear isolation of N200, whereas the auditory stimuli used could not evoke an N200. Apparently N200 is not only modality- but also stimulus-specific parameter (it is enhanced by the highest similarity between the “frequent” stimulus and the events, which confirms earlier findings related to the "mismatch negativity" (Tiitinen et al., 1997).

There was no significant difference between the latencies of the visual (upon 200' events) and auditory (upon 8 kHz events) P3a component, nor was there a difference in topography, suggesting that this is one and the same component. P3a seems to be affected by the interstimulus time interval. Although it has been demonstrated that the active areas over the scalp after visual and auditory events are different (Rogers et al., 1991), we find that for both visual and auditory modalities, P3b component is maximal at the parietal lead and that the latencies of the P3b components to auditory and visual stimuli are not significantly different and show a high intrasubject correlation. This suggests that the source of P3b is also modality independent. It is active only when counting the events. The latencies of visual and auditory P3b evoked while stimuli of the other modality are presented, are not significantly different and show a high correlation, which adds to the suggestion that this is one and the same component.

**Conclusion**
The choice of 200' checkerboards at 10% contrast as events is optimal since it allows isolation of the N200, P3a, and P3b. This made a better characterization of the components available: occipital N200 is related to temporal irregularity of visual stimuli, deep central P3a is affected only by the interstimulus time interval of any (sensory) stimulus, while deep parietal P3b is the only component which is purely cognitive.

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