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The magnetic counterpart of the contingent negative variation

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Summary The magnetic counterpart of the CNV, the contingent magnetic variation (CMV), was investigated in an Go/No Go design: subjects moved their index finger to the offset of a 4 sec tone of a certain frequency in the Go condition and were asked not to move during presentation of a 4 sec tone of different frequency in the No Go condition. During the preparatory interval, both the CMV and the electrical wave form followed a similar time course and both produced an equally pronounced statistical difference between conditions (Go and No Go). Compared to the variability in the auditory evoked fields, the CMV showed considerably more variance in the field distribution across subjects. The polarity reversal across the temporal surface of the head and the pronounced amplitudes over inferior temporal areas led us to conclude that a significant temporal activity contributes to both the late and the early CMV. However, neither for the early nor for the late CMV component did a single equivalent dipole prove to be a satisfying model. The data are consistent with the suggestion that the earlier as well as the later aspects of the CMV are fed through distributed sources in motoric, sensory and association areas, a distribution with considerable intersubject variability.

Key words: MEG; Contingent negative variation (CNV); Contingent magnetic variation (CMV); DC field; DC potentials; Event-related potential; Event-related field

In 1964 Grey Walter and colleagues (Walter et al. 1964) discovered a slow change in the EEG baseline developed during the warned foreperiod of a reaction time task when a warning stimulus indicated that a second Go signal would occur a few seconds later. Further investigations soon revealed that a shift towards negativity appears in the interval between two contingent events, particularly if the second event requires a distinct response. Although the phenomenon may be a composite of various subcomponents, it has thereafter been referred to as "contingent negative variation" (CNV). Generally, the CNV has been divided into an early aspect, related to the processing of sensory input, and a terminal CNV (tCNV), related to action preparation (Rohrbaugh and Gaillard 1983). The CNV topography, as, for example, illustrated by Denoth et al. (1986), indicates a widely distributed bilateral negativity which peaks between the frontal (earlier aspect) and the central (tCNV) electrodes. The significance of such slow potentials, with respect to information processing, has received considerable interest (summaries by McCallum 1988; Rockstroh et al. 1989) as they may represent physiological correlates of psychological constructs such as expectancy, preparation and attention. What we see on the scalp or the surface of the cortex is primarily the summation of post-synaptic potentials at pyramidal cells. Depolarization of the apical dendrites lowers the *threshold for excitability* of neurons and will appear as a surface negativity. Therefore, we believe that slow brain potentials can serve as indicators of the regulation of excitability in cortical neural cell assemblies (Elbert and Rockstroh 1987; Elbert 1993). If we assume that brain structures are able to adjust firing thresholds in advance, threshold control could be considered a mechanism for directing attention to future action. The question arises whether the anticipatory negativity, and thus the tuning of controlled processing, would be restricted to motor areas, or whether it also appears in sensory and association areas. In sensory areas, tuning might facilitate selecting sensory input patterns. For the case of auditory stimuli, it is difficult to disentangle the sources in the sensory and motor areas by means of the EEG, as activation of the auditory cortex will project to fronto-central areas as much as will the preactivation of motor programs. For temporal sources, however, a

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magnetic recording should produce a polarity reversal over the lateral surface of the head, as it is well known for, e.g., the M100 wave of the auditory evoked field (e.g., Pantev et al. 1989a,b; Hari 1990).

The magnetic counterpart of the Bereitschaftspotential, the Bereitschaftsfield, has been studied extensively by Deecke et al. (1982, 1983). As much as the Bereitschaftspotential seems to be a variant of the tCNV, we might expect a comparable magnetic field. To our knowledge, the magnetic counterpart of the CNV has not yet been studied systematically in more than 2 subjects. Fenwick and coworkers (Vieth et al. 1991; Fenwick et al. 1992) and Fiumara et al. (1985) have reported preliminary observations. Peter Fenwick termed the phenomenon contingent magnetic variation (CMV), a name which we have adopted. Fiumara et al. as well as Fenwick et al. determined the location of the terminal (late) CMV in frontal areas. The equivalent dipole of the earlier part of the CMV was located in the occipital region. Our results indicate that such a location may erroneously arise from an inadequate combination of ingoing and outgoing field extrema, produced by bilateral temporal sources (see Discussion).

For the present investigation, we chose a tone lasting throughout the warning interval, in order to bind the subject's attention and to make it unambiguous to the subject, at any given moment, whether the current time is within a foreperiod or within the interstimulus interval [1]. Such a paradigm has been shown to reduce variability in the slow potentials when prolonged foreperiods are chosen (Rockstroh et al. 1989). The presentation of an ongoing tone is known to produce a sustained potential (Köhler and Wegener 1955) or field (Hari 1980; Pantev et al. 1994). The present Go/No Go design controls for such a slow shift when the differences between Go and No Go are observed.

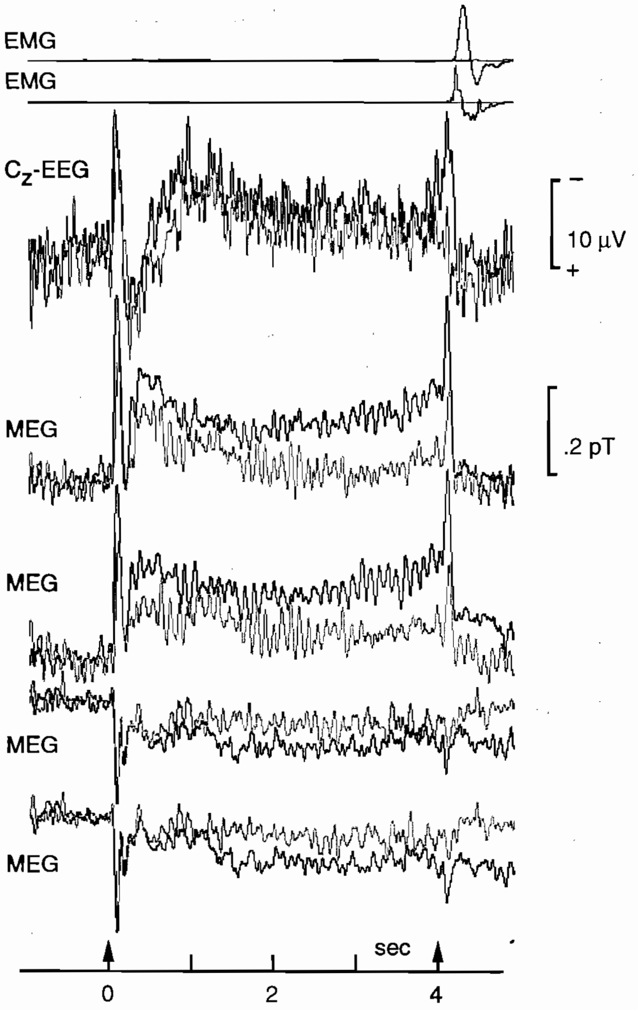

Fig. 1. Single subject averages for MEG channels selected to show the range of ingoing and outgoing fields (lower 4 traces) and in parallel the EEG (Cz-A2) and EMG (pars indices m. flexor digitorum longum). Dark lines correspond to the Go, grey lines to the No Go condition.

Method

Subjects

Nine men and 1 woman, all right-handed (as verified by a modified version of the Edinburgh handedness questionnaire, Oldfield 1971) and of good health, participated in the study. The ages ranged from 25 to 50 years (with an average of 34.8 ± 8.2 years). None of the subjects was under current medication at the time of testing. Prior to the experiment, each subject was given a detailed demonstration of the experimental procedure and apparatus.

Design and procedure

Within a constant foreperiod reaction time paradigm 2 different tones, a high-pitched (1000 Hz, 60 dB) and a low-pitched one (600 Hz, 60 dB), were presented in random order. Tones were switched on for intervals of 4 sec each, with 10 msec rise and decay time. (The tone interval will be called "warning stimulus" (WS) from hereon.) The interval between 2 subsequent tones varied randomly from 4 to 8 sec. Half of the subjects were asked to perform a flexion with their right index finger as fast as possible to the offset of the low tones ("Go trial"), but to repress any movement whenever the high tones were presented ("No Go trial"). The relationship between tone pitch and response (Go/No Go) was counterbalanced across subjects. The rectified EMG from the right forearm served as control for the subject's compliance with the instruction. A total of 192 trials (stimuli) were presented with an equal probability

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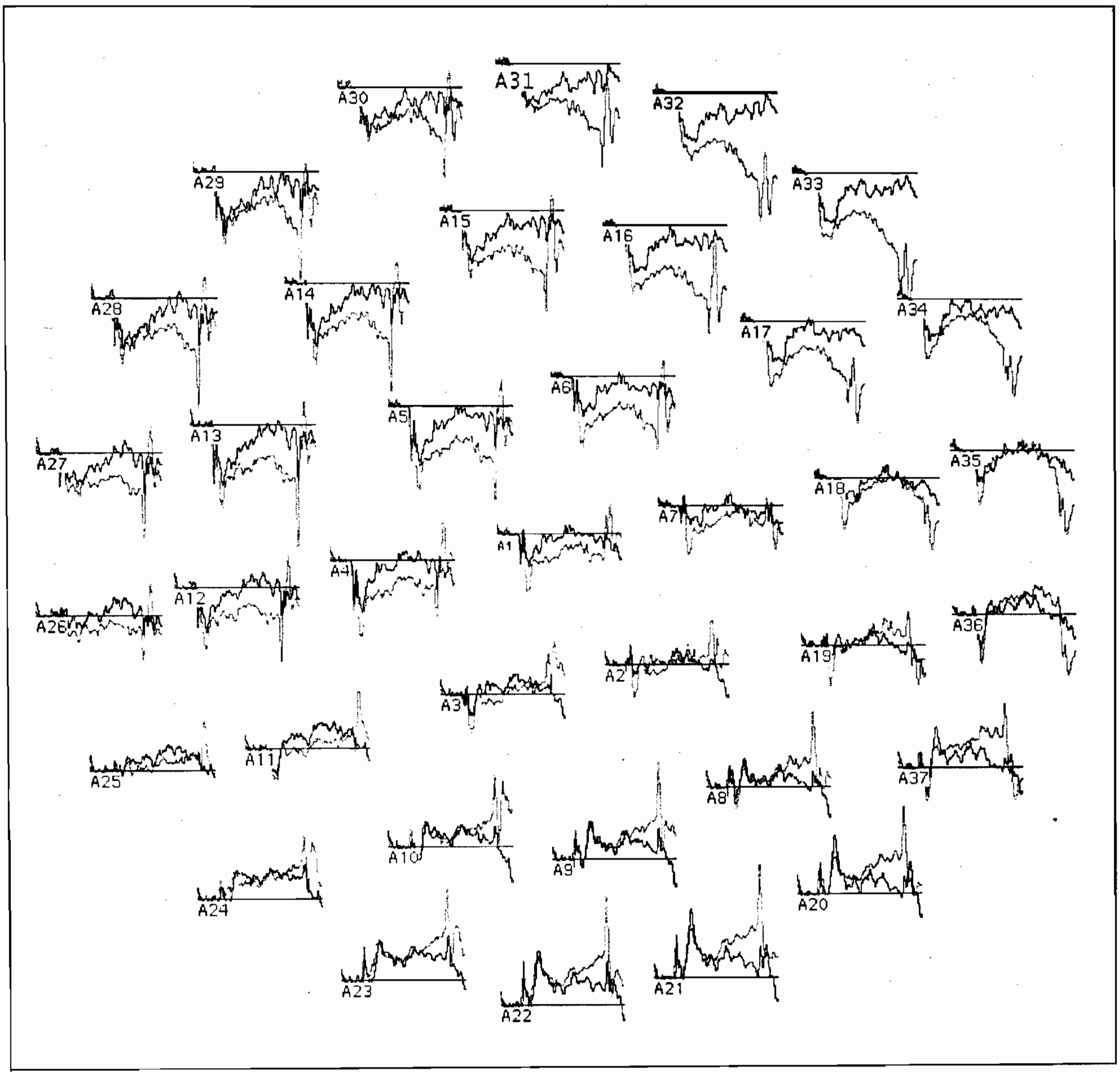
[1] When, for instance brief tone pulses are used as warning stimuli, the subject may sometimes be uncertain whether or not he/she has missed the warning stimulus.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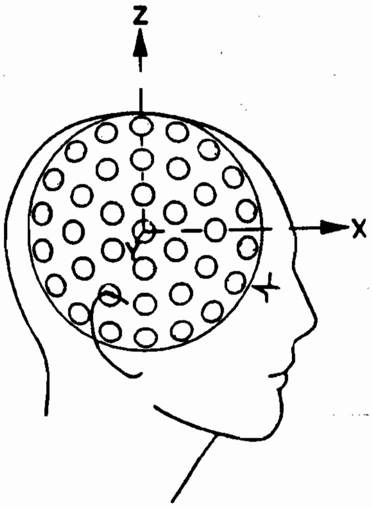
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for the 2 different frequencies to occur. Thus, the recording time lasted for 32 min; another 40 min were needed for preparation of the recording, familiarizing the subject, etc.

Apparatus and physiological recording

Tones were delivered to the subject's left ear through a non-magnetic and echo-free stimulus delivery system with a linear frequency characteristic between 200 and 4000 Hz. The tones reached the subject's ear 16 msec after the electrical pulse had been sent to the speaker. A latency of 0 msec refers to the arrival of the sound wave at the subject's ear.

The rectified surface EMG was measured from 2 electrodes attached over the active muscles (pars indices m. flexor digitorum longum). A ground electrode was attached to the same arm.

Using a 37-channel neuromagnetometer (BTi), magnetic fields were recorded from 37 locations centered over the right hemisphere, i.e., contralateral to the site of stimulation but ipsilateral to the movement. (The right hemisphere was chosen in order to minimize artefacts which arise from the heart, and furthermore, to minimize fields from the primary motor projections of the right hand.) The stability of the subject's position was assured using vacuum casts. This also ensured that breathing did not produce any change in position of the head, which would cause movement-related artefacts.

In the BTi system, the detection coils are arranged in a circular array (diameter 14.4 cm) on a spherical surface (with 12.2 cm radius). The coil diameter is 2.0 cm, the distance between the center of two adjacent coils is 2.2 cm. The sensors are configured as first-order axial gradiometers with a baseline of 5.0 cm.

The EEG was monitored from the vertex, referred to the right mastoid, using ZAK Ag/AgCl electrodes. The skin below the electrodes was prepared by cleaning with alcohol and abrading the outer layers of the skin in order to keep the electrode impedance below 5 kΩ. Grass EC2 served as conducting agent.

MEG and EEG were amplified from DC to 200 Hz and sampled at a rate of 860 points/sec.

Analyses of the magnetic event-related field

Trials were excluded from the analysis if the difference between the maximum and the minimum, computed across the whole 6 sec epoch exceeded 3.5 pT in any of the MEG channels or 100 μV in the EEG channel. This criterion also served to exclude larger eye movements or blinks, which would lead to excessive amplitudes in some of the more anterior channels. This left an average of 80 (minimal 65) Go and 72 (minimal 52) No Go trials (average rejection 20.8%).

For the artefact-free trials magnetic responses were averaged for every subject, separately across Go and No Go trials.

Parameters of the CMV were extracted from the time course of the root mean square (RMS) calculated across the 37 recording channels. From this course the following components were determined to characterize the CMV. The early component was determined as the mean change in magnetic field, referred to prestimulus baseline, during the interval 0.75–1.0 sec following tone onset. A middle component (that would allow the evaluation of the sustained field) was determined as the mean change in the magnetic field during the interval 1.75–2.0 sec following tone onset. The mean amplitude during the last 250 msec prior to tone offset served as a measure for the tCMV. The M100 (magnetic counterpart of N1) to tone onset was determined at 2 different instances: at the point in time, when the RMS reached its maximum around 100 msec, and at the point of maximal correlation between the measured field and the estimated model. The location of the respective equivalent dipole was determined for reference purposes in the subsequent analyses.

Analyses of topographic pattern of the magnetic event-related field

The exact position of the dewar with respect to the head and the individual head shape was determined using a sensor position indicator. For each subject a local sphere was fitted to the digitized head shape. Due to technical limitations this information was complete in only 8 of the 10 subjects. For these, a single moving dipole was fitted to the measured field distributions and the location and moment of this equivalent current dipole were estimated for each point in time. The origin of the head-based coordinate system (determined by the sensor position indicator) was the midpoint between the preauricular points. The x axis joined the origin of the nasion; the y axis (latero-medial) passed between the preauricular points with positive values towards the left preauricular point. The z axis was perpendicular to the x-y plane. Correlations between the theoretical field generated by the model and the observed field were squared to estimate which

Fig. 2. Example of the magnetic field, recorded with the 37-channel neuromagnetometer, according to the sensor layout. Superimposed are the single subject averages for the Go (larger amplitude) and No Go (lower in amplitude towards the tone offset) trials. Apart from the CMV, disitnct on- and off-responses also become visible. The subject was arbitrarily selected, but different from the one chosen for Fig. 1, to indicate another typical response.

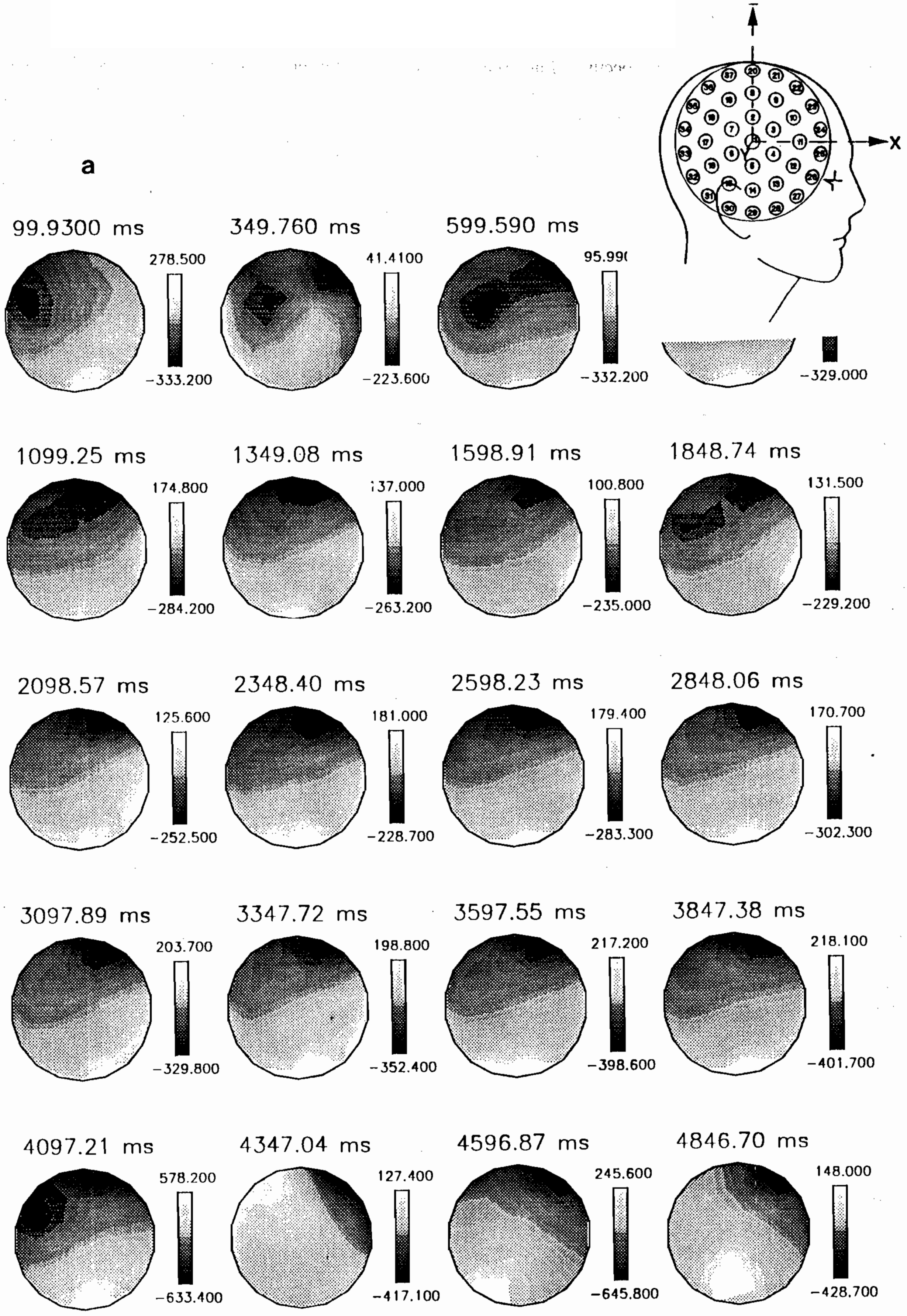

Fig. 3. Contour plots for 3 different (a, b, c) subjects during the time course of the Go trials. As can be seen, the pattern varies a great deal across time and across subjects, being only in a few instances dipolar.

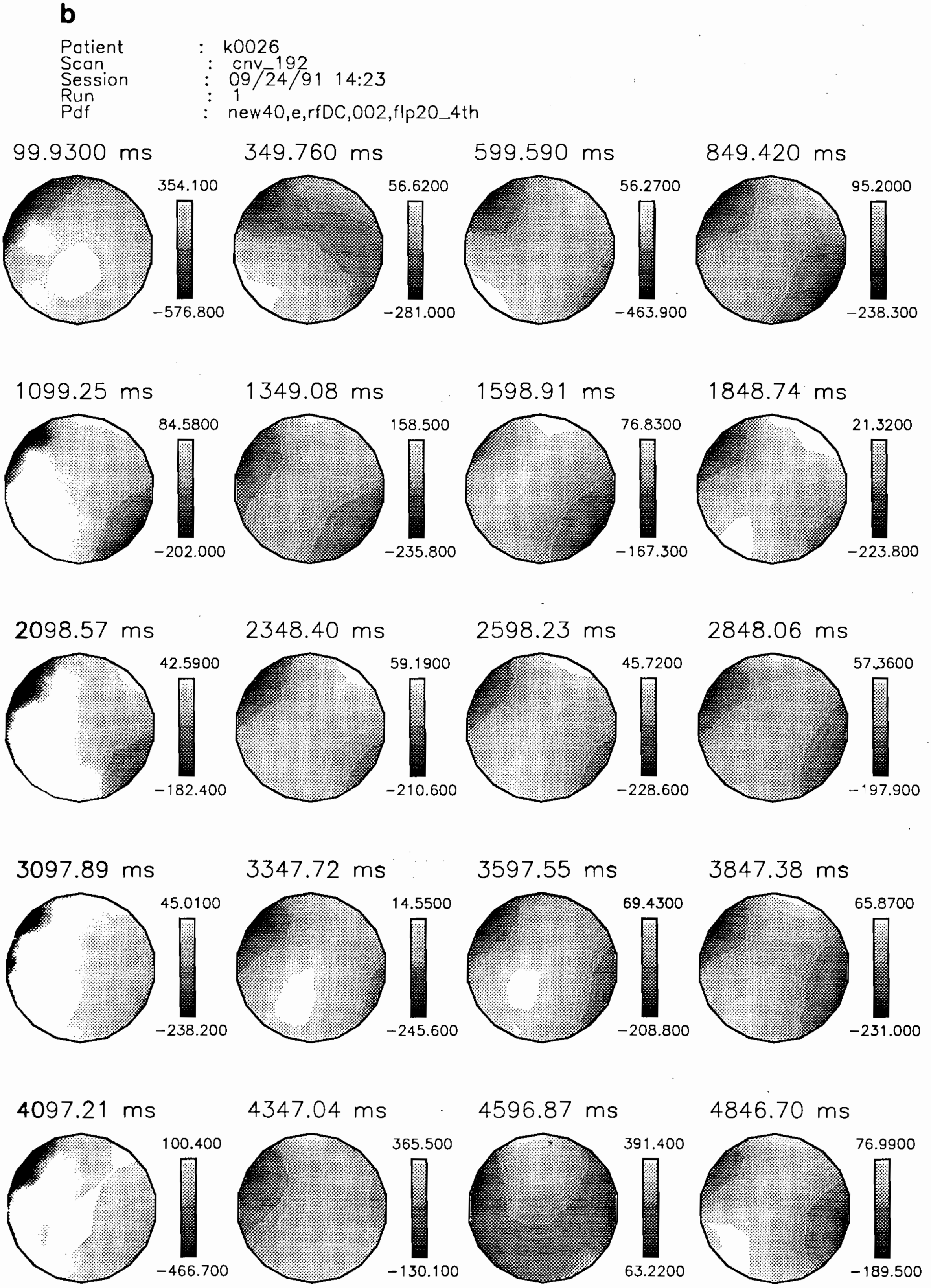

Fig. 3 (continued).

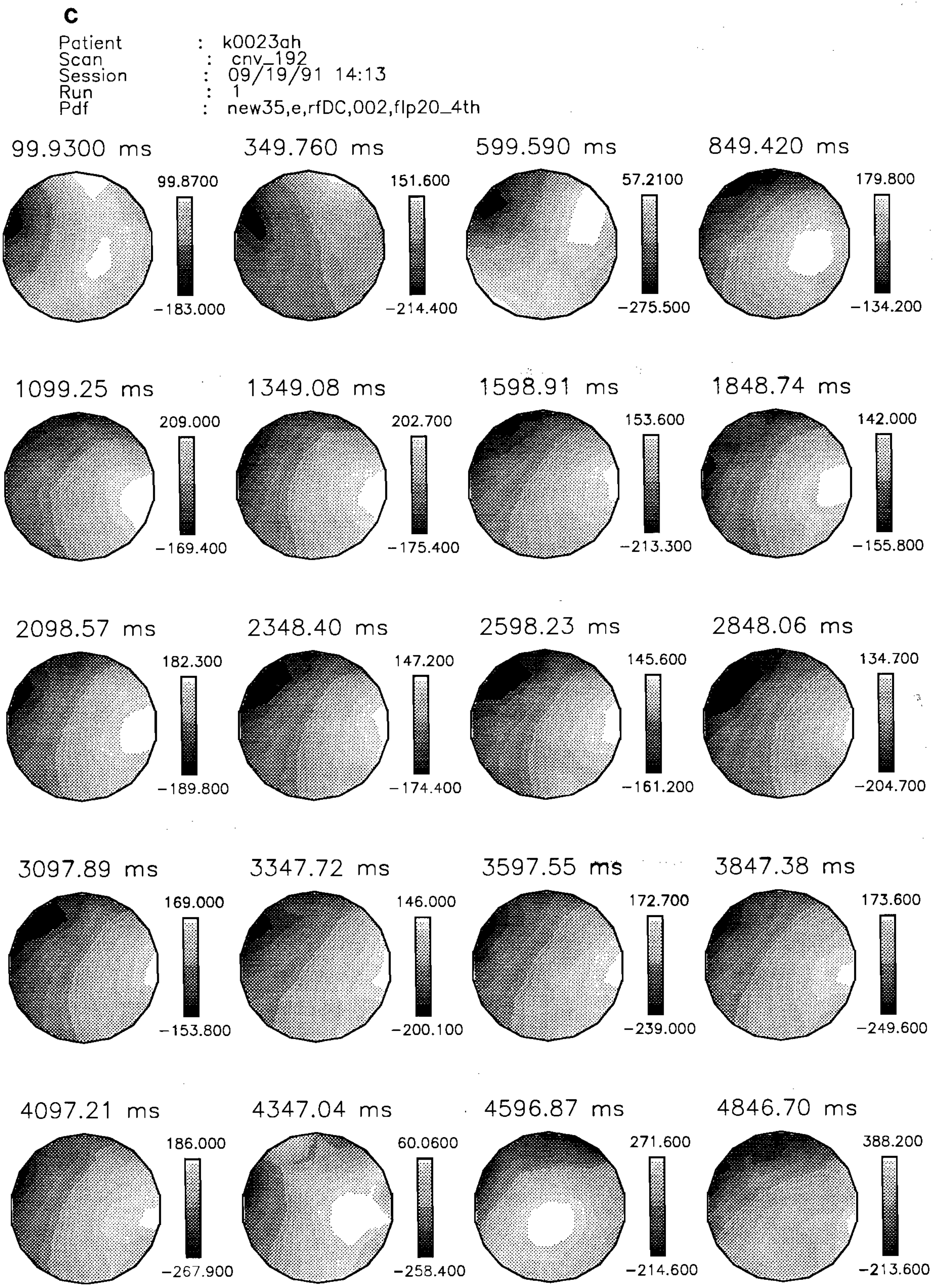

Fig. 3 (continued).

proportion of the variance of the measured field can be accounted for by the single equivalent dipole.

Where necessary, statistical differences between Go and No Go trials were evaluated by means of ANOVAs and post hoc *t* tests. Means ± standard errors are presented.

Results

Compliant with the instructions, a muscle twitch occurred only in Go trials, with a small but noticeable preparatory increase during the warning interval. The onset of the twitch (median across Go trials) ranged from 175 msec to 389 msec (average across subjects: 268 ± 23 msec).

In the electrical recordings, the well-known biphasic wave shapes were observed with larger tCNV under Go than under No Go conditions in all 10 subjects. All 10 subjects also showed distinct wave forms in the averaged fields during the 4 sec warning interval, with the more pronounced field extrema under Go compared to No Go conditions towards the end of the warning interval. Fig. 1 presents examples of selected magnetic channels and electrical (Cz) recording and the parallel EMG response. Magnetic channels were selected to illustrate the range of responses, which include ingoing and outgoing fields. Such a polarity reversal [2] from ingoing to outgoing magnetic fields across the temporally located sensor array is displayed for a representative subject separately for Go (solid) and No Go (dotted) conditions in Fig. 2. A comparable polarity reversal was obvious in 8 of the 10 subjects for the terminal CMV which showed up in the Go condition only. The pattern for the early CMV — though very similar for Go and No Go conditions — was less consistent across subjects with only 50% of the sample displaying a polarity reversal across the sensor array. The isofield contour maps of 3 subjects, representing the spectrum of variability, are displayed in Fig. 3a–c.

The M100 reached its maximum in the RMS at a latency of 105.4 ± 1.4 msec on Go and with 111.2 ± 1.3 msec later on No Go trials. For *all* subjects, these extrema were more pronounced on Go trials (241 ± 22 fT) than on No Go trials (196 ± 27 fT). The maxima for the correlation between modeled and measured field and the corresponding goodness of fit were consistently earlier than for those detected in the course of the RMS (mean 94 ± 5 msec) [3].

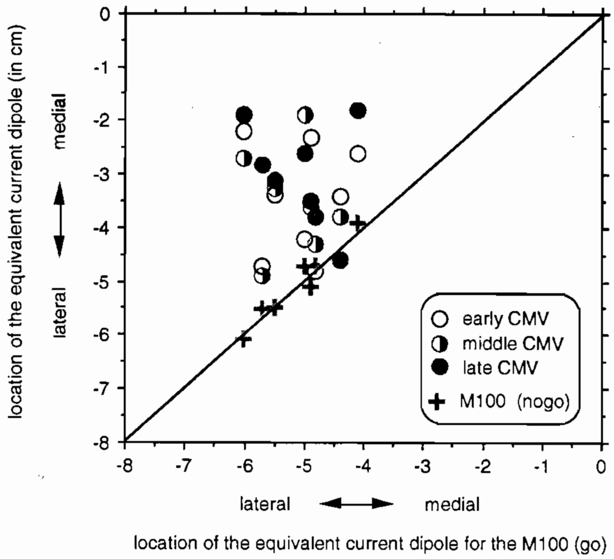

Fig. 4. Locations of single equivalent current dipoles of the early, middle and late component of the CMV (circles, ordinate) and the M100 (No Go, crosses, ordinate) are plotted as a function for the M100 (Go condition, abscissa). In the head based coordinate system the medio-lateral (y-)axis, passes between the preauricular points. Zero corresponds to values in the x-z plane, which includes the midpoint between the preauricular points; the right preauricular point lies in the negative direction (around 8–9 cm, depending on the particular head size). M100 ECDs for the Go condition are located along the diagonal. M100 ECDs for the No Go conditions (crosses) are located close to those of the Go condition, i.e., close to the diagonal. This scattergram shows that the locations for the CMV ECDs are shifted medial with respect to Heschl's gyrus, where M100 ECDs are known to be clustered, i.e., some of the ECDs are located in structures which correspond to the location of white matter.

All CMV measures were larger for Go than for No Go. The following statistic is presented for the subgroup of 8 subjects for which also equivalent dipole fits were obtained, in order to allow comparisons. The scores were submitted to an analysis of variance with the within-subjects factors time segment and Go/No Go. Post hoc *t* tests revealed that the Go responses were larger for every time segment than No Go responses (main effect: F (1, 7) = 24.92, $P < 0.01$, early CMV: 113 ± 13 fT vs. 86 ± 11 fT, t (7) = 4.78, $P < 0.01$; middle CMV: 98 ± 10 fT vs. 68 ± 6 fT, t (7) = 3.79, $P < 0.01$; late CMV: 137 ± 20 fT vs. 61 ± 5 fT, t (7) = 4.26, $P < 0.01$). The Go scores became larger, while the No Go scores diminished towards the end of the

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[2] Polarity reversals in magnetic recordings are of particular interest as the zero line in a contour plot, i.e., the location where the field changes its sign, indicates the location of the equivalent current dipole: for a dipolar field the current dipole points in the direction of the zero line and lies underneath it at some depth.

[3] As suggested by one reviewer, the fact that RMS maximum and best dipole fit occurred at different times indicates multiple generators overlapping both in space and time.

tone interval (F (2, 14) = 8.5, $P < 0.05$, Greenhouse-Geisser corrected for the corresponding interaction).

The M100 wave was well described by a single equivalent dipole which can explain an average 97% of the field variance (Go and No Go). For the other components, i.e., the CMV activities, a moving single equivalent dipole accounted for less than 80% of the variance in 4 out of the 8 subjects. In only 3 subjects could the single dipole model explain more than 90% of the measured CMV fields (which was then true for every component and both conditions). The moderate to unsatisfying fit in 5 of the 8 subjects indicates that at no time interval did the CMV result exclusively from just one focal (dipolar) source.

The calculated locations of the equivalent current dipole differed between the M100 and the CMV in a consistent manner along – and only along – the medio-lateral axis (Fig. 4). For all CMV components the dipole is considerably more scattered than for the M100. When Go and No Go conditions are compared, the locations for the M100 are strongly correlated; in 7 out of the 8 cases locations for the early CMV were closer to the head's surface under No Go than under Go conditions. No consistent relationships were found for the late aspects of the CMV.

Discussion

To our knowledge, the present study provides the first (group) study of the contingent magnetic variation (CMV). During the preparatory interval, a clear-cut magnetic variation is obvious for all 10 subjects. The CMV resembled the electrical wave form in its biphasic appearance. The difference in amplitude between conditions with (Go) and without (No Go) motor response requirements was obvious in the magnetic as well as in the electric recordings. Compared to the AEF variability, the CMV showed considerably more variance in the field distribution across subjects.

The polarity reversal across the temporal surface of the head and the pronounced amplitudes over inferior temporal areas lead us to conclude that a significant temporal activity contributes to both the late and the early CMV. However, neither for the early nor for the late CMV component has a focal source proven to be a satisfying model, due to the following reasons.

(1) In contrast to the M100, in 4 out of 8 subjects no satisfying fit for a moving equivalent current dipole (ECD) could be obtained, this being true under Go and No Go conditions.

(2) In all subjects, irrespectively of the goodness of fit for the ECD, it was located as much as 4 cm medial to the M100 for early and late CMV (Fig. 4). It is well known that the equivalent dipole of the M100 is located in the auditory cortex (e.g., Pantev et al. 1989a; Hari 1990). It can therefore be taken as a reference mark for the interpretation of other dipolar sources. Consequently, some of the more medially oriented sources of the CMV could not have their main sources in cortical grey matter. None of the deeply located anatomical structures are likely to generate magnetic fields strong enough to explain the observed activities: the area of synchronous activations producing parallel vector components of current dipoles is not large enough (Braun et al. 1990). Furthermore, the magnetic fields produced outside of the head vanish with increasing depth of the source.

(3) The Go condition, compared to No Go trials, shifted the ECD location towards the center of the head. It seems less plausible to assume a deeper generator for a "Go CMV" than to assume that additional generators contributed to the measured field.

Altogether, it is more likely that the observed fields result from summated activity of multiple, spatially distributed sources. This conclusion supports our earlier view based on electrophysiological data and biophysical considerations (Rockstroh et al. 1989; Braun et al. 1990; Elbert 1992, 1993).

The data are consistent with a model in which the early component of CMV (as well as CNV) results from an overlap of temporal and frontal sources. Two bilateral temporal sources give rise to 4 field extrema: on the right side, they produce an ingoing field maximum over posterior regions and an anterior outgoing field maximum which is more inferior. Over the left hemisphere the contour plot is similar except for a reversal in polarity. The field distribution bears resemblance to that of the M100 though somewhat more superior. If viewed from above the more superiorly located posterior field extrema dominate the contour plot. We believe that these ingoing and outgoing field maxima for the M100, for example, result from two different sources, one in each hemisphere. The assumption that these two maxima result from one underlying dipole produces a fictive occipital location. Fenwick et al. (1992) report dipoles of the early component to be concentrated in the occipital region. The present results demonstrate that a single moving dipole model does not produce a meaningful result when contour maps centered over the vertex are fitted. This would also be true for the terminal (late) CMV if we assume, for instance, that two bilateral sources in the motor cortex overlap. Two bilateral generators have been suggested in studies of the Bereitschaftsfield (motor field) prior to unilateral movement, e.g., by Cheyne and Weinberg (1989) and by Kristeva et al. (1991). Such findings do not support an exclusively frontal location of the late CMV, as suggested by Fiumara et al. (1985) or Fenwick et al. (1992).

Furthermore, the present data suggest that temporal sources contribute to the late component. In the present study, a tone was continuously presented during the entire preparatory interval, and this continuous stimulation may have activated temporal generators related to the sustained field (Pantev et al. 1994). However, tones were equally present during Go and No Go trials and, therefore, the difference between these two conditions should reduce the impact of the sustained field. On the other hand, it may be argued that the strength of the sustained field generators may be modulated by attentional demands. In this case, these generators may be active during Go trials but be switched off during No Go trials. Such speculations, however, must be substantiated by further studies.

It has been shown that modeling magnetic fields generated by multiple sources with a single equivalent dipole can result in serious localization errors (Nunez 1986; Lütkenhöner et al. 1990, 1991). Since the study of Helmholtz (1885) it is well known that any given electrical or magnetical distribution on the surface of a volume conductor may have an infinite number of possible generator structures. Only additional assumptions allow to come up with a unique solution for the generator structure. For distributed sources, neither a single nor a multiple dipole model will provide adequate information. A meaningful restriction for endogenous components like the CNV/CMV might be to allow only current dipoles in grey matter and perpendicularly oriented to the cortical surface (which then needs to be constructed on an individual basis from MRT data). Such modeling awaits its technical realization.

In summary, the data are consistent with the suggestion that the early CMV and the terminal CMV, in particular, are generated by distributed sources in motor, sensory and association areas. The data would not be consistent with a single moving dipole model.

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