Review

Electric source imaging of human brain functions

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Abstract

We review recent methodological advances in electromagnetic source imaging and present EEG data from our laboratory obtained by application of these methods. There are two principal steps in our analysis of multichannel electromagnetic recordings: (i) the determination of functionally relevant time periods in the ongoing electric activity and (ii) the localization of the sources in the brain that generate these activities recorded on the scalp. We propose a temporal segmentation of the time-varying activity, which is based on determination of changes in the topography of the electric fields, as an approach to the first step, and a distributed linear inverse solution based on realistic head models as an approach to the second step. Data from studies of visual motion perception, visuo-motor transfer, mental imagery, semantic decision, and cognitive interference illustrate that this analysis allows us to define the patterns of electric activity that are present at given time periods after stimulus presentation, as well as those time periods where significantly different patterns appear between different stimuli and tasks. The presented data show rapid and parallel activation of different areas within complex neuronal networks, including early activity of brain regions remote from the primary sensory areas. In addition, the data indicate information exchange between homologous areas of the two hemispheres in cases where unilateral stimulus presentation requires interhemispheric transfer. © 2001 Elsevier Science B.V. All rights reserved.

Theme: Neural basis of behaviour

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Contents

1. Introduction

During the last 20 years, we have witnessed an explosion of research on sensory and cognitive brain functions

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using functional imaging techniques, first with single photon emission computer tomography (SPECT) and positron emission tomography (PET), and then with functional magnetic resonance imaging (fMRI). A recent review by Cabeza and Nyberg [10] summarizes 275 PET and fMRI studies on human cognition, documenting this tremendous activity. In their review the authors conclude that several brain regions are usually activated by a given cognitive task and that some brain regions are involved in several different tasks. This is in line with the notion that cognitive functions are based on large-scale neural network interactions and the role of each brain area in this network is governed by its dynamic interactions with the others [41].

The study of dynamic interactions between different brain areas poses a challenge to standard functional imaging techniques because of their low temporal resolution. New approaches such as covariance-based analysis of PET images [39] and the study of the hemodynamic response of single-trial event-related fMRI [40] solve this problem only partially: covariance-based analysis of PET data cannot give information about the direction of activation, and event-related fMRI can provide such information only if areas are activated in a strictly sequential manner without feedback loops.

At present, the only available non-invasive technique to study the temporal dynamics of brain function is the recording of the electromagnetic activity on the scalp by means of event-related electric potentials or magnetic fields recorded with the electroencephalogram (EEG) or the magnetoencephalogram (MEG). Because the temporal resolution is in the one millisecond range or faster, these techniques permit the determination of the sequence of activity of cognitive brain functions in real time. In addition, with the recent developments in electromagnetic source imaging, valuable information on the localization of these functions has become available. We here describe one such analysis method of electromagnetic recordings and its application to several different data sets.

2. Methods

2.1. Electromagnetic source imaging

Attempts to localize the electric neuronal activity in the brain that produces a certain surface electric field are faced with the so-called 'inverse problem' which has, by definition, no unique solution. Different intracranial generator configurations can result in the same distribution of the electromagnetic field on the scalp surface. However, if physiologically and physically valid a priori assumptions are introduced, the inverse problem can be solved and estimations of the sources become possible. Of course, the correctness of the solution depends on the correctness of the assumptions. Thus, it must always be kept in mind that

the localization of sources in the brain using surface EEG and MEG is based on modeling and not on direct recording of these sources.

Most commonly, one or a few equivalent current dipoles are employed as an a priori model and iterative numerical methods are used to search for the best-fitting dipole(s) at a given time point, or for a time-varying collection of such dipolar sources [46,54]. Dipole models can be well suited for some types of data (e.g. epileptic activity [15,26,54] or early sensory and motor evoked responses [1,4,8,17]), but the fact that the number of sources has to be known in advance makes them poorly suited for cognitive event-related potentials where parallel activation of an unknown number of areas is expected. Therefore, we and other groups have developed inverse solutions which estimate the current distribution in the full three-dimensional space of the brain (for reviews see Refs. [16,19,21,23,43]). These solutions yield blurred source images in contrast to over-focalized point sources as derived by dipole methods. Distributed inverse solutions have been extensively tested in many simulations and have been repeatedly applied to the localization of epileptic foci [5,16,34,43,61], of sensorimotor [3,58,59] and visual [45,47,60] areas, as well as to studies on higher cognitive functions such as language [28,30,32] memory [33], attention [2,7,29], and face recognition [51]. There is no doubt that electromagnetic source imaging can provide valuable spatial information, with a spatial resolution comparable to other functional imaging procedures (at least for superficial sources). Thereby, MEG and EEG are comparable in terms of the amount of information they provide about the sources as long as the same number of electrodes/sensors is used in the two techniques [37].

We used different distributed linear inverse solutions in the original publications of the studies that are presented in this review (LORETA [47] in Refs. [29,30,49,59] and ELECTRA [20] in Refs. [45,57]). Spherical head models were used in all cases. We reanalyzed the data for this review using a local auto-regressive average (LAURA) solution based on interpolation formulas as described in Refs. [21,22]. In addition, a realistic model of the head is constructed on the basis of an average brain of 152 MRIs provided by the Statistical Parametric Mapping (SPM, Welcome Department UK) software. It is important to note that this new source reconstruction did not change the principal findings reported in the original articles, but did provide more possibilities for anatomical interpretation of the results.

2.2. Functional microstates of the brain

A pre-requisite for electromagnetic source imaging is the identification of the relevant time points or time periods in the event-related potentials (ERP). The traditional determination of peaks and troughs in ERP waveforms at certain channels becomes difficult with

multichannel recordings. The sometimes proposed averaging of the electric activity over fixed time periods produces unpredictable results if the stability of the field configurations within these periods is not assured by objective criteria. We therefore propose analysis of multichannel recordings solely by examination of the configuration of the electromagnetic surface fields over time, since any change of the configuration of these fields will be directly due to a change of the active neuronal populations in the brain. Looking at ERP signals as a map series instead of waveforms reveals that the map configurations do not randomly change over time. They remain rather stable for certain time periods (several tens of milliseconds), and then rapidly change to a new configuration in which they again remain stable [35].

Since different map configurations are produced by different neuronal populations in the brain, it has been proposed that they reflect different activation patterns of the neuronal network implied in a given task, i.e. different functional microstate during information processing [6,35,42]. We have developed the following methods to both identify the different ERP map configurations that appear over time and to test their statistical significance within and between different cognitive tasks.

First, group-averaged evoked potentials are calculated for each stimulus condition of a given task. A spatio-temporal cluster-analysis is then applied to this data in order to define the different electric field configurations (ERP maps) that predominate over time [48]. On the basis of cross-validation criteria, the cluster analysis defines the optimal number of ERP maps that explain the whole data set and the time period during which they occur. The second step consists of statistical analysis across the individual subjects in order to define the significance of each map for a given task. For this purpose the maps, defined by the cluster analysis, are fit to each individual ERP (in terms of spatial correlation). This provides information on the goodness of this fit as well as the duration during which a given map was present in a given condition in each subject. Statistical analysis then allows us to determine the maps (microstates) that are crucial for the task demand because they appear significantly more dominant or longer in a given condition compared to another [28,45,49,58], or because the goodness of fit or duration correlates with the behavior of the subjects, e.g. the reaction time [29,49]. Inverse solutions applied to these maps finally reveal the brain areas that are activated during each functional microstate. Some examples using this analysis method are illustrated below.

3. Applications

3.1. A third functional pathway important in visual motion processing

Two important processing pathways are known to exist in the primate visual system: the parvocellular pathway (P) and cortical ventral stream, which is particularly involved in color and form processing, and the magnocellular pathway (M) and cortical dorsal stream that is of particular relevance in motion processing. Key structures of these pathways in the extrastriate cortical areas are known as V4 and V5/MT, respectively [36]. However, these two pathways are not strictly segregated on the cortical level. It is known that motion information can be treated under isoluminant conditions [14], and that a dense network of corticocortical interconnections between the different visual areas of the dorsal and ventral stream exists, allowing fast and parallel activation of striate and extrastriate areas through feedforward and feedback mechanisms [53,55]. In addition, recent work suggests that a third retinogeniculocortical pathway, the koniocellular (K) pathway [11], also contributes to motion processing in a non-negligible way. This pathway relays blue-on signals driven by S-cone input and projects directly to the color-selective blobs in area V1, and to extrastriate areas like the motion area V5/MT [12,25]. There is still little knowledge of the functional role of the koniocellular pathway and large species difference makes it difficult to infer from animal experiments the role of this pathway in humans.

Using the spatio-temporal analysis methods described above, we have studied the cortical functional network activated by stimuli that are exclusively carried through the koniocellular pathway [45]. These so-called isoluminant tritonopic stimuli proposed by Cavanagh et al. [12] are created by the superposition of a blue image on a uniform bright yellow field (appearing as a white/yellowish image on a yellow background). The yellow field drives the response of the L and M cones of the retina to a saturated level so that only the S cones respond differentially to the information contained in the variation of the blue image. In our study we generated these stimuli on a computer monitor by differential modulation of only the monitor's blue phosphor, while red and green phosphors were set at maximum levels, producing 28, 3 and 2% cone contrast in S, M and L cones, respectively. The mean luminance for both the white and the yellow fields was 75 cd/m^2. The stimulus pattern was a sinusoidal grating with a spatial frequency of 1.1 cycles/deg which moved horizontally from left to right at a velocity of 12 deg/s, on for 200 ms and off for 800 ms. We compared these stimuli to gratings produced along a luminance axis from black to white (17% contrast for S, M and L cones and luminance ranging from 2 to 80 cd/m^2) with otherwise identical physical properties. These latter stimuli are presumably mainly carried by the magnocellular pathway. Multichannel ERPs were recorded in 17 subjects while watching these stimuli.

The sequence of activation evoked by luminance- and tritonopic-defined motion stimuli are shown in Fig. 1, each map representing a functional microstate as defined by the segmentation procedure. In general, we found fast activations of striate and bilateral extrastriate areas, probably V5/MT. A very early specific electric field for moving
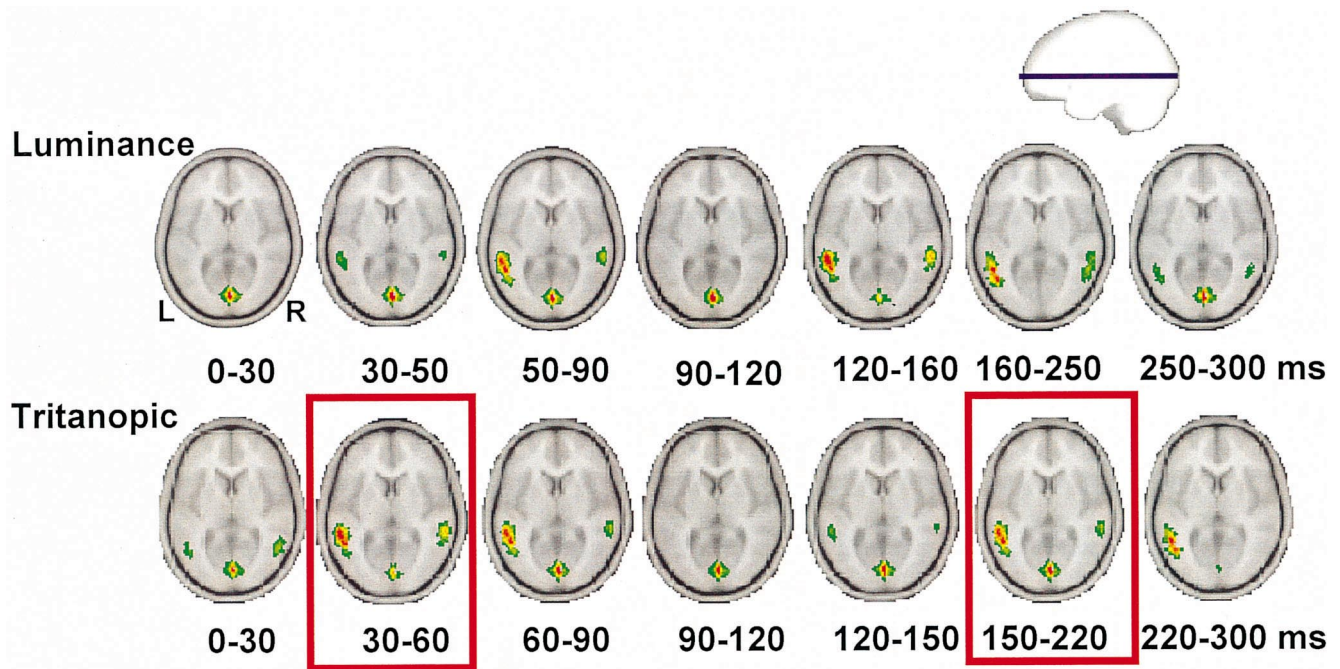
Fig. 1. Temporal sequence of electric brain activity evoked by visual motion stimuli. Upper row: black-white sinusoidal gratings activating the magnocellular pathway. Lower row: isoluminant tritanopic sinusoidal gratings activating the koniocellular pathway. The different time periods were defined by a segmentation procedure based on the scalp surface maps [48] and the localization was estimated by a linear distributed inverse solution based on a local autoregressive average model (LAURA [22]). Sources are computed on a realistic head model based on the averaged MRI used by the Statistical Parametric Mapping (SPM) software. The horizontal slice level is given in the inset. The right hemisphere is to the right. Red boxes surround the time periods that were found to activate unique surface maps for the tritanopic motion condition. Very early strong activation of extrastriate areas was found for both stimulation conditions, but weaker for luminance-defined motion stimuli (see Ref. [45] for details).
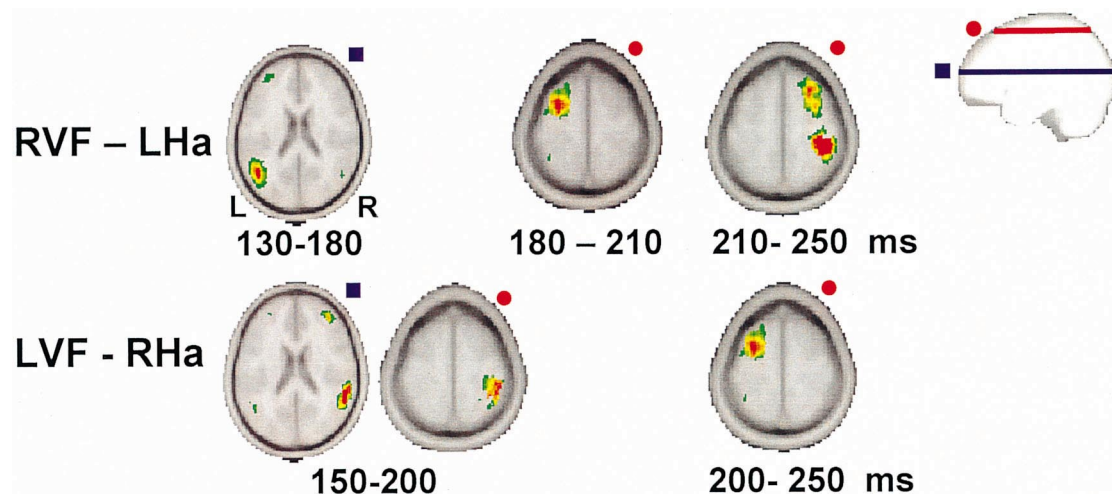

Fig. 2. Temporal sequence of electric activity in visuo-motor transfer tasks. Upper row: right visual field presentation followed by left hand response (RVF-LHa). Lower row: left visual field presentation followed by right hand response (LVF-RHa). Both conditions require a transfer of information from the stimulated to the responding hemisphere. Maps of the functional microstates that were significantly present in the relevant time period are shown. Source localizations were computed as described in Fig. 1. The slice level is given in the inset and marked with symbols on each slice. The RVF-LHa condition revealed three successive microstates, the first with maximal activity in left occipital areas, the second in left central areas, and the third in right central areas. These three distinct functional states were activated within ~100 ms. For the other crossed condition, only two microstates were found within these 100 ms. The first showed simultaneous activity of the right occipital and right central areas, while the second showed dominant activity in left central areas. These results strongly suggest that visuo-to-motor transfer is performed on the motor and not on the visual level (see Ref. [59] for details).

tritanopic stimuli was observed, peaking at 40 ± 31 ms. At this early time period, the difference of the maps between the two motion conditions is explained by differences in the strength of activation of striate and extrastriate areas: the tritanopic stimuli evoked strongest activation of the presumed areas V5/MT, while the luminance-defined motion stimuli show strongest activation of striate areas. Striate areas were reactivated later in time by both stimuli, which is in line with the notion of feedforward and feedback mechanisms in the visual cerebral cortex [53]. Our data confirm previous reports of fast and parallel activation of extrastriate areas [8,56] and support the particular role of the K-pathway in motion perception under isoluminant tritanopic conditions [14].

3.2. Interhemispheric visuo-to-motor transfer is performed on the motor level

The functional specialization of the two cerebral hemispheres requires a considerable transfer of information from one hemisphere to the other, which is mainly carried across the corpus callosum. At the visuo-motor level, a simple task that requires interhemispheric transfer is the so-called 'Poffenberger-paradigm' where subjects respond with one index finger to lateralized visual stimuli. In such a task, subjects react faster when stimuli are presented on the side of the responding hand (uncrossed condition) than when presented on the opposite side (crossed condition). The crossed–uncrossed difference in reaction times, generally ~5 ms, is thought to reflect interhemispheric transfer time [38]. When, where and at what functional level this transfer is performed is still a matter of debate [18,27].

We have addressed this question by analyzing ERP map series in 12 right-handed subjects who performed the Poffenberger-paradigm [59]. Each subject was tested in four blocks. In all blocks, small black dots appeared on a screen for 60 ms every 5–6 s in random order either to the left visual field (LVF) or the right visual field (RVF). The stimuli were presented at 4° of horizontal eccentricity from the central cross and subtended an angle of 0.5°. The central cross preceded the stimulus by 3–4 s and remained visible until the end of the response. In half of the blocks, the subjects were asked to press a button with the index finger of the left hand (LHa), in the other half with the index finger of the right hand (RHa). The EEG traces of each single trial were aligned off-line (a) to the time point of stimulus onset (stimulus-locked data) and (b) to the time point of the response (response-locked data). These two different alignments allowed better identification of those ERP maps that reflect stimulus processing because they differed between LVF and RVF presentation, and those maps that reflect motor control because they differed between LHa and RHa response. Since we were interested in the crucial time period after perception ended and before the motor response began we selected the last vision-related maps of the LVF and RVF presentations and the

first motor-related maps of the LHa and RHa response, and fitted these four maps to the individual ERPs of each subject. This analysis clearly confirmed the unilateral activity in the non-crossed conditions: only the LVF and the LHa maps or the RVF and RHa maps were found in the transmission period. However, in one of the crossed conditions (RVF-LHa), one additional map was found in-between the RVF- and the LHa-map. In ten out of the 12 subjects, this additional map was the motor map of the RHa condition and not the visual map of the LVF condition. Source localization of the maps showed a sequence of activity from left occipital to left central and then to right central (Fig. 2). In the other uncrossed condition (LVF-RHa), no additional map was found, i.e. the visual map was directly followed by the motor map. Source localization of the LVF map indicated simultaneous activity in right occipital and right central areas for the visual map followed by right central activity for the motor map. The observed faster transfer from the right to the left hemisphere in right-handed subjects [38] might be the reason for the simultaneous activation in this segment map, since it averages several milliseconds. In summary, we concluded from these results that the interhemispheric transfer in this task occurred at a functional motor level, at least for left-to-right interhemispheric transfer. Although it cannot be ruled out from our data that other areas of the non-stimulated hemisphere are activated briefly at early time points, they suggest that such activity is not relevant for the initiation of the motor response. Such activity appears to fade before the visual information is integrated into the motor command.

We confirmed activation of frontal motor areas early in time in a later study with direct intracranial recordings in epileptic patients [57] and proposed that this early activity also reflects visual processing in frontal motor areas, supporting the multifunctional properties of brain areas seen in other imagery studies [10].

3.3. Visual mental imagery is performed with the right hemisphere

Clinically, the functional specialization of the two cerebral hemispheres is best seen in patients with unilateral lesions. For example, left frontal and temporal areas are dominant for language, whereas right posterior parietal areas are particularly important for visual spatial orientation. Behavioral tasks that reliably probe these areas are highly desirable for clinical neuropsychological exams. A frequently performed test to probe right parietal functioning is the mental rotation task where subjects have to decide whether pairs of letters or line drawings with one member of the pairs being rotated with respect to the other are identical. It has repeatedly been shown that reaction times increase linearly with the degree of rotation of the figure, consistent with the idea that subjects mentally carry out a rotation of the figure to the normal position before

making the comparison. While functional imagery and EEG/MEG studies consistently reported posterior activation during this mental imagery task [13,44,50,52], these studies provided less convincing evidence for a right hemispheric dominance as suggested by initial clinical studies.

We performed an ERP mapping study on the mental rotation task in an attempt to unravel the different processes involved in the task [49]. Multichannel EEG was recorded in 12 right-handed subjects while they performed a mental rotation task using alphabetic characters. Pairs of uppercase letters (F, G, J, L, N, P, or R) were presented on a computer screen, the first item of the pair being always an upright, non-rotated cue. The second item was a normal (same) or mirror-reversed (different) stimulus, rotated by 0, 50, 100 or 150° clockwise. Cues were always presented centrally whereas the stimuli were presented either in the center, or to the left or right visual field. A fixation cross remained visible throughout the session on which the subjects were asked to maintain their gaze. For central presentations, the stimulus would appear just beneath the fixation cross. When stimuli were presented laterally, the border of the stimulus closest to the midline was at 1° of eccentricity and subtended a visual angle of 4°. The stimuli were presented for 225 ms. A gap of 1050 ms separated the two members of a pair and was followed by 1625 ms during which the subjects were instructed to respond 'same' or 'different' as quickly as possible by pressing a button with their right hand. Half the subjects responded 'same' by pressing a button with their index finger and 'different' with their middle finger, the other half responded in the reverse manner. A total of 840 pairs were presented. There was an equal number of normal and mirror reversed stimuli, every one appearing the same number of times in each presentation field and at each angle.

The microstate segmentation procedure applied to the ERPs evoked by the target letter revealed differences in the electric field maps within the first 300 ms. For each visual field presentation, however, the ERPs showed no differences with respect to the different angles of rotation. After 300 ms, the same maps were found for the different fields of presentation. However, one of these microstates, appearing between 400 and 600 ms, increased significantly in duration with greater angles of rotation, mirroring reaction time. The source localization strongly suggested that the dominant activity of the map during this microstate was located in the posterior cortex of the right hemisphere for all three presentation conditions. While the location estimation in the original study [49] was relatively crude because of a spherical head model, the re-analysis of the data with another localization algorithm and a realistic head model now suggests activation of the right parietal cortex for this time period (Fig. 3), corresponding to the intraparietal sulcus (Brodmann area 7) that has recently been described in a PET study on mental rotation where the same type of

alphanumeric characters and a similar stimulation paradigm were used [24].

This ERP study best exemplifies the power of the temporal segmentation procedure combined with source imaging methods: the temporal dynamics of the network can be unraveled, and the time period and the underlying brain activity that is crucial for the task can be determined because it co-varies with task demand and reaction time.

3.4. Rapid transfer of language information from the right to the left hemisphere

To characterize the network involved in left hemisphere tasks, we performed a study similar to the mental rotation experiment, but now engaging subjects in a semantic decision task [30]. We examined whether transfer mechanisms similar to those observed in the mental imagery experiment are seen after unilateral presentation of words, but in this case from the right to the left hemisphere. We recorded multichannel ERPs from 15 right-handed subjects during a categorization task of sequentially presented word pairs. In this task, pairs of high frequency, imaginable nouns with a length of four to seven letters were sequentially presented on a computer screen (stimulus duration: 150 ms, inter-stimulus interval: 700 ms, interval between word pairs: 2 s). The word pairs were either semantically related (e.g. apple paired with grape), or they were not related (e.g. ring paired with grape). The second words were the same in the related and unrelated conditions so that the ERPs of the two conditions were produced by physically identical stimuli. From a central fixation cross, the word pairs were presented randomly to the LVF or to the RVF subtending 1–5° of visual angles in length and a maximum of 1.3° in height. Anticipation of the visual field of presentation was avoided by adding a crossed presentation condition, where the first word was presented to one and the target word to the other hemisphere. The subjects' task was to mentally judge whether the second word of the pair was or was not semantically related to the previous word. No manual response was required. However, in order to ensure that the subjects were carrying out the task, 5% of the pairs were followed by a question mark to which a verbal response concerning the semantic relatedness was required.

The ERP analysis in terms of temporal segmentation of the map series elicited by the target words revealed different map configurations for LVF and RVF presentation up to 400 ms. However, source analysis of the grand mean data (Fig. 4) as well as the statistical analysis of the individual data (in terms of the amount of activity within different regions of interest), showed a predominance of electric activity in the left hemisphere already at ~200 ms. The strong and sustained activity of the left posterior temporal areas from this time period on suggests a prominent processing of the semantic information within this region independent of the visual field. The crossing to
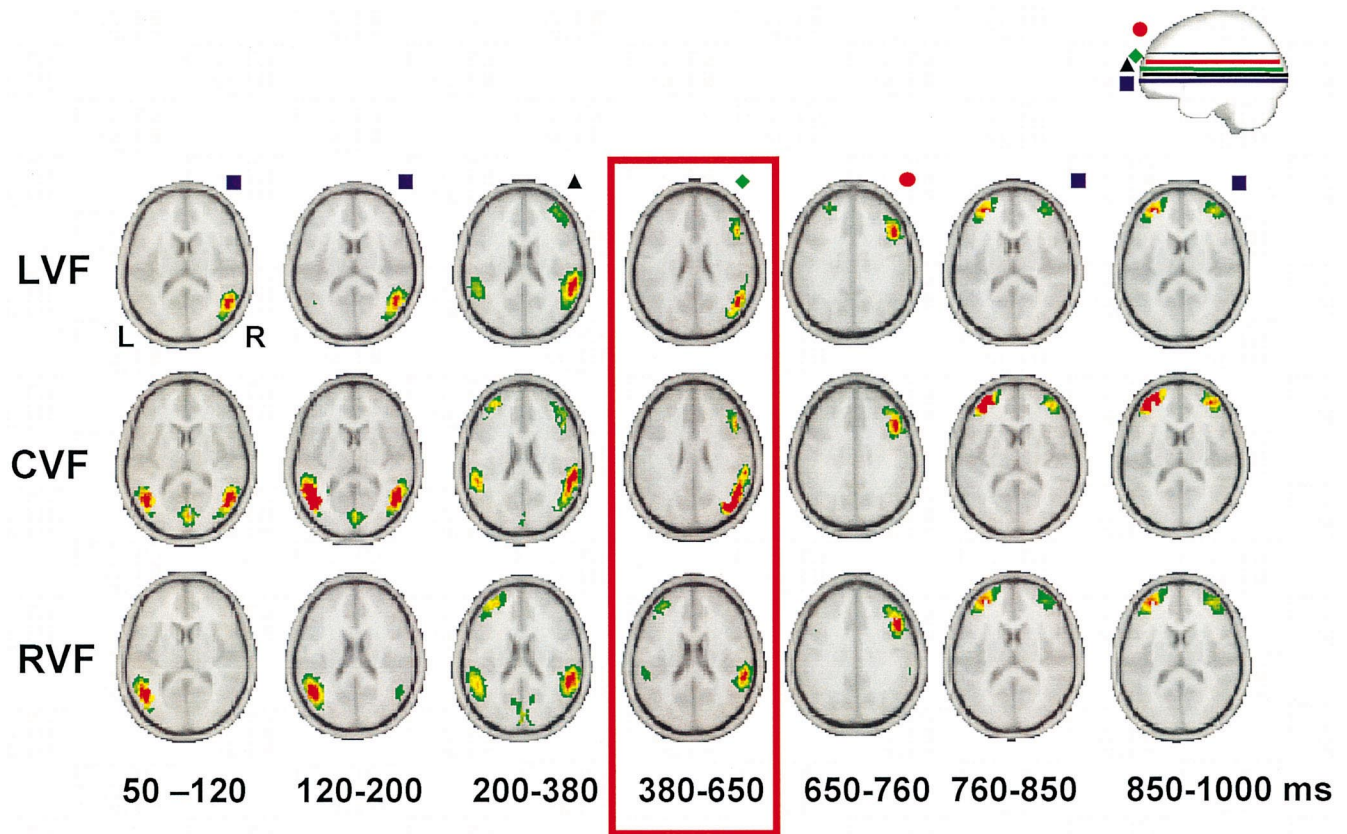
Fig. 3. Temporal sequence of electric activity in a mental rotation task. The three rows show the activation sequence for rotated letters presented to the left (LVF), centrally (CVF) and to the right visual field (RVF). The time periods were determined on temporal segmentation of the surface electric fields, which revealed seven functional microstates appearing over time. The electric sources for each microstate were computed as described in Fig. 1. The slice level is given in the inset and marked with symbols on each slice. It remained the same for the three rows. While the two first time periods showed activation of the occipital cortex of the corresponding hemisphere, subsequent time periods showed similar activation patterns for all three presentation conditions. The maps surrounded by a red box mark the microstate that increased in duration with increasing rotation angle of the stimulus, mirroring reaction time. For this crucial time period, dominant activity was found in the right parietal lobe for all three stimulation conditions. In case of RVF presentation, a hemispheric transfer to this area appeared on the preceding microstate from a homologous area of the left hemisphere. Pre-frontal activity dominated the microstates that appeared after the mental rotation had been performed (see Ref. [49] for details).

the left hemisphere in the case of LVF presentation is seen considerably earlier than the reversed crossing in the mental rotation task and at more inferior temporal sites (between 110 and 160 ms as compared to 200–380 ms in the mental rotation task). Interestingly, the difference in map configuration between the LVF and RVF presentation could be explained by activation differences in the prefrontal cortex. As confirmed by region-of-interest analyses on the individual data, the left visual field presentation seems to activate first left and then right prefrontal areas while the reverse appeared for right visual field presentation. It remains to be seen in replication studies whether the hemispheric differences of prefrontal areas depending on side of stimulus input can be confirmed. Nevertheless, the important activation of prefrontal areas in this as well as in the previous mental rotation task confirms many other functional imaging studies where the prefrontal cortex was found to be involved in almost all high-level cognitive tasks, particularly involving working memory and memory retrieval [10]. In the semantic decision as well as in the

mental rotation task we found that these prefrontal areas already become activated ~200 ms after stimulus presentation, i.e. very early in time. A more detailed analysis of the different regions of the prefrontal cortex and the hemispheric functional differences of these areas is mandatory.

3.5. Hemispheric specialization of the prefrontal cortex

A classical paradigm used in neuropsychology to test prefrontal brain functions is the Stroop task. In this task, subjects who are asked to report the color in which a word is displayed, are influenced by word meaning even though it is irrelevant to the task. Reaction times and error rate increase in the so-called 'interference condition', as is the case when the word 'red' is displayed in the color blue. Numerous variations of the Stroop task have been used and confirmed the robustness of the interference effect. Both clinical and functional imaging studies strongly suggest the involvement of frontal brain regions, in particular the
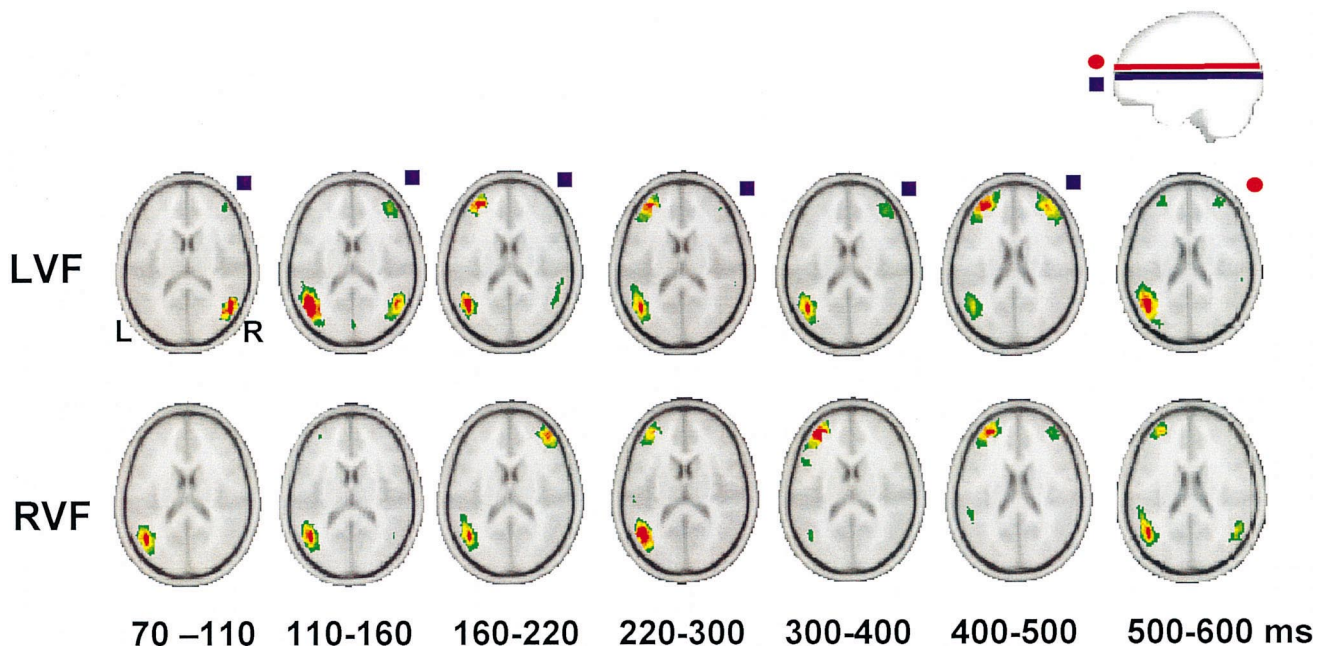
Fig. 4. Temporal sequence of electric activity in a semantic decision task. The target words were presented either to the LVF (upper row) or to the RVF (lower row). Temporal segmentation of the surface electric fields revealed seven functional microstates appearing over time. The electric sources for each microstate were computed as described in Fig. 1. The slice level is given in the inset and marked with symbols on each slice. It remained the same for the two rows. As for the mental rotation task (Fig. 3), initial activity was found in the occipital areas of the stimulated hemisphere. In the LVF condition, a transfer to the left hemisphere was observed, starting at ~150 ms, and involving rather inferior temporo-occipital areas. After this transfer, similar strong left temporal activity was seen for both stimulation conditions, sustaining over several microstates. Simultaneously, bilateral but more pronounced left prefrontal areas were activated during several time segments (see Ref. [30] for details).

anterior cingulate cortex, suggesting the importance of this area in cognitive interference, attention, and response selection [9]. We performed a ERP mapping study in such a task. In view of the result of the mental rotation study described above, we expected to find an electric activity pattern that correlates in terms of goodness of fit or duration with the reaction time in the interference condition. In our version of the Stroop paradigm, subjects had to decide whether a word was written in the same color as a patch shown just before. The interference condition consisted of presenting the patch and word in the same color, while the word was an incongruent name (e.g. a blue
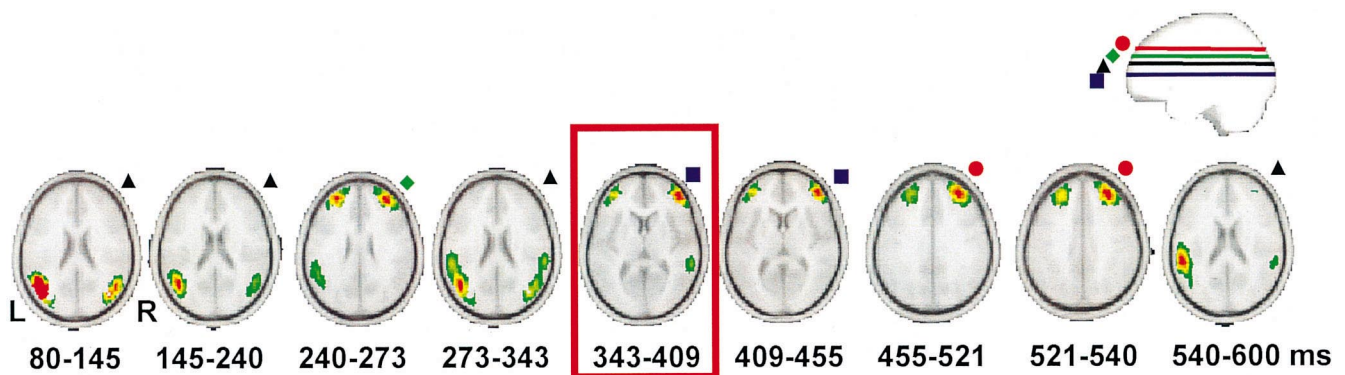

Fig. 5. Temporal sequence of electric activity in a Stroop task. The task required subjects to decide whether a color-name was written in the same color as a previously presented color patch. Stimuli were always presented centrally. The ERP data of the interference condition is illustrated here, where incorrect words were correctly colored. Reaction time increased in this condition as compared to congruent condition. Temporal segmentation of the surface electric fields revealed nine functional microstates appearing over time. The electric sources for each microstate were computed as described in Fig. 1. The slice level is given in the inset and marked with symbols on each slice. The map surrounded by a red box represent the microstate which correlated in duration with the reaction time. The activation sequence shows first occipital and then frontal activity. The activation of the prefrontal areas was seen already at ~200 ms, first bilaterally and later more dominantly in the right hemisphere. Region-of-interest analysis of the source localization in the individual subjects statistically confirmed a dominant right prefrontal activity at the crucial time segment of this task that appeared between 343 and 409 ms (see Ref. [29] for details).

patch followed by the word 'red' written in blue). In the interference condition, colored rectangles were followed by the names of other colors but written in the same color as the rectangles (e.g. blue rectangle followed by the word 'red' written in blue). In a third (neutral) condition, colored rectangles were followed by Xs presented in the same color as the reference rectangle (e.g. blue rectangle with blue 'XXXXX'). Stimuli were presented centrally for 150 ms. A gap of 300 ms separated the rectangles from the target stimuli and 1500 ms separated two pairs.

A total of ten right-handed subjects were recorded with multichannel EEG while performing the task [29]. The analysis of the behavioral data showed the expected significant increase in reaction time for incongruent as compared to congruent and neutral stimuli. The ERP analysis revealed a functional microstate appearing in the 300-ms time range that was activated longer in the interference condition and that correlated in duration with the reaction time. Source analysis of the maps that represent the successive functional microstates indicate a strong and sustained activation of the frontal lobe, first in rather inferior and then in more superior areas (Fig. 5). Activation of frontal areas again had already started ~200 ms after stimulus presentation, first bilaterally and then more dominantly on the right side. This right-sided dominance was particularly strong for the microstate that correlated in duration with reaction time. Region of interest analysis in the single subjects statistically confirmed the dominance of the right frontal activity in this time period, a result that corresponds to several other clinical and imaging studies [9,31] and supports the notion of a major role of the right prefrontal cortex in attention.

4. Conclusions

The temporal segmentation of the electric fields on the scalp surface into functional microstates and the subsequent localization of the sources that generated the electric field of each microstate represent a possible strategy to unravel the temporal dynamics of the functional neuronal network involved in cognitive tasks. This approach results in a limited number of maps representing the global electric brain activity during a certain time period after stimulus presentation. Each of these periods is proposed to reflect a particular functional microstate within which a certain stimulus treatment is performed. Statistical analysis and correlation with behavioral measures allows us to determine those time periods and activity patterns that are particularly important to complete a given task.

From the studies described in this review, we draw the following conclusions: (i) the speed of information processing of the human brain is due to very fast and simultaneous activation of different brain areas: striate and extrastriate areas are activated in parallel by simple visual stimulation, occipital and frontal areas are activated simul-

taneously in visuo-motor tasks, and sustained and early prefrontal activity is seen in higher-level cognitive tasks; (ii) visual stimuli presented to only one hemifield do not evoke activation of completely different neuronal networks. Interhemispheric transfer reaches unilateral functionally specialized areas and this transfer is carried out by the homologous area of the stimulated hemisphere, i.e. between the motor areas in visuo-motor tasks, parietal areas in mental imagery tasks, temporal areas in language tasks, and frontal areas in attentional tasks.

However, since electromagnetic source imaging is based on modeling procedures and not on direct recordings within the brain, the validity of the localization results may always be questioned. The required proof can only come from investigation using similar tasks with other brain imaging techniques, or (if possible) using direct intracranial recordings in man or animals. Since all techniques have their advantages and limitations, none of them alone will resolve all questions that have to be asked if one wants to understand the functioning of the human brain.

Acknowledgements

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