Spatiotemporal Dynamics of Human Cognition

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It is still largely unknown how the complex cortical neural network of the human brain can process information so rapidly. Multichannel evoked potential recordings with millisecond time resolution and spatiotemporal analysis methods now allow us to address this question and to unravel the temporal dynamics of the large-scale neurocognitive networks.

Functional brain imaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), have opened new possibilities for studying cognitive brain functions in humans. Although the first studies mainly confirmed what was already known from neuropsychological investigations of brain-lesioned patients, more recent reports give new insights into the complexity and diversity of the functional states of the brain during cognitive processes. Probably the most important finding is that many different parts of the brain are usually active in a certain task, even if very sophisticated subtraction paradigms are employed that are thought to isolate some unifocal functions. This confirms the concept that large-scale neurocogni-
tive networks are usually “at work” during specific cognitive functions and that many different modules within these complex networks continuously exchange information (6). To unravel the temporal dynamics of these networks, brain activity has to be recorded at the speed of neural transfer, i.e., in millisecond resolution. The measurement of cerebral electric responses evoked by external stimulation (event-related potentials; ERPs) provides this temporal resolution. Thus ERP recordings offer the unique possibility of studying the speed with which the human brain performs complex cognitive tasks and of defining the different functional states that lead from perception to action within fractions of seconds, a time resolution that is not achievable by more conventional techniques, e.g., PET or fMRI.

Brain electric potentials

The appearance of a stimulus evokes neural responses that are related to the processing of this stimulus. The more important or relevant the stimulus for an individual, the more intensive the analysis will be. The processing may end with the perception of the stimulus, or it may involve all cognitive and motor processes that are needed to execute an adequate response. These different processing levels are manifested by neural activity of several brain regions, either in parallel or in series. Such neural activities generate electric current flow in the brain; therefore, all processing levels are manifested by global spatiotemporal current flow alterations. Because the brain is a volume conductor, the sum of all currents at any given moment in time is expressed by an electric potential distribution on the scalp, i.e., a momentary electric field. The electroencephalogram (EEG) is the recording of this electric field potential at discrete scalp positions. The averaging of these signals after repeated presentation of visual, auditory, or somatosensory stimuli allows the delineation of those responses that are time-locked to the event and thus reflect the stimulus-evoked responses of the brain, the ERPs.

Mapping of the scalp electric field

The recording of the electric activity from many different sites simultaneously allows the construction of topographic maps of the momentary electric activity on the scalp as well as the study of the time series of these maps with millisecond resolution. In contrast to the traditional analysis of ERP waveforms at certain electrode positions, ERP mapping attempts to determine points in time when map configurations change and/or when they differ between experimental conditions (1). Such an approach relies on the fact that, whenever the spatial configuration of the electric field on the scalp differs, different neuronal populations are active in the brain, reflecting an alteration of the functional state of the brain. Thus ERP mapping refers to the search for the different functional states of the brain that are activated during information processing by analyzing the spatial configuration of the scalp electric field over time (4). Consequently, spatial pattern recognition algorithms replace conventional time series analysis methods in this approach.

Three-dimensional localization of the electric activity in the brain

Topographic mapping of the potential distribution on the scalp is the precursor of those approaches that attempt to localize the neuronal activity in the brain that gave rise to the surface map. However, the relation between map configuration on the scalp and the source configuration in the brain is not that simple. Many electric sources at different locations and with different orientations might have contributed to a certain potential map on the surface. In fact, infinite numbers of source distributions can lead to identical electric fields. Therefore, localization attempts face the so-called “inverse problem” that has, by definition, no unique solution. Because of this nonuniqueness, a priori assumptions about the source configuration have to be introduced. In some cases, such a priori information is available from current physiological knowledge and allows a restriction of the type, the number, and the position of the sources (for example, a few dipolar sources can be assumed for early sensory processes). If such knowledge is not available (as in the case of higher cognitive functions), constraints that are less restrictive in terms of the number of sources must be used. Recent models have thus employed generalized inverse solutions that estimate the current distribution in the full three-dimensional space of the brain. Most of these distributed pseudoinverse procedures use some sort of minimum norm criterion to achieve a unique solution, resulting in spatially diffuse (blurred) pseudotomographic images of the current distribution in the brain (2, 3, 9).

Information is processed by discrete sequential functional microstates

The example in Fig.1 shows a time series of evoked potential maps in a experimental paradigm in which subjects had to decide whether a simple abstract visual stimulus was relevant or not (8). These relevant stimuli (vertical rectangles)
were randomly distributed with 33% probability in a series of identical irrelevant stimuli (horizontal rectangles). Subjects had to count the relevant stimuli silently and report the total number of stimuli at the end of the trial. By inspecting the ERP map series evoked by the relevant stimuli, a very basic phenomenon can be observed: maps have a tendency to remain in a certain spatial configuration for a certain period of time, then change rapidly to a new configuration in which they stay stable again for a while. During a stable period, maps increase and decrease in strength, as can be seen by the increased number of equipotential lines, but the topography remains unchanged. This spatiotemporal behavior of the electrical potential maps has been repeatedly described for spontaneous as well as for evoked brain activity, and it has been the basis of the concept of functional microstates of the brain introduced by Dietrich Lehmann (for review, see Ref. 4). The idea behind this model is that information-processing steps or, more general, “mind states” are characterized by periods of synchronous activity of neural populations and that these activity states are represented by certain electric potential patterns on the scalp. Different microstates are defined by different potential configurations because, as mentioned above, different map topographies must have been produced by at least partially different neural popu-

FIGURE 1. Example of a time series of 42-channel event-related scalp potential maps. Head is seen from top with nose up, left ear on left. Time point zero indicates the appearance of a white rectangle on the screen. The subjects’ task was to count all rectangles with the same orientation (see Ref. 7 for details of experiment). Maps are shown here every 8 ms, even though data were collected at 250 Hz. Small insets in the maps mark the position of the centroid of the positive and negative potentials. A clustering procedure was used to determine time segments of stable map configuration. These segments are marked with bars under the map series. Graph, bottom, is the global field power trace over time, a value that indicates the strength of the potential map. Under this curve, the different segments are marked again. The mean map of each segment is given below the curve. The 6 maps are supposed to represent the electric potential maps that are characteristic for the different functional microstate of the brain during processing of these stimuli (see Ref. 4 for review).
From stimulus perception to content identification in a few brain states

The observation that ERP map series are characterized by a finite number of successive field patterns naturally leads to the idea of defining the time points where these field patterns change, or in other words, defining the beginning and the end of the different functional microstates of the brain during treatment of the information delivered by a stimulus (1, 4, 5, 7, 8, 10, 11). Algorithms developed for pattern recognition can be used to achieve this goal, and statistical approaches such as clustering methods and cross validation criteria can be utilized to define the optimal number of different map configurations to explain the data (10). In the example given in Fig.1, the microstate analysis led to six different map configurations that best describe the whole map series, i.e., the 552 ms after presentation of the relevant stimuli. The trace of the global field power, a measure of the field strength, shows the typical peaks known from the traditional ERP literature with a strong component at ~120 ms (the so-called P100), a second one at ~200 ms, and a strong and broad component between 300 and 400 ms (the so-called P300 component). In contrast to the definition of such peaks, the spatiotemporal segmentation approach determines segments of a certain duration that represent the different processing steps. In this example, six different functional states led from perception to identification of relevance of the stimulus.

Continuous, rapid short-term memory update

The following example illustrates the spatiotemporal ERP analysis approach in a task in which subjects were watching briefly (700 ms) presented single digits on a screen appearing in pseudorandom order at high speed (7). They had to press a button whenever three successive digits were either odd or even. This continuous performance task requires several processes to correctly respond to the task demands: Stimuli are perceived. They are stored in short-term memory either as numbers or as category (odd or even). They are compared with the previous digit to decide whether they belong to the same category. If two digits are of the same category, the probability for a triplet increases and attention is temporarily increased. If three digits are of the same type, then the decision and the motor response take place. Figure 2 illustrates how these different processing steps are retrieved in the ERP recordings during the task. ERPs were averaged for four different types of stimulus triplets: 1) control triplets consisting of alternating odd and even digits; 2) three digits of the same type that were correctly detected; 3) two digits of the same type followed by one of the other type; and 4) three digits of the same type that were missed ( omission error). EEG (47 channel) was collected from 24 subjects while they performed the task. Data of all subjects were averaged for this illustration. A total of 2,080 ERP maps (520 maps = 2,080 ms for each of the 4 conditions) were subjected to the statistical segmentation procedure described in Ref. 10. The analysis revealed the same sequence of maps for all three digits of the control condition and the first digit in the other conditions. These microstates probably reflect general processing steps that are performed with all “neutral” stimuli, such as perception, categorization (odd or even), comparison with information stored from the previous stimulus, and memorization of the new information. All these processes are performed within 700 ms to be ready for the next stimulus. In fact, the processes are even performed much faster, as we have shown in earlier experiments with even higher stimulus presentation rates.

Attention and the prediction of errors before they appear

The experiment shown in Fig. 2 also illustrates that the brain is able to rapidly increase attention and to prepare for a forthcoming stimulus to speed up the response. In the cases in which the subjects realized that the second digit was of the same type as the previous one, the ERPs were characterized by a new map configuration that started ~400 ms after the stimulus and continuously increased in strength. ERP literature knows this component as the “contingent negative variation” (CNV), a prestimulus functional state reflecting preparation. Interestingly, this microstate was also present when the subjects afterwards failed to respond to a triplet, but it stayed at very low strength and was eventually replaced by the microstate seen in the nonspecific conditions. This finding demonstrates the importance of attention and preparation for an adequate response and illustrates a case in which errors are already predictable from the ERP maps before they occur. More generally, we have found in different experiments that the functional state at the time of stimulus presentation crucially influences the way the stimulus is processed afterwards (5).
Match and mismatch produce different brain states

The evoked responses to the third digits of triplets were clearly different if this third stimulus matched with the previous two than if it did not. In case of a match, particular map configurations were found that represent those microstates that were related to the identification of relevance of this stimulus with respect to the task demand, i.e., the identification of a match. The maps resemble what is known as the P300 component in the ERP literature. These maps were not present when the third digit was of the other category and the subjects correctly withhold their motor response. In these cases, another microstate with a particular map configuration appeared after ~400 ms. The configuration of the map reminds us of the so-called N400 component, a component that is supposed to reflect expectancy mismatch in language tasks. It is not astonishing that similar expectancy mismatch functions are evoked in our task, but direct comparisons are needed to check for similarities of these functional states. Nevertheless, the example shown here illustrates how microstates can be related to very specific functional processes that take place during very rapid cognitive stimulus processing.

Unraveling the cerebral dynamics of mental imagery

There is an ongoing debate in cognitive neuroscience of whether mental imagery involves the same neural circuits as those employed in processing real stimuli. Is the motor cortex activated when we imagine riding a bicycle? Is the auditory cortex involved when we imagine a song? Is the visual cortex used when we imagine...
an object being turned in space? Shepard and his colleagues concluded from a series of behavioral experiments on mental rotation that, at least for visual imagery, this correspondence seems to be the case (see, e.g., Ref. 15). Their conclusion was based mainly on the following experimental paradigm. Subjects briefly view a drawing on the screen. After a short interval, a second drawing is briefly presented. The subjects' task is to press one button if the two drawings are the same or a second button if they are mirror imaged. To force mental imagery, the second stimulus is rotated by a certain angle with respect to the first stimulus. The classic finding is that reaction time linearly increases with rotation angle and that this increased time is caused by the time needed to mentally rotate the stimulus back in the upright position. Although this correspondence strongly suggests that the machinery of the visual system is involved in the imagery task, functional brain-imaging experiments failed to prove a unique involvement of the visual cortex. One reason might again be that these techniques provide a static “snapshot” image of the brain activity involved in the task and that the temporal compression of distinct events might result in a compound image of all processes that are taking place but that are not necessarily all related to the mental rotation process per se. EEG recordings with their high time resolution are ideal for recording the brain activity in Shepard's mental rotation task because of the possibility of relating the duration of certain brain processes to the behavioral indexes of task completion, i.e., to the time needed to make the decision. Such a relation has been demonstrated for an ERP microstate that increased in duration with the increase of the rotation angle of the target figure (11). Figure 3 illustrates a part of the results of this experiment that was conducted with 12 subjects recorded with a 41-channel EEG. The figure shows that a series of similar map configurations were evoked by the target stimuli independent of the rotation angle, with the exception of one segment that appeared at ~400-600 ms. This segment was only found for stimuli that were rotated, and it lasted longer the more the angle of rotation increased. In this study, methods were...

“...the second stimulus is rotated by a certain angle....”

FIGURE 3. Spatiotemporal analysis of the scalp electric fields in a mental rotation task. The subject's task was to decide whether the second letter of a pair was only a rotated, or a rotated and mirror-reflected, version of the first letter. Event-related potentials (ERPs) were averaged separately for 4 different angles of rotation of the stimuli. The 4 graphs show the ERPs for these 4 conditions in the same way as in the previous figures. The same microstates were found for all 4 conditions, except for 1 new microstate that appeared for the strongly rotated letters only and that lasted longer the more the letter was rotated (segment labeled with R). Under the curves, the scalp potential maps for 5 segments are shown and, at bottom, the estimated localization of the current density in the brain using a distributed inverse solution (9). Only the solution on 1 slice is illustrated here. Adapted from Ref. 11; see original publication and text for more details.
applied that allowed testing for whether this observation statistically holds over subjects: the maps that represent the different segments were fitted to each individual ERP and the onset, offset, and duration of "best fit" were defined for each map. This analysis indeed showed that only this "segment R" as labeled in Fig. 3 increased statistically significantly with increasing rotation angle. Similar results were found when the stimuli were presented to left or right visual field only, and the map of segment R showed topography similar to that with central presentation.

Right hemispheric lateralization of mental rotation

In view of the debate on the location of this mental imagery process in the brain, it would be most compelling to be able to localize the generators in the brain that produced this segment R, because the segmentation analysis clearly indicated that this functional microstate reflects the mental rotation process per se, whereas the other segments are nonspecific functions needed to perform the task.

We applied one of the distributed inverse solutions, which we called low-resolution electromagnetic tomography (9). The inverse solution is calculated for each of the potential maps that represent the different sequential microstates. The solutions suggest different areas being activated over time, starting with bilateral occipital activity, then left occipital, left posterior, bilateral temporal, and, finally, frontal activity. The activity for the map representing segment R is estimated to be dominant in the right postero-temporal cortex. It would thus support the hypothesis that the extrastriate visual cortical areas are involved in mental imagery, and it would propose a dominance of this activity in the right hemisphere, confirming some of the earlier lesion and functional imaging studies.

Intracranial evoked potentials in humans

The procedures discussed above allow the monitoring of cognitive processes in healthy humans noninvasively with high temporal precision. The localization procedures in combination with other imaging methods allow the estimation of putative generators in the brain that are involved in these processes. However, localization will always remain indirect and will need validation by other, more direct techniques.

Still, most of our knowledge about precise localization of functionally selective neuronal activity comes from intracranial and intracellular recordings in the animal brain. Although these studies can give important information about the cortical organization of perception, they are of limited use when it comes to higher cognitive functions. This is why the above-explained noninvasive methods are of such importance. There is, however, a rare possibility of directly recording from intracranial electrodes in humans while they perform cognitive tasks. Epileptic patients with medically intractable epilepsy who might be candidates for a surgical resection of the primary epileptogenic focus are eventually evaluated with intracranial subdural or depth electrodes to better pinpoint the pathological area and to differentiate against eloquent cortex. As in scalp ERP studies, event-related potentials can be recorded simultaneously from several intracranial electrode sites. Of course, even with large multichannel systems, spatial sampling remains restricted, and thus evoked responses might be missed because the area was not covered by electrodes. However, if evoked responses are found, the active neurons can be localized very close to the electrode contact, especially if the gradient between neighboring electrodes is high or if phase inversions between adjacent electrodes are observed.

The speed of visual perception and cognition

Intracranial evoked potential components have been described not only for sensory and motor functions but also for several cognitive tasks such as face recognition (14). An example of a subdural ERP recording in a face recognition task is shown in Fig. 4, illustrating the high specificity of the responses. Electrodes with <1-cm distance can show very different responses to the stimuli. Figure 4 also illustrates that the same electrodes can show differential responses to repeated versus nonrepeated faces at different latencies, indicating a reactivation of the same areas at different periods of information processing. Such findings strongly support the results from surface ERP microstate analysis, in which reappearance of the same map configurations at different latencies is not unusual. The activation of large-scale neurocognitive networks with a continuous exchange of information between the different modules (6) would explain such findings. Figure 4 shows another important result: recognition of a repeated face already appears very early in time. Evidence for very fast face recognition has been found in seven patients from whom depth ERP recordings were made in this face recognition paradigm (13). Although late differential responses, appearing between 190 and 600 ms after stimulus, were found at electrodes in different locations in the right and left hemisphere, the early responses, appearing between 50 and 90
ms, were more frequently found in the right hemisphere. Both responses were more frequent in the temporal lobe, underlining its role as a major contributor to these fast and highly efficient visual recognition networks in humans. Even more evidence for these very fast cognitive processes has been given by the fact that the same early differential responses (~70-90 ms) have been found in 12 healthy subjects from which surface evoked potentials were recorded in the same paradigm. Because cognitive ERP studies very rarely explore possible differential responses before 100 ms, further studies will be needed to define whether these early responses are specific for face stimuli or whether other cognitive functions also show this very fast activation. At least for language processing, several new studies using the spatiotemporal analysis techniques that we review here indicate that language stimuli also seem to be processed much faster than previously thought.

Outlook

The spatiotemporal analysis of multichannel evoked potentials is the method of choice if the temporal dynamics of human brain functions are to be studied. It is the only method that allows the unfolding of the complex neural networks involved in cognitive processes and determining with high temporal resolution when such processes are performed. The new localization approaches allow an approximation of the putative generators for each of the processes needed to perform a certain task. However, the limitations of the localization procedures cannot be neglected. Because surface EEG as well as the magnetic recordings (magnetoencephalogram, MEG) do not provide unique three-dimensional tomographic solution, localization results always must be interpreted with care and must be compared with anatomofunctional knowledge derived from other sources, such as lesion studies, intracranial recordings, and other non-EEG functional imaging approaches. Most appealing are those studies that try to combine noninvasive imaging methods with high spatial and high temporal resolution. Such a combination is now offered by the possibility of directly recording multichannel EEG within the MRI machine, opening a new dimension of precise spatiotem-

FIGURE 4. Intracranial recording of ERPs in a face recognition paradigm. The patient's task was to press one button if a face of a pair was shown in the pair before and another button if both faces were new (see Ref. 12 for details). The data shown here were recorded from a pharmacoresistant epileptic patient who had electrodes implanted for diagnostic reasons. A subdural grid of 8 x 8 contact and a few additional 8-contact strips were surgically placed on the cortex of the left hemisphere. Center-to-center electrode distance was 0.8 cm. Three ERP traces are illustrated here from contacts that exclusively showed responses to face stimuli (solid lines, mean; dotted lines, standard error). A phase inversion is seen between electrodes 62 and 63 for the component at ~200 ms, suggesting active neurons directly underlying this region. The trace for electrode 53 shows very early differences between repeated and nonrepeated faces (starting at 50 ms with a maximum at ~120 ms) but also latency and amplitude differences appearing between 250 and 300 ms.

“...allows the unfolding of the complex neural networks...”
poral analysis of brain functions (12). It is our hope that such combinations will replace invasive recordings even for answering clinically important questions such as the localization of crucial brain functions before surgery.

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References