31. Neurocognitive Functions and the EEG

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> According to the results of our investigations of the human EEG, we are confronted with material processes of smallest dimensions linked to psychological processes, yet these being the most wonderful and the most powerful phenomena on this planet. [Hans Berger 1938, p. 306]

The significance of the electroencephalogram (EEG) for investigating neurocognitive functions was already recognized by its discoverer, Hans Berger himself. In his first communication on the human EEG he introduced the topic of this chapter as a question: "Will it be possible to demonstrate intellectual processes by means of the EEG?" (1929, p. 569). And he gave a positive answer in the very same publication when he described the alpha-blockade during cognitive processing as a first objective correlate of mental states. Thus, the "Berger-effect" was the starting point of neurocognitive EEG-research.

In this discipline, the parallelism of methodological improvements and scientific progress can clearly be demonstrated: following Berger's work, research first focused on the relation between EEG frequencies and behavior. The development of averaging-techniques and the ensuing improvement of the signal-to-noise ratio was the prerequisite for the discovery of the small endogenous event-related potential shifts (ERPs), ranging within a few microvolts in amplitude, and reflecting neurocognitive processes. Improvements in direct current (DC) recording techniques during the mid-1980s encouraged several groups to investigate sustained DC-potential shifts in relation to complex cognitive processes. The rapid improvement of other brain-imaging methods such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) in the late 1980s forced EEG researchers to compete with or utilize these techniques (Wikswo et al., 1993). This development resulted in an increasing number of cooperating research teams, using co-registration of EEG and magnetoencephalography (MEG), PET, fMRI, and transcranial magnetic stimulation to solve their scientific questions. We are convinced that the future of our discipline lies in a synergistic use of methods providing the excellent temporal resolution of EEG and MEG, and the excellent spatial resolution of MRI and PET.

This chapter provides a systematic review of the field of EEG correlates of neurocognitive processes. It cannot be exhaustive, but nevertheless tries to distill the important general information on neurocognitive EEG research and the most significant recent contributions to this area from a huge body of literature. Some aspects have been reviewed in detail recently. We refer to a concise review article in the new *Handbook of Neuropsychology* by Münte et al. (2000) and to a recently published book, *The Cognitive Electrophysiology of Mind and Brain*, edited by Alberto Zani and Alice Mado Proverbio (2002).

According to the methodological criteria mentioned above, the different approaches of EEG research and the new developments of combined applications of methods in psychophysiology will be presented in separate sections:

(a) the analysis of EEG-frequencies, (b) the endogenous event-related potentials (ERPs), (c) the sustained cortical DC-potential shifts prior to or during mental performance, and (d) the combination of EEG and other brain imaging methods in psychophysiology

EEG Frequencies and Neurocognitive Processes

Neurocognitive research by analysis of the EEG frequencies started with Hans Berger's observation of the alpha-blockade during the performance of mental arithmetic. The electrophysiological basis of wave generation is not completely clarified, but there is general agreement that synchronous discharges of cortical cell assemblies driven by afferent thalamocortical inputs play an important role (see Chapter 2 by Speckmann and Elger). The thalamic pacemakers AQ1 in turn are controlled by the inhibitory inputs from the substantia reticularis in the midbrain. Activation of the substantia reticularis leads to disinhibition of the thalamic pacemakers and causes desynchronization of the EEG (Singer and Dräger, 1972).

It has been demonstrated that alpha-blocking or event-related desynchronization (ERD) (Pfurtscheler and Aranibar, AQ2 1977) is related to arousal mechanisms mediated by the reticular activating system (Lindsley et al., 1949; Moruzzi and Magoun, 1949). The close relationship of ERD with the orienting response is reflected by the fact that ERD is habituating over trials, but recovers when the stimulus changes in quality (Simons et al., 1987). In searching for electrophysiological correlates of focal cortical activation, the topographical distribution of ERD in relation to different mental tasks involving the two hemispheres specifically soon attracted interest. The introduction of the fast Fourier transform algorithm in 1965 facilitated the data analysis and contributed to a wider utilization of frequency analysis in psychophysiological research. Overall, the results were disappointing, exhibiting only small effects that often could not be reproduced by different investigators (Donchin et al., 1977; Gevins et al., 1979). In consequence, many researchers switched over to the developing field of endogenous ERP.

In the past decade, promoted by a rapidly increasing number of manufacturers offering commercial mapping systems that include multichannel frequency analysis and algorithms calculating the interelectrode coherence, mapping has experienced a renaissance. Furthermore, the concept that periodic neural activity in the high-frequency range (>20 Hz) may indicate specific cognitive processes has given new impulses to frequency analysis of the ongoing EEG and MEG (Singer and Gray, 1995). Presently, there is evidence (Engel and Singer, 2001) that neuronal oscillations and synchronization in the gamma frequency range (30-70 Hz) distributed over multiple cortical regions provide a general platform for functional cooperation or large-scale integration, which is an essential requirement for the successful accomplishment of any complex cognitive task (Varela et al., 2001).

However, the results produced by spectral mapping and coherence analysis of the surface EEG have to be interpreted cautiously, since a virtually indefinite number of parameters within variable frequency bands can be generated. Due to methodological and theoretical reasons, a direct comparison of results obtained with scalp electrodes in humans to data from intracortical multielectrode recordings in animals remains questionable.

Local Changes in Frequency and Coherence: Correlation to Mental Performance

Hemispheric differences in alpha power in relation to tasks requiring predominant processing in one hemisphere were observed by many investigators. Diminution of alpha power over the left hemisphere was found during mental arithmetic (Butler and Glass, 1987; Morgan et al., 1974), word search tasks (McKee et al., 1973), verbal fluency tasks (Beaumont et al., 1978), and listening to a tape recording of speech (Duffy et al., 1981). Reading elicited bilateral AQ2 occipital and parietal alpha diminution (Pfurtscheler and Klimesch, 1987). Diminution of the alpha power over the right hemisphere could be observed during spatial imagery (Rebert and Low, 1978) and music processing (Duffy et al., 1981; McKee et al., 1973). At a closer look, these apparently clear results were far from consistent. The sources of divergent results are manifold: the cognitive demands were confounded with motor task demands (Gevins et al., 1979); the number of electrodes was too small or bipolar recordings were used (Petsche et al., 1986); only narrow bands of the whole alpha activity were preselected (Jürgens et al., 1995); different methods of data analysis, especially the transformation of data into left/right ratios, obscured the results (Donchin et al., 1977); finally, varying definitions of "resting states" representing the baseline were used. Unfortunately, due to the lack of generally accepted standardized methods of data aquisition and data analysis, this Babylonian confusion has further increased and the comparison of results from different laboratories has become more and more difficult.

A recent development in neurocognitive EEG research is the increasing interest in the high-frequency gamma band (>20 Hz). Berger's (1929) hypothesis that high-frequency oscillations may indicate mental processes was nurtured by findings that coherent periodic neural activity in the 40-Hz range accompanies information processing in the visual cortex of vertebrates (Eckhorn et al., 1988). In animal experiments, neuronal oscillations in this frequency range could be related to feature linking and gestalt perception (Singer and Gray, 1995). EEG measurements in humans revealed local enhancement of cortical gamma band activity during preparation and execution of movements (Kristeva-Feige, 1993) during language processing (Pulvermüller et al., 1996), during visual tasks (Tallon et al., 1995), and during music perception, especially in professional musicians (Bhattacharya et al., 2001).

In elegant EEG and MEG experiments, Pulvermüller et al. (1996) could demonstrate that spectral responses in the 30-Hz range were specifically elicited by linguistic processing of meaningful words, but not of meaningless nonwords. Spectral responses to meaningful gestalt-like figures, such as Kanisza's triangle, produced a similar increase in 30-Hz power, but not the responses to matched figures that did not constitute a coherent gestalt (Tallon et al., 1995). In contrast, processing of simple stimuli affects the spectral power in the higher frequency range of the gamma band. Tones or moving bars, as well as preparation and performance of simple repetitive movements, are usually accompanied by enhanced spectral activity in the 40-Hz range or above (Pantev, 1995). It therefore seems that task-related high-frequency oscillations can be subdivided into two functionally separated entities, a 30-Hz and a 40-Hz component. As an explanation, Pulvermüller (1995) proposes that in complex cognitive tasks, e.g., during language processing, Hebbian neuronal cell assemblies are activated—"ignited"—and form a loop from Broca's region to Wernicke's region and back. The round-trip time in such a loop will be 20 to 40 msec or less, equaling a circulation frequency of 25 to 30 Hz. In contrast, if cell assemblies are less widely dispersed, as it can be assumed in primary sensory processing, round-trip times may be substantially shorter so that high-frequency oscillatory cortical activity in the 40- to 60-Hz range will be generated. There are still many questions unresolved with respect to the functional significance of increased gamma activity. Recent studies suggest that an increase in gamma power phase synchronization of induced gamma activity may represent a general mechanism enabling transient associations of neural assemblies. New findings indicate, furthermore, that synchronized gamma activity is specifically involved in selective attention. While feature binding appears to depend primarily on induced gamma synchronization, attentional processes seem to involve both induced and evoked gamma oscillations (Fell et al., 2003). The growing importance of even faster ("ultrafast," 80–1,000 Hz) frequencies has become evident during the first years of the 21st century (see Chapter 26 by Curio). AQ1

Endogenous Event-Related Potentials (ERPs) and Neurocognitive Functions

While the early portions of the evoked potential waveform are mainly dependent on physical stimulus characteristics such as loudness or brightness and are therefore often called exogenous potentials, the later portions of the evoked potential have been shown to vary with a variety of psychological variables. Therefore, these later parts (from 100

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msec onward) are often called (late, endogenous) ERPs. This is due to the fact that they depend largely on psychological variables, while physical stimulus properties play little or no role in their generation. In relation to the ongoing background EEG, the ERPs exhibit very small amplitudes ranging between 2 and 20 μVs in magnitude. Analysis of ERPs, therefore, requires an improvement of the signal-to-noise ratio, which is usually achieved by simple signal averaging (Münte et al., 2000). This procedure leads to time-voltage diagrams, which are characterized by positive and negative deflections, each of which with a specific scalp topography. Several systems of labeling the peaks and troughs of the ERP waveform coexist. Most often, the polarity of a component is denoted by the letters "N" (i.e., negative) or "P" (i.e., positive). The different negative and positive deflections are then labeled in the order of their appearance (e.g., P1, N1, P2, N2, etc.), by their characteristic peak latencies (e.g., N100 or P300), or by their actual peak latencies in a specific experiment (e.g., N148, P125; see Fig. 31.1 for a systematic overview). One has to keep in mind, however, that the label "P1" signifies completely different neurophysiological phenomena in somatosensory, visual, or auditory modalities. Also, sometimes peaks labeled according to their characteristic latencies might occur considerably earlier or later. For example, in difficult visual classification experiments, the P300 effect is often seen as late as 800 msec. In everyday use, the ERP peaks are often identified as components. This is somewhat misleading, since originally the term *component* had been reserved for ERP phenomena that show a unique behavior as a function of experimental manipulations. Therefore, a component might span several ERP peaks ("N2/P3" component) or, because of the dipolar nature of the underlying electromagnetic sources, may manifest itself as a negative peak at one recording site and as a positive peak in others. For example, the mismatch "negativity" component has actually a positive polarity at subsylvian recording sites when a nose-tip reference is employed.

While a lot of ERP research in the past has been devoted to the delineation of the cognitive correlates of certain components, more recent work has circumvented the difficulties of the definition of components by operationally defining ERP effects as markers for task-dependent differences in cognitive processes without making too much reference to the classic components. A case in point is the so-called *Dm* effect [for difference based on later memory performance (Paller et al., 1987); see memory section below]. We have therefore decided to organize this chapter according to the cognitive processes under study and not according to the ERP components. These will be mentioned at the appropriate places.

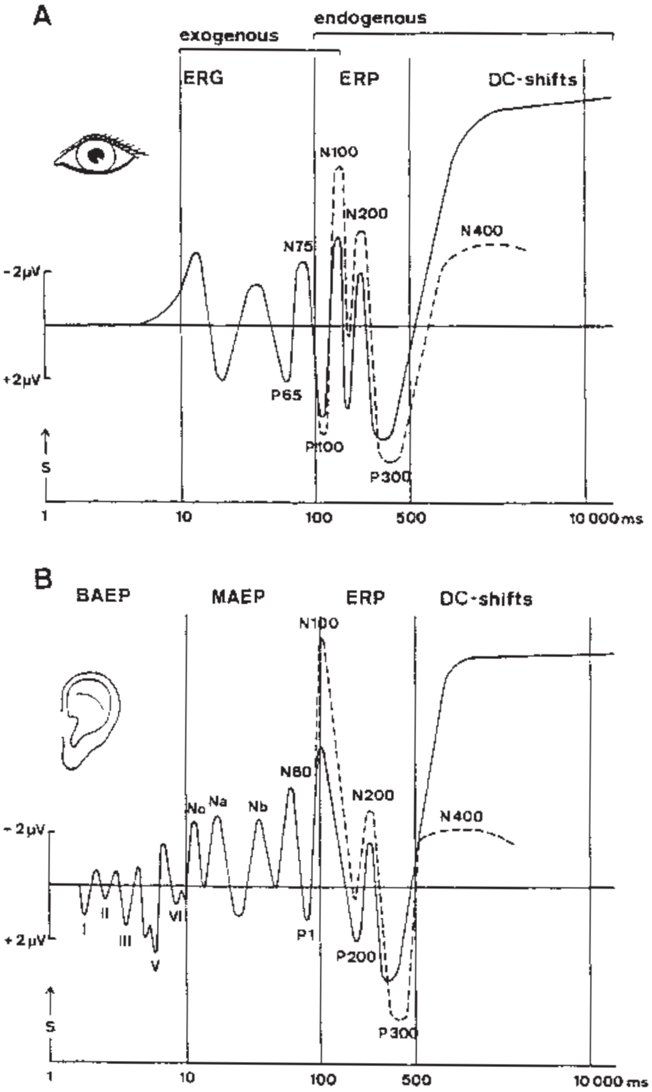

Figure 31.1. Averaged event-related responses to visual **(A)** and acoustic **(B)** stimuli. Schematic potential traces on a logarithmic time-scale. **A:** Exogenous components comprise the electroretinogram (ERG) and the P 65 and N 75. Components with latencies longer than 100-msec latency are considered as endogenous components. The P 100 and N 100 component can be modified by orienting and selective attention *(dashed lines)*, the N 200 by stimulus evaluation and the P 300 by context updating. The N 400 is related to semantic expectancy. Large direct current (DC) shifts occur when complex cognitive tasks have to be solved. **B:** In the acoustic modality exogenous components comprise the acoustic brainstem auditory evoked potentials (BAEPs) and the midlatency auditory evoked potentials (MAEPs). Endogenous components can be modified analogous to the visual modality but have a tendency toward shorter latencies. Whereas exogenous event-related potentials (ERPs) exhibit modality-specific potential traces, endogenous components are very similar in both modalities.

Neural Generators

While ERPs afford exquisite time resolution on the order of 1 msec, a major drawback has been the lack of knowledge regarding the anatomical generators responsible for the different effects. With the advent of multichannel recordings, the topographical definition of ERP effects has been greatly improved. Nevertheless, it has been known since von Helmholtz (1853) that the problem of recovering the current sources from superficial electromagnetic measurements is intrinsically based with great difficulties. It is impossible to uniquely determine the spatial configuration of neural activity based on EEG recordings alone (Nunez, 1981). This is also known as the inverse problem.

In spite of this dictum, significant progress has been made in source localization by making certain a priori assumptions about the solution. For example, a common ap-

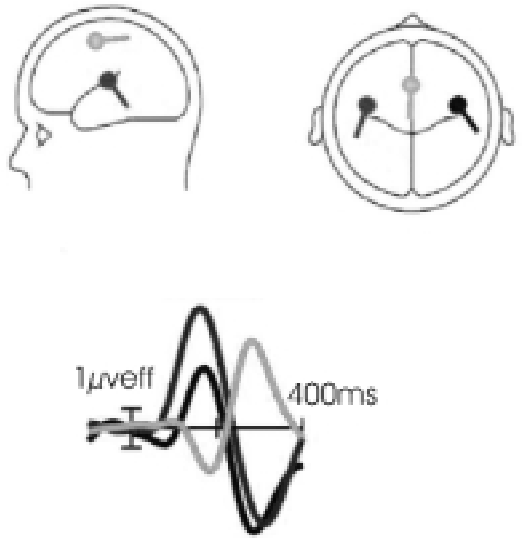

Figure 31.2. Example of the estimation of neural generators of ERPs using multiple equivalent current dipoles as implemented by the brain electric source analysis program package (e.g., Scherg et al., 1999). Data are from a study in which a combined mismatch negativity and P3a response was found for deviant stimuli (Nager et al., 2003). **Upper panel:** Three dipoles were found in an iterative procedure. Two symmetrical dipoles in the auditory cortex explained the activity related to the mismatch negativity. A third frontal source was associated with the P3a. **Lower panel:** Activity of these point dipoles over time.

proach is to assume that an ERP is generated by a small number of focal sources, which can be modeled by equivalent current point dipoles (ECD) (Scherg and Ebersole, 1994; Scherg et al., 1999). The location, orientation, and activity over time of each ECD is iteratively determined by minimizing the difference between the predicted and the actual ERP. This approach, implemented in the popular BESA software, has been successful when comparatively early ERP effects with a circumscribed scalp topography were targeted (Fig. 31.2). For late and widely distributed ERP effects, for which many spatially and temporally overlapping sources can be assumed, this approach becomes increasingly problematic for computational and plausibility reasons.

Another approach, therefore, is to consider a priori all possible fixed source locations. In such continuous current source models the strength of each dipole is estimated according to some mathematical constraint. A unique solution is obtained by minimizing the deviation from these constraints. A number of approaches have been proposed including (among others) weighted minimum L2 norm, i.e. a least squares approach (Brooks et al.,1999; Hämäläinen and Ilmoniemi, 1994; Sarvas, 1987), and maximum smoothness. The latter is implemented in the *low-resolution electromagnetic tomography* (LORETA) software package (Pascual-Marqui, 1999; Pascual-Marqui et al.,1994; see Chapter 59 by Lopes da Silva). AQ1

Neuroanatomical considerations suggest that sources of brain electromagnetic activity should be located in gray matter and, because of the orientation of the cortical columns, oriented orthogonally to the cortical sheet. Moreover, they should be locally coherent, leading to "smooth" activity along the cortical sheet. These considerations can be used to further constrain the solution space (Phillips et al., 2002) by using realistic head models derived from actual brain anatomy. For example, the current version of LORETA computes the current distribution across 2,394 voxels distributed only in gray matter as determined from a standard average brain template provided by the Montreal Neurological Institute.

Stimulus Selection: Attentive and Preattentive Mechanisms

One of the core tasks of our nervous system is to select important information and to discard stimuli that are not deemed important. This filtering out of information has been termed selective attention. At the same time it is also necessary to scan the environment for novel or deviant events in order to redirect attention towards these possibly important stimuli.

Visual Attention

In a typical visual selective attention task, stimuli are represented rapidly in at least two "channels" defined by, for example, their spatial location. Paying attention to stimuli from one channel in order to perform a target detection task ("look and see!" in colloquial English; editorial comment, E. Niedermeyer) gives rise to enhanced amplitudes of several ERP peaks, compared with ERPs to the same stimuli when the other location is detected. The earliest component to be affected by visuospatial attention is an occipitotemporal positivity component that has a latency of about 120 msec (P1) (Fig. 31.3). This component has been shown to be generated in secondary visual cortex (Gomez-Gonzalez et al., 1994) and is followed by a similarly enhanced negativity

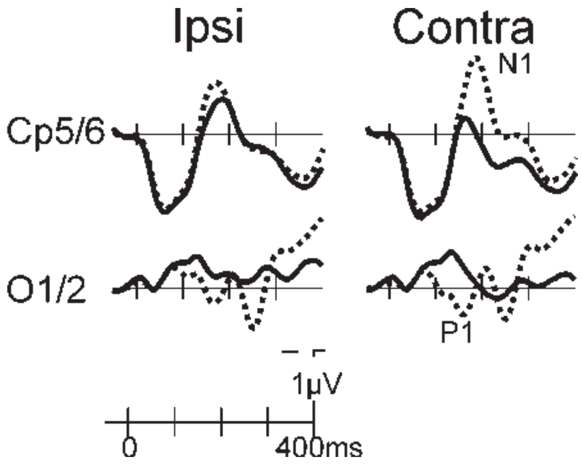

Figure 31.3. Visual ERPs in a selective spatial attention task requiring the subjects to fixate the center of a video screen and to attend either to stimuli appearing to the right or to the left of the fixation cross in order to identify rare target stimuli. ERPs from left and right visual fields are averaged together yielding ERPs for electrodes ipsi- and contralateral to the stimuli. The first attention-modulated ERP component is the occipital P1 component, which is more pronounced for attended stimuli. This is followed by a centroparietal N1 component that is similarly enhanced (unpublished data by Nager and Münte).

at about 170 msec (N1). While visuospatial attention modulates the amplitude of obligatory components of the ERP, the attention to other stimulus features such as motion, color, or stimulus orientation results in the elicitation of so-called selection negativities (Hillyard and Münte, 1984). These differ in their specific scalp topography, and source modeling suggests that these effects are generated by secondary visual areas dedicated to the processing of the corresponding stimulus features. When multidimensional stimuli are used, e.g., stimuli that are characterized by their location and color, a hierarchical dependency of color selection on location selection has been shown using ERPs.

In addition to maintaining an attentional focus at a specific location or on another specific stimulus feature, a subject often also has to direct the attentional spotlight either as a function of an alerting stimulus or voluntarily. This directive aspect of attention has been studied in cuing tasks, in which a target stimulus is preceded by an attention-directing cue. In such tasks some target stimuli are preceded by valid cues, i.e., the target appears at the designated location, while in a minority of trials the cue is invalid, i.e., the target appears on the other side. Under such circumstances again an attention-dependent modulation of the P1 and N1 components is found (Mangun and Hillyard, 1987).

While attention in the visual domain has been discussed mostly in relation to attention to specific features, more recently it has been stressed that whole objects in the environment may be attended selectively and thus perceived as unified ensembles of their constituent features. In a combined ERP/fMRI study that required subjects to attend to one of two superimposed transparent surfaces formed by arrays of dots moving in opposite directions, neural activity was found for an irrelevant feature (color) of an attended object. This activity could be localized to the color area of the fusiform gyrus. Thus, these ERP data suggest that attention links relevant and irrelevant features to form a unified perceptual object (Schoenfeld et al., 2003).

Auditory Attention

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In the auditory modality, selective attention tasks have been conducted using ERPs that are quite similar in design to the visual tasks mentioned above. (An example taken from Irving Berlin's song, "White Christmas": " . . . and children listen to hear sleigh bells in the snow"; editorial comment, E. Niedermeyer.) For example, subjects are instructed to attend to one of two concurrent auditory streams of information defined by their location or pitch in order to detect slightly deviant target tones. In such a scenario, which is similar to the dichotic listening task that has been extensively used in cognitive psychology, the ERPs to stimuli in the attended stimulus "channel" are associated with a more negative waveform starting approximately 100 msec after the onset of the stimulus (Hansen and Hillyard, 1980, 1983; Hillyard et al., 1973). This processing negativity often extends for several hundred milliseconds and can be subdivided into subcomponents. While spatial location has a special status in the visual modality, this is not the case in the auditory modality, as the processing negativity is very similar for the selection according to different auditory features (e.g., pitch, timbre, loudness, duration; Fig. 31.4). It has been used to investigate the processing of multidimensional auditory stimuli, i.e., situations in which stimulus channels are characterized by the factorial combination of different stimulus attributes (e.g., location and pitch; Hansen and Hillyard, 1983). Moreover, a number of studies have addressed the spatial gradient of auditory attention in central and peripheral auditory space (e.g., Teder-Sälejärvi and Hillyard, 1998). Interestingly, the gradient of auditory spatial attention in peripheral auditory space has been found to be much steeper in congenitally blind subjects (Röder et al., 1999) as well as in professional music conductors (Münte et al., 2001; Nager et al., 2003).

Preattentive Auditory Processing

It is of exquisite importance to humans as well as other species to screen the auditory environment for potentially important events. This global surveillance function is conducted without the use of attentional resources and this processing mode therefore has been labeled "preattentive." Two important ERP effects have been investigated in relation to preattentive auditory processing: the mismatch negativity (MMN) and the P3a response.

The MMN is found exclusively in the auditory domain. It is elicited by rare deviant stimuli that deviate physically from a monotonous context, e.g., in duration, pitch, timbre, or loudness. Importantly, the MMN is also found, if the subjects attend elsewhere. Experimentally, this is achieved by having subjects watching a movie or reading a book (reviewed in Näätänen and Winkler, 1999; Picton et al., 2001). The onset latency of the MMN varies but is typically around 130 msec with regard to the stimulus onset. Its duration is between 100 and 200 msec. The MMN shows a frontocen-

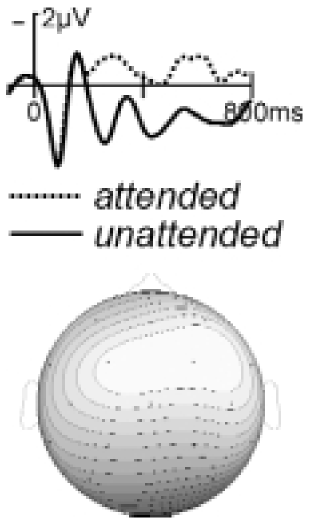

Figure 31.4. Auditory selective attention effect. Data are from a study requiring subjects to attend to one of two interspersed streams of stimuli defined by their pitch in order to identify target stimuli within the attended stream. Attended stimuli give rise to a long-standing negativity (**upper panel,** processing negativity), which has been interpreted as indicating prolonged processing of the attended stimuli. **Lower panel:** A spline-interpolated isovoltage map of the processing negativity is displayed with darker colors indicating positive and lighter colors negative voltage.

tral maximum and, if recorded against a nose-tip reference, a polarity inversion around the sylvian fissure suggesting a generator in the auditory cortex, which has been confirmed by dipole modeling and brain imaging studies (Opitz et al., 2002). In the classical experiments the deviant stimuli were presented against uniform standard stimuli. It therefore has been proposed that the invariant features of the standard stimuli form some kind of memory trace against which the incoming stimuli are compared. If a mismatch between the features of the actual stimulus and the memory trace is detected, an MMN is triggered. More recently, it has been shown that the MMN can also be elicited if repetitive sequences (e.g., tonal scales) are used to create the standard background stimuli (Tervaniemi et al., 1994). Thus, memory formation at the level of the auditory cortex includes the ability to extract complex sequential information (Picton et al., 2001).

A different mode of preattentive auditory processing is marked by the P3a component (Fig. 31.5). This is typically observed for so-called novel stimuli (e.g., the honking of a car, a dog's bark) occurring out of context in a series of stimuli. The P3a is a positivity with a peak latency of about 200 to 250 msec and thus considerably earlier than that of the classical P3b (P300) component. It has a frontocentral distribution. Combined fMRI/ERP recordings have suggested that the main neural generators of the P3a are in the superior temporal gyrus bilaterally and in the right frontal cortex (Opitz et al., 1999). The P3a response has been interpreted as an electrophysiological correlate of the orienting response (Squires et al., 1975, 1977), which helps the subject to direct attention toward potentially important sources of information (Schröger, 1997).

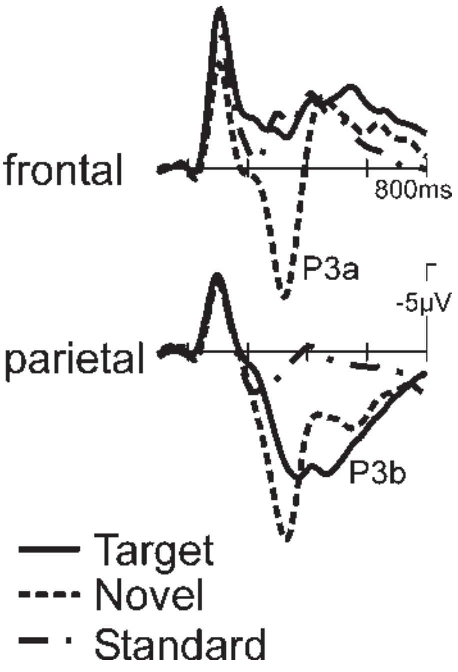

Figure 31.5. ERPs from a modified auditory oddball study: within a series of frequent "standard" stimuli (1,000 Hz, 80% probability) subjects had to identify by button press rare target stimuli (1,500 Hz, 10% probability). These target stimuli give rise to a typical P3b component, which is maximal at parietal recording sites. In addition, 10% of the stimuli comprised so-called novel stimuli; these were environmental noises that were not repeated during the experiment. These novel stimuli are associated with an earlier positivity (P3a) that is maximal at frontal and central recording sites.

Somatosensory Attention

If series of electric shocks are presented in a random sequence to different fingers of both hands with one of the fingers being relevant for the task, shocks in the attended "channel" produce an enhanced N140 component of the somatosensory evoked potential (SEP) (Desmedt and Tomberg, 1989). The topographical distribution reveals a maximal amplitude over the prefrontal cortex. In addition to this effect on the N140, earlier ERP signs of selective attention have been demonstrated in the somatosensory modality. At a latency of 30 msec an attention-related positive wave of small amplitude can be recorded over the contralateral parietal lobe (Desmedt and Tomberg, 1989). More recent investigations, combining multichannel recordings with spatiotemporal source modeling have shown attention-dependent modulations of the SEP waveform between 30 and 260 msec. Dipole modeling revealed six brain regions related to selective attention, among them the contralateral postcentral gyrus, the contralateral mesial frontal gyrus, the right posterior parietal cortex and the anterior cingulate gyrus. This suggests that attentional gain setting mechanisms act on different levels of the somatosensory pathway.

Memory

Psychological models distinguish between different memory systems that are presumably subserved by different neural systems and show differential involvement in neurological diseases. Memory systems can be classified according to whether or not their content can be verbalized (the declarative vs. procedural distinction) or whether or not the subject voluntarily accesses the memory content (explicit vs. implicit distinction). Further distinctions refer to the span that an item is kept in memory (working vs. short-term vs. long-term memory) and to the different processes involved in the administration of a memory trace (encoding vs. maintenance vs. retrieval). All of these different levels have been studied using ERPs over the past two decades (for reviews see Friedman and Johnson, 2000; Rugg and Allan, 2000; Rugg and Coles, 1995). Here we can highlight only a number of selected findings.

Event-Related Potential Effects During Retrieval

An important paradigm for memory research calls for the serial presentation of words, faces, or objects in a list with some of the items being repeated during the list. The task of the subject is to explicitly decide by button-press whether a given item is old (repeated) or new (first presentation). Across studies, three ERP effects distinguishing old and new items have been consistently observed: first, a decrease of the amplitude of the N400 component (between 300 and 500 msec, see language section of this chapter); second, an increase of a parietal positive slow wave (between 500 and 800 msec) that has been given different labels such as *late positive component, P300, late positivity,* or *parietal* *old/new effect.* Finally, in a number of studies a right frontal positivity has been found in paradigms that extend beyond simple recognition judgments and involve the retrieval of source information (i.e., under what circumstances was the item learned), or require postretrieval decision-making processes. A large body of research (summarized in Münte et al., 2000) has been directed at determining the relation of these three components to different qualities of recognition such as recollection and familiarity. Moreover, it has been asked which of these components is related to repetition in the absence of conscious recognition and which is related to repetition in the presence of conscious recognition. To answer these questions, variants of the old/new task have been used. For example, Düzel et al. (1997) required subjects to perform an old/new recognition judgment in some blocks of their study (explicit task), while in other blocks subjects had to make a living/nonliving judgment. In these latter runs the occasional repetition of items was not task-relevant (implicit task). In the explicit task both the N400 and late positive component were modulated by repetition, while in the implicit task only the N400 effect was seen. This suggests that the N400 modulation indexes repetition independent of recognition.

In so-called source monitoring tasks subjects are required not only to decide whether they have encountered an item before or not, but also to decide about specific aspects of the encoding episode of that item (e.g., the visual background or the speaker's voice). Wilding and Rugg (1996) found a right frontal positivity for those items that were classified as new and attributed to the right source. Consequently, this ERP effect has been discussed as reflecting retrieval of specific perceptual information regarding the memory source.

Effects During Encoding

Instead of presenting words or other stimuli in a continuous series, it is also possible to devise experiments with separate *study* and *test (retrieval)* phases. The registration of EEG during the study phase affords the possibility of averaging the single-trial activity according to whether or not the specific item was subsequently remembered during the retrieval phase. Using this method, Paller et al. (1987) found an increased late positivity (between approximately 300 and 800 msec) for those items that were later remembered, which was termed the Dm effect (see above). When words during the study phase had to be processed at a deep, semantic level (requiring a living, nonliving distinction), the Dm effect was larger and the memory performance better compared to a condition that used a shallow, nonsemantic task (first and last letter of word in alphabetical order). The Dm during encoding, therefore, appears to reflect the retrieval of information about the item from long-term memory.

Working Memory

It can be said that working memory holds, tags, and/or activates sensory information of the information retrieved from long-term memory for current processing. Working memory also actively maintains information, and this information can be changed or updated. An influential view posits that the P300 ERP component reflects this information processing function (Donchin and Coles, 1988), although not everybody agrees with this view (Verleger, 1988).

Typically the P300 is elicited by low probability deviant stimuli in a series of standard, higher probability stimuli when the deviants have to be attended and actively answered. This is called an oddball paradigm. The P300 is widely distributed but is most pronounced over parietal scalp regions. The amplitude of the P300 to the target events in an oddball sequence is inversely related to the global probability of its occurrence. The P300 amplitude is also modulated by the temporal interval between targets and by the local structure of the series (local probability). In an oddball task, in which more than two different stimuli are involved, the P300 amplitude is determined by the probability of the relevant stimulus category (target or standard) and not by the probability of the individual stimulus.

The relation to working memory becomes clearer if one assumes that whenever a target stimulus is encountered in an oddball task, the current target count maintained in working memory must be incremented, leading to an update of the model of the environment. Fine-grained inspection of the P300 "complex" often reveals different portions, which have been labeled P3a, P3b, and slow wave. Intracranial recordings have revealed multiple sites showing P300-like activity (Smith et al., 1990). The latency of the P3b component has been shown to vary systematically with task difficulty in stimulus categorization tasks. Thus, in a very difficult task, the P3b peak latency may well extend beyond 600 msec (Kutas et al., 1977). While manipulations of the difficulty of stimulus classification have profound effects on P3b latency, manipulation of the response selection difficulty has virtually no effect (McCarthy and Donchin, 1981). The P3b latency, therefore, can be used as an index of the timing of information processing as well as to assign task manipulations either to the stimulus evaluation or response selection stages.

Besides the updating of working memory, presumably indexed by the P300 response, information also needs to be actively maintained in working memory. Following Baddeley (1986), the working memory system comprises three major components: the central executive, the visuospatial sketchpad, and the phonological loop. The latter two systems are thought to maintain information over several seconds. In a series of studies Ruchkin and colleagues (1997) found that the scalp topography of the slow ERPs recorded during the retention interval depended on the type of material to be maintained. For example, retention of phonological material leads to a slow wave topography with a left frontal maximum, while retention of visuospatial material leads to a maximum over the right parietal scalp, suggesting that these effects index the activity of the visuospatial sketchpad and the phonological loop.

Language Comprehension and Production

Among all cognitive processes language is unique, as this function is available only to humans. Neurophysiological studies of language, therefore, are confined to humans and have to take advantage of noninvasive measures such as brain potential recordings. Linguists and psycholinguists have dissected the language faculty into several subdomains. While different theories make varying assumptions regarding the exact functional architecture of the language comprehension and production systems, there is a consensus that different types of information are needed that require specialized processing routines. These types of information have been identified as semantic, syntactic, pragmatic, phonological, and prosodic.

Semantic and Pragmatic Effects

A hallmark finding in the development of a neurophysiology of language has been the discovery of the N400 component by Kutas and Hillyard (1980). This is a widely distributed centroparietal negativity with a maximum at 400 msec (Fig. 31.6), which was first found in a sentence reading study. Terminal words that did not match the preceding context (e.g., "I drink my coffee with cream and <u>mud</u>") were associated with an N400, while congruous terminal words (" . . . with cream and <u>sugar</u>") were not. While this component was originally thought of as a marker of semantic incongruency, further research has shown that the N400 amplitude varies as a function of a number of factors (reviewed in Kutas et al., 2000). For example, the semantic incongruency effect is modulated by the relatedness of the expected word to the actual incongruent word such that a smaller N400 effect is obtained for the sentence "The pizza is too hot to drink" than for the sentence "The pizza is too hot too sing." Another factor is word frequency: words that are more common give rise to a smaller N400. Also, within a sentence the N400 amplitude decreases as a function of the serial position of the eliciting word within the sentence.

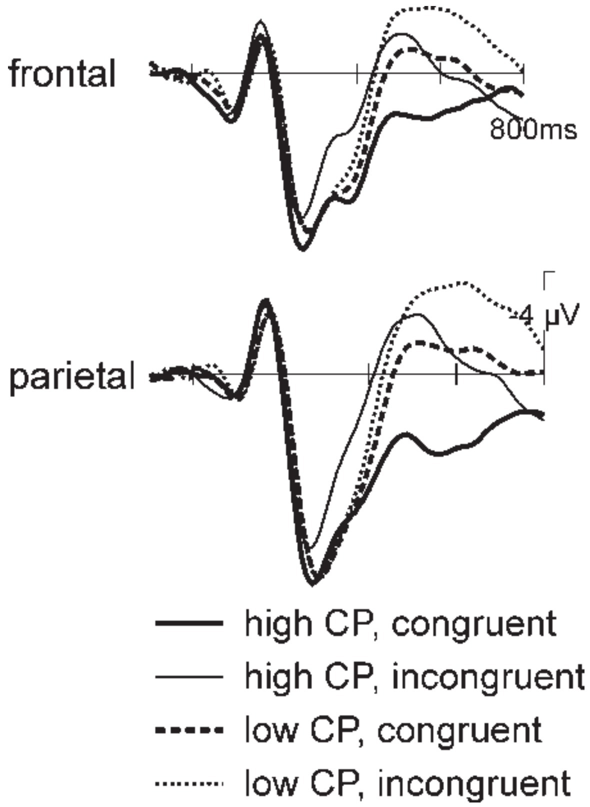

Figure 31.6. ERPs from a sentence processing study. All words except for the terminal word of a sentence were presented visually on a computer monitor. The last word of the sentence was presented via loudspeakers. Sentences were either highly coherent, leading to a high predictability of the terminal word (e.g., "The programmer was unhappy with his new computer": high CP sentence), or were less predictable (e.g., "He went to the store because he needed new socks": low CP sentence). Terminal words of low CP sentences are associated with an increased negativity (N400), which is maximal at parietal sites. In addition, terminal words were manipulated for semantic congruency. Incongruent words (e.g., "The programmer was unhappy with his new cockroach"; "He went to the store because he needed new love") lead to additional negativity in the N400 range.

The N400 is reduced by the repetition of a word even if a number of other words are presented in between. Recently, it has been shown that N400 is sensitive to processes that require integration of information across several sentences (van Berkum et al., 2001). It has also been found that the AQ5 N400 varies with pragmatic factors, i.e., with the difficulty of integrating a piece of discourse with general world knowledge (St. George et al., 1994). Taken together, the N400 amplitude appears to be negatively correlated with the ease with which an incoming stimulus can be integrated in the preceding context.

Syntax and Morphology

To establish links between words and ultimately to determine "who did what to whom" in a sentence, syntax is required. Many ERP studies in the syntactic domain have used the violation paradigm, i.e., the induction of grammatical errors. In relation to such errors a late positivity with an onset of approximately 500 msec with a maximum at 600 msec after onset of the critical word at centroparietal sites has been reported (P600 or syntactic positive shift). Syntactic errors that induce a P600 effect can be simple, such as in number agreement violations ("The cat chase_ the dog," Hagoort et al., 1993). The P600 is also observed in situations, in which a highly likely initial reading of a sentence has to be revised ("The woman persuaded to answer the door . . . ," Osterhout and Holcomb, 1992). The initial reading of the word *persuaded* is that it is very likely the verb of the main clause. This becomes untenable at the word *to*. Now, the syntactic interpretation of the sentence needs to be revised, with *persuaded* being the first word of a truncated relative clause. Precisely upon the presentation of the word *to*, a P600 is obtained in the ERP.

Concerning the functional significance of this P600 effect, it therefore has been proposed as a marker for syntactic reanalysis (Friederici, 1995), or syntactic integration difficulty (Kaan et al., 2000). Although no consensus has been reached yet on the exact functional significance of the P600, common to these views is that the P600 is primarily associated with syntactic processing. Evidence that is challenging this view has been presented, however (Kolk et al., 2003; Münte et al., 1998). A second component that is sometimes observed in grammatical errors is a left anterior negativity, which occurs with an earlier latency but seems to be less stable (King and Kutas, 1995; Kluender and Kutas, 1993; Münte et al., 1993).

Phonology and Prosody

Spoken language allows the speaker to code both syntactic information (e.g., whether a sentence is a question or a simple declarative sentence) and emotional information (e.g., whether he/she is sad or happy) by modulating the pitch of his/her voice. This is called prosody. An ERP effect, termed the closure positive shift, has been found that indexes an intonational phrase boundary (Steinhauer et al., 1999). These boundaries can be used to guide the initial syntactic analysis of spoken language.

Executive Functions

The term *executive function* denotes a heterogeneous group of higher order, "meta-cognitive" functions that are needed orchestrate and supervise the behavior of humans (Smith and Jonides, 1999). These functions include planning, supervising, self-monitoring, the ability to inhibit a prepotent response, and the ability to shift a mental set, among others. Two processes, inhibition and self-monitoring, are briefly discussed here.

Inhibition

A popular paradigm to investigate inhibition is the so-called go/no-go task, in which one class of trials requires a response (go trial), while a motor response has to be withheld for another, similar class. No-go trials are characterized by a frontal negativity of about 1 to 4 μV in amplitude. The onset and peak latency of this no-go N200 effect depend on the time at which the information determining the go/no-go decision becomes available (Gemba and Sasaki, 1989; Kok, 1986; Simson et al., 1977). Several lines of evidence link this frontal "N200" to inhibitory processes. For example, invasive studies in behaving monkeys have revealed activity related to response inhibition in the prefrontal cortex in a go/no-go paradigm that gives rise to an N200 in humans (Sasaki et al., 1989). Also, destruction of prefrontal cortex in animals has been found to lead to a profound disturbance of performance in delayed response tasks (Fuster, 1989), and to an enhancement of disinhibition and impulsive behavior (Luria, 1973). Finally, brain imaging (fMRI) has pinpointed the frontal lobe as being important for inhibition in go/no-go trials (Garavan et al., 1999; Konishi et al., 1999).

Self-Monitoring

Recent ERP investigations of executive processes have focused on error detection and action monitoring. By averaging time-locked to the motor response in a cognitive task rather than to the stimulus onset, a negative component has been isolated appearing immediately after committing errors that therefore has been labeled error-related negativity (ERN) (Falkenstein et al., 2000; Gehring et al., 1993). One model associates the ERN to an error-detection mechanism (Falkenstein et al., 2000; Gehring et al., 1993), which compares an internal goal (a computed "best response") with the predicted consequences of the actual response. An internal "error signal" is generated if a mismatch is detected by the system. An alternative interpretation holds that the ERN merely reflects the degree of response conflict experienced by subjects (Botvinick et al., 1999). It has been shown that the process indexed by the ERN is also important for error correction (Rodriguez-Fornells et al., 2002a). Importantly, source modeling techniques have suggested that the ERN emanates from the anterior cingulate gyrus (ACG). This coincides with findings from fMRI investigations, which also have found activations of the ACG in error trials and conditions that induced a high degree of response conflict (Carter et al., 1998).

Clinical Applications of Event-Related Brain Potentials

Clinical studies with ERPs have not fulfilled initial hopes and, as a general rule of thumb, ERPs have no utility in the diagnostic process of an individual patient. Nevertheless, a great number of ERP studies in clinical populations have been published, which have revealed important information about the information processing deficits of certain neuropsychichatric conditions.

P300 studies with normal elderly subjects have shown that the latency of the P300 becomes longer with increasing age and that this latency increase correlates with the general neuropsychological status of a subject (Polich and Kok, 1995). In patients with dementia, this latency increase is even more pronounced and a number of studies have provided evidence for a correlation between the cognitive decline and P300 latency. It is has been debated whether the latency increase might provide a useful clinical indicator (Polich, 1998).

Some studies have suggested that P300 amplitude and latency are valuable to distinguish between subcortical (e.g., Parkinson's disease, Huntington's disease) and cortical dementias such as Alzheimer's disease (Goodin and Aminoff, 1986). Another replicated finding is that the P300 can reliably distinguish between patients with dementia and those with a pseudo-dementia in the course of depression (Patterson et al., 1988). Other studies have used the P300 to investigate information processing in a variety of neuropsychiatric disorders, such as alcoholism, schizophrenia, depression, and multiple sclerosis. In general, a prolonged latency and/or amplitude decrement was seen for the patient groups. Thus, the P300 appears to be a very general measure to characterize information processing deficits in neuropsychiatric diseases. It lacks diagnostic specificity, however, which limits its use for differential diagnosis.

Mismatch Negativity (MMN)

In recent years, the MMN has been the most widely used ERP component in clinical studies. This is due to its good reproducibility and to the fact that the subject does not have to fulfill a task. It has been demonstrated in newborns (Kraus and Cheour, 2000) and therefore is of potential use for the investigation of developmental problems in the auditory system (Leppänen and Lyytinen, 1997). Another potential application is in the investigation of comatose patients (Kane et al., 1993) and it has been proposed that the MMN might be a superior predictor of outcome compared to other measures.

The MMN has been shown in group studies to reflect developmental problems in the perception of phonemes, which are related to a disturbed language development (Leppänen and Lyytinen, 1997) and developmental dyslexia (Kujala and Näätänen, 2001). In one study, Schulte-Körne and colleagues (1998) compared the MMN elicited by the syllables

/da/ and /ba/ with the MMN elicited by sine-wave tones of different frequencies. Dyslexic subjects showed a smaller MMN than controls for the syllables but a normal MMN for the sine waves. A strong genetic component has been revealed for dyslexia. In this regard the findings of Näätänen (2003) that babies of dyslexic parents already show abnormalities in the MMN to syllables is of great importance.

Only occasional reports concern the use of other ERP components in clinical context. An interesting study shows the potential utility of the N400 component for the characterization of aphasic disorders (Swaab et al., 1998). In this study Broca aphasics and normal control subjects were exposed to sentences ending with a potentially ambiguous word (e.g., “I put my money in the bank”). This sentence was followed by a test word that either was related to the meaning of the word primed by the sentence (e.g., *robber*) or to the alternative meaning (e.g., *river*). The word related to the alternative meaning gave rise to an N400 in normal subjects, suggesting that this meaning had been blocked by the sentence. In aphasics there was no N400 when the test word was presented immediately after the sentence, but the N400 was present when the word was presented with a considerable delay, indicating a temporal delay in sentence processing in the aphasics.

Slow Cortical DC Potentials in Neurocognitive Research

During the past two decades the investigation of cortical DC-potential shifts related to neuropsychological phenomena has increasingly attracted interest. The history of DC recordings supposedly dates back to 1875, when Caton was able to record epicortical DC potentials related to sensory stimulation in animals (a highly arguable claim). After Berger’s discovery, EEG research in humans focused on the phasic phenomena and was soon restricted to AC-coupled recordings (i.e., a time constant in the range of 0.3 to 1.5 seconds was used), but physiologists continued the tradition of DC recordings. In 1959, Caspers and Schulze demonstrated in long-term DC recordings the increase in negative cortical DC potential during the transition from sleep to awakeness and to motor activity in the freely moving rat. Astonishingly, although DC recordings during sensory stimulation and cortical processing of stimuli were pursued by physiologists (e.g., David et al., 1969), this method was not adopted by psychologists and neurophysiologists in testing more complex cortical functions and fell into oblivion for more than 10 years. The renaissance of DC recordings during cognitive, sensory, and motor processing in the late 1980s and in the 1990s was in part due to improved amplifier and electrode technology, which facilitated the recording and the management of artifacts (Bauer et al., 1989; Hennighausen et al., 1993; Tucker, 1993). However, in recent years fMRI has replaced EEG in most experiments investigating integrated neurocognitive functions on a longer time scale.

Therefore, we only briefly discuss the negative shifts in cortical DC potential during cognitive processing, and thereafter in anticipation of psychological or behavioral events.

Slow Waves and DC Potential Shifts During the Performance Interval as Correlates of Complex Cognitive Processing

When cognitive processing requires 1 second or longer, a large increase in the surface-negative cortical DC potential occurs. The topographical distribution of these DC potential shifts or “slow potentials” reveals task-specific patterns related to the cortical structures predominantly involved in processing of the required task. Thus, local changes in DC potential can be used for the functional brain imaging. Compared to short-latency event-related potentials up to 500 msec, the slow DC shifts reflect more global task-related processes. In Fig. 31.7 examples of task-specific activation

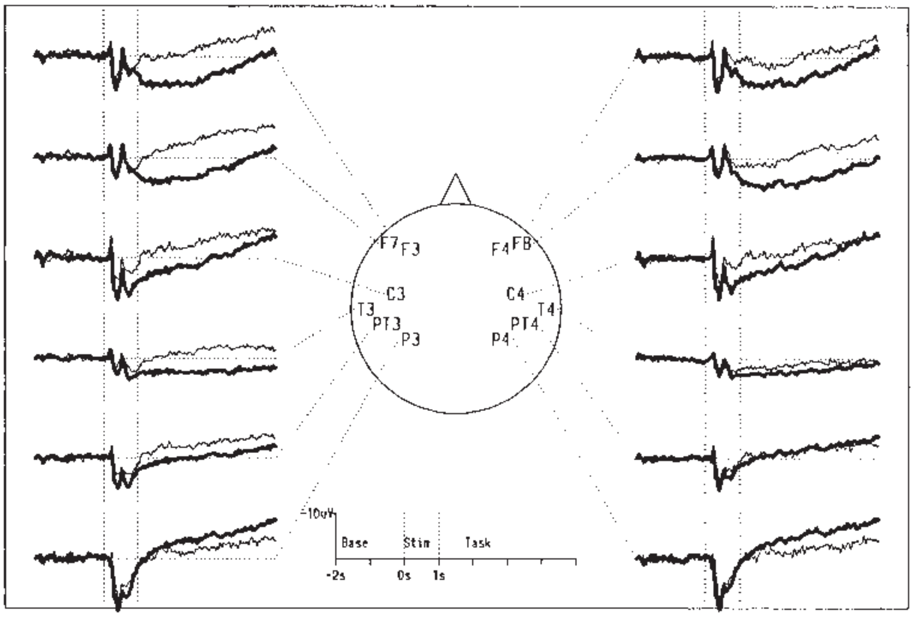

Figure 31.7. Grand-averages of DC-potential shifts during search for synonyms *(thin lines)* and during mental rotation of cubes *(thick lines)* in 16 male right-handed subjects. After recording of a 2-second baseline, stimuli are presented on a computer screen during 1 second. Subsequently, subjects perform the tasks during 4 seconds. Linguistic processing produces a marked increase in surface negativity over inferior left frontolateral brain regions, whereas visuospatial processing produces bilateral parietal activation.

patterns recorded with DC-EEG are displayed topographically. A linguistic task (thin lines) requiring mental search of synonyms to visually presented nouns and a visuospatial task (thick lines) requiring mental rotation of visually presented cubes are compared. The linguistic task causes an increase in DC negativity over the left inferior prefrontal cortex (electrode-position F7). In contrast, the mental rotation task produces maximal activation over the left and the right posterior parietal lobe (electrode positions P3 to P4).

The neurophysiological basis of slow negative DC shifts are long-lasting excitatory postsynaptic potentials at the apical cortical dendrites associated with a surface-negative, depth-positive electric dipole. The depolarization of apical dendrites, in turn, is dependent on sustained afferent input to layer I and/or simultaneous depolarization of large pools of pyramidal neurons (Caspers et al., 1984). The folding of about two thirds of the human cortex renders this simple relationship more complicated: negative-going DC shifts can only be recorded from scalp electrodes, when the sum vector of electric dipoles is perpendicular to the skull. This is the case when large cortical areas are activated during complex and sustained cognitive processes. In contrast, an activation of the planum temporale during decoding of verbal material produces an electric dipole tangentially to the surface of the temporal skull, which may be missed in surface electrode recordings from temporal or parietal locations. These restrictions, however, are common to all electrophysiological investigations of brain activity by means of scalp electrodes. Combination of EEG and MEG measurements, improvement of spatial resolution by multichannel recordings, and application of source localization algorithms with neurophysiologically guided modeling of sources (e.g., Scherg and Ebersole, 1993) have contributed to solve this problem in many respects (see Time and Space: Co-Registration of Synergistic Brain Imaging Results, below).

DC Potentials Related to Language Processing

DC potentials related to language processing were investigated with paradigms ensuring a sustained cognitive activity for several seconds (Altenmüller, 1989; Jung et al., 1984). As demonstrated above, mental search for synonyms produced a predominant activation over the left inferior prefrontal cortex, whereas the semantic category influenced activation patterns (Altenmüller et al., 1993a). Compared to abstract stimuli, search of synonyms to concrete semantic categories generated larger amplitudes over the parietal areas, due to an additional activation of visual association areas when processing highly imaginable words. The predominant activation of the left inferior frontal region is caused by inner speech, i.e., the subjects are silently formulating the synonyms. Correspondingly, in cerebral blood flow studies silent word processing produced an activation of the same cortical areas (Price et al., 1996). Investigation of right- and left-handed patients with known hemispheric dominance revealed that the frontal lateralization of sustained negative DC potential corresponds to hemispheric dominance for language (Altenmüller et al., 1993b); 93% of right-handed subjects ($n = 60$) but only 67% of left-handed subjects ($n = 45$) revealed left-hemispheric lateralization. Developmental changes of cortical activation patterns were found in experiments performed in 6- to 12-year-old children. In contrast to adults, only 60% of right-handed children exhibited left-hemispheric lateralization during the search for synonyms (Altenmüller et al., 1993c). This result supports Lenneberg's (1967) equipotentiality hypothesis, assuming a bilateral language representation in early infancy and a gradually increasing lateralization toward the left hemisphere during intellectual maturation.

Another aspect of language processing was investigated in a study on cortical activation patterns during processing of affective speech prosody (Pihan et al., 2000). Subjects had to identify the emotional category of sentences presented with happy, sad, or neutral intonation. While listening to these sentences, a right hemispheric frontotemporal activation occurred, suggesting that the right hemisphere has a dominant role for the evaluation of the emotional content of language.

Follow-up studies in patients with language disorders can give new insights into cerebral plasticity. In patients with anomic aphasia following left temporoparietal ischemia, DC potentials during the search for synonyms revealed an additional right frontocentral activation in the acute phase of the stroke. Along with complete clinical recovery, a marked decrease of right frontocentral negativity was found (Thomas et al., 1997). The transient activation of the right hemisphere in acute anomic aphasia might be due to an initial disinhibition of contralateral homologous areas and subsequent collateral sprouting and synaptic modulation. Alternatively, an activation of subordinate brain structures related to language processing may occur.

DC Potentials Related to Other Cognitive Functions

EEG correlates of music processing were investigated in a series of experiments. During melody processing, brain activation depends on musical expertise; nonmusicians tended to activate predominantly the right frontotemporal cortex, whereas professional musicians revealed an additional activation of left-hemispheric auditory areas (Altenmüller, 1986). These variations in auditory activation patterns were ascribed to different cognitive strategies and mental representations of music in trained or untrained listeners. Untrained subjects analyzed melodies in a contour-based global manner, a cognitive strategy that relies mainly on right-hemispheric neuronal networks (Heinze et al., 1994). Professionally trained listeners are able to use verbal strategies and inner speech. Furthermore, trained musicians tend to analyze melodies in a sequential interval-based manner, a strategy depending predominantly on left-hemispheric neuronal networks (Altenmüller, 2003). Besides musical expertise, emotional valence during music listening may influence lateralization patterns. When music is eliciting positive feelings, a left-sided frontotemporal lateralization can be observed, and negative feelings are accompanied by a right hemispheric preponderance (Altenmüller et al., 2002). These EEG-findings support the valence hypothesis of affective processing, saying that positive emotions are primarily processed in the left hemisphere and negative in the right hemisphere (Davidson, 1999).

In longitudinal studies during acquisition of musical skills, it could be demonstrated not only that brain plasticity during learning can be monitored with EEG, but also that the method is sensitive enough to record differences in declarative and procedural processing strategies (Altenmüller et al., 2000). The impact of specific musical skills on brain activation patterns is impressively documented in longitudinal studies during piano training. Piano playing requires high-speed control of complex movement patterns under continuous auditory feedback. As a prerequisite, audiomotor integration at cortical and probably subcortical levels has to be established. This audiomotor coupling, which is comparable to the oral-aural loop in language processing, is established after as little as 20 minutes of training, demonstrated by topographic analysis of DC-EEG potentials (Bangert and Altenmüller, 2003). After the first training session, there was additional activity over motor areas while subjects listened to simple piano tunes. Likewise, finger movements on a mute keyboard were associated with an increase of activity over auditory areas. The effect could be enhanced and stabilized during 5 weeks of training. Similar coactivation has also been demonstrated in professional pianists, who displayed magnetoencephalographic activity in sensorimotor cortical regions while listening to piano music (Haueisen and Knösche, 2001). These neural networks thus appear to behave similarly to the so-called mirror neurons in monkey frontal cortex (area F5) that are active during the execution of complex movements as well as the visual observation of the same movements (Umilta et al., 2001).

DC potentials during different learning paradigms were investigated by the Vienna group. M. Lang et al. (1987) demonstrated a task-specific left frontal negativation when subjects had to learn to transform letters into Morse code. Similarly, a left frontal negativation occurred when subjects had to learn word pairs and nonword pairs. Compared to nonwords, the left frontal negativation was considerably larger when meaningful word pairs had to be learned (W. Lang et al., 1988). In a subsequent study, Uhl et al. (1990) were able to demonstrate that frontal activation during paired associate learning is sensitive to interference; when the word pairs to be learned interfered with previously learned word pairs, the left frontal negativation was significantly more pronounced during learning compared to the no-interference condition. The role of the left frontal lobe in the learning studies cited above remains speculative. As discussed in this paper and in accordance with experiments assessing DC shifts during search for synonyms (Altenmüller, 1989), it is probable that silent speech during internal reverberation contributes to the left frontal activation.

Long-term memory function is another field investigated with DC-EEG recordings. Rösler and co-workers (1993, 1997) found during long-term memory retrieval a task-specific topography of surface negative slow potentials. A plateau-like negativity was found over frontal areas with semantic material, over parietal areas with spatial material, and over occipital areas with color material. The amplitude of the negative DC potential was found to be systematically related to the difficulty of the retrieval process. From the results it can be concluded that cortical neuronal networks involved during explicit memory retrieval are also those necessary for perception.

In conclusion, the measurement of sustained cortical DC potentials provides an excellent tool for the noninvasive assessment of cortical activation patterns during various types of cognitive processing. Furthermore, monitoring of the dynamic changes in cortical activation patterns provides information on neural mechanisms underlying learning and cerebral plasticity.

Slow Potentials in Anticipation of Events: The Contingent Negative Variation and the Bereitschaftspotential

As mentioned above, changes in cortical DC potential during sensory processing were known from physiological experiments but were ignored by neurologists and psychologists for a long time. In the middle and late 1960s, their research focused on slow potential shifts in anticipation of motor or cognitive performance. In 1964, Grey Walter and co-workers recorded a negative-going DC shift when a first stimulus or warning stimulus (S1) was followed by a second stimulus or imperative stimulus (S2) that required a motor response. The negativity started to rise 200 to 500 msec after S1 and terminated after S2. This slow potential shift was termed by Walter et al. (1964) the "contingent negative variation" (CNV) and was believed to be related to conditioning, preparation, and expectancy (therefore labeled sometimes "expectancy wave"). Around the same time, Kornhuber and Deecke (1965) described a negative-going slow potential shift starting about 800 to 1,000 msec prior to self-initiated movements. This potential was named "Bereitschaftspotential" (readiness potential) and was related to the "internal event" of a decision to act. We will give only a brief summary concerning their psychophysiological aspects. CNV studies in the field of psychiatric and neurological disorders will not be reviewed here.

The CNV: Expectancy and the Allocation of Cortical Resources

The experimental paradigm that most reliably elicits a CNV consists of a warning stimulus (S1) followed by an imperative stimulus (S2) one or several seconds later to which the subject is required to respond. This response does not need to be motor, and can be any type of cognitive performance, e.g., mental arithmetic. In general, the amplitude of the CNV increases with increasing probability of the occurrence of S2 and with increasing difficulty to discriminate S2. An aversive S2 causes higher amplitudes when compared to a neutral one (Knott and Tecce, 1978). Equally, a highly incentive value of the response produces an increase in amplitude, whereas no task or response following the S2 causes a decrease of CNV negativity. When the S1-S2 interval is extended to 3 or more seconds, a biphasic CNV with an initial negative peak, an intermittent positive slope, and a terminal negative slope emerge. The topography of these two negative components can be distinguished. Whereas the initial negative wave, also termed iCNV, exhibits an almost modality-independent distribution with the largest amplitudes over the frontal lobes, the terminal negative slope (tCNV) reveals a widespread surface distribution with maximal amplitudes over the brain regions involved in the anticipated tasks (Rohrbaugh et al., 1976, reviewed in Rockstroh et al., 1989, pp. 99-125). A motor response with the right hand, for example, elicits a maximal tCNV over the contralateral precentral region. The cerebral generator structures of the CNV cannot be localized with certainty. Animal experiments show that a CNV linked to a motor response is generated in the prestriate and prefrontal cortices contralateral to the moving hand. This activation, however, depends on an intact cerebrocerebellar loop and is abolished when cerebellar hemispherectomies are performed (Sasaki and Gemba, 1984). In humans, it is thought to be controlled by the basal ganglia-thalamocortical loop involving a complex interaction among incoming sensory inputs, motor initiation, output, and personal expectations (Ikeda et al., 1994).

Different and in many conditions certainly overlapping psychophysiological mechanisms seem to underlie the CNV. Walter and colleagues interpreted the CNV as a sign of expectancy. Evidence was provided by the increasing amplitude of the CNV with increasing stimulus probability. Tecce and co-workers related the early negative wave of the CNV to arousal, and the late negative slope to attentional processes. Finally, considering that an aversive S2 or a highly incentive S2, e.g., in the context of monetary reward, yields larger amplitudes of the CNV, the CNV was supposed to reflect motivational states (Rebert et al., 1967). An interesting feature of the late negative slope of the CNV is its area-specific cortical distribution, which apparently reflects task-specific preparation and allocation of resources (Birbaumer et al., 1981, 1988; Lutzenberger et al., 1985). The term *resources* has to be understood as the amount of processing facilities available in a defined time interval to optimize cortical function. The implications of this anticipatory activation is discussed below in the context of the threshold regulation model (Birbaumer et al., 1994).

The Bereitschaftspotential (BP) and the Decision to Act

The Bereitschaftspotential (BP) is a ramp-like negative-going DC shift that precedes a self-paced voluntary motor activity. According to the time course and the scalp topography, Deecke et al. (1969) distinguished four components of the BP: (a) a bilaterally symmetrical negative going ramp-like potential with maximal amplitude over the vertex starting 500 to 1,000 msec prior to electromyogram (EMG) onset (BP in the strict sense); (b) a contralateral preponderance of negativity over the precentral and parietal areas, starting about 200 to 500 msec prior to EMG onset; (c) a small positive deflection beginning around 90 msec prior to the EMG onset with a maximal amplitude over the postcentral areas (premotion positivity, PMP); and (d) a smaller negative potential starting about 50 msec prior to EMG and predominating over the primary motor cortex (motor potential, MP). It must be stressed that these four components are not present in all subjects and that superimposition may complicate the scalp configuration of the compound potential. There is still some debate on the generator structures of these components. The first bilateral negative shift seems to be generated in the supplementary motor area within the mesial cortical surface of both hemispheres (Deecke and Kornhuber, 1978; Kristeva et al., 1991). The second lateralizing component is probably generated in the primary motor and the postrolandic sensory areas (Neshige et al., 1988). The generator structures of the PMP are not clear. This component is supposed to reflect the deactivation of precentral areas (Deecke et al., 1984), but animal experiments and MEG studies could not prove this hypothesis so far. The motor potential finally seems to be closely related to the pyramidal tract volley, initiating the movement.

According to the generating structures, the amplitude and topography of the BP depend on the type of movement and on the muscle group to be activated, but complicating the situation to a large extent are psychological variables. In most studies, the BP amplitude is positively correlated with the force of different voluntary isometric contractions (Becker and Kristeva, 1980; Wilke and Lansing, 1973). However, as discussed by Rockstroh et al. (1989, pp. 95-98), it is not easy to decide whether the physical parameters themselves or psychological variables, e.g., motivation or attention, cause these effects. McAdam and Seales (1969) showed that BP amplitudes were larger when the motor response was associated with a financial reward. The outcome result of the movement considerably influences the amplitudes of the BP. When the voluntary response was followed by a painful shock, the BP amplitude was four times higher as compared to the responses followed by a neutral tone (Elbert et al., 1984). Task complexity, skillfulness of the movement, and learning influence the amplitude of the BP as well. Rockstroh et al. (1989, p. 98) pointed out that “the BP should rather be considered in terms of action-preparatory processes in which motor preparation may be but one component.”

Traditionally, the BP was related to the intentional decision processes of willed action. In intriguing experiments Benjamin Libet et al. (1983) demonstrated that the BP starts about 350 msec prior to conscious awareness of the intention to act. When the subjects “vetoed” their decision to act, the BP, which had normally developed prior to this veto, collapsed and no motion occurred. Libet (1985) concluded that voluntary acts can be initiated by unconscious cerebral processes before conscious intention appears, but that conscious control over the actual motor performance of the acts remain possible. This experimental design has had a long and often controversial history; after all, it has remained unclear whether the urge to act and the action itself represent actual differences in brain states (for a concise review see Eagleman, 2004).

Slow Potentials and the Cortical Threshold Regulation Model

In all the studies presented so far, changes in brain potentials were considered as a dependent variable associated with varying behavior. A different approach was chosen by Bauer (1975) when he developed the “brain-trigger design.” He presented a learning task in which the subjects had to learn nonsense syllables. The task presentation was triggered by either the absence or presence of alpha activity. Bauer was able to demonstrate that the ability to learn is increased in the absence of alpha but reduced in the presence of alpha. In a further-developed approach, the level of cortical DC potential was used as a trigger. During high-level cortical negativation, paired associate learning of syllables and numbers was considerably facilitated as compared to learning during positive shifts (Bauer and Nirnberger, 1980). Similar results were obtained in experiments manipulating the local distribution of negative DC potentials with biofeedback (Elbert et al., 1980). Subjects were required to watch a television display on which a small rocket moved from left to right over a period of 6 seconds. The task was to direct the rocket into one of two goals; which goal to take was indicated by a simultaneously presented high- or low-pitched tone. Without the subject's knowledge, the trajectory of the rocket was governed by the DC shift produced during watching the rocket. Within 60 to 160 feedback trials on the average, subjects had learned to control their DC level and were able to direct the rocket into the goal required.

Further experiments demonstrated that subjects could acquire hemisphere-specific control of DC potentials mainly over the central region. The level of surface-negative potential influenced behavior and speed of cognitive processing. Left precentral negativity improved tactile performance and response speed of the right hand and vice versa (Rockstroh et al., 1990). Birbaumer and colleagues (1994) interpret these results in the context of a threshold regulation model; whether a given neuronal network or cell assembly will be activated—"ignited"—by a stimulus or not depends on the threshold of the neuronal assembly. Cortical DC potentials are the objective measure of such thresholds: negativity represents lowering and positivity represents augmenting of thresholds. The local threshold of a certain neuronal assembly is determined by priming: stimuli indicating that a certain cognitive operation will be required in the future initiate a local lowering of thresholds reflected in an increase in negative DC potential. Threshold regulation can be trained via biofeedback. Using operant conditioning, Birbaumer and colleagues developed a thought translation device that trains locked-in patients to self-regulate slow cortical potentials of their electroencephalogram. After training, patients otherwise unable to communicate can select letters, words, or pictograms in a computerized language support program (Kübler et al., 2001).

Time and Space: Co-Registration of Synergistic Brain Imaging Results

> All our space-time verifications invariably amount to a determination of space-time coincidences. (Einstein, 1916)

As Albert Einstein pointed out, the timing of events, particularly their simultaneity, has no meaning except in relation to a given coordinate system. With respect to the study of complex brain functions, we may translate this into the necessity of considering both the time course and the topographical distribution of neuronal activation. Especially for the understanding of higher cognitive functions, technologies are required that are capable of measuring moment-by-moment changes in the distributed networks that are adaptively configured in response to environmental demands and in the context of purposeful behavior.

During the past 20 years, rapid advances have been made in functional neuroimaging techniques such as PET and fMRI. Their spatial resolution reaches several millimeters, but their effective temporal resolution has remained in the range of seconds or minutes. Only EEG and MEG provide a temporal resolution in the millisecond range, and thus can be used to analyze the rapidly changing neuronal activity that generates complex behavior. The amount of spatial information that can be recovered from the scalp-recorded EEG or MEG has often been underestimated. In the last decade, this situation has prompted a number of research laboratories to aim at an improved spatial resolution of these techniques. Without questioning the fundamental limitations of inferences about electrical sources that may be obtained from scalp-recorded brain electrical or magnetic activity, we have learned that cortical generators of EEG or MEG signals can be determined with centimeter or even subcentimeter accuracy (Cohen et al., 1990; Gevins et al., 1994; Gerloff et al., 1997c).

There are at least three general approaches that have been utilized to increase the reliability of spatial information obtained from scalp recordings: (a) improving the spatial accuracy of the electrical or magnetic data themselves; (b) comparative electrophysiological and imaging studies (Cohen et al., 1997; Manganotti et al., 1998; Rodriguez-Fornells et al., 2002b); and (c) direct co-registration techniques to combine results from different neuroimaging techniques, e.g., EEG and fMRI (Gerloff et al., 1996; Ullsperger and von Cramon, 2001; Opitz et al., 1999, 2002), or MEG and PET (Walter et al., 1992).

Improving the Spatial Accuracy of EEG and MEG

The traditional 10–20 system of electrode placement with only 19 channels results in interelectrode distances of typically 6 to 7 cm, and limits the spatial resolution of the EEG substantially. The major advances in computer technology within the past 20 years now allow recordings of more than a hundred channels simultaneously (currently up to 256 for EEG, up to 306 for MEG), so that with both EEG and MEG whole-head recordings at interelectrode distances of 3 cm and less can be practically accomplished. This is within the 3-dB point on the cortex to point on the scalp spread function, that is, within the size of the scalp representation of a small, discrete neuronal source at the level of the cortex (Gevins, 1990). The appropriate number of channels, however, is not an absolute number. It relates to the spatial distribution of the EEG or MEG component under study. The optimal interelectrode spacing for any given component can be mathematically determined by means of the spatial Nyquist value (Spitzer et al., 1989; Gerloff et al., 1997b). Figure 31.8 illustrates the gain of topographic resolution for a movement-related cortical potential (MRCP), when the channel number is increased from 28 to 122. Only with high-resolution EEG, it is possible to differentiate between discrete bilateral activation foci over the sensorimotor regions.

In addition to the appropriate number of recording channels, the surface-recorded electrical or magnetic signals can be spatially deblurred. This is particularly important for EEG data, since the inhomogeneous volume conduction properties of the different compartments of the human head distort the electrical field on its way from the brain to the

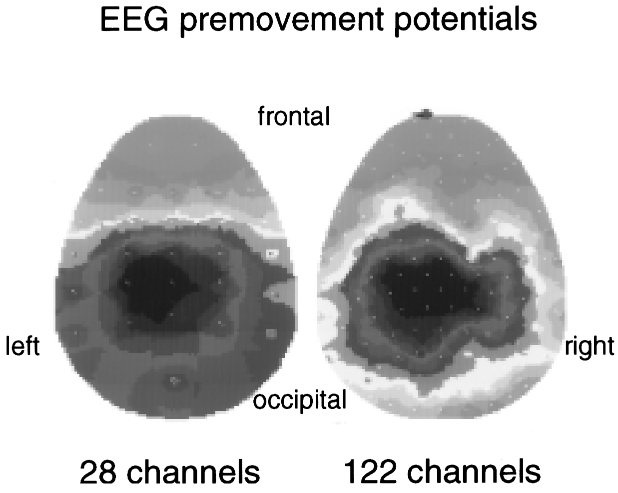

Figure 31.8. Topographic maps of the premovement component [60 msec before electromyogram (EMG) onset] of movement-related cortical potentials associated with finger extensions of the right hand at a movement rate of 2 Hz (Gerloff et al., 1997). Data from one subject. Only the 122-channel recording discriminates clearly two separate activation maxima (negative peaks, blue) over the sensorimotor region of the left and right hemisphere. With 28 channels, the potential map could as well be generated by a single activity focus in the left hemisphere close to the midline.

outside of the head. There are a number of methods for reducing this distortion, from the computationally simple to the very complex. The spatial *Laplacian operator* lies at the simpler end. As the second derivative of the potential field in space, it is proportional to the current entering and exiting the scalp at each electrode site, and makes the recorded field independent of the location of the reference electrode. A simplified version of computing the Laplacian derivation assumes an equidistant and rectangular electrode montage AQ7 (Hjorth, 1975), but computations based on the true interelectrode relations have become available and are more accurate AQ7 (Le et al., 1994). Computationally more demanding are methods such as finite element deblurring (FED) (Gevins et AQ7 al., 1994), a mathematical spatial enhancement procedure that uses an anatomically realistic model of the passive conducting properties of each subject's head and the finite element method to estimate potentials at the cortical surface from scalp potentials. The more sophisticated spatial localization methods have in common that they take into account the individual anatomy of each subject studied (Yvert et al., AQ7 1995; Bara-Jimenez et al., 1998, Mirkovic et al., 2003), so that they inherently require co-registration of electrophysiological and anatomical (MRI) data. Figure 31.9 shows a three-dimensional (3D) reconstructed cortical surface together with the corresponding realistic head model, which was computed on the basis of the MRI (Curry software, by Philips, Germany).

Comparative Electrophysiological and Imaging Studies

In many instances, fMRI or PET studies have identified brain regions that are activated during a particular task, but left questions open with regard to the time course of activation, the functional coupling ("crosstalk") between activated areas, and the functional relevance of each regional activation for successful behavioral output. Evidently, all of the latter aspects are essential in order to reveal the cortical processes underlying complex cognitive behavior. The missing information can often be obtained from comparative electrophysiological studies. While it is desirable but not always mandatory to study the same group of subjects with the different methods, the paradigms must be designed as similarly as possible to allow for correlative interpretation of the results.

A good example of how comparative electrophysiological and imaging studies can complement each other is a set of PET, EEG, and transcranial magnetic stimulation experiments that were aimed at the understanding of neuronal plasticity across different sensory modalities in blindness (Sadato et al., 1996; Cohen et al., 1997, 1999; Koyama et al., 1997). AQ7 Blind subjects who lost their vision early in life have an extraordinary capability for tactile discrimination. The most impressive evidence for that is the speed at which they read Braille. The neural basis for this particularly developed skill has not been known until recently. The first finding in this series of experiments was that the primary visual cortex showed increased regional cerebral blood flow (rCBF) during Braille reading in group of blind subjects, but not in a sighted control cohort (Sadato et al., 1996). AQ7 This was rather unexpected and exciting since the visual cortex in these blind subjects had never received any meaningful visual input and was thought to be mute. It was therefore suggested that, as a consequence of plastic reorganization of the "blind brain," the visual cortex might have acquired so-

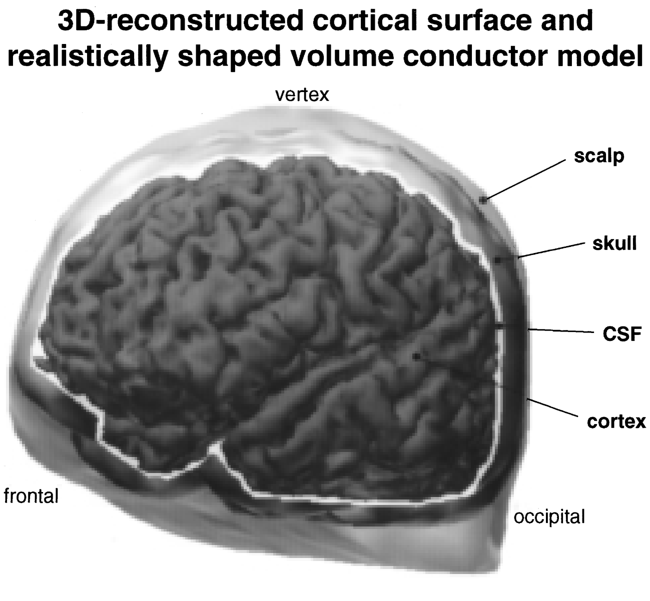

Figure 31.9. Three-dimensional reconstruction of the cortical surface, embedded in a realistic head model. Both were computed on the basis of magnetic resonance imaging (MRI) data that were acquired in a conventional 1.5-Tesla scanner. Note the variable thickness of each single layer [cerebrospinal fluid (CSF); skull; scalp] of the head model. This approximation of the true anatomical head shape and individual anatomical details enhances the spatial accuracy of inverse problem solutions substantially.

matosensory functions. From the PET data alone, it could not be determined if the visual cortex is in fact part of the functionally coupled network that mediates Braille reading. A subsequent EEG study demonstrated coherent oscillatory activity between occipital and central regions during Braille reading in the blind (Koyama et al., 1997), supporting the hypothesis that the activation of the visual cortex is functionally coupled with the activation of the sensorimotor cortex and therefore most likely behaviorally meaningful.

The remaining question, namely, how crucial is this regional activation and network-like integration of the visual cortex for the behavioral output, could be addressed using repetitive transcranial magnetic stimulation (rTMS) over the visual cortex (Cohen et al., 1997). Stimulation of cortical areas with rTMS can transiently disrupt specific cognitive functions, such as naming objects (Pascual-Leone et al., 1991), performing complex finger movement sequences on a piano (Gerloff et al., 1997a, 1998), or sensory functions, e.g., auditory perception (Plewnia et al., 2003). Cohen et al. (1997) showed that temporary disruption of the function of the visual cortex induced errors during Braille reading in blind subjects, but did not interfere with any form of tactile discrimination in the sighted control group.

The integration of PET, EEG, and rTMS provided, therefore, for the first time, evidence that brain plasticity across sensory modalities is involved in functional compensation. Figure 31.10 gives a schematic drawing of combined PET, EEG, and TMS results in a blind subject.

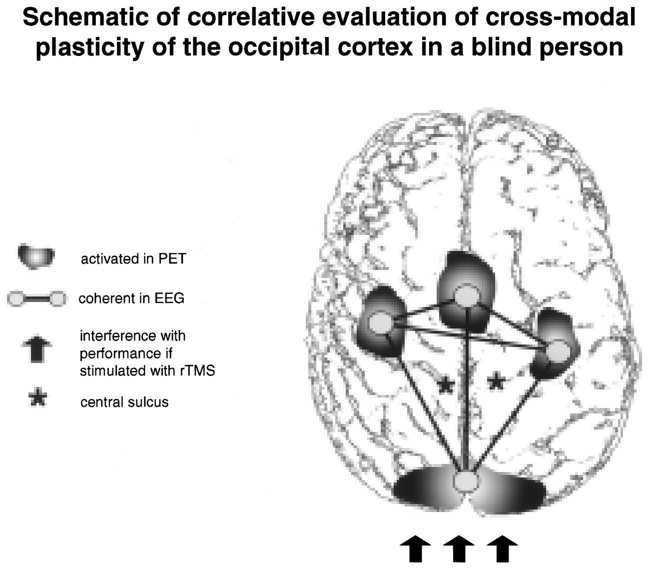

Figure 31.10. Plastic reorganization of the visuomotor system. Schematic of correlative positron emission tomography (PET), EEG, and repetitive transcranial magnetic stimulation (rTMS) results in a blind subject. The multimodal approach allows for a detailed analysis of the phenomenon of cross-modal plasticity. The occipital ("visual") cortex in people who lost their vision early in life appears to be integrated into the cortical network that mediates tactile discrimination skills (e.g., Braille reading). This type of plasticity is most likely relevant for functional compensation (Sadato et al., 1996; Cohen et al., 1997; Koyama et al., 1997).

Co-Registration

Other than with comparative group studies, formal co-registration must be based on the acquisition of data with different techniques in the same individuals. Since task-related neuronal activation patterns and, to a certain extent, even anatomical features in an individual brain are subject to dynamic changes, the data to merge should be acquired within a narrow time window.

A first and fundamental step of co-registration is to combine functional and anatomical images. For example, Gevins et al. (1990) have mapped the spatial distribution of scalp-recorded EEG data onto the cortical surface, and Reite et al., (1988) have mapped MEG dipole sources onto MR images. Commercial software is now available to accomplish this type of co-registration, which most likely will become a standard procedure in whole-head MEG and high-resolution EEG in the near future. Figure 31.11 gives an example of MEG-MRI co-registration in a motor paradigm (Gerloff et al., 1997c). Less well established is the technique of co-registering several types of functional data together with anatomical images (Walter et al., 1992; Toro et al., 1994; Beisteiner et al., 1995; Gerloff et al., 1996; Wassermann et al., 1996). The latter, however, provides the most comprehensive view into complex brain function, since it allows for a coherent description of subsecond changes in neuronal activity with subcentimeter spatial accuracy (Nunez and Silberstein, 2000; Thees et al., 2003).

Any given 3D measurement (e.g., EEG potentials distributed over the scalp, rCBF changes in the brain as demonstrated by PET) has its own reference coordinate system. Two or more 3D measurements can be brought together by

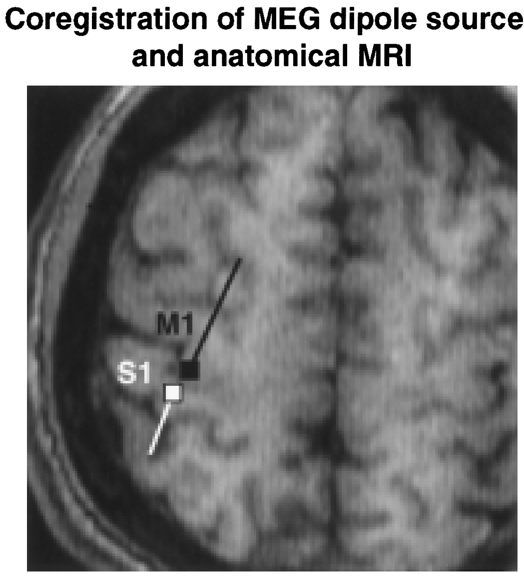

Figure 31.11. Co-registration of the equivalent current dipoles (ECDs) in the primary motor (M1) and primary sensory (S1) cortex. The ECDs were computed from movement-related magnetic fields associated with repetitive movements of the right thumb and co-registered with the high-resolution anatomical MRI of the individual subject. Note how M1 and S1 ECDs are located just anterior and posterior to the central sulcus of the left hemisphere.

matching a minimum of three common points, usually referred to as *fiducial markers*. Typical fiducial markers are the nasion, the left and right preauricular points, and the inion. For EEG and MEG measurements, these points can be registered together with electrode or sensor positions by means of a commercial magnetic digitizer, with an accuracy of about 3 mm (Gevins et al., 1994). Since the position of a 3D volume in space is unambiguously defined by three points, this approach is theoretically accurate and simple to implement. In practice, its disadvantage is that for co-registration the landmarks need to be localized in the anatomical MRI by hand (with a cursor). This can be ambiguous and cause inaccuracies in the centimeter range, particularly with respect to the anterior-to-posterior position of the preauricular points and to the lateral position of the nasion or inion. It is therefore recommended to mark the reference points with a paramagnetic (MR signal-intense) substance (e.g., vitamin E capsules; commercially available adhesive "fiducial markers"), before the subject is studied in the MR scanner.

Alternatively, it is possible to digitize a large number (e.g., 1,000) of randomly located points on the scalp surface. The head surface reconstructed from these points can be mathematically matched with the head surface of the same individual as extracted from the high-resolution MRI. This method of determining a "best fit" between digitized and MRI-derived head surfaces is computationally intensive but less subjective, and the spatial co-registration errors are as small as 2 to 3 mm (Wang et al., 1994). Once the digitized coordinate system of the ("real world") head has been matched with the anatomical MR images, the electrophysiological data can be mapped onto the scalp surface, and can be related to the underlying brain tissue or the underlying activation foci in PET or fMRI. Despite the known coupling of neuronal activity and rCBF, it is rather unclear if we should really expect that electrical sources and rCBF maxima are exactly in the same location in the brain. For example, in a variety of studies cortical generators of movement-related electrical or magnetic fields were no closer to the centers of rCBF maxima than 4.0 to 20.0 mm (EEG vs. PET) (Toro et al., 1994), 18.6 ± 7.6 mm (EEG vs. fMRI) (Gerloff et al., 1996), 17.3 ± 6.3 mm (MEG vs. PET) (Walter et al., 1992), and 16.7 ± 6.8 mm (MEG vs. fMRI) (Beisteiner et al., 1995). Similarly, the localization of the primary motor cortex with transcranial magnetic stimulation differed by 5.0 to 22.0 mm from the corresponding PET activation maxima (Wassermann et al., 1996). It is likely that these discrepancies are mostly related to co-registration problems and the use of simple spheric rather than realistically shaped head models for dipole calculations. Other sources of co-registration inaccuracies include head motion during data acquisition in MRI and PET (Lee et al., 1996; Picard and Thompson, 1997), distortion of the real anatomy in MR images (Maurer et al., 1996; West et al., 1997), and changes of the brain position inside the skull depending on the head position (e.g., upright for EEG vs. supine in the MR scanner). Finally and perhaps most importantly, there might be a systematic difference between rCBF maxima and electrical generator locations, which needs to be further determined.

Recently, the correlations between electrical neuronal activity and rCBF (more specifically, the BOLD signal of fMRI) have been studied by simultaneous recordings from depth electrodes and metabolic changes inside a high-field 4.7-T MRI scanner in monkeys (Logothetis et al., 2001). These findings suggested that the fMRI signal reflects the input and intracortical processing of a given area rather than its spiking output. This is encouraging for EEG-fMRI co-registration because the EEG signal also reflects the processing of afferent information in apical dendrites [excitatory postsynaptic potential (EPSPs)] of pyramidal cells rather than spiking output. Thus, taking fMRI or PET data as a (tentative) reference for adequacy of locating regional activation noninvasively in the human brain with EEG, MEG, or magnetic stimulation is a valuable approach and should be aimed at in future experiments.

Despite the enormous progress in this field, co-registration of different functional imaging results still remains an experimental procedure. It needs further improvement, not only with respect to technical aspects, but even more so regarding our understanding of the different parameters measured, such as equivalent dipole sources of electrical and magnetic fields, the neural substrates of magnetic stimulation effects, and the relation of neuronal activity to rCBF and blood oxygenation level changes in different brain regions. It is important to be aware of some intrinsic limits for each single method that may, for theoretical reasons, be impossible to overcome. For example, increasing the EEG channel number further or improving the deblurring algorithms cannot master the mathematical problem of the ambiguity of inverse problem solutions. Or, with relevance to PET and fMRI, task-related rCBF changes occur relatively slowly and with some delay, which blurs the intrinsic hemodynamic response (Kim et al., 1997; Logothetis et al. 2001, 2004) so that rapid changes of neuronal activity within a few milliseconds will probably always go undetected in PET or fMRI. At present, co-registration techniques and comparative study designs, based on high-resolution electrophysiological and imaging methods, offer promising ways to bypass these limitations and thereby "relate time and space" in psychophysiological research.

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AQ1: AU: Pls verify chapter x-ref.
AQ2: AU: Ref list has Pfurtscheller, not Pfurtscheler. Align sp.
AQ3: AU: If the s in μVs stands for something, pls define; if it merely a pluralization, delete it. Units of measure that follow a number are not pluralized.
AQ4: AU: Dr. Neidermeyer: Quoting song lyrics is a tricky business because in some cases even very short quotations require permission. Irving Berlin, when he was alive, was notorious for turning down all requests to quote from his songs. If you want to keep this quotation, you will need to contact Berlin's publisher (Irving Berlin Music Company, part of the Hal Leonard group) to inquire about permission. It is easier just to delete this quotation.
AQ5: AU: ref list has 1999 for van Berkum et al., not 2001. Align hear.
AQ6: AU: ref list has 2001 for Botvinick et al., not 1999. ALign year.
AQ7: AU: supply reference.
AQ8: AU: define DFG.
AQ9: AU: Pls cite in text or delete the following 37 references: Bara-Jimenez, W., Catalan, M.J., Hallett, M., and Gerloff, C. 1998. Abnormal somatosensory homunculus in dystonia of the hand. Ann. Neurol. 44: 826–821
AQ10: AU: is 1993 OK for Hennighausen? You have 1992 and 1993 here, but text cites 1993.
AQ11: AU: Fix page range.