The future of high-resolution EEGs in assessing neurocognitive effects of mild head injury

The existence of a resting electroencephalogram (EEG) marker of mild head injury (MHI) has recently been demonstrated using recording and analysis techniques that are over 20 years old. The most advanced EEGs use information from magnetic resonance imaging to produce images of superficial cortical activity with split-second resolution of neurocognitive processes such as attention and working memory, and with spatial detail approaching that of O15 positron emission tomography scans. When they become more widely available in a few years, these high-resolution EEGs may prove quite useful in detecting and characterizing the often elusive cognitive disabilities of patients with MHI.

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APPROXIMATELY 800,000 people in the United States suffer a "minor" or "mild" head injury (MHI) each year, and up to 650,000 may suffer persistent cognitive, physiologic, and emotional symptoms.[1] For many decades, the medical validity of patients' complaints has been the subject of debate, since neurologic exams are typically normal,[2] and the extent of the complaints often seems disproportionate to the severity of the injury.[3] In recent years, however, neuropsychological studies have clearly documented deficits of visuomotor problem solving, immediate and delayed memory, and attention.[3-7] Neurologic explanations for these cognitive effects are largely derived from animal experiments, which have shown that the shear and tensile forces associated

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even with a minor traumatic event can cause axonal damage throughout the neuroaxis.[8-11] In humans, morphologic damage, when detectable on computed tomography (CT) or magnetic resonance imaging (MRI) scans[12,13] most often involves frontotemporal cortical regions. The site, extent, and persistence of damage is highly correlated with the severity of neurobehavioral deficits.[12] In most cases of MHI, however, persistent neurobehavioral symptoms are reported without corroborating evidence of structural damage.

Although there has been significant recent progress, many questions about MHI remain unanswered. For example, what is the neuronal basis for the fact that symptoms persist in some patients and not in others with seemingly comparable traumas? Is there a neuronal basis for differences in cognitive symptomatology, for example, deficits in selective attention, working memory, concentration, etc? Are there neuronal markers that are predictive of the degree of recovery to the preinjury level of cognitive functioning? Are there neuronal signs of the mechanism of recovery, that is, the degree to which functional reorganization takes place? Advances in imaging brain function may well hold the answer to these questions.

BRAIN IMAGING

PET and SPECT

Current techniques for imaging brain metabolism, such as positron emission tomography (PET) or single photon emission computed tomography (SPECT) are well suited for addressing many of these issues; but these imaging modalities have not yet been applied to study MHI in a substantial number of patients (see J.T.L. Wilson and D. Wyper, "Neuroimaging and Neuropsychological Functioning Following Closed Head Injury," in this issue for a detailed discussion). Changes in cerebral blood flow in moderate to severe concussion are biphasic, with an initial increase followed by about a 15% decrease several days postinjury.[14] In the few instances in which PET scans have been obtained in moderate to severe head injuries,[7,15] PET seemed to provide more information about the nature and location of pathology than either CT or MRI. Even with the detailed three-dimensional information about brain function that metabolic measurements could potentially provide about MHI, these techniques have a number of disadvantages, including an inability to provide the split-second temporal resolution needed to measure fundamental neurocognitive processes, such as preparatory attention and working memory, use of ionizing radiation, and high cost and relatively limited availability of scanner facilities.

EEG

Although measures of central nervous system activity from electroencephalograms (EEGs) have been made for over 60 years, the EEG's full potential as a brain-imaging modality is only now being realized due to accumulated advances in signal processing and computer technologies.[16-21] While even advanced EEGs [or magnetoencephalograms (MEGs)][22] cannot provide three-dimensional images throughout the neuroaxis in the same sense as those obtained with PET and SPECT, they have a number of compensating advantages of their own. Electrophysiologic measures are easily obtained, noninvasive, and inexpensive. They can be repeated as often as is necessary, and they provide a temporal resolution in the millisecond range needed to study fundamental cognitive processes that may be affected by MHI. Their spatial resolution of superficial cortical activity has also been dramatically improved recently, with 124 channel recordings and ap-

plication of signal enhancing procedures to reduce blur distortion due to transmission through the skull and other tissues.[23-25] Additionally, development and application of computerized pattern recognition procedures has produced new means of measuring the distributed cortical networks of neurocognitive functions (Gevins, unpublished data, 1992).[26-32] Thus, quantitative electrophysiologic techniques hold significant promise for the study of MHI.[33]

In general, the more advanced the quantitative EEG technology, the clearer and stronger the results in studies of MHI. For example, traditional qualitative clinical EEG polygraph evaluations have not been informative in MHI cases, generally reporting normal or equivocal findings.[33] By contrast, spectral analysis of the resting EEG (a simple computerized method of quantifying activity into different frequency bands) has revealed a lowering of the alpha band frequency and a reduction in the power of higher frequency beta band activity.[34]

Averaged sensory evoked potentials (EPs—another simple form of quantification in which the EEG is averaged to repetitive presentations of a stimulus) have proven more useful than qualitative EEG evaluations for assessing sensory dysfunction, monitoring progress, and predicting clinical outcome in the earlier stages of moderate to severe head injury.[35-38] Sensory EPs have been less sensitive to MHIs,[33] however, possibly because they measure subcortical and primary cortical sensory processing and not higher-order cognitive functions. Studies of other EP peaks and waves, which reflect aspects of attentional and cognitive processes while subjects perform tasks, have shown attenuation of N100 and P200 amplitudes, prolongation of P300 latencies, and marked changes in the contingent negative variation (CNV—a marker of preparatory attention) in patients with varying degrees of head injury as compared with healthy control subjects.[39-41]

Recently, an impressive quantitative EEG study was reported that performed spectral analysis on resting EEGs recorded at 19 scalp locations from 608 patients with MHIs.[42] Remarkably, there was about a 90% ability to discriminate MHI patients from controls in several independent replications. Furthermore, a high degree of accuracy was obtained in predicting the clinical outcome in patients with moderate to severe injuries.[43] The strength of these findings strongly suggests that there are consistent neurophysiologic markers of MHI. The authors propose a reasonable explanation of the significance of these findings, that is, that the findings signify "decreased cortical functional differentiation" due to diffuse axonal injury and localized contusions of grey matter. Further studies will be required, however, to verify this intriguing hypothesis. Considering that such promising results were obtained using recording and analysis technologies that are over 20 years old,[19] it is certain that application of more advanced recording and analytic methods to EEGs recorded while patients were engaged in tasks that tax the impaired cognitive functions will yield an abundance of new information about the neuronal basis of MHI.

HIGH-RESOLUTION EEG METHODS

Improved spatial sampling: Scalp electrode arrays with many channels

Until recently it was widely assumed that, due to the smearing effects of volume conduction through the skull, the 19 to 21 recording sites traditionally used in clinical EEG recordings were sufficient for sampling the useful spatial information contained in EEG signals. This is not the case, as has been clearly demonstrated by several investigators.[44-47] With 19 recording sites, the typical distance between electrodes on an average adult male head is about 6 cm; with 124 sites

(the largest number that has been used so far), the typical distance is 2.25 cm. This is a good improvement in sampling resolution, but further improvements are possible and needed. For example, use of 256 channels provides an interelectrode distance of about 1.6 cm.

Previous articles have described our traditional methods for recording EEGs from 124 scalp sites and measuring the three-dimensional position of each electrode.[24,46] Advanced systems for very rapid electrode placement and position measurement are currently being refined and tested, since the traditional method of manually attaching each electrode takes too long for routine use when over 30 or so electrodes are used.

Registering scalp electrode positions with underlying anatomical structures

In order to visualize the brain areas underlying the scalp electrodes, a procedure is needed for aligning scalp electrode positions and underlying anatomical structures. This first requires producing an accurate anatomical representation of a subject's brain from the MRI. To do this, we developed methods and software for automated two-dimensional contouring of individual MR images, with optional manual editing, followed by the construction of triangular three-dimensional surface elements between contours in adjacent images. Renderings of these surface models are created by using standard three-dimensional computer graphics techniques (see Fig 1). Previous articles have described our EEG-MRI alignment procedures, as well as our basic MRI analysis, recognition, and visualization methods.[24]

Spatial enhancement

Electrical currents generated in the brain are volume conducted through brain cerebrospinal fluid (CSF), skull, and scalp to the recording electrodes. Because of this, potentials due to a localized generator are spread over a considerable area of scalp, and the potential measured at a scalp site represents the summation of signals from many generators over much of the brain. We have developed two spatial enhancement methods to correct this blur distortion without a priori assumption of an arbitrary generator model.

The simpler method computes an accurate estimate of the surface Laplacian derivation (LD), which is proportional to local current flow into and out of the scalp.[49,50] This has the advantage of eliminating the effect of the reference electrode used for recording, and of eliminating much of the common activity due to either the reference electrode or volume conduction from distant sources. The disadvantages are that the LD does not produce valid values at the outermost ring of scalp electrodes, and it does not correct for local differences in skull thickness and conduction properties. The most accurate surface LD, which we have implemented, uses the measured-electrode positions and estimates the LD over the actual shape of the head using a three-dimensional spline interpolation algorithm.[25]

A further improvement in distortion reduction is possible by using a finite element electrical-structural model of the cortex, CSF, skull, and scalp to estimate the potentials that would actually be recorded on the surface of the brain. We call our implementation of this method finite element model deblurring (FEMDB) or simply deblurring (DB).[25] The price of the improvement offered by DB is that MRIs have to be recorded and processed and many more calculations have to be performed. DB is a true "downward continuation" method in that, without prior knowledge or assumptions about the number or location of generating sources, the cortical potential distribution is derived given the scalp potential distribution and a realistic model of the conducting volume between the scalp and cortical surfaces.

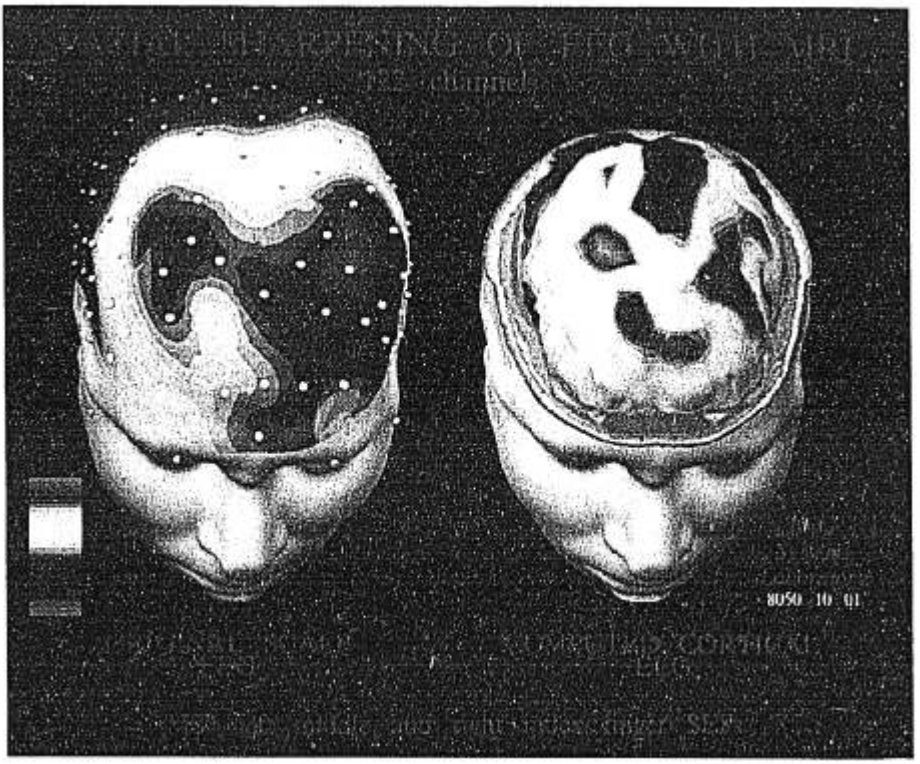
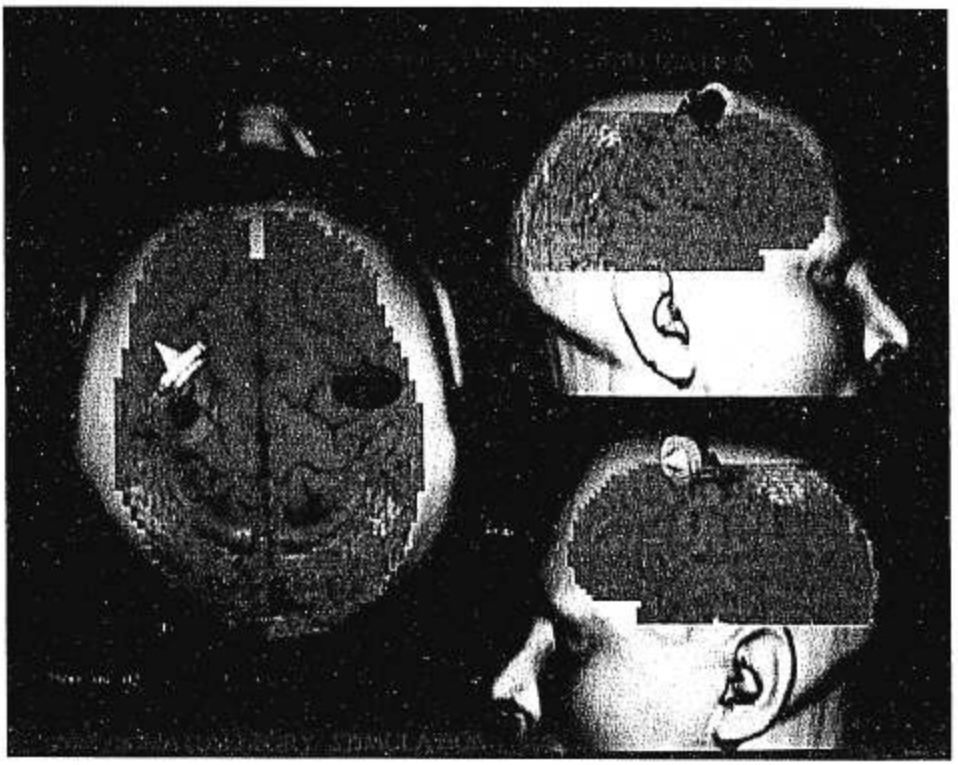


Fig 1



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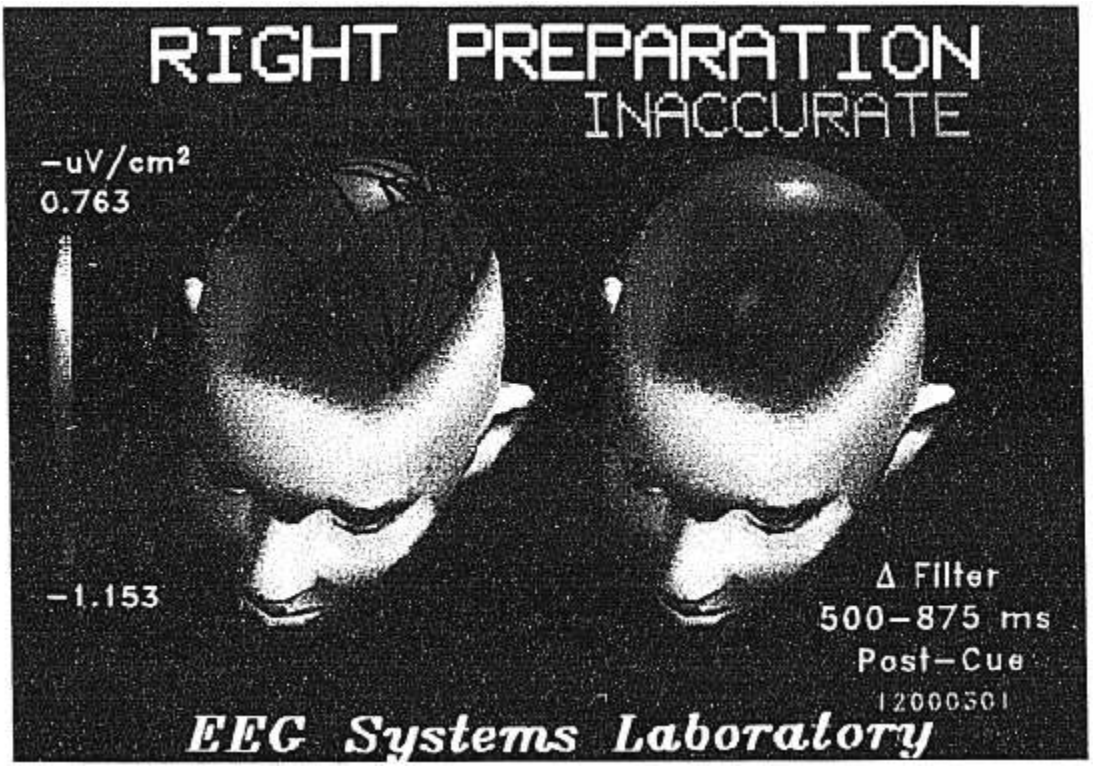
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Fig 3

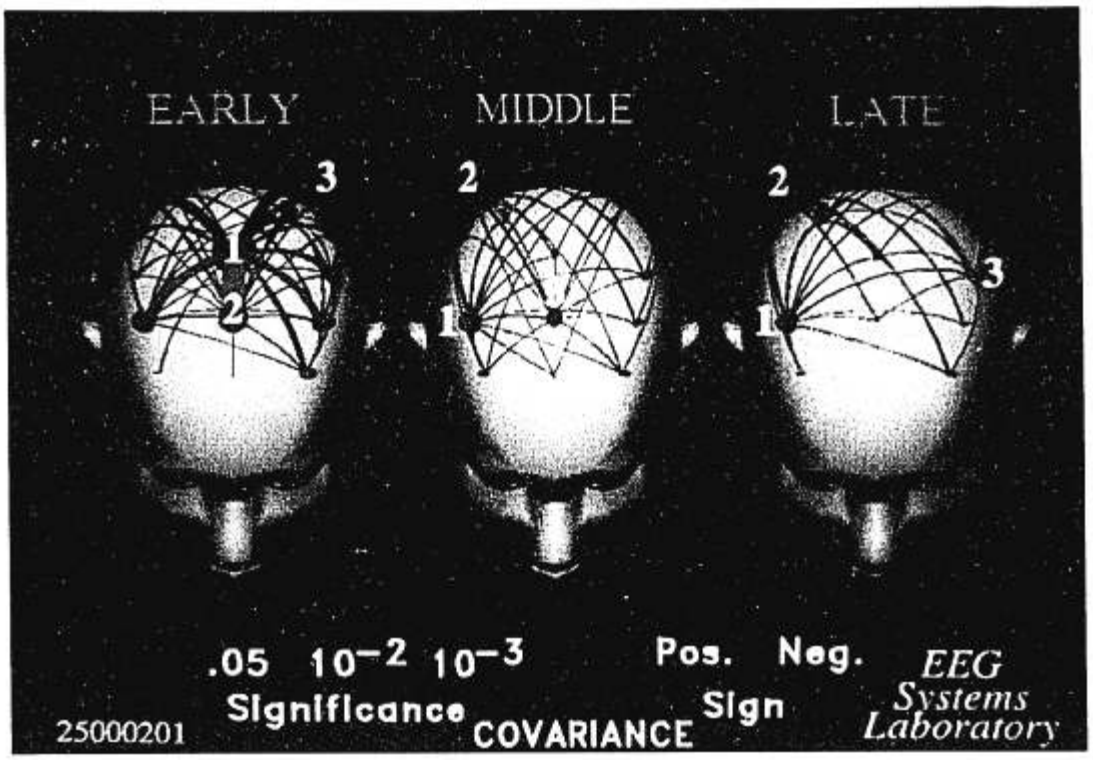
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Fig 4

An example of DB is shown in Fig 1 for a normal male subject whose left middle and right index fingers were stimulated electrically at 15 Hz. There is a major improvement in detail over the original scalp EEG data, and responses to the left and right fingers are appropriately lateralized and distinctly separated. Analogous results were obtained with

Fig 1. Steady-state EPs elicited by 15-Hz stimulation of left middle and right index fingers of a healthy control subject. The original scalp data, recorded from the 122 locations indicated by white dots, are shown on the left. The deblurred (computed cortical) EPs are shown on the right. An obvious improvement in detail is apparent in the deblurred EPs in that responses to the left and right fingers are more localized and are distinctly separated.

Fig 2. Point dipole modeling for each of three 15-Hz somatosensory stimulus conditions (left middle and right middle and index fingers—see Fig 1). Dipoles are shown with respect to the scalp surface and a cubic brain model constructed from the subject's MRIs. Each dipole is represented as a disk with its center on the dipole's location and with a cone pointing in the dipole's direction. Dipole color indicates stimulus as follows: left middle finger (blue), right middle (red), and right forefinger (yellow). Each dipole appears in the contralateral hemisphere, and the dipole for the forefinger is located slightly more lateral than that for the middle finger, consistent with the known locations of the somatosensory projection areas. Reprinted with permission from Gevins AS, Le J, Brickett P, Reutter B, Desmond J. Seeing through the skull: advanced EEGs accurately measure cortical activity from the scalp. *Brain Topogr.* 1992. In press. © 1992 by Plenum.

Fig 3. Preparatory cortical functional association patterns (colored lines) preceding, by 0.5 to 1 second, accurate (left) and inaccurate (right) responses. Data are shown from seven right-handed men. The thickness of an "event-related covariance" line is proportional to its significance (from .05 to .005). A violet line indicates the covariance is positive, while a blue line is negative. Functional associations involving left frontal, midline precentral, and appropriately contralateral central and parietal sites are prominent in patterns for subsequently accurate right-hand responses. When this pattern is weak or absent, subjects' responses are likely to be inaccurate. Many errors, it seems, result from a failure to concentrate properly during the split-second before action. It would be most interesting to study patients with MHIs as they performed this task to assess subtle changes in their preparatory neurocognitive cortical networks. Reprinted with permission from Gevins AS. Distributed neuroelectric patterns of human neocortex during simple cognitive tasks. In: Uylings HB, Van Eden CG, De Bruin JP, Corner MA, Feenstra MG, eds. *Progress in Brain Research.* Amsterdam, Netherlands: Elsevier; 1990. © 1990 by Elsevier.

Fig 4. Prestimulus cortical functional association patterns of a working memory task recorded from 5 highly practiced subjects during a 14-hour period. The Early period (left) was during the first 6 hours; the Middle (center) was during hours 7 to 9, before performance had deteriorated; and the Late (right) was during hours 10 to 14, when performance was impaired. The pattern globally declined in magnitude from Early to Middle to Late periods. The configuration of the pattern also changed, however, with the emphasis shifting from the midline central (1), midline precentral (2), and left parietal (3) sites to right hemisphere sites. This suggests that, in addition to the well-known global decrease in neural activity accompanying prolonged mental work, there are also changes in the topology of task-specific functional networks. Since MHI patients often report symptoms similar in many respects to those of mental fatigue, it would seem that this type of analytic paradigm would be quite useful in these cases. Reprinted with permission from Gevins AS, Bressler SL, Cutillo BA, et al. Effects of prolonged mental work on functional brain topography. *Electroencephalogr Clin Neurophysiol.* 1990;76:339–350. © 1990 by Elsevier.

partial visual field and auditory stimuli.[25] Results of applying DB to the data from a patient with pharmacologically intractable seizures demonstrate good agreement with the actual cortical evoked potentials measured with a grid of subdural electrodes.[25]

Equivalent point source localization

As used in brain imaging, a dipole is a mathematical model of hypothetical point source of electricity that can account for the EEG measured at the scalp.[51] Although dipole models are not physiologically realistic, they are nonetheless useful for locating the center of mass of primary sensory cortex activated by a stimulus. Dipole modeling was performed for each of the two finger stimulus conditions described previously plus stimulation of the right index finger. Fig 2 shows the dipoles with respect to the scalp surface and a cubic brain model constructed from the subject's MRI.[24] Each dipole appears in the contralateral hemisphere, and the dipole for the right forefinger is located slightly more lateral than that for the right middle finger, consistent with the known locations of the sensory projection areas.

Eliminating artifacts

It is essential to eliminate artifactual contaminants from EEG recordings prior to quantitative analysis. These artifacts can arise from both physiologic (eg, eye and head movements) and instrumental (eg, bad electrode) sources. Although many automated methods have been developed to do this, they are still far from perfect,[52] and visual review of the raw data on a graphics terminal is still necessary to confirm and improve the computer's detections as needed. In our studies with clinically healthy, young adult subjects, there is about 10% to 15% data attrition due to artifacts.

Preparing data sets to test for clinical effects

After the data have been cleared of artifacts, data sets are usually formed in pairs to test specific hypotheses, for example, normal versus impaired attention. In forming these data sets, it is of course crucial that the major differences between the two sets are related to the hypothesis being tested, and not to other irrelevant factors. While it is standard practice to try to eliminate irrelevant differences by careful experimental design, there is always the chance that some remaining factors differ between sets. These uncontrolled factors can include small residual eye-movement contaminants, arousal level, and response movement parameters (eg, force or reaction time), all of which are known to affect EEG signals. To ascertain that the major source of variance is actually related to the hypothesis, the statistical distribution of these possibly uncontrolled factors in the two sets of data must be examined and outlier observations, discarded. The net effect of these procedures is the certainty that when an EEG difference related to an experimental or clinical condition is found, the difference actually relates to the hypothesis under consideration.[53] This is not a point of only academic significance, since many published clinical studies using EEG (or PET) measures are less than satisfactory in this regard.

MEASURING NEUROCOGNITIVE PATTERNS

Model of the neural substrate of cognition

Our experiments are based on the idea that the neural substrate of cognition involves the integration of local processing across dynamic, distributed neuronal networks that are configured in response to task demands and prior experience.[26-31] The nature of our measurements stresses the split-

second dynamics of the cortical nodes of such networks. Other lines of research have also produced evidence supporting this idea. Metabolic methods such as regional cerebral blood flow (rCBF) and PET[54-56] have shown that each of the many types of mental tasks that have been studied ". . . increases blood flow in multiple cortical fields in homotypical cortical zones outside the immediate sensory association areas and, predictably, the constellation of cortical areas activated differs with different types of thinking or internal operations."[57] Based on clinical and neuroanatomic data, Mesulam[58] has formulated a model of interactive, multifocal neural systems, whose processing is both localized and distributed, and which specifies the networks likely to be involved in such a model for attention, language, and memory. We are empirically developing this type of model by directly measuring the formation and adaptation of neurocognitive cortical networks.

Measuring functional associations in distributed cortical networks

A stimulus induces a reorganization of ongoing neural activity as subsets of neural populations in specific loci become involved in stimulus-related processing.[58-61] The systematic relationship between pulse probability and extracellular field potentials[62] provides the basis for observing aspects of this reorganization in changes in EEG or EP amplitude or timing and relationships between sites.[63-68] In the case of a cognitive task stimulus, the time course of this reorganization manifests metastable configurations or "macrostates" that last up to several hundred milliseconds, demarcated by the stable topography of EP peaks and waves.[44] During each of these macrostates, a number of cortical and subcortical areas are active as nodes in a distributed processing network. We call measurements of the temporal coordination of processing between cortical nodes of these networks "functional associations." The term "functional associations" denotes a statistically significant, task-associated, concurrent activation of two cortical areas. We measure functional association by calculating the event-related covariance (ERC), which is the covariance between individual peaks and waves of spatially and temporally enhanced EPs for all pairs of recording electrodes. A "functional topography" is then determined as the pattern of significant functional associations. (See refs. 29 and 68 for descriptions of the computations involved and qualifications to their interpretation. The basic idea is that the EP waveform delineates the time course of stimulus-related mass activity of a neural population, so that if two populations are functionally related, their EPs should line up in time, perhaps with some delay. If so, this can be measured by the lagged covariance between the EPs, or portions of the EPs, from different regions.)

Over the past 10 years, we have used successive generations of this type of measure to study visuomotor coordination, attention, intention, decision, working memory, language, and mental fatigue (Gevins, unpublished data, 1992).[26-31,53] Two results, most relevant to the study of MHI, will be mentioned here.

In one study, subjects performed a task requiring continually adjusted fine pressure responses with right or left index fingers to visual numeric stimuli from one to nine. Evidence was found of involvement of left prefrontal cortex in a hand-specific "preparatory cortical network," which varied as a function of the accuracy of subsequent responses (see Fig 3).[28,29] Following feedback stimuli, which showed the subject how accurate the performance had been, these same left frontal sites were prominent only in those cases in which performance was inaccurate, consistent with the idea that more ad-

justment of prefrontal cortex is required following disconfirming feedback.[57,69–71] It would be most interesting to study patients with MHIs as they performed this task to assess subtle changes in their preparatory and feedback cortical networks.

The effects of mental fatigue on preparatory attention and working memory, stimulus processing, and response inhibition were studied using a similar type of finger pressure task, except that responses were made to previously seen numbers.[31] Striking changes occurred in cortical functional association patterns after an average of 7 to 9 hours of task performance, but before performance deteriorated. Pattern strength was reduced in a fraction-of-a-second-long prestimulus preparatory interval over midline precentral areas and over the entire left hemisphere (see Fig 4). By contrast, pattern strength in a poststimulus response inhibition interval was reduced over all areas. This suggests that, in addition to the well-known global reduction in neuroelectric signal strength, functional cortical networks are selectively affected by sustained mental work in specific fraction-of-a-second task intervals. Since MHI patients often report symptoms similar in many respects to those of mental fatigue, it would seem that this type of analytic paradigm would be quite useful in these cases.

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Patient welfare, prolonged medical and legal expenses, and other costs to society, all provide compelling reasons for research on improved assessment and treatment of the neurocognitive effects of MHI. Quantitative EEG studies, using 20-year-old methods, have already demonstrated the existence of an electrophysiologic marker of MHI. Modern high-resolution EEGs thus hold great promise for even more sensitive detection and characterization of the subtle and persistent neurocognitive effects of MHI. This type of brain imaging modality has the advantage of providing images of superficial cortical electrical activity with very high temporal resolution and spatial detail approaching that of O15 PET scans at low cost and without use of ionizing radiation.

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