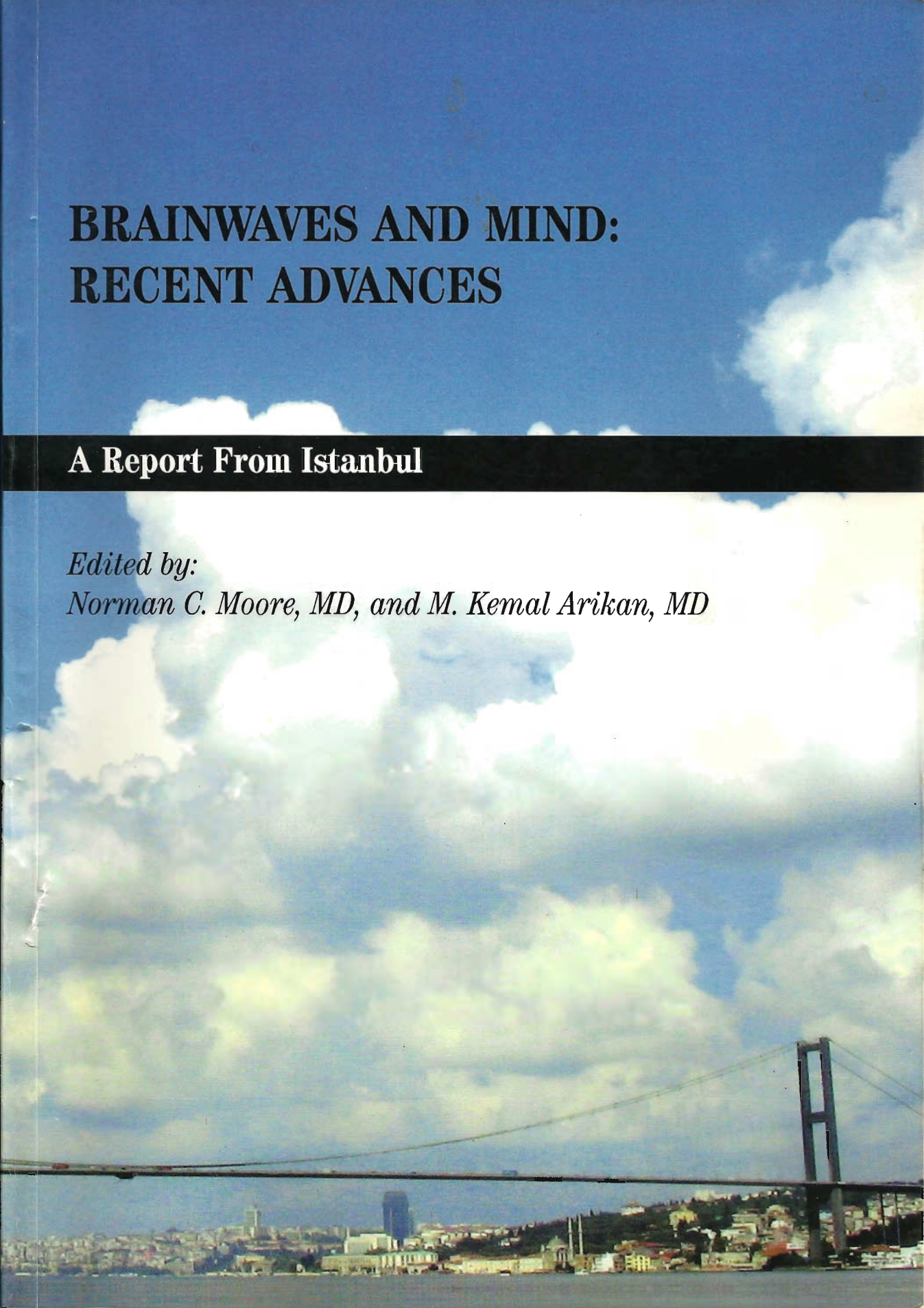
BRAINWAVES AND MIND: RECENT ADVANCES

A Report From Istanbul

Edited by:
Norman C. Moore, MD, and M. Kemal Arikan, MD



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Preface

Editors:
Norman C. Moore, MD, and M. Kemal Arikan, MD

Istanbul is both the nearest Asian city to Europe and the nearest European city to Asia, connecting continents, cultures and religions. It is a city of 11 million people living on a hill surrounded by two seas. It was the capital city of both Byzantine and Ottoman Empires, and trade paths passed through the city for thousands of years. It was therefore appropriate for scientists and clinicians from all over the world to meet in Istanbul in June 2001, for a conference "Electrophysiology in clinical practice and research." This book consists of selected papers, which are representative of the lectures given at the meeting. The authors have updated and rewritten the chosen presentations, which were then subjected to peer review and appropriate revision.

Kemal Arikan had the idea to host the conference, and asked Norman Moore, then President of the EEG and Clinical Neuroscience Society (ECNS), to assist with the organization. He hoped that Turkish electrophysiologists would benefit from observing the reasoning and problem solving of leading scientists. He also wanted them to develop personal relationships with these leaders and other colleagues. Finally, he was confident that, by presenting their own work, they would enhance their own and Turkey's reputation in the science of electrophysiology. We are pleased to report that all these goals were met. The successful meeting could not have been held without the support and assistance of many. These include Roche Turkey, which gave a generous educational grant, and the University of Istanbul, which assisted with administration. Wyeth Turkey, Turkcell and Turkiye Is Bankasi provided invaluable funding for organization expenses. The Turkish Company, Interium, did an excellent job of organizing the Conference. All members of the former Turkish Society of Electrophysiological Psychometry contributed greatly to the meeting.

THEORY

Biology of Brain Waves: Natural History and Evolution of an Information-Rich Sign of Activity

Theodore Holmes Bullock, University of California San Diego, La Jolla, California, USA

ABSTRACT

Using "brain waves" and "EEG" broadly for ongoing electrical activity and stimulus- or event-related activity of organized masses of neural tissue, as seen by wideband amplifiers and macro-, micro- or semi-microelectrodes within or in electrical contact with the central nervous system, I consider the character of these signs in animals of many phyla, by various descriptors, emphasizing local field potentials, pregnant questions and research opportunities.

We still have inadequate or hardly tested ideas of why most invertebrates, large and small, have inconspicuous slow waves (<50 Hz) and conspicuous spikes. They can, however, show slow waves under certain conditions, somewhat reminiscent of spinal cord, cerebellum or retina.

We have even less tested explanations of the strong similarity of all vertebrates: fish, amphibians, reptiles, birds and mammals, large and small — with respect to the power spectrum of conspicuous slow and inconspicuous spikes (until hunted by microelectrodes). Amplitude is the only obvious difference among vertebrate classes, mammals being highest. This may come from an evolution of the prevalence of synchrony, attributable, if true, to a generally higher coherence between pairs of sites in reptiles, birds and especially mammals.

The strong similarity in the power spectrum, among taxa with and without a cortex, is only one of several reasons to believe that we have not found the most relevant measures to reveal the real structure of the time series, in space and time. Fine structure in the millimeter and fractional second domains, in the seemingly stochastic, wideband component of activity, is probably widespread and greater in mammals than in fish. It has properties that are not obvious, such as nonlinear quadratic phase couplings and pseudo-periodicities, locally and episodically. Wavelet analysis, independent component analysis and other tools that might reveal nonrhythmic fine structure have not yet been applied to evolutionary studies.

A new tool, the Period-Specific-Average (PSA) can show real rhythms even when the power spectrum does not and shows absence of rhythms at some frequencies where the power spectrum peaks show Fourier components of irregular transients. The PSA shows that most of the spectrum, most of the time, in most human cortex is without significant rhythms. Special conditions bring out episodes of delta, theta, alpha, beta and gamma waves and their subtypes, usually only one or two at once, while most of the energy is wideband and seemingly stochastic. Between episodes of one or two rhythms there are major periods of time in normal human life without any significant rhythm in cortical surface (subdural) and depth electrodes. In spite of many kinds of sophisticated analyses, gross mappings, and models, with our present understanding, we cannot yet anticipate the character of scalp or subdural surface or macroelectrode depth recordings from microelectrode data or vice versa. Also lacking, so far, is any general understanding of the relation of slower, local field potentials and spike firing. Examples are known of strong positive correlations and others show no correlation. Communication among neurons by subthreshold, nonsynaptic routes is probably important in some evolving places and times.

The relative neglect of the basic biology, natural history, evolution, and system identification of local field potentials at different scales in different places is undeserved and a prime opportunity for new tools .

If a living organism moves or emits light, electricity, secretions, or sound, whether it sings or buzzes or ticks, if it squirts or flowers or lays eggs, biologists ask three kinds of questions: what, how and whence. The first question may be stated: what is the most adequate description of whatever is happening? The second question: how does it work? The third question is where did it come from — ontogenetically and phylogenetically? The task I set myself here is to look at what we neuroscientists have done and comment on the proposition that we haven't done much on any of these three fronts with respect to one form of action, the electrical activity of the nervous systems of humans and other animals.

Our descriptions of brain waves (a term which I will use as shorthand for ongoing electrical activity of the central nervous system, whether seen from the scalp, or on, or in the brain) have usually been in terms of the power spectrum. This may be about as adequate as describing an opera in terms of its power spectrum.

Chaos analysis and mutual information and bispectrum and all the rest have surely not adequately described the fine structure in space and time and the cooperativity of the myriad electrical generators in the depths of the brain. Still less have we an understanding of either how the brain waves are generated or what their roles may be — that is, whether they are purely the noise of the engine or can sometimes in some places also act as causes, able to influence cells in a field.

I find in some current literature that the EEG is the summation of action potentials! More often it is considered to be the summed synaptic potentials. We certainly know a number of other kinds of potentials that are at least candidate contributors and we can suspect still others. Even farther behind is any big picture of the evolution of brain waves — who has them, what they are like and how come? I will make some remarks on each of these three areas, as seen by a comparative biologist.

THE "HOW IT WORKS" QUESTION

First, let me deal with the how question — because there is little more to say. We think that most of the generators are cellular or subcellular, that is the cell membrane of one part of the cell changes its impedance or leakiness, relative to other parts of the cell. The impedances face standing potentials across the membrane, which may vary from place to place. This subcellular differentiation of one part from another, changing in time, is essential to explain the extracellular field activity, because if the whole cell stood or changed together we would have a closed system and could see nothing in the external field. We suppose that each of several kinds of membrane changes contributes to the summed external field: all-or-none action potentials (as far as they can invade the somata, dendrites and axon terminals), graded slow (ca. 0.1-50 Hz), subthreshold and infraslow changes in the membranes, pacemaker potentials, both rhythmic and nonrhythmic, local potentials, synaptic potentials, miniature, even quantal events peculiar to axonal terminal arbors or to dendrites or somata.

Some neurons — perhaps quite a few — never or rarely have all-or-none action potentials — which I may hereafter call spikes. Neuroglia of several kinds are also candidate generators. We cannot exclude other sources such as streaming potentials at the walls of blood vessels and epithelial potentials at the ependymal and pial surfaces. Empirically we find that events contribute over a wide spectrum of durations, from fractional milliseconds to many seconds and even minutes. The cellular and subcellular generators act as dipoles or multipoles in the size range from a few up to at least dozens of micrometers, and they have some more or less consistent orientations to help determine their contributions to the sum. The extracellular volume conductor is a complex configuration of interstices that cannot be assumed to be homogenous. Most of this is a guess and we might have a quite distorted idea of the true situation.[10,11,13,14,17,18,20] Of course, there is an enormous literature on brain waves; a great deal has been learned — mostly clinical correlations. Here we deal with general biological questions.

In particular I would underline that we have little basis to judge the relative importance of spikes and synaptic communication on the one hand and of non-spike, nonsynaptic communication between cells on the other — especially since their qualitative roles are no doubt quite different in the kind or meaning of the communications they mediate.

The diversity of kinds of neurons must have some role and consequence in the summed activity of organized assemblies. Uniquely among all the organ systems of the body, the nervous system has units with widely different or only slightly, but importantly, different receptive fields and projection fields as well as subthreshold behavior and spiking properties from never spiking to two kinds of spikes.[9]

Synchrony among some proportion of the active cells, whether firing spikes or undergoing subthreshold fluctuations, due to intrinsic cellular spontaneity or to impinging input, must be a major variable. Probably several distinct kinds of synchronization coexist, largely by way of the phase locking of slow fluctuations and thence of spikes or bursts.

Non-synaptic field effects are probably a major part of the communication between cells, besides the classical spikes and synapses, usually the only channel considered. Non-synaptic influences include direct electrical subthreshold interaction of slower fluctuations, some very slow and spoken of as "DC" or "infraslow" potentials.[16,17,31]

The infraslow potentials are often greater in voltage than all the rest of the activity and almost certainly exert strong modulatory influences upon spiking frequencies of many cells.[2,5,6,18,28,29,35,36,39,42,43,46]

As already stated, we have no basis for estimating the relative importance of spike and synapse vs non-spike, non-synaptic information processing and communication in neuropile and gray matter. Long distance communication that depends on spikes is certainly important but may be the postal service to the more continuous, decisive, integrative communication within the board rooms, auditoriums, offices and homes of the neurons and the glia. I hope it is obvious by now that the aim is to lift up for attention some questions of broad general interest that have been relatively neglected and offer attractive opportunities for new research.

NEURONAL INTEGRATIVE MECHANISMS

Instead of a code of the brain, several or many codes, including non-spike codes, operate in parallel. The long list of integrative mechanisms, cellular and subcellular,

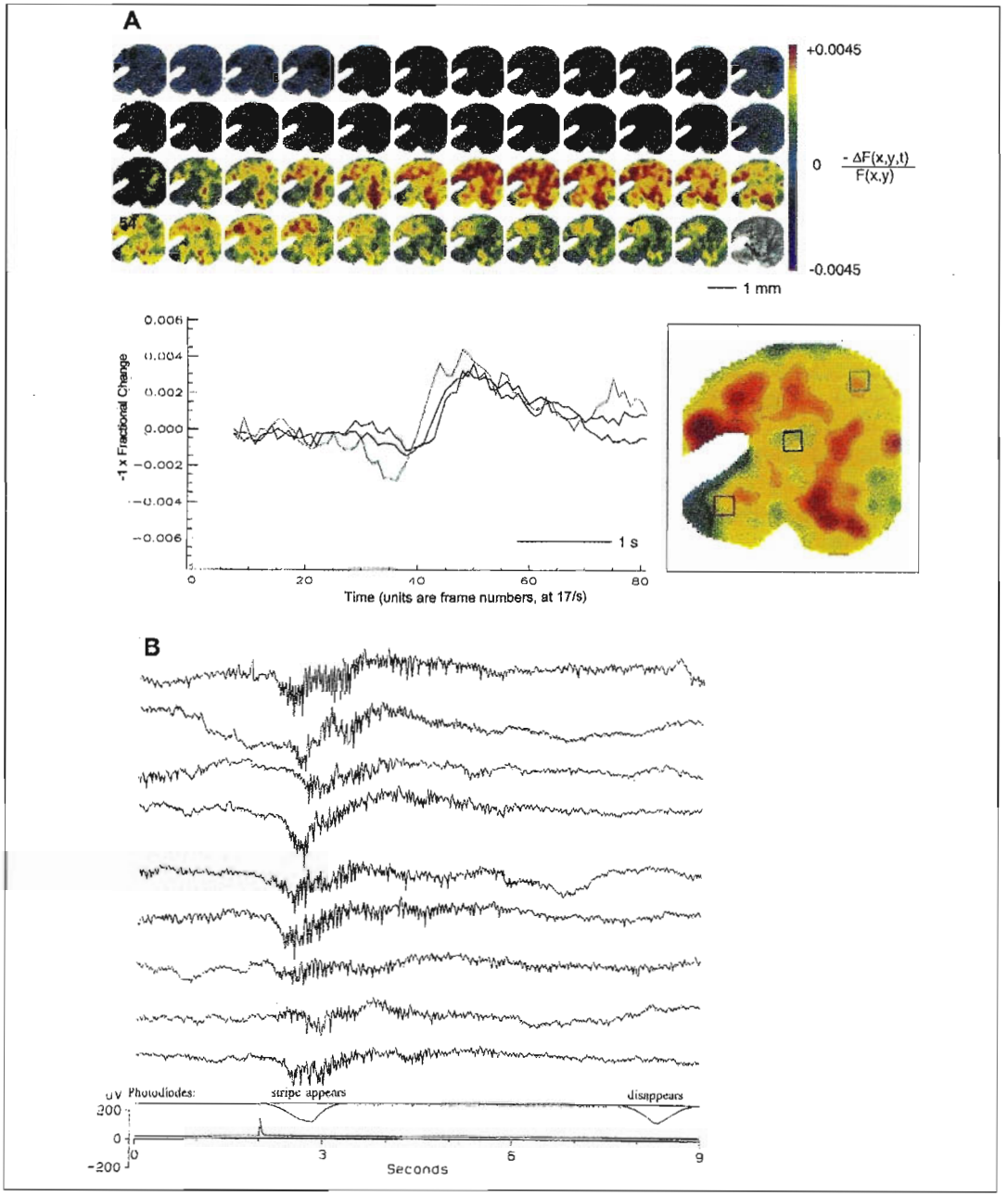

Figure 1..

A. Optically recorded visual evoked potentials from turtle dorsal cortex. Upper: 4 rows of 12 photographs of the brain surface, left to right, top to bottom, during 2.7 s of a video sequence of the stimulated membrane voltage changes. Each frame is a pseudo-colored image of 1.7 x 1.7 mm of the right visual area; rostral = right, lateral = up, white profile coming in from lower left = electrode. The moving visual stimulus starts in frame #30 (first of second row), causing a net hyperpolarization (dark blue) in frames 32-37, followed by depolarizations at a few loci which expand in caudal and lateral directions in frames 43-49; that is the figure shows a traveling wave. Bottom left: emission changes vs time from 3 loci indicated by the color-coded boxes in the enlarged frame #53, bottom right. The timing difference among the 3 plots reflects the spread of excitation. Responses imaged by epi-illumination with a CCD camera, 17 frames/s, after application of the fluorescent voltage-sensitive dye, RH795. Kindness of J.C. Prechtl (see Prechtl et al. (1997).[40] B. Raw data from 9 single sweeps of a similar preparation that shows the ON response, a "gamma" burst (ca. 20 Hz at 25°C), not time-locked and hence disappearing in an average — superimposed on a slow wave; no OFF effect. Turtle intracortical EEG; stimulus is a slowly moving visible stripe. Kindness of J.C. Prechtl.

whereby converging influences upon a neuron, excitatory and inhibitory, are weighted, and facilitate over time or disfacilitate with shorter or longer time-constants, or both — this list is already well above fifty (Bullock 1993,[16] p.16) and increases with nearly every issue of the journals. These integrative mechanisms act at many levels: protein synthesis, intracellular messengers, release of modulators of many kinds, gate opening and closing rates, transfer functions and non-linearities of many steps. Something similar probably happens with respect to small or medium populations of cells and more or less discrete circuits. By something similar, I mean there are probably several levels of integration and parallel as well as serial operations. My guess is that the brain is a reservoir of unfamiliar principles of system organization, waiting to be discovered.

The operations of the brain and of its constituent parts, nuclei, laminae, and circuits are not well understandable simply by unraveling the connectivity or hard wiring. We require also a major set of specifications of properties for each unit and site of interaction, mostly dynamical and plastic properties. I call them personality traits of the neurons and glia and sets of them. They represent formulae, equations and graphs of time dependence and state dependence, as additional determinants of output. The expression "circuits," even "local circuits," in the usual electronic engineering sense is a quite inadequate analog and terminology.

For this most complex of all systems, except systems of brains, we lack appropriate familiar terminology and analogs. Sometimes I find it heuristic to liken the organization of a brain to that of a complex human institution such as the government or a university. Many similar individuals perform a few similar acts — writing, speaking, filing and transporting materials, with many levels of integration, degrees of uniqueness and redundancy, plastic connectivity, serial and parallel. But, the analogy is limited.

Still speaking to the problem of how it works, the science cannot afford to wait for information about single cells and lower levels to accumulate sufficiently to permit bottom-up explanation or prediction of organized assembly dynamics. Emergents have already spiced up the history of brain physiology and are the only sure prediction in our science. Even hundred-channel recording of units, even if each channel were, as never before, wideband to allow both spikes and slow signals to be seen, is unlikely to make interpretation easier. Multichannel unit recording, with high resolution in space and time, is certainly the wave of the future and a white hope for new insights, stipulating technical problems yet to be solved. But it will overlap with multiunit extracellular field potential, wideband recordings — which I am here advocating in spite of the relative neglect and low opinion of some physiologists who are still making important discoveries from unit spike recordings. Another outstanding need today is for models of the nervous tissue, realistic with respect to geometry of subcellular generators, volume conduction, both spike-like and subthreshold, slow activity — on which to test ideas about synchrony, rhythms, field effects and redundancy.

THE "WHAT" QUESTION – AN ADEQUATE DESCRIPTION?

This view of how it works does not give any clues to what we should measure or look for in the time series and their spatial distributions in various parts of the brain and different species to provide an adequate description of brain waves. Now that the brain is regarded as central to behavior and mental life, we can not be satisfied with statistical measures of Gaussianity, Fourier analyses of energy at each equivalent frequency component, or estimates of dimensionality. Expecting nonlinearity and nonstationarity to be characeristic, except in special states, we do well to seek any evidence of microstructure, temporal as well as spatial.

Whether one considers the ongoing unstimulated background activity or the activity related to stimuli or to mental events or to changes in state, an array of extracellular, semimicro-probes, each detecting the wideband activity of a small volume overlapping with that of neighbors offers an array of information-rich time-series that challenges our ingenuity to find tools that might uncover nonrandomness potentially related to behavior or state. If the array is fortunately situated we may be able to recognize some of that rich information, although it will in the general case be as difficult to interpret as would an array of microphones at a political convention in a foreign language; indeed, even more difficult, since the number of units in the brain is many times greater. One concept that embraces many approaches and relevant measures is called cooperativity — any aspect of the assembly considered as though it were an interacting group.

Figure 1A shows one current state-of-the-art method of visualizing cooperativity of traveling brain waves in a plane by using voltage sensitive dyes and optical recording via an array of ca. 20 x 20 sensors. Without averaging, but confined to the near-surface plane, ca. 60 ms and 80 μm temporal and spatial resolution is permitted in this favorable case by the optical noise reduction of replacing blood with corpuscle-free saline in a suitably tolerant species, the pond turtle.

Coherence is a first order, linear form of cooperativity measured for pairs of places at each frequency in the Fourier space. Although on the average it is high between electrodes a few cell diameters apart, in our measurements of rabbit cortex it is commonly low and varies widely second by second and pair by pair a few millimeters apart.[21,25,26] Average coherence falls rapidly

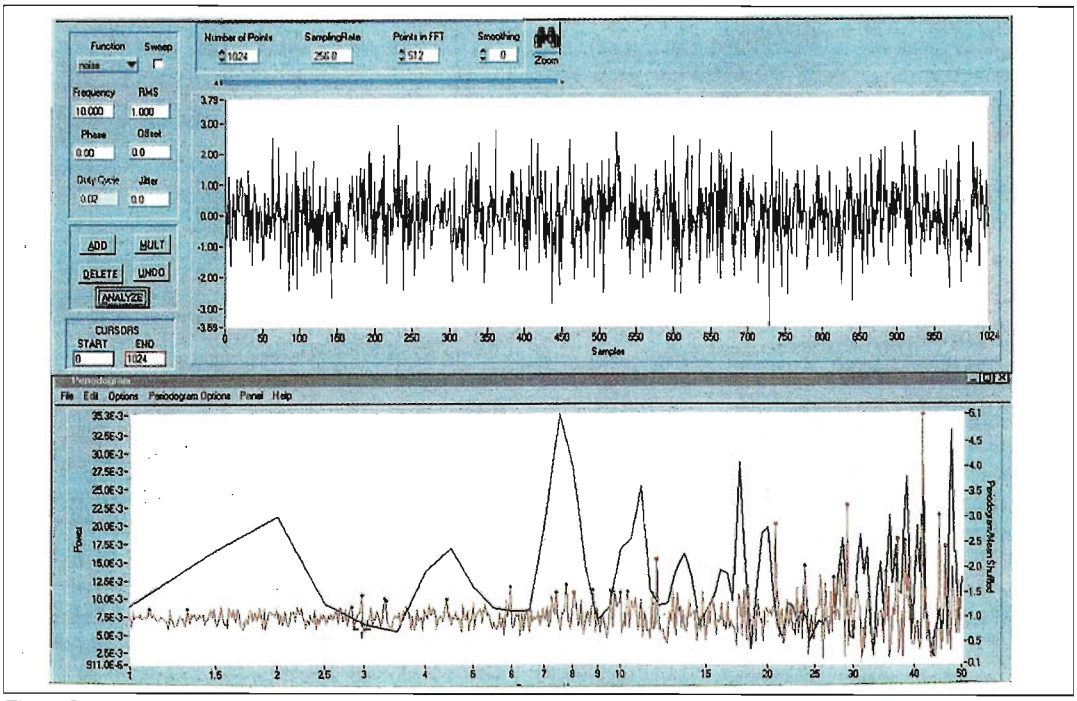

Figure 2.

Power spectrum peaks (black) in 4 s of 1-100 Hz noise (upper panel) do not necessarily represent rhythms, by any common sense definition. The high-lighted peaks of the red trace mean average PSA (Period-Specific-Average) periodicities (red), i.e., chance sequences of waves in the brief noise sample that satisfy a definition of rhythms. Red dots = 99% confidence, blue diamonds = 95% confidence. The time series is segmented and averaged at each period shown. The variance of each average is plotted and normalized by dividing the control value into the data value. Control values (the expectation by chance) were computed in two ways: (i) the same time series was segmented with random starting times, and (ii) the phases of each segment were randomized. The resulting curves have nearly identical 95 and 99% confidence points. Note many power peaks that do not correspond to PSA peaks and some good rhythms occur where power is weak. Abscissa of upper panel (data), at 256 samples per second, represents 4 s; abscissa of lower panel is in hertz. (Programs "Datgen" for generating artificial data, and "Periodity" for analysis by M.C. McClune.)

with distance when recording with small electrodes — to chance level within ca. 10 mm. This is true for all frequencies, except for theta during episodes of high theta or for alpha during episodes of high alpha. The evidence of local fine structure and dynamic changes is much less true with larger electrodes or with surface electrodes on the pia or dura or outside the skull.

Somehow the average coherence of local field potentials is able to rise to quite significant levels on the scalp, even at separations as great as 40 mm between electrodes — each of which "sees" a large cone of active tissue overlapping with its neighbors. Neither result, the fine structure at the micro level or the macro structure from the surface could predict the other. Finer microelectrodes within the cortex or most subcortical regions, apparently, on average, show relatively more energy at higher frequencies and less coherence at a given distance plus many sharp discontinuities of coherence between one pair of electrodes and another close by. As one approaches the cellular level, one often finds high agreement but often finds the opposite. There are large regional differences, even between cortical laminae, such as those of the optic tectum and of the cerebellum, but we really know little about regional distribution and lack a solid body of data recorded and analyzed in the same way.

We have found fine structure in space and time also with the unrelated, nonlinear and higher order measures called bicoherence and bispectrum, which depend on quadratic phase coupling between nonharmonic frequencies in the same or in different channels (electrodes). They also show episodic, transient increases very locally, suggestive that these may characterize some states or places, in the domains of seconds and millimeters.[23]

Other measures, such as partial coherence, mutual information, dimensionality and chaos, entropy, wavelet analysis, and the Fourier spectrum have been used, principally via scalp electrodes on humans, looking at large cones of brain tissue. Much needed are searches

for wave or spike burst packages with a degree of complexity that recur now and then, permitting efforts to find their correlates. Quite possibly some programs might be useful from the libraries of the search for nonrandom patterns in radio frequencies from extraterrestrial sources.

Particularly promising is the recently introduced Independent Component Analysis (ICA) which allows searching for localized sources of distinct time series at the resolution of the spacing of electrodes.[34] It has not to my knowledge been applied intracranially or to laboratory animals or non-mammals.

HOW MUCH IS LOCAL BRAIN ACTIVITY RHYTHMIC?

At present my colleagues and I are exploring rhythms (= oscillations) in human subdural and depth as well as scalp recordings, non-human and non-mammalian and invertebrate recordings, with a new method that permits the distinction between real rhythms and peaks of Fourier components which may not represent rhythms but Fourier components of irregular transients.[22,27] It is an additive periodogram we call Period Specific Averaging (PSA), based on the method of Enright[30]; the time series sample is segmented at an arbitrary period and these are averaged; this is repeated at every possible period between chosen limits, at a resolution of <1% of the period. The variance of each average is plotted against the period. Periodicities can be revealed which are missed by the FFT as well as, more often, absence of periodicity revealed where the FFT has a peak. PSA is nearly independent of wave form or duration of a repetitive event. It can show up to several nonharmonically related rhythms anywhere in a chosen range, such as 2-50 Hz, even in brief sample epochs. It works even when the stochastic background is many times higher than the rhythmic signal, i.e., with a signal to noise ratio of 1/4 or 1/5. If the rhythm is sloppy or frequency-jittered by 10 or 20 percent it is still useful though less sensitive. The control is the same time series segmented with randomized phase or randomized start times, permitting peaks to be highlighted when they are 95% or 99% confident. Figure 2 shows a short sample of band-passed noise and the absence of confident rhythms at some periods with FFT peaks.

The idea is to provide another descriptor potentially discriminating or characterizing places in the brain, or states, stages and species or taxa. So far this method has shown that: (a) much of the time most electrodes see no rhythm, (b) rhythms are often short lived — appearing in one 4 s epoch and not the next, (c) clear rhythms in the human are usually narrow-peaked, rarely sloppy or otherwise frequency modulated, (d) generally, if there is a rhythm at all there is only one that stands out or lasts for some time; but a second, third or fourth not harmonically related can occur, usually for a short time. The method has many limitations and the plots are not easy to read, as yet.

We see the classical rhythms — delta (1-3 Hz), theta (4-7 Hz), alpha (8-13 Hz), beta (14-29 Hz) and gamma (30-80+ Hz), with their subtypes, each under the special circumstances that conduce to their appearance.[7,8,15,19,32,38] Those special circumstances are not present most of the time, so that most local fields seen with subdural or depth macroelectrodes are most of the time without any rhythm that is statistically confident. Figures 3 and 4 show samples of human EEG with PSA and power spectrum.

Even though much of the EEG, especially the intracerebral local field potentials, are largely the stochastic result of independent fluctuations of many cells, I posit that it also hides nonrandom and nonrhythmic features in time and space. The challenge, as I see it, is similar to deciphering voices from babble on the radio or in a cocktail party. A human listener is likely to be able to say within seconds: "I hear something that sounds like Japanese from over there and something that sounds like Russian from over here — although I do not know either language." You can tell classical from pop music — but we don't know how you do it — or how to tell a computer to search for a non-stochastic pattern of unspecified form, except by wavelet analysis. We recognize and discriminate voices, handwriting, faces, even caricatures. We have fast, parallel filters for biologically important complex stimuli. But how do we uncover more of the spatiotemporal structure in the EEG? We have hardly begun.

I imagine that two or three human listeners given suitably transposed audio versions of the independent components extracted from multichannel brain recordings might, with some hours of training, learn to discern agreed upon differences among the parts of the brain and between states of the brain. The result seems likely to be vastly more informative than images of local blood flow or positron emission. Particularly interesting, because my intuition fails me, is the question whether local field potential recording from small volumes or from the pial surface or the scalp would be more likely to reveal patterned or unpatterned signals. A large step in the informative direction will be to estimate the volume of the independent sources, comparing two kinds of recordings, one being multiple semimicroelectrode arrays within the brain, and the other being macroelectrodes on the pia or outside the skull, in monkeys or cats where we can do both.

So much for the "what" and the "how" questions, a view of the nature of brain waves and a series of hypotheses posed as existence theorems, in short, physiological natural history. Any substantial departure from the view I have outlined, once compelled by the evidence, would

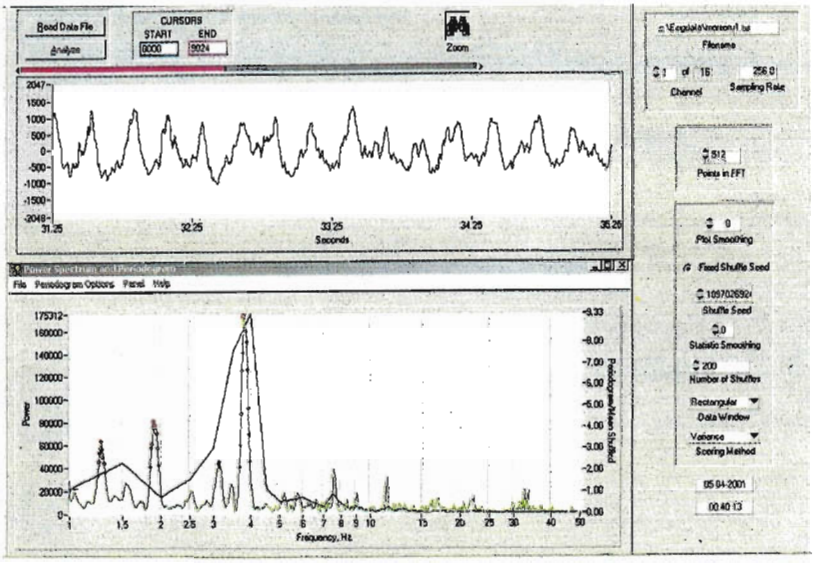

Figure 3.
Human subdural EEG data, 4 s in mid-seizure, during a strong theta epoch. As in the usual case, the power spectrum peak agrees with the periodicity peak — slightly less than 4 Hz. The periodicity analysis also shows smaller peaks at subharmonics just below 2 and 1.3 Hz, but this does not mean there are rhythms at those frequencies. To decide, we examine the averaged wave form at those periods.

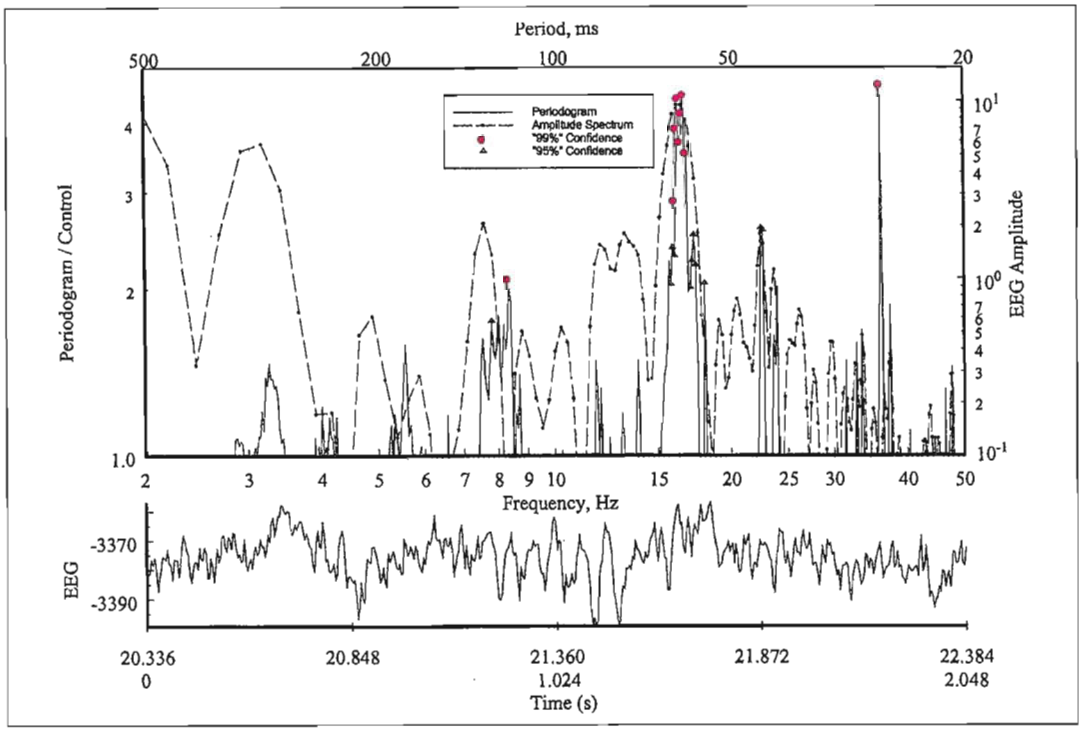

Figure 4.
Human scalp EEG; normal subject looking at a target image (a classical illusion, the "non-Kanizsa square"; subject is instructed to count targets) among several visual stimuli that include the Kanizsa square, Kanizsa triangle, and non-Kanizsa triangle images. Electrode is the one placed at (O4). Data kindly provided by C. Herrmann et al. (1999)[33] who showed brief periods of enhanced gamma activity at ca. 75-150 ms and 200-400 ms after stimulus onset. Here, analyzing the whole 2 s epoch, representing a single trial, without averaging, we see a significant gamma peak at 36 Hz where power is very low and a strong rhythm at ca. 16 Hz in both measures. Other power peaks do not represent rhythms. The upper time axis under the data is the elapsed time since the start of a stimulus series. Ordinate on the left is the PSA periodogram divided by the control from 200 randomized segment starts; 1.0 is the expectation from chance, given stochastic data with the same power spectrum.

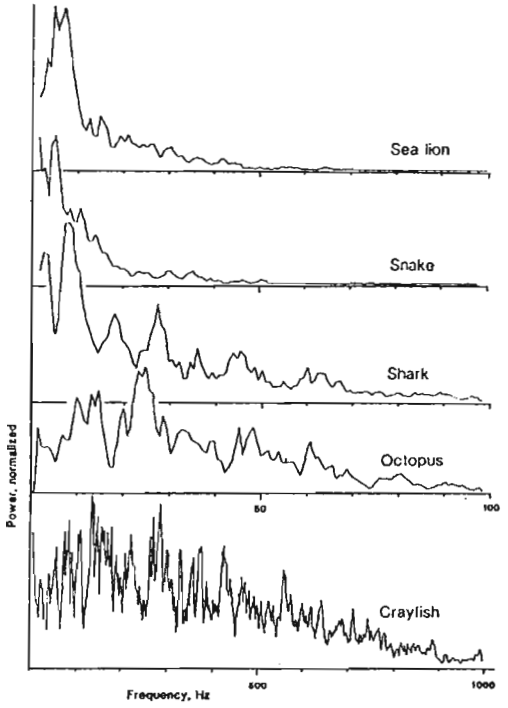

Figure 5..
Power spectra of EEG from various taxa. Upper three, vertebrates of different classes, with and without a cerebral cortex, share the pattern of maximum power below 10 Hz, steeply falling at higher frequencies. Note the ten-fold change in X-axis scale for the fifth trace, from crayfish. Octopus is closer to the vertebrate pattern.

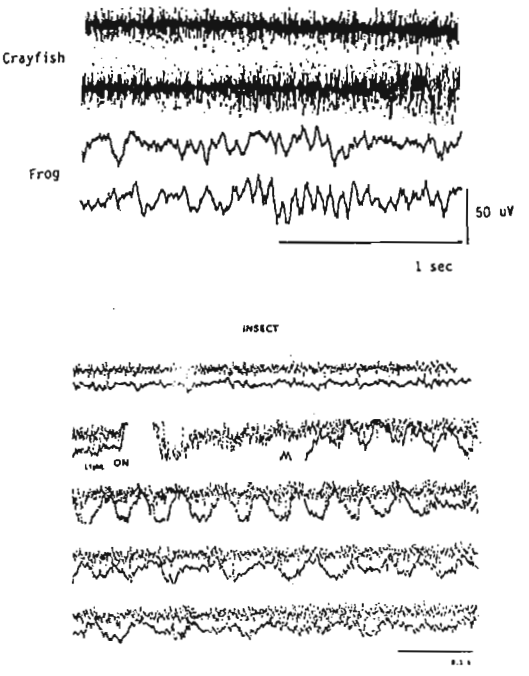

Figure 6..
Comparison of invertebrate and vertebrate EEGs. Upper panel, crayfish and frog wideband recordings from the surface of the brain, using similar wire macroelectrodes. Lower panel, locust optic ganglia of the brain, adapted to moderate light; additional light at "ON" caused a local field potential oscillation at ca. 18 Hz, damping out in a few seconds. The two channels are low-pass and high-pass filtered from the same wire recording macroelectrode. Invertebrates can show slow waves, probably manifesting synchrony of many neurons, under special conditions. See also Adrian, (1931).[3]

be more of an advance in scientific understanding than a finding that is compatible with this view.

THE QUESTION "WHENCE"

The third question "whence?" is also descriptive but adds the dimensions of evolutionary time and phylogenetic relationships. I will here omit discussion of the ontogenetic dimension. Formulating the goal more modestly, until the day when we have a sufficient data base: what are brain waves like in some birds, reptiles, amphibians, fish and invertebrates of various phyla — especially the molluscs, arthropods, and annelids because they have concentrated and differentiated brains?

In spite of a paucity of studies,[3,4,12,13,16,20] we know enough to raise basic and interesting questions. I will pose two in particular. (1) Firstly, what can be the relevant physiological or anatomical differences between vertebrates and invertebrates that explain a drastic difference in the EEGs from their respective higher brain centers — almost any recording from any species of either group? The major exception is the cephalopods, which have EEGs more like those of vertebrates than those of other invertebrates. (2) Secondly, what can it mean that vertebrates, fish, frogs and man, show essentially indistinguishable EEGs, if we look at the midbrain tectum or the cerebral pallium or the cerebellum or the olfactory bulbs? I can be only a little more specific on each of these two puzzles in the space available. But I believe they are important and potentially illuminating differences.

(1) The first evolutionary puzzle I want to mention is what can it mean that a consistent difference in the power spectrum of the EEG appears to be general, comparing any vertebrate with any invertebrate, apart from the cephalopods, such as octopus and cuttlefish? The typical invertebrate record of ongoing electrical activity is spiky with single unit and compound spikes of one or a few milliseconds width, riding on slow waves that are usually inconspicuous (Figures 5 and 6). One doesn't have to hunt for spikes. In both surface and depth recordings, whether by microelec-

trodes or gross electrodes, from intact, behaving animals or isolated cerebral ganglia removed from the body, whether the subject is the brain of a snail, a slug, the marine tectibranch Aplysia, a cockroach, a bee, an adult moth or a larva (caterpillar), a crayfish, stomatopod (mantis shrimp), earthworm, or polychaete annelid, they all, except cephalopods, show omnipresent, simple or compound multiunit spikes overriding small slow waves.

In certain conditions — poorly understood — slow waves can become prominent in the invertebrates (Figure 6, lower; Schütt et al.[44,45]) whereas in all vertebrates and most regions of their brain, slow waves are omnipresent and relatively stronger; and spikes have to be sought by careful positioning. The power spectra are quite different. Vertebrates, as we just noted, almost invariably have a maximum between 5 and 15 Hz and fall off at higher frequencies, typically more than a factor of two for each octave to about 1/10 at 100 Hz. In the invertebrates power commonly stays up and even rises to a broad maximum above 100 Hz.

One wonders whether two general differences exist. One might be in the tissue impedance — vertebrates having more cell membranes and capacitance, tending to short out the high frequencies. The impedance has not been measured, to my knowledge, in the millimeter range.

The other candidate for a general difference is synchrony. This has been estimated in a preliminary way in our own sampling of coherence as a function of distance between pairs of electrodes referenced to a common and demonstrably inactive electrode. Averaging over many sample periods of 5-10 s and many pairs of electrodes of each separation, the means in mammals fall from ca.0.8-1.0 (perfect coherence) at 1-2 mm to a level indistinguishable from a stochastic control at a separation of ca.10-20 mm in rabbit and human (macroelectrodes on the pia or dura mater). This is true for all frequencies between ca. 2 and 50 Hz. The more sensitive measure is the distance for mean coherence equal to 0.5, but it demands large scale averaging of many pairs with different separation, and is impractical in most preparations. I found, roughly, that it lies in the range of 5-10 mm in rabbit cortex, ca.3-4 mm in the lizard (Gecko) cortex, only 1-3 mm in a ray optic tectum (Platyrhinoides), and less than 1 mm in the gastropod, Aplysia.[12] It will require many more samples to establish whether this is a valid trend. For the present we can only suggest that there may be a significant evolution in the degree and distribution of slow wave synchrony.

(2) The second puzzle is this. The raw recordings and the power spectra look alike in all the vertebrates, (Figure 5) except for the RMS amplitude, if we compare subdural surface recordings or intracerebral needle or fine wire recordings in the waking animal, between ca. 0.3 and 100 Hz. The main features are: (a) absence of spikes (except for certain places such as a deep layer in the cerebellar cortex and in other places if a fine electrode is micromanipulated through the tissue) and (b) a power spectrum falling quite steeply on each side of a maximum around 5-15 Hz (Figure 5).

The presence of a cortex makes no generalized difference in the form of the power spectrum, as yet demonstrated, and the same is true for the size of the brain and for its degree of microscopic differentiation. Amplitude is generally lower in the nonmammalian species but is doubtfully different among mammals, from mouse to dolphin — but we don't yet know what the key factors are. Many factors influence amplitude and selecting comparable samples is difficult.

Some features that might be expected to play a large role can be shown not to do so — for example lamination. The cerebellar cortex has low amplitude slow waves. Species of fish and reptiles having highly laminated optic tecta show low EEG amplitudes — something like a third to a sixth of that of a mammal comparably recorded. Local field potentials of poorly or not at all laminated subcortical mammalian gray matter typically exceed the amplitude of any cerebral region of fish or reptiles, or even the well laminated tectum. The wide differences in EEG amplitude that seem on the present data to be generalizable between mammals and fish or amphibians might possibly be understood if synchrony of slow waves is also generally lower in fish and amphibians. I return to this below.

Some evidence points to a lower coherence at the same distance between electrodes in reptiles than in mammals and a still lower coherence in teleosts and elasmobranchs. If this is borne out with a larger sample of species, we could attempt the generalization that degrees of synchrony tend to increase in the more complex brains.

The large mystery I want to highlight is the lack of other differences between the form, power spectrum and dynamics of the EEGs among the vertebrate classes, to parallel the great changes in brain anatomy and behavioral ethograms. Even the first order form and distribution of sensory evoked potentials[41] and event-related potentials[24] in fish are surprisingly similar to those of mammals. I must conclude that we are missing major features in our description of EEGs — features hiding in the temporal and spatial fine structure of the time series, perhaps like the firing patterns of Abeles et al.[1] or slow wave patterns of Lopes da Silva.[37] This is the most important take-home message and it seems not to have been noticed or to have attracted much attention heretofore. The challenge is tantalizing — what instructions can we give our high speed

computers to seek dynamical features that distinguish a set of sample mammalian EEGs from a set of reptilian or teleostean EEGs, as generalizable as the six-layered cortex? I believe there are such features and that they are specific and measurable, not intangible or vague. They probably involve new integrative levels of complexity of the meaning of similar neuronal activity — like the meaning of "yes" pronounced by the chancellor of a university and by the principal of a small middle school.

To emphasize this point, I will confess that a major disappointment in my career has been my failure to accumulate good digitized recordings from such a range of taxa, with adequately comparable conditions, including the state of the animal, the kind of electrodes and their placement in equivalent regions of the brain, so that I could now push such data through the programs we have that can spit out comparative findings on many traits in the sadly neglected area of dynamical properties of organized assemblies of neurons.

REFERENCES

1. Abeles M, Bergman H, Margalit E, Vaadia E. Spatiotemporal firing patterns in the frontal cortex of behaving monkeys. J Neurophysiol 1993; 70: 1629-1638.
2. Adey WR. Slow electrical phenomena in the central nervous system. Neurosci Res Prog Bull 1969; 7:75-180, (including a 20 page bibliography).
3. Adrian ED. Potential changes in the isolated nervous system of Dytiscus marginalis. J Physiol 1931; 72: 132-151.
4. Adrian ED, Buytendijk FJJ. Potential changes in the isolated brain stem of the goldfish. J Physiol 1931; 71: 121-135.
5. Aladzhalova NA. Electrographic study of pharmacologically induced changes in the ultra-slow waves of the cortical potentials. Sechenov Physiol J USSR 1958; 44: 757-764.
6. Albrecht D, Gabriel S. very slow oscillations of activity in geniculate neurones of urethane-anaesthetized rats. NeuroReport 1994; 5: 1909-1912.
7. Başar E. EEG and synergetics of neural populations. In: Başar E, Flohr H, Haken H, Mandell AJ, (eds). Synergetics of the Brain. Berlin: Springer-Verlag; 1983: 183-200.
8. Başar E, Bullock TH. Induced Rhythms in the Brain. Boston: Birkhäuser; 1992.
9. Bullock TH. Reassessment of neural connectivity and its specification. In: Pinsker HM, Willis WD Jr, (eds). Information Processing in the Nervous System. New York: Raven Press; 1980: 199-220.
10. Bullock TH. Compound potentials of the brain, ongoing and evoked: perspectives from comparative neurology. In: Başar E, (ed). Dynamics of Sensory and Cognitive Processing by the Brain. Berlin: Springer-Verlag; 1988: 3-18.
11. Bullock TH. The micro-EEG represents varied degrees of cooperativity among wide-band generators: spatial and temporal microstructure of field potentials. In: Başar E, Bullock TH, (eds). Brain Dynamics: Progress and Perspectives. Berlin: Springer-Verlag; 1989a: 5-12.
12. Bullock TH. Evolution of compound field potentials in the brain. In: Başar E, Bullock TH, (eds). Brain Dynamics: Progress and Perspectives. Berlin: Springer-Verlag; 1989b: 258-266.
13. Bullock TH. Signs of dynamic processes in organized neural tissue: extracting order from chaotic data. In: Başar E, Bullock TH, (eds). Brain Dynamics: Progress and Perspectives. Berlin: Springer-Verlag; 1989c: 539-547.
14. Bullock TH. New descriptors for the activity of brain cell assemblies: requirements and opportunities. In: Schuster HG, (ed). Nonlinear Dynamics and Neuronal Networks. Weinheim, Germany: VCH Verlagsgesellschaft; 1991: 257-266.
15. Bullock TH. Introduction to induced rhythms: a widespread, heterogeneous class of oscillations. In: Başar E, Bullock TH, (eds). Induced Rhythms in the Brain. Boston: Birkhäuser; 1992: 1-26.
16. Bullock TH. How Do Brains Work? Papers of a Neurophysiologist. Boston: Birkhäuser; 1993.
17. Bullock TH. Signals and signs in the nervous system: the dynamic anatomy of electrical activity is probably information-rich. Proc Natl Acad Sci USA 1997; 94: 1-6.
18. Bullock TH. Slow potentials in the brain: still little understood but gradually getting analytical attention. Brain Res Bull 1999; 50: 315-316.
19. Bullock TH, Achimowicz JZ. A comparative survey of oscillatory brain activity, especially gamma-band rhythms. In: Pantev C, Elbert T, Lütkenhöner B, (eds). Oscillatory Event-Related Brain Dynamics. NATO A: Life Sciences series. New York: Plenum Press; 1994: 11-26.
20. Bullock TH, Başar E. Comparison of ongoing compound field potentials in the brains of invertebrates and vertebrates. Brain Res Rev 1988; 13: 57-75.
21. Bullock TH, McClune MC. Lateral coherence of the electrocorticogram: a new measure of brain synchrony. Electroencephalogr Clin Neurophysiol 1989; 73: 479-498.
22. Bullock TH, Enright JT, Chong KM. Forays with the additive periodogram applied to the EEG. It gives a different picture of brain rhythms from the power spectrum. Proc.5th Joint Symp Neural Computation. Univ. of Calif., San Diego; 1998a; 8: 25-28.
23. Bullock TH, Achimowicz JZ, Duckrow RB, Spencer SS, Iragui-Madoz VJ. Bicoherence of intracranial EEG in sleep, wakefulness and seizures. Electroencephalogr Clin Neurophysiol 1998b; 103: 661-678.
24. Bullock TH, Hofmann MH, Nahm FK, New JG, Prechtl JC. Event-related potentials in the retina and optic tectum of fish. J Neurophysiol 1990; 64: 903-914.
25. Bullock TH, McClune MC, Achimowicz JZ, Iragui-Madoz VJ, Duckrow RB, Spencer SS. EEG coherence has struc-

ture in the millimeter domain: subdural and hippocampal recordings from epileptic patients. Electroencephalogr Clin Neurophysiol 1995a; 95: 161-177.

26. Bullock TH, McClune MC, Achimowicz JZ, Iragui-Madoz VJ, Duckrow RB, Spencer SS. Temporal fluctuations in coherence of brain waves. Proc Natl Acad Sci USA 1995b; 92: 11568-11572.
27. Bullock TH, McClune MC, Enright JT. Rhythms in the human EEG are occasional. Proc Seventh Joint Symp Neural Computation, Inst Neural Computation, UCSD, La Jolla, CA; 2000; 10: 18-20.
28. Devrim M, Demiralp T, Kurt A, Yücesir I. Slow cortical potential shifts modulate the sensory threshold in human visual system. Neurosci Lett 1999; 270: 17-20.
29. Elbert T. Slow cortical potentials reflect the regulation of cortical excitability. In: McCallum WC, (ed). Slow Potential Changes in the Human Brain. New York: Plenum Press; 1993: 235-251.
30. Enright JT. The search for rhythmicity in biological time-series. J Theoret Biol 1965; 8: 426-468.
31. Ezrokhi VL, Voronin LL. Non-synaptic synchronizing effects of endogenous single neuron activity on spike activity of a neighboring neuron. (Personal commuication); 2001.
32. Gray CM. Synchronous oscillations in neuronal systems: mechanisms and functions. J Computat Neurosci 1994; 1: 11-38.
33. Herrmann CS, Mecklinger A, Pfeifer E. Gamma responses and ERPs in a visual classification task. Clin Neurophysiol 1999; 110: 636-642.
34. Jung TP, Makeig S, McKeown, Bell AJ, Lee TW, Sejnowski TJ. Imaging brain dynamics using independent component analysis. Proc IEEE 2001; 89: 1107-1122.
35. Lang W, Starr A, Lang V, Lindinger G, Deecke L. Cortical DC potential shifts accompanying auditory and visual short-term memory. Electroencephalogr Clin Neurophysiol 1992; 82: 285-295.
36. Lickey ME. Localization and habituation of sensory evoked DC responses in cat cortex. Exp Neurol 1966; 15: 437-454.
37. Lopes da Silva F H. Pattern recognition and automatic EEG analysis. Trends Neurosci 1981; 4: 272-297.
38. Lopes da Silva F H, van Rotterdam A, Barts P, Van Heusden E, Burr W. Models of neuronal populations: the basic mechanisms of rhythmicity. Prog Brain Res 1976; 45: 281-308.
39. O'Leary JL, Goldring S. D-C potentials of the brain. Physiol Rev 1964; 44: 91-125.
40. Prechtl JC, Cohen LB, Pesaran B, Mitra PP, Kleinfeld D. Visual stimuli induce waves of electrical activity in turtle cortex. Proc Natl Acad Sci USA 1997; 94: 7621-7626.
41. Prechtl JC, von der Emde G, Wolfart J, Karamürsel S, Akoev GN, Andrianov YN, Bullock TH. Sensory processing in the pallium of a mormyrid fish. J Neurosci 1998; 18: 7381-7393.
42. Rowland V. Steady potential phenomena of cortex. In: Quarton GC, Melnechuk T, Schmitt FO, (eds). The Neurosciences: a Study Program. New York: The Rockefeller Univ Press; 1967: 482-495.
43. Rowland V. Cortical steady potential (direct current potential) in reinforcement and learning. In: Stellar E, Sprague J, (eds). Progress in Physiological Psychology. New York: Academic Press; 1968: 1-70.
44. Schütt A, Başar E, Bullock TH. Power spectra of ongoing activity of the snail brain can discriminate odorants. Comp Biochem Physiol A 1999a; 123: 95-110.
45. Schütt A, Bullock TH, Başar E. Dynamics of potentials from invertebrate brains. In: Başar E, (ed). Brain Functions and Oscillations. II: IntegrativeBrain Function. Neurophysiology and Cognitive Processes. Berlin: Springer; 1999b: 91-108.
46. Speckmann E-J, Elger CE. Introduction to the neurophysiological basis of the EEG and DC potentials. In: Niedermeyer E, Lopes da Silva F, (eds). Electroencephalography: Basic Principles, Clinical Applications and Related Fields. Baltimore-Munich: Urban & Schwarzenberg; 1987: 1-13.

Neuropsychology of P3a and P3b: A Theoretical Overview

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ABSTRACT

This chapter outlines the cognitive theory and neuropsychological origins of the P300 event-related brain potential (ERP) by reviewing the basis for the distinction between the P3a and P3b subcomponents. The methodological and empirical foundations underlying these ERPs are sketched, with candidate neurophysiological generator mechanisms proffered. These structures are used to articulate a theoretical perspective that specifies the interaction between P3a and P3b in terms of frontal attention with working memory processes and subsequent attentional resource allocation during temporal/parietal memory storage operations. The neuroelectric basis for these effects is then outlined. Finally, practical guidelines for recording P300 in clinical settings are presented, with a view toward defining standard paradigms that can be developed for evaluating the neurocognitive efficiency of individual subjects.

NEUROPSYCHOLOGY OF P3A AND P3B: A THEORETICAL OVERVIEW

The P300 event-related brain potential (ERP) has demonstrated considerable utility in the study of normal cognitive function as well as for assessing a variety of mental disorders. Despite the plethora of ERP studies on these topics, the usefulness of P300 (or "P3b" as described below) as an assessment tool has been limited in part because its neural generators are as yet ill defined so that formulation of a comprehensive theoretical perspective has been limited. However, recent empirical advances on the relationship between the P3a and P3b ERPs have suggested a plausible approach to how these subcomponents may contribute to overall P300 generation. The purpose of the present chapter is to outline the issues surrounding these developments. The review is organized into several sections: First, the empirical background of the P3a and P3b subcomponent distinction is sketched. Second, a theoretical perspective of P300 is presented. Third, the neuropsychological basis for the P300 component is outlined in terms of how these subcomponents may be related. Fourth, the neuroelectric basis for P300 generation is summarized. The chapter concludes with suggestions for clinical applications.

P3a and P3b

The P300 was discovered over 35 years ago and has provided much fundamental information on the neural underpinnings of normal and dysfunctional cognition.[14,150] This ERP component is often elicited using the "oddball" paradigm, wherein two stimuli are presented in a random order, with one occurring more frequently than the other. Figure 1 illustrates this task situation in the upper panel. The subject is required to discriminate an infrequent target stimulus from the frequent standard stimulus by responding covertly or overtly to the target—typically a relatively easy discrimination.[109,118] The target elicits the P300, which is not apparent in the ERP from the standard stimulus.

The "three-stimulus" paradigm is a modification of the oddball task in which "distractor" stimuli are inserted into the sequence of target and standard stimuli. Figure 1 schematically illustrates the task situation in the lower panel. When "novel" stimuli (e.g., dog barks, color forms, etc.) are presented as distractors in the series of more "typical" target and standard stimuli (e.g., tones, letters of the alphabet, etc.), a P300 component that is large over the frontal/central areas can be produced with auditory, visual, and somatosensory stimuli.[22,74,161] This "novelty" P300 is sometimes called the "P3a,"[21,150] and with recent analyses confirming that these two potentials are the same component (cf. Simons et al[145]; Spencer et al[148]). The parietal maximum P300 from the target stimulus is sometimes called the "P3b." As the P3a exhibits an anterior scalp distribution, relatively short peak latency, and rapidly habituates, it is thought to reflect frontal lobe function[39,78] and can be elicited in a variety of populations.[36,40,160]

In another variant of the three-stimulus paradigm, infrequent-nontarget "typical" visual stimuli (i.e., not novel) that are easily recognized (i.e., not novel) have been found to elicit a P300 with maximum amplitude over the central/parietal rather than frontal/central areas.[19,20] This component is sometimes referred to as a "no-go" P300, because subjects do not respond to the infrequent nontargets.[37,105] In the auditory modality, infrequent nontarget tone stimuli that are readily perceived (i.e., not novel) inserted into the traditional oddball sequence also elicit a central/parietal maximum P300 (cf. Katayama and Polich[63]; Pfefferbaum and Ford[104]). When both an infrequent nontarget tone and a novel sound are presented, the novel stimuli elicit a central maximum P300 and the infrequent nontarget tone elicits a central/parietal P300, the amplitude of which is smaller than that of the

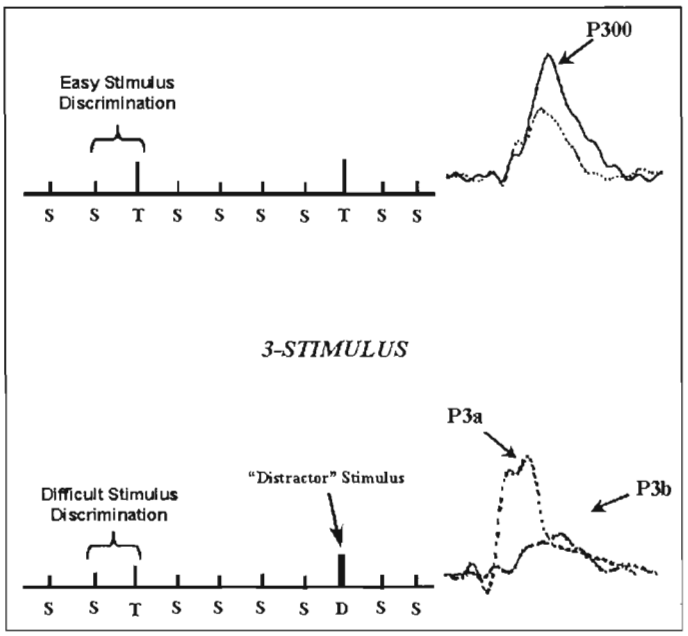

Figure 1.
Schematic illustration of the oddball (upper panel) and three-stimulus paradigms (lower panel) paradigms, with the ERPs from the stimuli of each task presented at the right. The oddball task presents two different stimuli in a random sequence, with one occurring less frequently than the other (target = "T", standard = "S"). The three-stimulus task also presents a compelling (not necessarily novel) "distractor" (D) stimulus that occurs infrequently, to which the subject does not respond but which elicits the "P3a" subcomponent. In each task, the subject typically responds only to the target stimulus, which elicits the "P3b".

novel stimulus potential (cf. Grillon et al[43]; Verbaten et al[154]). Thus, P300 from both auditory and visual stimuli can vary in amplitude and timing, because the intra-paradigm stimulus relationships in conjunction with presentation probability define the stimulus and task context (cf. Katayama and Polich[64]; Suwazono et al[163]).

Stimulus Context

Katayama and Polich[65] assessed the role of task difficulty in the three-stimulus paradigm to examine more closely the effects of stimulus context on P300 component scalp topography distribution. In this study, the perceptual distinctiveness between the target and standard stimuli was manipulated in an auditory task by using typical tone stimuli that varied in pitch. When the target/standard discrimination was easy and the distractor stimulus was highly discrepant, P300 target amplitude was larger than distractor stimulus amplitude across the midline electrode sites, and both component types were largest over the parietal sites. However, when the target/standard discrimination was difficult and the distractor stimulus was highly discrepant, the nontarget distractor stimulus elicited a P300 that was greater in amplitude frontally and shorter in latency than the target P300. Additional studies have found that the repeated distractor "typical" stimulus elicits a P3a component that is larger in amplitude over the frontal/central locations and shorter in latency than the target P3b components.[17,18] These results suggest that the engagement of frontal lobe attentional mechanisms elicited by a difficult target stimulus detection task is a defining aspect of the stimulus context that contributes to P3a generation using the three-stimulus paradigm (see Figure 2).

This hypothesis has been assessed systematically by comparing "typical" with "novel" distractor stimuli under easy vs. difficult target/standard discrimination tasks. Figure 2 provides an illustration of the critical ERP results from a study that compared several distractor types in a visual three-stimulus task.[27,110] The distractor stimuli were either a blue square that was the same for each trial or variegated colored patterns that changed on each trial, with both distractor stimuli much larger than the target and standard. The "easy" (target stimulus "A" from the standard letter "B") compared to the "difficult" (a target stimulus 5.0 cm diameter circle from a 4.5 cm circle) task conditions produced both the P3a and P3b components across distractor stimulus types (23.0 cm on a side). However, when the discrimination task was difficult, the blue square and novel patterns produced P3a and P3b ERP components that were virtually identical, such that the P3a components from the large squares were remarkably similar to those previously reported for "novel" stimuli.[21,145,150] It is therefore reasonable to suppose that stimulus context – the relative perceptual distinctiveness among stimuli – determines both distractor and target P300 amplitude since each stimulus type produces distinct scalp topographic distributions,[65,148,153] which implies that each potential is generated by different neural structures (see Figure 2).

P300 THEORY

Context Updating

P300 amplitude is thought to index brain activity that is "required in the maintenance of working memory" when the mental model of the stimulus context is updated (Donchin et al,[30] p. 256). Figure 3 illustrates this theoreti-

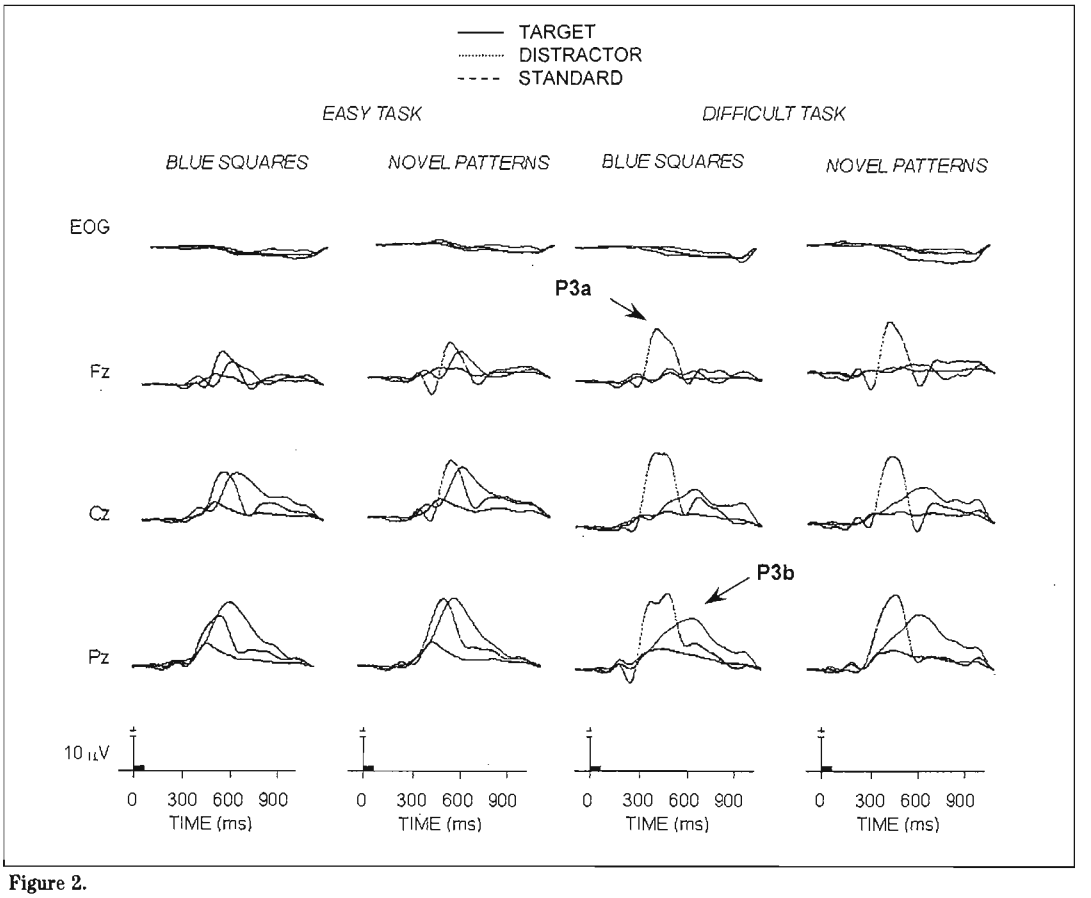

Figure 2.

Grand average ERPs (n=12) from selected three-stimulus oddball stimulus conditions. The EASY TASK required subjects to respond to the target letter "A" and not respond to the standard stimulus letter "B" or distractor stimuli. The DIFFICULT TASK required subjects to respond to a 5.5 cm diameter target circle and not respond to the 5.0 cm diameter standard stimulus or distractor stimuli. The distractor stimuli were 23.0 cm squares that were either all blue and always the same or different color novel patterns, with the two- distractor stimulus types presented in separate conditions. Note that the P3a and P3b ERPs are not as distinct in the EASY compared to DIFFICULT tasks (after Polich and Comerchero, 2003[119]).

cal perspective and schematically portrays the updating processes hypothesized to produce the canonical P300 during oddball task performance. After initial sensory stimulus processing, a memory comparison evaluation is performed in which the current stimulus of the oddball sequence is compared to the previous stimulus. If no change in stimulus attributes is detected, the old "schema" or neural model of the stimulus environment is maintained, and just the sensory evoked potentials recorded. However, if a new stimulus is processed the system engages attentional mechanisms to "update" the neural representation of the stimulus context—and the P300 (P3b) is elicited, which is thought to index the ensuing memory storage operations. This assertion is supported by findings that larger P300 amplitudes are related to memory for previous stimulus presentations.[34,61,101] A variety of cognitive factors have been delineated for this view, with information content, stimulus probability structure, task relevance/difficulty, and stimulus properties all found to affect P300 measures.[23,20,59,97,147,156]

P300 latency is considered to be a measure of stimulus classification speed unrelated to response selection processes,[85,89,106] such that its timing is independent of behavioral reaction time.[32,52,155] Indeed, it is these properties that make P300 a valuable tool for assessing cognition: Because P300 latency is an index of the processing time that occurs before response generation, it provides a temporal measure of the neural activity underlying the processes of attention allocation and immediate memory. Further, component timing is negatively correlated with mental function efficiency in normal subjects: Shorter latencies are associated with superior cognitive performance from neuropsychological tests that assess how rapidly attentional resources can be allocated for memory

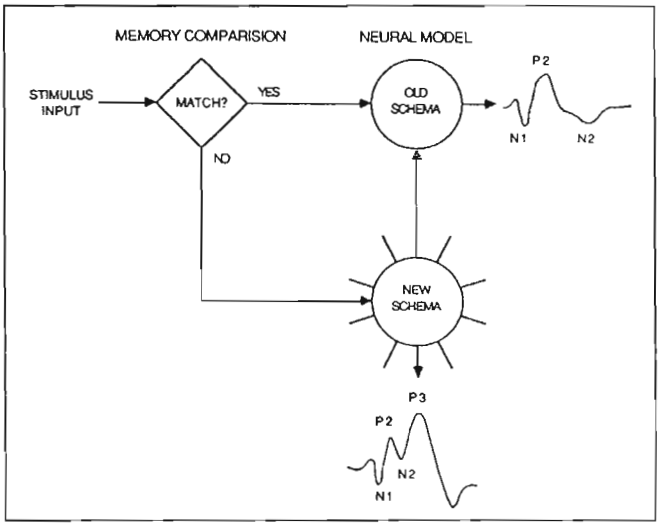

Figure 3.
Schematic illustration of the context-updating model for P300 theory. Stimuli enter the processing system and a memory comparison process is engaged that ascertains whether the current stimulus is either the same as the previous stimulus or not (i.e., a standard or a target stimulus in the oddball task). If the incoming stimulus is the same, the neural model or schema of the stimulus environment is unchanged and single signal averaging of the EEG reveals sensory evoked potentials (N1, P2, N2). If the incoming stimulus is not the same and the subject discriminates the target from the preceding standard stimulus, the neural model of the stimulus environment is changed or "updated," such that a P3(00) potential is generated in addition to the sensory evoked potentials.

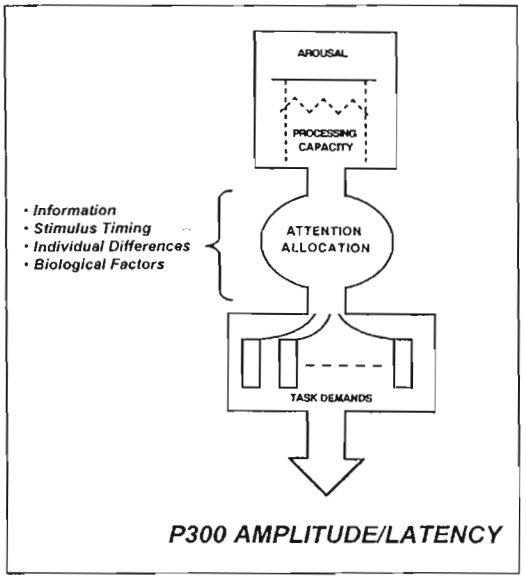

Figure 4.
Schematic illustration of the resource allocation model for P300 theory. Arousal governs the amount of processing capacity that can be allocated as attentional resources to a given task. The attention allocation governs P300 amplitude and latency in a manner that can help account for cognitive and biological variables that affect ERPs (after Kahneman, 1973[62]).

processing (e.g.[33,51,123,125,128,140,151]). This association is also found in clinical studies that indicate P300 latency increases as mental capability is compromised by dementing illness (e.g.[50,96,127,129,134]).

Attentional Resource Allocation

As the P300 is derived from neural activity, it is necessarily affected by the physical state of its underlying physiology that can be subsumed under the rubric of arousal in two ways: (1) a general arousing effect and (2) a specific or idiosyncratic effect that contributes to a complex pattern of activation that modulates information processing.[81,136] Figure 4 illustrates a theoretical model of how arousal affects P300 measures (cf. Kahneman[62]; Kok[82]). Arousal's tonic changes usually involve time periods on the order of minutes or hours and are manifestations of relatively slow fluctuations in the general or non-specific background arousal state of the individual, whereas phasic responses reflect the organism's energetic reaction to specific stimulus events. In this framework, tonic and phasic arousal effects originate from situational or spontaneous factors and affect the cognitive operations of attention and memory updating – i.e., the same processes hypothesized to underlie P300 generation.[122]

Dual-task effects also support the effects of biological influences on P300. Performance of a secondary cognitive (but not motor) task while executing the primary typical auditory or visual oddball paradigm will decrease or increase P300 amplitude in direct proportion to the attentional resources allocated to the secondary task (e.g.[55,84,168]). Hence, for any task situation in which arousal is hypothesized to be operating, attentional resources are allocated such that P300 amplitude is altered relative to a non-arousal state.[82] As suggested by Figure 4, both P300 amplitude and latency from a given task situation will reflect how the processing system provides general attentional resources in the evaluation of incoming stimuli. This theoretical interpretation is consonant with the context-updating view of P300 generation but additionally specifies a more general explanatory mechanism for the cognitive variables that affect this ERP component (cf. Donchin et al[30]; Hillyard and Picton[40]; Johnson[57]; Picton[109]; Pritchard[137]).

Table 1

P300 amplitude and latency biological determinants

Factor	Amplitude	Latency	Comment
Natural			
Circadian	Indirect	Indirect	Circadian body changes affect P300 measures
Body Temperature	No	Yes	Increased temperature, decreased latency
Heart Rate	No	Yes	Faster heart rate, decreased latency
Food Intake	Yes	Some	Amplitude increases, latency shorter
Activity Time	Yes	Some	Food interacts with activity preference time
Ultradian	Some	Yes	90 min latency cycles
Seasonal	Yes	No	Seasons with light, increased amplitude
Menstrual	No	No	Neutral stimuli, no effects
Induced			
Exercise	Indirect	Direct	Affects overall arousal level
Tonic	Yes	Yes	Increases amplitude, decreases latency
Chronic	No	Yes	Decreased latency, variable results across studies
Fatigue	Yes	Yes	Decreased amplitude, increased latency
Drugs (Common)	Yes	Yes	Specific drug, arousal level, tonic/chronic use
Caffeine	Some	Yes	Amplitude increases if fatigued, latency decreases
Nicotine	Small	Yes	Weak amplitude effects, latency decreases
Alcohol			
Acute	Yes	Yes	Amplitude decreases, latency increases
Chronic	No	No	Social drinking: no permanent long-term effects
Alcoholism Risk	Yes	No	At-risk: smaller amplitudes with visual tasks
Constitutional			
Age	Yes	Yes	Modality, task, response parameters important
Children	Yes	Yes	Amplitude increases, latency decreases
Adults	Yes	Yes	Amplitude decreases, latency increases
Intelligence	Yes	Yes	Amplitude from complex tasks smaller for more intelligent, latency shorter for perceptual/speeded classification tasks for more intelligent
Handedness	Yes	Yes	Amplitude: left > right for frontal/central sites Latency: left < right for frontal/central sites
Gender	Small	Small	Amplitude: female > male, latency: female < male
Personality	Yes	No	Amplitude: introverts < extroverts
Genetic	Yes	Yes	Amplitude and latency genetically determined

Adapted from Polich and Kok, 1995.[120]

Table 1 summarizes a variety of arousal-related "biological determinants" of P300 measures that been reviewed in detail elsewhere.[118] These factors reflect the action of independent variables that can contribute to both within and between-subjects designs, which can be controlled to reduce individual variation and increase experimental sensitivity.[117] The intra-subject test-retest correlation coefficients for P300 amplitude are .50 to .80 and peak latency are .40 to .70.[35,111,144] This test-retest variability may reflect the influence of ultradian rhythms on ERP measures.[87,138] To date only the P3b has been systematically assessed, with P3a normative data needed (cf. Knight[76]; Polich et al[126]). Despite this variation, however, P300 measures are as sensitive as other clinical assays, directly index individual cognitive capability for both normal and patient populations, and are relatively easy and inexpensive to obtain.[120]

NEUROPSYCHOLOGY OF P300

P300 and the Hippocampal Formation

The precise neural origins and, therefore, the neuropsychological meaning of the P300 are as yet unknown, although appreciable progress has been made in the last 20 years. Given the theoretical association of attentional and memory operations with P300, the first human studies on the neural origins of this ERP focused on the hippocampal formation. Initial reports employed depth electrodes that were implanted to help identify sources of epileptic foci in neurological patients. These recordings suggested that at least some portion of the P300 (P3b) is generated in the hip-

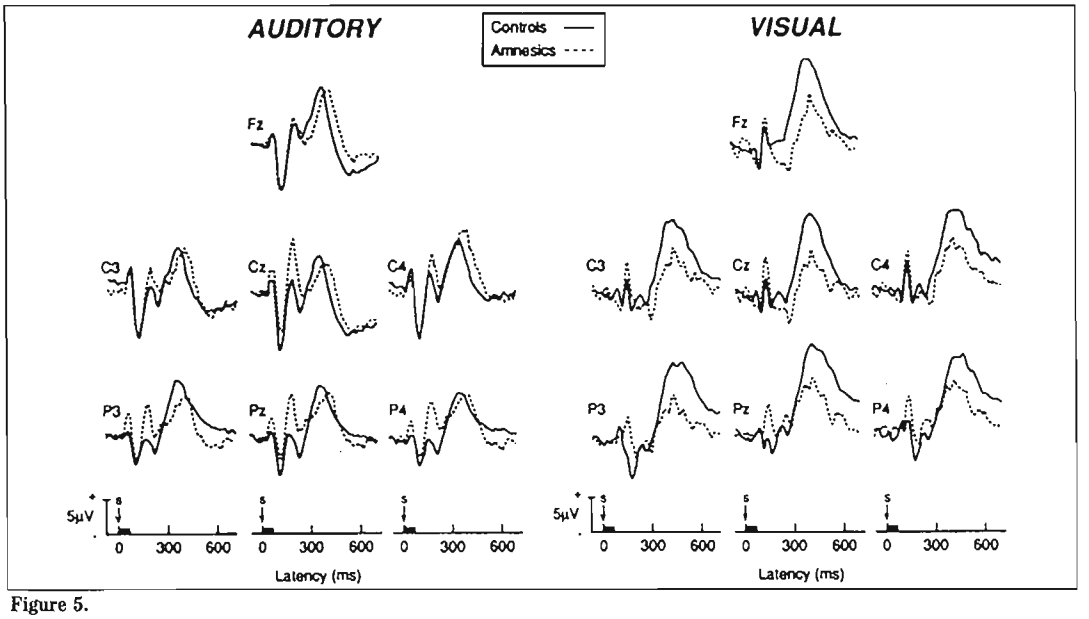

Figure 5.
Grand averaged auditory and visual oddball ERPs from normal controls (n=20) and bilateral hippocampal lesion amnesic patients (n=5). No statistically reliable differences were obtained for either P300 amplitude or latency between the controls and patients (after Polich and Squire, 1993[124]).

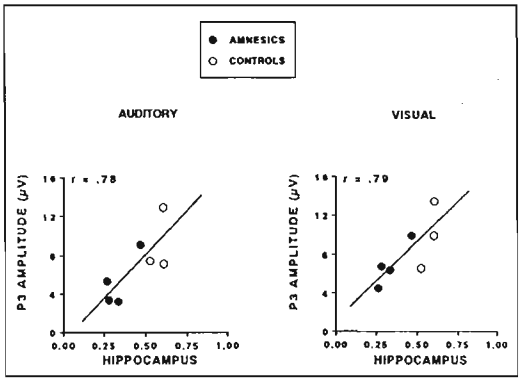

Figure 6.
Scattergrams of P300 amplitude from the auditory and visual ERP tasks plotted against relative hippocampus size (as assessed through MRI measures) from a subset of controls and bilateral hippocampal lesion amnesic patients for whom the brain area measures were available (previously unpublished from Polich and Squire, 1993[124]).

pocampal areas of the medial temporal lobe.[44,90] However, subsequent investigations using scalp recordings on individuals after temporal lobectomy,[58,146] experimental excisions in monkeys,[100,102] and patients with severe medial temporal lobe damage[98,141] found that the hippocampal formation does not contribute directly to the generation of P300.[95]

Figure 5 provides an example of these effects and illustrates ERPs from auditory and visual stimuli in an oddball task recorded from normal matched controls and patients with bilateral hippocampal lesions. Although general morphological differences were observed, no statistically reliable P300 amplitude or latency group effects were found.[124] Figure 6 illustrates additional observations from a subset of these patients and controls from the same study whose MRI hippocampal size measures were available. P300 amplitude from each modality is positively correlated with the proportional size of the hippocampal formation relative to the temporal lobe size from MRI measures and suggests that larger hippocampal size is associated with larger P300 amplitudes. Furthermore, other studies of lesion patients have found that the integrity of the temporal-parietal lobe junction is involved with either transmission or generation processes subsequent to hippocampal activity and contributes to component recordings at the scalp (cf. Johnson[60]; Knight et al[80]; Yamaguchi and Knight[162]; Verleger et al[157]). Taken together, these findings suggest that although relative absence of the hippocampus does not eliminate the P300, its presence and/or connection with temporal-parietal lobe function does influence P300 generation.

P3a Neural Substrates

As outlined above, the P3a subcomponent is produced when the attentional focus required for the primary discrimination task is interrupted by an infrequent nontarget stimulus event, which does not have to be perceptually novel.[18,119] ERP studies on humans with frontal lobe lesions have demonstrated that P3a requires frontal lobe func-

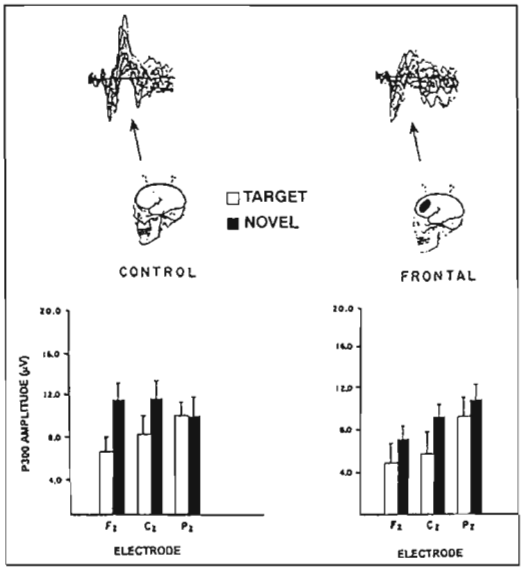

Figure 7.
Top: Overlapped single-subject ERPs from the auditory novel stimuli used to elicit the P3a from normal control and frontal lesion patients (n=10/group). Bottom: P300 amplitude from the target and novel stimulus conditions plotted as a function of the midline electrode positions for each subject group. Note that controls demonstrate the typical P300 frontal/central maximum for the novel stimulus P3a (black bars) and parietal maximum for target stimulus P3b (open bars), whereas the patients evince a greatly reduced frontal P3a but relatively normal P3b amplitude patterns (after Knight, 1984[74]).

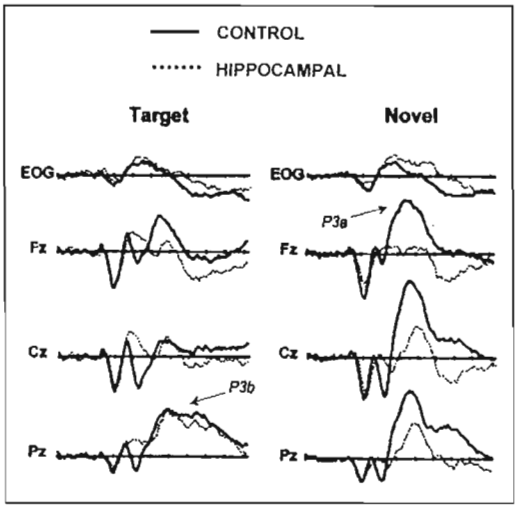

Figure 8.
Grand average auditory target and novel stimulus ERPs from normal controls and bilateral hippocampal lesion patients (n=7/group). Controls demonstrate robust P3a and P3b components, whereas hippocampal patients demonstrate highly reduced P3a components over the frontal recording site (after Knight, 1996[77]).

tion. Figure 7 illustrates this effect, with unaffected controls compared to frontal lobe lesion patients.[74] P3a from the novel distractor stimulus for the controls evinced frontal-central maximum amplitude, whereas P3b from the target stimulus produced a parietal maximum topographic scalp distribution. However, the frontal lesion patients demonstrated a clear diminution of the P3a subcomponent for the distractor stimulus, and the usual parietal maximum for the P3b from the target stimulus. These results imply that frontal lobe engagement is necessary for P3a generation, and that such activity contributes to the larger role of these mechanisms in attentional control.[76,78,79]

However, frontal lobe activity is not the only neural source for the P3a, as the hippocampal formation has been associated with the ERP processing of "novelty" in patients with focal hippocampal lesions.[77] Figure 8 illustrates the primary findings. P3a amplitude from novel auditory distractor stimuli for the controls yields the typical frontal-central maximum scalp topography, whereas for the patients this subcomponent is virtually eliminated over frontal electrode sites. P3b amplitude from the target stimulus is generally similar between the groups at the parietal site, as observed previously. Thus, P3a generation requires frontal lobe attentional mechanisms and hippocampal processes driven by novelty information processing.

Frontal-to-Parietal Lobe Interactions

Given this background, possible neuropsychological mechanisms for P3a and P3b generation can be developed. Figure 9 presents a graphic illustration of candidate neural generators. Discrimination between target and standard stimuli in an oddball paradigm is hypothesized to initiate frontal lobe activity that reflects the attentional focus required by task performance,[101,131,132] with ERP and neuroimaging findings demonstrating frontal lobe activity for the detection of rare or alerting stimuli.[90,135,154] P3a is related to the neural changes in the anterior cingulate when incoming stimuli replace the contents of working memory, and communication of this representational change is transmitted to infero-temporal lobe stimulus maintenance mechanisms.[28] P3b reflects the operation of memory storage operations that are then initiated in the hippocampal formation with the updated output transmitted to parietal cortex.[77,149] Although the exact pathways are not yet clear,[45,46] a variety of evidence suggests that the hippocampal formation contributes to these events, even though it is not necessary for P300 generation.[58,124] In summary, when a demanding stimulus commands frontal lobe attention, a P3a is produced; when attentional resources are allocated for subsequent memory updating after stimulus evaluation, a P3b is produced to establish the connection with storage areas in associational cortex.

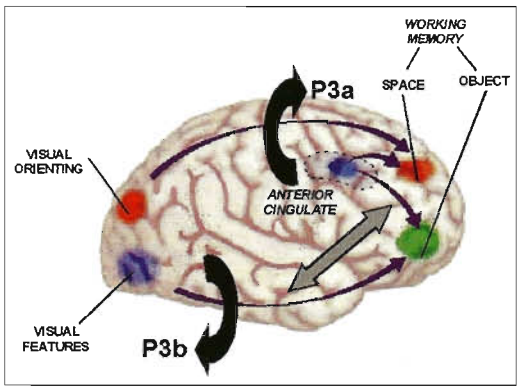

Figure 9.
Candidate neural generators for the P300 subcomponents: P3a reflects activity of the anterior cingulate when new stimuli are processed into working memory.; P3b reflects the subsequent activation of the hippocampal formation when frontal lobe mechanisms communicate with the temporal/parietal lobe connection. See text for explanation. (Figure based on Posner and Raichle,[133] and illustrated in Gazzaniga, Ivry, and Mangun,[41] p. 460)

Figure 10 presents a schematic outline portrait of this P300 neural generating system. As the model suggests, the neuroelectric events that underlie P300 generation stem from the interaction between frontal lobe and hippocampal/temporal-parietal function as outlined above (cf. Kirino et al[67]; Knight[77]). ERP and fMRI studies using oddball tasks have obtained patterns consistent with this frontal-to-temporal and parietal lobe activation pattern.[47,66,92,99,148] Further support comes from magnetic resonance imaging (MRI) of gray matter volumes that suggest individual variation in P3a amplitude from distractor stimuli is correlated with frontal lobe area size, whereas P3b amplitude from target stimuli is correlated with parietal area size[38] – a finding that may underlie individual variability for observing P3a and P3b subcomponents from simple oddball tasks (cf. Polich[113]; Squires et al[150]).

It also should be noted that the initial neural activation during auditory discrimination appears to originate from right frontal cortex,[130] and that P300 amplitude is larger over the right compared to left frontal/central areas.[5,6,93] Hence, after initial frontal processing of the incoming stimulus, activity is propagated between the cerebral hemispheres across the corpus callosum.[8,15,143] This hypothesis is supported by evidence that larger callosal fiber tracts are associated with greater P300 amplitudes and shorter latencies,[3,4,121] most likely because of increased inter-hemispheric communication (cf. Witelson[159]; Driesen and Raz[31]). Thus, the P3a and P3b are distinct ERP components that arise from the interaction between frontal lobe attentional control over the contents of working memory and the subsequent long-term storage operations.

NEUROELECTRIC BASIS OF P3A AND P3B

EEG, ERD, and P300

Conventionally, ERP analyses are performed in the time domain by assessing the amplitudes and latencies of prominent peaks in the averaged potentials and searching for correlates of information processing mechanisms. However, portions of P300 variability also can stem from individual differences in background electroencephalographic (EEG) spectral power and frequency, which have been found to contribute to ERP values.[116] For example, a positive relationship between pre-stimulus EEG power (theta and alpha) and P300 amplitude has been reported.[9,53] Several studies also have suggested that EEG and P300 measures interact during information processing tasks: When subjects exhibit relatively large amounts of alpha, their P300 amplitude also is large.[91,148] Taken together, these findings indicate that the underlying EEG rhythmicities are strong determinants of P300 generation (cf. Başar[11]; Başar et al[12]; Başar-Eroglu et al[13]; Klimesch et al[71]; Polich[115]).

Event-related desynchronization (ERD) analysis also has been used to quantify alpha frequencies during ERP processes.[107,108] A major finding is that different alpha frequencies have specific functional meanings, with slow alpha ERD (8-10 Hz) related primarily to attention and fast alpha ERD (10-12 Hz) associated with memory operations.[68,69,70,72,73] More important, the differentiation between slow and fast alpha ERDs has been shown to be sensitive to individual variation for P300 measures from an auditory oddball task: Slow alpha ERD is delayed and enhanced, whereas fast alpha ERD is inhibited in relation to larger and shorter P300 components across subjects (cf. Kolev et al[83]; Yordanova et al[166]). Such findings point to a tendency of sustaining the oscillatory mode of alpha activity at anterior sites,[42] and indicate that an important difference exists between the slow and fast alpha frequencies for P300 production.[163-165] Thus, P300 cognitive operations tasks index neural information processing related to alpha power and frequency.

Wavelet Transformation and P3a/P3b

Although analysis of EEG/ERP in the frequency domain has revealed that EEG rhythms across frequency ranges are functionally related to information processing and behavior (e.g.,[7,94]), the manifestly different time-scales or frequency contents of the transient ERP waves indicate that the time-scale at which the transient signal is expressed is itself an important index of the functional interpretation.[49,139] Hence, employing only temporal/spatial ERP analyses can obscure signal information, so that analyses that can characterize the relevant signal features in both time and frequency are necessary to consider. The wavelet transform (WT) is an efficient time-frequency (time-scale) decomposition method,[24,88] which has recently been systematically applied to ERP signals.[1,25,26] The major advan-

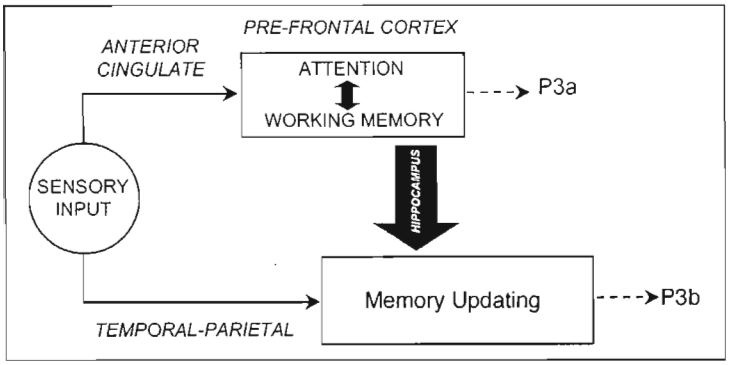

Figure 10.
Schematic model of candidate neural generator activity. Sensory input is processed in parallel streams, with frontal lobe activation from attention-driven working memory changes producing P3a and temporal/parietal lobe activation from memory updating operations producing P3b. See text for explanation.

tage of the WT is its multi-resolution property that employs shorter time windows for higher frequencies and longer time windows for lower frequencies — an attribute that closely matches the structural properties of ERP signals.[2,142]

This attribute of the WT has been applied to assess the P3a and P3b subcomponents elicited with the three-stimulus visual task described above.[27,119] The P3a components from the distractor stimuli for both the colored "novel" and "typical" blue square conditions produced comparable scalp topographies (see Figure 2), but the WT analysis revealed statistically greater increases in theta band activity for the novel relative to the blue square stimuli. These findings imply that despite similar ERP topographic distributions for the eliciting distractor stimuli, the underlying EEG signals differed appreciably and primarily in the theta frequencies. Reliable effects for the novelty stimulus condition were also found for alpha frequencies, but these were weaker than those from the theta band and primarily reflect scalp topography differences (cf. Spencer and Polich[148]; Kolev et al[83]; Yordanova and Kolev[164,165]; Yordanova et al[166]). Thus, the distractor stimulus contributes to P3a amplitude topography and is affected by discrimination difficulty for the ERP task, but novelty differentially changes the theta and alpha frequencies of the underlying EEG in the same task conditions.

These neuroelectric processes contribute to component variability across subjects, since P3a measures reflect primarily theta and early alpha activity,[27,54] whereas P3b measures index variation in delta and late alpha.[116,148] Given that ERPs consist of sequential as well as parallel activation of different neuronal groups, temporally overlapping activations can contribute to ERP generation. Hence, time-domain representations of ERPs contain signal components that occur in different frequency ranges, so that a simple topographic interpretation of ERP data employing a spatial decomposition is necessarily limited.[10,86] Because cognitive activity can be represented by partially overlapping large-scale neural networks, characterization of the dynamics of the underlying neural structures is necessary in order to decompose the surface ERPs into functional and meaningful neuronal substrates. Although this level of analysis is just beginning, understanding how the EEG determines the P3a and P3b subcomponents is a necessary step toward understanding the neuropsychology of P300.

PRACTICAL SUGGESTIONS FOR P300 CLINICAL APPLICATION

P3a and P3b Task Parameters

Brain disorders that affect the attention allocation and immediate memory will influence P300 measures by reducing amplitude and/or increasing latency.[118,120] The present chapter has attempted to specify a more detailed description of the neuropsychological origins and relationship between the P3a and P3b, so that the clinical utility of these ERP subcomponents can be developed as neuroelectric measures of cognitive efficiency – i.e., how well an individual's CNS can process and incorporate incoming stimulus information. However, clinical applications require specification of stimulus factors and task parameters for P3a and P3b tasks. Additional issues surrounding subject variables, alternative clinical P300 paradigms, and electrophysiological recording methods are discussed elsewhere.[117]

Table 2 summarizes stimulus and task parameters that can readily elicit P3a and P3b subcomponents. These conditions are based on a series of studies that have evaluated the P3a using the three-stimulus paradigm described above.[17,18,119] From these and additional unpublished data, the primary considerations for stimulus conditions in the P3a paradigm are to make the target/standard sensory discrimination challenging enough to produce a consistent task performance error rate of about 8-12% (which reflects the necessary task difficulty) and present a distractor stimulus that is physically quite distinct from the target and standard (cf. Katayama and Polich[65]; Polich and Comerchero[119]; Comerchero and Polich[18]). Novel stimuli are not needed for the distractor and perhaps should be avoided to minimize variability, since coercing the subject to focus attention by manipulating stimulus parameters with relatively small target/standard sensory differences will elicit strong P3a responses. The suggested P3b

Table 2

Recommended stimulus and task parameters for P3a and P3b auditory and visual paradigms (see text for explanation)

Modality	Auditory		Visual	
Stimulus (probability)	P3a	P3b	P3a	P3b
◯ Target (.15)	1000 Hz	1000 Hz	5.5 cm	5.5 cm
○ Standard (.70)	900 Hz	500 Hz	5.0 cm	3.0 cm
□ Distractor (.15)	4000 Hz		23.0 cm	

P3a auditory parameters are designed to produce about 10% error rates; a white noise burst may be used for distractor. Intensities of 70 dB SPL, durations of 60 ms (including 10 r/f), and binaural presentations produce excellent ERPs; minor variations on these values change P3a relatively little. Visual stimuli are solid, filled-in shapes; stimulus sizes are indicated by the width in cm. Brightness is medium and constant across conditions, duration of 60 msec is sufficient, viewing distance is about 1 m. For both modalities, inter-stimulus intervals of 2 sec, a button-press response to the target stimuli, with response time as well as performance accuracy recorded are typical procedures.

conditions employ a relatively easy target/standard discrimination task comparable to clinical ERP paradigms used previously (e.g.,[114,116]). Note that the target stimulus is identical within modalities. It is useful to collect ERPs using each task, as the P3b from the three-stimulus paradigm does reflect typical oddball P300 outcomes.

The nature of the stimulus and task conditions can be varied within the constraints of ensuring a difficult task for the P3a and an easy task for the P3b, as well as sufficient numbers of artifact-free trials obtained to stabilize ERP measures.[16,112] The auditory distractor should be a high-pitched tone or white noise sound burst, and the visual distractor should be a physically large square shape. The main distractor characteristic is that it should provide an attention-demanding interruption to the difficult target/standard discrimination task. The auditory distractor can be presented with greater intensity than the target or standard (e.g., 90 vs. 70 dB), and the visual distractor stimuli can be a large form of any color that presents a distinct perceptual contrast to the background color (e.g., blue on gray). Passive presentation procedures for visual stimuli also yield reliable P3a measures.[56] In general, as long as the target/standard discrimination engages attentional focus and the distractor is compelling, reliable P3a components will be obtained.

Clinical Applications

The goals of employing such procedures are twofold: (1) to characterize normative variation for P3a and P3b for the commonly used auditory and visual modalities, and (2) to apply the same methods to clinical populations. Given the theoretical considerations outlined above, the three-stimulus P3a measures should reflect neurocognitive measures related to frontal lobe function, whereas the oddball P3b measures will index attentional allocation capabilities across individuals.[78,122] Although application of these paradigms needs to be empirically expanded, a comprehensive P3a/P3b evaluation of appropriate control and patient populations will be of considerable clinical interest. Thus, use of P3a/P3b methods will produce reliable P300 subcomponents that can be used in a variety of applied circumstances.

CONCLUSIONS

This overview has attempted to limn the mechanisms underlying P3a and P3b generation. As these brain potentials are related to fundamental aspects of mental function, they offer significant promise as a means to assess normative cognition as well as impaired cognitive capability in patients. Further assessment of their neuropsychological foundations will provide additional insight into the cognitive meaning of P300. Analysis of the neuroelectric oscillations that govern ERP generation will make observation of the connection between brain and mind a reality. The theoretical and methodological approaches outlined here are an attempt to provide a basis for this development and are derived from contemporary research findings on factors that govern the P3a and P3b production. By controlling these variables and incorporating them into the design of applied studies, greater sensitivity for the P300 brain potential will be obtained and its utility as an index of individual cognitive efficiency increased. Thus, as the neuropsychology of P3a and P3b unfolds, understanding how these potentials contribute to "P300" will expand the theoretical and functional significance of this ubiquitous but still esoteric brain event.

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REFERENCES

1. Ademoglu A, Micheli-Tzanakou E, Istefanopulos Y. Analysis of pattern reversal visual evoked potentials (PRVEP's) by spline wavelets. IEEE Trans Biomed Engineer 1997; 44: 881-890.
2. Ademoglu A, Demiralp T, Yordanova J, Kolev V, Devrim M. Decomposition of event-related brain potentials into multicomponents using wavelet transform. Appl Signal Process 1998; 5: 142-151.
3. Alexander JE, Polich J. P300 differences between sinistrals and dextrals. Cogn Brain Res 1995; 2: 277-282.
4. Alexander JE, Polich J. Handedness and P300 from auditory stimuli. Brain Cogn 1997; 35: 259-270.
5. Alexander JE, Bauer LO, Kuperman S, Rohrbaugh J, Morzorati S, et al. Hemispheric differences for P300 amplitude from an auditory oddball task. Int J Psychophysiol 1996; 21: 189-196.
6. Alexander JE, Porjesz B, Bauer LO, Kuperman S, Mozarati S, O'Connor SJ, et al. P300 amplitude hemispheric asymmetries from a visual discrimination task. Psychophysiol 1995; 32: 467-475.
7. Anokhin AP, Lutzenberger W, Birbaumer N. Spatiotemporal organization of brain dynamics and intelligence: an EEG study in adolescents. Int J Psychophysiol 1999; 33: 259-273.
8. Barcelo F, Suwazono S, Knight RT. Prefrontal modulation of visual processing in humans. Nature Neurosci 2000; 3: 399-403.
9. Başar E, Schürmann M, Başar-Eroglu C, Demiralp T. Theta and delta responses in cognitive event-related potential paradigms and their possible psychophysiological correlates. In: Heinze HJ, Munte TF, Mangun GR, (eds). Cognitive Electrophysiology. Boston: Birkhauser, 1994: 334-367.
10. Başar E, Demiralp T, Schürmann M, Başar-Eroglu C, Ademoglu A. Oscillatory brain dynamics, wavelet analysis and cognition. Br Lang 1999; 66: 146-183.
11. Başar E. Brain Function and Oscillations. I. Brain Oscillations. Principles and Approaches. Springer Series in Synergetics. Berlin-Heidelberg-New York: Springer; 1998.
12. Başar E, Hari R, Lopes Da Silva FH, Schürmann M. Brain alpha activity: new aspects and functional correlates. Int J Psychophysiol 1997; 26: 353-368.
13. Başar-Eroglu C, Başar E, Demiralp T, Schürmann M. P300-response: possible psychophysiological correlates in delta and theta frequency channels: a review. Int J Psychophysiology 1992; 13: 161-179.
14. Bashore TR, van der Molen M. Discovery of P300: a tribute. Biol Psychol 1991; 32: 155-171.
15. Baudena P, Halgren E, Heit G, Clarke JM. Intracerebal potentials to rare target and distractor auditory and visual stimuli. III. Frontal cortex. Electroencephalogr Clin Neurophysiol 1995; 94: 251-264.
16. Cohen J, Polich J. On the number of trials needed for P300. Int J Psychophysiol 1997; 25: 249-255.
17. Comerchero MD, Polich J. P3a, perceptual distinctiveness, and stimulus modality. Cogn Br Res 1998; 7: 41-48.
18. Comerchero MD, Polich J. P3a and P3b from typical auditory and visual stimuli. Clin Neurophysiol 1999; 110: 24-30.
19. Courchesne E. Changes in P3 waves with event repetition: long-term effects on scalp distribution and amplitude. Electroencephalogr Clin Neurophysiol 1978; 45: 754-766.
20. Courchesne E, Courchesne RY, Hillyard SA. The effect of stimulus deviation on P3 waves to easily recognized stimuli. Neuropsychologia 1978; 16: 189-199.
21. Courchesne E, Hillyard SA, Galambos R. Stimulus novelty, task relevance and the visual evoked potential in man. Electroencephalogr Clin Neurophysiol 1975; 39: 131-143.
22. Courchesne E, Kilman BA, Galambos R, Lincoln A. Autism: processing of novel auditory information assessed by event-related brain potentials. Electroencephalogr Clin Neurophysiol 1984; 59: 238-248.
23. Covington JW, Polich J. P300, stimulus intensity, and modality. Electroencephalogr Clin Neurophysiol 1996; 100: 579-584
24. Daubechies I. The wavelet transform, time-frequency localization and signal analysis. IEEE Trans on Inform Theory 1990; 36: 961-1005.
25. Demiralp T, Ademoglu A, Schürmann M, Başar-Eroglu C, Başar E. Detection of P300 waves in single trials by the wavelet transform. Br Lang 1999a; 66: 108-128.
26. Demiralp T, Yordanova J, Kolev V, Ademoglu A, Devrim M. Time-frequency analysis of single-sweep event-related potentials by means of fast wavelet transform. Br Lang 1999b; 66: 129-145.
27. Demiralp T, Ademoglu A, Comerchero M, Polich J. Wavelet analysis of P3a and P3b. Br Topogr 2001; 13: 251-267.
28. Desimone R, Miller EK, Chelazzi L, Lueschow A. Multiple memory systems in the visual cortex. In: Gazzaniga MS, (ed). The Cognitive Neurosciences. Cambridge, Mass: MIT Press; 1995: 475-486.
29. Donchin E, Coles MGH. Is the P300 component a manifestation of context updating? Behav Br Sci 1988; 11: 357-374.
30. Donchin E, Karis D, Bashore TR, Coles MGH, Gratton G. Cognitive psychophysiology and human information processing. In: Coles MGH, Donchin E, Porges SW, (eds). Psychophysiology: Systems, Processes, and Applications. New York: The Guilford Press; 1986: 244-267.
31. Driesen NR, Raz N. The influence of sex, age, and handedness of corpus callosum morphology: a meta-analysis. Psychobiology 1995; 23: 240-247.
32. Duncan-Johnson CC. P300 latency: a new metric of information processing. Psychophysiology 1981; 18: 207-215.
33. Emmerson R, Dustman R, Shearer D, Turner C. P300 latency and symbol digit correlations in aging. Experimental Aging Res 1990; 15: 151-159.
34. Fabiani M, Karis D, Donchin E. Effects of mneumonic strategy manipulation in a von Restorff paradigm. Electroencephalogr Clin Neurophysiol 1990; 75: 22-35.
35. Fabiani M, Gratton G, Karis D, Donchin E. The definition, identification, and reliability of measurement of the P300 component of the event-related brain potential. In: Ackles PK, Jennings JR, Coles MGH, (eds). Advances in Psychophysiology. Greenwich, CT: JAI Press; 1987; 2: 1-78.
36. Fabiani M, Friedman D, Ching J. Individual differences in P3 scalp distribution in older adults, and their relationship to frontal lobe function. Psychophysiology 1998; 35: 698-708.
37. Falkenstein M, Koshlykova NA, Kiroj VN, Hoormann J, Hohnsbein J. Late ERP components in visual and auditory go/nogo tasks. Electroencephalogr Clin Neurophysiol 1995; 96: 36-43.

38. Ford JM, Sullivan E, Marsh L, White P, Lim K, Pfefferbaum A. The relationship between P300 amplitude and regional gray matter volumes depends on the attentional system engaged. Electroencephalogr Clin Neurophysiol 1994; 90: 214-228.

39. Friedman D, Simpson G. ERP amplitude and scalp distribution to target and novel events: effects of temporal order in young, middle-age, and older adults. Cogn Br Res 1994; 2: 49-63.

40. Friedman D, Kazmerski VA, Cycowicz YM. Effects of aging on the novelty P3 during attend and ignore oddball tasks. Psychophysiology 1998; 35: 508-520.

41. Gazzaniga MS, Ivry RB, Mangun GR. Cognitive neuroscience: The biology of the mind. New York: W.W. Norton & Company, 1998.

42. Gevins A, Smith ME, McEvoy L, Yu D. High-resolution EEG mapping of cortical activation related to working memory: effects of task difficulty, type of processing, and practice. Cerebral Cortex 1997; 7: 374-385.

43. Grillon C, Courchesne E, Ameli R, Elmasian R, Braff D. Effects of rare non-target stimuli on brain electrophysiological activity and performance. Int J Psychophysiol 1990; 9: 257-267.

44. Halgren E, Squires NK, Wilson C, Rohrbaugh J, Babb T, Crandall P. Endogenous potentials in the human hippocampal formation and amygdala by infrequent events. Science 1980; 210: 803-805.

45. Halgren E, Baudena P, Clarke JM, Heit G, Liegeois C, Chauvel P, Musolino A. Intracerebral potentials to rare target and distractor auditory and visual stimuli. I. Superior temporal plane and parietal lobe. Electroencephalogr Clin Neurophysiol 1995a; 94: 191-220.

46. Halgren E, Baudena P, Clarke J M, Heit G, Marinkovic K, Devaux B, et al. Intracerebral potentials to rare target and distractor auditory and visual stimuli. II. Medial, lateral and posterior temporal lobe. Electroencephalogr Clin Neurophysiol 1995b; 94; 229-250.

47. He B, Lian J, Spencer KM, Dien J, Donchin E. A cortical potential imaging analysis of the P300 and novelty P3 components. Human Br Map 2001; 12: 120-130.

48. Hillyard SA, Picton TW. Electrophysiology of cognition. In: Geiger SR, (ed). Handbook of Physiology: A Critical, Comprehensive Presentation of Physiological Knowledge and Concepts (Section 1: The nervous system). New York: American Physiology Association 1986; 5: 519-584.

49. Hillyard SA, Picton TW. Electrophysiology of cognition. In: Plum F, (ed). Handbook of Physiology. Baltimore: American Physiological Society 1987: 519-584.

50. Homberg V, Hefter H, Granseyer G, Strauss W, Lange H, Hennerici M. Event-related potentials in patients with Huntington's disease and relatives at risk in relation to detailed psychometry. Electroencephalogr Clin Neurophysiol 1986; 63: 552-569.

51. Houlihan M, Stelmack R, Campbell K. Intelligence 1998; 26: 9-25.

52. Ilan AB, Polich J. P300 and response time from a manual Stroop task. Clin Neurophysiol 1999; 110: 367-373.

53. Intriligator J, Polich J. On the relationship between background EEG and the P300 event-related potential. Biol Psychol 1994; 37: 207-218.

54. Intriligator J, Polich J. On the relationship between EEG and ERP variability. Int J Psychophysiol 1995; 20: 59-74.

55. Israel JB, Chesney GL, Wickens CD, Donchin E. P300 and tracking difficulty: evidence for multiple resources in dual-task performance. Psychophysiology 1980; 17: 259-273.

56. Jeon Y-W, Polich J. P3a from a passive visual paradigm. Clin Neurophysiol 2001; 112: 2202-2208.

57. Johnson R. A triarchic model of P300 amplitude. Psychophysiology 1986; 23: 367-384.

58. Johnson R. Scalp-recorded P300 activity in patients following unilateral temporal lobectomy. Brain 1988a; 111: 1517-20.

59. Johnson R. The amplitude of the P300 component of the event-related potential: review and synthesis. In: Ackles P, Jennings JR, Coles MGH, (eds). Advances in Psychophysiology: A Research Annual. Greenwich, CT: JAI Press, Inc; 1988b; 3: 69-137.

60. Johnson R. On the neural generators of the P300 component of the event-related potential. Psychophysiology 1993; 30: 90-97.

61. Johnson R. Event-related potential insights into the neurobiology of memory systems. In: Boller F, Grafman J, (eds). Handbook of Neuropsychology. Amsterdam: Elsevier 1995; 10: 135-163.

62. Kahneman D. Attention and Effort. Englewood-Cliffs. NJ: Prentis Hall 1973.

63. Katayama J, Polich J. P300 from one-, two-, and three-stimulus auditory paradigms. Int J Psychophysiol 1996a; 23: 33-40.

64. Katayama J, Polich J. P300, probability, and the three-tone paradigm. Electroencephalogr Clin Neurophysiol 1996b; 100: 555-562.

65. Katayama J, Polich J. Stimulus context determines P3a and P3b. Psychophysiology 1998; 35: 23-33.

66. Kiehl KA, Laurens KR, Duty TL, Forster BB, Liddle PF. Neural sources involved in auditory target detection and novelty processing: an event-related fMRI study. Psychophysiology 2001; 38: 133-142.

67. Kirino E, Belger A, Goldman-Rakic P, McCarthy, G. Prefrontal activation evoked by infrequent target and novel stimuli in a visual target detection task: an event-related functional magnetic resonance study. J Neurosci 2000; 20: 6612-6618.

68. Klimesch W. EEG-alpha rhythms and memory processes. Int J Psychophysiol 1997; 26: 319-340.

69. Klimesch W. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. Br Res Rev 1999; 29: 169-195.

70. Klimesch W, Doppelmayr M, Pachinger T, Russegger H. Event-related desynchronization in the alpha band and the processing of semantic information. Cogn Br Res 1997; 6: 83-94.

71. Klimesch W, Doppelmayr M, Russegger H, Pachinger T, Schwaiger J. Induced alpha band power changes in the human EEG and attention. Neurosci Lett 1998; 244: 73-76.

72. Klimesch W, Schimke H, Schwaiger J. Episodic and semantic memory: an analysis in the EEG theta and alpha band. Electroencephalogr Clin Neurophysiol 1994; 91: 428–441.

73. Klimesch W, Dopplemayr M, Schwaiger J, Winkler T, Gruber W. Theta oscillations and the ERP old/new effect: independent phenomena? Clin Neurophysiol 2000; 111: 781-793.

74. Knight RT. Decreased response to novel stimuli after prefrontal lesions in man. Electroencephalogr Clin Neurophysiol 1984; 59: 9-20.

75. Knight RT. Aging decreases auditory event-related potentials to unexpected stimuli in humans. Neurobiol Aging 1987; 8: 109-113.

76. Knight RT. Neural mechanisms of event-related potentials from human lesion studies. In: Rohrbaugh J, Parasuraman R, Johnson R, (eds). Event-related Brain Potentials: Basic Issues and Applications. New York: Oxford Press; 1990: 3-18.

77. Knight RT. Contribution of human hippocampal region to novelty detection. Nature 1996; 383: 256-259.

78. Knight RT. Distributed cortical network for visual attention. J Cogn Neurosci 1997; 9: 75-91.

79. Knight R, Grabowecky M, Scabini D. Role of human prefrontal cortex in attention control. Adv Neurol 1995; 66: 21-34.

80. Knight RT, Scabini D, Woods D, Clayworth C. Contributions of temporal-parietal junction to the human auditory P3. Br Res 1989; 502: 109-116.

81. Kok A. Internal and external control: a two-factor model of amplitude change of event-related potentials. Biol Psychol 1990; 74: 203-236.

82. Kok A. Event-related potential (ERP) reflections of mental resources: a review and synthesis. Biol Psychol 1997; 45: 19-56.

83. Kolev V, Yordanova J, Schürmann M, Başar E. Event-related alpha oscillations in task processing. Clin Neurophysiol 1999; 110: 1784-1792.

84. Kramer AF, Strayer DL. Assessing the development of automatic processing: an application of dual-track and event-related brain potential methodologies. Biol Psychol 1988; 26: 231-267.

85. Kutas M, McCarthy G, Donchin E. Augmenting mental chronometry: the P300 as a measure of stimulus evaluation. Science 1977; 197: 792-795.

86. LaBar KS, Gitelman DR, Parrish TB, Mesulam MM. Neuroanatomic overlap of working memory and spatial attention networks: a functional MRI comparison within subjects. NeuroImage 1999; 10: 695-704.

87. Lin E, Polich J. P300 habituation patterns: individual differences and ultradian rhythms. Percept Motor Skills 1999; 88: 1111-1125.

88. Mallat S. A theory for multiresolution signal decomposition: the wavelet representation. IEEE Trans Pattern Analy Machine Intelligence 1989; 11: 674-693.

89. McCarthy G, Donchin E. A metric for thought: a comparison of P300 latency and reaction time. Science 1981; 211: 77-80.

90. McCarthy G, Wood CC, Williamson PD, Spencer D. Task-dependent field potentials in human hippocampal formation. J Neurosci 1989; 9: 4235-4268.

91. Mecklinger A, Kramer AF, Strayer DL. Event-related potentials and EEG components in a semantic memory search task. Psychophysiology 1992; 29: 104-119.

92. Mecklinger A, Maess B, Opitz B, Pfeifer E, Cheyne D, Weinberg H. A MEG analysis of the P300 in visual discrimination tasks. Electroencephalogr Clin Neurophysiol 1998; 108: 45-56.

93. Mertens R, Polich J. P300 hemispheric differences from oddball, verbal, and spatial tasks. Psychophysiology 1997; 34: S64. Abstract.

94. McEvoy LK, Smith ME, Gevins A. Test-retest reliability of cognitive EEG. Clin Neurophysiol 2000; 111: 457-463.

95. Molnár M. On the origin of the P300 event-related potential component. Int J Psychophysiol 1994; 17: 129-44.

96. O'Donnell BF, Friedman S, Swearer JM, Drachman D. Active and passive P300 latency and psychometric performance: influence of age and individual differences. Int J Psychophysiol 1992; 12: 187-195.

97. Oken BS. Endogenous event-related potentials. In: Chiappa KH, (ed). Evoked Potentials in Clinical Medicine. Raven Press: New York; 1989: 563-592.

98. Onofrj M, Fulgente T, Nobiolio D, Malatesta G, Bazzano S, Colamartino P, Gambi D. P300 recordings in patients with bilateral temporal lobe lesions. Neurology 1992; 42: 1762-1767.

99. Opitz B, Mecklinger A, Von Cramon DY, Kruggel F. Combining electrophysiological and hemodynamic measures of the auditory oddball. Psychophysiology 1999; 36: 142-147.

100. Paller KA, McCarthy G, Roessler E, Allison T, Wood CC. Potentials evoked in human and monkey medial temporal lobe during auditory and visual oddball paradigms. Electroencephalogr Clin Neurophysiol 1992; 84: 269-279.

101. Paller KA, McCarthy G, Wood CC. ERPs predictive of subsequent recall and recognition performance. Biol Psychol 1988a; 26: 269-276.

102. Paller KA, Zola-Morgan S, Squire LR, Hillyard SA. P3-like brain waves in normal monkeys and in monkeys with medial temporal lesions. Behav Neurosci 1988b; 102: 714-725.

103. Pardo JV, Fox P, Raichle M. Localization of human system for sustained attention by positron emission tomography. Nature 1991; 349: 61-64.

104. Pfefferbaum A, Ford JM. ERPs to stimuli requiring response production and inhibition: effects of age, probability and visual noise. Electroencephalogr Clin Neurophysiol 1988; 71: 55-63.

105. Pfefferbaum A, Ford JM, Weller BJ, Kopell BS. ERPs to response production and inhibition. Electroencephalogr Clin Neurophysiol 1985; 60: 423-434.

106. Pfefferbaum A, Christensen C, Ford JM, Kopell B. Apparent response incompatibility effects on P300 latency depend on the task. Electroencephalogr Clin Neurophysiol 1986; 64: 424-437.

107. Pfurtscheller G, Klimesch W. Event-related synchronization and desynchronization of alpha and beta waves in a cognitive task. In: Basar E, Bullock TH, (eds). Induced Rhythms in the Brain. Boston: Birkhäuser; 1992: 117-128.

108. Pfurtscheller G, Lopes da Silva FH. Event-related EEG/MEG synchronization and desynchronization: basic principles. Clin Neurophysiol 1999; 110: 1842-1857.

109. Picton TW. The P300 wave of the human event-related potential. J Clin Neurophysiol 1992; 9: 456-479.

110. Polich J. Attention, probability, and task demands as determinants of P300 latency in ERPs from auditory stimuli. Electroencephalogr Clin Neurophysiol 1986a; 63: 251-259.

111. Polich J. Normal variation of P300 from auditory stimuli. Electroencephalogr Clin Neurophysiol 1986b; 65: 236-240.

112. Polich J. P300 development from auditory stimuli. Psychophysiology 1986c; 23: 590-597.

113. Polich J. Bifurcated P300 peaks: P3a and P3b revisited? Jour Clin Neurophysiol 1988; 5: 287-294.

114. Polich J. Meta-analysis of P300 normative aging studies. Psychophysiology 1996; 33: 334-353.

115. Polich J. EEG and ERP assessment of normal aging. Electroencephalogr Clin Neurophysiol 1997a; 104: 228-243.

116. Polich, J. On the relationship between EEG and P300: Individual differences, aging, and ultradian rhythms. Int J Psychophysiol 1997b; 26: 299-317.

117. Polich, J. P300 clinical utility and control of variability. J Clin Neurophysiol 1998; 15: 14-33.

118. Polich J. P300 in clinical applications. In: Niedermeyer E, Lopes da Silva F, (eds). Electroencephalography: Basic Principles, Clinical Applications and Related Fields. 4th ed. Baltimore-Munich: Urban & Schwarzenberg; 1999: 1073-1091.

119. Polich J. Comerchero MD. P3a from visual stimuli; typicality, task and topography. Br Topogr 2003; 15: 141-152.

120. Polich J, Herbst KL. P300 as a clinical assay: rationale, evaluation, and findings. Int J Psychophysiol 2000; 38: 3-19.

121. Polich J, Hoffman LD. P300 and handedness: on the possible contribution of corpus callosal size to ERPs. Psychophysiology 1998; 35: 497-507.

122. Polich J, Kok A. Cognitive and biological determinants of P300: An integrative review. Biol Psychol 1995; 41: 103-146.

123. Polich J, Martin S. P300, cognitive capability, and personality: a correlational study of university undergraduates. Personality Individ Differ 1992; 13: 533-543.

124. Polich J, Squire L. P300 from amnesic patients with bilateral hippocampal lesions. Electroencephalogr Clin Neurophysiol 1993; 86: 408-417.

125. Polich J, Howard L, Starr A. P300 latency correlates with digit span. Psychophysiology 1983; 20: 665-669.

126. Polich J, Howard L, Starr A. Aging effects on the P300 component of the event-related potential from auditory stimuli: peak definition, variation, and measurement. J Gerontol 1985; 40; 721-726.

127. Polich J, Ladish C, Bloom FE. P300 assessment of early Alzheimer's disease. Electroencephalogr Clin Neurophysiol 1990a; 77: 179-189.

128. Polich J, Ladish C, Burns T. Normal variation of P300 in children: age, memory span, and head size. Int J Psychophysiol 1990b; 9: 237-248.

129. Polich J, Ehlers CL, Otis S, Mandell AJ, Bloom FE. P300 latency reflects cognitive decline in dementing illness. Electroencephalogr Clin Neurophysiol 1986; 63: 138-144.

130. Polich J, Alexander JE, Bauer LO, Kuperman S, Rohrbaugh J, Mozarati S, et al. P300 topography of amplitude/latency correlations. Br Topogr 1997; 9: 275-282.

131. Posner MI. Attention as a cognitive neural system. Curr Direct Psychol Sci 1992; 1: 11-14.

132. Posner MI, Petersen SE. The attention system of the human brain. Ann Rev Psychol 1990; 13: 25-42.

133. Posner MI, Raichle ME. Images of Mind. New York: Oxford University Press; 1994.

134. Potter D D, Barrett K. Assessment of mild head injury with ERPs and neuropsychological tasks. J Psychophysiol 1999; 13: 173-189.

135. Potts GF, Liotti M, Tucker DM, Posner MI. Frontal and inferior temporal cortical activity in visual target detection: evidence from high spatially sampled event-related potentials. Br Topogr 1996; 9: 3-14.

136. Pribram KH, McGuinness D. Arousal, activation, and effort in the control of attention. Psychol Rev 1975; 82: 116-149.

137. Pritchard WS. Psychophysiology of the P300. Psychol Bull 1981; 89: 506-540.

138. Ravden D, Polich J. On P300 measurement stability: habituation, intra-trial block variation, and ultradian rhythms. Biol Psychol 1999; 51: 59-76.

139. Regan D. Human brain electrophysiology: evoked potentials and evoked magnetic fields in science and medicine. Amsterdam: Elsevier; 1989.

140. Reinvang, I. Cognitive event-related potentials in neuropsychological assessment. Neuropsychol Rev 1999; 9: 231-248.

141. Rugg MD, Pckles C, Potter D, Roberts. Normal P300 following extensive damage to the left medial temporal lobe. J Neurol Neurosurg Psychiat 1991; 54: 217-222.

142. Samar VJ, Swartz KP, Raghuveer MR. Multiresolution analysis of event-related potentials by wavelet decomposition. Br Cogn 1995; 27: 398-438.

143. Satomi K, Horai T, Kinoshita Y, Wakazono A. Hemispheric asymmetry of event-related potentials in a patient with callosal disconnection syndrome: a comparison of auditory, visual, and somatosensory modalities. Electroencephalogr Clin Neurophysiol 1995; 94: 440-449.

144. Segalowitz S, Barnes K. The reliability of ERP components in the auditory oddball paradigm. Psychophysiol 1993; 30: 451-459.

145. Simons RF, Graham FK, Miles MA, Chen X. On the relationship of P3a and the Novelty-P3. Biol Psychol 2001; 56: 207-218.

146. Smith ME, Halgren E. Dissociation of recognition memory components following temporal lobe lesions. J Exper Psychol Gen 1989; 15: 50-60.

147. Sommer W, Leuthold H, Matt J. The expectancies that govern P300 amplitude are mostly automatic and unconscious. Behav Br Sci 1998; 21: 149-150.

148. Spencer K, Polich J. Post-stimulus EEG spectral analysis and P300: attention, task, and probability. Psychophysiol 1999; 36: 220-232.

149. Squire LR, Kandel ER. Memory from mind to molecules. New York: Scientific American Library; 1999.

150. Squires NK, Squires K, Hillyard S. Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli in man. Electroencephalogr Clin Neurophysiol 1975; 38: 387-401.

151. Stelmack RM, Houlihan M. Event-related potentials, personality and intelligence: concepts, issues, and evidence. In: Saklofske DH, Zaidner M, (eds). International Handbook Personality and Intelligence. New York: Plenum Press; 1994: 349-365.

152. Sutton S, Braren M, Zubin J, John ER. Evoked potential correlates of stimulus uncertainty. Science 1965; 150: 1187-1188.

153. Suwazono S, Machado L, Knight RT. Predictive value of novel stimuli modifies visual event-related potentials and behavior. Clin Neurophysiol 2000; 111: 29-39.

154. Verbaten MN, Huyben MA, Kemner C. Processing capacity and the frontal P3. Int J Psychophysiol 1997; 25: 237-248.

155. Verleger R. On the utility of P3 latency as an index of mental chronometry. Psychophysiology 1997;34: 131-156.

156. Verleger R. Event-related potentials and cognition: a critique of the context updating hypothesis and an alternative interpretation of P3. Behav Br Sci 1988; 11: 343-356.

157. Verleger R, Heide W, Butt C, Kömpf D. Reduction of P3b in patients with temporo-parietal lesions. Cogn Br Res 1994; 2: 103-116.

158. Wickens C, Kramer A, Vanesse L, Donchin E. The performance of concurrent tasks: a psychophysiological analysis of the reciprocity of information processing resources. Science 1983; 221: 1080-1082.

159. Witelson SF. Cognitive neuroanatomy: a new era. Neurology 1992; 42: 709-713.

160. Yamaguchi S, Knight R. Age effects on the P300 to novel somatosensory stimuli. Electroencephalogr Clin Neurophysiol 1991a; 78: 297-301.

161. Yamaguchi S, Knight RT. P300 generation by novel somatosensory stimuli. Electroencephalogr Clin Neurophysiol 1991b; 78: 50-55.

162. Yamaguchi S, Knight RT. Effects of temporal-parietal lesions on the somatosensory P3 to lower limb stimulation. Electroencephalogr Clin Neurophysiol 1992; 84: 139-148.

163. Yordanova J, Kolev V. Developmental changes in the relationship between EEG theta response and P300. Electroencephalogr Clin Neurophysiol 1997; 104: 418-430.

164. Yordanova J, Kolev V. A single-sweep analysis of the theta frequency band during an auditory oddball task. Psychophysiol 1998a; 35: 116-126.

165. Yordanova J, Kolev V. Event-related alpha oscillations are functionally associated with P300 during information processing. NeuroReport 1998b; 9: 3159-3164.

166. Yordanova J, Kolev V, Polich J. P300 and alpha event-related desynchronization (ERD). Psychophysiol 2001; 38: 143-152.

NON-CLINICAL

Digital Signal Processing and Single Trial Evoked Potentials: Accomplishments, Limitations and Promises

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ABSTRACT

Digital signal processing (DSP) involves converting the analog EEG signal into a digital sequence ("sampling"), followed by computer-based processing. Early DSP methods were aimed at improving ensemble averaging, which relies on the rather unrealistic assumptions that the EP is time-locked to the stimulus, does not vary between trials, and is not correlated with the ongoing EEG. These days, much attention is devoted to single trial analysis. Two basic approaches are being explored: inverse filtering, and decomposition.

Inverse filtering uses a model for EEG generation. Once the model parameters have been adapted to reproduce the pre-stimulus EEG, post-stimulus EEG/EP is input to the inverse model, resulting in an attenuation of the post-stimulus, spontaneous EEG. Models chosen for their mathematical convenience or neurophysiological relevance have been used with moderate success, as will be illustrated by examples.

Decomposition methods take the single trial EEG/EP apart into its constituent rhythms. Band-pass filtering is one approach, but may introduce misleading artifacts, as we will show. The wavelet transform shows promise, but the decomposition depends sensitively on the choice of the "mother wavelet." The author's laboratory developed the piecewise Prony method (PPM), and results of its application to auditory EPs are presented.

INTRODUCTION

Ever since the introduction of ensemble averaging, about 35 years ago, computers, and more specifically, digital signal processing (DSP) methods have played a major role in evoked potential (EP) analysis. DSP involves converting the analog EEG signal into a digital sequence ("sampling"), followed by computer-based processing. DSP methods are implemented in software, providing flexibility not attainable in implementations using analog circuitry.

Early DSP methods were aimed at improving ensemble averaging, which relies on the rather unrealistic assumptions that the EP is time-locked to the stimulus, does not vary between trials, and is independent (or at least uncorrelated) with the ongoing EEG. Examples include latency-corrected averaging[23] and Wiener filtering.[31]

Veritable single trial analysis methods can be divided into two categories: inverse filtering methods, and decomposition methods. Inverse filtering involves the use of a model for EEG generation, which is adapted to reproduce the pre-stimulus EEG. Post-stimulus EEG/EP is input to the inverse model, resulting in an attenuation of the post-stimulus, spontaneous EEG. Inverse filtering is reviewed below.

Regardless of the choice of model, all inverse filtering methods assume that the event related activity is additive to the spontaneous EEG activity. However, there is mounting evidence that the EEG and EP are not two independent processes, but that the event related activity is due to an interaction between spontaneous neural activity and specific afferent activity. This interaction may result in the emergence of new frequency components, attenuation or augmentation of EEG rhythms present pre-stimulus, or phase resetting of certain components (or a combination of all or some of these). Decomposition methods are well-suited to uncover which of these processes underlie EP generation. Next, several decomposition methods are reviewed and their strengths and weaknesses are discussed. Then an application of a new decomposition method for single trial auditory EPs is presented, and a discussion concludes this presentation.

INVERSE FILTERING

One class of single trial EP analysis methods involves the use of filters, designed to attenuate the ongoing EEG activity while leaving the EP activity unaffected. A variety of such methods have been developed, many involving Wiener filtering.[8,19] A theoretical review of such methods was presented by de Weerd,[28] who also introduced a time-varying method.[29] Other filtering approaches rely on linear, and especially autoregressive, modeling.[15] Applications to EP enhancement are reported using single EEG/EP trials.[7,22,26] The basic idea is to fit a model to pre-stimulus EEG and to pass the

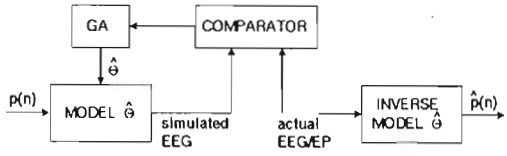

Figure 1
Inverse modeling approach to EP enhancement. MODEL: cortical column model of EEG generation, with model behavior governed by parameters that will have to be estimated from actual EEG data; INVERSE MODEL: inverse version of MODEL; COMPARATOR: trajectory-based comparator; GA: genetic algorithm-based model parameter estimator.

stimulus response through the inverse version of the model. Ideally, the ongoing EEG component of the brain activity following stimulation would be suppressed. A weakness of these methods is that they use models selected primarily for their ease of use, without regard to neurophysiology.

Recently, our laboratory developed an inverse filtering method[20] using a mathematical, but neurophysiologically-based model of EEG generation.[18,19] The model is defined by six coupled, nonlinear differential equations. The type of activity produced by the model depends on six "free" parameters — m, α, C, A, B, v_0 (collectively referred to as Θ)— the values of which have to be determined experimentally.

This model is used in the inverse filtering method outlined in Figure 1. The model parameters are estimated from the pre-stimulus segment of the recorded EEG/EP, which may be assumed to contain relevant information about the background activity only. The nonlinearity of the model equations makes it difficult to efficiently compute the model parameters, such that the model output matches actually observed cortical activity. A common approach for estimating parameters in nonlinear models involves the iterative minimization of a "loss function," which quantifies the difference between the target (the time series to be modeled) and the estimated data (the model-generated time series). Here we use a genetic algorithm[32] to iteratively minimize a trajectory-based loss function.[17]

Next, the inverse model is constructed and EEG/EP segments containing both pre-stimulus and post-stimulus activity are passed through it. Theoretically, the inverse model will remove the ongoing EEG component, thus enhancing the stimulus-specific activity.

Flash visual evoked potentials (FVEP) obtained from three adult male subjects, referred to as CE, MB and MS, respectively, were used.[5] The subjects viewed identical photo-flashes through closed eyelids. The inter-stimulus interval was randomly chosen between two and six (whole) seconds. Monopolar recordings

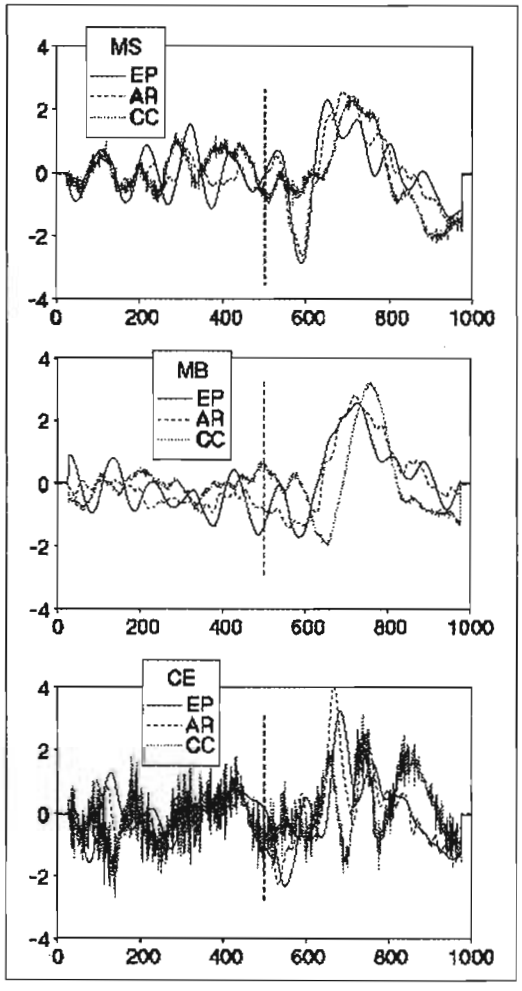

Figure 2
Averaged EPs obtained using conventional ensemble averages (solid line –EP–), inverse AR modeling (dashed line –AR–), and neurophysiological modeling (dotted line, –CC–). All averages are normalized by subtracting the mean and dividing by the standard deviation. Vertical dotted line indicates moment of stimulus delivery. MS, MB and CE refer to three male subjects.

were taken from the PO_z electrode site (midway between P_z and O_z) and the reference electrode at the linked earlobes. The data were sampled at 1000 Hz. Ten single trials were selected from each subject and the mean was removed for each trial.

The model parameters were estimated from the 0.5 s segment immediately prior to stimulus delivery. Ten estimates of the model parameters were obtained for each trial, and ensemble averaged to reduce the variance in the model parameter estimates. An inverse model was constructed from the mean estimated parameter set, and the corresponding single trial was passed through this

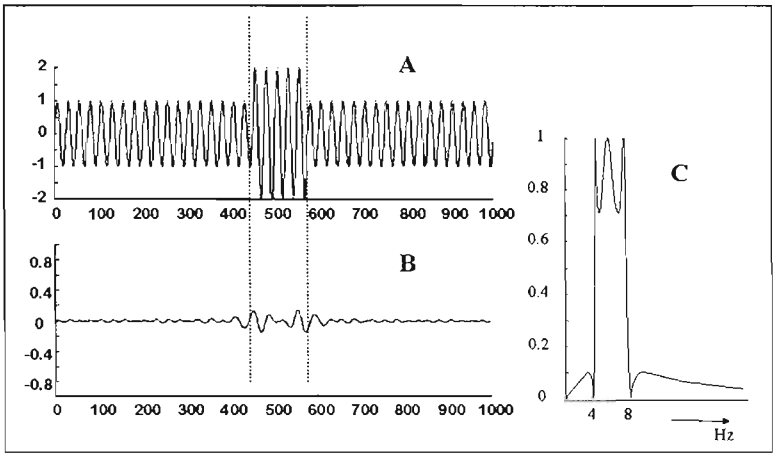

Figure 3
A) 10 Hz sine wave, undergoing sudden increase and decrease in amplitude (dotted lines).

B) Result of passing the signal shown in A through the filter shown in C).

C) Amplitude response of 4-8 Hz band-pass filter.

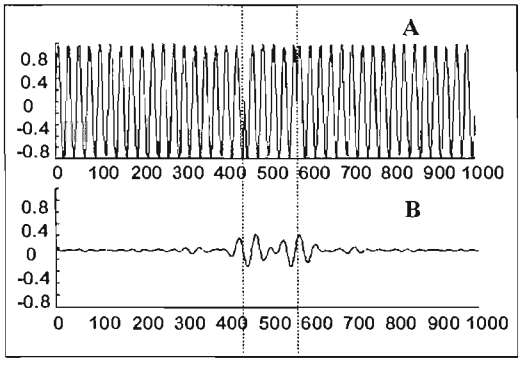

Figure 4
A) Constant amplitude 10 Hz sine wave, undergoing sudden increase and decrease in phase (dotted lines). B) Result of passing the signal shown in A through the filter shown in Figure 3C.

inverse model. Next, the model outputs for all ten trials of a single subject were ensemble averaged. By design, the inverse model acts as a "whitening" filter, hence the model output will contain large amounts of (white) noise whenever the post-stimulus EEG activity has frequency characteristics similar to the pre-stimulus EEG. Deviations from whiteness, thought to point to stimulus-related EEG changes, were enhanced by low pass filtering the model output with a 51-point moving average.

For comparison purposes, we also present results obtained with an inverse modeling approach not based on neurophysiology. A fifth-order AR model was fitted to each of the 0.5 *s* pre-stimulus EEG segments, downsampled to a sampling frequency of 100 Hz. (A fifth order model can adequately represent EEG signals of the type used here.[16]) The inverse AR model outputs were obtained, ensemble averaged and low pass filtered in the same manner as the previously described method. To facilitate comparison, the ensemble averages obtained for conventional averaging, inverse AR modeling, and inverse filtering using the neurophysiologically-inspired model, were normalized by subtracting the mean and dividing by the standard deviation, and are presented in Figure 2.

As can be seen from Figure 2, the neurophysiological model-based approach does a commendable job of suppressing pre-stimulus EEG activity. For example, the conventional ensemble average of subjects MB and MS, which displayed large amount of pre-stimulus alpha activity, have significant amounts of alpha activity both pre- and post-stimulus. The AR model attenuates alpha activity to some degree, but fair amounts of alpha activity remain in the pre-stimulus segment of the ensemble average. In contrast, the ensemble average of the inverse model is essentially void of this type of activity.

DECOMPOSITION METHODS

Decomposition methods take the EEG/EP apart into its constituent rhythms. Band-pass filtering is one approach, and quite interesting results can be obtained with this relatively simple method.[3] A problem with this method is that narrow pass-band filters with a steep roll-off are required to achieve good frequency resolution. Unfortunately, the steeper the roll-off, the worse the time resolution becomes. Also, such filters display excessive "ringing," which may introduce misleading artifacts. For example, Figure 3 presents a 10 Hz sine-wave signal, which undergoes a sudden, temporary amplitude increase (see panel A). This signal is passed through a 4-8 Hz pass-band filter with amplitude response as presented in panel C. The output of the filter is shown in panel B. Ideally, the filter's output should be close to zero throughout the time course of the signal of Figure 3A. However, fairly prominent, transient oscillations caused by "ringing" are observed around the instances where the signal's amplitude is suddenly increased or decreased. A similar effect is seen when the amplitude is kept constant, but the signal undergoes a sudden phase change, as shown in Figure 4.

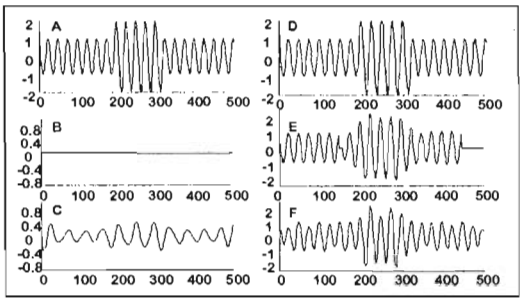

Figure 5
Comparison of wavelet transforms and piecewise Prony method for 10 Hz sine wave, undergoing sudden increase and decrease in amplitude (panels A and D). PPM results in the 4-8 Hz band (B) and 8-16 Hz band (E). WT results in the 4-8 Hz band (C) and 8-16 Hz band (F).

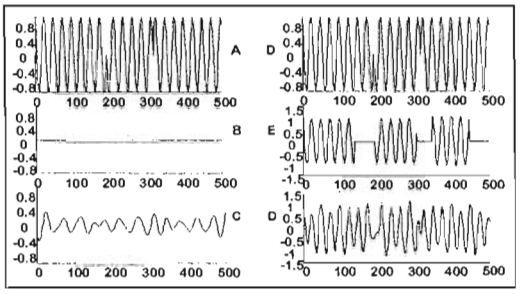

Figure 6
Comparison of wavelet transforms and piecewise Prony method for 10 Hz sine wave, undergoing sudden increase and decrease in phase (panels A and D). PPM results in the 4-8 Hz band (B) and 8-16 Hz band (E). WT results in the 4-8 Hz band (C) and 8-16 Hz band (F).

Wavelet transform-based decomposition has been used successfully for EP analysis.[2,9,27] The basis approach involves the repeated application of complimentary high and low-pass filters followed by downsampling the output of the low-pass filter. The advantage over band-pass filtering approaches is that less "ringing" will occur because of the use of low- and high-pass filters. However, loss of time resolution will still be a problem. Another problem with these methods is that they depend sensitively on the choice of the "mother wavelet," which often shows little or no resemblance to EP signal characteristics. Figures 5 and 6 present the wavelet transform results obtained using the Daubechies 9-tap filter for 10 Hz sine waves undergoing sudden amplitude change and phase change, respectively. As one can see, a substantial amount of activity is seen in the 4-8 Hz band (Figures 5C, 6C), even though no such activity is present in the signal at hand. Also, the wavelet transform produces an 8-16 Hz decomposition that shows considerable amplitude variability (Figures 5F, 6F).

An alternative method for single trial analysis was recently introduced.[13] This method, referred to as the piecewise Prony method (PPM), reduces the signal to a sum of elementary signals, very much like a chemist may split a molecule into atoms. The method we developed is somewhat similar to a Fourier series expansion, where a signal is represented as a sum of weighted cosines and sinusoids. However, we follow a variant originally developed by Baron de Prony,[25] who proposed to use exponentially decaying sinusoids as elementary signals. Using such signals for EEG and EP modeling is attractive, because it has been observed that intra-cortical EP activity resembles decaying oscillations.[12,14] In the original Prony method, the sinusoids have a duration equal to the length of the signal to be modeled, and all components are monotonically increasing or decreasing. In our variant, we allow the components to start and terminate at any time during the interval to be decomposed, and the components can turn from decaying to increasing and vice versa. In this regard, PPM resembles a wavelet transform. However, an important difference is that a *redundant* representation is obtained, with the signal components not orthogonal to each other. This results in less "leakage" than observed for non-redundant representations such as the Fourier transform and the wavelet transform. This is illustrated in Figures 5B and 6B, which show that the PPM produces a zero-amplitude component in the 4-8 Hz range when decomposing a 10 Hz sine wave undergoing sudden amplitude or phase changes, respectively. As shown before, the wavelet transform incorrectly produced appreciable output in this frequency range (Figures 5C and 6C). Furthermore, the PPM also produces an accurate estimate of the amplitude of the 10 Hz signal component, as can be seen from Figures 5E and 6E. A drawback is that the PPM fails to accurately model the signal around the instances where the signal characteristics undergo a sudden change.

PPM ANALYSIS OF SINGLE TRIAL AUDITORY EPS

Subjects and recording procedure

Twenty paid healthy volunteers and nineteen chronic schizophrenia patients were subjected to a double click paradigm. All patients had negative drug screens on admission, and all were on neuroleptics (typical or atypical, but none were on clozapine) at the time of the study. Pairs of identical 1500 Hz clicks were produced by a Grass auditory stimulator and were delivered through head phones, with 400 msec to 600 msec between the first (S_1) and the second (S_2) click. The inter-stimulus intervals were randomized by the computer. A sampling rate of 1000 Hz was used for digitization. Pairs of clicks were separated by at least 8 sec. Monopolar recordings

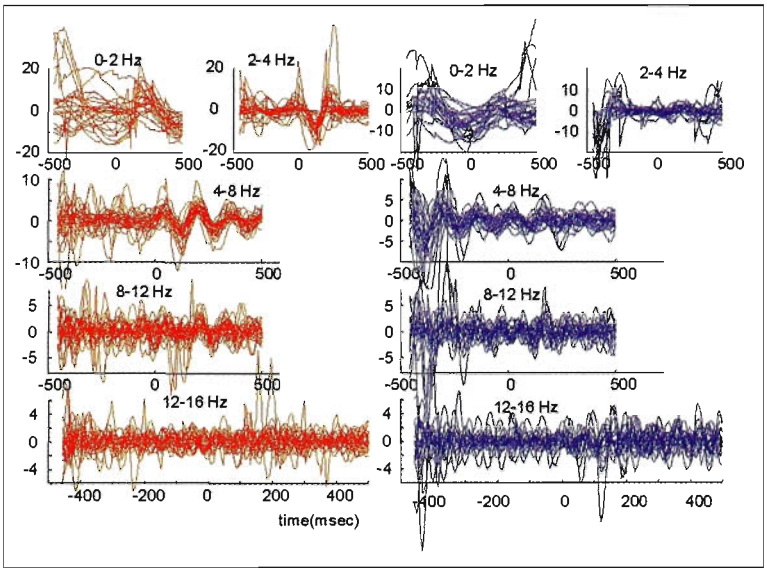

Figure 7
Components from 25 trials of normal subject A for all frequency bands. Upper left panel is 0-2 Hz band, upper right is 2-4 Hz. Second from top is 4-8 Hz, next to bottom is 8-12 Hz and 12-16 Hz is at the bottom. Left: stimulus S1; Right: stimulus S2. Stimulus is presented at 0 msec, and 500 msec pre- and post-stimulus activity is presented in each frequency band.

were made from gold-disk electrodes affixed to the Fz, Cz, Pz, F1, F2, T3, T4 locations, referenced to linked ears. Twenty-five artifact-free trials were selected from each subject for the single trial analysis.

Data processing and analysis

The Cz lead only was analyzed and all data were downsampled to 250 Hz before being input to the PPM. The PPM was applied from 500 msec pre-stimulus to 500 msec post-stimulus, for S1and S2 separately. The single trials were decomposed to obtain components in the 0-2 Hz, 2-4 Hz, 4-8 Hz, 8-12 Hz, and 12-16 Hz bands. Since very little useful signal was observed in the 12-16 Hz band, we present results primarily from the 0 Hz through 12 Hz frequency range. The single trial auditory evoked potentials were decomposed into exponentially increasing and/or decreasing sinusoidal components. The decomposition was done iteratively, modeling lower frequencies first, which were then removed from the signal before moving to the next frequency band. The effect of the stimulus on the ongoing EEG can be observed directly by graphing the components found in a number of trials in a specific frequency band.

RESULTS

For the normal population, it was generally observed that phase synchronization occurs in the delta and theta band. Specifically only four subjects did not show any phase resetting at all in these bands. This phase synchronization was much more pronounced for the S_1 stimulus than for S_2. While some of the schizophrenic patients behaved much like normal subjects, in general, schizophrenic patients displayed much less phase synchronization than normal subjects; only eight subjects phase synchronized in response to S_1 in the delta/theta bands. The schizophrenic patients showed much more variation in their responses and six showed more phase resetting for the S_2 stimulus than for S_1, something which was not seen in any of the normal subjects.

We present graphs of the components found in the various frequency bands for representative subjects. The first case shows phase synchronization in the 0-2 Hz, 2-4 Hz and 4-8 Hz bands (see Figure 7) in a normal subject. The 0-2 Hz synchronization lasts for a very long time, starting around 150 msec post-stimulus and continuing beyond 500 msec. The 2-4 Hz band synchronization starts quite early comparatively, but its effect dies out much sooner. S_2 has very little or no effect on the phase. A certain amount of variability is also observed among the different trials in the same band. For example, in the theta band (4-8 Hz), there are some trials which seem unaffected by the S_1 stimulus.

A second normal subject displayed strong S_1 phase synchronization in all but the 0-2 Hz and 12-16 Hz bands (Figure 8). S_2 also had a phase synchronizing effect, but to a lesser degree and primarily confined to the 4-12 Hz range.

One subset of the schizophrenic subjects did not show phase synchronization in response to either stimulus. See, for example, the overlay plots for schizophrenic subject B shown in Figure 9.

On the other hand, some of the schizophrenic patients behaved much like normal subjects. For example, schizophrenic subject D showed much more phase synchronization for S_1 than S_2, as one can see from Figure10.

CONCLUSIONS

Digital signal processing can provide powerful tools for single trial evoked potential analysis. However, one

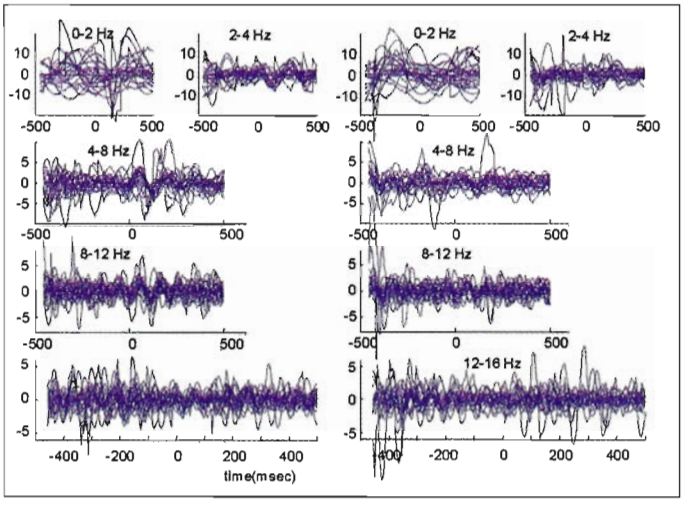

Figure 8
Components from 25 trials of normal subject C for all frequency bands. Upper left panel is 0-2 Hz band, upper right is 2-4 Hz. Second from top is 4-8 Hz, next to bottom is 8-12 Hz and 12-16 Hz is at the bottom. Left: stimulus S1; Right: stimulus S2. Stimulus is presented at 0 msec, and 500 msec pre- and post-stimulus activity is presented in each frequency band.

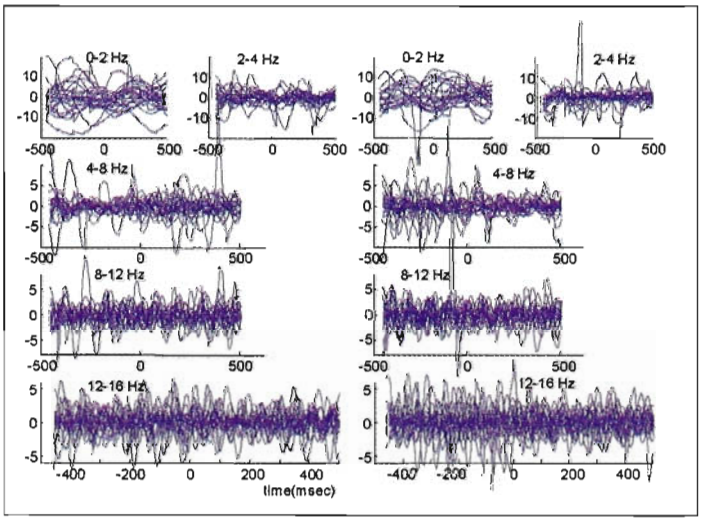

Figure 9
Components from 25 trials of schizophrenic subject B for all frequency bands. Upper left panel is 0-2 Hz band, upper right is 2-4 Hz. Second from top is 4-8 Hz, next to bottom is 8-12 Hz and 12-16 Hz is at the bottom. Left: stimulus S1; Right: stimulus S2. Stimulus is presented at 0 msec, and 500 msec pre- and post-stimulus activity is presented in each frequency band.

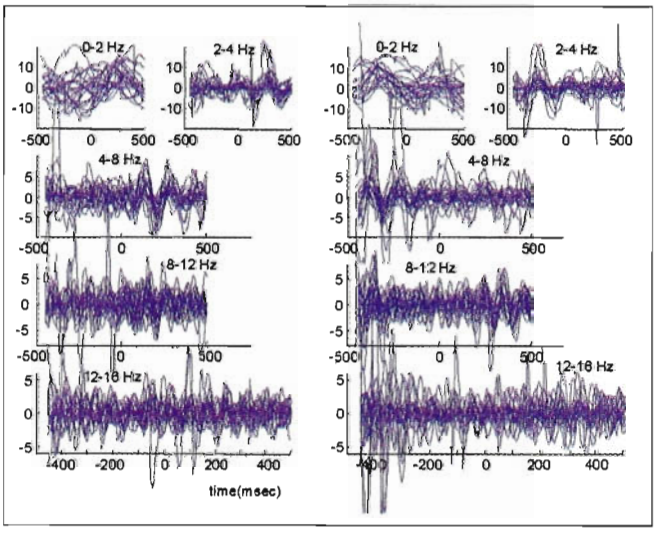

Figure 10
Components from 25 trials of schizophrenic subject D for all frequency bands. Upper left panel is 0-2 Hz band, upper right is 2-4 Hz. Second from top is 4-8 Hz, next to bottom is 8-12 Hz and 12-16 Hz is at the bottom. Left: stimulus S1; Right: stimulus S2. Stimulus is presented at 0 msec, and 500 msec pre- and post-stimulus activity is presented in each frequency band.

should be careful interpreting the results. As we have shown here, changes in amplitude and/or phase of the signal being processed by band-pass filters could produce short bursts of oscillatory activity. It is quite easy to mistakenly interpret such bursts as genuine EEG activity. This problem is especially acute when searching for small amplitude activity, such as event-related gamma activity, "hidden" in much larger, nonstationary scalp-recorded EEG.

Wavelet transforms are less sensitive to the "ringing" artifact produced by band-pass filters, but the time and frequency resolution that can be obtained with such methods still leaves much to be desired. The less than satisfactory performance is, at least in part, due to the choice of the "mother wavelet," which is typically chosen for its mathematical convenience rather than its suitability for EP analysis. We believe that especially the frequency resolution characteristics can be improved by dropping the requirement that a non-redundant signal representation is obtained. This requirement is at the root of the power leakage problem. The PPM method we have developed to address these issues has a demonstrable better performance on simulated data than either wavelet transforms or band-pass filtering.

The PPM was used to investigate auditory EPs from normal and schizophrenic individuals. The schizophrenia population showed phase synchronization deficiencies to the S1 response primarily in the 4-8 Hz and 8-12 Hz band. These results are in concordance with an earlier report, in which a different method was used to show that the capability to phase reorganize is deficient in certain groups of psychiatric subjects as compared to normal subjects.[30]

Most of the deficiencies were observed 60-100 msec after stimulus presentation. This interval coincides with the P50 and N100 latency. Since lower levels of phase synchronization give rise to smaller amplitude EP components, our results support previous findings that the attenuation of the amplitude of the P50 and the N100 evoked potentials with stimulus repetition was significantly decreased in schizophrenia patients as compared to normal control subjects.[1,4,6,11,24,30]

The normal population produces strong phase synchronization in response to S_1 in the 2-12 Hz range. This matches previously reported evidence of auditory stimulus-induced phase resetting in the 3-20 Hz band in normal subjects.[21]

In summary, we have demonstrated that advanced digital signal processing methods can be used to analyze single trial auditory EPs.

ACKNOWLEDGMENT

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Parts of the work presented in the Inverse Filtering section will appear in Reference 20.

REFERENCES

1. Adler LE, Waldo MC, Freedman R. Neurophysiologic studies of sensory gating in schizophrenia: comparison of auditory and visual responses. Biol. Psychiatry 1985;20:1284-1296.
2. Bartnik EA, Blinowska KJ, Durka P. Single evoked potential reconstruction by means of wavelet transform. Biol Cybern 1992;67:175-181.
3. Başar E. EEG-Brain Dynamics: Relation between EEG and brain evoked potentials. Elsevier Biomedical Press, The Netherlands, 1980.
4. Boutros NN, Zouridakis G, Overall J. Replication and extension of P50 findings in schizophrenia. Clin Electroencephal 1991; 22:40-45.
5. Brandt ME, Jansen BH, Carbonari JP. Pre-stimulus spectral EEG patterns and the visual evoked response. Electroencephal Clin Neurophysiol 1991;80:16-20.
6. Buchsbaum MS. The middle evoked response components and schizophrenia. Schizophren Bull 1977;3:93-104.
7. Cerutti S, Baselli G, Liberati D, Pavesi G. Single sweep analysis of visual evoked potentials through a model of parametric identification. Biol. Cybernet 1987;56:111-20.
8. Cerutti S, Bersani V, Carrara A, Liberati D. Analysis of visual evoked potentials through Wiener filtering applied to a small number of sweeps. J Biomed Engng 1987;9;3-12.
9. Demiralp T, Ademoglu A, Schürmann M., Canan B., Ba_ar E. Detection of P300 waves in sinle trials by the wavelet transform (WT). Brain Lang. 1999;66:108-128.
10. Doyle DJ. Some comments on the use of Wiener filtering for the estimation of evoked potentials. Electroencephalogr Clin Neurophysiol 1975;38:533-34.
11. Ford JM, White P, Lim KO, Pfefferbaum A. Schizophrenics have fewer and smaller P300s: A single trial analysis. Biol Psychiat 1994;35:96-103.
12. Freeman WJ. The electrical activity of a primary sensory cortex: analysis of EEG waves. Int Rev Neurobiol 1963;5:53-119.
13. Garoosi V, Jansen BH. Development and evaluation of the piecewise Prony method for evoked potential analysis. IEEE T-BME 2000;47:1549-1554.

14. Horowitz SM. Evoked activity of single units and neural populations in the hippocampus of the cat. Electroencephal clin Neurophysiol 1972;32:227-240.

15. Jansen BH. Analysis of biomedical signals by means of linear modeling. CRC Crit Rev Bioengng 1985;12:343-92.

16. Jansen BH, Bourne JR, Ward JW. Autoregressive estimation of short segment spectra for computerized EEG analysis. IEEE T-BME 1981;28:630-38.

17. Jansen BH, Nyberg HN. Measuring the similarity between trajectories using clustering techniques. Chaos 1993;43:143-51.

18. Jansen BH, Zouridakis G, Brandt ME. A neurophysiologically based mathematical model of flash visual evoked potentials. Biol. Cybern 1993;68:275-83.

19. Jansen BH, Rit VG. EEG and visual evoked potential generation in a mathematical model of coupled cortical columns. Biol. Cybern 1995;73: 357-66.

20. Jansen BH, , Kavaipatti AB, Markusson O. A model-based approach to evoked potential enhancement. Meth Inform Med 2001; 40: 338-345.

21. Laskaris NA, Ioannides AA. Exploratory data analysis of evoked response single trials based on minimal spanning tree. Clin Neurophysiol 2000;112:698-712.

22. Liberati D, Bedarida L, Brandazza P, Cerutti S. A model for the cortico-cortical neural interaction in multisensory-evoked potentials. IEEE T-BME 1991;38:879-89.

23. McGillem CD, Aunon JI, Pomalaza CA. Improved waveform estimation procedures for event related potentials. IEEE T-BME 1985;32:371-79.

24. Müller MM, Keil A, Kissler J, Gruber T. Suppression of the auditory middle-latency response and evoked gamma-band response in a paired-click paradigm. Exp Brain Res 2001;136:474-479.

25. Prony GR Baron de. Essai Expérimental et analytique: sur les lois de la dilatabilité de fluides elastiques et sur celles de la force expansive de la vapeur de l'eau et de la vapeur de l'alkool, à différentes temperatures. J L'Ecole Polytech 1795;1:24-76.

26. Solomon G, Barford J. A new concept of vertex ERA and EEG analysis applying inverse filtering. Acta Otolar 1977;83:200-10.

27. Thakor NV, Xin-Rong G, Yi-Chun S, Hanley DF. Multiresolution wavelet analysis of evoked potentials. IEEE T-BME 1993;40:1085-1094.

28. Weerd JPC de. Facts and fancies about a posteriori "Wiener" filtering. IEEE T-BME 1981;28:252-57.

29. Weerd JPC de. A posteriori time-varying filtering of averaged evoked potentials, I. Introduction and conceptual basis. Biol Cybern 1981;41:211-22.

30. Winterer G, Ziller M, Dorn H, Frick K, Mulert C, Wuebben Y, Herrmann WM, Coppola R. Schizophrenia: reduced signal-to-noise ratio and impaired phase-locking during information processing. Clin Neurophysiol 2000;111:837-849.

31. Woody CD. Characterization of an adaptive filter for the analysis of variable latency neuroelectric signals. Med Biol Engng 1967;5:539-53.

32. Yao L, Sethares WA. Nonlinear parameter estimation via the genetic algorithm. IEEE T-SP 1994;42:927-35.

On the Existence and Functional Properties of Perisaccadic Occipital Gamma Range EEG in Humans

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ABSTRACT

The time honored method of describing the human EEG is by specifying the amplitude of different frequency bands below the classical beta range. In recent years it became possible to evaluate the presence of higher frequency bands. In this paper we review our experimental data, which show that high frequency, gamma range posterior activity reflects physiological properties in response to visual stimuli and to voluntary saccades in the absence of visual stimulation. To analyze the high frequency components to visually evoked responses we used discrete wavelet transform (DWT) while to quantify gamma responses when subjects perform voluntary saccades even in the absence of visual stimulation, we applied continuous wavelet transform (CWT).

The experimental results reveal that in response to visual stimuli the lower gamma band represents a mechanism which is foveally centered and spatially relatively broadly tuned and reflects paracentral retinopathy. The higher gamma band is also foveally centered, it is spatially narrowly tuned and reflects purely on foveal processing.

We show that a burst of high frequency, gamma range (centered on 37 hertz) posterior activity occurs when observers execute saccades. We have applied continuous wavelet transform to the EEG, dividing the perisaccadic period into four segments, preceding, during and following each saccade. Only intrasaccadic periods show consistent bursts of gamma starting around 40-50 ms following saccade onset and lasting about 20 ms beyond new fixation. The functional significance of the gamma band is shown by its laterality and topography, dependent on saccade timing and direction.

Properties of occipital gamma activity following visual stimuli and occurring in association with saccades demonstrate the "true" existence of gamma range activity in the human EEG. The proof is the strong dependence of the classical gamma, and not of lower frequencies, on physiological variables.

INTRODUCTION

The time honored method of describing the human EEG is by specifying the amplitude and occurrence of different frequency bands. Prior to the computer age visual inspection of different frequencies allowed only discerning coarse differences over the scalp and across the hemispheres. With the availability of *fast computation* new methods of quantification entered the armamentarium of EEG analysis. In particular, Fourier analysis allows the precise determination of the power and phase of different frequency bands. With the availability of *digital recording* methods at high sampling rates, it became possible to evaluate the presence of high frequency bands in addition to the classical beta and lower frequency bands. However, when visual inspection is no longer sufficient to confirm the presence of high frequency components, it is healthy to wonder whether these signals are "really" present or they simply result from linear decomposition of periodic signals.

In this chapter we review our experimental data, which show that high frequency, gamma range posterior activity "truly" exists in the human EEG. What does it mean that a periodic signal "truly" exists? For instance, a square wave function can be described by its amplitude versus time course, or equivalently by its frequency spectrum, containing all the odd harmonics of the fundamental sine wave. Do the higher frequencies truly exist or are they only artificial constructs of linear decomposition of a periodic signal with rapid transitions? Of course the higher frequencies truly exist if one describes say a square wave or an edge in the frequency domain. Without adding the high frequency components to the fundamental sine wave the square wave would be a different function in the time domain as well (rounded edges). Hence both descriptions are real and the method of quantification is a matter of choice. The question for truth is rather, whether or not the frequency component identified has a biological, functional significance independent of other frequency components. In this chapter we shall review our arguments that high frequency components of the EEG indeed exist. Our argument is based on the separate functional properties of low gamma (encompassing the classical beta range) and gamma range EEG centered on 37 Hz. We demonstrate the functional significance of each of these bands by showing their independent variance with visual input and relevance to voluntary saccades. Specifically, we shall argue

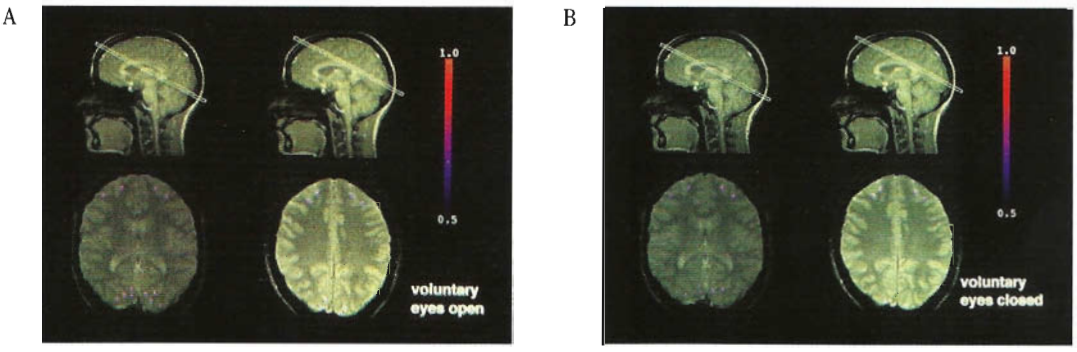

Figure 1.
T*2 weighted oblique transversal MR images of two sections of the same subject with superimposed activation maps (TR/TE=63/30 ms, alpha=10 degrees) associated with voluntary eye movements in light (A) and in dark (B). The scout is shown on the top of the transverse images. The color coded correlation coefficient scale ranges from 0.5 (blue) to a maximum of 1.0 (orange). When voluntary saccades are executed the posterior median frontal gyrus (FEF), the median part of the superior frontal gyrus (SEF) show, as expected, activation. In addition, the visual cortex shows robust activity. Note similar activation patterns of the visual cortex in light and in dark (no visual stimulus present) suggesting the role of the visual cortex in executed voluntary saccades (from Bodis-Wollner et al.[5]) For further details see text.

that only one of these bands is limited to foveal processing and linked to preparation for new fixation when quick voluntary eye movements are executed.

I. THE VISUAL, FUNCTIONAL SIGNIFICANCE OF BETA AND HIGHER RANGE POSTERIOR EEG

Methods

The EEG was recorded with conventional methods using a sixteen channel (Dantec Concerto) digital EEG and subsequent averaging. The data were transferred to a PC and analyzed using Matlab software.[26] To analyze the high frequency components we used discrete wavelet transform (DWT).[9,18] The choice of DWT was based on its ability, as opposed to extended, Fourier analysis, to decompose several seconds or only tens of milliseconds long EEG signals into orthogonal, equal bandwidth components. Previous studies have applied DWT to the descriptive quantification of primary visual evoked potentials.[1,2] However, with DWT we could not only quantify and compare peak energy and peak energy timing of different frequency bands, "detail functions" in the parlance of DWT, but primarily, evaluate if different gamma bands reflect different aspects of visual processing. Beyond great descriptive power, DWT provides a method to provide new information regarding the frequency and timing of cortical electrophysiological activity and visual input. After comparing various filters, using the entropy criterion, we applied a Coifflet II filter to the EEG data. DWT was centered on the conventional visual evoked potential (VEP) peaks. Six healthy normal observers in the age range of 18-62, with a visual acuity better than 20/20, participated. Viewing was binocular.

Visual stimuli were vertical sinusoidal gratings in the spatial frequency range of 1.1 to 6.9 cycles/degree (cpd). Contrast was 55 percent, calibrated on the screen of a high resolution black and white monitor, using the methods described by Bodis-Wollner and Hendley.[7] They were presented in the on-off mode (700 msec/300 msec)

The stimulus field was either a bipartite half field of 9 degrees in diameter (the results fully reported by Tzelepi et al.[26]) or a full field of 18 degrees. Mean luminance was 180 cd/meter square.

Results

Visual processing of elementary visual stimuli and the lower gamma band

The 18-28 hertz band showed peak energy from 70-90 milliseconds following the onset of the visual stimulus. Both power and latency of peak power depended on spatial frequency. There was little power for 1.1 cpd and peak power occurred to a 2.3 cpd stimulus, except in one observer (4.6 cpd).

For full field (18 degrees) stimuli peak power occurred at the midline occipital electrode with a symmetrical fall-off over lateral occipital electrodes (placed 17 and 34 % of the inion-nasion distance). For half field (9 degrees paracentral) stimuli peak power was elicited by the same spatial frequencies, however, the locus of peak power shifted to either the near (17%) or far (34%) occipital electrodes (For details, including statistics see Tzelepi et al.[26]).

Visual processing of elementary visual stimuli and the higher gamma band

Timing of peak energy in the 28 to 56 hertz band in respect to spatial frequency of stimulation was similar to the results in the lower band.

Differences in the visual stimulus dependence of the lower and higher gamma bands

One noteworthy difference in the functional properties of the lower and higher gamma band in the Tzelepi et

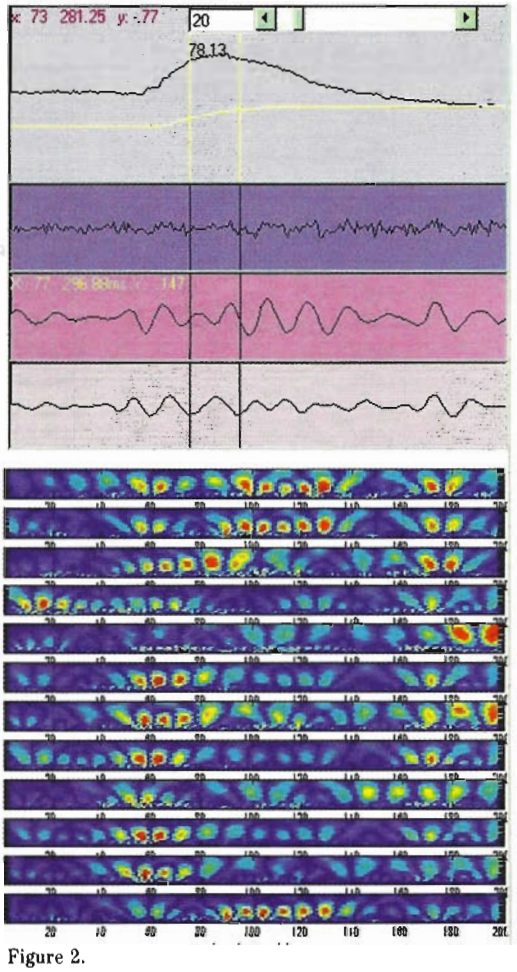

Figure 2.
The subject executed a single voluntary saccade over a distance of 30 degrees from left to right of fixation. The EOG trace, reflecting eye movement velocity, is shown in the top trace, while eye position, as recorded with the infrared reflection technique, is shown in the second trace. There is a 16 msec delay between EOG and eye position trace. Cursors were placed to indicate a period of 78 msec encompassing the new fixation, but starting prior to arriving at the the new fixation aim. The next trace is recorded over the occiput, without any filtering. Recording sites were referred to a midfrontal location, and in addition to a mastoid location. The subsequent two traces show the EEG recorded over the left and right occiput, following continuous wavelet transform (CWT, see text). The rows showing 37 Hz centered activity in occipital and parieto-occipital channels. The top row shows the midline occipital recording, while the subsequent channels represent left alternating with right-sided recording over near and then far occiput, parieto-occipital, parietal skull. The last channel represents the wavelet EEG recorded over the left occiput with a different reference electrode. Note the asymmetry particularly evident in the cursored period over the left and right occiput. Color coding represents wavelet coefficient magnitude (red =high, blue=low). For quantitative results see text. (After Bodis-Wollner et al.2002[8])

al.[25] study was that the response fell below noise in five of six observers at lateral electrodes, suggesting that the higher band is closely linked to foveal processing and reflects poorly on paracentral stimuli. This was true even at the lowest spatial frequency, with known strong paracentral representation in the cortical retinotopical map.[25]

The most functionally important difference of lower and higher gamma band responses is their spatial frequency bandwidth selectivity. We[7] evaluated the spatial frequency response curve of the two bands. (For statistical details see Tzelepi et al.[26] and Bodis-Wollner et al.[7]) The results showed that power in the lower band peaks to between 1.1 and 2.3 cpd at the inion, while in the higher band it peaks to 4.6 cpd. Even more significantly, not only peak tuning differs, but spatial frequency bandwidth. The lower band has a bandwidth of over one octave, while the higher band has the remarkably narrow bandwidth of 0.15 octave. All these differences between the simultaneously obtained responses in the lower and "classical" gamma range oscillatory responses may be therefore summarized as such: both reflect fixational and spatial frequency selective mechanisms, however, (a) the lower gamma band in vision represents a mechanism that is foveally centered and spatially but relatively broadly and furthermore reflects paracentral retinotopy, and (b) the higher gamma band is also foveally centered; it is spatially narrowly tuned and reflects purely on foveal processing.

II. THE ROLE OF THE FOVEAL GAMMA DURING SACCADIC EYE MOVEMENTS

It has been shown that the striate cortex is linked to visual processing strategies associated with saccades, operating even without active visual input. We[5,6] have studied in 12 normal observers cortical activity associated with voluntary saccades, using functional magnetic imaging (fMRI) with electro-oculogram monitoring. The activity associated with blinks was registered during the recording of voluntary saccades in the same session (alternating blinks, saccades and rest).

The results showed that voluntary blinks are associated with significant activation of the frontal (FEF) and supplementary eye fields (SEF), the parietal eye field (PEF) and of the primary visual cortex. (Figure 1). Several other subsequent studies show visual cortical changes in association with saccades.[17,20] However, whether occipital activity in association with saccades occurs prior to, during or following saccades is not revealed by conventional fMRI studies. We therefore explored perisaccadic changes in the EEG, in particular those in the higher frequencies. In the past several electrophysiological presaccadic signal changes have been recorded over the occipital cortex. An attenuation of two different frequency bands of the EEG (alpha and some beta) prior to visually triggered saccades is known. Higher than 25Hz activity associated with voluntary saccades was

Table 1

This Table shows the statistical results for Type 3 tests for fixed effects

Effect	Num DF	Den DF	F Value	Pr > F
Light vs Dark	1	14E3	0.69	0.4058
Saccade	1	14E3	9.04	0.0026
Light Dark vs Saccade	1	14E3	4.48	0.0343
Eye Position	3	14E3	13.36	<0.0001
Light Dark vs Eye Position	3	14E3	5.89	0.0005
Saccade vs Eye Position	3	14E3	8.44	<0.0001
Light Dark vs Saccade vs Eye Position	3	14E3	0.36	0.7820
Channel	11	14E3	252.26	<0.0001
Light Dark vs Channel	11	14E3	7.76	<0.0001
Saccade vs Channel	11	14E3	3.12	0.0003
Light Dark vs Saccade vs Channel	11	14E3	0.94	0.4968
Eye Position vs Channel	33	14E3	0.62	0.9550
Light Dark vs Eye Position vs Channel	33	14E3	0.49	0.9939
Saccade vs Eye Position vs Channel	33	14E3	2.31	<0.0001
Light Dark vs Saccade vs Eye Position vs Channel	33	14E3	0.53	0.9877

The analysis, based on Coifflet II coefficients, shows that there is a significant difference ($F_{1, 14000} = 7.76$, $p < 0.0001$) in gamma activity between light and dark trials with relation to specific channels and also between saccade direction and channel location ($F_{1, 14000} = 3.12$, $p < 0.0003$). Gamma activity differed depending on channel location ($F_{1, 14000} = 252.26.76$, $p < 0.0001$). Gamma activity also differed in light and dark depending on time window ($F_{1, 14000} = 5.89$, $p = 0.0005$). Significant difference ($F_{1, 14000} = 13.36$, $p < 0.0001$) in gamma activity exists between different perisaccadic time windows (presaccade, intrasaccade first half, intrasaccade second half just including fixation and postsaccade). There is interaction between saccade direction and perisaccadic time window ($F_{1, 14000} = 8.44$, $p < 0.0001$). Interaction of saccade direction with perisaccadic time window (pre-, intra- and post) and channel location was also significant ($F_{1, 14000} = 2.31$, $p < 0.0001$). No other effects, listed in the Table, were significant.

not carefully studied. However, high frequency activity may be necessary to signal changes during saccades: the duration of an average saccade rarely exceeds 100 msec. Low frequency, such as alpha range activity, could not well represent intrasaccadic changes as a typical saccade duration is less than 100 msec. We have therefore investigated if gamma range occipital EEG signals are associated with voluntary saccades, and if so, at which point in time, in reference to a saccade, do they occur.[8]

Method

In our first study the EEG was recorded over 64 evenly distributed electrodes.[10] Using power spectral analysis, it was evident that there is alpha decrease preceding, as well as following, voluntary sacccades. There was significant gamma power following a saccade over occipital leads, but not anteriorly. Whether or not this asymmetry is related to an intrasaccadic change was evaluated in 10 observers using a 16 channel recording and subsequent continuous wavelet transform (CWT). CWT is similar to DWT in that it allows precise comparison of different frequency bands in their time and power. However, it is like a sliding window, without a fixed reference point. We again applied the Coifflet II filter. Coefficients for different bands, distances and electrode locations were evaluated using standard multivariate statistics.

We applied CWT, and not DWT as in the first study, for the following reason. In looking for gamma range responses time locked with the visual stimulus, we had a natural time marker. In looking for gamma activity in association with saccades, we could not a priori decide whether saccade onset, duration or end will determine when gamma occurs. Hence CWT seemed more appropriate, not being biased to a discrete time event. Thirteen channels were devoted to the posterior EEG using the montage applied by Bodis-Wollner et al.[4] The three remaining channels were devoted for the horizontal and vertical EOG and to the eye position recording, using a pupil/cornea infrared method with a sampling rate of 128 Hz. Subjects were executing horizontal saccades over various distances ranging from 8 to 38 degrees across fixation.

Results

We report the results of analyzing the "classical" gamma band by applying CWT. We have obtained evidence for the intrasaccadic modulation of gamma centered on 37 Hz. The lower band, identified in our visual study (see above) revealed a more complex behavior and will not be further discussed. Of relevance, though, is that while the higher band exhibits a constant relationship to executed saccades, the lower band does not

reveal occipital saccadic modulation. What we have found is a highly statistically significant difference in gamma over the left and right occipital hemisphere preceding the new fixation. Gamma synchronization starts about 40 msec into the saccade and outlasts the new fixation. In Figure 2, one can see the results of a single trial, showing the horizontal EOG, the eye position recording and the color coded output of the coefficients over 13 channels for the 37 Hz component. Table 1 shows the statistical significance of side-to-side difference for the occipital leads for the 37 Hz component for multiple trials in 10 observers (seven saccades each).

DISCUSSION

We have recently shown (Tzelepi et al.[26]) and reviewed above the functional differences between subbands of high frequency brain wave activity in reference to retinotopical representation in the visual cortex. Our recent results also show that high frequency activity may be necessary to signal changes during saccades. The duration of an average saccade rarely exceeds 100 msec, and our results show that gamma modulation occurs for perhaps 60-70 msec. Low frequency, such as alpha range activity, is unlikely to represent intrasaccadic changes. Consistent with earlier suggestions, our hypothesis is that associated with saccades an occipital gamma burst represents modulation of lateral interconnections in the visual cortex.

Gamma was first described in multiunit recordings in cats[14] and monkeys,[10] and it has received increasingly more attention in human studies. Based on the original suggestions of W. Singer and colleagues,[11,22] it has been inferred that binding of neuronal activity by a temporal code is one effective way the cortex integrates distributed activity, and thus gamma represents cortical activity related to perception of closure[24] and binding of visual features.

Saccades (and blinks) occur continuously in humans who are awake. Yet one is not aware either of their occurrence, or of a shift of the visual scene, during saccades or blanking out of vision during blinks. How, and which cortical mechanisms ensure visual stability associated with saccades is still unknown, even though much has been learned in recent years of saccade related receptive field changes of individual neurons in the frontal and lateral parietal cortices. We have discovered that the occipital cortex, hitherto not thought to be part of the circuit participating in saccades is active in association with voluntary saccades, even in the dark, in the absence of visual input. Our electrophysiological data show that at least during saccades, the occipital cortex is physiologically active. The properties of the intrasaccadic gamma range EEG suggest that one of the functions of the occipital cortex is to prepare for the new fixation. Whether this preparation represents the reorganization of the connectivity of visually responsive neurons to alter their spatial summation properties or visuo-spatial attention has not been evaluated by our studies. Nevertheless, saccade preparatory attention is unlikely to explain the results. A relationship between saccadic eye movements and spatial attention has been always seen as eminently reasonable. Over the last decades an increasing number of experiments and theoretical models support the view of a direct connection between them. One current theory postulates that the trigger for saccades is a disengagement of attention from a particular visual target, or lack of focus on a target. In this view, once a new target emerges its location is computed during a disengagement or unfocused stage,[12,13] the saccadic eye movement is triggered. Since our data show changes in gamma are initiated, following the saccade, this type of attention related explanation for the intrasaccadic gamma is not very likely.

The possible relationship of intrasaccadic gamma changes to perisaccadic changes in visual sensitivity is more likely. Vision during, and for a short time prior to and following saccades[16,27,28] is "suppressed." Based on experimental evidence Ross, Morrone and Burr[20] and Ross et al.[21] suggested that visibility of stimuli preferentially exciting "magnocellular" pathways is suppressed. The psychophysical evidence is consistent with the perceptual observation that when saccades bring the fovea to a new target the objects in the scanpath do not appear to move. Ever since the pioneering concept of Helmholtz (1866)[15] the notion of "corollary discharge"[23] and "Reafferenzprinzip"[29] postulate that the cortical organization responsible for saccades generates signals prior to the eye movement. The purpose of these signals is to prepare the visual cortices to cancel the shift of the visual frame and maintain stable perception. It has been suggested by Ross et al.[20,21] that the concept of selective attenuation of "magnocellular" signals provides a more parsimonious explanation of perceptual stability during saccades, than cancellation due to the "corollary signal" does. Our data show that the occipital cortex generates intrasaccadic sensory preparatory signals. If indeed gamma reflects interneuronal binding, as neurophysiological studies suggest, then our results may be interpreted as representing short term (60-70 milliseconds) activity dependent plasticity in neuronal connectivity.

Irrespective of the explanation, however, taking into consideration the properties of occipital gamma activity following visual stimuli and occurring in association with saccades demonstrates the "true" existence of gamma range activity in the human EEG. The proof is the strong dependence of the classical gamma, and not of lower frequencies, on physiological variables.

REFERENCES

1. Ademoglu A, Micheli-Tzanakou E, Istefanopulos Y. Analysis of pattern reversal visual evoked potentials (PRVEP's) by spline wavelets. IEEE Trans Biomed Eng 1997; 44: 881-901.
2. Başar E, Demiralp T, Schurmann M, Başar-Eroglu C, Ademoglu A. Oscillatory brain dynamics, wavelet analysis, and cognition. Brain Lang 1999; 66: 146-183.
3. Bodis-Wollner I, Hendley CD. On the separability of two mechanisms involved in the detection of grating patterns in humans. J Physiology 1979; 291: 251-263.
4. Bodis-Wollner I, Mylin L, Frkovic S. The topography of the N70 component of the visual evoked potential in humans. In: Maurer K, (ed). Topographic Brain Mapping of EEG and Evoked Potentials. Berlin, Heidelberg: Springer-Verlag; 1989: 396-406.
5. Bodis-Wollner I, Bucher SF, Seelos KC, Paulus W, Reiser M, Oertel WH. Functional MRI mapping of occipital and frontal cortical activity during voluntary and imagined saccades. Neurology 1997; 49: 416-420.
6. Bodis Wollner I, Bucher SF, Seelos KC. Cortical activation patterns during voluntary blinks and voluntary saccades. Neurology 1999; 53: 1800-1805.
7. Bodis-Wollner I, Jiang D, Tzelepi A, Bezerianos T. Wavelet transform of the EEG reveals differences in low and high gamma responses to elementary visual stimuli. Clin Electroencephalogr 2001; 32: 139-144.
8. Bodis-Wollner I, von Gizycki M, Avitable Z, Hussain A, Javeid A, Habib A, Raza A, Sabet M. Perisaccadic occipital EEG changes quantified with wavelet analysis. Ann NY Acad Sci 2002; 956: 464-467.
9. Daubechies I. The wavelet transform, time-frequency localization and signal analysis. IEEE Trans Inform Theory 1990; 36: 961-1004.
10. Eckhorn R, Frien A, Bauer R, Woelbern T, Kehr H. High frequency (60-90 Hz) oscillations in primary visual cortex of awake monkey. NeuroReport 1993; 4: 243-246.
11. Engel AK, Koenig P, Kreiter AK, Schillen TB, and Singer W. Temporal coding in the visual cortex: new vistas on integration in the nervous system. Trend Neurosci 1992; 15: 218-226.
12. Fischer B, Weber H. Characteristics of 'anti' saccades. Exp Brain Res 1992; 89: 415-424.
13. Fischer B, Weber H. Express saccades and visual behavior. Brain Sci 1993; 16: 553-567.
14. Gray C, Singer W. Stimulus-specific neuronal oscillations in orientation columns of cat visual cortex. Proc Natl Acad Sci USA 1989; 86: 1698-1702.
15. Helmholtz HV. Handbuch der Physiologischen Optik. In: Southhall JPC, (ed). A Treatise on Physiological Optics 1866. New York: Dover; 1986.
16. Latour PL. Vision during voluntary saccadic eye movements. Vision Research 1962; 2: 261-262.
17. Law I, Svarer C, Rostrup E, Paulson O B. Parieto-occipital cortex activation during self-generated eye movements in the dark. Brain 1998; 121: 2189-2200.
18. Mallat S. A theory for multi-resolution signal decomposition: the wavelet representation. IEEE Trans Pattern Anal Machine Intell 1989; 11: 674-693.
19. Mari Z, Mima T, Gerloff C, Hallett M, Bodis-Wollner I. Perisaccadic high frequency EEG changes in frontal and occipital regions are similar in light and dark. J Physiol (London) 2000; 25S: 526.
20. Ross J, Morrone MC, Burr DC. Compression of visual space before saccades. Nature 1997; 386: 598-601.
21. Ross J, Morrone MC, Goldberg E, Burr DC. Changes in visual perception at the time of saccades. Neuroscience 2001; 24: 113-121.
22. Singer W. Synchronization of cortical activity and its putative role in information processing and learning. Annu Rev Physiol 1993; 55: 349-374.
23. Sperry RW. Neural basis of the optokinetic response produced by visual inversion. J Comp Psych Physiol 1950; 43: 482-489.
24. Tallon-Baudry C, Bertrand O, Delpuech C, Permier. Oscillatory gamma-band (30-70 Hz) activity induced by a visual search task in humans. J Neurosci 1997; 17: 722-734.
25. Tootell R B H, Silverman M S, Hamilton S L, Switkes E, De Valois R L. Functional anatomy of macaque striate cortex. V. Spatial frequency. J Neurosci 1988; 8: 1610-1624.
26. Tzelepi A, Bezerianos T, Bodis-Wollner I. Functional properties of sub-bands of oscillatory brain waves to pattern visual stimulation in man. Clin Neurophysiol 2000; 111: 259-269.
27. Volkmann F. Vision during voluntary saccadic eye movements. J Opt Soc Am 1962; 52: 571-578.
28. Volkmann FC, Riggs LA, Moore RK. Eyeblinks and visual suppression. Science 1980; 207: 900-902.
29. Von Holst E, Mittelstaedt H. Das Reafferenzprinzip. Naturwissenschaften1950; 37: 464-476.
30. Wenzel R, Wobst P, Heekeren HH, Kwong KK, Brandt SA, Kohl M, Obrig H, Dirnagl U, Villringer A. Saccadic suppression induces focal hypooxygenation in the occipital cortex. J Cereb Blood Flow Metab 2000; 20: 1103-1110.

Time-Frequency Analysis of VEPs for Interhemispheric Transfer Time

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ABSTRACT

This paper aims to use time frequency analysis in order to determine interhemispheric transfer time (IHTT) for different frequency bands. For this purpose, the correlation of the VEP at left and right occipital sites to lateralized stimuli is used. Previously, in literature the IHTT was determined by comparing the latencies of the P100 and N160 peaks at different bands. The technique that we use gave us the opportunity to compare VEP pairs as a whole, and this increases robustness in determination of IHTT.

INTRODUCTION

The human brain is made of two hemispheres, each being functionally specialized for certain cognitive processes. Besides some subcortical connections between hemispheres, the corpus callosum (CC), as the largest fiber tract in the brain, seems to have the greatest responsibility for the integration of hemispheric functions.[8,9] CC contains fibers different in axonal diameters.[1] This suggests that CC has different types of channels, relating to the kind of information transferred from one hemisphere to the other.[5]

Many studies have been performed in order to understand the function of CC. In these studies, the subjects are presented by a stimulus from their left or right half visual field causing the stimulus to reach both hemispheres through the natural crossings of the visual pathways. The hemisphere at the opposite side of the visual field where the stimulus is presented is stimulated directly, whereas the hemisphere at the same side is stimulated indirectly. The response of the brain is recorded as EEG signals from both hemispheres, and these signals are called Visual Evoked Potentials (VEP). The term "Direct VEP (DVEP)" is used here to represent the VEP produced at the contralateral hemi-visual field and "Indirect VEP (IVEP)" is used for the VEP produced at the other hemisphere mostly via CC.

Many researchers interested in callosal function have dealt with interhemispheric transfer time (IHTT), which is the time delay between the DVEP and IVEP.[3,13,14] Nalçacı et al.[11] have suggested that the VEPs give us a rough estimation of the IHTT, and different IHTT of the fibers in different diameters could be estimated using time and frequency analysis of VEP.

Nalçacı et al.[11] recently suggested that even though different estimations of IHTT have been found depending on the type of paradigms and the measuring sites, only a latency difference has been measured between two peaks of complex waves in each VEP study. However, these complex waves of VEP were most probably formed by different generators of neural populations, which act through different frequency channels.[2] The slow and fast components of VEPs are entirely generated in cortical layers.[7] Nalçaci et al.[11] hypothesized that if the main peaks of VEP were established by different types of generators, which can also be connected to each other by different types of callosal fibers, a wide range of IHTT could be estimated by measuring the latency between time-locked peaks of narrow band-pass filtered VEP.

Nalçaci et al.[11,12] carried out an experiment in order to test this hypothesis, and subjects were presented with a reversal of checkerboard pattern as stimuli at right visual field (RVF) or left visual field (LVF), and EEG was recorded at O1, O2. In Figure 1 grand-averaged DVEP and IVEP obtained from the occipital site of a subject are shown. The stimulus is presented at time t=0, and the signals in the Figure are plotted from 50 msec before the stimulus to 250 msec after the stimulus.

These grand-averaged VEPs were transformed to the frequency domain by means of the Fast Fourier Transform to obtain the amplitude frequency characteristics. Band-pass filters were chosen adequately according to tuning frequencies indicated by clear peaks in the amplitude frequency characteristics. The chosen band pass filters [4-8 Hz (θ), 8-15 Hz (α), 15-20 Hz ($\beta 1$), 20-32 Hz ($\beta 2$)] were applied to the VEP of the subjects, and 4 different components of DVEP and IVEP were obtained. The latency of P100 and N160 of unfiltered VEP was measured. In the band-pass digital filter applied VEPs, positive and negative peaks, which are consistent with P100 and N160, were measured for each subject. The P100 latency was defined as the latency of the greatest positivity between 80 and 130 ms. The N160 latency was defined as the latency of the greatest nega-

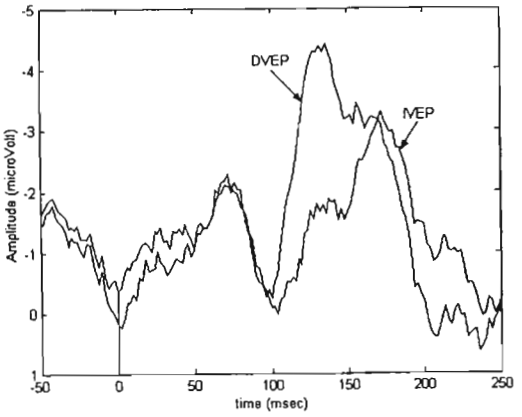

Figure 1.
An example of DVEP and IVEP obtained from the occipital site of a subject. Vertical axis shows amplitude in μV and horizontal axis shows time in msec.

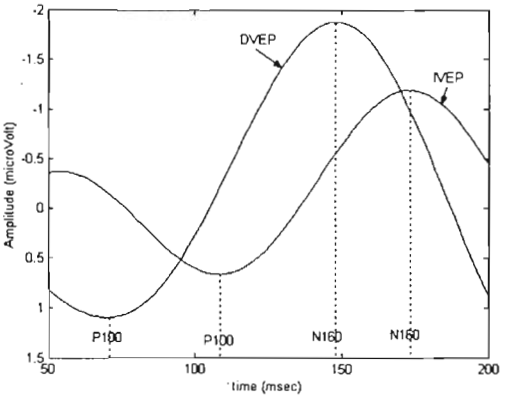

Figure 2.
Theta band of DVEP and IVEP of a subject. Horizontal-axis is the time in msec, and vertical axis is the amplitude in μV.

tivity between 130 and 190 ms. In Figure 2, P100 and N160 peaks can be seen clearly on both signals, which are DVEP and IVEP of theta band of a subject.

In the 20-32 Hz band, the largest amplitudes of negative and positive peaks were observed between 70 and 120 ms. The first high negative peak was defined as N80 and the first high positive peak was defined as P100. These peaks were selected for evaluation. Latency differences between hemispheres for digitally unfiltered and filtered VEPs were manually determined to estimate IHTT. In the different frequency bands, different IHTTs were estimated, ranging from 3 ms to 30 ms. Approximately 16 ms for θ band, 11 ms for α band, 6 ms for β1and 3 ms for β2 bands were found.

The aim of this study is to improve the previous report using some methods in time-frequency domain. For determining the interhemispheric delay for each band, the correlation of the filtered VEP pairs are considered for the whole time not just for the peaks. In the Methods section, it is explained how the delay of the signal is determined using correlation between signals. In the next section, results are presented, and in the final section these results are discussed.

METHODS

The data set

VEP pairs (i.e., pairs of DVEP and IVEP) used in this study were taken from the same experimental data set of Nalçacı et al.,[12] in which eight right-handed men (n=8) and eight women (n=8) between the ages 19 and 30 years served as subjects. The stimuli reversals of 55° checkerboard pattern were presented as a window 8.5 x 8.5 cm². The medial edge of the stimulus was 2" to the left or right of the central point. Nalçaci et al.[12] carried out two different blocks of experiments in the following way: stimuli were presented to the right visual hemi-field (RVF), or the left visual hemi-field (LVF). In each block, 120 stimuli were presented, and 120 trials results were collected. Inter-stimulus intervals varied randomly between 2.5 and 3.5 sec.

EEG was recorded with Ag/AgCI electrodes positioned at O1, O2 of the 10/20 system. The linked ear lobes (A1+A2) served as reference. Two channels of EOG were recorded from electrodes placed on the outer canthus of the right eye and above the right eyebrow, in order to measure horizontal and vertical eye movements. Electrode impedances were below 5 kOhm. EEGs were amplified by Nihon Kohden (EEG-4421) EEG apparatus with band limits 0.1-70 Hz (24 dB/octave). An additional 50 Hz notch filter was also applied to the data to remove main interference. EEG records began 1s prior to stimuli onset and extended 1 s post-stimulus, and each channel was digitized on line with a sampling rate of 500 samples per second and stored on computer disc for later averaging.

In respect of EOG amplitude, any EEG trials associated with artifacts were automatically rejected. In addition to this rejection procedure, single sweep analysis was carried out on each of the EOG channels, and EEG trials associated with blink and saccadic eye movements were eliminated before averaging.

In our analysis, we used the part corresponding to the interval starting from 0 to 1 seconds just after the stimulus was applied. DVEPs and IVEPs were separated into *θ*, *α*, *β1* and *β2* bands using ideal digital band pass filters. For this purpose, first Fast Fourier Transforms (FFT) of the signals are taken. Then in frequency domain, signals are multiplied by ideal square wave band pass filters where bands are consistent with *θ*, *α*, *β1* and *β2* band frequencies. Finally signals are transformed to time domain by inverse fast Fourier transformation (IFFT).

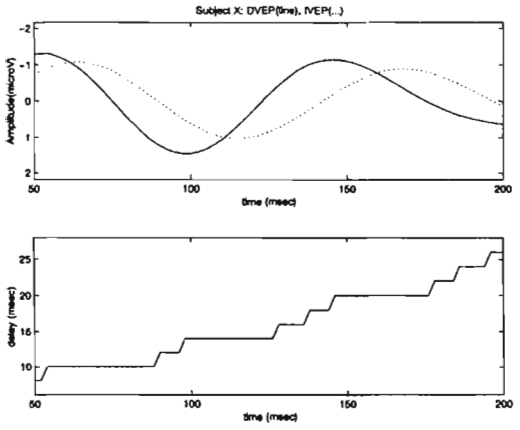

Figure 3
Top: Theta band amplitude (μV) with respect to time (msec) for DVEP (straight line) and IVEP (dotted line) of a subject; Bottom: Delays (msec) calculated for each time separately for the interval from 50 msec to 200 msec using the windowed correlation method.

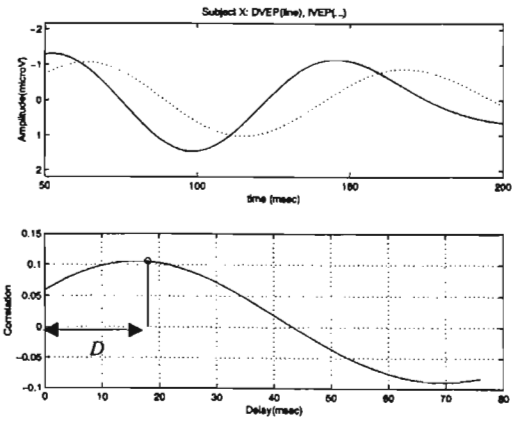

Figure 4
Top: Theta band of DVEP (straight line) and IVEP (dotted line) of a subject. Bottom: Correlation results calculated considering the whole signal for different delays. D_b is the delay value for which the correlation gives maximum.

This procedure is the same as taking convolution of the signals and band-pass filters in time domain.

Inter-hemispheric Transfer Time

For determining the interhemispheric delay for each band, the correlation *C(DVEP(t), IVEP(t))* of the filtered VEP pairs was considered. Let Δ_b be the window size at band $b=\{\theta, \alpha, \beta 1, \beta 2\}$. In this study, it was chosen as Δ_θ=128 msec, Δ_α=64 msec, $\Delta_{\beta 1}$=32 msec, $\Delta_{\beta 2}$=16 msec, such that it covered at least a cycle of the signal. Let $DVEP_b[s, \Delta_b]$ represent the portion of the DVEP at chosen band b, containing $\Delta_b/2$ sample points (since it is sampled at 500 Hz) starting from time $s-\Delta_b/2$, i.e., the window is centered at time s. Let $IVEP_b[s, \Delta_b]$ represent similarly for IVEP. Since the correlation of VEP pairs observed to be low before s<50 msec and after s>200 msec, we restricted 50 msec≤ s ≤ 200 msec. The interhemispheric transfer may not begin before 50 msec and the transfer is almost completed after 200 msec. Thus, for each t in interval (50 msec, 200 msec) we determined the delay d_b such that the correlation $C(DVEP_b[t,\Delta_b], IVEP_b[t+d_b, \Delta_b])$ was maximum with respect to argument d_b (1,2). Since the window sizes are related to the frequency content of the bands, meaningful parts of the signals are included in the windows used in correlation.

$$d_b(t) = \arg\max_d C(DVEP_b[t,\Delta_b], IVEP_b[t+d,\Delta_b]) \quad (1)$$

$$C(DVEP_b[t,\Delta_b], IVEP_b[t+d,\Delta_b]) = \int_{t-\Delta b/2}^{t+\Delta b/2} (DVEP_b(t)-\text{mean}(DVEP_b))(IVEP_b(t+d)-\text{mean}(IVEP_b))dt \quad (2)$$

where, and are, the mean of the DVEP and IVEP, respectively.

In this way, delay values are determined automatically and not by only checking the peak points but by considering a time window around peaks. Also, delay values are calculated not only at peak points such as P100 or N160 but for all points in the interval from 50 msec to 200 msec, and this is done automatically. In Figure 3, the theta band of DVEP and IVEP of a subject are plotted at the upper plot and the delay values found for each time are plotted at the bottom plot. As can be observed from the Figure, IVEP is delayed in time and smaller in amplitude with respect to DVEP. Also the delay through time varies from the delay values at P100 and N160.

Furthermore, we considered the correlation of VEPs as a whole in order to find out a single delay value for each band. This delay, D_b, is determined as in (3). Here the whole signal between 50 msec and 200 msec is selected for the DVEP where the window is centered at 125 msec, and different delays, d, are assumed for IVEP. The d for which the correlation result gives the maximum is chosen to be the delay between the signals, i.e., D_b.

$$D_b = \arg\max_d C(DVEP_b[125,150], IVEP_b[125+d,150]) \quad (3)$$

In Figure 4 the theta band of DVEP and IVEP is given in the top image and the bottom image shows the correlation of the whole signals for different d's. In this Figure, D_b is the delay value at which the correlation is maximum for this band (i.e., theta).

RESULTS

The averages of the results obtained from 16 subjects for VEPs at O1 and O2 are summarized in Table 1. The first column shows the half visual fields where the

Table 1

The means and standart deviations of the results averaged over 16 subjects for both visual fields (LVF and RVF), for all bands (theta, alpha, beta1, beta2). Latencies at P100 and N160, delays calculated using windowed correlation method at P100 and N160 (d_b at P100 and d_b at N160 columns) and delay calculated for the whole signal (D_b) are tabulated

Visual Field	Band	Latency at P100 (msec)	d_b at P100 (msec)	Latency at N160 (msec)	d_b at N160* (msec)	D_b (msec)
		90.5	8,909	164,545	8,000	15,273
	theta	±16.3	±8.455	±12.267	±7.266	±15.239
		106.9	6,727	149,000	5,400	7,273
Left	alpha	±8.8	±9.392	±12.481	±10.373	±10.631
(LVF)		107.0	5,000	137,200	3,400	8,200
	beta1	±12.1	±10.551	±11.745	±10.113	±9.589
		107.2	3,200	87,400	3,800	2,000
	beta2	±11.0	±6.408	±10.287	±6.563	±7.376
		91.7	17,111	159,111	20,667	22,667
	theta	±11.8	±10.105	±10.398	±16.432	±14.967
		100.6	9,600	146,400	9,600	11,800
Right	alpha	±6.8	±5.948	±8.733	±8.208	±7.391
(RVF)		104.0	7,800	132,600	7,200	10,000
	beta1	±6.1	±6.070	±7.720	±5.827	±11.419
		106.2	3,800	84,800	2,800	3,000
	beta2	±9.5	±5.770	±8.651	±5.594	±5.354

*(t_{N80} for beta2)

stimulus is presented. The second column shows the bands. In the third, fourth, fifth and sixth columns, latencies at P100 for DVEPs, delay values found at these points, latencies at N160 for DVEPs and delay values for these points are listed, respectively. In the last column the delays found for the whole signal are given. One thing should be mentioned here: for the beta2 band, the first negative peak occurs before the first positive peak. Since the negative peak occurs sometimes around 80 msec after the onset of the stimulus it is called N80.

DISCUSSION

Our results replicated the previous report,[12] indicating that time frequency analysis of VEP to lateralized stimuli gives us additional information in estimate of IHTT. In the report of Nalçacı et al.[12] the IHTT was determined by comparing the latencies of the peak points manually. Since band-pass filtered signals are similar to sinusoids, and they are almost flat around the peak points, it is difficult to determine the exact position of the peaks, and this results in uncertainties in the estimated delay. In this paper this is done automatically and more accurately.

Since the peaks show us the points where the highest number of neurons responds to a stimulus, most of the research studies on this subject were dealing with those peaks only. However, in whole oscillation related neuronal pools are active and callosal transfer continues. Callosal transfer begins earlier than peaks and damps later than peaks. In this study, we considered all times in the interval (i.e., from 50 msec to 200 msec after the onset of the stimulus) and calculated delay values for each time step, using meaningful window lengths for each band separately. We also used the whole signal interval to determine the delay between DVEP and IVEP. With the help of obtained results, we can have an idea about the delay behavior through time for each band and a more realistic estimate for the whole signal delay. Also, in future studies, the behavior of the bands through time could be investigated with the delay information through time.

The correlation analysis of the whole signal yielded slightly different results in comparison to results obtained by comparing latencies of P100 or N160 peaks in VEP pairs. The result obtained by this new approach could be more reliable than the estimate of IHTT depending on comparing the peaks. The differences between IHTT at different frequency bands appear to be more clear with this method. For an example, IHTT at theta band was estimated by correlation as larger when compared to IHTT found by comparing peak latencies.

Also, the results show that there is an asymmetry between the LVF and RVF delays, which is also consistent with the literature. Asymmetric IHTT was first suggested by Marzi et al.[10] who did meta-analysis on 16 simple RT studies. They found RT advantages for the LVF, indicating faster transfer from the right-to-left

hemisphere than from the left-to-right. Meta-analysis of VEP-IHTT by Brown et al.[4] supported this report of Marzi, indicating the similar directionally asymmetric transmission. Our study supported the previous findings about asymmetric callosal transfer, indicating faster transfer from the right hemisphere to the left.

In this study, our main aim was to perform delay calculation for a long period of time automatically, and this was successful. In future studies, we plan to do the same analysis with more subjects and to understand the behavior of delay through time for each band and behavior of delay among bands.

REFERENCES

1. Aboitiz F, Scheibel AB, Fisher RS, Zaidel E. Fiber composition of the human corpus callosum. Brain Res 1992; 598: 143-153.
2. Başar E. EEG-dynamics and evoked potentials in sensory and cognitive processing by the brain. In: Başar E (ed). Dynamics of Sensory and Cognitive Processing by the Brain. Berlin: Springer; 1988: 30-55.
3. Brown WS, Jeeves MA. Bilateral visual field processing and evoked potential inter-hemispheric transmission time. Neuropsychologia 1993; 31: 1267-1281.
4. Brown WS, Larson EB, Jeeves MA. Directional asymmetries in interhemispheric transmission time: evidence from visual evoked potentials. Neuropsychologia 1994; 32: 439-448.
5. Clarke JM, Zaidel E. Anatomical-behavioural relationships: corpus callosum morphometry and hemispheric specialization. Behav Br Res 1994; 64: 185-202.
6. Davidson RJ, Saron C. Evoked potential measures of interhemispheric transfer time in reading disabled and normal boys. Develop Neuropsychology 1992; 22: 353-364.
7. Ducati A, Fava E, Motti EDF. Neuronal generators of the visual evoked potentials: intracerebral recording in awake humans. Electroencephalogr Clin Neurophysiol 1988; 71: 89-99.
8. Hoptman MJ, Davidson RJ. How and why do two cerebral hemispheres interact? Psychol Bull 1994; 116: 195-219.
9. Innocenti GM, Aggound-Zouaouni D, Lehman P. Cellular aspects of callosal connections and their development. Neuropsychologia 1995; 33: 961-987.
10. Marzi CA, Bisiacchi P, Nicoletti R. Is interhemispheric transfer of visuomotor information asymmetric? A meta-analysis. Neuropsychologia 1991; 29: 1163-1177.
11. Nalçacı E, Başar-Eroğlu C, Stadler M. Visual evoked potential interhemispheric transfer time in different frequency bands. Clin Neurophysiol 1999; 110: 71-81.
12. Nalçacı E, Başar-Eroğlu C, Stadler M. VEP-interhemispheric transfer time in 20-32 Hz band in man. NeuroReport 1999; 10: 3105-3109.
13. Rugg MD, Lines CR, Milner AD. Visual evoked potentials to lateralized stimuli and the measurement of interhemispheric transmission time. Neuropsychologia 1984; 22: 215-225.
14. Saron CD, Davidson RJ. Visual evoked potentials measures of interhemispheric transfer time in humans. Behav Neurosci 1989; 103: 1115-1138.

Properties of Multistable Perception During Long Term EEG Recordings

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ABSTRACT

In previous studies, we showed that a positive wave appeared approximately 250 ms prior to the button press of the subjects, indicating the perceptual reversal during the observation of the Necker cube figure. The most dominant features in the delta and alpha band were found to represent the perceptual reversal related positivity. In the present study, we aim to analyze the changes in the alpha frequency band during the perceptual reversal by using the Necker cube paradigm during long term EEG recordings. After the determination of the Individual Alpha Frequency (IAF), the properties of the alpha activity have been measured in three alpha sub-bands: Lower-1 alpha (6-8 Hz), lower-2 alpha (8-10 Hz) and upper alpha (10-12 Hz). The Root Mean Square (RMS) values of the alpha frequency band were measured for two time periods: ±3 SD around the mean peak latency of the perceptual reversal related positivity and a time window of the same length before the perceptual reversal related positivity. We obtained the behavioral properties of the alpha power during the long term EEG recordings by using the multistable perception paradigm.

INTRODUCTION

Since Berger's[9] discovery of the alpha blocking response, several investigators assumed alpha activity to be generated in the visual cortex as an idling rhythm of the visual cortex, because it is blocked by opening the eyes.[11-14,18,19,31-33,36]

Alpha desynchronization probably is the best known phenomenon in the human electroencephalograph. Event-related desynchronization or ERD coined by Pfurtscheller and Aranibar[37] is described as the attenuation or blocking within the alpha and the other frequency bands. ERD was observed during visual stimulation, voluntary movement and cognitive activity by several investigators. Recent research on event-related changes in alpha band power suggests that desynchronization in the alpha frequency range is associated with active information processing, and that different alpha frequencies have quite different functions.[26,27]

Because of outstanding features of the alpha frequency band, many researchers have assumed that alpha may play a key role in understanding other EEG phenomena. For the alpha range, a variety of functional correlates have been found, some of which appear in the following classification (extending a previous version by Galambos[15]; by Başar[1,5]; Başar et al.[4]: 1) The alpha rhythm is more than just a spontaneous rhythm. It is the prototype of spontaneous brain rhythms. According to Başar et al.,[3] it is a prototype of a dynamic process that governs a large ensemble of integrative brain functions. 2) Alpha patterns can be induced, i.e., initiated by, but not closely time-locked to a stimulus.[2,3] 3) Alpha patterns can be evoked, i.e., precisely time-locked to a stimulus.[3] 4) Alpha patterns can be movement-related and also memory-related.[37] 5) Finally, alpha patterns can be emitted. Well trained subjects emitted time-locked bursts of alpha band energy for up to a full second before the delivery of an expected target. The alpha locking to the future moment, when a target will be delivered, is robust and statistically significant.[3]

Reversible or ambiguous figures like the Necker cube make up a well known class of visual phenomena, leading to spontaneous alternations between different stable percepts or interpretations without a physical change of the stimulus.[34] In previous studies, the correlates of the perceptual reversibility from one stable to the other was found related to the alpha and delta frequency bands.[6-8,16,17,41]

The aim of the present study is to test the relationship between the perceptual reversal related positivity and the alpha desynchronization on the sub-bands of alpha range by applying the Necker cube as a multistable figure during the long term EEG recordings.

METHOD

Subjects

Fifteen healthy, right-handed volunteers participated in this study. Subjects were eight men and seven women ranging in age from 21 to 31 years. They were psychology students and members of the university. All subjects had normal or corrected vision, and none of them had neurological disorders. They were instructed to keep their eyes open and to maintain fixation all the time, to minimize blinking and eye movements.

Stimulus pattern

We used a reversible Necker cube as stimulus during the recording time (Figure 1). The stimulus was continuously projected on a computer monitor for a time peri-

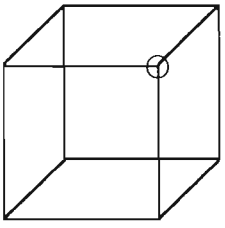

Figure 1.
The stimulus paradigm: ambiguous Necker cube. "0" indicates the fixation point.

od of 400 sec. The line length of the outline cube was 10 cm. The viewing distance was 150 cm, and visual angle was 3.81 deg. The stimulus was presented as white lines on a black background.

Experimental procedure

The subjects sat in a soundproof and echo-free room, which was dimly lit. They were informed about the perceptual reversal of the Necker cube. The subjects were instructed to look at the fixation point all the time and to press a button immediately following reversal. They indicated the onset of the perceptual reversal by shortly and slightly pressing down their right index finger, thus breaking a contact impinging on one channel of the EEG-writer. An additional electromyographic (EMG) recording was carried out in order to estimate the contribution of the motor potentials to the main recording.

Electrophysiological recording

The EEG was registered at recording sites Fz, Cz, Pz, and Oz according to the International 10/20 System. Linked earlobe electrodes served as a reference. All electrode impedances were maintained at less than 5 kOhm. The electrooculogram (EOG) was also registered from medial upper and lateral orbital rim of the right eye. The EEG was amplified by means of a Nihon Kohden (EEG 4421 G) apparatus with band limits at 0.1-70 Hz (24 dB/octave). An additional notch filter (36 dB/octave) was also applied to remove the main interferences. For the recording of EOG, the time constant was set at 0.3 sec and a low pass filter at 70 Hz were applied. All channels were displayed on paper and on-line by monitor scope in order to observe both single trials and averaged trials. The EEG was digitized with a sampling rate of 256 points/s and stored on computer disc memory. Each button press was also recorded as a simple on-off signal on one EEG channel. Furthermore, the EMG was recorded from the right forearm, which served as trigger point for the data analysis. The recording time was about a hundred minutes with 2000 sweep number.

Data analysis

To eliminate muscle and eye movement artifacts, manual off-line selective averaging procedure was applied. Then the remaining epochs were averaged time-locked to the onset of the finger movement. The mean number of the sweeps after artifact elimination was between 800-1000 for each recording. The number of sweeps was equalized from the artifact-free sweeps as 800 sweeps for each subject.

For each subject the peak frequency of the dominant EEG frequency in the alpha band for all recordings sites was used as an anchor point. The mean Individual Alpha Frequency (IAF) was defined as the mean frequency calculated over the entire EEG epochs of each subject individually.[24,25] Table 1 shows the mean frequency windows averaged over the entire sample of 15 subjects as well as the values for the subjects with the highest and the lowest IAF. The frequency windows had a standard bandwidth of 2 Hz and were the same for all of the subjects.[24,25] Three alpha frequency sub-bands with a bandwidth of 2 Hz each were defined by using IAF as the individual anchor point: (IAF-4) to (IAF-2), (IAF-2) to IAF and IAF to (IAF+2), termed lower-1 alpha (6-8 Hz), lower-2 alpha (8-10 Hz) and upper-alpha (10-12 Hz). Averaged over the entire sample of subjects, IAF was 10.37 Hz (see Table 1).[24,25]

The mean latencies of the perceptual reversal related positivity (261.41 ± 60.9 ms) were measured on the average sweeps to determine the latency ranges where alpha power changes related with the perceptual reversal should be measured. The RMS values of the alpha frequency band were computed on the average sweeps for three alpha frequency sub-bands; termed lower-1 alpha (6-8 Hz), lower-2 alpha (8-10 Hz) and upper-alpha (10-12 Hz). This procedure was applied for two time periods: ±3 SD around the mean peak latency (261.41 ± 60.9 ms) of the perceptual reversal related positivity (t2: 440-80 ms before button press), and a time window of the same length before the time window of the perceptual reversal related positivity (t1: 800-440 ms before button press) was used for this purpose.

Statistical analyses

Statistical analyses were carried out on the alpha RMS values of the averaged sweeps by multivariate analysis of variance (MANOVA) test for repeated measures with three factors (frequency, period-effect of perceptual reversal, channel).

RESULTS

Figure 2 shows the grand averages of the artifact-free sweeps of all subjects recorded from Fz, Cz, Pz and Oz channels. The averages of the artifact-free sweeps showed a positive wave approximately 250 ms prior to the finger movement of the subjects marking the onset of the perceptual reversal.

Figure 3 shows the properties of the broad range of alpha power (6-12 Hz) in the latency range of the perceptual reversal-related positivity recorded from the Fz, Cz, Pz and Oz channels of a representative subject. It can be clearly observed that the alpha desynchronization occurs in a precise temporal relation with the perceptual reversal related positivity.

Table 1

The mean frequency windows averaged over the entire sample of 15 subjects, and the values for the subjects with the highest and the lowest Individual Alpha Frequency (IAF)

		Lower-1 Alpha		Lower-2 alpha		Upper-Alpha	
	IAF	From	To	From	To	From	To
Lowest IAF	8.98	6.0	8.0	8.0	10.0	10.0	12.0
Highest IAF	12.77	6.0	8.0	8.0	10.0	10.0	12.0
IAF of 15 subj.	10.37	6.0	8.0	8.0	10.0	10.0	12.0

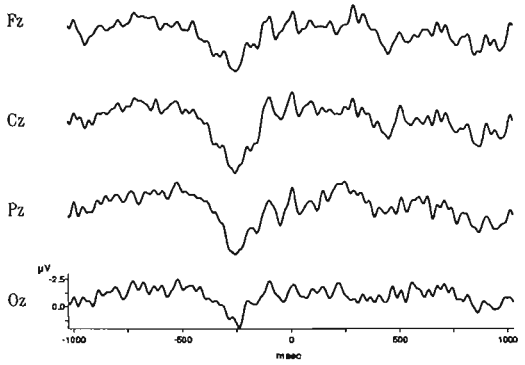

Figure 2.
Shows the grand averages of the artifact-free sweeps of all subjects recorded from Fz, Cz, Pz and Oz channels. The averages of the artifact-free sweeps showed a positive wave approximately 250 ms prior to the button press of the subjects marking the onset of the perceptual reversal. "0" indicates the time of the button press. The time window of the perceptual reversal related positivity (t2) is shown as 440-80 ms before button press, and the time window before the perceptual reversal related positivity (t1) is shown as 800-440 ms before button press in the time scale.

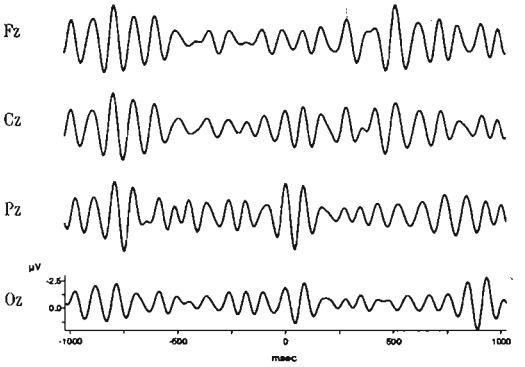

Figure 3.
Shows the properties of the broad range of alpha power (6-12 Hz) in the latency range of the perceptual reversal-related positivity recorded from the Fz, Cz, Pz and Oz channels of a representative subject. It can be clearly observed that the alpha desynchronization occurs in a precise temporal relation with the perceptual reversal related positivity.

To analyze the alpha band correlates of the perceptual reversal statistically, averaged sweeps were filtered in the three alpha sub-bands (lower-1, 6-8 Hz; lower-2, 8-10 Hz and upper, 10-12 Hz), and the RMS amplitude of the alpha activity was measured in two time windows during (t2) and before perceptual reversal related positivity (t1). The time window ± 3 SD around the mean peak latency (260. 45 ± 60.5 ms) of the positive wave (t2: 440-80 ms before button press) and a time window of the same length before the perceptual reversal related response (t1: 800-440 ms before button press) were used. The effect of the perceptual reversal positivity on the RMS amplitude of the three alpha sub-bands (lower-1 alpha, 6-8 Hz; lower-2 alpha, 8-10 Hz and upper alpha, 10-12 Hz) were analyzed statistically. There was a significant perceptual reversal effect ($F(12, 1) = 71.93$; $p< 0.0001$; t1 > t2) on the alpha RMS values.

There also was frequency effect ($F(24, 2)= 2.02$; $p< 0.001$; t1 > t2) on the alpha RMS values, especially for the lower-1 alpha ($t= -0.811$; $p< 0.001$; t1 > t2) and the lower-2 alpha ($t=-1.908$; $p< 0.001$; t1 > t2) (Figures 4, 5).

The effect of the channel on the alpha RMS amplitude was significant ($F(36, 3)= 1.40$; $p< 0.01$; t1 > t2), especially for the Fz ($t=0.932$; $p< 0.01$; t1 > t2), Cz ($t=0.243$; $p< 0.01$; t1 > t2) and Pz ($t=-2.160$; $p< 0.01$; t1 > t2) on the lower-1 alpha and the lower-2 alpha bands (Figures 4 and 5).

The time x frequency effect was significant ($F(24, 2)=8.41$; $p< 0.002$; t1 > t2), especially for the lower-1 alpha ($t=1.503$; $p< 0.01$; t1 > t2) and lower-2 alpha (($t=4.930$; $p< 0.0003$; t1 > t2). The time x channel factor also was significant ($F(36, 3)=1.81$; $p< 0.01$; t1 > t2), especially for the Fz ($t=-1.714$; $p< 0.003$; t1 > t2), Cz ($t=0.747$; $p< 0.03$; t1 > t2) and Pz channels($t=1.514$; $p< 0.04$; t1 > t2).

The factors of the time, frequency, channel, time x frequency, time x channel interactions had no significant effect on the upper alpha RMS amplitudes (Figure 6).

DISCUSSION

In previous studies, we showed a slow positive wave 250 ms before the reaction of the subject mark-

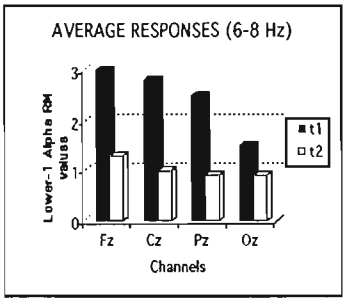

Figure 4.
The RMS values of lower-1 alpha band (6-8 Hz) for Fz, Cz, Pz and Oz channels were evaluated in two time windows (t1: -800 to –440 ms, dark columns; t2:-440 to –80 ms before the button press, light columns). There was a significant decrease of the lower-1 alpha amplitudes during the perceptual reversal related positivity, especially for the Fz, Cz and Pz channels ($p < 0.0001$; t1 > t2).

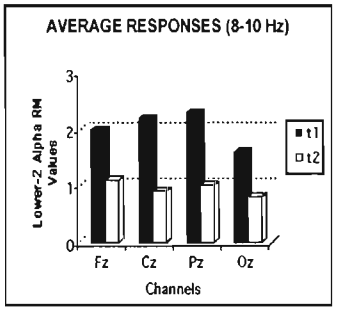

Figure 5.
The RMS values of lower-2 alpha band (8-10 Hz) for Fz, Cz, Pz and Oz channels were evaluated in two time windows (t1: -800 to –440 ms, dark columns; t2:-440 to –80 ms before the button press, light columns). There was a significant decrease of the lower-2 alpha amplitudes during the perceptual reversal related positivity, especially for the Fz, Cz and Pz channels ($p < 0.0001$; t1 > t2).

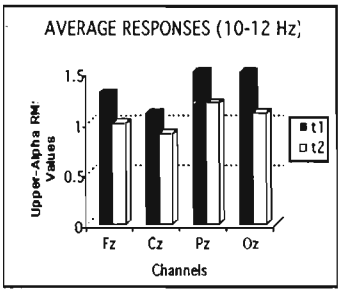

Figure 6.
The RMS values of upper alpha band (10-12 Hz) for Fz, Cz, Pz and Oz channels were evaluated in two time windows (t1: -800 to –440 ms, dark columns; t2:-440 to –80 ms before the button press, light columns). The factors of the time, frequency, channel interactions had no significant effect on the upper alpha RMS amplitudes.

ing the occurrence of a perceptual reversal during continuous observation of a Necker cube and the correlates of the perceptual reversibility from one stable to the other found related to the alpha and delta frequency bands.[6-8,16,17]

According to the Gestalt psychologist Wolfgang Kohler, the investigation of reversal figures serves as a methodological window to the neurocognitive dynamics of perceptual organization.[27] The spontaneous oscillation between different stable percepts of the same physical pattern elucidates the fundamental role of instability as a process characteristic for the autonomous order formation in perception.[29] It has been shown by means of psychophysical experiments that perceptual multistability is an appropriate paradigm for research on cognitive self-organization.[30]

The oldest and classical concept is that the alpha activity is an idling rhythm desynchronized during evoked and/or cognitive processes.[10,31,35-37,39,40] According to this view, alpha desynchronization is characteristic of an activated brain state and can be seen as an electrophysiological correlate of activated or excited cortical neurons, whereas a synchronized activity within the alpha band can be interpreted as a neurophysiological correlate of decreased cortical exitability or even of inhibition of neuronal populations.

Pfurtscheller and Klimesch[38] have shown that exogenous or endogenous stimuli can evoke ERD and ERS with about the same latency at different locations on the scalp. For example, alpha band activity can be enhanced over the visual region and desynchronized over the sensorimotor region during a motor task, whereas occipital alpha is desynchronized and the sensorymotor alpha is enhanced during a visual task. This means that ERD and ERS both form a spatiotemporal pattern, in which the localization of ERD characterizes cortical areas in preparation to process sensory information or ready and prepared to execute a motor command, and ERS marks cortical areas at rest or idling state.[20-23]

In short, the common results of these studies is that the alpha band activities of the EEG react to sensory inputs or cognitive and motor processes. These may appear as a desynchronization or increase of amplitude under certain conditions and over certain brain regions.

There are different approaches to the range of the alpha frequency band, as division into the smaller alpha sub-bands. Klimesch et al.[22,24,26] and Klimesch[25] have reported that the upper alpha band (10-12 Hz) is specifically related to semantic memory processes, the lower-1 alpha (6-8 Hz) is related to attentional processes and the lower-2 alpha band (8-10 Hz) seems to reflect expectancy.[26] Krause et al.[28] suggested that the lower and upper alpha bands differ in the 10-12 Hz frequency band exhibiting reactivity to the presence of linguistic content while the 8-10 Hz band shows an unspecific response. Considering recent studies showing the significance of alpha band power changes during cognitive processes, in the present study we investigated the changes in the RMS amplitude of alpha sub-bands during perceptual reversals.

However, there are few studies[7,8,16,17] performed to understand the Necker cube reversal mechanism using

the EEG measurements. The alpha range we use covers the whole alpha band (6-12 Hz), which allows us to observe the most general characteristics of Necker cube phenomenon. In the second step, the features observed in the broad alpha range were investigated in the alpha sub-bands as lower-1 alpha, lower-2 alpha and upper alpha.

Our findings indicate that a significant decrease of the alpha amplitude during perceptual reversal related positivity was obtained when compared with other parts of the recordings, where subjects observed the same pattern but no reversal occurred. Additionally, the desynchronization effect of the perceptual reversal increased significantly on the lower-1 alpha and lower-2 alpha sub-bands, especially for the Fz, Cz and Pz channels.

According to Başar et al.,[4] a unique frequency component is generally not sufficient to find the exact electrical correlation of brain function. With general interpretation it can be said: different cognitive processes are reflected by band power changes in different frequency bands over localized regions in the brain. The change of two different sub-bands of alpha range might be attributed to two different sub-processes underlying perceptual reversal related positivity.

Our findings indicate that the slow positivity is accompanied by wide-spread alpha desynchronization during perceptual reversal. There is a relationship between the behavior of perceptual reversals and alpha frequency sub-bands of the ERP during the long term EEG recordings by using the Necker cube. This compound reactivity in both the lower-1 alpha and lower-2 alpha frequency bands, which could attribute to the presence of a cognitive process, is not affected by fatigue after such long term recording sessions.

Cognitive processes may influence brain processes. It is often asked how this might be possible without violating the physical conservation laws. The common hypothesis is that the mental effort influences the brain activity at the moment when it is in a highly unstable state. Multistable stimuli offer the possibility to investigate visual awareness, since they evoke spontaneous alternations between different perceptual interpretations of the same stimulus. In the present study, we used the Necker cube as a multistable figure and compared the properties of the perceptual reversals time window with the other parts of the recordings. Our findings indicate that the desynchronization effect of the perceptual reversal increased significantly on the lower-1 alpha and lower-2 alpha sub-bands. This property of the alpha desynchronization may reflect a process of destabilization of the actual percept until a switch of visual awareness occurs.

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REFERENCES

1. Başar E. EEG-Brain dynamics: relation between EEG and brain evoked potentials. Amsterdam: Elsevier; 1980.
2. Başar E. Brain natural frequencies are causal factors for resonances and induced rhythms. In: Başar E, Bullock TH, (eds). Induced Rhythms in the Brain. Boston, Basel, Berlin: Birkhauser; 1992.
3. Başar E, Başar-Eroglu C, Parnefjord R, Rahn E, Schurmann M. Evoked potentials: ensembles of brain induced rhythmicities in the alpha, theta and gamma ranges. In: Başar E, Bullock TH (eds). Induced Rhythms in the Brain. Boston, Basel, Berlin: Birkhauser; 1992: 155-181.
4. Başar E, Schurmann M, Başar-Eroglu C, Karakas S. Alpha oscillations in brain functioning: an integrative theory. Int J Psychophysiol 1997; 26: 5-29.
5. Başar E. Functional alphas selectively distributed in the brain-A theory. In: Başar E, (ed). Brain Function and Oscillations. II. Integrative Brain Function. Neurophysiology and Cognitive Processes. Berlin: Springer-Verlag; 1999: 331-351.
6. Başar-Eroglu C, Struber D, Stadler M, Kruse P. Multistable visual perception induces a slow positive EEG wave. Int J Neurosci 1993; 73: 139-151.
7. Başar-Eroglu C, Struber D, Stadler M, Kruse P, Greitschus, F. Slow positive potentials in the EEG during multistable visual perception. In: Kruse P, Stadler M, (eds). Ambiguity in Mind and Nature. Multistable Cognitive Phenomena. Berlin: Springer-Verlag; 1995: 391-340.
8. Başar-Eroglu C, Struber D, Kruse P, Başar E, Stadler M. Frontal gamma band enhancement during multistable visual perception. Int J Psychophysiol 1996; 24: 113-125.
9. Berger H. Uber das Elektroenkephalogramm des Menschen. I Mitteilung Arch Psychiatr Nervenkr 1929; 87: 527-570.
10. Brandt M. Visual and auditory phase resetting of the alpha EEG. Int J Psychophysiol 1997; 26: 285-298.
11. Chatrian GE, Petersen MC, Lazarete JA. The blocking of the rolandic wicket rhythm and some central changes related to movement. Electroencephalogr Clin Neurophysiol 1959; 11: 497-510.

12. Cohen D. Magnetoencephalography: evidence of magnetic field produced by alpha rhythm currents. Science 1968; 161: 784-786.

13. Creutzfeldt OD, Watanabe S, Lux HD. Relations between EEG phenomena and potentials of single cortical cells. I. Evoked responses after thalamic and epicortical stimulation. Electroencephalogr Clin Neurophysiol 1966; 20: 1-18.

14. Creutzfeldt OD, Rosina A, Ito M, Probst W. Visual evoked response of single cells and of EEG in primary visual area of the cat. J Neurophysiol 1969; 32: 127-139.

15. Galambos R. A comparison of certain gamma band (40-Hz) brain rhythms in cat and man. In: Başar E, Bullock TH, (eds). Induced Rhythms in the Brain. Boston, Basel, Berlin: Birkhauser; 1992.

16. Isoglu-Alkac U, Başar-Eroglu C, Ademoglu A, Demiralp T, Miener M, Stadler M. Analysis of the EEG activity during the Necker cube reversals by means of the Wavelet Transform (WT). Biol Cybern 1998; 79: 437-442.

17. Isoglu-Alkac U, Başar-Eroglu C, Ademoglu A, Demiralp T, Miener M, Stadler M. Alpha activity decreases during the perception of Necker cube reversals: an application of wavelet transform. Biol Cybern 2000; 82: 313-320.

18. Jasper HH, Penfield W. Electrocorticograms in man: effect of the voluntary movement upon the electrical activity of the precentral gyrus. Arch Psychiat Z Neurol 1949; 183: 163-174.

19. Kaufman L, Schwarz B, Salustri C, Williamson S. Modulation of spontaneous brain activity during mental imagery. J Cogn Neurosci 1990; 2: 124-132.

20. Klimesch W, Doppelmayer M, Pachinger T, Russegger H. Event-related desynchronization in the alpha band and the processing of semantic information. Brain Res Cogn Brain Res 1997a; 6: 83-94.

21. Klimesch W, Doppelmayr M, Schimke H, Ripper B. Theta synchronization and alpha desynchronization in a memory task. Psychophysiology 1997b; 34: 169-176.

22. Klimesch W, Doppelmayr M, Pachinger T, Russegger H. Event-related desynchronization in the alpha band and the processing of semantic information. Brain Res Cogn Brain Res1997c; 6: 83-94.

23. Klimesch W. EEG alpha rhythms and memory processes. In: Başar E, Hari R, Lopes da Silva FH, Schurmann M, (eds). Brain Alpha Activity-New Aspects and Functional Correlates. Int J Psychophysiol 1997; 26: 319-340.

24. Klimesch W, Doppelmayr M, Russegger H, Pachinger T, Schwaiger J. Induced alpha band power changes in the human EEG and attention. Neurosci Lett 1998; 244: 73-76.

25. Klimesch W. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. Brain Res Cogn Brain Res 1999; 29: 169-195.

26. Klimesch W, Doppelmayr M, Röhm D, Pöllhuber D, Stadler W. Simultaneous desynchronization and synchronization of different alpha responses in the human electroencephalograph: a neglected paradox? Neurosci Lett 2000 284: 97-100.

27. Kohler W. Dynamics in Psychology. New York: Liveright; 1940.

28. Krause CM, Porn B, Lang AH, Laine M. Relative alpha desynchronization and synchronization during speech perception. Brain Res Cogn Brain Res 1997; 5: 295-299.

29. Kruse P, Stadler M, Struber D. Psychological modification and synergetic modelling of perceptual oscillations. In: Haken H, Stadler M, (eds). Synergetics of Cognition. Berlin: Springer 1991: 299-311.

30. Kruse P, Struber D, Stadler M. The significance of perceptual multistability for research on cognitive self-organization. In: Kruse P, Stadler M, (eds). Ambiguity in Mind and Nature, Multistable Cognitive Phenomena. Berlin: Springer; 1995: 69-84.

31. Lopes da Silva FH, Van Lierop THMT, Schrijer CF, Storm van Leeuwen W. Organization of thalamic and cortical alpha rhythms: spectra and coherences. Electroencephalogr Clin Neurophysiol 1973; 35: 626-639.

32. Lopes da Silva FH. Neural mechanisms underlying brain waves: from neural membranes to networks. Electroenceph Clin Neurophysiol 1991; 79: 81-93.

33. Lopes da Silva FH, Pijn JP, Velis D, Nijssen PCG. Alpha rhythms: noise, dynamics and models. Int J Psychophysiol 1997; 26: 237-249.

34. Necker LA. Observations on some remarkable phenomenon which occurs on viewing a figure of a crystal or geometrical solid. The London and Edinburgh Philosophical Magazine and J Science 1832; 3: 329-337.

35. Niedermeyer E. The normal EEG of the waking adult. In: Niedermeyer E, Lopes da Silva FH, (eds). Electroencephalography: Basic Principles, Clinical Applications and Related Fields. Baltimore, MD: Williams & Wilkins; 1993: 131-152.

36. Niedermeyer E. Alpha rhythms as physiological and abnormal phenomena. Int J Psychophysiol 1997; 26: 5-29.

37. Pfurtscheller G, Aranibar A. Event-related cortical desynchronization detected by power measurements of scalp EEG. Electroencephalogr Clin Neurophysiol 1977; 42: 817-826.

38. Pfurtscheller G, Klimesch W. Event-related desynchronization and desynchronization of alpha and beta waves in a cognitive task. In: Başar E, Bullock TH, (eds). Induced Rhythms in the Brain. Boston, Basel, Berlin, Birkhauser; 1992.

39. Regan D. Same characteristic of average steady-state and transient responses evoked by modulated light. Electroencephalogr Clin Neurophysiol 1966; 20: 238-248.

40. Regan D. Human Brain Electrophysiology: Evoked Potentials and Evoked Magnetic Fields in Science and Medicine. Amsterdam: Elsevier; 1989.

41. Struber D, Başar-Eroglu C, Hoff E, Stadler M. Reversal-rate dependent differences in the EEG gamma-band during multistable visual perception. Int J Psychophysiol 2000; 38: 243-52.

Cognitive Potentials to Visual and Auditory Discrimination Tasks in Children and Adolescents

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ABSTRACT

This chapter presents methodological and developmental aspects of studies carried out on the late endogenous event related potentials, especially P300, in developmental age. The method of eliciting P300 to visual and auditory stimuli has been developed by the Chair and Department of Developmental Neurology in the University of Medical Sciences in Poznan, Poland, and introduced into clinical diagnosis. The investigations were performed on 80 healthy children and adolescents age 8 to 18 years. Auditory and visual oddball paradigms were used. The latencies of P300 showed differences dependent on modality. The significant negative correlation between P300 latencies and age was found at Pz derivation. Visual stimuli produced longer latencies than the auditory task. There were no significant differences between boys and girls in the examined parameters of P300 and no statistical relationship between N1, P2 and N2 latencies and amplitudes for auditory and visual stimulus and age, as well for their P300 amplitudes. These data confirm P300 latency changes related to maturity.

INTRODUCTION AND OBJECTIVES

In 1965 Sutton et al.[37] first described P300 as an event related potential (ERP) associated with cognitive function. The P300 wave is accepted as an objective method of mental processing involved in the allocation of attention resources when immediate memory is engaged. Many studies showed that it provided a modern electrophysiological tool for studying mental processing. Chen and Donchin[2] related P300 to the process of "context update," or the updating of an internal model in the subject's brain that was required when the external situation had changed significantly. Verleger[41] suggested that P300 reflected the "context closure" that occurred when the meaningful, awaited stimulus had been detected. Because processes involve the modification of memory traces, they should be linked with excitatory activity. However, simultaneous recordings from single neurons and from the surface of the skull indicated that the surface positive waves originated mainly from the hyperpolarization of apical dendrites of cortical cells. Thus, they should correspond to periods of reduced cortical excitability. The putative excitatory phenomena could be masked by stronger inhibitory processes. Desmedt[6] suggested that the P300 potential reflected an inhibitory input of prefrontal cortex to the activating reticular formation. Alternatively, Elbert and Rockstroh[7,33] suggested that this potential reflected a threshold regulation mechanism in the cortex. Rockstroh's hypothesis is interesting because it pertains to the principles of neuronal network operation rather than to the psychological meaning of the P300 potential. This does not contradict other theories, but it leads to a number of conclusions that can be experimentally tested.[21]

P300 is considered to be a manifestation of intellectual effort, including memory processing functions, decision making and attention processes. An endogenous component of P300 reflects the moment of the intellectual solution process as indicated by problem stimulus. Therefore, it is considered to be a bioelectric parameter of cognitive processes. P300 is a clinically relevant method to study the cognitive function in all age groups including children and adolescents.[27,30] The P300 component is often elicited with a simple discrimination task (oddball paradigm). Auditory or visual stimuli have been used to elicit the P300.[13,16,17,38,42]

This paper presents methodological and developmental aspects of studies carried out on P300 in developmental age. The age-related changes were also studied.

METHODS

The method of eliciting the late endogenous event related potentials of P300 to visual and auditory stimuli has been developed by the Chair and Department of Developmental Neurology in the University of Medical Sciences in Poznan, Poland, and introduced into clinical diagnosis. ERPs to visual and auditory stimuli were performed on 80 healthy children and adolescents (40 boys, 40 girls) age 8 to 18 years.

According to the IFCN recommendation standards, the auditory oddball paradigm was used to elicit ERPs.[14] ERPs were averaged with Multiliner (Toennies, Germany) equipment. The method included two different tones, 1000 Hz for frequent (non-target) and 2000 Hz

Table 1

The values of ERP parameters in children and adolescents

Parameter	Latency [ms]	
	Auditory	Visual
P300	311.7±17.4	387.2±22.8*
N1	96.0±13.9	102.7±13.4
P2	164.0±20.9	169.1±20.1
N2	218.3±18.1	224.2±18.3
	Amplitudes [μV]	
N1-P2	10.6± 4.0	11.9± 5.3
P2-N2	7.2 ± 3.3	7.6± 4.4
N2-P300	13.2± 3.4	13.4± 3.4

- values are presented mean ±SD
*significant differences between parameters

for rare (target) stimuli pseudorandomly presented. The tones were presented binaurally through headphones with a stimulus duration of 50 ms (rise/fall 10 ms, plateau 30ms) and intensity level of 50 dB above hearing threshold. The repetition rate was 0.5 /s. Each session consisted of 110 tones (30 - rare, 80 - frequent). ERPs were recorded at Fz, Cz and Pz according to the International 10-20 System with Ag/AgCl electrodes, referred to linked earlobes. An additional surface electrode was placed infraorbitally (IO) to record an electro-oculogram (EOG) to monitor artifacts. The filter bandpass was 0.1-70 Hz. Trials with eye movements and with EEG activity of more than 50 μV were automatically rejected. ERPs for target and non-target stimuli were averaged separately. The patients were asked to count the rare tones silently and required to press a button whenever this tone was heard. To assess performance accuracy, at the end of each session the patient's count was compared with the actual number of target tones presented.

On account of different methodology used for visual ERP recordings the particular visual oddball paradigm was applied. Recordings were performed with the same Multiliner (Toennies, Germany) equipment and computerized system developed for visual stimuli. In all patients, visual acuity of each eye was determined before testing to make sure these were normal (or to be corrected).

The method included two stimuli, frequent and rare generated on a screen; (O) was the frequent stimulus and (X) the rare stimulus. The frequent stimulus was red in color and the rare was yellow, each lasting for 50ms. The monitor was placed 1 meter from the subject. The stimulus subtended a visual angle of 10°. Each session consisted of 200 flashes (15% rare, 85% frequent) in random order of red and yellow. The subjects were asked to focus on the central fixation, try to avoid blinks and press a button if a target stimuli (X) was seen. To assess performance accuracy at the end of each session the subject's count was compared with the actual number of targets presented. ERPs for target and non-target stimuli were averaged separately. The major positive peak between 250 and 500 ms for the rare tones was regarded as the cognitive evoked potential (P300).

The latencies of the N1, P2, N2 and P300 waves were determined for each subject, as well as peak-to-peak amplitudes of N1-P2, P2-N2, N2-P300. Latency values were obtained from the intersection of extrapolated lines from the ascending and descending slopes of each peak. Student's t-test was used to compare parameters of ERP produced by visual and auditory stimuli.

RESULTS

The latencies of N1, P2, N2, P300 and the inter-peak amplitudes to visual and auditory stimuli are shown separately in Table 1. The latencies of P300 show differences dependent on modality. Visual stimuli produced statistically significant longer latencies than the auditory task. The latencies of P300, N1, P2, N2 and interpeak amplitudes N1-P2, P2-N2, N2-P3 were scored regarding gender. There were no significant differences between boys and girls in examined parameters of ERP for auditory and visual stimuli (Tables 2 and 3). The obtained results of ERP parameters were age-corrected. The significant negative correlation between P300 latencies and age in auditory and visual stimulation was found at Pz (auditory>$Y=-6.8X+360.8$ $R=-0.75$ $p<0.05$, visual>$Y=-4.3X+389.4$ $R=-0.62$ $p<0.05$). This latency decreased by 6.8 ms per year from 8-18 years of age for auditory stimuli and 4.3 ms for visual stimuli (Figure 1). There was no statistical relationship between N1, P2 and N2 latencies and amplitudes for auditory and visual stimuli and age, as well as for P300 amplitudes.

DISCUSSION

Various authors define endogenous P300 potentials in different ways. Schreiber et al.[36] describe it as a positive component with the highest amplitude at Pz derivation and with latency of 280-500 ms. However, in many research studies done among children of the same age, the average P300 latency is characterized by a different value. Johnson[17] defines P300 as the potential of the highest amplitude recorded at Pz between 300-800 ms after the stimulus presentation. On the basis of his research, the standard defined for 7-year-old children is equal to 640 ms. Pearce et al.[26] defined P300 in children as well as adolescents, as a component of latency between 280-500 ms. As a result of regressive analysis, they established the standard as 400 ms. Schreiber et al.[36] described P300 as a late positive component with the latency of 300-800 ms and maximum amplitude originating in the parietal region. Courchesne[5] claims that P300 latency at children is so high that it is not possible to record it between 280-500 ms. He thinks that endogenous response of maximum amplitude appears at Pz

Table 2

The latencies of P300, N1, N2 of auditory and visual ERP regarding gender

Parameter	Latency [ms]	
	AUDITORY	
	Female	Male
P300	310.5±19.2	312.9±15.6
N1	95.9±13.2	96.1±14.6
P2	164.6±17.8	163.4±24.0
N2	222.1±17.7	214.4±18.4
	VISUAL	
P300	385.5±23.2	388.9±22.3
N1	103.9±14.4	101.4±13.6
P2	173.8±18.1	178.4±22.1
N2	245.2±19.3	249.2±17.3

- values are presented mean ±SD

Table 3

The inter-peak amplitudes of N1-P2, P2-N2, N2-P300 of auditory and visual ERP in girls and boys

Parameter	Amplitudes [μV]	
	AUDITORY	
	Female	Male
N1-P2	10.6±3.8	10.5±4.8
P2-N2	8.2±2.4	6.1±4.2
N2-P3	13.5±3.5	12.8±3.3
	VISUAL	
N1-P2	11.5±4.8	12.3±5.7
P2-N2	7.3±3.4	8.2±5.3
N2-P3	12.9±4.3	13.9±4.4

- values are presented mean ±SD

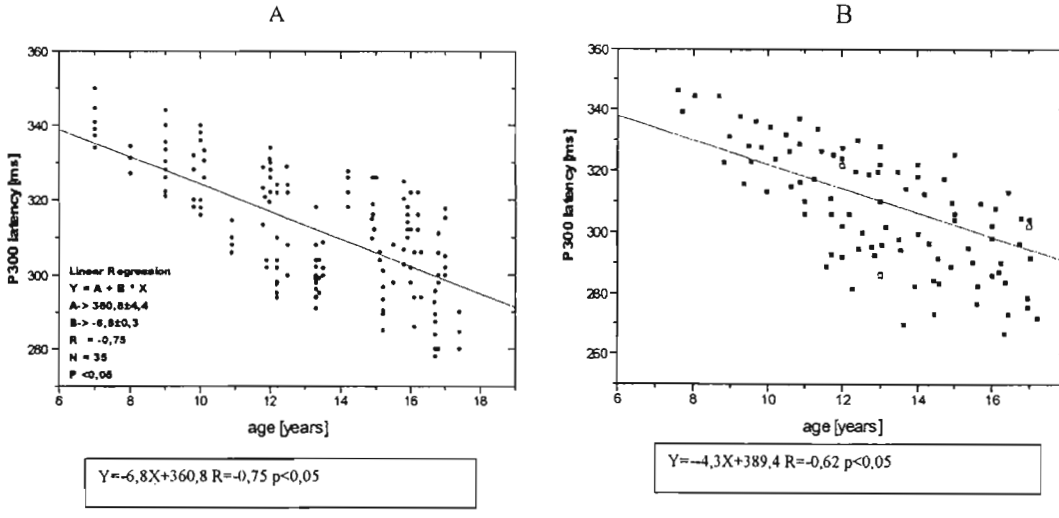

Figure 1.
Relationship between P300 latencies for auditory (A) and visual (B) stimulus and age

between 200-1200 ms. Enoki et al.[9,10] defined P300 as a maximum positive component between 250-500 ms. In their research, P300 was recorded in all subjects above the age of 6. Our own examinations, in the group of children and adolescents between age 8-18, showed that the P300 potential appears in the range of 280-350 ms after the stimulus has been activated.

The question of age influence on P300 component latency has been discussed in many articles. Generally, P300 latency and amplitude decrease gradually with age, reaching the constant value at adult age.[10,14,22,28,30] Finley et al.[12] examined a group of 35 persons age 5-16 demonstrating the decline of P300 latency at 3.6 ms/year.

Polich and Heine[31] analyzing P300 latencies in 26 examined patients with 13 at the age below age 10 recorded the fall of 7.8 ms/year. Goodin et al.[14] observed a decrease of 18.4 ms/year in a group of 48 children among whom 5 patients were under age 10. Johnson[17] showed the drop of latencies at 13.8 ms/year in 40 girls at the age between 7-20.

Enoki[9] examined P300 in 164 patients age 4-77, among whom there were 88 children under 15 years of age, recording the decline of latency at 9.4 ms/year in patients below age 15. Naganuma et al.[23] examining 53 children at ages under 15, found a decrease of latency at 9.8 ms/ year.

Finley et al.[12] and Chen and Donchin[2] found about a 19 ms/ drop in P300 latency for children under age 15. Patients between 6-23 years of age showed a latency decrease of 8.15 ms/year. Karrer and Ackles[18] stated that P300 latency with auditory stimulation increases at 1.8 ms/year between 15-76 years of age.

These examinations were confirmed by Syndulko et al.,[30] Brown et al.,[1] Pfefferbaum et al.,[27] and Picton et al.[28]

Our own examinations demonstrated the decrease of P300 latency at 6.7 ms/year for auditory stimulus and 4.3 ms for visual stimulus. The above considerations lead to the conclusion that P300 latency decreases from the start of life, reaches the minimum value in the last stage of puberty and then increases with age. The decrease of P300 latency in the developmental age is connected with the maturation of neuroanatomic structures and neuropsychological functions.[32]

The histological observations made by Cohen and Polich[3] show that forming dendrites in the cerebral cortex takes place at the age of 10. Yakovlev and Lecours[43] stated that the development of anatomical structures responsible for higher nervous system activities takes place progressively up to the end of puberty.

Consequently, it may be concluded that physiological and anatomical changes of cerebral structures are responsible for the decrease of latency progressing with the age of children and adolescents. P300 has been generally considered to be independent of gender.[19,20,35] There were also no statistically significant differences in ERP parameters regarding gender in our study.

Literature describes many methods of visual stimulation eliciting the generation of endogenous P300 potential. Nash and Fernandez[24] applied two luminescent diodes of various colors in their examinations. The subject was to react to a stimulus of a defined color that appeared rarely, a method which is technically simple to administer. The disadvantage of this method for generating P300 may be the weak light intensity emitted from a single diode, which makes the differentiation of colors more difficult. This type of stimulation should not be used for examination of children.

Evers et al.[11] and Grotemeyer et al.[15] developing this type of stimulation, elaborated on a method in which alternating colors (respectively for the "oddball paradigm" method) appeared on the computer screen. Changing colors presented as computer flashes were used by Picton et al.[28] in their examinations. They used stimuli of 50 ms duration and red color (rare) and green color (frequent). This type of stimulation reduces the difficulty in discriminating the characteristics; therefore, it may be successfully used in examination of children and adolescents.

The next step in developing the examining methods of P300 endogenous potentials with the use of visual stimulation was the introduction of graphic elements as trigger stimuli. Pfefferbaum et al.[27] used two symbols "+" and "–" and a patient reacted to a "–" symbol.

Linking a computer with the research equipment allowed our group to use more complex methods of stimulation. Complicated graphic symbols appeared on the screen, such as figures, letters and drawings. In their examinations Onofrj et al.[25] used as a stimulus horizontal lines (frequent) and vertical (rare), appearing on the screen with probability of 0.3. Comerchero and Polich[4] applied black-and-white stripes of different width appearing on the screen at random. Moreover, Polich[29] describes a method using a chessboard and stripes as stimulating elements. Uberall et al.[40] used geometric figures as stimulating elements. They applied a procedure in which a distinguished stimulus was generated at the same time as a sequence of a figure circumference and then its full picture. Simultaneously, the reduction of amplitude and elongation of P300 latency were observed. The modification of this method was the introduction of a definite object and subsequent picture of its name as stimuli.[34]

Complexity of the subtitle, which was to be recognized as proper, seemed to have great influence on the value of ERP latency. Suwazano et al.[38] administered an innovative technique using a triangle with the base upward or downward. Sangal and Sangal[35] used S and H letters as elements eliciting a response. The subject reacted by pushing the button while seeing S.

The procedure used by the Chair and Department of Developmental Neurology at the University of Medical Sciences consists of two stimuli, X and O symbols. The age of patients undergoing ERP examinations in our Department requires the introduction of stimulation. Therefore, except for the discrimination of patterns, every letter is a different color, allowing examination of children who do not yet know letters or figures.

A similar technique was used by Johnson[17] Emmerson[8] and Rosenberg et al.[34] However, these authors used monochromatic patterns, reducing the applicability of this method. The P300 component is closely associated with the degree of difficulty in recognition of the X or O symbols presented. The more difficult the task is, the longer the latency of the potential. The application of the complex set, consisting of changes in colors of presented letters, results not only in neurophysiological measurement of selective attention, but in the process of scanning memory.

The effects on modality used for ERP were similar to previous reports by Polich and Heine[31] and Ramero and Polich.[32] They observed smaller amplitude and shorter latency of P300 parameters for auditory stimulus. In our work, we found statistically significant differences only in latency without changes in amplitude. The technical parameters used for visual stimulation can be an important factor influencing the differences from previous reports.

CONCLUSIONS

These data confirm P300 latency changes related to maturity. Differences between procedures of ERPs per-

formance and subject age can affect P300 latencies. EPR parameters were independent of gender. We found that ERP is an objective and non-invasive procedure for evaluating cognitive function in developmental age.

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REFERENCES

1. Brown W, Marsh J, Laure A. Exponential electrophysiological aging: P3 latency. Electroencephalogr Clin Neurophysiol 1983; 55: 264-271.
2. Chen G, Donchin E. Predictions, their confirmation, and the P300 component. Psychophysiology 1979; 16: 174.
3. Cohen J, Polich J. On the number of trials needed for P300. Int J Psychophysiol 1997; 25: 249-255.
4. Comerchero MD, Polich J. P3a and P3b from typical auditory and visual stimuli. Clin Neurophysiol 1999; 110: 24-30.
5. Courchesne E. Cognitive components of the event-related brain potential: changes associated with development. In: Gaillard AWK, Ritter W, (eds). Tutorials in Event-Related Potential Research; Endogenous Components. Amsterdam: North Holland, 1983: 329-344.
6. Desmedt J. P300 in serial tasks: an essential post-decision closure mechanism. Prog Brain Res 1980; 54: 682-686.
7. Elbert T, Rockstroh B. Threshold regulation: a key to the understanding of the combined dynamics of EEG and event-related potentials. J Psychophysiol 1987; 4: 317-333.
8. Emmerson R. P3 latency and symbol digit correlations in aging. Exp Aging Res 1990; 15: 151-159.
9. Enoki H. P300 of auditory event-related potentials: the effects of development and aging in humans. Jpn J EEG EMG 1990; 18: 60-67.
10. Enoki H, Sanada S, Yoshinaga H, Oka E, Ohtahara S. The effects of age on the N200 component of the auditory event-related potentials. Cogn Brain Res 1993; 1: 161-167.
11. Evers S, Bauer B, Grotemeyer K-H, Kurlemann G, Husstedt IW. Event-related potentials (P300) in primary headache in childhood and adolescence. J Child Neurol 1998; 13: 322-326.
12. Finley W, Faux S, Hutcheson J, Amstutz L. Long-latency event-related potentials in the evaluation of cognitive function in children. Neurology 1985; 35: 323-327.
13. Galas-Zgorzalewicz B, Nowak R, Zgorzalewicz M. Event related potentials to visual stimuli in school children and adolescents. Clin Neurophysiol 2000; 111(suppl 1): 15.
14. Goodin D, Desmedt J, Maurer K, Nuwer M. IFCN recommended standards for long-latency auditory event-related potentials: report of an IFCN committee. Electroencephalogr Clin Neurophysiol 1994; 91: 18-20.
15. Grotemeyer K, Husstedt IW, Brundermann H, Busch H, Schlake HP, Zidek In. Event-related potentials in HIV-infected out-patients. AIDS Res Hum Retroviruses 1991; 7: 629-635.
16. Heinz G, Rau I, Schneider B. Visuell ausgelöste P300-wellen. Z EEG-EMG 1991; 22: 209-216.
17. Johnson R. Developmental evidence for modality-dependent P300 generators: a normative study. Psychophysiology 1989; 26: 651-666.
18. Karrer R, Ackles P. Visual event related potentials of infants during a modified oddball procedure. In: Johnson R, Rohrbaugh JW, Parsurman R, (eds). Current Trends in Event-Related Potential Research. Amsterdam: Elsevier 1987; (EEG suppl 40): 603-608.
19. Kosmidis MH, Duncan CC, Mirsky AF. Sex differences in seasonal variations in P300. Biol Psychol 1998; 49: 249-268.
20. Kugler CF. Interrelation of age, sensory functions and human brain signal processing. J Gerontol A Biol Med Sci 1999; 54: 231-238.
21. Michalski A. Novel environment as a stress-inducing factor. An event-related potentials study. Acta Neurobiol Exp 1998; 58: 199-205.
22. Mullis R, Holcomb PJ, Diner BC, Dykman RA. The effects of aging on the P300 component of the visual event related potential. Electroencephalogr Clin Neurophysiol 1985; 62: 141-149.
23. Naganuma Y, Konishi T, Hongou K, Murakami M, Yamatani M, Yagi S, Okada T. Auditory event-related potentials in benign childhood epilepsy with centrotemporal spike: the effects of carbamazepine. Clin Electroencephalogr 1994; 25: 8-12.
24. Nash A, Fernandez M. P300 and allocation of attention in dual-tasks. Int J Psychophysiol 1996; 23: 171-180.
25. Onofrj M, Fulgente T, Nobilio D, Bazzano S, Colamarino P. Mapping of event-related potentials to auditory and visual odd-ball paradigms in controls. Eur Neurol 1991; 31: 220-228.
26. Pearce J, Crowell D, Tokioka A, Pacheco G. Childhood developmental changes in the auditory P300. J Child Neurol 1989: 4: 100-106.
27. Pfefferbaum A, Ford J, Roth W, Kopell B. Age differences in P3 reaction time associations. Electroencephalogr Clin Neurophysiol 1984; 59: 85-103.
28. Picton T, Stuss D, Champagnne S, Nelson R. The effects on age on human event related potentials. Psychophysiolology 1984; 21: 312-325.
29. Polich J. Meta-analysis of P300 normative aging studies. Psychophysiology 1998; 33: 334-353.
30. Polich J, Ladish C, Burns T. Normal variation of P300 in children: age, memory span and head size Int J Psychophysiol 1990; 3: 237-248.
31. Polich J, Heine M. P300 topography and modality effects from a single stimulus paradigm. Psychophysiology 1996; 33: 747-752.

32. Ramero R, Polich J. P300 habituation from auditory and visual stimuli. Physiol Behav 1996; 59: 517-522.

33. Rockstroh B, Müller M, Cohen R, Elbert T. Probing the functional brain state during P300 evocation. J Psychophysiol 1992; 6: 175-184.

34. Rosenberg C, Nudleman K, Starr A. Cognitive evoked potentials (P300) in early Huntington's disease. Arch Neurol 1985; 42: 984-987.

35. Sangal B, Sangal J. Topography of auditory and visual P300 in normal adults. Clin Electroencephalogr 1996; 27: 145-150.

36. Schreiber H, Stolz-Born J, Rothmeier J, Kornhuber A. Endogenous event-related brain potentials and psychometric performance in children at risk for schizophrenia. Biol Psychiatr 1991; 30: 177-189.

37. Sutton S, Braren M, Zubin J, John ER. Evoked potential correlates of stimulus uncertainty. Science 1965; 1187-1188.

38. Suwazano S, Machado L, Knight T. Predictive value of novel stimuli modifies visual event-related potentials and behaviour. Clin Neurophysiol 2000; 111: 29-39.

39. Syndulko K, Hansch E, Cohen S, Pearce J, Goldberg Z, Montana B, Tourtellote W, Potvin A. Long latency event related potentials in normal aging and dementia. In: Courgan J, Mauguire F, Revol M, (eds). Clinical Application of Evoked Potentials in Neurology. New York: Raven Press; 1982: 126-178.

40. Uberall M, Brandt U, Wenzel D. Stimulus specificity of P300. Neuropediatrics 1993; 24: 324-331.

41. Verleger R. Event-related potentials and cognition: a critique of the context updating hypothesis and an alternative interpretation of P3. Behav Brain Science 1998; 11: 343-356.

42. Vesco K, Bone R, Ryan J, Polich J. P300 in young and elderly subjects: auditory frequency and intensity effects. Electroencephalogr Clin Neurophysiol 1993; 88: 302-308.

43. Yakovlev P, Lecours A. The myelogenetic cycles of regional maturation of the brain In: Minkowski A (ed). Regional Development of the Brain in Early Life. Oxford: Blackwell Scientific Publ; 1967: 3-70.

CLINICAL

Diagnostic Utility of Electrophysiological Testing: Approaches and Obstacles

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ABSTRACT

Diagnosis in psychiatry remains dependent on subjective reports by patients, and it continues to be difficult to quantify observations of aberrant behavior. A number of biological aberrations have been identified in various psychiatric populations. The translation of these research findings into clinical applications is complex. Two approaches for such translational effort are described. The first approach is the development and progressive refinement of appropriate "battery" tests for specific differential diagnostic questions. The second approach is to develop discriminant functions to help differentiate between disorders. The simplest technique is to start with a large number of parameters with the basic assumption that the presumed illness will be reflected with a statistical significance in some of these variables. Advantages and disadvantages of each approach are discussed.

INTRODUCTION

Diagnosis in psychiatry remains dependent on subjective reports by patients and it continues to be difficult to quantify observations of aberrant behavior. Currently identified biological markers, when used in isolation, do not have the performance characteristics to be useful in clinical medicine. Diagnosis in psychiatry remains the major limiting-step in biological research and in treatment studies.[26] Despite the evolution of our classification system and methods of assessment, questions about accuracy of diagnosis persist. As Spitzer[22] and others have pointed out, there is no diagnostic "gold standard" for psychopathology, and we may never have one. Instruments used to ascertain the presence of a diagnosis are limited by their imperfect application. The accuracy of clinical diagnoses, based solely on structured or unstructured interviews, remains questionable.[10] Inconsistencies in format, differing levels of examiner expertise, and bias in interpretation of data all are sources of decreased reliability of diagnosis.

Recent data by Roy et al[18] and earlier by Leckman et al[11] have shown that diagnoses based solely on clinical data, and using the best available expertise and a multilevel evaluation to arrive at a consensus best estimate diagnosis, can only reach a kappa for agreement of 0.69. Clinically based diagnoses have also been found to contain diagnostic bias.[12] The literature suggests that even in the best hands and utilizing prohibitively long clinical evaluations (up to 26 hours/patient) the current diagnostic system, solely based on clinical data, lacks a high degree of reliability and accuracy. Steiner et al[23] examined the agreement between diagnoses generated by the Structured Clinical Interview for DSM-IIIR and by non-structured psychiatric interviews. Overall reliability between the SCID and the clinicians, as determined by weighted kappa, was poor. Agreements for schizophrenia were among the highest (r=.69), moderate for major depression (r=.38) and lowest for schizoaffective disorder (r=.17). Prospective studies designed to examine the effects of misdiagnosis have not been done.

Differentiating patients from non-patients with a high degree of reliability is an essential first step. Clinical situations where this differentiation is essential are not infrequent.[1] In fact, the labeling of a non-patient as a patient (particularly as schizophrenic) is likely to stigmatize this person for life. Each case, when the insanity defense is invoked, is a reminder of such need. Recent studies strongly suggest that such differentiation can be attained with currently available technology. In the next section we briefly describe two approaches for applying electrophysiological data to the differential diagnosis process in psychiatry. Early studies, using either approach, seem highly promising.

APPROACHES

The biggest challenge in differential diagnosis is the misclassification problem. Many approaches for the solution are proposed and used according to the data handled.

The first approach is the development and progressive refinement of appropriate "battery" tests for specific differential diagnostic questions, each test component of the test-battery having already been demonstrated to be abnormal in one or the other of the illnesses to be differentiated from one another. As is the case in most identified biological abnormalities in psychiatric disorders, such abnormalities can be detected in more than one disorder. If an abnormality is equally prevalent in two disorders, this particular abnormality will most likely not contribute to the differential diagnostic value of the test-battery. Abnormalities with differential prevalence among

disorders to be differentiated should be useful components of the test-battery. In this approach, decision trees are used, and programs like the Classification and Regression Trees (CART) may be helpful.[2] Bayesian analysis techniques are very informative in this kind of approach.[6] We will refer to this approach as the Battery Approach. A good example of the battery approach was conducted by Shagass and his colleagues[21] in the mid-eighties showing that, using a battery of the non-invasively recorded brain evoked potentials (EPs), groups of normal controls can be differentiated from patients with axis-I diagnoses. There are no published replication attempts. Moreover, the electrophysiology battery used in this study was limited to evoked potentials.[21] Other test modalities like sleep recording, EEG, and eye movement recordings can be added to the battery with possible usefulness.

The second approach is to develop discriminant functions to help differentiate between disorders. The simplest technique is to start with a large number of parameters, with the basic assumption that the presumed illness will be reflected with a statistical significance in some of these variables. A set of bivariate comparisons in this first phase of analyze is necessary. A more flexible level of "p" must be preferred ($p = 0.10$) in this parameter elimination phase. Another important side of these comparisons is to remember that electrophysiological variables are generally well behaved and normally distributed without using any transformations.[24] After getting rid of redundant or nondiscriminative parameters, various discrimination functions can be developed. With this new list of "probably independent and discriminative" parameters, some appropriate methods within a large scale of discriminative techniques may be applied (we will refer to this approach as the Discriminant Function Approach). The main criticism usually directed at this approach is that it requires intense statistical calculations that the average clinician cannot understand. John et al.[9] used a different strategy than that used by Shagass et al.[21] They started with a large number of measures/variables and progressively narrowed the comparisons by eliminating redundant or un-useful information. John et al.,[9] in addition to reaffirming the powerful ability of EP and EEG measures to differentiate between normal subjects and patients with schizophrenia, provided evidence that EEG/EP measures can be used to develop a number of stable and reproducible electrophysiological profiles within a group of patients with schizophrenia. Such profiles may not coincide or correlate with clinically established disease subtypes and may provide new avenues in investigating complex heterogeneous disorders like schizophrenia.

Whatever the approach, a perfect discrimination is always never reached, and misclassifications are present. Some approaches are used to correct the error rate of classification techniques. The cross-validation method is a preferred one. Because the same observations are used both to define and to evaluate the discriminant model, the resultant error-count estimate is believed to have an "optimistic" bias. To reduce this bias a cross validation may be used in which "n-1" out of "n" training observations are treated as a training set. The discriminant functions based on these n-1 observations are determined and the functions are applied to classify the observation left out. This is done for each of the n observations. The misclassification rate for research groups is the proportion of sample observations in that group that are misclassified.[7]

Electrophysiology has a great potential as a differential diagnostic tool: Electrophysiological recordings from the scalp, whether electroencephalography (EEG) or evoked potentials (EPs), are completely noninvasive, and without risks to human subjects.[25] The techniques are also relatively inexpensive compared with other procedures such as magnetic resonance imaging (MRI) and positron emission tomography (PET). The above two attributes are essential if a test modality is to become clinically useful. Essential, also, is evidence that the objective test data can significantly and meaningfully improve the clinical care of a particular patient.

The P300 ERP is a large positive response appearing between 250-450 msec most commonly elicited by an odd stimulus imbedded among common or frequent stimuli. Evidence for an abnormally small P300 in schizophrenia is substantial.[5] In a discussion of the usefulness of the P300 in diagnosing schizophrenia, it was shown that a criterion P300 amplitude can be established, above which one can rule out the diagnosis of schizophrenia (+1.6 SD), but no criterion amplitude can reasonably establish a positive diagnosis of schizophrenia.[5]

Evidence for abnormal mid-latency auditory evoked responses (MLAERs) in schizophrenia has also been accumulating for the last three decades.[3] Iwanami et al. studied 27 medicated individuals with schizophrenia.[8] They found the amplitude of the MLAER N100 to be decreased at Cz as compared to normal controls. Roth et al.[17] using long interstimulus intervals also showed the N100 to be decreased in amplitude in schizophrenia. Other researchers have also found similar decreases in N100 amplitudes in schizophrenia.[13-16] In contrast, the P200 was found to be decreased in amplitude in schizophrenia patients by some investigators, but not by others.[4,17] Shagass et al.[20] studied somatosensory, auditory, and visual EPs in 102 patients, 50 of whom were diagnosed with schizophrenia.[19] They found that the EPs of overtly psychotic patients (schizophrenics, depressives or manics) differed markedly from the EPs of normal control subjects. Psychotic patients had significantly decreased amplitudes of events occurring 100 ms or later after stimulation. While most of the above listed

abnormalities have been repeatedly and independently replicated (particularly the P300 amplitude abnormality in schizophrenia), their clinical usefulness has not been demonstrated. Problems with sensitivity and specificity are most frequently cited as reasons. More recently, the mis-match negativity has also emerged as another promising variable that has potential for differentiating among psychotic disorders like schizophrenia and bipolar disorders.

In conclusion, the authors of this chapter believe that both approaches may have different utilities and are likely to be complementary. Familiarity with both approaches seems necessary. Further research, particularly using the Battery Approach, will require that researchers be more adept in a number of electrophysiological research methodologies (e.g., sleep, QEEG, ERP...) or be able to develop close collaborative research relationships allowing the development of such batteries.

REFERENCES

1. Boutros NN, Nasrallah H, Leighty R, Torello M, Tueting P, Olson S. The mid-latency auditory evoked responses clinical vs. research applications. Psychiatry Res 1997; 69: 183-195.
2. Breiman L, Friedman JH, Olshen RA, Stone CJ. Classification and Regression Trees. New York: Chapman and Hall Publishers; 1984.
3. Buchsbaum MS. The middle evoked response components and schizophrenia. Schizophr Bull 1977; 3(1): 93-104.
4. Faux SF, Shenton ME, McCarley RW, Torello MW, Duffy FH. P200 topographic alterations in schizophrenia: evidence for left temporal-centroparietal region deficits. In: Johnson R Jr, Rohrbaugh JW, Parasuraman R, (eds). Current Trends in Event-related Potential Research. (EEG suppl 40). Elsevier Science Publishers VV (Biomedical Division); 1987.
5. Ford JM, Roth WT, Pfefferbaum A. P3 and schizophrenia. In: Friedman D, Bruder G, (eds). Psychophysiology and Experimental Psychopathology: A Tribute to Sam Sutton. NY Acad Sci 1992: 146-162.
6. Gelman A, Carlin JB, Stern HS, Rubin DB. Bayesian Data Analysis. New York: Chapman and Hall/CRC; 1995.
7. Hora SC, Wilcox JB. Estimation of error rates in several-population discriminant analysis.J Market Res 1982; 19: 57-61.
8. Iwanami A, Suga I, Kanamori R. N1 component derived from the temporal region during an auditory passive event-related potential paradigm in schizophrenics. Clin Electroencephalogr 1994; 25: 50-53.
9. John ER, Prichep LS, Alper KR, Mas FG, Cancro R, Easton P, Sverdlow L. Quantitative electrophysiological characteristics and subtyping of schizophrenia. Biol Psychiatry 1994; 36(12): 801-826.
10. Kosten TA, Rounsaville BJ. Sensitivity of psychiatric diagnosis based on the best estimate procedure. Am J Psychiatry 1992; 149:1225-1227.
11. Leckman JF, Sholomskas D, Thompson D, et al. Best estimate of life time psychiatric diagnosis. Arch Gen Psychiatry 1982; 39:879-883.
12. Meziade M, Roy MA, Fournier JP, et al. Reliability of best-estimate diagnosis in genetic-linkage studies of major psychoses: results from the Quebec pedigree studies. Am J Psych 1992; 149: 1674-1686.
13. Pfefferbaum A, Ford JM, White P, Roth WT. P3 in schizophrenia is affected by stimulus modality, response requirements, medication status and negative symptoms. Arch Gen Psychiatry 1989; 46: 1035-1046.
14. Pfefferbaum, A., Horvath, T., Roth, W.T., Tinklenberg, J.R., Kopell BS. Auditory brainstem and cortical evoked potentials in schizophrenia. Biol Psychiatry 1980;15: 209-223.
15. Roemer RA, Shagass C. Replication of an evoked potential study of lateralized hemispheric dysfunction in schizophrenics. Biol Psychiatry 1990; 28: 275-291.
16. Roth WT, Goodale J, Pfefferbaum A. Auditory event-related potentials and electrodermal activity in medicated and unmedicated schizophrenics. Biol Psychiatry 1991; 29: 585-599.
17. Roth WT, Horvath TB, Pfefferbaum A, Kopell VS. Event related potentials in schizophrenics. Electroencephalogr Clin Neurophysiol 1980; 48:127-138.
18. Roy MA, Lanctot G, Merette C, et al. Clinical and methodological factors related to reliability of the best-estimate diagnostic procedure. Am J Psych 1997; 154:1726-1733.
19. Shagass C, Roemer R. Evoked potential tomography in unmedicated and medicated schizophrenics. Int J Psychophys 1991; 10: 213-224.
20. Shagass C, Roemer RA, Straumanis JJ, Amadeo M. Evoked potential correlates of psychosis. Biol Psychiatry 1978; 13(2): 3-184.
21. Shagass C, Roemer RA, Straumanis JJ, Josiassen RC. Combinations of evoked potential amplitude measurements in relation to psychiatric diagnosis. Biol Psychiatry 1985; 20: 701-722.
22. Spitzer RL. Psychiatric diagnosis: are clinicians still necessary? Compr Psychaitry 1983; 24: 399-411.
23. Steiner JL, Tebes JK, Sledge WH, Walker ML. A comparison of the structured clinical interview for DSM-IIIR and clinical diagnosis. J Nerv Ment Dis 1995; 183:365-369.
24. Thatcher RW, Walker RA, Gerson I, Geisler FH. EEG discriminant analyses of mild head trauma. Electroencephalogr Clin Neurophysiol 1989; 73: 94-106.
25. Tueting PA. Electrophysiology of schizophrenia: EEG and ERPs. Curr Opin Psychiatry 1991; 4: 7-11.
26. Van Praag HM. Over the main stream: diagnostic requirements for biological psychiatric research. Psychiatry Res 1997; 72: 201-212.

Electric Brain Activity in Psychiatry: Research Tools with Clinical Value

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ABSTRACT

Electroencephalography (EEG) and evoked potentials (EP) directly reflect cortical neuronal activity with high temporal resolution. Brain electric activity is influenced by cortically released neurotransmitters and by effects of neuromodulators on cortical neuronal function. Using modern techniques of EEG and EP recording and analysis, these instruments are not only important research tools in neuroscience, but can also be helpful in the clnical diagnosis and monitoring of functional neuropsychiatric disorders. The clinical application of neurophysiological assessments will be demonstrated in patients with dementia and depression to provide evidence that neurophysiology can be of clinical relevance in early diagnosis, drug monitoring, or even in prediction of treatment response.

INTRODUCTION

Looking at the number and the ranking of relevant medical publications (e.g., in *Medline*) of the last 5 years, there has been a reviving interest in electroencephalography (EEG) and evoked potentials (EP) as important clinical and research instruments in psychiatry.

This development reflects the strategic role of EEG and/or EP for the investigation of brain function in psychiatric patients: 1) EEG/EP are instruments, *directly* reflecting cortical neuronal activity, 2) EEG/EP are the only methods with a sufficiently *high* time resolution for the analysis of the dynamic patterns of neuronal brain activity, e.g., synchronization and desynchronization, oscillation, coherence, gamma band activity, latency of event related activity, etc., which are crucial for a deeper understanding of functional (neurophysiological) correlates of cognitive, emotional and behavioral disturbances in psychiatric patients.

These characteristics are substantial advantages of electrophysiology over functional neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), or single photon emission computed tomography (SPECT), which are *indirect* measures of neuronal activity with a comparatively *low* time resolution.

Conventional and quantitative electroencephalography are often underutilized in the evaluation of psychiatric disorders but nevertheless can be most useful and highly effective in the diagnostic workup of confusional states, delirium, dementias and other neuropsychiatric conditions. In their excellent and comprehensive review of more than 200 significant EEG studies in neuropsychiatry, Hughes and John[13] provided evidence that the application of electroencephalography can even be helpful in particular psychiatric problems, such as early diagnosis and estimation of prognosis (e.g., dementia) and the prediction of drug responses or treatment monitoring.

Recent methodological advances of electrophysiological techniques have further improved and strengthened the position of EEG/EP concerning clinical application. Results from two research areas regarding two event related evoked potentials (ERP), the auditory evoked P300 and the N1P2 component of auditory evoked potentials, will be summarized: 1) Auditory P300 dipole activity turned out to be one of the best biological markers for the early diagnosis and differential diagnosis of Alzheimer's disease (AD); P300 parameters were correlated with a favorable outcome to a treatment with donepezil and might become a clinically useful response predictor. 2) The loudness dependency of the N1P2 component of auditory evoked potentials (LDAEP) is one of the best validated indicators of central serotonergic function. It is a replicated finding that LDAEP is useful for the prediciton of the individual clinical response to serotonergic medication in depressed patients.

ELECTROPHYSIOLOGY IN (EARLY) DIAGNOSIS, DIFFERENTIAL DIAGNOSIS AND TREATMENT MONITORING OF DEMENTIAS: THE VALUE OF AUDITORY EVENT RELATED POTENTIALS (P300)

Diagnosis

As new antidementive treatment strategies will become available in the future, there is an emergent need for a reliable and efficient noninvasive method for the early diagnosis of Alzheimer's disease and for the detection of patients at risk for the development of dementia. In addition, expensive antidementive treatments require objective measures of intraindividual efficacy.

In a prospective, confirmatory study to evaluate the clinical relevance of event-related P300 in the early diagnosis of AD, Frodl et al.[3] have investigated 30 patients with AD, 26 patients with mild cognitive impairment (MCI) and 26 age-matched healthy controls (HC). A new

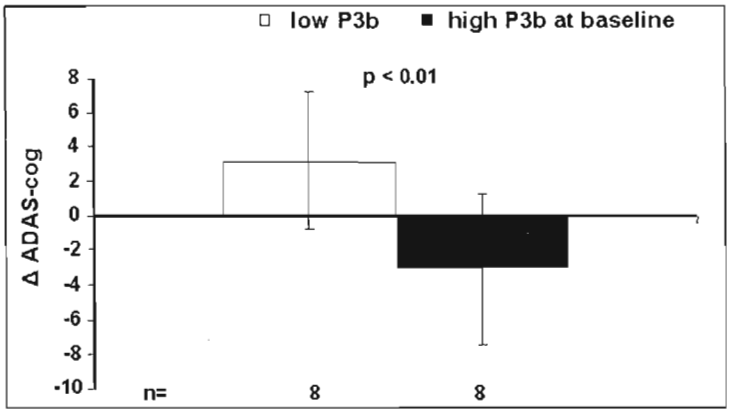

Figure 1.
Treatment response of 16 patients with Alzheimer's disease to a 12 week treatment with donepezil: patients with higher temporobasal P300 dipole amplitudes at baseline improved the most on cognition as determined by ADAS-cog scores (negative Δ-ADAS-cog denotes improvement); differences between the groups: p<.01.

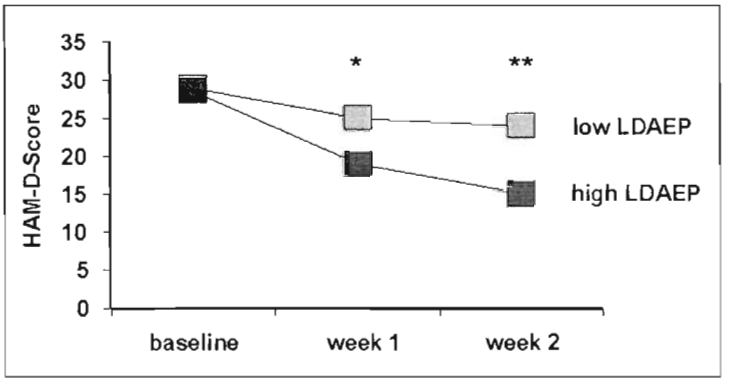

Figure 2.
HAM-D-scores of patients with depression at baseline and under treatment with paroxetine: treatment response after stratification of the patients according to high (n=14) or low (n=15) LDAEP at baseline; differences between the groups – *p<.01, **p<.05 (modified from Gallinat et al. 2000[5]): patients with high LDAEP (low serotonergic activity) at baseline showed a statistically significant better response to serotonergic drugs as compared to patients with a low LDAEP (normal or high serotonergic activity).

method for analyzing P300 recordings has been applied, using Brain Electrical Source Analysis (BESA,[27]). This technique allows separation of two different P300-subcomponents, a temporo-superior (TS-P300) and a temporo-basal component (TB-P300), and thus enhances the test-retest reliability as compared to single channel data.[11] In a pilot, exploratory study with this method in 11 AD patients, there were tendencies for significantly reduced TB-P300-amplitudes in comparison to age- and sex-matched healthy controls, and the latencies of the TS-P300 components were significantly prolonged.[4]

In the confirmatory study the amplitudes of temporo-basal dipoles (TB-P300) were statistically significantly decreased in AD as compared to HC and MCI. Furthermore, the latencies of temporo-superior dipoles (TS-P300) were significantly prolonged in AD compared with HC.[3] The significant differences remained stable after stratification of the patients regarding the severity of the disease: Even patients with mild AD showed marked, significant reductions in temporo-basal dipole amplitudes. The sensitivity and specificity for the differentiation of AD patients and HC using TB-P300-amplitudes and TS-P300-latencies were 86.7%, and 76.7%, respectively.

These prospectively evaluated, confirmatory data are comparable or even higher than other (often less validated) biological diagnostic markers in AD: the sensitivity and specificity of CSF-tau protein was 80-90% in most studies.[1] The discrimination based on MRI volumetry resulted in sensitivity and specificity values of about 90%.[6,14,18,19,22] In functional imaging studies with PET, sensitivities and specificities were reported higher than 85%,[21] and SPECT studies showed sensitivities and specificities between 50% and 88% for AD patients.[12,15,20]

Treatment Studies

An exploratory EEG/EP study in AD patients who underwent a 12 week treatment with either choline esterase inhibitors or placebo showed first evidence for the value of the P300 regarding prediction of treatment response[26]: 30 AD patients were investigated, who received electrophysiological evaluations (P300, auditory oddball paradigm, dipole-source-analysis) during a 12 week double-blind, placebo-controlled treatment with donepezil. Treatment response (change in ADAS-cog) was analyzed after stratification of donepezil and placebo patients (n=16 and 14, respectively) according to high/low TB-P300 dipole amplitudes at baseline. There was a significant association between the P300 parame-

ters at baseline and the mean change in ADAS-cog scores after 12 weeks on treamtent: patients with a high P300 amplitude at baseline showed a statistically significant better treatment response after 12 weeks on verum medication ($p<0.01$) (Figure 1). The corresponding analyses in the placebo group did not show statistically significant differences. This pilot study data provided preliminary evidence that P300 and dipole source analysis may be a useful tool to predict treatment response in AD patients.

In summary, the event-related P300 presents an easy to perform, non-invasive and reliable diagnostic tool and might offer complementary information on AD, even for those patients with mild AD. The P300 diagnostic instruments are accurate, clinically available, nonexpensive, noninvasive and reliable markers for AD and might be useful for the prediciton of treatment response.

ASSESSMENT OF THE CENTRAL SEROTONERGIC FUNCTIONING USING EVOKED POTENTIALS: LDAEP FOR RESPONSE PREDICTION AND TREATMENT MONITORING

In many depressed patients, there is a need for drug trials with several different antidepressants, in order to reach a successful treatment at last. To finally evaluate the definite non-response of the individual patient to a certain medication, therapists have to await a period of at least two to three weeks, due to the known latency of the antidepressant drug effects. In case of non-response, requiring repeated drug trials, this procedure is not only time consuming, but furthermore leads to increasing distress for the patient and may even raise the risk of self-harm and suicide.

The development of a neurobiological parameter, as a reliable instrument for the prediction of the individual response to antidepressive drugs would allow to immediately provide adequate treatment, to shorten the disease process and thus to prevent possible chronification or therapy-resistance. Additionally, indirect and direct cost of treatment could significantly be reduced.

On the basis of today's pathophysiological knowledge of depression, there is a rising number of antidepressant drugs that selectively influence either the central serotonergic or noradrenergic neurotransmission - such as SSRI or NARI. The use of serotonergic medication should primarily be administered in patients, whose disease is a consequence of a low central serotonergic activity. However, the identification of this group of patients is difficult using biochemical markers that mainly reflect the peripheral seronotergic activity.

Within the last years, several preclinical and clinical studies showed that the loudness dependence of auditory evoked potentials (LDAEP) is a valid indicator of the central serotonergic system.[9,10,16,17] The N1P2 subcomponent of the AEP, which can be identified using the dipole source analysis (BESA[28]), showed a strong relationship to the functioning of the serotonergic system: the LDAEP of the N1P2 components of the primary auditory cortex is *high*, when the activity of the serotonergic system is *low*, and *vice versa*. The clinical value of this variable for prediction of treatment with serotonergic antidepressants has already been confirmed in several clinical studies.

Patients with a *strong* LDAEP before therapy, i.e., *low* serotonergic activity, showed a favorable response to fluoxetine,[24] fluvoxamine,[9] fenfluramine,[2] paroxetine,[5] and to the acute antidepressive or relapse prophylactic treatment with lithium,[7,8] compared to patients with a *weak* LDAEP, indicating a rather *high* or *normal* serotonergic activity (Figure 2). It is currently under investigation whether these latter patients (weak LDEAP, i.e., normal serotonergic activity) respond best to noradrenergic, rather than serotonergic drugs.[21,26]

A reliable prediction of antidepressive treatment response is of greatest clinical relevance by avoiding important unfavorable factors (i.e., sustained suffering of the patient, increased suicide risk, risk of therapy-resistency and chronicity, high direct and indirect cost of treatment). A considerable number of studies show, right now, that the response to antidepressive pharmacotherapy (esp. to SSRI) can successfully be predicted by LDAEP- which is by far the best validated indicator of the central serotonergic system to date. Our own experiences have shown that this easily available tool is of value in clinical practice to estimate the success of serotonergic medication.

In conclusion, these two research areas in psychiatry highlight the use and applicability of modern electrophysiology (evoked potentials) in patient management and care and show that these techniques provide benefit not only for research but also for daily clinical routine.

REFERENCES

1. Andreasen N, Vanmechelen E, Van de Voorde A, Davidsson P, Hesse C, Tarvonen S, et al. Cerebrospinal fluid tau protein as a biochemical marker for Alzheimer's disease: a community based follow up study. J Neurol Neurosurg Psychiatry 1998; 64: 298-305.
2. Bruneau N, Barthelemy C, Roux S, Jouve J, Lelord G. Auditory evoked potential modifications according to clinical and biochemical responsiveness to fenfluramine treatment in children with autistic behavior. Neuropsychobiology 1989; 21: 48-52.
3. Frodl T, Hampel H, Juckel G, Bürger K, Padberg F, Engel RR, et al. Value of event-related P300 subcomponents in the clinical diagnosis of mild cognitive impairment and Alzheimer's disease? Psychophysiology 2002; 39: 175-181.
4. Frodl-Bauch T, Clotz F, Padberg F, Juckel G, Stübner S, Bürger K, Hampel H, et al. Auditory evoked P300 subcomponents in patients with probable dementia of the Alzheimer's type (DAT). Pharmacopsychiatry 1997; 30: 168.
5. Gallinat J, Bottlender R, Juckel G, Munke-Puchner A, Stotz G, Kuss HJ, et al. The loudness dependency of the auditory evoked N1/P2-component as a predictor of the acute SSRI response in depression. Psychopharmacology 2000; 148: 404-411.
6. Golebiowski M, Barcikowska M, Pfeffer A. Magnetic resonance imaging-based hippocampal volumetry in patients with dementia of the Alzheimer type. Dement Geriat Cogn Disorder 1992; 10: 284-288.
7. Hegerl U, Herrmann WM, Ulrich G, Muller-Oerlinghausen B. Effects of lithium on auditory evoked potentials in healthy subjects. Biol Psychiatry 1990; 27: 555-560.
8. Hegerl U, Wulff H, Muller-Oerlinghausen B. Intensity dependence of auditory evoked potentials and clinical response to prophylactic lithium medication: a replication study. Psychiatry Res 1992; 44: 181-190.
9. Hegerl U, Juckel G. Intensity dependence of auditory evoked potentials as an indicator of central serotonergic neurotransmission: a new hypothesis. Biol Psychiatry 1993; 33: 173-187.
10. Hegerl U, Juckel G. Auditory evoked dipole source activity: indicator of central serotonergic dysfunction in psychiatric patients? Pharmacopsychiatry 1994; 27: 75-78.
11. Hegerl U, Frodl-Bauch T. Dipole source analysis of P300 component of the auditory evoked potential: a methodological advance? Psychiatry Res 1997; 74: 109-118.
12. Holman BL, Johnson KA, Gerada B, Carvalho PA, Satlin A. The scintigraphic appearance of Alzheimer's disease: a prospective study using Technetium-99mSPECT. J Nuclear Med 1992; 33: 181-185.
13. Hughes JR, John ER. Conventional and quantitative electroencephalography in psychiatry. J Neuropsychiatry Clin Neurosci 1999; 11: 190-208.
14. Jack CR, Peterson RC, O'Brien P, Tanaglos EG. MR-based hippocampal volumetry in the diagnosis of Alzheimer's disease. Neurology 1992; 42: 83-88.
15. Johnson KA, Holman BL, Rosen TJ, Nagel JS, English RJ, Growdon JH. Iofetamine I 123 single photon emission computed tomography is accurate in the diagnosis of Alzheimer's disease. Arch Intern Med 1990; 150: 752-756.
16. Juckel G, Hegerl U, Molnar M, Csepe V, Karmos G. Auditory evoked potentials reflect serotonergic neuronal activity — a study in behaving cats administered drugs acting on 5-HT1A autoreceptors in the dorsal raphe nucleus. Neuropsychopharmacology 1999; 21: 710-716.
17. Juckel G, Molnar M, Hegerl U, Csepe V, Karmos G. Auditory-evoked potentials as indicator of brain serotonergic activity — first evidence in behaving cats. Biol Psychiatry 1997; 41: 1181-95.
18. Kesslack JP, Nalcioglu O, Cotman CW. Quantification of magnetic resonance scans for hippocampal and parahippocampal atrophy in Alzheimer's disease. Neurology 1991; 41: 51-54.
19. Laakso MP, Soininen H, Partanen K, Lehtovirta M, Hallikainen M, Hanninen T, et al. MRI of the hippocampus in Alzheimer's disease: sensitivity, specificity, and analysis of the incorrectly classified subjects. Neurobiol Aging 1998; 19: 23-31.
20. Müller H, Möller HJ, Stippel A. SPECT patterns in probable Alzheimer's disease. Eur Arch Psychiat Clin Neurosci 1999; 249: 190-196.
21. Mulert C, Pogarell O, Brunnmeier M, Juckel G, Hegerl U. Prediction of treatment response in major depression: the relationship between the serotonin-related LDAEP and the unspecific prediction related to anterior cingulate cortex activity. Pharmacopsychiatry 2003; 36: 248-249.
22. O'Brien JT, Desmond P, Ames D, Schweitzer I, Chiu E, Tress B (1997). Temporal lobe magnetic resonance imaging can differentiate Alzheimer's disease from normal ageing, depression, vascular dementia and other causes of cognitive impairment. Psychological Medicine, 27:1267-1275.
23. Ohyama M, Senda M, Mishina M, Kitamura S, Tanizaki N, Ishii K, Katayama Y (2000). Semi-automatic ROI placement system for analysis of brain PET images based on elastic model: application to diagnosis of Alzheimer's disease. Keio Journal of Medicine, 49:105-106.
24. Paige SR, Fitzpatrick DF, Kline JP, Balogh SE, Hendricks SE (1994).Event-related potential amplitude/intensity slopes predict response to antidepressants. Neuropsychobiology, 30:197-201.
25. Pogarell O, Schulz C, Juckel G, Mueller-Siecheneder F, Laux G, Bahra R, Zhang R, Hegerl U (2001). Auditory evoked P300 and treatment response to donepezil in patients with Alzheimer's disease. World J Biol Psychiatry, 2:264.
26. Pogarell O, Müller-Siecheneder F, Mulert C, Folkerts M, Frodl T, Juckel G, Hegerl U. Effects of citalopram and reboxetine on the loudness dependence of auditory evoked potentials in patients with major depression. Pharmacopsychiatry 2003; 36: 253.
27. Scherg M, von Cramon D (1985). A new interpretation of the generators of BAEP waves I-V: results of a spatio-temporal dipole model. Electroencephalographic Clinical Neurophysiology, 62:290-299.
28. Scherg M, Picton TW (1991). Separation and identification of event-related potential components by brain electrical source analysis. In. Brunia CHM, Mulder G, Verbraten MN (eds.). Event-related brain Research. (EEG suppl 42.), Elsevier, Amsterdam, pp. 24-37.

Reliability of Brain Responses to a Person's Own Name in Healthy Subjects and Patients with Brain Damage

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ABSTRACT

Event related brain responses to a person's own name were compared to responses to another similar word of the same probability. Both group and individual analyses were performed in order to test the overall consistency of the own name effect and the applicability of this effect for testing individual patients. Whereas group data in healthy subjects demonstrate consistent differential response to a person's own name in terms of the increased amplitude of the N1 and P3 waves, no such response was found in individual waveforms of 6 out of 14 healthy subjects and in 3 out of 5 patients. Thus, the presence of a differential brain response to a person's own name may be regarded as an important sign of cortical reactivity, but its absence cannot be interpreted unequivocally.

INTRODUCTION

In an oddball paradigm wherein two stimuli are presented in a random order, one of which occurs less frequently than the other, a large P300 in response to the rare stimulus is elicited.[2,10] Subjects typically respond to rare stimuli by either counting them or pressing a button. In a passive oddball paradigm in which no task is required, a P300 to the rare stimuli has also been obtained.[13,18,19] But the P300 amplitude is significantly larger in active discrimination tasks than in the passive condition due to the factor of task relevance which contributes to the magnitude of this component.[8,9] This task relevance effect on P300 underlies the idea of using stimuli of particular subjective significance in order to obtain a particularly large and/or stable P300.

An example of such a stimulus supposedly possessing intrinsic meaningfulness, even in the absence of any task, is the subject's own name. It is known that a person's own name has an emotional content and is meaningful due to life-long repetition.[4,26] Berlad and Pratt[1] used a passive two-word oddball paradigm, where the low-probability word was the subject's first name, and a passive three-word oddball paradigm entailing two low-probability words, one of which was the name. They found a larger P300 to the own name than to the other improbable word. Other authors[16] presented eight subjects with eight names, one of them being always the own name of the given subject, and the other being first names of the other participants. Both N2 and P300 waves were significantly enhanced in response to the own name relative to other names, regardless of whether an active task was required or not. The fact that the person's name, even in the absence of any explicit instruction, elicited a larger P300 as compared with other stimuli of the same probability is interpreted as evidence that subjects implicitly process their name as a target stimulus.[1,5,16]

Because of the emotional content of a subject's own name, it can be used for testing cortical processing in states of anesthesia and sleep,[17] as well as in neurological patients having attention deficits[5] or difficulties in motor expression.[22] Signorino et al[22] reported that presentation of verbal stimuli with emotional content (including a patient's own name) after tones increased the probability of obtaining P300 in comatose patients.

A major problem of these reports, however, is that their conclusions are largely based on group results, which is in contrast to the claim that this paradigm can be used for assessment of the responsivity of individual patients. Thus, in the present study, we intended first to replicate the principal findings of Berlad and Pratt[1] using another sample and a slightly different design. Second, we sought to analyze individual subject's responses. Third, we sought to apply the oddball design with the patient's own name in patients with severe disorders of consciousness.

SUBJECTS AND METHODS

Fourteen healthy subjects, aged 20-47 (mean 27.4), with no history of neurological or hearing disorders participated in the experiment and were paid (DM 15/hour) for their participation. During the study, subjects were comfortably seated in a sound-attenuated and electromagnetically-shielded room. Subjects were presented a list of motor activities and asked to indicate their preferred hand or leg when they perform these activities. Their responses indicated that all of them were strongly right-handed. Neuropsychological assessment of the subjects revealed that they all had above-average scores in general IQ, Wisconsin Card Sorting Test, and paper-and-pencil attention tests.

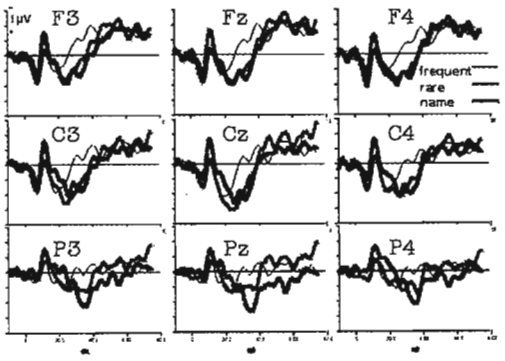

Figure 1.
Grand mean event-related potentials in the three-stimulus oddball task (average across 14 healthy subjects). Thin line: frequent stimulus. Thick dark line: the subject's own name (rare stimulus). Light-gray line: another (irrelevant) rare stimulus. Zero point on the time scale indicates stimulus onset. Negativity is up.

Five* patients (three female, aged 18-28; duration of the lesion between 10 months and 4 years) suspected of being in persistent vegetative state after closed head injuries (traffic accidents) were investigated at their bedsides. CT data indicated diffuse cortical lesions extending over both hemispheres in all patients. Further, all of them were characterized by moderate EEG slowing with the dominant rhythm being between 5 and 7 Hz, without prominent delta activity. Finally, patients were required to have normal brain stem auditory evoked potentials in order to rule out pathology of the conducting pathways.

Auditory stimuli were presented through air-tube earphones with an intensity of about 75 dB above average threshold estimated in a group of healthy subjects. Stimuli were the subject's own name and two irrelevant words spoken by a female voice. All three words were always of the same length. One of the two irrelevant words had the frequency of occurrence of 70%; the frequency of the two other words (including the subject's own name) was 15 % each. Words were presented at a rate of one per 0.9 s. A total of 300 trials was presented.

The EEG was recorded using sintered† Ag-Ag/Cl electrodes placed on and around the midline: Fz, Cz, Pz, F3, F4, C3, C4, P3, and P4. All electrodes were referred to two reference electrodes placed on the left and right mastoids and linked by a 15 kΩ shunt. In addition, the vertical and horizontal eletrooculogram was recorded by means of two pairs of electrodes placed above and below one eye and at the left and right orbital rim. Epochs of 900 ms starting 100 ms prior to stimulus onset were digitized (digitalization rate: 200 Hz; band pass: 0.1 – 70 Hz, subsequently low-pass filtered at 30 Hz with 12 dB/octave). Blinks and eye movements were corrected using a regression procedure.[6] After this, all epochs containing out-of-scale values or EEG amplitudes > 150 μV were discarded, resulting in 42-44 valid responses to each of the rare stimuli per subject.

An inspection of the data revealed three prominent ERP peaks: N1 (80-180 ms post-stimulus), P2 (150-230 ms), and P300 (290-600 ms). Since no stimulus dependent variation was found with respect to P2, our analysis will be restricted to N1 and P300. These two components were measured as the areas within the corresponding time windows. In addition, the P300 peak latency was measured. In healthy subjects, this latency tended to correlate with age (r = .41, p < .10), but did not vary as a function of stimuli. In contrast, the amplitude measures were not correlated with age (all rs < .20). Therefore, no age correction was applied.

RESULTS

Healthy participants

A mulitivariate analysis of variance (MANOVA) with factors Condition (3 levels: frequent, rare, name), Site (3 levels: frontal, central, parietal), and Laterality (3 levels: left, midline, right) was performed with the N1 and P300 amplitudes being analyzed jointly. The main effect of Condition was significant (F(4/46) = 4.53, p = .002). Notably, the difference between the person's own name and the other rare word was also significant (F(2/11) = 4.51, p = .037), demonstrating that the Condition effect could not be reduced to the overall oddball effect but was, at least in part, name-specific (see Figure 1).

Next, standard repeated-measures ANOVAs were carried out for the two waves separately. Significant effects were further examined using Bonferroni-corrected t-tests to compare the stimuli pairwise. A significant main effect of Condition on N1 amplitude (F(2/26) = 4.33, p = .027§) was mainly due to a larger amplitude to the subject's own name as compared with the frequent word (p = .008). The N1 to the rare word was of an intermediate amplitude and did not significantly differ from the frequent condition. The difference between the responses to the subject's own name and to the other rare word approached significance (p = .078). Likewise, the main Condition effect was significant for the P300 wave measured as the area under the curve

*Initially six patients were examined, but data of one of them were eliminated because of numerous movement artifacts.

†That is, covered by small powder particles, which makes electrode surface porous thereby improving its mechanical properties.

§All p-values in ANOVAs are shown after Greenhouse-Geisser non-sphericity correction.

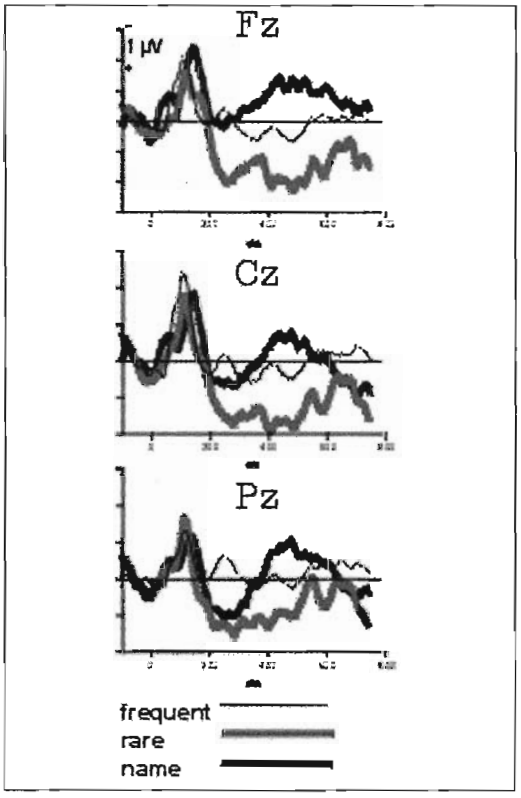

Figure 2.
Event-related brain potentials of patient 5 in the same three-stimulus oddball task, recorded at midline electrode sites. The legend see Figure 1. Note a large (highly significant) fronto-central negativity in response to the own name, instead of the expected enhanced P300.

($F(2/26) = 5.96$, $p = .009$) and as peak amplitude ($F(2/26) = 5.62$, $p = .011$). Both rare words elicited larger P300 amplitudes than the frequent word ($p < .001$), but the difference between the two rare conditions did not approach significance ($p = .30$).

A careful inspection of the data revealed a subject whose P300 amplitude to the rare stimulus exceeded the mean plus three standard deviations of the remaining thirteen subjects. Thus the group analysis was repeated with the data of that subject being dismissed. The main effects of Condition on both N1 and P300 remained highly significant. However, there was no differences in terms of the N1 amplitude between the two rare words any longer ($p = .36$). On the other hand, the corresponding difference for the P300 amplitude proved to be significant ($F(1/12) = 7.58$, $p = .018$), indicating the larger P300 to the person's own name than to the other stimulus of the same probability.

The significance of name-related effects in individual waveforms was first tested using univariate statistics identical to those employed for group analysis. That is, the mean amplitude was measured in single trials in the same N1 and P300 time windows. This was followed by an ANOVA with within-subject factors Site (frontal, central, and parietal) and Laterality (left, midline, right). Condition (3 levels: frequent, rare, name) was here regarded as a "between-subject" factor, as "subject" in this analysis was equivalent to a single trial.

Although the main effect of Condition and/or its interactions with topographical factors was significant in 12 of 14 subjects, in 5 subjects this effect was attributed solely to a larger P300 amplitude to both rare stimuli as compared with the frequent stimulus, thus indicating only the well-known oddball effect without a specific reaction to the own name. Only in 7 subjects (50%) the P300 was significantly larger to the subject's own name versus the other rare stimulus [$F(1/87)$ ranging from 3.47 to 12.31, with p-values ranging from .066 to .0001].

The differences in the N1 window did not attain the .05 level of significance in the univariate analysis of individual responses. However, it was possible that these differences would additionally contribute to separation of responses to the person's own name versus irrelevant rare stimuli. For this sake a discriminant analysis was conducted with 18 independent variables (9 electrodes by two time windows) and Condition (name versus rare) as a criterion variable. Like in the univariate analysis, single trials (42-44 in each condition) were taken as the units of the analysis.

Of the 7 subjects with significant univariate results depicted above, 6 also demonstrated a statistically significant stimulus effect in the discriminant analysis (p from .040 to .0001). In 5 of them lower p-values were obtained in the discriminant analysis than in the unvariate analysis (in one subject, both techniques resulted in $p < .0001$), thus suggesting that discriminant analysis had greater power in this context. Furthermore, significant differences between the responses to the subject's own name and to the other rare word were obtained in two additional participants [$F(1/87) = 4.77$, $p = .032$; and $F(1/87) = 5.79$, $p = .019$] who did not show this effect with univariate analysis. On the other hand, one subject with a significantly larger P300 amplitude to the name than to the other rare word ($F(1/87) = 4.81$, $p = .031$) failed to attain statistical significance in the discriminant analysis. Identical results were obtained when a multivariate analysis of variance (MANOVA) with single-trial data was performed.

Patients

The same 3-way analysis of variance with factors Condition, Site, and Laterality was carried out for each patient on the basis of single trial data. Importantly, the intercept in the ANOVA for the N1 time window was highly significant in all five patients (p-values < .001). This intercept tests whether the general mean value of

the analyzed data is different from zero. Therefore, its significance demonstrates that the patients' values were, indeed, negative, that is, that exogenous cortical ERP components were present. No effect of Condition on the N1 or P300 was found in three of five patients. In patient 4, the main effect of Condition ($p = .021$) was mostly due to a much larger P300 amplitude to this patient's own name than to the frequent stimulus ($p = .005$). The P300 to the patient's name also tended to be larger than to the other rare stimulus ($p = .10$).

In patient 5 (f, 24, four years since head injury with a questionable vegetative state), substantial differences in both N1 and P300 intervals were found. The analysis of N1 amplitude resulted in a highly significant Condition x Laterality interaction ($p = .007$), which was attributed to a larger N1 to the patient's own name as compared with the frequent word over the right hemisphere ($p = .033$). Furthermore, the response to the patient's name was characterized by a large fronto-central negative wave during the P300 interval (see Figure 2). At the same time, the rare irrelevant word elicited, as expected, a large positive wave with a parietal maximum. This resulted in a significant main effect of Condition ($p = .014$) as well as a Site x Condition interaction ($p = .022$). As can be seen in Figure 2, this effect was mainly due to a large and highly-significant difference between the two rare stimuli ($p = .002$).

This result is indirectly validated by the fact that this patient also exhibited reliable P300 amplitude differences between rare and frequent stimuli in oddball tasks with two vowels (Site x Condition interaction, $p = .022$, indicating a parietal P300 effect) and with two chords (main effect of Condition, $p = .053$).

DISCUSSION

First of all, the present data agree with the previous findings[1] indicating a larger P300 to the person's own name in healthy subjects. Previous studies also found a small but consistent increase of the N1 amplitude to the own name (see also,[14] for a similar finding in a different paradigm). This finding was also replicated in the present experiment. Thus ERP responses to a person's own name are shown to consistently differ from the responses to other similar stimuli, notwithstanding numerous methodological differences among the studies which included different control words, different interstimulus intervals, cultural/language differences between subjects (e.g., German in the present study vs. Hebrew in [1]), etc.

The fact that N1 amplitude was increased (with an onset latency of about 80-90 ms) indicates an important role of very early attentional processes in the processing of a person's own name. Probably, after a couple of presentations subjects recognized the significance of their own names immediately after the presentation of the first phoneme. A magnetoencephalographic (MEG) study is now being prepared with the purpose of localizing the brain structures responsible for this very early processing.

On the other hand, the data of individual participants indicate that these consistent group effects (i.e., the increment of the amplitudes of the N1 and P300 components) can be attributed to a relatively small number (slightly more than 50%) of the subjects. Not only were there outliers like the person mentioned above who exhibited an extremely high P300 amplitude to the irrelevant rare word, but a quite usual amplitude to his own name. Also some other subjects' ERPs did not statistically differ between these subjects' own names and the other stimulus of the same probability. In their post-experimental verbal reports, these completely healthy subjects reported that they fully recognized their names and wondered why it was necessary to adjust the stimulation program especially for them. Nevertheless, these cognitions were not reflected in their brain waves. Moreover, visual inspection of these waves suggests that this negative finding is probably not due to the low statistical power of the tests, and, thus, it is improbable that this result would improve with an increased number of trials. Furthermore, the lack of ERP differences cannot be attributed to topographical distribution of the components. If topographical effects attained significance (usually, this was a Site x Condition interaction), they simply reflected the well-known oddball effect, that is, a larger P300 over the parietal cortex in response to both rare words as compared with the frequent word.

Regarding the patients' data, it should first be noted that the small patient sample was rather homogenous with respect to age (young), etiology (head trauma), behavioral status (complete or nearly complete non-responsiveness), course (chronic), CT findings (diffuse cortical lesions), and the EEG pattern (predominant theta activity). Normal brain stem potentials as well as the highly significant N1 component clearly indicate that acoustic information did arrive at the auditory cortex of these patients.

In three patients, in which no differential response to their own name was found, no endogenous ERP activity such as P300 or mismatch negativity was observed in oddball tasks. In contrast, in the other two patients an oddball effect was evident. In one of them the P300 amplitude to this patient's own name tended to be larger than to the other rare stimulus, and in that case the difference might have attained the .05 significance level if more trials were used. In the other patient, her own name elicited not an enhanced P300 but rather a large slow negativity, similar to an N400 wave or to the post-imperative negative variation found in schizophrenia[25,27] and other psychiatric and neurological disorders.[24,28,29] Of course, this effect cannot be explained on the basis

of a single observation. However, it should be stressed that this patient's responses significantly differentiated among the three types of stimuli, i.e., the frequent word, the rare word, and her own name. These findings may be interpreted as evidence that the last two patients were in a better condition than the first three, despite the similar clinical and behavioral appearance. The consistency in the patients' ERP findings should, however, be taken with caution given the small size of the patient group.

It should be further noted that the last patient (i.e., the one with the most consistent cortical responses) was also one with the longest history of the disease (4 years). This observation is at odds with what may be expected on the basis of such terms as "persistent" or "permanent" vegetative state. It also indicates a possible discrepancy between the state and the prognosis. Thus in acute coma, numerous data have been accumulated to date which demonstrate the predictive value of EEG parameters, evoked potentials, and endogenous ERP components;[3,7,11,15,24] roughly speaking, the more normal the brain waves, the better the prognosis. Unfortunately, this relation seems less evident regarding patients in the chronic condition, because both electrophysiological[12,10] and positron emission tomography data[20,21] indicate that, in general, patients who are more responsive at the time point of an examination may not be those who make more progress in follow-up.

To summarize, the three-word oddball paradigm with the subject's own name can be used for assessment of higher cortical functions in severely damaged patients, but its results should be interpreted with caution. While positive findings unequivocally indicate the ability to differentiate between frequent and rare stimuli (the classical oddball effect) or to perceive significant stimuli differently (a differential response to the own name), negative findings are meaningless, as the lack of ERP differences with respect to a person's own name can be observed in many healthy subjects who are surely able to perceive words and to behaviorally respond to their name when necessary.

ACKNOWLEDGMENTS

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REFERENCES

1. Berlad I, Pratt H. P300 in response to the subject's own name. Electroencephalogr Clin Neurophysiol 1995; 96: 472-474.
2. Duncan-Johnson CC,Donchin E. The P300 component of the event-related brain potential as an index of information processing. Biol Psychol 1982; 14: 1-52.
3. Fischer C, Morlet D, Giard MH. Mismatch negativity and N100 in comatose patients. Audiol Neuro-Otology 2000; 5: 192-197.
4. Fischler I, Jin Y, Boaz T, Perry NW, Childers DG. Brain potentials related to seeing one's own name. Brain Lang 1987; 30: 245-262
5. Folmer R, Yingling C. Auditory P3 responses to name stimuli. Brain Lang 1997; 56: 306-311.
6. Gratton G, Coles MGH,Donchin E. A new method for off-line removal of ocular artifacts. Electroencephalogr Clin Neurophysiol 1983; 55: 468-484
7. Guerit JM, Verougstraete D, Tourtchaninoff M, Debatisse D, Witdoeckt C. ERPs obtained with the auditory oddball paradigm in coma and altered states of consciousness: clinical relationships prognostic value and origin of components. Clin Neurophysiol 1999; 110: 1260-1269.
8. Johnson R. The amplitude of the P300 component of the event-related potential: review and synthesis. In: Ackles PK, Jennings JR, Coles MGH, (eds). Advances in Psychophysiology. Greenwich, CT: JAI Press; 1988: 69-138.
9. Johnson R. A triarchic model of P300 amplitude. Psychophysiology 1986; 23: 367-384.
10. Johnson R, Donchin E. Sequential expectancies and decision making in a changing environment: an electrophysiological approach. Psychophysiology 1982; 19: 183-200.
11. Kane NM, Moss TH, Curry SH, Butler, SR. Quantitative electroencephalographic evaluation of non-fatal and fatal traumatic coma. Electroencephalogr Clin Neurophysiol 1998; 106: 244-250.
12. Kotchoubey B, Lang S, Baales R, Herb E, Maurer P, Mezger G, et al. Brain potentials in human patients with severe diffuse brain damage. Neurosci Lett 2001; 301: 37-40.
13. Lang S, Kotchoubey B, Lutz A, Birbaumer N. Was tut man, wenn man nichts tut? Kognitive EKP-Komponenten ohne kognitive Aufgabe. [What are you doing while you are doing nothing? Cognitive ERP components without a cognitive task]. Zeitschrift Experiment Psychol 1997; 44: 138-162.
14. Müller HM, Kutas M. What's in a name? Electrophysiological differences between spoken nouns proper names and one's own name. NeuroReport 1996; 8: 221-225.
15. Mutschler V, Chaumeil CG, Marcoux L, Wioland N, Tempe JD, Kurtz D. Etude du P300 auditif chez des sujets en coma post-anoxique. Donnees preliminaires. [A study of auditory P300 in subjects with anoxic coma: preliminary data]. Neurophysiol Clin 1996; 26: 158-163.
16. Perrin F, Garcia-Larrea L, Mauguiere F, Bastuji H. A differential brain response to the subject's own name persists during sleep. Clin Neurophysiol 1999; 110: 2153-2164.

17. Perrin F, Bastuji H, Mauguiere F, Garcia-Larrea L. Functional dissociation of the early and late portions of human K-complexes. NeuroReport 2000; 11: 1637-1640.

18. Polich J. Comparison of P300 from a passive tone sequence paradigm and an active discrimination task. Psychophysiology 1987; 24: 41-46.

19. Polich J. P300 from a passive auditory paradigm. Electroencephalogr Clin Neurophysiol 1989; 74: 312-320.

20. Rudolf J. Beitrag der Positronen - Emissionstomographie zur diagnostischen Zuordnung und prognostischen Einschätzung postanoxischer Hirnschäden. [A contribution of positron emission tomography to the diagnosis and prognosis of hypoxical brain injuries]. Fortschritte Neurologie Psychiatrie 2000; 68: 344-351.

21. Rudolf J, Ghaemi M, Haupt WF, Szelies B, Heiss WD. Cerebral glucose metabolism in acute and persistent vegetative state. J Neurosurg Anesthesiol 1999; 11: 17-24.

22. Signorino M, D'Acunto S, Cercaci S, Pietropaoli P, Angeleri F. The P300 in traumatic coma: conditioning of the oddball paradigm. J Psychophysiol 1997; 11: 59-70.

23. Siniatchkin M, Gerber WD, Kropp P, Vein A. Contingent negative variation in patients with chronic daily headache. Cephalgia 1998; 18: 565-569.

24. Thatcher RW, Cantor DS, McAlaster R, Geisler F, Krause P. Comprehensive predictions of outcome in closed head injured patients: the development of prognostic equations. Ann NY Acad Sci 1991; 620: 82-101.

25. Verleger R, Wascher E, Arolt V, Daase C, Strohm A, Kömpf D. Slow EEG potentials (contingent negative variation and post-imperative negative variation) in schizophrenia: their association to the present state and to Parkinsonian medication effects. Clin Neurophysiol 1999; 110: 1175-1192.

26. Voss U, Harsh J. Information processing and coping style during the wake/sleep transition. J Sleep Res 1998; 7: 225-232.

27. Wagner M, Rendtorff N, Kathmann N, Engel RR. CNV, PINV and probe-evoked potentioals in schizophrenics. Electroencephalogr Clin Neurophysiol1996; 98: 130-143.

28. Yordanova J, Dumais-Huber C, Rothenberger A, Woerner W. Frontocortical activity in children with comorbidity of tic disorder and attention-deficit hyperactivity disorder. Biol Psychiat 1997; 41: 585-594.

29. Zapolli R, Versari A, Arnetoli G, Paganini M, Nuscas G, Arneodo M, et al. Topographic CNV activity mapping, presenile mild primary cognitive decline and Alzheimer-type dementia. Neurophysiol Clin 1991; 21: 473-483.

30. Zeitlhofer J, Steiner M, Oder W, Obergottsberger S, Mayr N, Deecke L. Prognostische Wertigkeit evozierter Potentiale in der neurologischen Frührehabilitation bei Patienten im apallischen Syndrom. Predictive value of evoked potentials in the early neurological rehabilitation of apallic syndrome (in German). Zeitschrift EEG - EMG 1991; 22: 10-14.

Psychogenic Dysphagia and Globus Sensation

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ABSTRACT

Globus sensation may be the first complaint of patients having mechanical, neurologic or psychogenic disorders. The mechanical causes are often evaluated by video-fluoroscopic manometric methods. However, globus sensation and psychogenic dysphagia may not be differentiated from a neurogenic dysphagia. Some neurophysiological methods are described for this purpose.

The test of dysphagia limit was found to be a very useful clinical and neurophysiological tool to differ the neurogenic dysphagia from those patients with psychogenic dysphagia and global sensation. It was proposed that the corticobulbar neurons and the brain stem CPG are intact in psychogenic dysphagia, but the cortical neural processes related with swallowing are considerably slower. Sometimes a transient failure of a tonic descending inhibition may occur in the distal swallowing apparatus in globus sensation and psychogenic dysphagia.

INTRODUCTION

The relationship between psychological disorders and gastrointestinal system is well known. Although the deglutition and the psychological and psychosomatic aspects of individuals have been the subject of numerous studies, we still felt the need to clarify this topic, which is important to differential diagnosis, i.e., organic versus functional nature of the swallowing disorders.

So far, two kinds of basic swallowing problems have been established in relation to psychiatry. One of them is known to every physician since the era of Hippocrates.[42] This is so-called "Globus Hystericus." This term describes the frequent feeling of a lump, fullness or "tickle" in the throat that typically does not interfere with swallowing and may even be relieved by swallows. It also implies, often inaccurately, that patients with these symptoms have hysterical personalities. The diagnosis of "globus" should never be made without a thorough investigation for a lesion in the pharynx or neck and for organic esophageal diseases such as reflux or an hypertensive upper and/or lower esophageal sphincter. In fact, globus sensation has been described in patients with either of these conditions.[4,25,30,38,42,49,50,51,53] On the other hand, globus sensation was found to be the most common initial complaint in a general otolaryngological clinic, i.e., 4.1 percent of 4330 consecutive first visit patients.[41] It must be born in mind that the incidence of globus sensation solely psychogenic in nature is far less frequent than globus sensation caused by various organic reasons. However, the globus sensation has been an attractive subject for the psychoanalytic and psychiatric views in the past. Ferenczi (1964) (cited by Moser et al[42]) proposed that globus sensation resulted from a "peripheral materialization of a repressed idea and a subconscious desire for oral sexual practice." Weis and English (1949) thought that "the hysterical symptoms of swallowing over a lump is one of the most widely recognized indications of nervous illness," and another explanation was "a physical manifestation of suppressed emotion, specifically holding back tears."[27] It has even been proposed that the globus sensation is a useful single-symptom model for the study of conversion disorders.[51] In contrast to these assumptions and claims, patients with the globus sensation were found to have no more hysterical traits than healthy persons.[7,36,45] or otolaryngological outpatients with a wide variety of complaints, and patients with esophageal motor disorders .[42] The personality characteristics and mood states, in particular, anxiety, depression, hypochondriasis, hysteria and even stress, are unlikely to be of etiologic significance, and the term "hystericus" must be avoided because not only it is a misnomer but also bears the temptation to refrain from searching for the cause of globus sensations.

The second group of swallowing disorders related to psychiatry can be referred as "Psychogenic Dysphagia." Contrary to the globus sensation, the dysphagia complaints appear during swallowing. The general characteristics of the psychogenic dysphagia include[3,35,46]: 1) Frequently female gender; 2) Young and mid-adult age range; 3) Complaints of difficulty initiating swallowing and/or things sticking in the throat during swallowing; non-cardiac chest pain, substernal pressure sensation, hearthburn sensation and adynophagia (painful swallowing) were also described by some patients; 4) Absence of dysphagia complications other than weight loss; 5) Absence of speech disorders and other neurological symptoms; 6) Occasionally marked fluctuations of dysphagia; 7) Absence of stroke risk factors and other underlying diseases; 8) Normal findings in neurological examination; 9) Normal videofluoroscopy of swallowing other than complex, nonpropulsive tongue movement during attempted swallowing; 10) Normal neurological studies including brain MRI; 11) Most frequent psychiatric symptoms are anxiety, depression, hypochondriasis, somatoform disorders, conversion disorder and eating disorders. It follows that, in psychogenic dysphagia there are no objective clinical and laboratory findings of neurological or

gastroenterological nature or ENT specialty. We do not know how they are developed, since the somatization, depression and anxiety are frequently found both in patients with so-called psychogenic dysphagia and in patients with an organic cause of dysphagia.[36] However, patients with psychogenic dysphagia did not subsequently manifest neurologic disorders or other likely medical causes of dysphagia over a median follow-up period of 5 years.[43]

An important point is that some psycotrophic drugs may cause a reduction in saliva production. Because of anticholinergic effects of these drugs, xerostomia or dry mouth occurs and this may give rise to difficulty in triggering swallowing in the mouth, and the oropharyngeal swallowing may give a sensation of sticking in the throat.[33] This side effect of psycho-pharmacological treatment should be differentiated from two conditions, i.e., globus sensation and psychogenic dysphagia. Recently, a different form of psychogenic dysphagia was described and called "phagophobia." These patients are presented with either an acute or chronic dysphagia secondary to fear of swallowing.[47]

Because the management techniques are so different in mechanical, neurological and psychogenic dysphagia, the first task in the evaluation of any suspected dysphagia is to distinguish between the structural, neurological and functional etiologies. The first task is to eliminate any structural abnormality by using endoscopic and radiological methods. However, they require non-neurological and/or non-psychiatrical expertise, and are expensive and time consuming. We have described some electrophysiological methods[12,13] to investigate the nature of swallowing and its disorders, and shown that it is possible to diagnose objectively the existence of neurogenic dysphagia in suspected cases by using electrophysiological methods such as dysphagia limit.[13,14,16,20] We have investigated 14 patients with globus sensation and 15 patients with so-called "psychogenic dysphagia" by clinical and electrophysiological methods. Below we will first summarize our electrophysiological methods and then discuss the clinical and electrophysiological results obtained from 29 patients.

METHODS

The seated patient was instructed to hold his or her head in the neutral upright position during the procedure. Mechanical upward and downward laryngeal movements during swallowing were detected by means of a piezoelectric sensor designed in our laboratory.[44] This was a single piezoelectric wafer with a 4 X 2.5 mm rubber bulge fixed to its center. The rubber bulge was placed on the coniotomy region between the cricoid and thyroid cartilages at the midline. The sensor was taped onto the neck and its output signal was filtred (bandpass 0.01-20 Hz) and fed into one of the channels of the electromyography (EMG) apparatus (Medelec, Mystro, MS-20, Surrey UK). The submental EMG (SM-EMG) was recorded by bipolar silver chloride electroencephalogram (EEG) electrode taped under the chin over the submental muscle complex (mylohyoid, geniohyoid and anterior digastricus muscles). Signals were filtered (bandpass 100 Hz-10 KHz), amplified, rectified and integrated. Crycopharyngeal (CP) muscle activity of the upper esophageal sphincter (UES) was recorded similarly with a sterile needle electrode (disposable needle electrode. DMC-37. Medelec) inserted through the skin at the level of cricoid cartilage about 1.5 cm lateral to its palpable lateral border in the posteromedian direction.[12,16,18]

By using these electrophysiological parameters, the phenomena of piecemeal deglutition and dysphagia limit[13,14,16] have been investigated. The recording of the first upward and second downward movement deflection of the laryngeal sensor was used to stabilize the reading on the oscilloscope screen using the delay line technique, so that throughout successive recordings, the deflections appeared at the same location of each sweep. In this way all electromechanical events were displayed synchronously, i.e., SM-EMG together with the deflections of the laryngeal upward/downward movements. The sweep duration was set at 10 seconds with the delay-line starting at 2 seconds. After a certain amount of water had been ingested, the effect of bolus was measured for 8 seconds. The subjects were given 1,3,5,10,15 and 20 ml of water and ossiloscopic traces were initiated at the examiner's order to swallow. The laryngeal sensor signals and the integrated activities of the SM-EMG and/or crico-pharyngeal EMG (CP-EMG) were recorded from the beginning of these long sweeps. The patient was requested to swallow all the liquid given in a single effort. Any swallowing related recurrence of the EMG activity and the laryngeal sensor signal within the 8 seconds after the onset of the sweep was accepted as piecemeal deglutition or as a sign of dysphagia limit. However, as piecemeal deglutition is observed physiologically in normal subjects when swallowing more than 20 ml. of water, duplication or multiplication of the swallowing at or below 20 ml of water is referred to as the dysphagia limit.[14]

Normal control subjects were selected within the same age decades as the patients' group. Thirty-eight normal control subjects (23 females and 15 males) were investigated within the age range of 17-40 years (mean age: 27.8). However, for comparison of the CP-sphincter EMG results another group of 21 normal adult subjects within the age range of 30 to 75 years was also examined. Eleven of them were female.

PATIENTS

All 29 patients with globus sensation or psychogenic dysphagia have attended our laboratory after being investigated by gastroenterologists and/or ENT specialists and absolved of abnormalities in these specialty domains. They were separated into two groups according to their history and symptoms: 1) Complaints related to swallowing were accepted as psychogenic dysphagia; 2) Complaints not

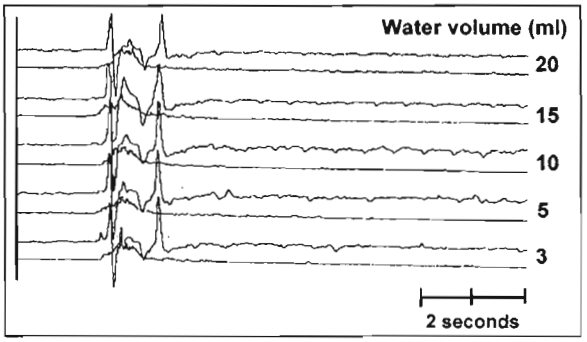

Figure 1.
"Dysphagia limit" obtained from a patient with psychogenic dysphagia. Laryngeal sensor signals (top trace of each pair) and integrated SM-EMG activities (lower trace of each pair) are recorded during swallowing of different amounts of water (3-20 ml from bottom to top). Note that the volume swallowed in a single attempt was up to 20 ml. Total analysis time was 10 seconds.

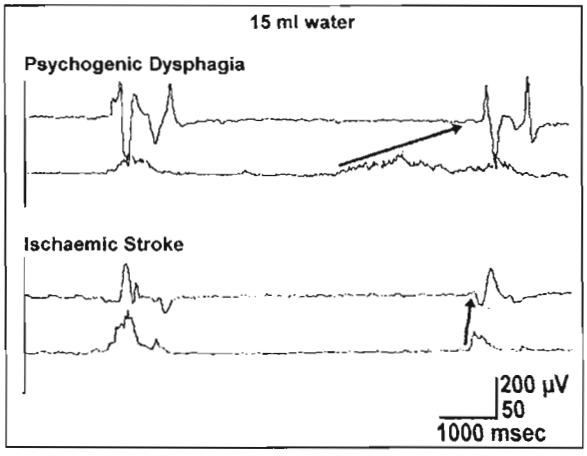

Figure-2
Same patient with psychogenic dysphagia (in Figure 1) has sometimes shown the double swallows as it is shown in top traces. A patient with neurogenic dysphagia (ischaemic stroke) is compared at the bottom traces. The second swallows were observed within the 8 seconds after the first swallows. Note the triggering time is very short for ischaemic stroke (arrow) while the triggering time is extremely prolonged in psychogenic dysphagia (arrow) in the attempt of 15 ml water swallowing.

linked to swallowing were accepted as globus sensation. These complaints and symptoms were classical as we have mentioned in previous pages. They were all neurologically normal and their EMG and neuroimaging investigations were within the normal limits when they were performed. Psychogenic dysphagia was found in 15 patients, 6 of them male. The other 14 patients were accepted as having globus sensation, 2 of them male. The mean age of all 29 patients (8 male, 21 female) was 34.5 years and ranged between 20 to 47 years. Their complaints were quite variable and lasted from 30 days to 7 years, but most of them described their symptoms lasting for over a year. The serial investigations of the swallowing and its disorders were approved by the ethical committee of our university hospital and all subjects provided informed consent.

RESULTS AND COMMENT

The dysphagia limit was above 20 ml of water in all normal subjects investigated and in all patients but one with psychogenic dysphagia or globus sensation (Figure 1); contrary to the neurogenic dysphagia in which cases the dysphagia limit was definitely pathological and below 20 ml water volume, as we know from previous studies (Ertekin et al,[14,16] and others). In one patient with psychogenic dysphagia the water volumes of 15-20 ml appeared to be divided into the pieces as the duplication of bolus (Figure 2). This electrophysiological finding may indicate an objective and organic nature of dysphagia in this patient as in the case of ischemic stroke shown in the bottom of the Figure 2. However, even if in two cases we noticed the second swallow, there was one major difference between these two cases of second swallow: A-O interval was very short in the patients with neurogenic dysphagia (arrow in lower traces), while in the patient with psychogenic dysphagia, it was severely prolonged before the oropharyngeal swallowing occurs (arrow in upper traces). This observation may indicate that the psychological patient could have forced herself voluntarily to produce another swallow within 8 seconds. As we have shown, the triggering of the pharyngeal phase of swallowing is measured from the onset of SM-EMG until the onset of first deflection of the laryngeal upward movement and is briefly defined as A-O interval. This phase of the swallowing is shown to be controlled by corticobulbar excitatory drives.[18,19,24] Therefore, the second swallow in the psychogenic dysphagia is a kind of voluntary effort and under the control of the cortical influences, not an objective sign of dysphagia as readily demonstrated in neurogenic dysphagia. Indeed, when this patient has repeated the test later, the dysphagia limit became normal, over the 20 ml of water as it was shown in Figure 1. The results show that the test for dysphagia limit is a very useful clinical and neurophysiological tool to differentiate neurogenic from psychogenic dysphagia and from globus sensation. This simple

Table 1

The summary of statistical results of oropharyngeal swallowing in normal subjects and patients with globus sensation / psychogenic dysphagia

	Normal Control Group (n=38)		Patients Group (n=29)		p-value
	Mean ± SEM	SD	Mean ± SEM	SD	
1. Triggering Time of swallowing (A-O interval)	254 ± 17	106 msec	300 ± 21	110 msec	p<0.01
2. Pharyngeal Phase of swallowing reflex (O-2 interval)	565 ± 16	97 msec	683 ± 21	114 msec	p<0.001
3. SM-EMG duration (A-C interval)	860 ± 19	119 msec	948 ± 45	241 msec	p>0.05
4. Amplitude of SM-EMG	76 ± 6.0	36 microV	66 ± 4.0	23 microV	p<0.001
5. CP-EMG Pause (n = 21)	462 ± 18	82 msec	479 ± 26	106 msec	p>0.05

test while noninvasive and inexpensive is very sensitive in demonstrating the oropharyngeal neurogenic dysphagia without time consuming procedures.

Single bolus analysis of SM-EMG and laryngeal sensor movement during 3 ml water swallowing has always been very useful in understanding the pathophysiological mechanism of oropharyngeal dysphagia of neurological nature.[16-19,22] These methods of measuring the components of the oropharyngeal swallowing did not potentially facilitate the diagnosis or differential diagnosis in a clinical sense, but they were able to demonstrate the physiological and/or pathophysiological nature of oropharyngeal swallowing in a given case or in a series of patients with the same etiology. In 29 patients with psychogenic dysphagia, the triggering time of oropharyngeal swallowing, the time necessary for the pharyngeal phase of swallowing reflex and SM-EMG duration and amplitude and CP-EMG pause, were all measured and compared statistically with the normal age matched groups. The summary of the results of swallowing components is shown in Table 1.

Triggering time from oral phase to swallowing reflex was denoted as A-O time interval. This time interval is mostly under cortical control and the cortico-bulbar pyramidal system during voluntarily initiated swallows as we have mentioned before. It is interesting that this time interval was found to be statistically prolonged in patients with psychogenic dysphagia and/or globus sensation ($p< 0.01$). However, individually, the prolongation of the triggering of the oropharyngeal swallows was found in 5 patients in whom this interval was slightly longer than 400 msec. This slowing down was not as high as that encountered in patients with corticobulbar involvement such as ALS and multiple lacunar states.[18,19] Thus, this kind of prolongation may indicate that the cortical processes related to the triggering of the bolus in the mouth driven by the corticobulbar pyramidal fibers is normal, but the slow action in these cases can be prior to corticobulbar neuronal firing.

The pharyngeal phase of swallowing is demonstrated by the onsets of two laryngeal deflections and denoted as O-2 interval. This interval is thought to reflect the time necessary for the elevation, closure and upward relocation of the larynx.[12,13,16,18] This is a physiological event, that is, one of the important components of the swallowing reflex.[8,32,37] This time interval was statistically found to be prolonged in psychogenic patients/globus sensation compared to normal control subjects ($p< 0.001$). Figure 3 shows the oropharyngeal components of swallowing recordings from a normal subject (upper traces) and from a patient with psychogenic dysphagia (lower traces). Patients appeared to have a slower pharyngeal phase of swallowing with longer O-2 interval and SM-EMG duration. Nevertheless, such a pathological swallowing reflex surpassing the value of 800 msec was only encountered in 5 of 29 patients (about 17 percent of patients). In neurogenic dysphagia, slowing in the pharyngeal phase is encountered especially in patients with neuromuscular disorders[16-18] and extrapyramidal disorders such as Parkinson's disease.[16] However, in these above-mentioned disorders, dysphagia is associated with the abnormal dysphagia limits contrary to that of psychogenic dysphagia. The longer pharyngeal phase of swallowing was not supported statistically by the SM-EMG duration in that there was no significant prolongation compared to the normal subjects (Table 1, $p> 0.05$). This finding is also different from the data obtained from the patients with neuromuscular and extrapyramidal disorders[16,17] in whom both O-2 and A-C time intervals were prolonged. Taken together, these data may be explained by the effect of the limbic system and its descending motor fibers on the bulbar swallowing center[31] in psychogenic dysphagia. This speculation is needed to be clarified by further studies.

The amplitude of SM-EMG is statistically lower than the normal control group. This may also support the view that the SM-muscles were excited by the mild asynchronous descending motor drives avoiding the great temporal

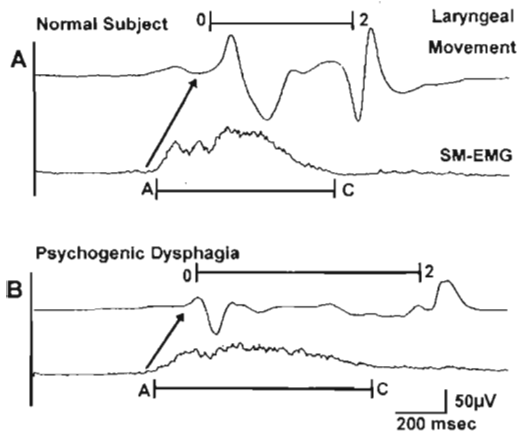

Figure-3

Laryngeal sensor signals and integrated SM-EMG obtained from a normal subject (A) and one patient with psychogenic dysphagia (B). Note the significant prolongation of the pharyngeal phase of oropharyngeal swallowing (denoted by 0-2 time interval) in patient with psychogenic dysphagia. All traces are averages of five responses.

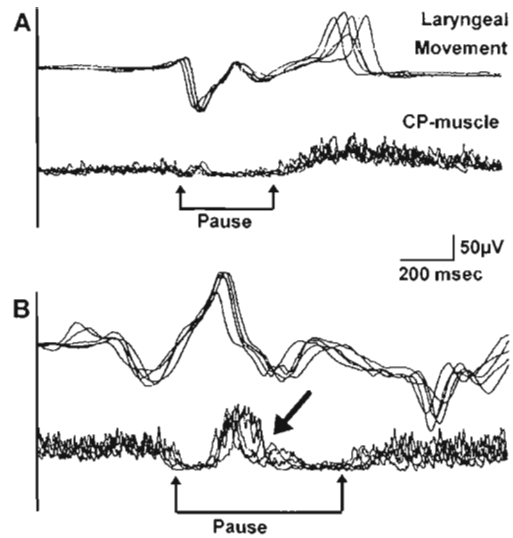

Figure-4

Laryngeal sensor signals and CP sphincter muscle EMGs recorded from two patients with psychogenic dysphagia (A and B). The traces are the superimposition of five responses. EMG traces are rectified and integrated. CP sphincter muscle is normal in both patients, except the unexpected burst of motor unit action potentials during swallowing pause of the cricopharyngeal muscle (oblique arrow in B) in the other patient.

dispersion of the oropharyngeal muscles excitation in both oral phase and pharyngeal phase. How could such mild asynchronous descending motor drives affect the central pattern generator of the bulbar swallowing center? This question also remains to be elucidated.

CP-sphincter muscle-EMG was investigated in 17 patients with psychogenic dysphagia or globus sensation. The cricopharyngeal sphincter like other sphincter muscles has special functions and properties that are different from those of skeletal muscles. Although it is a striated muscle, it is innervated by the vagus nerve, and therefore it is not readily controlled by the voluntary motor system and is closed at rest.[28,39,40] During a swallow, the UES opens and the tonic activity of the CP-muscle ceases simultaneously[11,12,18,20] as can be seen in Figure-4 (lower traces). The tonic activity in rest and the CP-EMG pause during swallowing did not differ in psychogenic dysphagia and in normal control subjects (Table 1, $p > 0.05$). However, in four patients with psychogenic dysphagia/globus sensation, an unexpected EMG burst activity during CP-EMG pause was encountered (see Figure 4 arrow in the lower traces). Four patients or 23.5 percent of all psychogenic patients investigated had an unexpected motor unit burst within the CP-EMG pause. A disordered contractile activity of the upper esophageal sphincter has been held responsible for the globus sensation in previous studies using manometric and/or videofluoroscopic evaluation.[1,2,30,49] However, there is considerable controversy on whether disorders of these types are in fact related to the symptoms of patients.[26,42,50,52] Recently, it was shown that in globus sensation (and probably in psychogenic dysphagia) there are no upper esophageal pressure changes.[56,33,48] Therefore, the unexpected EMG burst during CP-EMG pause may be a transient electrophysiological phenomenon probably related with the transient failure of the tonic inhibitory drive from the suprasegmental levels, which are partly responsible for the CP-EMG pause during voluntarily triggered swallowing.[18] The motor neurons of the CP-sphincter muscle pass directly (phasic)[23] and probably indirectly (tonic) descending neural connections from the cerebral motor cortex and some other supraspinal structures including limbic system and basal ganglia. The motor neurons of CP-sphincter muscle must be transiently and functionally released from the descending inhibitory control, and consequently such motor unit bursts may appear within the pause of the CP muscle during swallowing. The central pacemaker or central swallowing program at the bulbar center becomes transiently disturbed by removal of the inhibitory corticobulbar influences. A similar argument has been proposed in neurological patients with hyperreflexic CP-sphincter (i.e., ALS, lacunar states) with whom in addition to EMG bursts, there is also shortening of CP-EMG pause and premature closure of the upper esophageal sphincter. These findings are prevalent in cases of neurogenic dysphagia.[18,19] Occurrence of psychogenic patients with only EMG bursts strongly suggests that such an inhibition can occur from time to time functionally and above the bulbar swallowing center. The central pacemaker or central swal-

lowing program at the bulbar center, has been demonstrated to have such a functional inhibition even in normal conditions or in the experimental physiology.[9,10,39,54]

In conclusion, the psychogenic dysphagia and globus sensation can be differentiated from the neurogenic dysphagia by using the method of dysphagia limit. Dysphagia limit is normal in psychogenic patients, they can swallow the bolus volumes above 20 ml. water, while in neurogenic dysphagia, patients divide the bolus into two or more pieces and swallow successively within 8 seconds of analysis period. So, this simple electrophysiological method offers a new way to distinguish the psychogenic dysphagia from the neurological patients with oropharyngeal dysphagia.

The single bolus analysis by electrophysiological technique certainly is not useful for clinical purposes, but it has given some evidence about the peripheral nature of the psychogenic dysphagia/globus sensation. We can propose that in some patients, the corticobulbar drive to trigger the voluntarily initiated swallows is delayed, probably due to asynchronous firing of the swallowing-related cortical neurons. The corticobulbar neurons are certainly intact, but the cortical neural processes related to swallowing are comparatively slow preceding the firing of cortical motor neurons. Descending limbic motor cortex may also play a role in the prolongation of the oropharyngeal swallowing encountered in psychogenic dysphagia, but its nature is unknown to us at the present time. There is a suprasegmental cortical / limbic descending tonic-inhibitory action on the central pattern generator of the bulbar swallowing center. Sometimes a transient failure of this tonic inhibition may cause an unexpected EMG burst during CP-EMG pause of the voluntarily initiated swallows. The variable nature of the electrophysiological phenomena and the diversity of the complaints due to neurogenic dysphagia may well be linked to each other. It would be interesting to follow up these clinical and electrophysiological findings to see whether they would disappear altogether following an effective psychiatric treatment.

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REFERENCES

1. Batch AJG. Globus pharyngeus. Part-I. J Laryngol Otol 1988a; 102: 152.
2. Batch AJG. Globus pharyngeus. Part-II. J Laryngol Otol 1988b; 102: 227.
3. Buchholz DW. Neurogenic dysphagia: What is the cause when the cause is not obvious? Dysphagia 1994; 9: 245.
4. Castell DO. Dysphagia: a general approach to the patient. In: Gelfand DW, Richter JE, (eds). Dysphagia in Diagnosis and Treatment. NewYork, Tokyo: Igaku Shain; 1989: 3-9.
5. Cook IJ, Dent J, Shannon S, et al. Measurement of upper esophageal sphincter pressure, effect of acute emotional stress. Gastroenterology 1987; 93: 526.
6. Cook IJ, Shaker R, Dodds WJ, et al. Role of mechanical and chemical stimulation of the esophagus in globus sensation. Gastroenterology 1989; 86, A99.
7. Deary IJ, Wilson JA, Mitchell L, et al. Covert psychiatric disturbance in patients with globus pharyngis. Br J Med Psych 1989; 62: 381.
8. Donner MW, Bosma JF, Robertson DL. Anatomy and physiology of the pharynx. Gastrointest Radiol 1985; 10: 196-212.
9. Doty RW, Bosma JF. An electromyographic analysis of reflex deglutition. J Neurophysiol 1956; 19: 44.
10. Doty RW, Richmond WH, Storey AT. Effect of medullary lesions on coordination of deglutition. Exp Neurol 1967; 17: 91.
11. Elidan J, Shochina M, Gonen B, et al. Manometry and electromyography of the pharyngeal muscles in patients with dysphagia. Arch Otolaryngol Head Neck Surg 1990; 116: 910.
12. Ertekin C, Pehlivan M, Aydoğdu I, et al. An electrophysiological investigation of deglutition in man. Muscle and Nerve 1995; 18: 1177.
13. Ertekin C. Clinical diagnosis and electrodiagnosis of swallowing disorders. In: Swanson M, (ed). Disorders of Speech and Swallowing. Rochester: Johnson Printing Co; 1996: 23-33.
14. Ertekin C, Aydoğdu I, Yüceyar N. Piecemeal deglutition and dysphagia limit in normal subjects and in patients with swallowing disorders. J Neurol Neurosurg Psychiatry 1996; 61: 491.
15. Ertekin C, Aydoğdu I, Yüceyar N, et al. Effects of bolus volume on oropharyngeal swallowing: an electrophysiological study in man. Am J Gastroenterol 1997; 92: 2049.
16. Ertekin C, Aydoğdu I, Yüceyar N, et al. Electrodiagnostic methods for neurogenic dysphagia. Electroencephalogr Clin Neurophysiol 1998a; 109: 331.
17. Ertekin C, Yüceyar N, Aydoğdu I. Clinical and electrophysiological evaluation of dysphagia in myasthenia gravis. J Neurol Neurosurg Psychiatry 1998b; 65: 848.
18. Ertekin C, Aydoğdu I, Yüceyar N, et al. Pathophysiological mechanisms of oropharyngeal dysphagia in amyotrophic lateral sclerosis. Brain 2000a; 123: 125.
19. Ertekin C, Aydoğdu I, Tarlacı S, et al. Mechanisms of dysphagia in suprabulbar palsy with lacunar infarct. Stroke 2000b; 31: 1370.
20. Ertekin C, Palmer JB. Physiology and electromyography of swallowing and its disorders. Clin Neurophysiol 2000; 53 (suppl): 148.

21. Ertekin C, Kıylıoğlu N, Tarlacı S, et al. Effect of mucosal anesthesia on oropharyngeal swallowing. Neurogastroenterology Motility 2000c; 12: 567.

22. Ertekin C, Yüceyar N, Aydoğdu I, et al. Electrophysiological evaluation of oropharyngeal swallowing in myotonic dystrophy. J Neurol Neurosurg Psychiatry 2001a; 70: 363.

23. Ertekin C, Turman B, Tarlacı S, et al. Cricopharyngeal sphincter muscle response to transcranial magnetic stimulation in normal subjects and in patients with dysphagia. Clin Neurophysiol 2001b; 112: 86.

24. Ertekin C, Kıylıoğlu N, Tarlacı S, et al. Voluntary and reflex influences on the initiation of swallowing reflex in man. Dysphagia 2001c; 16: 40.

25. Freeland AP, Ardran GM, Emrys-Roberts E. Globus hystericus and reflux oesophagitis. J Laryngol Otol 1974; 88: 1025.

26. Fulbeck CL, Winship PH, Henson B. Upper esophageal manometric findings in globus hystericus Gastroenterology 1983; 84: 1161. Abstract.

27. Glaser JP, Engel GL. Psychodynamics, psychophysiology and gastrointestinal symptomatology. Clin Gastroenterol 1977; 6: 507.

28. Goyal RK. Disorders of the cricopharyngeus muscle. Otolaryngol Clin North Am 1984; 17: 115.

29. Goyal RK, Martin SB, Shapiro J, et al. The role of cricopharyngeus muscle in pharyngeesophageal disorders (Review). Dysphagia 1993; 8: 252.

30. Gray LP. The relationship of the "inferior constrictor swallow" and "globus hystericus" or the hypopharyngeal syndrome. J Laryngol Otol 1983; 97: 607.

31. Holstege G. Descending motor pathways and the spinal motor system: limbic and non-limbic components. Prog Brain Res 1991; 87: 307.

32. Jacob P, Kahrilas PJ, Logemann, et al. Upper esophageal sphincter opening and modulation during swallowing. Gastroenterology 1989; 97: 1469.

33. Kahrilas PJ, Kishk SM, Helm JF, et al. A comparison of pseudo-achalasia and achalasia. Am J Med 1987; 82: 439.

34. Kahrilas PJ. Motility disorders of the esophagus. In: Yamada T, et al. (eds). Textbook of Gastroenterology. Philadelphia: Lippincott; 1999: 1199-1230.

35. Kim CH, Hsu JJ, Williams DE, et al. A prospective psychological evaluation of patients with dysphagia of various etiologies. Dysphagia 1996; 11: 34.

36. Lehtinen V, Puhakka H. A psychosomatic approach to the globus hystericus syndrome. Acta Psychiatr Scand 1976; 53: 21.

37. Logeman JA. Evaluation and treatment of swallowing disorders. San Diego: College Hill Press; 1983.

38. Mair WS, Schroder KE, Modalsh B, et al. Aetiological aspects of the globus symptom. J Laryngol Oto 1974; 88: 1033.

39. Miller AJ. Deglutition (Review). Physiol Rev 1982; 62: 129.

40. Miller AJ. The search for the central swallowing pathway: the quest for clarity (Review). Dysphagia 1993; 8: 185.

41. Moloy PJ, Charter R. The globus symptom: incidence, therapeutic response and age and sex relationship. Arch Otolaryngol 1982; 108: 740.

42. Moser G, Vacariu, Granser GV, et al. High incidence of esophageal motor disorders in consecutive patients with globus sensation. Gastroenterology 1991; 101: 1512.

43. Neuman S, Buchholz D, Ravich W, Jones B. Psychogenic dysphagia: a long-term follow-up study. Dysphagia poster 25 DRS meeting, NewOrleans; 1998. Abstract.

44. Pehlivan M, Yüceyar N, Ertekin C, Çelebi G, Ertaş M, Kalaycı T, Aydoğdu I. An electronic technique measuring the frequency of spontaneous swallowing (Digital Phagometer). Dysphagia 1996; 11: 259.

45. Puhakka H, Lehtinen V, Aalto T. Globus hystericus-a psychosomatic disease? J Laryngol Otol 1976; 90: 1021.

46. Ravich WJ, Wilson RS, Jones B, et al. Psychogenic dysphagia and globus: reevaluation of 23 patients. Dysphagia 1989; 4: 35.

47. Shapiro J, Franko DL, Gagne A. Phagophobia: a form of psychogenic dysphagia: a new entity. Ann Otol Rhinol Laryngol 1997; 106: 286.

48. Vakil NB, Kahrilas PJ, Dodds WF, et al. Absence of an upper esophageal sphincter response to acid reflux. Am J Gastroenterol 1989; 84: 606.

49. Watson WC, Sullivan SN. Hypertonicity of the cricopharyngeal sphincter: a cause of globus sensation. Lancet 1974; 2: 1417-1419.

50. Wilson JA, Heading RC, Maran, et al. Globus sensation is not due to gastroesophageal reflux. Clin Otolaryngol 1987; 12: 271.

51. Wilson JA, Deary IJ, Maran AGD. Is globus hystericus? Br J Psychiatry 1988; 153: 335.

52. Wilson JA, Pryde A, Piris J, et al. Pharyngoesophageal dysmotility in globus sensation. Arch Otolaryngol Head Neck Surg 1989; 115: 1086.

53. Zerhouni EA, Bosma JF, Donner MW. Relationship of cervical spine disorders to dysphagia. Dysphagia 1987; 1: 129.

54. Zoungrana OR, Amri M, Car A, et al. Intracellular activity of motoneurons of the rostral nucleus ambiguus during swallowing in sheep. J Neurophysiol 1997; 77: 909.

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