

Event-related brain potentials in the study of human cognition and neuropsychology

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Introduction: understanding brain–behavior relationships

People, whether brain intact or brain-damaged, are information processors. They gather information during interactions with the environment, store it, extend it, transform it, combine it, retrieve it, transmit it, and use it as the basis for subsequent interactions. However, unlike computers, which are also information processors, humans carry out these informational transactions via biological mechanisms. Working out the details of biological information processing in order to understand perception, cognition, emotion, action, learning, and memory in intact and brain-damaged humans from the cradle to the grave is the neuropsychological enterprise.

On the view that the essential function of the relevant physical systems (peripheral and central nervous systems) is to process information, a satisfactory understanding of cognition will require a theory of the nervous system expressed in the vocabulary of the physical sciences, a theory of the functional system expressed in the vocabulary of information processing, and an account of the relation between the two. In this chapter we will show how scalp electrical potentials (or their magnetic counter-

parts) are especially useful in this enterprise because they are a product of ion flow across neural membranes — the currency of neural communication — that, conveniently, vary systematically with stimulus, processing and response parameters.

Cognitive models

Information processing (IP) models of the sort required by a mature cognitive neuroscience are still in their infancy with some resembling a digital computer and others resembling neurally-inspired networks. Digital computers are highly articulated artificial information processors that have proven astonishingly successful at doing things that would, until recently have been assumed to require sophisticated cognitive functions (playing chess, general problem solving). As a result cognitive science has 30 years of cognitive models that look like flow charts from an introductory computer programming course. Information is encoded in symbolic representations in the form of combinable chunks; these representations are stored by keeping the chunks in some suitable container from which they can be retrieved or otherwise processed in a sequential fashion according to general rules (e.g., Anderson, 1983; Baddeley, 1986; Feigenbaum and Feldman, 1995; Gernsbacher, 1990; Marr, 1982; Posner, 1978; Sternberg, 1969). These types of models are the basis for working hypothe-

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ses that can be used to generate testable predictions whatever the dependent measure.

Still, computers are not people: they sometimes do very well on tasks that give people trouble but at the same time have been much less successful in performing some tasks that people find very easy (e.g., identifying visual objects, learning a language). Indeed, during the 1980's, the strain of thinking about human information processing in the same terms as symbolic computer information processing led to a revival of interest in neural network (connectionist or parallel distributed processing) models of information processing (Elman, 1995; Rumelhart, McClelland and PDP Research Group, 1986; Smolensky, 1988). These alternatives, explicitly or implicitly guided by the structure of the nervous system, have yielded 20 years worth of network models consisting of many interconnected independent processing units operating in parallel. Information, if chunked at all, tends to be chunked at a finer grain, and not stored as a persistent representation in any particular list or tree-like data structure, but distributed throughout as patterns of connectivity or dynamic activation states or both. Information is stored to the extent that these states and connections persist through time and information is retrieved or otherwise processed in virtue of the effect it has on subsequent state changes in the nodes or connections of the network. It is within these frameworks (until quite recently predominantly information processing or IP) that event-related brain potential (ERP) studies of intact individuals and brain-damaged patients have been conducted and the results interpreted.

Details notwithstanding, any plausible cognitive model requires an information processing system that has some version of sensory and perceptual input processes, central processes such as attention, memory, language, and output processes such as movement. We will consider these processes in turn, illustrating how ERPs have been used to test cognitive hypotheses in experiments that differentially engage these putative processes or track their disintegration. This approach is risky because claims regarding relationships between specific scalp potentials and specific types of cognitive processes inherit the general uncertainty surrounding our understanding of the cognitive system. Nevertheless, it is likely that the range of general capacities and processes

reflected in the sections of this chapter on sensation, perception, attention, memory, language comprehension, and movement are to be found in any plausible cognitive model in some form.

Sensation and perception

The peripheral nervous system serves to provide information about the environment and, given the selective sensitivity of different types of peripheral receptors, this is a matter of communicating information about specific types of sensory features to the central nervous system. Selective sensitivities in the nervous system are now well established. As the ear drum is displaced at different frequencies, the cochlea resonates so that hair cells in particular regions of the basilar membrane fire. These cells are selectively sensitive to acoustic frequency, neurally encode acoustic frequency, and propagate this information up the auditory pathway to the central nervous system. Other familiar examples include selective sensitivity — and presumably neural encoding — of color, motion, and orientation by the visual system; pressure and temperature by the somatosensory system; five tastes by the gustatory system. Somehow, (not necessarily at some single point in time or single place in the brain) the features of the environment encoded by the peripheral nervous system are bound into coherent percepts: the individual objects, scenes, events that comprise our experience. Much research is dedicated to solving this binding problem.

Attention

The study of visual and auditory attention follows naturally upon study of the sensory input systems. In the normal adult cognitive system, the senses generally make available more information than is actually used. Having more information available than can be used is adaptive: not having the information available at all amounts to a form of blindness, deafness etc. which presumably increases vulnerability to predation. However, having a welter of sensory information poses a processing problem for the system: of the information currently available, what is to be recruited for immediate or delayed information processing, i.e., attended, and what is

to be ignored? What determines the effectiveness of selection? How extensively are ignored stimuli processed? How much perceptual analysis of simultaneous inputs is possible? When people orient to a sudden noise, attention has shifted involuntarily, but attention may also be directed voluntarily as when a person monitors a sensory channel for a particular event, e.g., a strange new noise in the car that only appears under acceleration. This observation raises another information processing problem: what mechanism is responsible for engaging and directing attention in such a way that it is sometimes, but not always, under voluntary control? A whole host of cognitive models of attention have articulated answers to these questions in a variety of ways including a filter (Broadbent, 1958), or attenuator (Treisman and Geffen, 1967) between sensory channels and central processes, general capacity limitations (Kahneman, 1973), and combinations of automatic and controlled processes (Schneider and Shiffrin, 1977). The actual details of attention, including its function, remain matters of considerable debate (see Allport, 1989 for a review). Also at issue is the extent to which it makes sense to talk about attention as if it were a unitary concept when some form of selection must occur at multiple levels (e.g., sensory inputs, decisions, memory retrieval, and actions), and damage to different brain areas/circuits leads to specific attentional deficits (orienting, shifting, focussing, dividing, among others).

Memory

The sensory system provides current information, some of which may be in the focus of attention. Somehow the system must also be able to retain information for subsequent processing, whether it comes from the sensory periphery or is generated internally. The general ability to retain information is memory and the nature of its representations and processes are central questions for cognitive neuroscientists. Data from a wide variety of human and animal studies suggest that mammalian memory systems encode, retain, access, and retrieve different types of information in different ways. This has led to the widespread view that there are multiple, distinct and, to some extent independent memory systems, where a memory system here is charac-

terized by its information processing properties. In some cases, anatomically distinct brain structures have been implicated for certain types of memory. In very general terms, at the information processing level, a container metaphor is generally assumed according to which either short or long term memory or both is a container into which information can be put (somehow), held (somehow) and subsequently retrieved (somehow); this is generally true even though reference to working memory and notions of short term memory as activation of items in long-term memory attempt to move psychologists away from the container metaphor. For discussion from different perspectives see e.g., Schacter (1999) and Squire and Knowlton (1995).

Although the devil is in the details, it seems likely that any satisfactory account of memory will have to include distinctions between sensory, short term, and long term memory. A fairly large capacity sensory register maintains a veridical representation of the environment at least for a fleeting instant (~1 second), before it is categorized, and/or crowded out by more sensory input; there seems to be one for each sensory modality. Control processes direct the information from the various sensory registers into short term memory: less fleeting (on the order of tens of seconds) encodings of sensory features as well their meaningful groupings into the more familiar objects of awareness such as objects, words, events. Short term memory stores information long enough to be categorized and to take part in various rehearsal, coding, retrieving, and decision-making processes. The capacity of the short term memory system is considerably less than that of either the sensory register or long term memory, although there seem to be several subgroupings, each with its own limited-capacity and functional organization. The combination of short term storage with concomitant processing has been termed 'working memory'; from the perspective of the processes involved, it is a temporary memory (e.g., Baddeley, 1986; Kutas and King, 1999). Finally, there is the information, general knowledge, e.g., facts and events, procedures, and skills, that forms our long term memory (hours, days, weeks, and years).

These general memory abilities can be cross-classified with the type of information stored, e.g., visual, auditory, verbal, non-verbal, meaningful, etc.;

the type of encoding, e.g., intentional memorization or mere exposure; the type of retrieval, e.g., free recall, cued recall and recognition; the characteristics of memory failure, e.g., forgetting and misremembering. There are similarities and differences between these that can be teased apart in the laboratory by manipulating experimental variables and/or subject groups.

Language

The information processes of sensation, perception, attention, and memory can be investigated not only in humans but in non-human animals, sometimes more easily. However, only in humans is it possible to study the remarkable ability to communicate with each other about what we perceive, learn, know, remember and believe via a written, spoken or signed language. The seeming effortlessness of communicating with language belies the range and complexity of the information processing involved. This complexity, however, becomes apparent when we consider the multiple representational and processing levels at which language can be described.

Each language has its own set of fundamental sounds (phonemes, smallest unit of speech input that makes a difference in a word's meaning) that can be combined to make words. All languages also include inventories of meaningful building blocks — 'morphemes', which are combinations of phonemes that have their own meaning. Many languages also have an orthographic system of 'graphemes' for representing the building blocks. Languages have systematic ways of combining these building blocks at each level to form meaningful expressions, i.e., a 'grammar'. There are endless possibilities for combining the building blocks of a language into larger, often novel, parts — from words to phrases to sentences to discourses. The meaning or 'semantics' of complex expressions depends on both the building blocks and the particular structural properties of the complex expression, where structure also occurs at multiple levels (e.g., phrase structure, thematic structure, referential structure). In the service of communication, meaningful expressions can be used in a variety of ways. The practical or 'pragmatic' communicative uses of language include literal uses such as stating facts, asking questions, and giving commands as

well as non-literal uses such as metaphor, irony, and fiction.

The important point for the purposes of the scientific investigation of language is that there are regularities of pronunciation, word construction, grammar, and use that far exceed the handful of simple prescriptive rules that are sometimes taught. As local regions of the speech signal do not constrain the phonological, semantic, or syntactic interpretation to uniqueness, the language comprehension system must use other information to constrain interpretation. How, when, and where in the brain these different types of information are processed and how this processing results in the interpretation it does is at the core of much of the neurocognitive studies of language.

Working out the correct meaning of the words and syntactic structures is especially complicated by the fact that language, whether spoken or read is input to the cognitive system serially such that the information available to the system for sorting out the interpretation unfolds over time and only partial information is available initially. Finally, language comprehension and production clearly require many of the same sensory (e.g., transduction) and cognitive resources (e.g., working memory) as other cognitive processes. At issue, therefore, is the relation between comprehension and production processes, and their modularity with respect to other cognitive and motor processes.

Motor systems

Sensory inputs and higher information processing capacities such as memory are recruited to guide goal-directed behavior. Behavior is fundamentally a matter of movements that can range from the commonplace to the exotic to the essential. The final output is via the motor system whether it is for highly practiced or novel acts of movement. Motor neurons in the spinal cord or brain stem control muscle contraction following the instructions from sensory neurons, interneurons, the cerebral cortex, and other CNS structures. There are over 300 muscles that determine how gracefully, and how efficiently we move.

Movements can be automatic or voluntary. Automatic motor responses include reflexes that are

stereotyped responses elicited by a specific sort of stimulus. Movements that are automatic, but not reflexive in this sense, include complex sequences of movements such as those produced by the skeletal muscles during bipedal locomotion or those produced by the musculature of the abdomen, throat, mouth, and face during the articulation of speech sounds. Voluntary movements include relatively simple movements such as of an individual digit as well as complex sequences of movements such as looking for an object, reaching for it, and grasping it which involves the head and neck, eyes, arm, hand and fingers. In cognitive terms, different types of movements depend on different information processing systems.

Automatic movements may depend on representations of the length of muscle fibers or the degree of force exerted on a muscle. Although the physical mechanisms may be neural, the terms 'length' and 'degree of force' characterize the type of information represented and are cognitive in the information processing sense. A voluntary movement may also involve the representation of a goal (e.g., pressing a button, grasping an object, or expressing a thought) and a means (e.g., moving a finger, reaching with an arm and hand, or producing a vocalization). Although the mechanisms are neural, the goals and means characterize types of information that the system is using.

The line between the sensory and motor systems can be fuzzy. There is much to be known about how the nervous system knows how hard to contract a muscle much less how to organize a coordinated movement. What is the nature of the information communication between sensory and motor systems? Can a movement be stopped once started? How do voluntary and involuntary movements differ from each other? What control parameters change as a movement goes from novel to well-practiced? What processes differentiate an expert from a novice? How important is sensory feedback to various movements? What aspects of movements can be prepared and which cannot?

Before looking at how ERPs have been used to examine sensory, cognitive, and motor processes in intact and brain-damaged individuals let us consider the physical and physiological basis of neural communication and the ERP.

Event-related brain potentials

The brain conducts its business via the electrochemical activity of neurons. The healthy adult human scalp crackles with cortically (and in a few cases subcortically) generated potentials on the order of 50 microvolts as seen in continuous electroencephalographic (EEG) recordings. Buried in these larger potentials are (much) smaller potentials generated by the brain in response to specific events. When these different types of external and internally generated events intercept the information processing trajectory of the neurocognitive system, they modulate the pattern of brain activity resulting, in a wide range of cases, in measurable differences in the electrical potentials that propagate to the scalp. To the extent that these events and the neurocognitive trajectories can be controlled in an experimental setting, scalp potentials can be used to test hypotheses about neurocognitive information processing. All the work that has been done in this area is a matter of refining the mappings between the neural activity, the cognitive processes, and the electrophysiological record at the scalp.

The electroencephalogram is a record of electrical potentials measured at the scalp across time. Notwithstanding artifacts introduced by other electrical sources on or off the head, the potentials evident in EEG are generated by neuronal activity in the CNS, and largely by the neocortex. This ongoing electrical activity at the scalp is known to vary systematically with the occurrence of specific events such as the onset or offset of a stimulus. When these stimuli impinge on the peripheral nervous system, the afferent volley drives characteristic activity in the neurons of the central nervous system, and is reflected in 'evoked' potentials recorded at the scalp. However neuronal activity visible at the scalp can also result from internally generated events, for instance when a person anticipates a stimulus that has not yet occurred, makes a decision, or prepares to execute a voluntary movement. The term 'evoked-potential' now tends to be used most widely in the context of perception research and clinical applications, while the term 'event-related potential' is more widely used in the context of experimental research into the so-called 'higher' cognitive functions — attention, memory, and language — etc., even when the scalp potentials of interest are in fact evoked by the onset of stimuli.

The specific properties of an event-related potential, the amplitude of its peaks and troughs, its frequency characteristics, its distribution over the scalp, etc., are all causally determined by the physical properties of the relevant tissues (neurons, membranes, ions, intracellular fluid, bone, skin, etc.) and the measuring equipment. At the same time, at least some of the relevant states and processes of the neurophysiological system are cognitive states and processes, i.e., states specified in a theoretical vocabulary of information processing and governed by laws relating them to other information processing functions including the encoding of information into stable representations, and storing these representations, using these representations in subsequent cognitive processes and overt actions.

Electrogenesis of scalp potentials

Although the value of much cognitive ERP research can be appreciated without reference to the details of brain function, a general understanding of the electrogenesis of scalp potentials helps clarify the motivation for certain methodological decisions and puts one in a better position to critically evaluate inferences based on recorded patterns of scalp potentials, particularly with respect to inferences about the underlying neuroelectrical activity.

There are three main types of electrical potentials that are measurable with macroscopic electrodes affixed to the scalp: potentials generated by electrochemical activity of brain neurons, potentials generated by electrochemical activity of muscles, and potentials generated by electrical sources off the body that induce potentials on the body. For present purposes, potentials arising from muscles and sources off the body are merely artifacts to be guarded against during EEG recording. Following Nunez (1981), the discussion below reviews some general principles of electrostatics (stationary electric charges) and their application to the special case of electrical fields (force per charge) generated by ionic currents in volume conducting media.

Electrostatics

Electric charge is a fundamental property of matter. Electrically charged bodies include protons (small-

est unit of positive charge) and electrons (smallest unit of negative charge) as well as ions (i.e., atoms that have an imbalance of protons and electrons, and hence a net electrical charge). Positively charged ions such as sodium (Na^+), potassium (K^+), and calcium (Ca^{2+}), and negatively charged ions such as chloride (Cl^-) play crucial roles in the electrochemical signaling between neurons that is the basic mechanism of neural information processing.

In classical physics, a stationary body with positive or negative electrical charge is surrounded by a field of electrical force. For a point charge in an infinite vacuum, the magnitude of the field at each point (x, y, z) in a 3-dimensional rectangular coordinate system is given by:

$$F(x, y, z) = \left(\frac{1}{4\pi\epsilon_0} \right) \left(\frac{q}{R(x, y, z)^2} \right) \quad (1)$$

where q is the charge at the origin of the coordinate system, the constant ϵ_0 is the permittivity of empty space, and $R(x, y, z)$ is the distance between the charge and the field point at (x, y, z) . The electric field around a proton or electron is continuous with lines that radiate out of a positive charge and into a negative charge. The strength of an electric field varies linearly with the charge and drops off as the square of the distance from the charge.

It takes energy to push like charges together or to pull unlike charges apart. Once this has been accomplished charged particles have the potential to do work (i.e., they have an electromotive force, emf). This potential to do work is a function of the charge and its position relative to the electric field; the potential work per unit charge is known as the electric potential (in volts). The potential can also be characterized as a field that surrounds a charged body.

When electrical fields change relatively slowly, as is the case for the electrical fields generated by ionic currents in the nervous system (Nunez, 1981), electromagnetic coupling can be ignored and Eq. 2 is a good approximation of the magnitude of electrical potential due to the point charge q at each point (x, y, z) in an infinite homogeneous medium:

$$\Phi(x, y, z) = \left(\frac{1}{4\pi\epsilon_0} \right) \left(\frac{q}{R(x, y, z)} \right) \quad (2)$$

Both the force Eq. 1 and the potential Eq. 2 quantify the idea that the more electric charge, the greater the

strength of the electric field, and the farther away from the charge, the weaker the field. An important consequence of this tradeoff between the magnitude of the charge and the distance from the charge is that the observed value of an electrical potential at a single point in space could be generated by a small charge nearby or a larger charge farther away. This indeterminacy has implications for inferring the location of electrical sources of the scalp potentials on the basis of observed scalp potentials alone and will be revisited below (see inverse problem).

The single charged body ('monopole') discussed above is a special case of spatially distributed sets of charges. Regardless of the number of charges or their positions relative to each other, the overall electrostatic force and potential fields are the linear sum of the individual fields of the charges. This idea can be expressed more formally by Eq. 3 in which the potential at each point (x, y, z) is given as the sum of all the n individual sources q_i :

$$\Phi(x, y, z) = \sum_{i=1}^n \left(\frac{1}{4\pi\epsilon_0} \right) \left(\frac{q_i}{R_i(x, y, z)} \right) \quad (3)$$

Here, q_i , is the i -th charge and $R_i(x, y, z)$ is the distance between that charge and the field point at (x, y, z) .

Electrical current

To do actual work, electric charges must move, and when they do move they produce electric current. Electrical current can be forced relatively easily through metal wires or with greater resistance through other conducting materials such as ionic solutions. In metals, the charged particles are electrons that skip from atom to atom, and in ionic solutions, e.g., salt water or the intra- and extracellular fluids of biological tissue, the charged particles that move are ions. By convention ionic current is given by the net flow of positive charge. In a three dimensional volume conductor, there may be different numbers of charges moving through different regions and the current flow at each point in the conductor is specified as the current density.

Although in principle, the potential at any point in a volume conductor is the linear sum of the fields associated with individual charges, at macroscopic scales there are huge numbers of charges and the

potential cannot be calculated on the basis of known charge locations. Furthermore, charges move differently in materials with different molecular compositions, and this means that the fields associated with the charges will differ as well. Nevertheless, by adding a term for this conductivity, it is possible to retain laws governing electric fields associated with current sources in volume conductors that have the same general form as Eqs. 2 and 3 for point charges. That is, for a point current source, I , in a homogeneous conducting medium of infinite extent, the potential is given by:

$$\Phi(x, y, z) = \left(\frac{1}{4\pi\sigma} \right) \left(\frac{I}{R(x, y, z)} \right) \quad (4)$$

where σ is the conductivity of the medium, I is the current flow, and $R(x, y, z)$ is the distance between the current source and the field point (x, y, z) . The 'source' I can either be a positive current source or a negative current source, i.e., a current sink. As the potentials due to multiple current sources sum linearly, in a homogeneous conducting medium the potential at point (x, y, z) for n sources is given by Eq. 5:

$$\Phi(x, y, z) = \sum_{i=1}^n \left(\frac{1}{4\pi\sigma} \right) \left(\frac{I_i}{R_i(x, y, z)} \right) \quad (5)$$

where I_i is the i -th current source or sink, and $R_i(x, y, z)$ is the distance between the field point and I_i . The upshot is that a current source acts like a positive static charge, a current sink acts like a negative charge and current paths in conducting media correspond to the field lines of electrostatic force in a vacuum. This parallel enables methods in classical electrostatics to be applied to calculate fields due to current source distributions in volume conductors.

Dipolar sources

Among the infinite number of possible configurations of current sources, the dipole and the dipole layer are of particular importance in discussions of neuroelectric fields because both have been recruited as candidates for modeling the neuroelectric generators of scalp potentials. A current dipole consists of a paired current source and current sink separated by a distance (d). In a dipole field, the direction of

the force at points close to the current source will be the sum of the larger force of repulsion away from the source and the smaller attractive force directed towards the distant current sink. At points equidistant from the two charges, the fields will sum to exactly zero. Furthermore, any point at a distance substantially greater than the separation between the source and the sink is approximately equidistant to both, so the source and sink contributions to the field are roughly equal, and they tend to cancel each other out. A consequence of this cancellation effect is that the potential field of a dipole falls off with distance much faster than the potential field of a single source. At distances large relative to the pole separation, the potential falls off approximately with the inverse square of the distance and this very rapid drop off is the salient point for present purposes.

A dipole layer consists of a sheet of current sources and sheet of current sinks oriented in parallel, separated by a distance (d). At distances far from the patch, the field falls off like a dipole, i.e., with the inverse square of the distance, whereas at distances close to the surface patch, the potential field is roughly constant over the entire patch except near the edge. At intermediate distances the field falls at a rate in between that of a monopole and a dipole. So, for a range of distances that are still fairly large relative to the pole separation, the single dipole and the dipole layer have different field properties at points in the vicinity of the current sources. An important implication of this is that when modeling electrical fields with current dipole approximations, the level of grain is important. The fields that result from a few large dipoles and those that result from many smaller dipoles distributed in a layer can have rather different properties at distances relevant to EEG recording, e.g., 1 cm above a 3 cm wide patch of neocortex. Thus, in the absence of other information, a measured potential could be the result of a small dipole very close by, a much larger dipole somewhat farther way, or dipole layer of moderate size at an intermediate distance (see Fig. 1).

The above outlines the potential field associated with three types of current sources: monopoles, dipoles, and dipole layers in homogeneous media of infinite extent. When the field is distributed through media with different conductances and the media are bounded at distances that are not good approxima-

tions to infinity, boundary conditions come into play and the distribution of the electrical field is not governed by a simple inverse square law. Anisotropic media, i.e., media with different conductances in different directions, complicate the behavior of the field still farther as a function of both the conductances and the geometry of the materials involved. For instance, if a current source is located in a volume conductor near the boundary with a non-conducting medium, the potential at the surface of the conductor will be larger than it would be if the conducting medium were infinite; these considerations are relevant when measuring potentials at the boundary of the conducting scalp and the relatively non-conducting air. Despite these complications, if the geometries and conductances of the different media are known, it is possible in principle to calculate the potential generated by known current sources at all points, including the surface, i.e., at the scalp-air boundary in the case of neuroelectric potentials.

Bioelectric fields

The same principles that govern current flow and volume conduction in electrolytic solutions govern electric fields in and on the head as a special case. In this instance the electrical sources are predominantly ionic currents in and around neurons. While several factors are at work to move ions, ion concentration gradients across neuron membranes are the primary contributor to the microscopic ionic currents that are ultimately responsible for the potentials recorded at the scalp with macroelectrodes.

A typical neuron consists of a cell body (soma) from which both smaller processes (basal and apical dendrites) as well as an elongated cylindrical process (axon) emerge. Structural and chemical differences notwithstanding, the mechanisms of electrochemical signaling operate on the same general principles for all neurons. The cell membrane itself is relatively impermeable to ions, but embedded in the cell membrane are proteins that selectively pass ions of a specific type or types across the membrane (i.e., ion channels). Ion channels in the vicinity of the synapse tend to be gated by neurotransmitters, whereas along the axon and at the axon hillock channels tend to be voltage-gated. At rest, there is a potential across the cell membrane, typically about -60 to -75 mV for

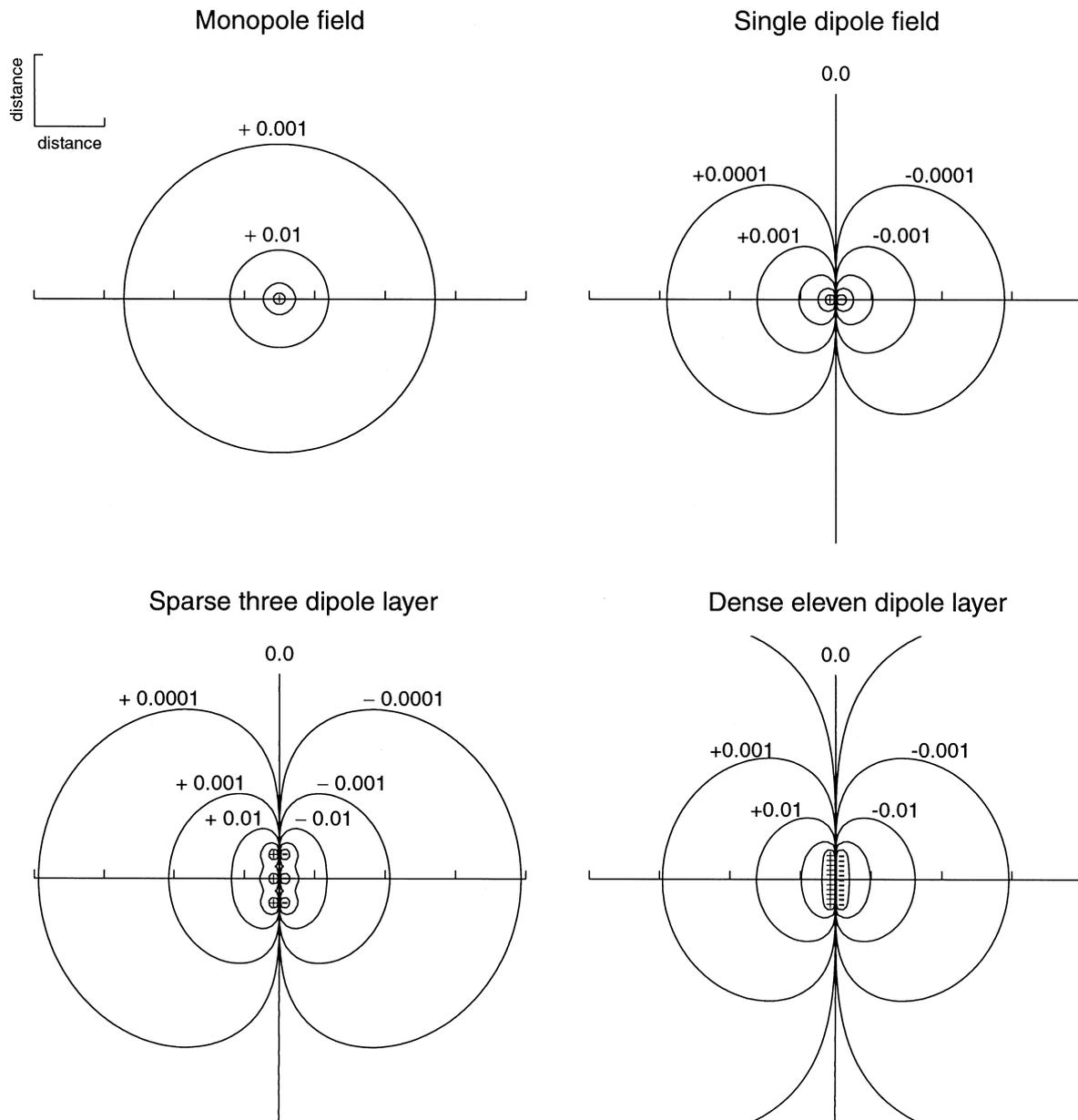


Fig. 1. The relative strengths of potential fields in an infinite homogeneous medium generated by different types of sources. The spatial scale is the same for all four fields. In all the sources, the point charges are of unit strength and the pole separation is twice the unit distance. The distance between adjacent dipoles in the sparse and dense dipole layers is three and one times the unit distance, respectively. Note that the single dipole and the dense dipole layer differ by about an order of magnitude in the vicinity of the source.

cortical neurons. This resting potential is the result of the ion concentration gradient across the membrane that arises from the combined action of electrostatic forces, diffusion across the semi-permeable

cell membrane through non-gated ion channels, and the cell actively pumping ions across the membrane.

When neurotransmitter is released from an excitatory synapse, gated ion channels in the postsynaptic

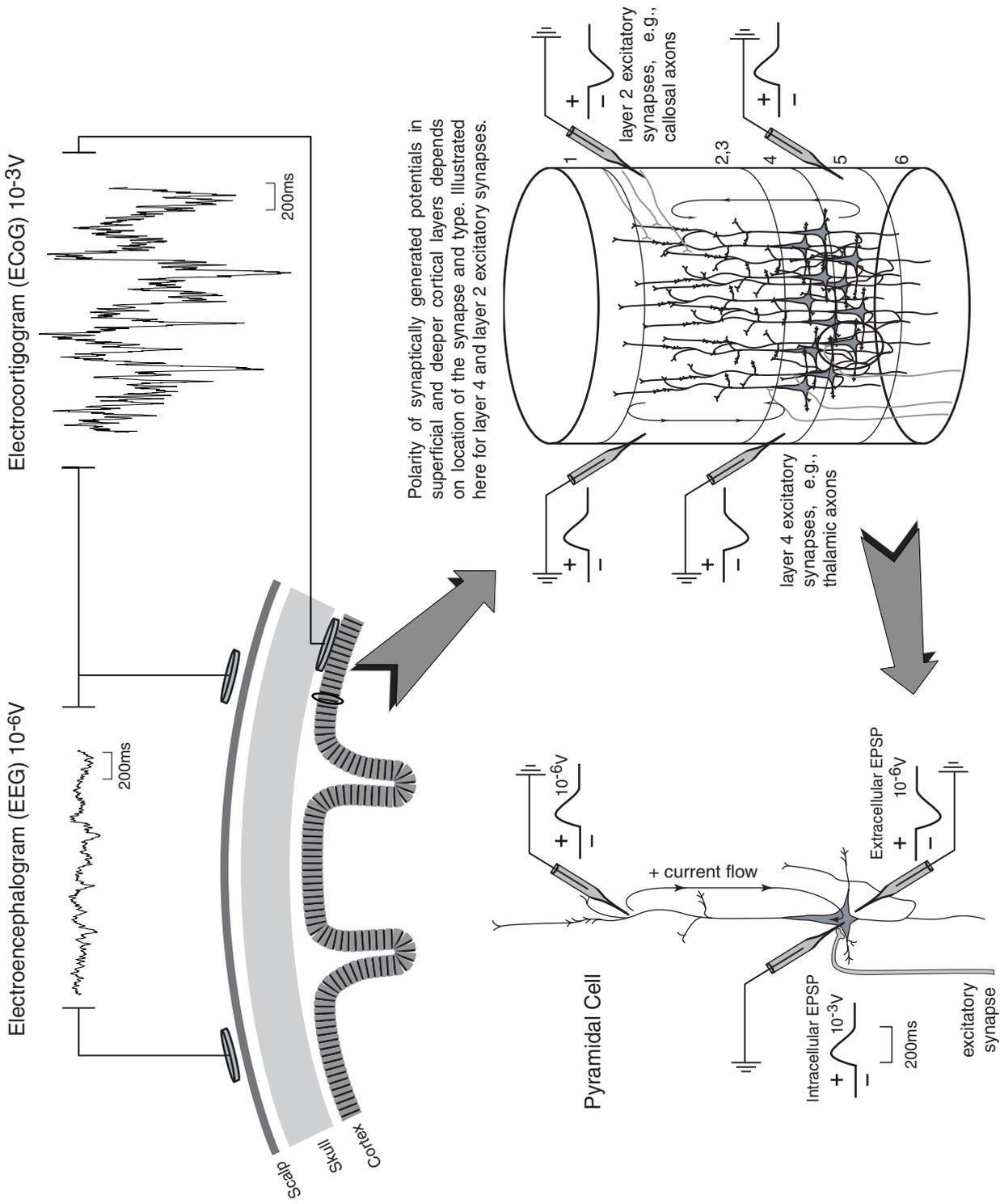


Fig. 2. Schematic overview of neuroelectric potentials at different locations and scales.

membrane open, and an influx of positive ions across the membrane induces a reduction of the potential across the postsynaptic membrane which passively spreads along the membrane. If the combination of enough of these 'excitatory' postsynaptic potentials (EPSPs) sufficiently depolarize the membrane in the vicinity of the axon hillock, voltage-gated ion channels open, triggering a chain reaction of voltage-gated ion channel openings that propagates along the axon, i.e., the action potential. When the action potential reaches the terminal regions of the neuron, it triggers the release of neurotransmitter, and this begins the process anew in the neuron on which it synapses. When positive ions move across the postsynaptic membrane in the area of an excitatory synapse, this area of the membrane becomes an ionic current sink and locations in other regions of the membrane where positive ions flow out become current sources.

These general facts about the propagation of electric fields in conductive media and neural electrochemistry constrain the possible generators of potentials recorded at the scalp with macroelectrodes. The rapid fall off of potential fields with distance and the fact that the skull is a poor conductor conspire to ensure that electrical fields in the cortex are greatly attenuated at the surface of the scalp. This rules out the possibility of seeing the fields generated by single neurons (with current technology). The microvolt level potentials measurable at the scalp thus are generated by large populations of neurons, and even so, only populations of neurons with a specific geometry. Although neurons that are not oriented in parallel or that do not fire together in large groups generate local microscopic electrical fields, these will either tend to cancel at macroscopic distances or be of insufficient strength to sum into fields that are large enough to be measurable at the scalp. On the other hand, structures that have many neurons that fire simultaneously and are oriented in parallel are plausible candidates for the generation of electrical fields measurable at the scalp.

Based on anatomical studies, top candidates are pyramidal cells in the cortical laminae, particularly the neocortex because of its relative proximity to the scalp. Pyramidal cells comprise perhaps three quarters of all the neurons in the cortex and tend to be oriented perpendicular to the layers, parallel to each

other. In addition, because of the local density of excitatory interneurons, it is likely that populations of these pyramidal cells can fire synchronously. Under these conditions, the ionic current sinks associated with the EPSPs and spatially separated corresponding sources can generate potential fields that, in sum, are of sufficient strength to conduct to the scalp where differences between one region of the scalp and another are on the order of tens of microvolts. Fig. 2 schematically illustrates electrical fields due to EPSPs at the level of the individual neuron (bottom left), the potential at the cortical surface resulting from the summed EPSPs of many neurons oriented in parallel in a cortical layer (top right), and the volume conducted potential measured at the scalp (top left).

Propagation of the action potential is the basic mechanism by which signals are communicated between neurons, and at a peak of perhaps 100 mV across the cell membrane, this potential is relatively large. However, given the geometry of neurons, in most cases, it is likely that it is the EPSPs responsible for triggering the action potentials rather than the action potentials themselves that sum to produce measurable scalp potentials.

Although potentials in the 50 μ V range recorded at the scalp in the electroencephalogram are largely generated by neurons in the neocortex, cells in structures farther from the scalp that have suitable geometries, such as the auditory nerve and some brainstem structures can also generate electrical fields of sufficient magnitude to be measurable at the scalp, although these potentials tend to be an order of magnitude smaller (less than 1 μ V).

Cognitive processes and ERPS

Input processes

Stimulation of various sensory receptors propagates neuroelectric activity through relay nuclei and into the primary sensory cortices. This cascade of electric activity conducts through the surrounding tissue, and in some cases, these sources of electrical activity generate potentials that can be measured at the surface of the skin. Detailed technical considerations and standards for recording evoked potentials can be found in publications by the American EEG

Society (1994), Picton, Bentin, Berg et al., 2000, Regan (1989) and Spehlmann (1985). Although the emphasis herein will be on ERPs in experimental cognitive research, sensory evoked potentials have important uses in basic research into the sensory systems as well as clinical applications (Aminoff, 1990, 1999; Chiappa, 1997; Nuwer, 1996, 1998). A brief examination of some basic findings can serve as a useful reminder that even in 'higher cognition' the properties of the stimulus and of the peripheral nervous system are important determinants of the morphology of scalp potentials, particularly in the first two hundred milliseconds following the onset of a stimulus.

Visual evoked potentials

In the visual modality, both diffuse stimuli such as a flash of light and patterned stimuli such as checkerboards and sine gratings evoke potentials that are easily measurable at scalp locations over visual cortex and other regions. Presenting stimuli at intervals longer than a second elicits a transient visual evoked potential, whereas presenting stimuli at a faster rate will, after a short period, drive the visual system into periodic activity that results in a steady state potential at the frequency of the stimulus presentation.

Different types of visual stimuli typically elicit characteristic evoked potential waveforms, but the specific morphology, even for a single type of stimulus, can vary with presentation conditions. Consider three visual events in which the stimulus is a circular black and white checkerboard pattern subtending 32° of visual angle with $50'$ checks: the stimulus onset when the checkerboard first appears, the stimulus offset when the checkerboard disappears, and the stimulus reversal when the white and dark squares are switched. As illustrated in Fig. 3, in healthy adults, all of these events evoke a potential recorded over primary visual cortex consisting of an initial negative peak at about 70–90 ms followed within about 20 ms by a larger positive going peak at about 100 ms post stimulus (P100).

The latency of the negative and positive peak amplitude maxima for offset and reversal events is comparable, but both occur about 20 ms later than the peaks evoked by the stimulus onset.

With position and duration parameters held constant, visual evoked potentials are also sensitive to

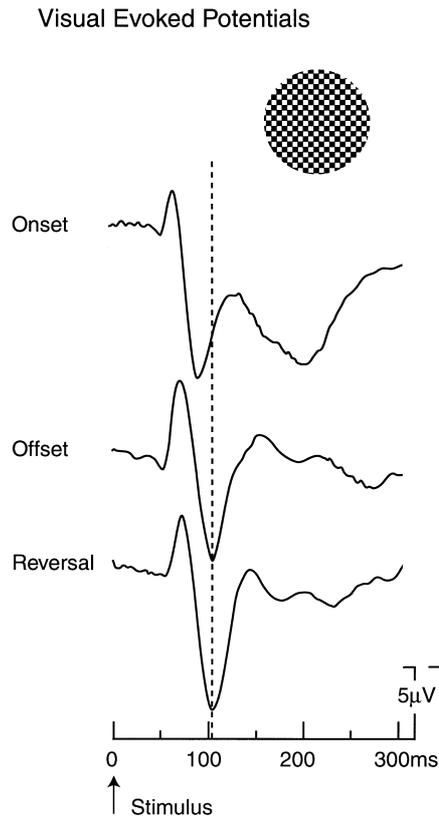


Fig. 3. Visual evoked onset, offset, and reversal potentials for a checkerboard stimulus recorded between midoccipital and mid-frontal electrodes. The waveforms share the same basic morphology, but the different aspects of the stimuli modulate the amplitude and latency of the peaks differently. These properties make the VEP a reliable and sensitive measure of early visual processing. Adapted from Kriss and Halliday, 1980.

fine-grained differences in the visual features of stimuli. For instance, the VEPs elicited by vertical and horizontal bars oriented at a range of relative angles are distinguished by different onset as well as offset potentials. Scalp potentials can provide quite fine-grained information about early visual processing. For example, MacKay (1984) showed that visual evoked potentials recorded from closely spaced montages (~ 1.5 cm apart) can distinguish retinal receptive fields with diameters of about $1-2^\circ$. These examples show the visual evoked potentials are sensitive to both the dynamics of stimulation — onset, offset, and type of change — as well as the location of stimulation in the visual field.

Neurologists routinely examine evoked potentials to passive stimulation to assess the integrity of the visual system from the retina, through the optic chiasm into primary visual cortex. At the retinal level, the electroretinogram (ERG) to flash and pattern-reversal stimuli can be recorded via gold foil, DTL fiber, or contact lens electrodes. It is customary to distinguish the a, b, and c waves as well as a DC component. To date, the ERG has been used primarily in the investigation of retinal diseases. Recent evidence, however, suggests that the reduced pattern ERG (especially to medium spatial frequencies, i.e., 2.7–4 cycles/degree) may provide a simple electrophysiological tool for evaluating dopaminergic retinal deficiency, specifically of the functioning of d2-receptors, in Parkinson's disease (Calzetti, Franchi, Taratufolo and Groppi, 1990; Peppe, Stanzione, Pierantozzi et al., 1998; Tagliati, Bodis-Wollner and Yahr, 1996).

Typically, a checkerboard stimulus reversing twice a second is used to evoke a steady state potential characterized by a large P100 (pattern reversal evoked potential). The morphological features of this peak can be diagnostic. With binocular stimulation, laterally asymmetric reductions in the post stimulus latency of the peak can help in the diagnosis of multiple sclerosis (MS) with optic neuritis (Nuwer, 1996). In principle, diagnosis of prechiasmal, chiasmal, and retrochiasmal lesions is possible, by combining binocular and monocular with full and half field stimulation, although MR-imaging provides a better alternative. Viggiano, Spinelli and Mecacci (1995) reported that pattern reversal EPs were normal in patients with visuospatial neglect implicating post-perceptual problems whereas Angelelli, De Luca and Spinelli (1996) concluded that early visual processing was abnormal in the neglected hemifield when assessed via steady state VEPs.

Auditory evoked potentials

Acoustic stimulation of the auditory system results in neural activity that propagates along the auditory pathway to the auditory cortex and scalp potentials track this progression. As illustrated in Fig. 4, AEPs are conventionally divided into three time-scales: 0–10 ms (auditory brainstem potentials), 0–50 ms (middle latency potentials) and 0–500 (long latency potentials).

Early AEPs. When scalp potentials are recorded following a click stimulus, a train of small ($\sim 1\text{--}2\ \mu\text{V}$) peaks or wavelets in the scalp potential between 2 and 8 ms post stimulus can be observed (Jewett, Romano and Williston, 1970). These peaks reflect the time course of activity through the major structures in the auditory pathway, with the caveat that the different structures may contribute to more than one peak. Wave I is attributed mainly to conduction in the auditory nerve lateral to the brain stem. The generation of Wave II is controversial and might be generated by the cochlear nucleus or auditory nerve or both in combination. Wave III is thought to be generated as the trapezoid body and superior olive are traversed. Waves IV and V are attributed to the upper pons and lower midbrain, probably the lateral lemniscus and inferior colliculus. Because of their high frequency, brainstem evoked potentials have to be recorded with high temporal resolution (AD-conversion of $>3000\ \text{Hz}$).

In clinical neurology and ear–nose–throat medicine, recording of auditory brainstem potentials (ABRs) a.k.a. brainstem evoked responses (BERs) has become a standard procedure for testing the integrity of the primary auditory pathway up to the midbrain level. They are commonly used because of their reliability and comparatively low intersubject variability in latency (especially the I–V, I–III and III–V interpeak intervals, and V/I amplitude ratio). The presence of waves I–V can be used in the diagnosis of acoustic neuroma, multiple sclerosis and for objective audiometry (Nuwer, 1998). Absence of Wave I indicates a peripheral deficit, whereas presence of Wave I and the absence of Wave V implicate the brain stem. Since ABRs can be recorded during sleep, they are suitable for use with infants, and are recommended for early detection of hearing deficits as infants are exposed to language, and of acoustic neuromas in individuals with sudden hearing loss (Saunders, Luxford, Devgan and Fetterman, 1995). In addition to transient auditory brainstem potentials, there is a steady state response in which the auditory system follows the frequency of an auditory stimulus, cf., the visual steady state evoked potential.

Several reports claiming an attentional sensitivity of brainstem evoked potentials (e.g., Galbraith and Doan, 1995), pointing to the existence and functional role of the olivo-cochlear-bundle in humans, have

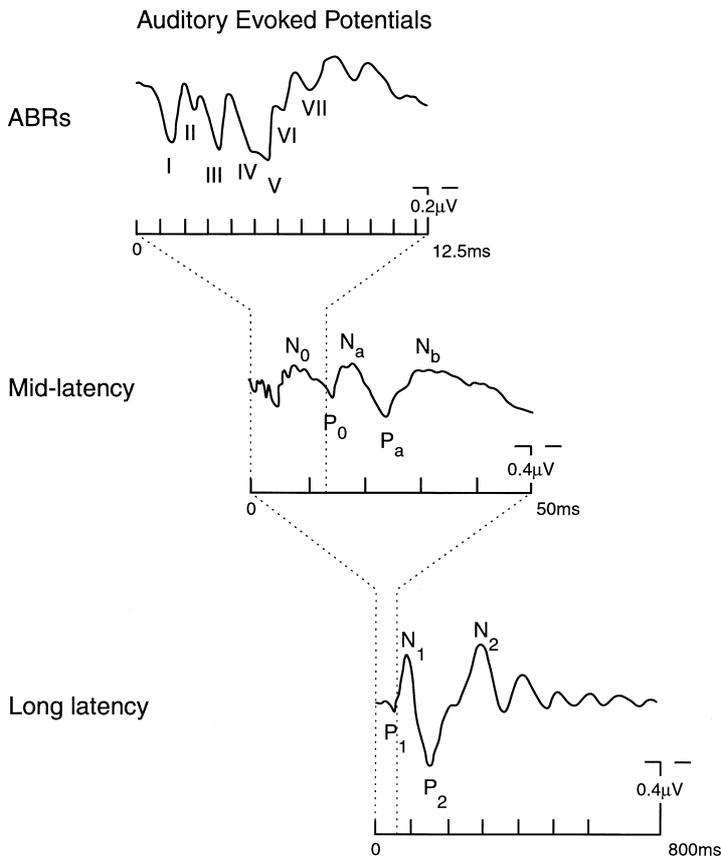


Fig. 4. Auditory evoked potentials recorded at the vertex electrode at different time scales and amplitude scales. Adapted from Picton and Smith (1978).

not been replicated (Hackley, Woldorff and Hillyard, 1990; Hirschhorn and Michie, 1990).

Middle and late latency AEPs. Auditory evoked potentials occurring between 10 and 50 ms are referred to as middle latency auditory evoked potentials (MLAEPs). Of the various components, the N_a and P_a (between 10–60 Hz) are the two that are clinically useful. These are usually recorded with particular two channel electrode montages and require at least 500 trials.

By the time the late latency auditory evoked potentials (LLAEP), i.e., those occurring after about 50 ms evolve, cortically generated scalp potentials reflect both the processing of sensory system outputs and ongoing cognitive processes such as attention. In fact, the neural processing of attended versus unattended information can differ significantly by 20 ms

or so, as reflected in mid-latency AEPs. The earliest effects of attention on the ascending auditory pathways are reflected in a greater positivity in the ERP to the attended ear tones called the P20–50, which according to combined ERP and MEG recordings is generated in the auditory cortex (Woldorff, Gallen, Hampson et al., 1993).

At longer latencies, the major features of the auditory evoked potential recorded at the vertex are a negative deflection at ~90–120 ms post stimulus (N_1 or N_{100}) followed by a positive deflection at about 170–200 ms (P_2 or P_{200}). The N_1 tends to be largest centrally, but can be seen at many sites, with the potential at any given site reflecting the combined effect of activity from at least three cortical sources: (1) activity in the auditory cortices on the supratemporal plane that results in a negative scalp potential that is largest fronto-centrally (Vaughan and Ritter,

1970); (2) activity in the auditory association cortex in the superior temporal gyrus that results in a positive peak at 105 ms and a negative peak at 155 ms (Wolpaw and Penry, 1975); (3) activity in the frontal motor and premotor cortex that results in a negative scalp potential at about 100 ms post stimulus (Näätänen and Picton, 1987). Both the N1 and P2 have been found to be abnormal in children with developmental language disorders and dyslexia (Leppanen and Lyytinen, 1997).

Somatosensory evoked potentials

Somatosensory evoked potentials (SEPs) include spinal (action potentials from receptors up to the cervicomedullary junction), subcortical, as well as early cortical potentials (see Fig. 5). The appropriate electrode montages are determined by the potentials of interest, but in all cases ground placement is crucial. The somatosensory evoked potential (SEP) components that have proved their clinical utility peak before 50 ms for upper limb stimulation and before 70 ms for lower limb stimulation.

By recording SEPs at different levels of the somatosensory pathways, it is possible to assess the transmission of the afferent volley from the periphery to the cortex. For example, SEPs can be a useful way of measuring peripheral conduction velocities when sensory nerve action potentials cannot be obtained at the periphery. The difference between the latencies of the N20 potentials obtained by stimu-

lating the same nerve at two different levels offers an estimate of the conduction velocity in the segment between the two stimulated points. SEPs can be used to test whether some inputs are reaching comatose patients and may help to differentiate apallic syndrome from locked-in states. SEPs are reportedly also informative in combination with EMG and nerve conduction velocity recordings in patients with Guillain-Barre syndrome, hereditary ataxias, traumatic lesions, spinal cord lesions, multiple sclerosis (MS), Huntington's disease, and ALS.

SEPs are helpful in the classification of patients with astereognosis (loss of ability to identify objects by touch in the absence of visual or auditory information); the contralateral parietal N20 and/or P27 to stimulation of the affected side are generally reduced in such patients (Mauguiere, Desmedt and Courjon, 1983).

Chemosensory evoked potentials

Although visual, auditory, and somatosensory evoked potentials are the canonical sensory evoked potentials, chemosensory evoked and event-related potentials are receiving increased attention, (reviewed in Lorig, 2000). In principle, recording scalp potentials evoked by an olfactory event is no different than recording any other sensory modality. In practice however, delivering an odorant at a precise moment is technically more difficult than irradiating the retina or displacing the eardrum. However,

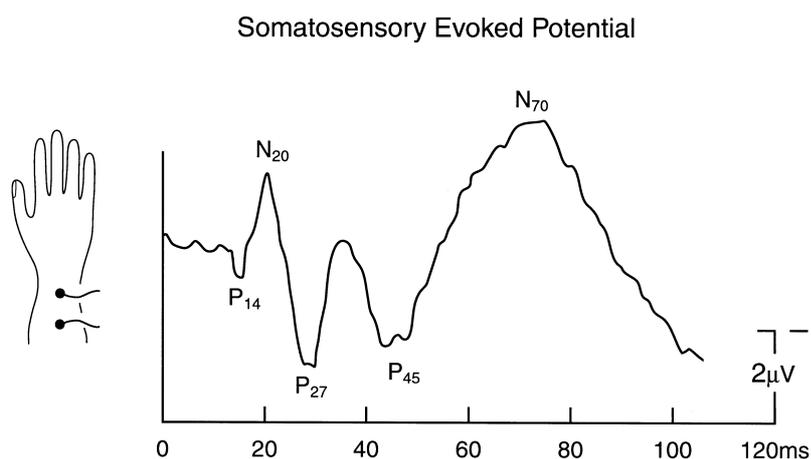


Fig. 5. Somatosensory evoked potential at right parietal scalp to 4 mA stimulation of the left median nerve at the wrist. Adapted from Desmedt and Brunko (1980).

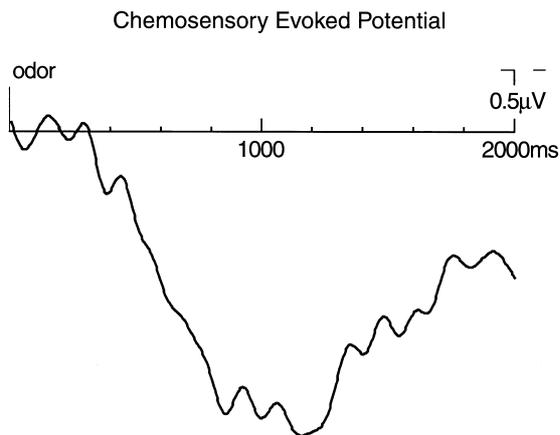


Fig. 6. Grand average chemosensory event-related potential at a midline parietal site (Pz) to the second administration of phenethyl alcohol (20%) following an interstimulus interval of 33.6 s (Lorig and Radil, 1998).

the technical obstacles can be surmounted (Evans, Kobal, Lorig and Prah, 1993), and with care, it is possible to record scalp potentials evoked by chemosensory sensory events (see Fig. 6).

The sharp peaks found in the first few hundred milliseconds for visual and auditory stimuli are not observed for olfactory stimuli, perhaps because of the variability in transduction time for different odors that is compounded by individual subject differences. However, as with visual and auditory sensory evoked potentials, the morphology of olfactory ERPs varies systematically with stimulus intensity, albeit at a somewhat longer latency. For instance, the amplitude of the positive peak about 400 ms post stimulus has been found to co-vary with the concentration of an odorant such as butanol (Lorig, Sapp, Campbell and William, 1993) and vanillin (Tateyama, Hummel, Roscher et al., 1998). Olfaction plays an important role in a range of sensory and cognitive processes and, in addition to basic research in olfaction, there are a wide range of possible applications of olfactory evoked potentials. Olfactory discrimination degrades with normal aging; olfactory impairment precedes cognitive impairment in the progression of Alzheimer's type dementias.

Gustatory evoked potentials also can be recorded by flowing gaseous gustatory substances over the tongue (acetic acid for sour, chloroform for sweet, thujone for bitter and ammonium chloride gaseous

particles for salty) or by using a laser beam device (sweet: sucrose; salty: sodium chloride; sour: tartaric acid; and bitter: quinine-HCl). Taste stimuli under the latter conditions, for example, elicit a P1 (50 ms) and a P2 (180 ms) component, of which only the P2 was considered specifically gustatory. Matern, Matthias and Mrowinski (1995) examined patients with olfactory disorders and suggested that olfactory evoked potentials (EOPs) combined with the contingent negative variation (CNV) allow a better assessment of odor perception and odor discrimination than traditional subjective tests (sniff test, gustatory smell test, and trigeminus test; see McCallum, Cheyne and Curry, 1993 and Walter, 1965 for discussion of CNV).

Central processes

We now turn to scalp potentials associated with cognitive processes that operate with and on the information provided by the sensory periphery. On the whole, these processes follow an afferent volley, but there is no sharp dividing line between 'sensory' potentials and higher 'cognitive' potentials. On the one hand, effects of attention, a presumably higher cognitive state/process, have been found to modulate scalp potentials at the latencies of 20–50 ms (e.g., auditory selective attention, Woldorff and Hillyard, 1991). And to the extent that subsequent processing, e.g., for a judgment-based response, depends on evaluating a stimulus, it is not surprising that physical stimulus features such as stimulus quality, visual brightness, and auditory pitch, would modulate scalp potentials at latencies well after one would expect the initial sensory processing to have been completed. Still, the distinction between stimulus-driven (also known as sensory or evoked potentials) 'exogenous' components in scalp potentials and 'endogenous' components that reflect information processing driven or elicited by central cognitive processes (Donchin, Ritter and McCallum, 1978) is a useful heuristic.

Perception and attention

In controlled experiments, there are clear differences observed when presenting stimuli to attended and unattended sensory channels, e.g., a visual hemifield or single ear. Stimuli presented in an attended

channel are typically processed more rapidly, and unattended stimuli may not be responded to at all if they do not recruit attention (see Pashler, 1998 for an overview). ERPs are particularly well suited to studies of attention because the technique provides data on brain activity not only for attended stimuli but also for unattended stimuli without requiring any behavioral response. Furthermore, since attentional processes can come into play more rapidly than even the fastest of speeded responses, a measure that provides continuous data on a millisecond timescale is invaluable. ERPs have proven to be sensitive to differences in tasks that differentially engage attentional processes and this sensitivity, in conjunction with carefully controlled experimental designs, has allowed the testing of models of visual and auditory attention at a level of grain as fine as any in cognitive neuroscience (see Hillyard, Mangun, Woldorff and Luck, 1995 and Näätänen, 1992 for reviews).

Visual perception and attention. For the neuropsychologist, the visual system is the origin of many notable abnormalities, including central achromatopsia (impairment of color perception), motion blindness, simultanagnosia (deficit affecting patients' ability to integrate the parts of a whole into a coherent unit), prosopagnosia (deficit in face recognition), object agnosias (disorder of object recognition), among others (e.g., Zeki, 1993). A wealth of clinical data regarding these symptoms has accumulated over the past 100 years or so. Yet, surprisingly little use has been made of electrophysiological techniques to analyze complex disorders of vision, even though these techniques can track visual processes at virtually every level.

Electrophysiological and behavioral investigations of non-human primates have implicated several dozen anatomically and functionally distinct areas in the processing of visual input. Within the monkey brain, it is now possible to delineate the timing and location of electrical activity related to the processing of spatial location, orientation, color, and motion of a stimulus, at both the single cell and ensemble levels (Chelazzi, 1995). Researchers also have identified single cells that appear to respond specifically to faces and even to the direction of gaze (Milders and Perrett, 1993). Functional imaging studies using PET and fMRI methodologies, likewise, have

provided insights into the anatomical organization of visual processing in humans (Heinze, Mangun, Burchert et al., 1994; Mangun, Buonocore, Girelli and Jha, 1998). It is against this rich background of research on vision and the brain that observations from non-invasive electrophysiological studies in intact and brain-damaged patients can be analyzed.

Visual selective attention. Early ERP studies of visual attention by Eason, Harter and White (1969) showed that differences in visual-spatial attentional result in measurable differences in the scalp potentials. In a typical selective attention task, visual stimuli are presented rapidly in at least two 'channels' defined by, e.g., their spatial location. Paying attention to one location in order to detect slightly altered target stimuli interspersed among similar frequent standard stimuli gives rise to enhanced amplitudes of several ERP components when compared with the same stimuli when they are unattended (for review see Hillyard et al., 1995). Focussed visuospatial attention is associated with an enhancement of the occipitotemporal P1 (latency about 120 ms) component emanating from the lateral extrastriate cortex (Gomez-Gonzalez, Clark, Fan et al., 1994; see also Woldorff, Fox, Matzke and Lancaster, 1997) followed by a similarly enhanced negative component (N1) with a peak latency of approximately 170 ms (see Fig. 7).

This N170 is modulated by dorsolateral prefrontal damage, being decreased in amplitude over the lesioned hemisphere for all types of stimuli, especially over posterior temporal sites (Knight, 1997). Such data have been taken as evidence for prefrontal modulation (specifically, providing ipsilateral facilitatory input) of visual processing in extrastriate areas during sustained attention tasks.

Attentional selection based on non-spatial features of visual stimuli such as color, orientation, spatial frequency, or conjunctions of such features does not modulate the amplitude of the P1 and N1 components. Rather they give rise to 'endogenous' ERP components that may appear to be superimposed upon the sensory-evoked potentials. Best seen in the attended minus unattended difference waveform, these so-called selection negativities (SN) or processing negativities (PN) tend to be of longer latency and prolonged duration relative to visuospatial ERP effects, although more recent work has revealed

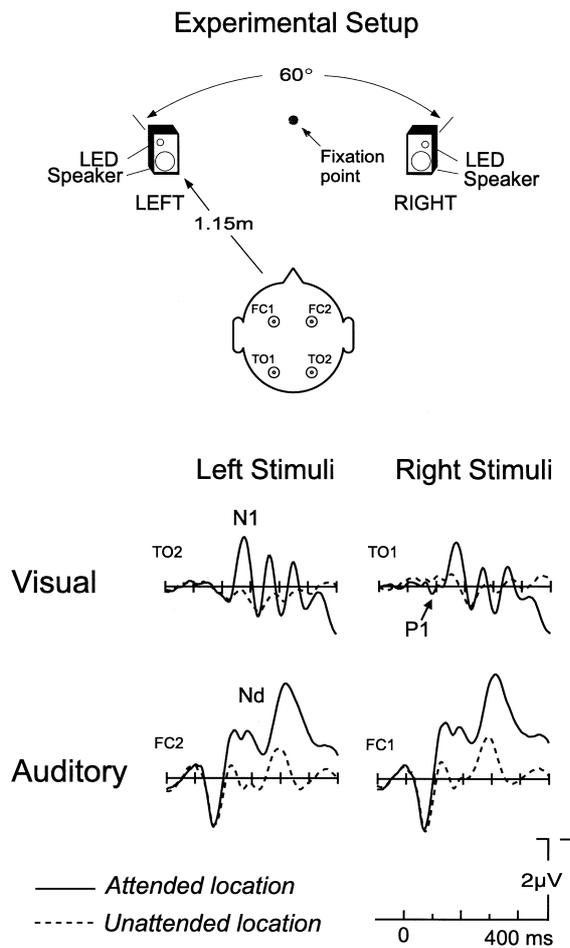


Fig. 7. Illustration of visual and auditory spatial selective attention effects. The upper part of the figure shows the experimental set-up. Subjects were asked to attend to either the visual (LEDs) or the auditory stimuli (bandpass filtered noise) on one side in order to detect slightly deviant targets in the attended channel. Visual spatial attention leads to a modulation of several successive components over the posterior scalp beginning at approximately 60 ms after stimulus onset with the enhancement of a contralateral P1 positivity. Other attention sensitive components are located over frontal brain areas. Auditory spatial attention leads to a prolonged fronto-central negativity for the attended stimuli (negative difference or Nd), beginning at about 100 ms and extending over several hundred milliseconds (adapted from Teder-Salejarvi, Münte, Sperlich and Hillyard, 1999).

both selection positivities and negativities of various latencies, durations, and maxima over the scalp (e.g., Michie, Karayanidis, Smith et al., 1999; Smid, Jakob and Heinze, 1999). For example, Anllo-Vento and

Hillyard (1996) found that attention to both color and motion features is accompanied by a negativity starting at about 150 ms and extending to about 250 ms. This negativity had a very similar timing and morphology regardless of which feature was attended, in spite of the fact that color is presumably processed by the so-called ventral stream, while motion is analyzed by the dorsal visual pathway (Haxby, Grady, Horwitz et al., 1991). It remains to be shown, whether subtle differences in scalp distribution of this selection negativity can be traced back to their presumably separate cortical origins. Additionally, as in previous reports of attention to multiple features of which one is location (e.g., Hillyard and Münte, 1984; Karayanidis and Michie, 1996), selection of color and motion was hierarchically dependent on prior selection of location; in other words, there was no evidence of processing for color or motion features for stimuli that appeared in the unattended location.

In contrast to the studies mentioned thus far, investigations of attention in neuropsychological populations have often used trial by trial cueing as exemplified by the Posner spatial-cueing task. In the spatial-cueing paradigm a cue stimulus is presented at the beginning of each trial and is followed by a target stimulus that is presented either at the cued location (valid trial) or at an uncued location (invalid trial). Typically, target detection and discrimination are better on valid than invalid trials. ERP-effects in spatial cueing tasks share many similarities in common with those obtained with a fixed attentional set across an entire experimental run: a central pre-cue indicating the likely site of an upcoming target event leads to larger amplitude P1s and N1s to targets on valid than on invalid trials (Mangun, Hansen and Hillyard, 1987). Verleger, Heide, Butt et al. (1996) followed up on neuropsychological observations indicating that right parietal patients had difficulties in this task, and found a selective reduction of the attention effect for the left cue/right target combination in a group of ten patients.

Visual search. Screening a complex visual scene for some relevant item or feature is a prerequisite for daily functioning (spotting a friend in a crowd, searching for a particular store on a street, locating a car in a parking lot). Experimental psychologists have distinguished what appear to be two different

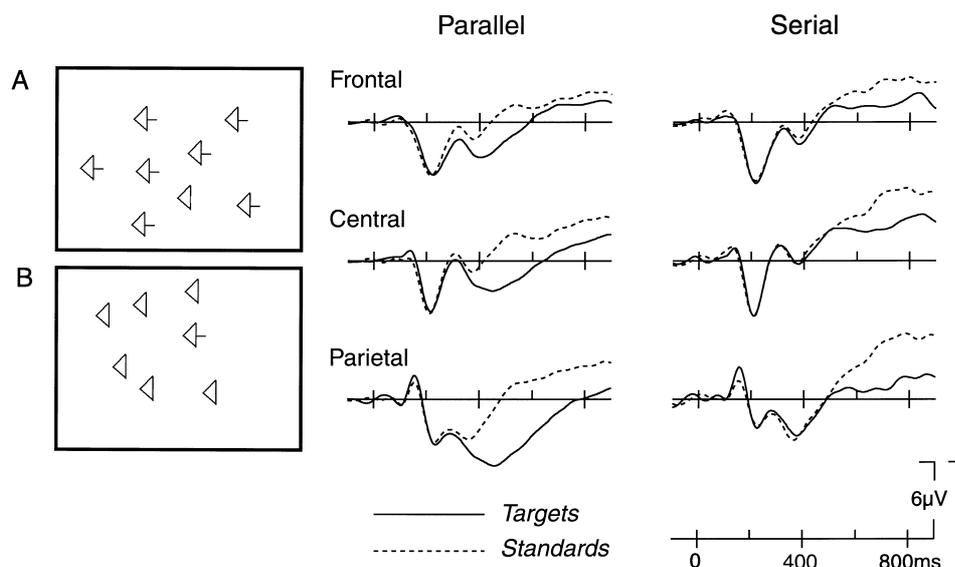


Fig. 8. Prototypical stimuli for a visual search experiment are shown on the left. (A) illustrates a serial search condition, in which the subject is asked to detect a missing feature, in this case a horizontal line against a background of non-target/standard triangles all of which have the horizontal line. In (B) a parallel search condition is illustrated. Here the subject is asked to detect the presence of a feature — a horizontal line, against a background of similar triangles none of which have the horizontal line. The target stimuli under parallel search elicit ERPs with a prominent P300 component that diverges from the standard ERP around 350 ms. During the serial search mode, there is no clear P300 and the ERPs to targets and standards diverge much later (~200 ms) than under parallel search, reflecting the longer time needed for target identification in this task (unpublished data of Lill and Münte).

classes of search behaviors. In visual search tasks, an observer is asked to find a target in a multi-element array, pressing one button if the target is present and another if it is not. The focus in these studies has been on how long it takes to detect targets (or the absence of targets) as a function of display set size; with ERPs it is possible to look at mechanism as well as timing. The rationale for this paradigm is that if an observer can search all the items in the display in parallel, then response times should not vary with the number of distractors, whereas if items must be processed sequentially, with attention focussed on each individual item to determine whether or not it is a target, then reaction times should increase linearly with the number of distractors. Some types of stimuli can be detected without serial application of attention; others cannot. When distractors are identical and the target differs from them in color, brightness, size, orientation or some other obvious feature, the search is affected little if at all by adding an extra display item. In any case, it is easier to find a target defined by the presence of a given feature than

it is to report the absence of the same feature. An example of a display that can be searched in parallel is illustrated in Fig. 8B. Subjects are asked to search for a distinguishing feature that is present only for the target item, in this case an extra line extending from the base of one triangle.

In Fig. 8A, all items, except for the target item, possess a feature, in this case the additional line; this display seems to require a serial search to notice the absence of a feature.

These sorts of tasks have been translated into the electrophysiological domain by Luck and Hillyard (1990, 1994a,b). They found that the latency and the amplitude of the P3 component were substantially different in feature-present (presumably parallel) and feature-absent (presumably serial) search. In the parallel search mode, target stimuli elicited a large P3 with a circumscribed peak, that increased in amplitude and latency with set size; in the serial task the ERPs to standard and target stimuli diverge significantly later than in parallel search task (see Fig. 8). This task has been used to investigate visual search

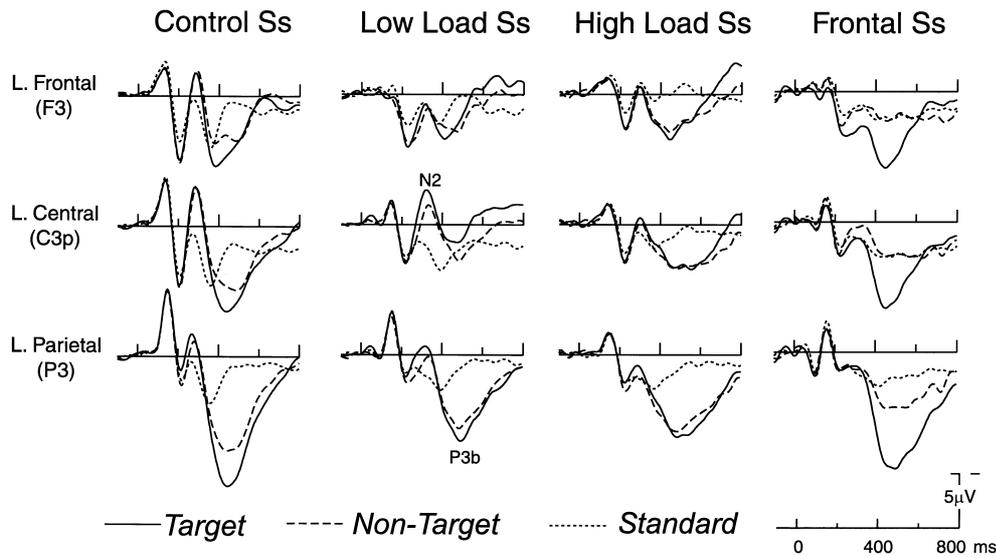


Fig. 9. A total of 34 patients with multiple sclerosis were assigned to *low load*, *high load*, and *frontal* groups according to the volume and location (diffuse or frontal) of their MS lesion as determined by a semi-automated procedure on T2-weighted MR-scans. Subjects viewed multi-item stimulus arrays of either standard stimuli containing 8 filled vertical bars at random locations, target stimuli with 7 filled and one unfilled vertical bars, or non-target, 'pop-out' stimuli with 7 filled vertical and one unfilled horizontal bar. The most obvious effect is the absence of the fronto-central N2 component, linked to automatic feature registration, for the target and non-target stimuli in both the high load and frontal groups (see Luck and Hillyard, 1990). N2 amplitude was correlated with the total lesion load on the MR-scans (unpublished data of Sailer, Heinze, Tendolkar and Münte).

in various neurological populations including individuals with brain injury (Heinze, Münte, Gobiet et al., 1992) and Huntington's disease (Münte, Rida-Alonso, Preinfalk et al., 1997b) and ALS (Münte, Schiltz and Kutas, 1998b). See Fig. 9 for visual search data in MS patients.

Luck and his colleagues have used a visual search paradigm to investigate the role of attention in visual perception. In several of these studies they measured attention via the N2-posterior-contralateral (N2pc) component of the ERP. The N2pc is a negative-going deflection coincident with the N2 complex (200–300 ms) observed at posterior scalp sites contralateral to the location of a visual search target; it is sensitive to target position and distractor density, and is typically observed for visual search arrays containing targets. Luck and Hillyard (1994a) proposed that it reflects the focussing of attention onto a target to filter out interfering information from nearby distractor items. The N2pc has been used to show that the same attentional mechanisms are invoked independent of the features (color, orientation, motion) that define the target even if these cut across parvocellular (color,

orientation) and magnocellular (motion) pathways specialized for processing those features.

Objects and hierarchical processing. In experimental psychology, a growing number of studies has suggested that objects themselves rather than their spatial locations can serve as the basis for attentional selection (Duncan, 1984; Vecera and Farah, 1994). Several studies using ERPs have examined this hypothesis (Czigler and Balazs, 1998; Valdes-Sosa, Bobes, Rodriguez and Pinilla, 1998; Weber, Kramer and Miller, 1997). In one such study, suppression of the P1/N1 components for objects occupying the same spatial location as the unattended object was taken to indicate that object-based attentional selection mechanisms act very early in the visual system (Valdes-Sosa et al., 1998). These types of paradigms have yet to be applied to brain-damaged patients with object agnosia or Balint's syndrome (simultaneous agnosia).

A sizeable literature within neuropsychology has addressed visual objects. While in the real world global (e.g., a forest) and local levels (e.g., the trees) are quite different, most experimental studies of

these aspects of visual objects have been composed of relatively similar elements at both levels (e.g., a large H made up of small A's). Results have shown that patients with lesions at the temporoparietal junction exhibit marked problems with the analysis of global aspects of such stimuli following right-hemisphere lesions and local aspects following left-hemisphere lesions (Robertson, 1995; Robertson, Lamb and Knight, 1988).

In addition to the temporoparietal areas, neuroimaging data have implicated secondary visual areas in the extrastriate cortex in global/local processing (Fink, Halligan, Marshall et al., 1997). It is important to note, however, that the inferences that can be drawn from neuroimaging studies are limited in that an individual's attention can be directed to only one level at a time. By contrast, in a divided attention task using electrophysiological measures, it is possible to study the concurrent processing of both the local and the global levels of the stimuli simultaneously. In so doing, Heinze and Münte (1993) found that a negativity between 150 and 300 ms with a maximum at temporoparietal sites was sensitive to the detection of target letters. This selection

negativity was greater over the left than right hemisphere for the detection of targets at the local level and larger over the right than left hemisphere for the detection of targets at the global level. While we cannot assume that potentials over one hemisphere are necessarily generated in the underlying hemisphere, these data do show differential lateralization for local and global visual processing. Heinze, Matzke, Dorfmueller and Smid (1997) used this same task to investigate patients with malignant brain tumors including the temporoparietal junction, and found a clear dissociation: right-hemisphere patients had a much-attenuated selection negativity for targets at the global level, while left hemisphere patients were characterized by the reverse pattern (see Fig. 10).

Face processing. Faces are visual objects of great personal and social significance. Researchers disagree on how different face processing is from processing of other highly practiced, complex visual objects. Evidence for a neural system specific to face recognition was first provided by individuals with mostly right-sided occipitotemporal damage, who had a specific impairment in face processing; such patients are referred to as prosopagnosics

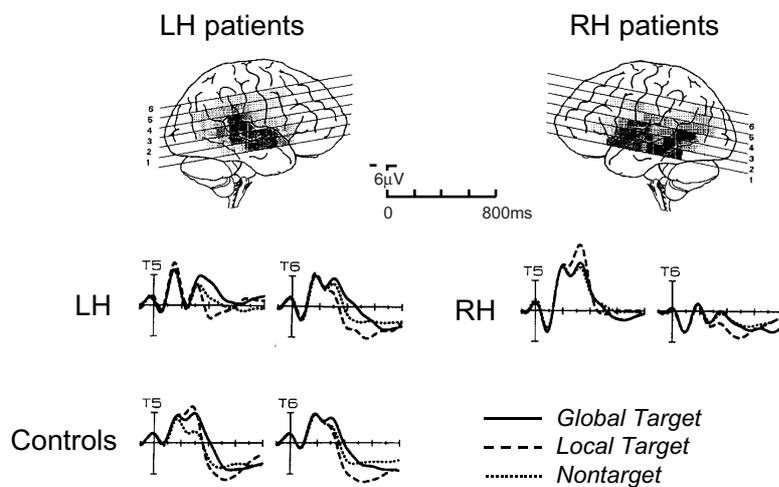


Fig. 10. Data from a task assessing global and local target detection. Stimuli comprised large letters (global level, e.g., the letter H) made up from smaller letters (local level, e.g., letter S). In any given run, one letter was designated as the target letter to which subjects were asked to press a button regardless of level. In control subjects, the response to target letters includes a prominent selection negativity around 200 to 350 ms over temporo-posterior scalp sites. This selection negativity is reduced in amplitude for targets at the local level in patients with left temporoparietal tumors and for targets at the global level in patients with right hemisphere lesions. This pattern of results is consistent with the proposed hemispheric specialization of the right and left hemispheres for global and local information processing, respectively (adapted from Heinze et al., 1997).

(Bodamer, 1947; De Renzi, 1996). While some prosopagnosics are specifically impaired in identifying familiar faces, others show selective deficits in the recognition of gaze direction (Campbell, Heywood, Cowey et al., 1990; Newcombe, 1979; Perrett, Smith, Potter et al., 1985), social expression (Kucucz and Feldmar, 1979) or lipreading (Campbell, Brooks, De Haan and Roberts, 1996; Campbell, Landis and Regard, 1986). In an attempt to account for these selective deficits, neuropsychological models have fractionated face recognition into several sub-functions (Bruce and Young, 1986). Facial features are specified and analyzed during an initial stage of structural encoding, the products of which then presumably are delivered to various independent modules dedicated to the analysis of facial expression and speech as well as face recognition. This type of model has found support in studies of neuropsychological patients and non-human primates (for review see Desimone, 1991). In humans, functional imaging studies using PET and fMRI have revealed bilateral albeit right predominant activation in the posterior fusiform gyrus in response to faces compared to other objects or textures (Clark, Keil, Maisog et al., 1996; Haxby, Horwitz, Ungerleider et al., 1994; Kanwisher, McDermott and Chun, 1997; McCarthy, Puce, Gore and Allison, 1997; Puce, Allison, Gore and McCarthy, 1995; Sergent, Ohta and MacDonald, 1992).

Electrophysiological studies in humans have helped to delineate the time course of the neural activity reflecting facial processing. Subdural recordings (in individuals with epilepsy) have revealed a negative potential at a latency of 200 ms (N200) in left and right fusiform and inferior temporal gyri in response to faces but not to other complex stimuli such as scrambled faces, cars or butterflies (Allison, Ginter, McCarthy et al., 1994; Puce, Allison, Spencer et al., 1997). Jeffreys (1989; Jeffreys and Tukmachi, 1992) described a vertex positive potential at the scalp with a peak latency of between 150 to 200 ms, which he suggests is specific to faces. Schendan, Ganis and Kutas (1998) found that the P150 amplitude varies with the cumulative experience people have discriminating among instances of specific categories of visual objects (e.g., words, faces), and suggested that it may be a scalp reflection of letter-string and face intracranial ERPs in posterior

fusiform gyrus. Bentin, Allison, Puce and McCarthy (1996) recorded a negative potential over posterior temporal sites at a latency of 172 ms (N170) that was selectively evoked by faces, however, as it was delayed by face inversion and significantly larger to isolated eyes, it might reflect eye-specific instead of whole face-processing.

Münte, Brack, Grootheer et al. (1998a) contrasted the ERPs elicited as individuals matched successively presented pairs of faces (frontal and side-views) for identity and for expression (see Fig. 11). Identity matching affected a fronto-central negativity in the 200–400 ms range, whereas expression matching had a later effect with a parietal maximum.

The combination of functional imaging and event-related brain potential data provide a very detailed picture of face processing in humans: Initial feature analysis and encoding, including the analysis of gaze seem to take place in secondary visual areas of the fusiform gyrus at latencies between 100 and 200 ms. Later visual analyses, such as the determination of a person's identity are carried out by anterior temporal and possibly frontal brain area at latencies beyond 200 ms. Later still, it appears likely that multiple brain regions are recruited in the analysis of emotional expression. These findings thus are of sufficient specificity to be useful for investigating prosopagnosic patients with various impairments.

In a recent report of a rare case of developmental prosopagnosia, Bentin, Deouell and Soroker (1999) found that the N170 component was elicited by all sorts of visual objects and thus was not specific to faces. This patient had an abnormally small right temporal lobe. These data suggest that at least this rare kind of prosopagnosia might arise from abnormal encoding of basic visual features. Finally, Renault, Signoret, Debrulle et al. (1989) have capitalized on the sensitivity of the P300 to categorization and subjective probability to demonstrate covert recognition of familiar faces in an individual with acquired prosopagnosia.

Auditory perception and attention.

Auditory selective attention. One of the most powerful paradigms in experimental psychology, based on dichotic listening, has been adapted for use in electrophysiological studies of selective attention. In the basic task at least two 'channels' of

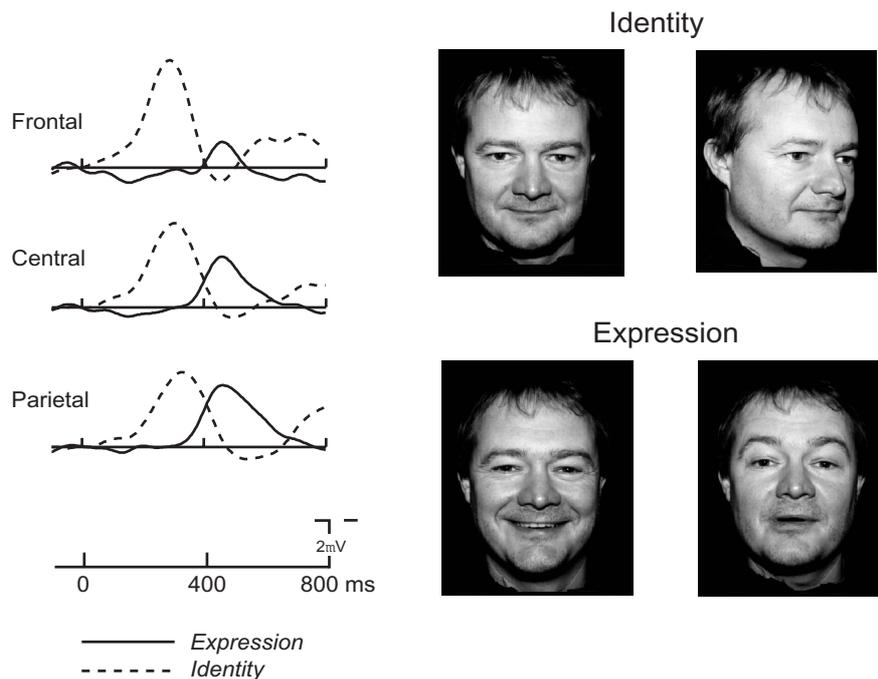


Fig. 11. In this study, young healthy adults were asked to compare pairs of successively presented faces either for identity (same person or not?) or for expression (same or different). Shown are the difference ERPs (nonmatching minus matching) for the second stimuli of the pairs. These difference ERPs show a very early effect of identity, beginning at about 150 ms, and a later effect of expression judgment (350 ms). Note the effects also differ in their scalp distribution (based on Münte et al., 1998a).

information are presented rapidly, e.g., tones in the left and right ears. Channels can be defined by location (Hansen and Hillyard, 1980), pitch (Alho, Sams, Paavilainen and Näätänen, 1986), movement (Okita, 1987) or a combination of features (Hansen and Hillyard, 1983). Participants are required to attend to one of the channels in order to detect relatively infrequent, target stimuli interspersed among the other, more frequent standard or background stimuli in the attended channel while ignoring all stimuli in the other channel. Attended tones (or in other experiments phonemes) give rise to a more negative ERP waveform starting approximately 100 ms after onset of the stimuli (see Fig. 7). There has been some controversy as to whether this includes both a modulation of the N1 generated in the superior temporal plane in the auditory cortex (the so-called N1 attention effect) and an endogenous negativity that overlaps the N1. This additional endogenous negativity called the negative difference (Nd) or processing negativity (PN) extends for several hundred

milliseconds (see Fig. 7). On the grounds of its scalp-distribution, the Nd has been divided into two subcomponents — an early part up to about 250 ms with a slightly contralateral distribution and a later, symmetrical aspect.

In contrast to the visual modality, wherein location has a special status relative to other features, ERP attention effects in the auditory modality are rather uniform in morphology for different auditory features (pitch, timbre, loudness, duration), although Nds associated with different features do have slightly different scalp distributions (Woods, Alho and Algazi, 1994). For example, Szymanski, Yund and Woods (1999) noted that the size of the asymmetry in the Nd elicited by the same consonant–vowel–consonants was a function of whether the task called for a phonetic discrimination or an intensity judgment. From these data, the authors concluded both hemispheres are specialized for phonetic analysis, but that special left hemisphere processes come into play during the final stages of phoneme processing.

One wonders how dyslexics and individuals with language deficits would respond in such a paradigm.

The Nd has also been used to study plasticity, specifically functional reorganization of auditory attention in the congenitally blind. Although neither the Nd nor the mismatch negativity (MMN, see below) were found to differ between the blind and sighted controls, there was a prolonged negativity that appeared only in the ERPs of the blind. The authors concluded that plasticity in these blind individuals involved progressive recruitment of parietal and then occipital regions (Liotti, Ryder and Woldorff, 1998).

Woods, Knight and Scabini (1993) observed reduced Nds over both hemispheres in patients with damage to the temporo-parietal junction and over the lesioned hemisphere in patients with damage to the inferior parietal lobe. Knight, Hillyard, Woods and Neville (1981) found that the auditory Nd was smaller than normal in patients with frontal brain lesions. Pursuing the notion that amyotrophic lateral sclerosis (ALS) patients also are somewhat impaired in tests that index frontal lobe functions, Vieregge, Wauschkuhn, Heberlein et al. (1999) likewise found reduced auditory Nds in their ALS patients, along with functional motor impairments. Parkinson's disease patients also generate smaller than normal auditory ERP attention effects, albeit only at slow presentation rates (1/s) (Vieregge, Verleger, Wascher et al., 1994). Taken together, these data suggest that disorders that involve the frontal lobe and more specifically the frontal supervisory attention system lead to difficulties with auditory attention. For those conditions, like Parkinson's disease, that can be treated pharmacologically, the question arises as to whether electrophysiological measures may aid in treatment decisions and supervision.

Auditory sequence processing. An electrophysiological phenomenon that has generated much theoretical and clinical interest is the mismatch negativity (MMN). The MMN is usually recorded in passive listening situations with individuals attending something other than the eliciting stimuli, e.g., reading a book while auditory stimuli are played in the background (reviewed in Näätänen, 1992). The MMN occurs with an onset latency of about 130 ms and lasts to about 250–300 ms. It is evoked by physically deviant stimuli (frequency, duration, intensity, rise time, phonetic structure) occurring among

frequent ('standard') stimuli (Näätänen, 1995). The MMN presumably reflects automatic detection of the change in the sequence (Näätänen, 1992).

It has been argued that the MMN is not merely a response to novelty that results from firing non-refractory neurons that are selectively responsive to new features because a large MMN also follows a reduction in stimulus intensity. The claim instead is that the MMN response reflects the change per se, against the background of information recently encoded in a short term sensory memory store (Näätänen, 1992, pp. 140–141). In other words, the MMN is presumably generated by a mismatch process between the sensory input from a deviant stimulus and a neural sensory-memory trace representing the physical features of the standard stimulus. It is not surprising that a sensory system that has evolved in a dynamic environment would be tuned to represent changes in that environment. This process, as well as sensory analysis of auditory input and its encoding into the memory trace, appear to be automatic since the MMN is elicited even when changes occur in stimuli that are unattended, such as during sleep (Loewy, Campbell and Bastien, 1996; Winter, Kok, Kenemans and Elton, 1995). In this respect, the MMN is unlike otherwise similar negative potentials evoked by deviant stimuli. For instance the broadly distributed central N2b is elicited by deviant stimuli but only when they are attended unless the deviation is unusually large (Näätänen, Simpson and Loveless, 1982).

More recently, it has been shown that the MMN also can be elicited by complex stimuli, e.g., mismatches in rhythmic patterns or systematic pitch changes (Alain, Achim and Woods, 1999a; Alain, Cortese and Picton, 1999b). The MMN thus offers the unique possibility of an objective measure of the central representation of a sound. The MMN paradigm also provides a means of assessing the discriminative capabilities of individuals whose auditory capacities are otherwise difficult to determine, including infants (Choer-Luhtanen et al., 1995), young children (Ceponiene, Cheour and Näätänen, 1998) and those with severe cognitive impairment or in coma (Fischer, Morlet, Bouchet et al., 1999). MMN also has been used to track cognitive changes in deaf subjects after implantation of a cochlear hearing device (Groenen, Snik and Van den Broek, 1996).

Both the temporoparietal and dorsolateral prefrontal cortex have been implicated in MMN modulation and/or generation. Temporoparietal lesions lead to a reduced MMN following stimulation of the ear contralateral to the lesioned hemisphere along with impaired performance, suggesting that auditory sensory memories are predominantly stored in auditory cortex contralateral to the ear of presentation. Dorsolateral prefrontal damage likewise impaired performance and reduced MMNs, albeit to deviant stimuli in either ear (Alain, Woods and Knight, 1998). Alain et al. (1998) proposed a temporoparietal and frontal neocortical network in the transient storage of auditory stimuli. These anatomical uncertainties notwithstanding, because of the minimal requirements with regard to patient cooperation and its well-defined psychological links, the MMN is one of the most promising components for future research in neuropsychology.

While the MMN indexes stimulus deviance, another ERP component, termed P3a, has been found to reflect stimulus novelty (Courchesne, Hillyard and Galambos, 1975). Knight, Scabini, Woods and Clayworth (1989) found that the P3a response was abolished by discrete unilateral lesions in the posterior superior temporal plane. Recent magnetoencephalographic recordings (Alho, Winkler, Escera et al., 1998) also have implicated the superior temporal plane of the auditory cortex in its generation. Intracerebral recordings in possible candidates for epilepsy surgery by Halgren, Baudena, Clarke et al. (1995a,b) have revealed a multifocal neural network (comprising the posterior cingulate, supramarginal gyrus, temporal pole, middle temporal area, posterior parahippocampal and fusiform gyrus) that exhibits characteristics similar to those of the scalp P3a.

A typical situation for the elicitation of the P3a is the presentation of occasional sounds, such as a dog's bark or the honking of a car, in a sequence of tone bursts. This situation has parallels to the conditions necessary to obtain an orienting response (Sokolov, 1990). The P3a has a more frontal distribution and a shorter latency (250–300 ms) than the P3b (P300) component. In keeping with neuropsychological evidence regarding the functions of prefrontal cortex, the P3a has been found to be attenuated in a group of patients with prefrontal cortex damage (Knight, 1984).

Music and disorders of music perception. Music is a highly structured multidimensional auditory signal. Disorders of music perception and production represent a largely neglected area of neuropsychology, due in part to the immense variability in musical skills across individuals. This has been remedied in recent years as a number of investigators have described specific disorders of music processing (e.g., Basso, 1999; Liegeois-Chauvel, Peretz, Babai et al., 1998; Schuppert, Münte, Wieringa and Altenmüller, 2000), and still others have examined neurophysiological correlates of music perception. In an elegant series of studies, Besson and co-workers (Besson, Faita and Requin, 1994; Besson and Macar, 1987; Patel, Gibson, Ratner et al., 1998) recorded ERPs to various musical incongruities (harmonic, rhythmic, melodic) in musicians and non-musicians, and observed late positivities of varying amplitudes in contrast to the negativity (N400) observed in parallel experiments with lexical semantic anomalies in the language domain. Although musicians were faster than untrained subjects in detecting these incongruities, their ERP congruity effects were similar to those observed in non-musicians, suggesting that similar processes are involved in 'making sense' of notes and the music of which they are a part.

Insofar as there are any, auditory processing differences between musicians and non-musicians, these occur in earlier, pre-semantic levels of processing. For example, Koelsch, Schröger and Tervaniemi (1999) and Tervaniemi, Ilvonen, Karma et al. (1997) found that musicians elicited larger MMNs (used as an index of preattentive auditory processing) to occasional changes in the temporal structure of a repetitive sound pattern than did non-musicians when each group read a book. In a different study of selective attention to pitch, the Nd as the correlate of selective auditory attention was found to be prolonged and of higher amplitude in musicians compared to non-musicians, suggesting that musicians processed the sounds more thoroughly and extensively.

In a group of unselected hemispheric stroke patients, Münte, Schuppert, Johannes et al. (1998c) recorded ERPs in a four stimulus oddball paradigm comprising frequent standard tones ($p = 0.7$), infrequent target tones ($p = 0.1$), infrequent irrelevant non-target tones ($p = 0.1$) and infrequent novel sounds ($p = 0.1$). All patients showed a decrease of

the P3b component, which was interpreted as an index of controlled processing. However, only patients who were identified via a test battery as having music processing difficulties showed an amplitude decrease for the P3a component, taken as an index of preattentive orienting to novel sounds. These data suggest that music perception deficits are more widespread than previously thought, with at least some arising from basic deficits in auditory processing.

As the neuropsychology of music is still in its infancy, so is the electrophysiology of amusia. ERPs might help to distinguish between lesions that involve domain general cognitive processes (such as the orienting and mismatch responses) and those that involve dysfunction(s) in a dedicated music processing network.

Memory

Memory is an important property of the mind/brain that impacts many aspects of information processing in all cognitive domains in both the short- and long-term (see Johnson, 1995 and Rugg, 1995 for reviews on the electrophysiology of memory).

Working memory: short-term memory process. Working memory holds, tags, or activates sensory input and information retrieved from long-term memory for current processing. A number of questions concerning the information processing properties of this short-term store have been addressed with ERPs. As already mentioned, changes in the contents of sensory memory can be reflected in components such as the MMN elicited by unattended deviant stimuli in a sequence of standard auditory stimuli.

Working memory also actively maintains information and this information can be changed or updated. It has been proposed that the P300 scalp potential — a positive waveform broadly distributed across the scalp with a posterior maximum and a peak around 300 ms post-stimulus for relatively simple categorization — indexes this information processing function (Donchin and Coles, 1988). The P300 can be elicited by low probability deviant stimuli in a sequence of standard, higher probability stimuli (i.e., an oddball paradigm) when the deviant events are attended (see Fig. 12), although it can be elicited by the absence of an expected stimulus as well.

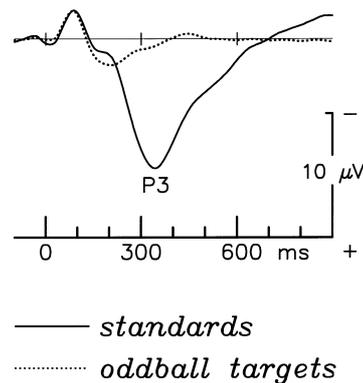


Fig. 12. Grand average ERP from midline parietal site (Pz) to a high frequency target or oddball tone occurring infrequently (20%) in a Bernoulli sequence interspersed with low frequency standard tones. Oddball tones were responded to by a button press. Note the large positivity (P3) around 400 ms to the oddball target.

As long as the stimulus sequence is attended, its amplitude to oddball or target events is inversely related its probability of occurrence; oddball P300 amplitude is also affected by the interval between targets (temporal probability), its global probability across an entire block of trials, the fine structure of the stimulus sequence (stimulus probability), as well as by the nature of the immediately preceding event (local probabilities). It is important to note that subjective probability is more important in determining P300 amplitude than is objective probability. For example, in an oddball task when more than two different stimuli are involved, P300 amplitude is determined by the probability of the relevant stimulus category rather than the probability of any given stimulus. It is assumed that when the deviants or targets are encountered in an oddball task, the current deviant count maintained in working memory must be incremented by one, and a model of the environment modified and updated as well; when this happens a P300 is elicited. The original reports talked in terms of resolution of uncertainty, and this notion is still valid (Sutton, Braren and Zubin, 1965). Similar effects, albeit with different distributions and latencies, have been found in visual, auditory (e.g., Squires, Squires and Hillyard, 1975), and olfactory (Pause, Sojka, Krauel and Ferstl, 1996) modalities (for review see Pritchard, 1981).

It seems unlikely that 'the P300' is 'the' at all; rather these widely observed positive wave-

forms seem to have multiple neuronal sources implicated in a variety of cognitive processes (e.g., Frodl-Bauch, Bottlender and Hegerl, 1999; Halgren et al., 1995a,b; Johnson, 1993; McCarthy, Nobre, Bentin and Spencer, 1995). Debates about the fine-grained cognitive interpretation of the waveforms notwithstanding, broadly distributed positive waveforms with peaks occurring after about 300 ms (or at least deflections that are more positive in an experimental condition relative to a suitable control condition) are reliably elicited by attended stimuli in a huge variety of experimental manipulations ranging from deviant tone pips in a sequence of standards through violations of rules of grammar in sentences (e.g., Coulson, King and Kutas, 1998).

What initially appeared to be a broadly distributed positivity can be dissociated into at least two (probably 3) major parts which have been labeled the P3a and the P3b (and slow wave or SW). The P3 complex is often preceded by a modality-dependent negativity (N200) and followed by a slow wave that is posteriorly positive and anteriorly negative. The P3 complex is most often used to address questions about the flow of information processing, especially mental chronometry. P3b latency varies systematically with the difficulty of the categorization task such that a very difficult categorization may well elicit a P3b with a peak latency around 600 ms (e.g., Kutas, McCarthy and Donchin, 1977). Variables such as stimulus-response compatibility that alter the timing of response processes have very little, if any effect on P3b latency, whereas manipulations that increase the difficulty of perceptual discriminations and categorizations do (McCarthy and Donchin, 1981). Thus the P3b, in particular, has been linked to stimulus evaluation and stimulus categorization processes. Its amplitude has traditionally been used to estimate the amount of attentional capacity that is being devoted to the categorization at hand, especially within dual task paradigms (Isreal, Chesney, Wickens and Donchin, 1980a; Isreal, Wickens, Chesney and Donchin, 1980b).

Although it has been proposed that the P3b indexes the update of working memory, not everyone agrees (Picton, 1992; Verleger, 1988). As always, the plausibility of the working memory update hypothesis, or any other, must be assessed against the enormous body of research with this paradigm. For

reviews and discussion see Johnson (1986), Polich and Kok (1995) and Verleger (1988, 1997). P3b recordings in patients with focal brain lesions and intracranially from individuals with temporal lobe epilepsy implicate many brain areas in P3b modulation if not its generation. Halgren et al. (1995a,b), for example, concluded that the P3 represents a widespread corticolimbic modulation of the systems responsible for orienting attention toward a possibly significant stimulus, as well as for the subsequent encoding of that stimulus into a cognitive event. Such findings are consistent with both the idea that the P3b reflects the activity of a general-purpose processor and the view that the scalp P3b reflects the sum of several different generators and associated processes (see Frodl-Bauch et al., 1999 for a review of neurochemical substrates of the P300).

Working memory retention. How information is actively maintained in working memory is a central question and Baddeley, for instance, has proposed distinct subsystems: a central executive, a visuo-spatial sketch pad for retaining visual information, and a phonological (nee articulatory) loop for maintaining a representation of verbal material (Baddeley, 1986, 1992). We all know that two good ways of maintaining information even temporarily is to rehearse the information or form some image of it. In a laboratory setting, Baddeley and colleagues found that many verbal short term memory effects could be explained in terms of an articulatory loop about 2 seconds long. In addition, there are some combinations of two or more tasks that can be performed simultaneously without much interference as long as one is non-verbal if the other is verbal. The lack of interference in such dual task situations thus points to the existence of independent short term buffers for verbal and non-verbal (e.g., spatial) information. Certainly, visual imagery and mental scanning effects call for some sort of spatial buffer.

Ruchkin and colleagues (Ruchkin, Berndt, Johnson et al., 1997, 1999; Ruchkin, Canoune, Johnson and Ritter, 1995; Ruchkin, Johnson, Grafman and Canoune, 1992) found that the scalp topography of slow wave activity (on the order of seconds) during the S1–S2 retention interval is sensitive to the type of information retained in a way that is consistent with the hypothesis that the different working memory subsystems differentially engage the vi-

sual and auditory cortices. In particular, during the retention interval the slow wave associated with retention of phonological information (pronounceable non-words) appears maximal over left-frontal scalp whereas that for visuo-spatial information the slow wave appears largest over right central parietal scalp.

Working memory search. In addition to retaining types of information for short periods of time, working memory is also thought to make information available to other cognitive processes. This raises the questions of how the information is made available and the nature of the search process. In an important series of reaction time memory scanning studies, Sternberg (1966, 1969, 1975) varied the number of digits to be retained in working memory. Upon presentation of a probe digit, volunteers were asked to decide whether or not the probe belonged to the memory set just presented. The standard finding is that negative determinations take longer overall but that both negative and positive determinations increase with set size at the same rate. This pattern of reaction time data can be explained if comparison of the probe with the contents of working memory is an exhaustive serial search (i.e., comparison of the probe with items in memory continues even after a match has been found) and the binary choice of a negative determination takes longer than the positive determination.

The latency of the late positive scalp potentials (P300) elicited by the probe digit in this paradigm also varies systematically with set size, but only at about half the rate of the reaction times (Ford, Roth, Mohs et al., 1979). Partial dissociations between ERPs and reaction time are commonplace (Coles, Smid, Scheffers and Otten, 1995). In any event, they must be explained by any theory of memory scanning in this particular case and by any account wherein a particular experimental manipulation is hypothesized to act at a specific locus of in the processing system in the more general case. Two measures provide more constraints on theorizing than one, and once a specific theory of normal information processing is articulated, its generalizability can be assessed within various patient subgroups presumed to have specific processing deficits.

Long term memory in healthy individual. Years of research have shown that how information is en-

coded has significant consequences on whether or not, and, if so, how readily that information is later remembered. ERP studies were the first to allow researchers to examine the time course of encoding for items as a function of subsequent success at memory retrieval — that is, to track encoding processes as they took place. As researchers traditionally record ERPs during study, this type of analysis requires that the events during encoding be averaged selectively as a function of later performance during the memory test. This type of analysis can be done not only for the memory of an item in its entirety but also for certain attributes of the item or the context wherein it occurred (i.e., source memory). Again, ERPs allow examination of the time course of the encoding and retrieval processes not just during successful attempts but, critically, during failed (unsuccessful and false memory) attempts as well.

By its nature, ERPs are well-suited for testing the various theories about different memory systems and different implicit and explicit memory processes. In fact, ERPs can be used to track learning within a session, across several sessions, or in a lifetime of normal or abnormal experiences. Of the many ERP studies of memory, we focus, here, on encoding and retrieval in brain intact individuals as well as in individuals with organic brain abnormalities including damage to the temporal lobes, epilepsy, and Alzheimer's dementia.

Encoding processes. From behavioral measures alone it is difficult to tease apart the contributions of encoding and retrieval processes on successful memory performance because the effects of encoding variables must be inferred from retrieval measures. By their very nature, therefore, behavioral indices can provide only an indirect measure of encoding manipulations. ERPs, on the other hand, provide a direct measure of brain activity during encoding and thus offer the possibility of isolating its specific contributions. In line with what has generally been assumed, ERP data collected to date indicate that brain activity during encoding is in fact critical in determining whether (and what aspects of) an item will be later remembered or forgotten.

According to the levels of processing framework, a memory trace is a by-product of perception and comprehension. Intent to remember, per se, is not important; rather what is remembered is a function

of what is encoded, which in turn is a function of how the event is initially processed (Craik and Lockhart, 1972). 'Deep' or semantic processing (e.g., living/nonliving or concrete/abstract judgments) is presumed to establish more links between the current episodic context and the experimental item than 'shallow' processing as in graphemic or orthographic judgments, thereby affecting the quality of the retrieval that is subsequently possible. When retrieval requires that a person explicitly reflect on the encoding experience, semantic processing leads to a better recognition and recall than nonsemantic processing. On the other hand, if memory is measured without direct reference to the encoding event, i.e., implicitly, as in a perceptual identification task, the nature of initial encoding seems to make little difference to memory performance (Gardiner, Java and Richardson-Klavehn, 1996; Graf and Schacter, 1985; Rajaram, 1993; Roediger, Weldon and Challis, 1989; Schacter, 1987).

The ERP to items processed deeply are more positive between 400 and 800 ms post stimulus onset than are those processed shallowly (Fabiani, Karis and Donchin, 1990; Paller, Kutas and Mayes, 1987; Sanquist, Rohrbaugh, Syndulko and Lindsley, 1980; Van Petten and Senkfor, 1996). Insofar as this late positivity reflects brain activity critical for successful encoding into episodic memory, we might expect it to be larger for items that are later remembered than for those that are later forgotten, and it is. Paller et al. (1987), for example, found that the ERPs to items during encoding did differ as a function of whether or not they were later remembered; this ERP encoding effect has been dubbed the difference due to memory or the ' D_m ' effect (Paller et al., 1987). In the Paller et al. study (as well as many others since) the D_m -effect comprised an increased late positivity for to-be-remembered words between 400 and 800 ms maximal over left parietal sites; this D_m was larger in the semantic task (living/nonliving?) than in the non-semantic alphabetic task (are the first and last letters of each word in alphabetical order?), and larger for items associated with an affirmative than a negative decision.

Van Petten and Senkfor (1996) hypothesized that the late positivities in these types of levels of processing memory tasks reflect the retrieval of information related to the to-be-remembered item from

'secondary' (long-term) memory. They tested this hypothesis by comparing the memory-related ERP effects to meaningless visual patterns to those for meaningful words. This contrast is predicated on the assumption that elaborative encoding could make contact with preexisting knowledge for words only, as no such knowledge exists for novel visual patterns. The results supported their hypothesis: words were associated with a large D_m effect whereas a comparison of the encoding ERPs to the novel visual patterns that were later remembered versus forgotten yielded none. Moreover, the D_m to words was larger in association with affirmative than negative decisions (see also Paller, McCarthy and Wood, 1988), which Craik and Tulving (1975) have attributed to a greater richness of elaboration for positive decisions. The data thus supported the conclusion that the amplitude of the late positivity during encoding in this type of experiment is an index of the richness of associative elaboration engendered by the to-be-remembered event, and that this elaboration relies on retrieval from long-term semantic memory.

It is important to note, however, that in different studies there may be different reasons, even if they are all encoding related, that an item may later be remembered or forgotten. Thus, there is no reason *a priori* to assume that all D_m effects reflect the same process. Certainly, they do not. Data collected across many different studies indicate substantial variability in the onset latency, duration, and scalp topography of D_m effects (Besson and Kutas, 1993; Fabiani and Donchin, 1995; Fabiani, Karis and Donchin, 1986; Fernandez, Weyerts, Tendolkar et al., 1998; Johnson, Pfefferbaum and Kopell, 1985; Karis, Fabiani and Donchin, 1984; Münte, Heinze, Scholz and Künkel, 1988; Neville, Kutas, Chesney and Schmidt, 1986; Paller, 1990; Paller and Kutas, 1992; Paller et al., 1987, 1988; Van Petten and Senkfor, 1996). For example, the D_m effect was observed to be larger over the right frontal sites in some studies (Fernandez et al., 1998) and larger over left parietal sites in others (Paller et al., 1987). It is best to think of the D_m effect as involving different neural structures depending on the nature of the encoding task and context.

Encoding processes also have been investigated in the context of a Von Restorff (1933) paradigm wherein occasional deviant items within an experi-

mental list appear to be preferentially encoded ('isolates'), and therefore better remembered (Donchin and Fabiani, 1991; Fabiani et al., 1986, 1990; Fabiani and Donchin, 1995; Karis et al., 1984). Whether physically or semantically deviant, the 'isolates' elicited P300s; the amplitude of the P300 to the isolates correlated with free recall performance. The authors proposed a two stage model of encoding wherein deviance in features first elicits an N400, which is followed by a context updating (elaborative) process indexed by the P300. Although not the same as Tulving's (Tulving, Markowitsch, Craik et al., 1996) two stage model of encoding of novel events, this proposal is similar in arguing for two stages.

Some evidence for two stages of encoding can be found in the report of Fernandez, Effern, Grunwald et al. (1999), who recorded ERPs from intracranial depth electrodes implanted in the medial temporal lobes of patients with therapy-resistant epilepsy. They observed a functional coupling between two distinct D_m effects: a perirhinal N400 and intrahippocampal late positivity, both of which were higher in amplitude during encoding of words that would subsequently be recalled versus those that would be forgotten.

Retrieval processes. The recent past has seen a significant increase in the number of electrophysiological investigations of memory retrieval processes. Some of these have been aimed at establishing ERP indices of retrieval processes during repetition and recognition so that these could then be used as tools for assessing the functional integrity of such processes in the damaged brain. Yet others have been aimed at using the ERP to provide a better understanding of the functional contribution of the various brain areas that neuroimaging studies have implicated in memory retrieval.

Electrophysiological studies of retrieval are conducted against a backdrop of a detailed and elaborate model of memory based on neuropsychological patients with selective memory deficits and associated areas of brain damage. These have revealed that there is no unitary cortical area dedicated solely to the storage of memory; rather, different aspects of events are stored at the specific cortical sites that analyzed those aspects initially. Amnesia results from damage to the midline diencephalon or the medial

temporal lobe which is specifically involved in memory consolidation. For example, bilateral lesions of the medial temporal lobes, as in H.M., are associated with a severe impairment in the ability to remember new events and facts (Milner, Squire and Kandel, 1998; Squire and Zola-Morgan, 1991). In these patients, this deficit in declarative memory can be contrasted with preserved nondeclarative memory such as normal procedural learning.

Tulving has proposed that declarative memory be further subdivided into episodic and semantic memory (Tulving, 1985; Wheeler, Stuss and Tulving, 1997). Episodic memory refers to context-rich, time- and space-stamped memories characterized by a mental 're-living' of personal episodes. Semantic memory refers to the world knowledge that lacks personal episodic contextual information. Recent evidence by Vargha-Khadem, Gadian, Watkins et al. (1997) suggests an anatomical distinction between the two: relatively isolated bilateral hippocampal damage that occurred early in life left one individual with no memory for personal episodes although he could acquire new facts (such as the names of new members of Parliament).

Episodic (autobiographical) memory is assessed via explicit tasks such as free recall, cued recall, and recognition. These forms of retrieval make reference to a particular episode in an individual's life (Jacoby and Dallas, 1981), and are considered direct (Johnson and Hasher, 1987), episodic (Tulving, 1972), explicit (Schacter and Graf, 1986) or intentional memory (for a review see Richardson-Klavehn and Bjork, 1988). Explicit tasks can be contrasted with implicit retrieval tasks (Schacter, 1987) which make no reference to a particular episode and tap nondeclarative memory processes. Implicit tasks make it possible to demonstrate that a prior event facilitates behavior without concurrent recognition, a phenomenon that is referred to as repetition priming (Tulving and Schacter, 1990). A hallmark of the human amnesic syndrome is the presence of a normal or near-to-normal priming on a number of implicit memory tests in the face of severely impaired performance on explicit tasks (Graf and Schacter, 1985; Squire and Zola, 1997; Warrington and Baddeley, 1974). The different patterns of brain activity involved in implicit and explicit retrieval have therefore been an important target of investigation in many ERP studies.

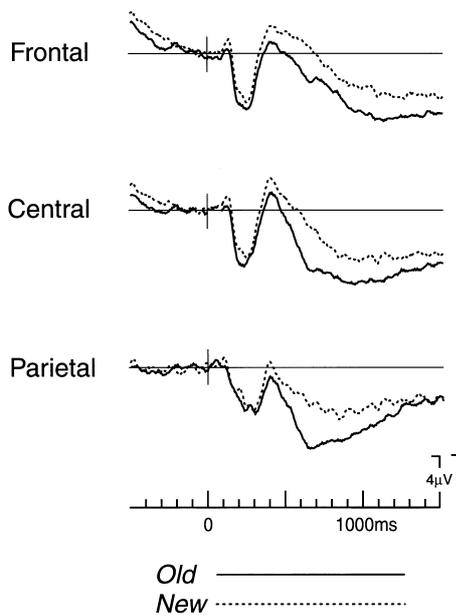


Fig. 13. Grand average ERPs from midline scalp to words correctly recognized as having been presented during a previous study session (Old) and to words correctly identified as not having been previously studied (New). The potentials elicited by the Old words are more positive, particularly over parietal scalp (Urbach, Payne and Blackwell, 1996).

Explicit and implicit recognition memory. In a typical retrieval paradigm items are presented twice and ERPs to first and second (i.e., repetition) presentations are compared. In an implicit memory test, subjects perform a task wherein old (repeated)/new distinction is irrelevant; these typically include lexical decision, semantic judgment, identification of visually degraded words. By contrast, in an explicit memory test subjects are asked to recognize and detect the repeated items (see Fig. 13).

As most repeated items are also recognized by healthy adults, even under implicit testing conditions, we refer to these as ERP repetition/recognition effects. Across studies, the ERPs to repeated/recognized items differ from those to newly presented ones in two and sometimes three features. In the order of their timing these are: (1) a decrease of the amplitude of a negativity between 300 and 500 ms (N400); (2) an increase in the amplitude of a late positivity between 500 and 800, referred to here LPC (Düzel, Cabeza, Picton et al., 1999; Düzel, Yonelinas, Mangun et al., 1997; Paller, Kutas and McIsaac,

1995; Sanquist et al., 1980) but also known as P300 (Donchin and Fabiani, 1991; Fabiani and Donchin, 1995), late positivity (Donaldson and Rugg, 1999) or 'parietal old/new effect' (Rugg, Schloerscheidt, Doyle et al., 1996); (3) a right frontal positivity from 300–1900 ms (Donaldson and Rugg, 1999; Düzel et al., 1997; Senkfor and Van Petten, 1998; Wilding and Rugg, 1996, 1997).

The exact functional roles of the processes leading to each of these effects at the scalp during memory retrieval are still under investigation. Some of the specific questions raised include: (1) which component(s) is correlated with repetition in the absence of conscious recognition and which is correlated with repetition in the presence of conscious recognition; (2) how do the various ERP effects relate to different qualities of recognition such as recollection and familiarity (Jacoby, Toth and Yonelinas, 1993), or remembering and knowing (Gardiner and Java, 1993). Does the behavior of various memory-related ERP effects provide any evidence for the proposed division of declarative memory into episodic and semantic?; (3) which if any of these memory-related components index post-recognition processes loosely called 'monitoring'? Some of the studies conducted to answer such questions are sampled below. These include studies not just of simple recognition judgment but also of source retrieval (Senkfor and Van Petten, 1998; Wilding and Rugg, 1996, 1997), retrieval of detailed item-information (Ranganath and Paller, 1999), manipulations of post-retrieval decision-making processes (Donaldson and Rugg, 1998; Düzel et al., 1997; Wilding and Rugg, 1996, 1997) and introspections about retrieval awareness within a remember/know paradigm (Düzel et al., 1997; Smith, 1993).

Repetition versus recognition. To assess which part of the ERP repetition/recognition effect signifies repetition as opposed to recognition, a direct comparison of implicit and explicit retrieval is necessary (Rugg, Mark, Walla et al., 1998a) as in Düzel et al. (1997). In the explicit condition subjects performed an old/new recognition judgment on a list of words half new and half repeated. In the implicit condition subjects made living/nonliving judgment on the same materials, except now repetition was task-irrelevant. Repetition modulated both the N400 and LPC in the explicit task but only the N400

in the implicit task. As the frontocentral portion of the N400 repetition effect was still present under implicit instructions, Düzel suggested that it may reflect repetition independent of recognition. Rugg, Walla, Schloerscheidt et al. (1998b) reached the same conclusion by comparing the ERPs to repeated words that were recognized versus those that were classified as 'new', and thus not associated with conscious recognition. They observed a repetition effect in the absence of conscious recognition at frontal sites; the N400 repetition at posterior sites was observed only if the subject recognized the repeated word. Although some researchers have questioned the assumptions of these studies, it appears that the N400 repetition/recognition effects reflects concurrent activity of distributed and functionally dissociable neural populations, and it may be that the frontal portion reflects solely repetition.

Dual processing accounts of recognition. The recent past has seen a proliferation of theories suggesting different types of recognition, presumably with different neural involvement. For example, according to some dual-processing theories of retrieval, recognition can be due either to familiarity (derived for example from perceptual fluency) or to recollection. According to the theory of episodic memory (e.g., Wheeler et al., 1997) episodic recognition or remembering is associated with autonoetic awareness, a recollective experience that is rich in context and characterized by a mental 're-living' of a past episode. Semantic recognition, or knowing is associated with noetic awareness as during the retrieval of factual knowledge that lacks personal episodic contextual information. These two types of recognition can be examined within the remember/know procedure (Gardiner et al., 1996; Rajaram, 1993; Richardson-Klavehn, Gardiner and Java, 1996, 1993). Distinctions between two different types of recognition are also made within the source-monitoring framework of Johnson and colleagues (Johnson, Hashtroudi and Lindsay, 1993). According to this framework, recollection and familiarity are distinguishable in terms of the contextual specificity of the activated memory information (Dodson and Johnson, 1996).

A number of ERP studies have sought evidence for episodic and nonepisodic recognition. Both the remember/know (R/K) and the source monitoring framework have been used (Düzel et al., 1997;

Smith, 1993; Senkfor and Van Petten, 1998; Wilding, Doyle and Rugg, 1995; Wilding and Rugg, 1996, 1997). The fundamental difference between the two approaches is that the R/K procedure is based on a purely subjective first person account of retrieval quality while the source monitoring framework requires the retrieval of a specific piece of contextual information from a particular experimental episode and hence implies retrieval quality from an objective, third person perspective.

Wilding and colleagues (Wilding et al., 1995; Wilding and Rugg, 1996, 1997) conducted a series of source retrieval paradigms in which recollection was conceptualized as successful source retrieval and familiarity as recognition with an incorrect source judgment. ERPs to recognized words with the correct source judgments elicited more positivity than to those with an incorrect source judgment; otherwise the ERPs were similar. Whether the source was based on modality (auditory/visual) or voice gender (man/woman), there was no qualitative distinction between responses based on recollection and familiarity.

Düzel et al. (1997) coupled the R/K procedure with a false memory paradigm (Roediger and McDermott, 1995). The ERPs to Remember and Know were distinguishable from those to correct rejections of new words: Remember but not Know responses showed a prominent late (600–1000 ms) left parieto-temporal old/new effect. Know responses on the other hand showed a prominent old/new effect in the region of the N400 followed by greater negativity than correct rejections in the LPC region. The same pattern emerged when subjects made R and K responses to false targets indicating that the ERPs reflect subjective rather than veridical accounts of memory. Remembering is clearly reflected in the LPC; knowing is more complicated. LPC amplitude is also sensitive to levels of processing manipulation, being larger for more deeply encoded items (Paller and Kutas, 1992; Paller et al., 1995; Rugg et al., 1998a). Taken together with the ERP data from source memory paradigms and R/K paradigms, these results suggest that episodic and nonepisodic (perhaps semantic) memory make independent contributions to recognition.

The right frontal contribution to memory. Several lines of evidence have implicated the frontal regions

in different memory-related processes. For example, frontal brain areas are important in elaborative and planned processing of information for encoding and during retrieval, metamemory skills (knowledge of the workings of memory and effectiveness of memory strategies), memory for the temporal order and frequency of events, and for source. Within the past few years neuroimaging studies have repeatedly shown right frontal blood flow changes during episodic retrieval supporting reports of memory impairments after right frontal lesions (Curran, Schacter, Norman and Galluccio, 1997; Levine, Black, Cabeza et al., 1998; Schacter, Curran, Galluccio and Milberg, 1996b).

Wilding et al. (1995) were among the first to observe right frontal ERP effects in a source retrieval paradigm, wherein subjects made a speeded recognition judgment followed by a source judgment for each word. Specifically, the ERP over the right frontal site was more positive for correctly recognized old as compared to correctly rejected new words from 200 ms on (~2 s duration). This finding has been replicated and extended in several laboratories. Düzel et al., for instance, observed that the greater right frontal positivity had an earlier onset when the recognized word was rated as remembered rather than merely known. It appears that this right frontal effect can be differentiated into an early part before the old/new judgment and a later part reflecting post-retrieval processes (e.g., Donaldson and Rugg, 1999). Such post-retrieval processes might include computations on the products of retrieval in the face of an upcoming source or remember/know judgment.

The finding of a right frontal ERP difference between correctly recognized (hits) and correctly rejected new words has ignited a discussion about the functional contribution of the frontal regions to episodic memory. The ERP data suggest that right frontal activity is affected by recognition success whereas hemodynamic studies show increased right frontal activity with episodic retrieval regardless of success (Buckner, Koutstaal, Schacter et al., 1998; Kapur, Craik, Jones et al., 1995; Nyberg, Tulving, Habib et al., 1995; Schacter, Alpert, Savage et al., 1996a; Wagner, Desmond, Glover and Gabrieli, 1998). The right frontal activity then presumably reflects an episodic retrieval mode — a mental set wherein a person thinks back on their per-

sonal past (Wheeler et al., 1997). This discrepancy between ERP and hemodynamic measures may be more apparent than real: episodic retrieval mode is a task-related, long-lasting process whereas episodic retrieval success is an item-specific, relatively short-lived process. Düzel et al. used DC recordings to test the hypothesis that brain areas that mediate task-related processes (e.g., episodic retrieval mode) are continuously active throughout the duration of a task, while brain areas that mediate item-related processes are transiently active with each successive test item. Volunteers studied a list of 20 words and were then tested with a list of 40 words and 20 nonwords. During the test, task instructions were changed every 4 words to either (a) episodic retrieval requiring an old/new discrimination, (b) semantic retrieval requiring a living/nonliving judgment on old and new words or (c) random button press. DC potentials were recorded over 10 second epochs from the onset of each task until 1.5 seconds after the presentation of the 4th (and last) word for that task. Whether words were old or new, episodic retrieval was associated with a prominent right frontopolar positive DC-shift that was absent in semantic retrieval. It is this right frontal DC shift that was taken to reflect episodic retrieval mode and was linked to hemodynamic changes typically observed in these types of paradigms.

Memory disorders associated with neuropathology.

Our understanding of the functional significance of ERP components associated with declarative memory processes in healthy individuals has increased to the extent that the ERP technique can now be used to assess various (especially declarative) memory disorders with greater specificity than ever before.

Bilateral damage to the medial temporal lobes yields a severe anterograde and a time-limited retrograde impairment in declarative memory (Milner et al., 1998). With extensive damage, as in the case of H.M. (Milner, 1972) this form of amnesia has an episodic component such as an inability to remember personal events and a semantic memory component characterized by an inability to learn new facts (Wheeler et al., 1997). With less severe damage, declarative amnesia refers to impaired episodic memory with relatively spared performance on tests of recognition memory (Aggleton and Shaw, 1996;

Brooks and Baddeley, 1976; Cohen and Squire, 1980; Hirst, Johnson, Kim et al., 1986; Vargha-Khadem et al., 1997). Using remember/know or the process-dissociation procedures, Yonelinas et al. (1998) have shown that familiarity is better preserved than recollection in amnesic patients of this type.

In patients with memory deficits with recognition intact, ERP data can complement behavioral data in helping to distinguish episodic from semantic memory. The LPC recognition effect is correlated with episodic recollection while the N400 recognition effect is correlated with conceptual priming according to some authors (Olichney et al., 2000) and familiarity according to others (Donaldson and Rugg, 1999; Düzel et al., 1997). Thus, to the extent that brain damage impairs episodic memory but leaves semantic memory intact, the N400 recognition effect should be preserved while the LPC recognition effect should be greatly diminished.

Although there is general agreement that declarative memory is divisible into episodic and semantic memory, there is an ongoing controversy as to whether an intact hippocampal formation is critical only for episodic and not for semantic memory (Mishkin, Vargha-Khadem and Gadian, 1998; Squire and Zola, 1998; Tulving and Markowitsch, 1998). According to one view, both types of memory are served equally by medial temporal lobe structures although episodic memory depends critically on intact frontal lobes as well (Squire and Zola, 1998; Squire and Zola-Morgan, 1991). An alternative view holds that the hippocampal formation is critical for episodic but not for semantic memory, which is instead served by structures in the parahippocampal gyrus (parahippocampal cortex and entorhinal cortex) together with the perirhinal cortex (Mishkin et al., 1998; Tulving and Markowitsch, 1998). The hippocampal formation, by virtue of its extensive projections to posterior neocortical association areas, is critical for context-rich associations that are the hallmark of episodic memories (Rolls, 1996). Insofar as an intact hippocampal formation is indeed critical for only episodic memory, we would expect to observe a dissociation between LPC and N400 components with isolated hippocampal damage: recognition based on recollection would be impaired while semantic memory use during language comprehension would be unaffected.

Epilepsy. A number of researchers have investigated the ERP memory effects in individuals with unilateral medial temporal lobe damage accompanying epilepsy and/or its surgical treatment (Grunwald, Elger, Lehnertz et al., 1995; Grunwald, Lehnertz, Heinze et al., 1998; Guillem, N'Kaoua, Rougier and Claverie, 1995; Rugg, Roberts, Potter et al., 1991; Smith and Halgren, 1989). Smith and Halgren (1989), for example, recorded ERPs during visual word recognition in nine patients after right and nine after left temporal lobectomy (TL) including removal of the anterior 5–7 cm of the temporal lobe (most of the hippocampus, uncus, basolateral amygdala and neocortical areas including anterior parts of the parahippocampal, fusiform, inferior, middle and superior temporal gyri, anterior temporal operculum and all of the temporal pole). Overall the left TL group showed significantly worse word recognition memory than the right TL group. The same 10 target words were repeated in 9 test blocks together with 10 new words in each block. Comparison of the ERPs to hits (correct recognition of target words) and correct rejections (of new words) revealed normal repetition/recognition effects from 250 to 650 ms in the normal controls and patients with right TL and the absence of such effects in left TL patients (although they did show some effects between 300–500 ms). Smith and Halgren (1989) argue that it is the contextual retrieval during recognition that is reflected in the repetition/recognition ERP effect and is absent in the left TL group. An alternative interpretation would be that the left TL group showed no ERP effects because they based their recognitions on item strength and fluency (i.e., familiarity).

Rugg et al. (1991) employed a continuous visual word recognition task wherein words were repeated after six intervening items and found that the ERP old/new difference was reduced in both right and left TL patients although only the left TL group was impaired in verbal paired associates learning. In patients with (unoperated) temporal lobe epilepsy, the ERP repetition/recognition effect was lateralized to the presumably unaffected temporal lobe. Given that temporal lobe epilepsy is frequently associated with unilateral hippocampal pathology (hippocampal sclerosis and/or atrophy) and dysfunction (Mathern, Babb, Leite et al., 1996; Vinters, Armstrong, Babb et al., 1993) often with no significant extrahippocampal

lesions, this finding suggests that an intact hippocampal formation may be necessary for the generation of the ERP repetition/recognition effect. The lack of difference between the left and right TL patient ERPs and the inconsistency with the Smith and Halgren results may be due to the small number (five) of recording sites used or the continuous recognition task, wherein recognition and retrieval phases overlap.

Hippocampal damage is also reflected in ERP indices of encoding (Grunwald et al., 1995). Using intracranial recordings inserted longitudinally into the hippocampi of patients with temporal lobe epilepsy for purposes of presurgical diagnosis, Grunwald observed an anterior mediotemporal (AMTL) N400 to newly presented visual words; its amplitude in the language dominant hemisphere correlated with recognition performance. In the presence of ipsilateral hippocampal sclerosis AMTL-N400 amplitude to words presented for the first time was abnormally small, even though it did show the normal reduction upon repetition. This was taken to suggest that in the presence of hippocampal dysfunction, anterior medial temporal processes of recognition are preserved, while novelty-detection may be impaired (Grunwald et al., 1998).

Unlike the ERP indices of explicit recognition, those reflecting implicit retrieval (e.g., repetition priming) appear to be normal in the presence of medial temporal lobe damage (Rugg et al., 1991). However, in the implicit condition repetitions were immediate, while in the explicit condition they occurred after a lag of six intervening words. It therefore remains unclear to what extent the dissociation between implicit and explicit ERP measures was due to repetition lag.

Brain damage due to hypoxia. Global hypoxia can lead to medial temporal lobe damage that affects the hippocampal formation and subcortical regions to a greater extent than subhippocampal structures (Rempel-Clower, Zola, Squire and Amaral, 1996). Recognition ERPs in individuals with memory disturbance after hypoxic episodes thus may be particularly useful in elucidating the distinct functional contributions of hippocampal and subhippocampal structures.

Mecklinger, Von Cramon and Matthes-Von Cramon (1998) asked eight patients who had experienced global hypoxia to memorize either four ob-

jects (line drawings) or their spatial location. During the recognition test, these objects or spatial locations were presented again randomly intermixed with new stimuli. For objects, there was an ERP repetition/recognition effect between 300 and 600 ms in normal control subjects but not in the hypoxic patients even for correctly recognized objects. This dissociation between recognition memory performance and ERP repetition/recognition effects is not compatible with the idea that the ERP effect indexes both familiarity and recollection. However, since participants were asked to remember only a small number (4) objects for a relatively short period (~20s), it is possible that recognition was based on working memory rather than long term familiarity or recollective processes. In any case, the extent of brain damage was not sufficiently detailed to allow specific correlations between ERP effect size and extent of hippocampal and extrahippocampal damage.

Data from Vargha-Khadem et al. (1997) on three individuals with early and relatively isolated bilateral hippocampal damage with no apparent structural damage in subhippocampal regions, however, do allow such a correlation. These patients have relatively preserved recognition memory without episodic recollection. Subjects made living/nonliving judgments on each of 20 visually presented words, followed by old/new judgments on these intermingled with 20 new words. The results from one of these patients, Jon, were similar to those for the normal controls in showing greater positivity between 300–500 ms to hits than to correct rejections; in other words, N400s were preserved despite the absence of functional hippocampi. However, Jon also showed a reverse old/new effect during the LPC; specifically, hits elicited a left fronto-temporal negativity compared to correct rejections. Apparently, in the absence of functional hippocampi the normal LPC effect of recognition was eliminated. This was taken as evidence that the hippocampal formation is critical for episodic recollection while the subhippocampal cortices suffice to support nonepisodic recognition on the basis of familiarity.

Alzheimer's disease. Alzheimer's disease (AD) is characterized by an insidious, progressive cognitive decline that disrupts memory, executive functions, visuospatial orientation, language and attention ultimately leading to amnesia, aphasia, agnosia, and

apraxia. An impairment in episodic memory function is one of the first symptoms, although at the time of clinical diagnosis most patients also have dysexecutive deficits (Baddeley, Della Sala and Spinnler, 1991). Currently, performance on delayed recall tests is considered to be one of the most important cognitive indices for judging whether an elderly individual with recent cognitive changes is likely to develop AD (Albert, 1996). These tests tap primarily episodic memory functions and there is evidence of medial temporal volume loss early in AD. In elderly individuals with mild cognitive impairment not (yet) diagnosed with AD, hippocampal atrophy is associated with lowered delayed recall performance (De Leon, George, Golomb et al., 1997). Laakso, Soininen, Partanen et al. (1998) reported that hippocampal volumes were atrophied in patients with early AD but not in patients with age-associated memory impairment. However, the most prominent locus of volume loss in AD is due to atrophy in the parahippocampal gyrus with the entorhinal cortex and not in the hippocampal formation (Juottonen, Laakso, Insausti et al., 1998; Pucci, Belardinelli, Regnicolo et al., 1998). Using the remember/know procedure, Dalla Barba (1997) found that early in the disease when AD patients can still perform recognition judgments their retrieval lacks recollective experience and is based primarily on stimulus familiarity.

Measuring ERP indices of explicit retrieval in AD is difficult, because most patients cannot easily comply with task instructions and recordings are subject to excessive blink and movement artifacts. A number of ERP studies have therefore investigated ERP indices of implicit retrieval (Friedman, Hamberger, Stern and Marder, 1992; Rugg, Pearl, Walker and Roberts, 1994) with one exception (Tendolkar, Schoenfeld, Golz et al., 1999). Rugg et al. (1994) examined the ERP indices of implicit word repetition with inter-item lags of one and six words as subjects detected occasional words denoting animals. Young, normal elderly and AD patients impaired in recognition and recall all showed greater positivity to repeated than new words, albeit later in the older subjects. The AD patients showed somewhat smaller repetition effects at the longest inter-item lags. All in all, it appears that the ERP repetition effect is preserved in AD, suggesting that implicit memory processes are preserved, at least, in

mildly affected patients (see also Friedman et al., 1992)

ERP word recognition effects in mild AD were studied by Tendolkar et al. (1999) in a paradigm including a source retrieval manipulation. Patients first studied a list of ten words that were displayed in green or red color, and then were asked to make old/new decisions for each word in a test list of the ten studied and ten new words all displayed in white. For words judged as old, participants also were asked to indicate the color in which it had been displayed (source retrieval). AD patients were able to recognize some of the repeated items but were unable to give correct source judgments. Their ERP repetition/recognition effect was small, confined to the 300–500 ms interval, and was maximal frontally, and not evident over left posterior scalp as in age-matched controls. The hippocampal volumes of the AD patients were reduced to approximately 75% of that of the control group. Thus, it seems that the memories of the AD patients have no episodic quality and are perhaps based mainly on familiarity.

Frontal lobe lesions. Patients with dorsolateral frontal lobe lesions have normal recognition memory, but they are impaired on recall of episodic information (Milner, 1995), and in free recall (Gershberg and Shimamura, 1995). This impairment is best seen in tasks that require source memory judgments (Shimamura, Janowsky and Squire, 1990), recency judgments (Milner, 1995), or self-ordered retrieval. Based on this pattern of impairment it has been proposed that an intact dorsolateral frontal lobe is important for metamemory judgments (Janowsky, Shimamura and Squire, 1989), and for its strategic role in organizing retrieval (Mangels, 1997; Shimamura et al., 1990). These patients also produce higher false recognition rates implicating additional impairment in processes that act upon the products of retrieval as well (Schacter et al., 1996b).

Neuroimaging studies also have implicated the left inferior prefrontal cortex (LIPC) in repetition priming. Swick (1998) examined ERP indices of implicit repetition in individuals with frontal lobe lesions (areas 9 and 46 and extending to areas 6, 8, 44, and 45 in some patients) in a continuous lexical decision task. The patient group showed preserved behavioral repetition priming together with reduced ERP repetition effects. Swick (1998) inter-

preted these results as evidence for a modulatory effect of frontal lobe areas on neural activity in posterior cortical regions. Note that such patients (with bilateral damage in areas 9 and 46) produce higher than normal false alarm rates in recognition task but show normal ERP repetition/recognition effects.

Language processing: comprehension and production and language-related ERP components (N400, SPS/P600, LAN, slow potentials)

The beauty of the ERP for language is that it can be used to track processing at various levels of linguistic analysis (word, sentence, discourse) simultaneously. Moreover, this monitoring can take place during word by word or phrase by phrase reading and natural speech with no need for any task besides comprehension. By combining ERP results from other cognitive domains such as attention, memory, motor preparation, it is possible to assess their contribution to language processing in real time. What we know influences not only what we talk about but how and how quickly we understand what we hear. Where do syntax and semantics come together? How does a spoken language differ from a signed language? What happens when a word from one language finds its way into an utterance? How and when do the different aspects of language develop? What language processing problems, if any, characterize dyslexics, aphasic individuals, individuals with Alzheimer's dementia, individuals with right hemisphere damage, or individuals in whom the corpus callosum has been severed? What's special about one's own name? We will not describe electrophysiological investigations of all these questions, but a look at the extant literature would turn up some data relevant to answering each.

Indeed, a large part of language processing is sensory analysis and integration with memory. Linguistic symbols without access to memory would be meaningless. Like other domains language can be analyzed within an information processing framework, and as such refer to sensory memory, attention, working memory, long term memory, among others. It is the questions and not the stimuli that determine whether a study is about language. Similarly, it is the nature of the result relative to the question under study not the ERP componentry that determines whether or not an experiment contributes to our

understanding of language processing. In fact, electrophysiological studies of language comprehension and production have utilized a variety of ERP measures, many of which have already been mentioned (N1, P2, MMN, Nd, PN, P3, LRP). There are other components that are traditionally assumed to be language-related in that they are typically elicited by certain manipulations within the context of language processing. These include N400, lexical processing negativity (LPN) a.k.a. frequency-sensitive negativity (FSN), left anterior negativity (LAN), syntactic positive shift (SPS) a.k.a. P600, clause-ending negativity (CEN), and various clause- or sentence-length potentials, among others (Kutas, 1997). Their language-specificity has yet to be proven and would first require a consensus as to what it means to be domain-specific in general and language-specific, in particular. Nonetheless, these components can be used under controlled conditions to answer some questions — questions which usually are about language processing per se although they need not be (for reviews see Kutas, Federmeier, Coulson et al., 2000 and Osterhout and Holcomb, 1995).

The N400 and its use for linguistic and non-linguistic issues. A case in point is the use of the N400 potential to adjudicate between two alternative views of the nature of processing during the attentional blink (Luck, Vogel and Shapiro, 1996; Vogel, Luck and Shapiro, 1998). The attentional blink is a short period of around half a second following the detection of a target item within a very rapid (3/s) stream of visual stimuli during which any subsequent targets are missed. The N400 is a negative going potential between 250–600 ms elicited in response to potentially meaningful stimuli (written or spoken sounds including words, pictures, faces). The N400 was first observed in response to a semantically anomalous word at the end of a sentence presented one word at a time and read for comprehension (Kutas and Hillyard, 1980). Similar (although not identical) effects have been observed in multiple languages, for written, spoken, and signed words presented at various positions within a sentence. Very similar effects (relative negativity to the anomalous word) are elicited whether words are presented visually, one at a time slowly (700–1500 ms) or quickly (10/s, albeit delayed in latency by ~80 ms) or in natural

speech (for review see Kutas and Van Petten, 1994). An N400 is elicited by words flashed in the middle of the screen as well as peripherally in the left and right visual fields, although the two hemispheres are differentially sensitive to degree of contextual constraint (Federmeier and Kutas, 1999a). These contextual effects on N400s to words indicate that RVF and central word presentations lead to similar processing, which differ from that invoked by LVF presentations. Such results suggest that visual half-field studies of this type (e.g., centrally presented context with lateralized endings) might prove very useful for examining the role of the two hemispheres in each of the different levels of linguistic analysis. Much research also has shown that words and pictures elicit N400-like activity even when the item is not semantically anomalous with its context.

Lexical properties and contextual constraints. In short, the N400 is not just a semantic violation detector. In fact, in a sentence all words may elicit some N400 activity with an amplitude determined by how expected the word is and thus how meaningfully it can be integrated with the current context (Kutas and Hillyard, 1984; Kutas, Lindamood and Hillyard, 1984). These expectations appear to be based on information at multiple levels including the single word, sentence, and discourse. In the absence of any coherent context, N400 amplitude is determined by word frequency and concreteness, being larger for low than high frequency words, thus generally larger for open than closed class items. The N400 is also sensitive to repetition, being smaller for a word on its second or third presentation, especially when it has been repeated at a relatively short lag (lag 1–6). The N400 is also larger for concrete than abstract words appearing in isolation (i.e., unrelated word lists).

These factors (frequency, concreteness, repetition) interact with each other and others (relatedness, congruity, contextual constraint) when words occur in word pairs or within sentences. For example, words at the beginning of a sentence have large N400s relative to those later in the sentence; and this effect of contextual constraint on N400 amplitude is a function of word frequency (Van Petten and Kutas, 1990, 1991). N400 is larger for low frequency words at the beginning of a sentence but by the middle of the sentence, the N400 is reduced equally for high

and low frequency words, which do not differ from each other. The sentence N400 congruity effect also can be overridden by repetition as long as the context remains constant (Besson and Kutas, 1993; Besson, Kutas and Van Petten, 1992). Thus, “dog” no longer elicits an N400 in “I take my coffee with cream and dog.” if the sentence is being read for the third time (second repetition). See Fig. 14 for an illustration of some of these N400 effects.

The majority of research work with the N400 has been done with ‘nouns’. There is evidence that the ERPs to nouns and verbs often differ from each other, not just in the N400 region (e.g., Koenig and Lehmann, 1996; Preissl, Pulvermüller, Lutzenberger and Birbaumer, 1995). From a methodological perspective this means that it is important either to hold certain factors constant or to match them across conditions: these include word class, frequency, number of occurrences (repetitions) within stimuli sets, and position within the sentence. Once catalogued, such differences also can serve to distinguish individuals with potentially different impairments as a consequence of focal brain damage.

With minimal context such as a word pair, the N400 to the second word is reduced not just by repeating the exact same word but also by a word that is orthographically, phonologically, morphologically or semantically related. Thus for example, in rhyme judgment tasks, rhyming word pairs elicit a smaller negativity than do nonrhyming words (Sanquist et al., 1980). Rugg and Barrett (1987) demonstrated that orthographic, and not just visual similarity modulates the N400. Morphological influences on word processing also have been observed in the ERP by 250 ms. In fact, the ERP effects due to violations of inflectional morphology (marking of case, number, tense) have been directed at the current theoretical debate concerning the extent to which the same computational algorithms and/or neural mechanisms can deal with the analyses of both regular and irregular word forms. Weyerts, Münte, Smid and Heinze (1995), for instance, compared ERPs to German past participles primed by themselves (exact priming) or by their respective infinitives (morphological priming), and found different patterns of ERP repetition for regular and irregular verb forms. Münte, Say, Clahsen et al. (1999) observed similar differences for a study of past tense in English. Investigations of

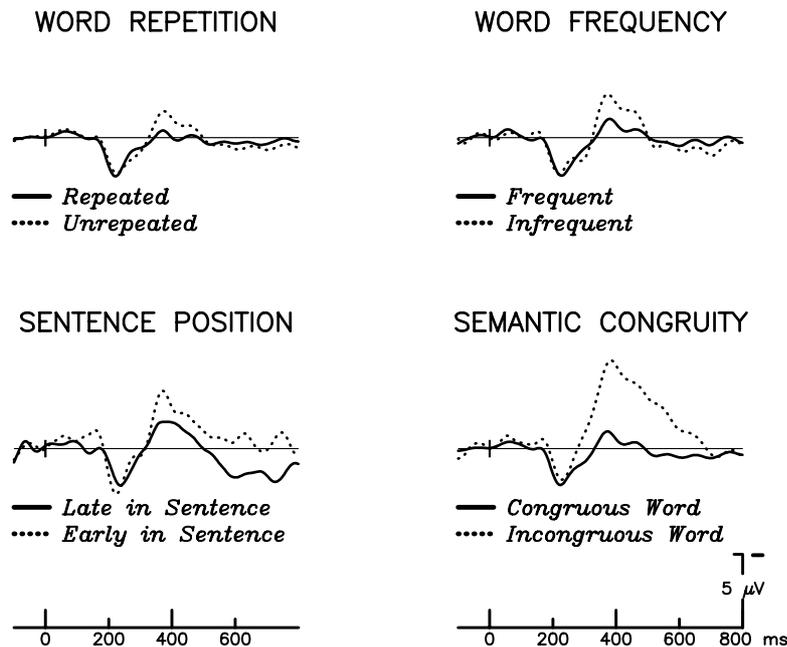


Fig. 14. Grand average ERPs recorded at a posterior site within a single experiment demonstrating some of the variables (semantic congruence with context, word frequency, repetition, ordinal word position within a sentence) that modulate the amplitude of the N400.

this sort in various patient populations known to have different patterns of deficits with regular and irregular word forms may help to resolve this issue, and show that the answer must go deeper than showing that some difference exists. These studies point to the inferential difficulty of going from a brain measure to neural mechanism or mental representation.

At a practical level, however, it is well-established that the amplitude of the negativity in the N400 region is reduced when the two words look alike, sound alike, or share morphemes. Again, this means that such similarities along these levels must be controlled for when the interest is on semantic or associative relatedness. Thus, all else being equal, the amplitude of the N400 to a noun is smaller if it has recently been preceded by a semantically related word than by an unrelated word (e.g., Anderson and Holcomb, 1995; Bentin, McCarthy and Wood, 1985; Holcomb, 1988).

It is this sensitivity of the N400 to semantic relationships that researchers have counted on to determine whether the attentional blink phenomenon is due to an impairment in pre- or post-perceptual processing (Luck et al., 1996). On one view the at-

tentional blink occurs because there is essentially a dead period following target detection during which another target cannot be perceived, because the sensory processing/perceptual system is overloaded. By a different account, however, the attentional blink results from a processing failure subsequent to perceptual analysis of the target. The sensitivity of N400 elicited by a word presented during the attentional blink interval to semantic relatedness thus could provide evidence as to the level to which the word was processed even when a person cannot report it accurately. In the experimental runs participants were presented with a stream of 20 seven character strings of letters or numbers at a very rapid rate (one string every 83 ms). For each stream, they reported the outcome of two decisions — whether the first target word (seventh or tenth item in the stream) was an odd or even digit and whether the probe word was semantically related or unrelated to the context word for that trial. The probe word was presented at various lags (1, 3, 7) after the first target; as expected, accuracy for the probe word was poorest (~11%) at lag 3. By contrast the N400 difference ERP (unrelated minus related probe word ERPs) was

unaffected by lag. In other words the attentional blink was not accompanied by a reduction in the N400 elicited by processing semantic relatedness, indicating that the probe word was analyzed to a semantic level even during the attentional blink. The results were taken to mean that the decline in probe discrimination accuracy during the attentional blink was not caused by suppression of perceptual processing but resulted instead from post-perceptual loss of information. Consistent with this conclusion, during the attentional blink interval there was also no suppression of early sensory components (P1 and N1) together with complete suppression of the P3 component (Vogel et al., 1998). From these data we cannot determine whether the probe words were identified without reaching awareness or if they momentarily reached awareness and were rapidly forgotten. Nonetheless these data do suggest that the meaning of a word can be extracted without necessarily being remembered 1–2 seconds later.

Of course while the N400 can be a useful measure of semantic processing in an otherwise non-linguistic experiment, its main utility has been as a measure of semantic analysis in investigations of various psycholinguistic issues in intact as well as neurologically impaired individuals (e.g., Hagoort and Kutas, 1995). Whereas the early work with the N400 focused on word level processing (as in lists and word pairs) and occasional sentence level processes (as in appreciation of semantic anomalies), more recent studies have begun to use the N400 to look at linguistic processes beyond the level of the word or even a single sentence, namely at the level of discourse without any obvious surface level anomalies or violations (e.g., Kutas and King, 1996).

St George, Mannes and Hoffman (1994), for example, asked college undergraduates to read short paragraphs about some topic. The paragraphs were constructed such that they were not easy to understand unless their topic was marked by a title. For example, the following paragraph:

“The best place is a large field or a parking lot, if it is big enough. A favorite time to do it is an hour or two before sunset, although sunrise is nice too. You need a few people, but not too many, or else you will never get anywhere. There is a lot of noise and it gets pretty hot. Everything is colorful and festive. There might be some apprehension if it is your first time. There is

material spread out everywhere. They are bigger and heavier than you might think, once you get up close. Eventually, the hot vapors rise and fill the material. Then the fun begins.”

proves much easier to understand and recall if it comes along with its title “Hot air ballooning” than without, as originally noted by Bransford and Johnson (1972). St George et al. reported that overall the N400 to words in the untitled paragraph was significantly larger than that to words in the titled paragraph. Neither strictly word nor sentence-level processes can explain these results. At minimum, it appears that discourse level information influences the semantic analysis of words in sentences. Moreover, the finding of discourse effects on the N400 are inconsistent with any strictly serial theories of language processing wherein word level effects precede sentence level effects which in turn are presumed to precede discourse level effects. Word, sentence, and discourse level constraints appear to act within the same time frame in reducing the N400 amplitude. In fact, more direct comparisons of the latency of the N400 effects in words, sentences, and discourse suggest a trend toward the exact opposite temporal pattern — discourse, then sentence, then word level effects. Kutas (1993) found that the latency of the N400 semantic relatedness effect in written sentences preceded the N400 semantic relatedness effect for the second word of word pairs. Likewise, it appears that the N400 effect for violations in isolated sentences is somewhat later than the N400 effect observed for semantically congruent words in sentences which are inconsistent with meaning at the discourse level.

A lovely example of this can be seen in a study by Van Berkum, Hagoort and Brown (1999). They asked subjects to read sentences word by word for meaning. The critical sentences were easy to understand and congruent when presented in isolation (e.g., “Jane told her brother that he was exceptionally slow.”), but semantically anomalous with respect to the wider discourse wherein “he” had in fact been very quick. The N400 was larger to the discourse anomalous word relative to a control; that is, the N400 was larger for the word that was inconsistent with discourse-based expectations. Such top-down discourse effects also appear to influence processing

of sentences at a structural level (Van Berkum et al., 1999).

Several research groups have recorded intracranial responses in patients undergoing evaluation for medically intractable epilepsy in situations that elicit N400 activity at the scalp. For example, McCarthy et al. (1995) and Nobre, Allison and McCarthy (1994) examined intracranial responses to semantically congruent and semantically anomalous endings in written sentences. Anomalous words were associated with a bilateral negative field potential in the anterior medial temporal lobe with a peak latency around 400 ms (AMTL-N400). At this same latency, electrodes near the collateral sulcus recorded positive potentials. The authors thus suggested that this voltage pattern was consistent with a source in or near parahippocampal and anterior fusiform cortices. The AMTL-N400 is also elicited by orthographically legal words, larger for open than closed class words, and reduced in amplitude by semantic priming. There are also potentials during the N400 time window in other parts of the brain (Guillem et al., 1995), although these tend to be studied more within the domain of memory (e.g., Elger, Grunwald, Lehnertz et al., 1997; Grunwald et al., 1995, 1998). Elger et al. (1997), for example, reported that N400s in the medial temporal gyrus predicted immediate recall performance, and the left AMTL-N400 predicted delayed verbal recall. In another study from the same laboratory, N400 amplitudes in the right AMTL predicted postoperative verbal recall performance in patients with left temporal lobe epilepsy.

Syntactic violations: SPS/P600 and LAN effects. Until relatively recently ERP studies of sentences focussed on the processing of a particular violation within a sentence. As previously mentioned, lexical semantic violations within written sentences elicit a posterior N400, slightly larger over the right than left hemisphere. Syntactic violations of various sorts including agreement of number, gender, and case, as well as phrase structure, subcategorization, and subadjacency elicit a late positivity around 500 ms or so variously referred to as the syntactic positive shift (SPS) or the P600. For example, the violation of subject–verb number agreement on the verb auxiliary in “The young child are throwing a tantrum” elicits a SPS/P600. Hagoort and Brown

(1994) observed essentially the same response even when the sentence wherein the violation occurred was completely semantically anomalous (e.g., The boiled hose *smoke the radio in the giraffe).

As in the case of the N400, violations are not necessary for eliciting an SPS/P600. A similar positivity also is elicited by a word which helps resolve a structural ambiguity in a sentence. At some general level, the positivity reflects the additional processing cost involved in resolving the ambiguity; the extra processing may reflect the rejection of the initial parse (structure) and the subsequent syntactic reassignment for the new parse, or the shift in the relative activations of the various alternative readings. In any case, there is no real violation at this point, but there is what appears to be a P600/SPS. This is exemplified by the response to the verb “noticed” in “The sheriff saw the indian and the cowboy noticed the horses in the bush” which includes a P600/SPS relative to when it appears in the same sentence with a comma after “indian”. Without the comma, it is unclear whether “the cowboy” is part of a complex noun phrase (“the indian and the cowboy”) that is the direct object of the verb “saw” or as it happens, “the cowboy” is the subject of the verb “noticed”. In other words, “the cowboy” is syntactically ambiguous and this structural ambiguity is not resolved until the verb “noticed” makes it clear; the processes involved are reflected in the presence of a P600/SPS at this point (Brown and Hagoort, 2000). The presence of a P600 in such sentences thus can be used to track the resolution of structural ambiguities and the types of information that help resolve them; just where and what these are, respectively, are major sources of contention in the psycholinguistic literature on parsing. Whether or not the P600/SPS is a syntax-specific response, its behavior under experimentally controlled conditions can serve to test various theories of human parsing and its breakdown following a brain insult.

Some syntactic violations also have been linked to a frontally-distributed negativity between 300 and 500 ms post stimulus onset referred to generally as a left anterior negativity (LAN), and by those who maintain that it comprises several subcomponents as the LAN and ELAN (Hahne and Friederici, 1999). As noted previously a morphosyntactic violation in so-called syntactic prose such as “Two mellow

graves freely sinks by the litany.” elicits a P600/SPS. The singular verb “sinks” violates the plural subject “graves” and elicits a P600 even though the sentence is incomprehensible. However, Münte, Matzke and Johannes (1997a) have shown that the P600/SPS effect disappears when the words in the syntactic prose are replaced with pseudowords (words with no meaning at all), as in “Twe mulloow grives/grive freely senks by the litune.”). There is still a frontal negativity to the morphosyntactic violation, however, perhaps reflecting a process that is specifically syntactic in nature. Indeed several authors have argued that there is an early LAN that is evoked uniquely by syntactic processing and a later, partially overlapping LAN that reflect the engagement of verbal working memory processes (King and Kutas, 1995; Kluender and Kutas, 1993).

Before reviewing the studies wherein a LAN effect occurs, it is important to distinguish the LAN from the lexical processing negativity (LPN, also known as the frequency sensitivity negativity) which also occurs between 200 and 400 ms post word onset and has a left frontal focus. It is one of a number of ERP effects that varies with various word features. Specifically, LPN latency varies with the eliciting word’s frequency of occurrence in the English language ($r = 0.96$), with high frequency words eliciting earlier LPNs (King and Kutas, 1998). The N280, which has been specifically linked to closed class or function words (Neville, Mills and Lawson, 1992) seems instead to be an instance of an early LPN due to the disproportionately higher average frequency of this class (e.g., articles prepositions, conjunctions) relative to the open class or content words (e.g., nouns, verbs, adjectives, adverbs). While these results demonstrate that the N280 is not specific to closed class words, just as the N400 is not specific to open class words, the ERPs to word classes do vary. For example, Ter Keurs, Brown, Hagoort and Stegeman (1999) found significant word class differences in brain intact individuals which were significantly reduced in aphasic patients.

The processing of a word with more than one meaning (lexical ambiguity) is likely to require more verbal working memory resources than processing a word that does not. Likewise, processing a word that has more than one antecedent in the preceding discourse (referential ambiguity) is likely to make

greater demands on verbal working memory than one that does not (e.g., King and Kutas, 1996). Both these types of ambiguities are associated with frontal negativities. In fact, the hypothesis that the LAN reflects working memory usage comes from electrophysiological investigations of sentences that are wholly grammatical, but difficult to process.

The fine temporal resolution of the ERP is especially well-suited to investigating the individual and combined influences of the structural, semantic, and discourse aspects of sentences. Indeed, no other brain imaging measure has yet to be able to track real time sentence processing with the precision and sensitivity of the ERP. Moreover, the results from electrophysiological studies that have done so indicate that the temporal dynamics of language processing warrant this type of analysis: the brain’s response changes systematically throughout the course of a sentence.

Cross-clause or cross-sentence potentials are best viewed after a low-pass digital filter is applied to the averaged data. These potentials tend to be of a lower frequency than the transient responses to individual words. Of the various ultra-slow potential effects that have been observed, a cumulative positivity (<0.2 Hz) has tentatively been linked to some executive function(s) of verbal working memory. King and Kutas (1995) observed modulation of this potential when comparing two types of sentences both of which contain a relative clause, but differ in how difficult the presence of the clause makes the sentence to process. Specifically, they compared sentences such as “The reporter [who the senator harshly attacked] admitted the error” with sentences such as “The reporter [who harshly attacked the senator] admitted the error”. Figuring out who did what to whom is more difficult in the so-called object relative sentence where the object “reporter” is missing from the relative clause (within the brackets) than in the so-called subject relative sentence where only the subject “reporter” is missing. The processing difficulty is hypothesized to result from a combination of the load placed on working memory due to the need to maintain information across multiple words in order to determine the grammatical identity of the missing noun phrase (“reporter”) and the greater number of shifts of focus in the object relative compared to the subject relative sentences. The electrophysiological data show large differences

between the two sentence types soon after the beginning of the relative clause which is much earlier than the reaction time effects that are typically observed; the more WM-taxing object relatives show greater negativity (less ultra-slow positivity) over left frontal sites. In addition to these slow potential effects, the response to the main clause verb (“admitted”) in object relatives is characterized by a large LAN relative to the response to the same verb in a subject relative, which in turn has a larger LAN than the response to the second verb in a sentence without any relative clauses. Of interest for potential application of this paradigm to neuropsychological populations is the finding of much larger differences between the two relative clause sentence types in good than poor readers.

The link between this left frontal slow potential effect and working memory usage was strengthened in a study by Münte et al. (1998b) contrasting across-clause ERPs to two sentence types that varied in working memory demands by virtue of the differences in conceptual knowledge activated by their initial words (Before vs. After).

As can be seen in Fig. 15, although the sentences are identical in all respects except their initial words, this has a striking effect on processing as reflected in the ERPs over frontal sites: the waveform to the After sentences, wherein the order of events is ex-

pressed in their natural order, goes positive whereas that to the more working memory taxing Before sentences, wherein the order of expressed events goes counter to that of their actual occurrence, goes negative. Moreover, the size of the ERP difference between the two sentence types over left frontal sites is highly correlated with individuals’ working memory span scores. This paradigm thus is well-suited for examining patient groups (e.g., Parkinson patients) in whom working memory resources are presumably compromised.

The majority of language comprehension studies have focussed on visual word recognition in isolation, word pairs, and occasionally in written sentences. Despite its obvious importance and evolutionary precedence, spoken language processing has received short shrift until quite recently. One example we will not detail here is an auditory version of the investigation comparing the object and subject relative clause sentences. Suffice it to say that the basic findings and variation due to individual differences in comprehension were in large part replicated (Müller, King and Kutas, 1997). This not only allows greater generalization of the conclusions but also provides a more user-friendly and natural way of testing neuropsychological patients. At least in this respect, spoken language processing is easier to deal with than visual language processing.

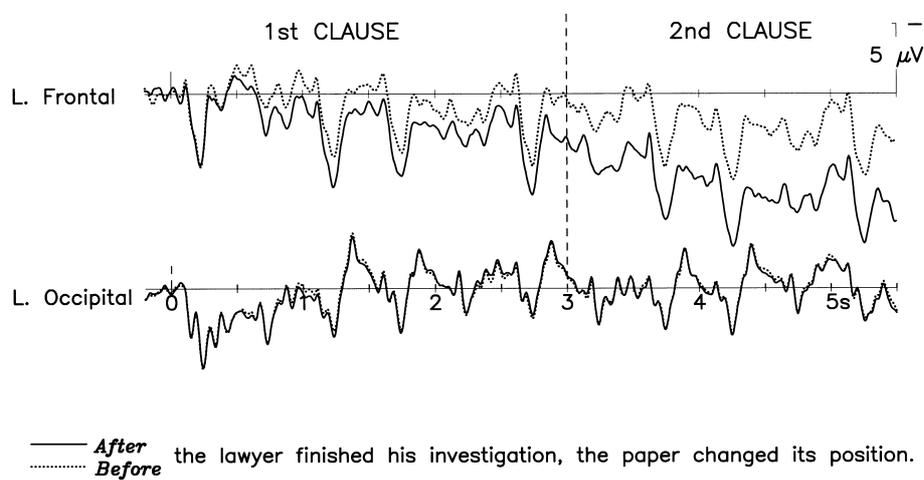


Fig. 15. Grand average ERPs across entire sentences (~5 s) recorded from a left frontal and a left occipital site from a group of young adults with relatively high verbal working memory spans. Overlapped are sentences that differ only in their initial word (Before/After). The dashed line demarcates the clause boundary between the two clauses of each sentence. Note the prolonged difference between the two sentence types starting approximately 300 ms following the onset of the sentence initial word. Data taken from Münte et al., 1998b.

Speech comprehension. An especially elegant example of the use of ERPs in speech processing is the work of Van Petten, Coulson, Rubin et al. (1999). Specifically, they capitalized on the fact that semantically incongruous words elicit an N400 to examine alternative hypotheses as to how much initial (sensory) processing must take place before a listener begins to process semantic meaning. One extreme is marked by serial models which specify that a word must first be identified from sensory input alone. Next its context free meaning is accessed, and only then can its meaning be integrated with the prior semantic context. At the other extreme are models wherein the semantic properties of all the words that are consistent with the first few phonemes of a word are accessed regardless of prior context (cal- low, calamity, calorie, calendar, after hearing “cal”). While these models vary on how early during a word’s analysis meaning is processed, both postpone integrating the word with its context beyond the point where the word is uniquely identified. As it happens a behavioral technique called gating provides a fairly precise measure of how much acoustic input (how much of a word) is required to identify that word. This so-called recognition point for any given word is the duration of the acoustic signal that must be presented in a gating task for a person to identify the word correctly. In a gating task people are presented with only the first 50 ms of a word and asked to guess what it might be, or presented with the first 100 ms, 150 ms, etc. until the end of the word. Most words (over 90%) can be identified before their offset. In the Van Petten et al. (1999) experiment, for example, mean word duration was 600 ms but the mean recognition point was around 350 ms.

After defining the recognition point of about 700 words, Van Petten et al. (1999) used the N400 semantic congruity effect to determine whether semantic integration (reflected in onset of N400 effect) occurred before or only after the recognition point as both of the above classes of theories propose. Van Petten et al. (1999) used four different types of sentence final words — congruous meaningful endings, semantically anomalous endings with no obvious phonological relationship to the congruous completions of those sentences, semantically anomalous words that shared (~3) initial phonemes with the congruous completions (dollars when dolphins was

expected), and semantically anomalous words that shared final phonemes with the congruous completions (i.e., rhymes such as furniture vs. premature).

The results clearly support models that place the effect of contextual integration prior to the recognition point. As expected, congruous endings elicited a much smaller N400 than anomalous endings, with the ERPs for the congruous and anomalous endings diverging around 200 ms. The N400 to the semantic anomalies that shared initial phonemes with the expected congruous endings was delayed relative to the N400 to the plain incongruous endings; the N400 congruity effect began around 375 ms after word onset, largely coincident with the mean recognition point (382 ms) for this set of words. This finding is consistent with the hypothesis that integration begins as soon as a word is uniquely identified or as soon as the acoustic input diverges from expected congruous endings as they are the same. They are not the same, however, in the case of the rhyming words — for which the recognition point was later (352 ms) than the point at which the acoustic input diverged from the expected congruous endings (at the beginning of the word). The timing of the N400 to anomalies that rhymed with the expected completions was indistinguishable from that to the plain anomalies. Thus the N400 congruity effect (~200 ms) preceded the recognition point (~350 ms) by 150 ms. The results indicate that semantic integration during speech comprehension begins before word recognition is complete (on partial, incomplete information). This finding and paradigm can be used to assess various theories regarding the use of context as a function of normal and abnormal development, aging, or after different sorts of brain damage. For instance, this paradigm could be used to test the hypothesis that poor language users rely more on context than do good language users.

Language and neuropathology. The N400 has also been used to test various theories about spoken language processing in aphasic patients with comprehension deficits regardless of their syndrome classification. Swaab, Brown and Hagoort (1997) recorded ERPs as subjects listened to sentences spoken at a normal rate, half of which ended with a word which was semantically anomalous with respect to the sentence context. Patients with damage to the

right hemisphere and aphasic patients with only a slight comprehension deficit showed N400 effects similar to those for age-matched control subjects. In contrast, the seven aphasic patients with moderate to severe comprehension deficits showed delayed N400 effects. As the nature of the ERP sentence congruity effect was quite similar in all the subjects, it seems that these aphasic patients' comprehension problems are not due to the loss of linguistic information in semantic memory per se or to impaired automatic access into the semantic lexicon. Rather, the results were interpreted as evidence for an impairment in the integration of word level information into a higher message level representation of the sentence. Lexical integration refers to the mapping of syntactic and semantic information at a lexical level onto a higher order representation of the whole utterance. This integration process apparently occurs less rapidly in aphasic patients. In sum, these N400 data show the aphasics' comprehension deficit is the result of slowed processing rather than the loss of knowledge (i.e., representational deficit).

A similar conclusion was reached by Schwartz, Kutas, Butters et al. (1996) in a test of the hy-

pothesis that Alzheimer's dementia (AD) results in a breakdown of semantic knowledge. Participants were primed with an auditory category name followed by the visually presented name of an imageable object and indicated whether the object was a category member; the category was either superordinate to, at, or subordinate to the basic level. All groups showed similar RT and N400 priming effects in response to the category manipulation, albeit varying in amplitude. N400 effects were largest in the young, smallest in the AD patients, but also smaller and later in the normal elderly (see Fig. 16). The presence of the N400 in the AD patients did not support a strong version of the strictly 'bottom-up' breakdown of semantic networks in individuals with Alzheimer's dementia, suggesting an important role for other factors such as processing speed, contextual support, etc.

Note also that in the Swaab et al. (1997) study, there were two control groups. The right hemisphere patients served as controls for non-specific effects of brain damage whereas the age-matched, brain intact individuals served to control for the effects of natural aging on N400 parameters. Indeed, several labora-

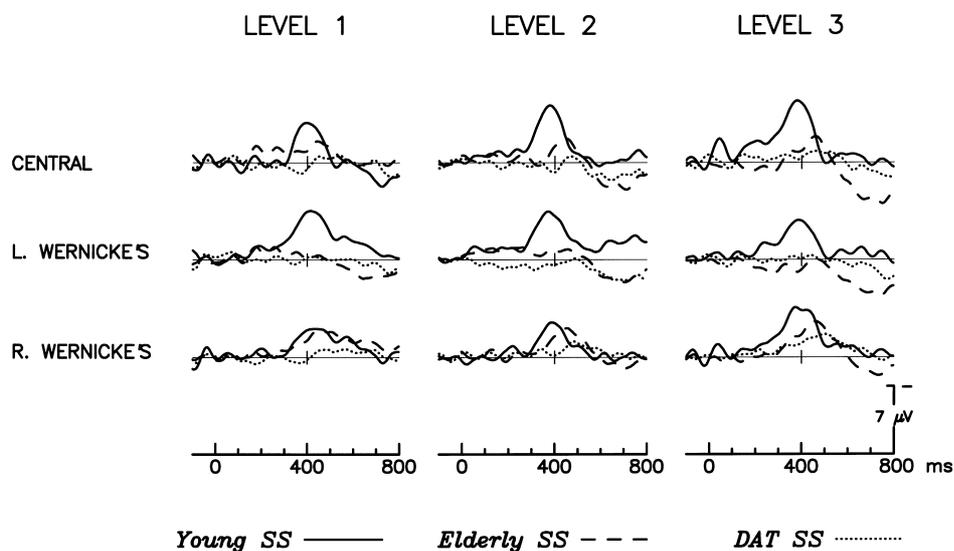


Fig. 16. Grand average difference ERPs (point by point difference between ERP to category non-member minus category member) over a central midline and two lateral posterior sites at 3 levels of category size, decreasing from level 1 to level 3. Overlapped are the difference ERPs in young adults, normal elderly, and patients with presumed Dementia of the Alzheimer's Type (DAT). Note that while the negativity (N400 effect) does get smaller and later with aging and DAT, the relative pattern across the category levels is similar in all three groups: largest effects for the smallest category (level 3), and smallest for the largest category (level 1). Data taken from Schwartz et al., 1996.

tories have found that the N400 congruity effect is reduced in amplitude and delayed in latency with advancing age (e.g., Gunter, Jackson and Mulder, 1995; Kutas and Iragui, 1998). When using the N400 as a dependent measure, it is also important to match participants on family history of left handedness, and most likely educational history, working memory span, and verbal fluency. In several studies word related activity such as the N400 was less lateralized in right-handers with a family history of left-handedness than those without (Kutas, Van Petten and Besson, 1988).

Prosody. While written and spoken language processing may share many processes in common, there are respects in which the two provide very different sorts of information. For example, spoken language includes prosodic information such as rhythm, pauses, accents, amplitude and pitch variations. Little is known about when and how these features are used by a listener to interpret the speech signal. Steinhauer, Alter and Friederici (1999) recorded a positive shift to an intonational phrase boundary and demonstrated that intonational phrasing guides the initial analysis of sentence structure. Applied to aphasic and right hemisphere damage patients, this type of task should prove useful in contrasting the proposed roles of the left and right hemispheres in propositional and prosodic analyses of speech, respectively.

Language production. The role of the brain in speaking sense or intentional nonsense has always been of interest to psycholinguists and neurolinguists. Given the differences between the hemispheres in language processing — once thought to be highly unequal and now thought to more equal but qualitatively different — the emphasis was on laterality studies. Many researchers have unsuccessfully attempted to use the ERP to localize the side of the brain (hemisphere) that controls speaking during the act — under the assumption that both hemispheres cannot do it, at least not simultaneously. Certainly, determining which hemisphere in any given individual controls speech would be of great clinical benefit, as anesthetizing one hemisphere with sodium amytal and seeing how this influences counting, natural speech, and naming is potentially dangerous.

Thus, any reliable and safe procedure for determining which hemisphere controls speech will make its mark in history. ERP recording has not yet proven effective for studying the expressive side of language processing — speaking and writing — because of contaminating artifacts. The muscles of the face, the tongue, the tongue touching fillings in teeth, etc. create potentials that are difficult to separate out from the signals of interest. This has been the primary drawback to studying actual speech-triggered ERPs. While this has not yet changed, it may be time for a new look at this problem using one of the spatial filtering approaches that are now available for separating signal from noise including spatial PCA, independent components analysis, and wavelet filtering (see section on ERP analysis).

Although there has been no progress on the overt speech production front, psycholinguists have begun to use ERPs to study language production processes by investigating preparation to name, in other words, the language process involved in saying a word or naming a picture. The idea is that except for the overt control of the effectors that actually control speaking, the processes involved in silently naming a picture are pretty much the same. At the least, they are considered similar enough by many investigators to allow testing of various theories about the relative order in which the production processes involved run their course.

According to Levelt's theory of speaking (Levelt, 1989), conceptualizing precedes formulation which includes grammatical processing and phonological processing. During conceptualization a speaker determines how to express the specific message s/he wants to express keeping in mind the situation, their intent, the speaker, etc. The form of the expression (statements or question, ironic) as well as the order in which information is to be disclosed are among the choices that the speaker must make. Formulation begins with the grammatical encoding during which words (lemmas — meanings plus syntactic properties such as word category and grammatical gender) that will best convey the intended message are selected from the mental lexicon and organized in a grammatical framework for the upcoming utterance. Grammatical encoding thus involves assigning words to their functions in the sentence and determining the order in which they will be spoken. Once the sur-

face form of an utterance is specified, its formulation proceeds with phonological encoding during which the sound pattern of the utterance is retrieved, so that a speaker has an articulatory (phonetic) plan for the utterance. In other words, the last part of the formulation process involves retrieving words, morphemes, segments, metrical structure. Then at some point phonological words are transformed into an ordered sequence of articulatory movements (one for each syllable). All these processes are completed as the phonetic plan is executed by the articulatory system yielding overt speech.

The time course of information processing in speech. Many different types of data, such as speech errors, tip of the tongue phenomena, and from neurological patients have been used to evaluate Levelt's theory. Relatively recently, two electrophysiological measures called the lateralized readiness potential (LRP) and the N200 have been co-opted for this purpose as well. About one second before a person voluntarily moves any muscle a negativity starts to build over the motor cortex. About half a second before the actual (hand and arm) movement this negative potential becomes laterally asymmetric. Its asymmetry reflects the organization of the motor system wherein the left half of the brain controls the right side of the body and vice versa. Kutas and Donchin (1980) showed that the readiness potential was sensitive to the presence of prior information about the response, with the lateralization of the RP dependent on the moment when choice of responding hand was made. Accordingly, the LRP has been used as an index of motor preparation. To be useful in this regard, it is critical that lateralized activity that is not specific to motor preparation be eliminated. This is achieved by first subtracting potentials from over left motor cortex from those over right motor cortex, and creating separate averages for right and left hand responses. Secondly, the average for left hand trials is subtracted from the average lateralization for right hand trials. Lateralization not specifically related to response preparation is presumed to be the same for both hands and thus zeroed out by the second subtraction (e.g., Coles, Gratton and Donchin, 1988).

Studies using lateralized readiness potential. The LRP has been used to detect transmission of partial information between perceptual and motor processes

(e.g., Coles et al., 1995). The most compelling evidence for response preparation on the basis of partial stimulus information comes from studies in which the LRP technique is combined with a two-choice go/no-go paradigm (e.g., Low and Miller, 1999; Osman, Bashore, Coles and Donchin, 1992). In this paradigm one stimulus attribute indicates a left or right hand response while a different attribute of the same stimulus indicates whether or not the response has to be given at all. If the attribute determining the responding hand is analyzed more quickly than that determining whether or no to go, then there is an LRP even on trials where a subject does not actually make a response. The latency of the onset of the LRP is determined by the amount of time needed to decide which hand will respond while the moment at which the go/no-go responses diverge is influenced by the discriminability of the go/no-go stimuli. Since the reverse is not true, this pattern of results indicates that the LRP is differentially sensitive to the time course of the processes that lead to response hand selection and those that lead to the go/no-go distinction. The LRP has been fruitfully combined with measurements of reaction times, muscle activity, and P300 to address many important issues about the dynamics of information processing and motor preparation. Of relevance here is its use in delineating the time course of speech production processes. See Fig. 17 for a sample LRP.

While normal speech is produced much too quickly to be the result of a set of processes that are wholly serial, there is still considerable debate over the temporal dynamics of speech production. Levelt, for example, hypothesizes that words to be uttered are first activated in the mental lexicon by conceptual input (the idea behind the utterance), and only later shaped into a phonetic representation; in other words, in speaking, conceptual processing is presumed to precede phonological encoding. Van Turenout, Hagoort and Brown (1997, 1998) used the LRP in a go/no-go response task to detect the moments at which semantic and phonological information became available for response preparation. Participants performed a go/no-go response task consisting of a semantic-phonological judgment on the name of the picture; the semantic judgment involved an animacy decision and the phonologi-

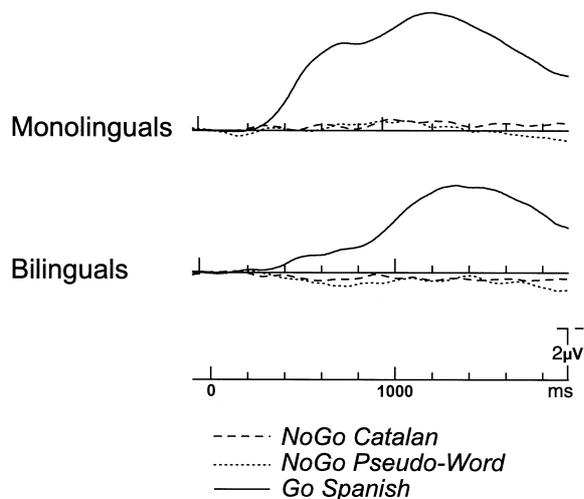


Fig. 17. Lateralized readiness potentials of thirteen monolingual Spanish speakers and thirteen bilingual Spanish/Catalan speakers. Subjects viewed series of letter strings and pressed a button, held in the right hand for half of the runs and in the left hand for the other half, whenever a Spanish word ($p = 0.5$) appeared, and withheld responding for Catalan words ($p = 0.25$) and pseudo-words ($p = 0.25$). A typical LRP only appeared for Spanish stimuli. The absence of an LRP for Catalan words in either subject group suggests that these bilinguals could effectively block out one of their languages when it was not task relevant (unpublished data of Rodriguez-Fornells and Münte).

cal task involved a phoneme decision (e.g., does the name of the pictured object start with an /s/ or a /b/?). The LRP was calculated as described above time-locked to the picture onset. The results showed that when semantic decision determined the response hand and the phonological decision determined go/no-go, an LRP developed not only on go trials as expected, but also on no-go trials on which no overt response was given. The same pattern was observed whether the go/no-go decision was based on the word-initial or word-final phoneme. Moreover, when the task demands were reversed such that the go/no-go decision was based on semantic information, and the response hand was based on phonological information, there was an LRP only on go (not on no-go) trials. Together, these results were taken to mean that speakers retrieve the semantic (conceptual) properties of a word before they have access to its phonological form. From the results of experiments with a similar design, Van Turenout, Hagoort and Brown (1999) concluded that in prepara-

tion to name a picture the name's syntactic gender is retrieved before its phonological properties.

Studies using the N200. The same issues concerning the temporal dynamics of information availability during language production (in this case via picture naming) have been addressed with measurements of the latency of the N200 component. No-go trials routinely elicit a large, frontally-distributed negativity called an N200. This N200 is presumably related to response inhibition rather than response preparation (see section on movement). Since an anticipated response cannot be stopped until the information on which the response depends is available, the latency of N200 can be measured to determine when that is.

Accordingly, Schmitt, Münte and Kutas (2000) used the latency of the N200 to test the serial model's prediction that semantics precedes syntax during speech production in the paradigm much like that of Van Turenout's experiment. Subjects were asked to make two decisions for each picture: a semantic decision as to whether the pictured item represents an animal or an object and a syntactic decision as to whether the syntactic gender of the pictured item's name in German is male or female. Again, in some conditions, the semantic decision determined which hand made the response while the syntactic decision determined whether or not any response was made, and vice versa. Whether the decision not to respond is based on semantic or syntactic information, withholding a response should elicit an N200 and it does; in both conditions, the no-go trials elicit an N200, albeit at different latencies. When semantic information halts the response, the N200 is much earlier (~ 90 ms) than when syntactic information halts the response. So, like the LRP data, the N200 data support a serial model for speech production — first one figures out what they want to say and then they choose exactly how to say it; conceptual encoding precedes phonological encoding by 90–120 ms, and precedes syntactic encoding by ~ 80 ms. The N200 effects are quite robust (relative to the LRP) and thus can be especially useful in investigations testing alternative theories as to the nature of the impairments in stutterers, children whose speech development is delayed, normal elderly, and various other patients with brain damage presumed to cause speaking, signing, and/or writing problems.

Output processes

Failure to initiate or inhibit movements is symptomatic of several neurological disorders, most notably basal ganglia diseases. Moreover, it appears to be the case that the difficulties in initiating and inhibiting actions extend to cognitive and executive processes as well (Elias and Treland, 1999). As a consequence, electrophysiological correlates of motor processes are of some interest to the neuropsychologist.

Motor preparation and execution

By averaging the EEG time-locked to the onset of self-paced movements, Kornhuber and Deecke discovered a slowly increasing cortical negativity, the readiness potential (RP or BSP, *Bereitschaftspotential* in German) that preceded the beginning of the actual movement by about 1 second (Deecke, Scheid and Kornhuber, 1969). Subsequent research has revealed that the RP can be divided into at least two distinct parts. The early, bilaterally symmetric portion has been shown by source modelling (Bocker, Brunia and Cluitmans, 1994; Praamstra, Stegeman, Horstink and Cools, 1996b) and cerebral blood flow studies (Cui, Huter, Lang and Deecke, 1999; Lang, Cheyne, Kristeva et al., 1991) to emanate from the supplementary motor area (SMA). The later part of the RP beginning approximately 200 ms before the movement is asymmetric with a contralateral maximum (at least for hand and finger movements). The generator of this latter portion of the RP has been localized to the primary motor cortex; its exact locus reflects the known organization of the motor homunculus. For example, RPs preceding foot movements tend to display a paradoxical ipsilateral distribution, which can be traced back to a generator in the contralateral crown of the primary motor cortex (Bocker et al., 1994).

Several studies have demonstrated RP differences between freely selected and repetitive movements that probably reflect the more demanding preparatory processes in the former. Dirnberger, Fickel, Lindinger et al. (1998), for instance, reported that the RPs to freely-selected movements were both larger in amplitude and more parietally-distributed than those preceding repetitive movements. The long-lasting DC shifts observed during sequential finger movements vary with the complexity of the task.

The fact that RP precedes voluntary but not involuntary movements (e.g., Trenkwalder, Bucher, Oertel et al., 1993) has generated considerable interest in the nature of its link to conscious awareness of movements. Libet, Wright and Gleason (1983), in particular, have developed a methodology for comparing the onset latency of the RP with the timing of the corresponding intent to perform the voluntary movement that elicited it. His estimations led Libet (1985) to conclude that the RP-onset precedes the time of conscious intention to move by about 350 ms, implying that 'voluntary' movements are initiated unconsciously. This conclusion has recently come under attack. Keller and Heckhausen (1990), for example, compared conditions that differed in the level of attention that subjects paid to the movements. Additionally, they observed different scalp distributions for RPs to unconscious and conscious movements which they attributed to the lateral and medial premotor system, respectively. They concluded further that the activation of the SMA and the urge to move coincide in time. Haggard and Eimer (1999) compared RPs and LRPs for trials with early and late time of awareness determined according to Libet et al. (1983). While the RPs to late awareness trials had an earlier RP onset than those to early awareness trials, the onset latency of the lateralized portion of the readiness potential (the LRP) showed a close relation to movement awareness. Haggard and Eimer thus suggested that the processes involved in the generation of the LRP also might be responsible for our awareness of movements.

The RP has been investigated in a number of different patient populations. In an early study Shibasaki, Shima and Kuroiwa (1978), for example, observed abnormal RPs in approximately 90% of the individuals with Parkinson's disease (PD) that they examined; their RPs were smaller in amplitude and earlier in onset than in intact individuals (also see Oishi, Mochizuki, Du and Takasu, 1995). Dick, Rothwell, Day et al. (1989) likewise observed a reduction in the early portion of the RP in individuals with Parkinson's Disease, which they attribute to abnormal activation of the SMA by the basal ganglia. Unlike previous reports, however, Dick et al. found that the later component of the RP of Parkinson patients was larger than normal, which they suggested might reflect compensatory activity

in other brain areas for the reduced output of the SMA.

Cunnington, Iansek and Bradshaw (1999) found that even the early part of the RP in Parkinson patients can be enhanced when attention is directed at aspects of the movements that are typically executed automatically. They therefore concluded that motor performance in PD could be improved not only by external cues but also by directing attention. On the other hand, Praamstra, Meyer, Cools et al. (1996a) found that unlike neurologically-intact individuals PD patients did not generate higher amplitude RPs before freely-selected relative to stereotypic movements. They attributed this lack of RP modulation in PD to diminished SMA activity in the more demanding free movement task.

Very few studies have examined RPs in individuals with some type of hyperkinetic movement disorder. Adler, Pecevich and Nagamoto (1989), for instance, compared a group of schizophrenics with tardive dyskinesia (TD) with a group of normal subjects and a group of medicated schizophrenics without movement disturbances. TD is a known complication of neuroleptic treatment involving involuntary hyperkinetic movements of perioral and limb muscles. The RPs to voluntary movements in the TD group were on average twice as large as those of the normal controls and schizophrenics without TD. Moreover, the amplitude of the RPs to voluntary movements in the TD group varied as a function of severity of involuntary movements assessed on an independent scale.

A different approach to the analysis of movements in a hyperkinetic disorder was taken by Trenkwalder et al. (1993) who recorded cortical activity time-locked to the characteristic leg-movements in patients with restless leg syndrome. These potentials were compared to those obtained for voluntary simulations of the leg movements by the patients and a control group. While voluntary simulation led to a typical RP, no RP was observed prior to the involuntary myoclonic leg movements in the patients suggesting a subcortical or spinal origin for these movements.

Motor inhibition

Even less is known about the electrophysiological basis of motor inhibition than motor preparation, al-

though as previously noted (see section on language production) promising results are rapidly accumulating from experiments using either a go/no-go or the so-called stop paradigm. When an individual is asked to respond to one class of stimuli (go trials) and to withhold responses to another (no-go trials), the ERP on no-go (relative to go) trials is characterized by a large negativity (1–4 μ V) between 100 and 300 ms after stimulus onset (N200), especially over fronto-central sites (Gemba and Sasaki, 1989; Kok, 1986; Pfefferbaum, Ford, Weller and Kopell, 1985; Sasaki, Gemba, Nambu and Matsuzaki, 1993; Simson, Vaughan and Ritter, 1977).

It has been hypothesized that N200 amplitude varies with the neuronal activity required for 'response inhibition' (Jodo and Kayama, 1992; Sasaki and Gemba, 1993). This hypothesis is supported by the results of studies with surface and depth (2.0–3.0 mm) electrodes in the prefrontal cortex of monkeys (Sasaki, Gemba and Tsujimoto, 1989). In this study, potentials were recorded as the animals performed a go/no-go task on color discrimination (e.g., pushing a button when a green light came on and giving no response when a red light came on). As expected, no-go trials elicited an N200 both at the scalp and in the prefrontal cortex. Sasaki et al. also found that they could mimic the brain processes associated with N200s on no-go trials by stimulating the prefrontal cortex during go trials. More specifically, they could suppress the overt response on go trials by electrically stimulating the prefrontal cortex at the time that an N200 would normally have developed on a no-go trial (see also Sasaki and Gemba, 1993 for a comparison of data from humans and monkeys). These results thus link the N200 elicited in a go/no-go paradigm to response inhibition processes, occurring, at least in part, in the prefrontal cortex.

Equally promising results with regard to the electrophysiology of motor inhibition come from employment of the stop paradigm (De Jong, Coles and Logan, 1995; Naito and Matsumura, 1996). In this paradigm, subjects are presented with stimuli that have to be responded to via speeded button presses. On a small proportion of the trials a second stimulus (the stop signal) is presented immediately following the go-stimulus. The stop stimulus gives rise to a frontal negativity that shares many properties with the go/no-go N200.

To date only the go/no-go paradigm has been used with patients with motor deficits. Mild to moderate Parkinson's patients asked to categorize pictures into objects and animals (with only one class requiring motor responses), i.e., a go/no-go paradigm, showed significantly lower N200 responses than age-matched controls (Münte, Matzke, Kazarians et al., 2000). These data illustrate that electrophysiological measures can be used to monitor inhibitory motor processes in patient populations.

Normal and pathological aging

As people live increasingly longer, there is a greater interest in characterizing the effects of normal aging on cognitive processing, and distinguishing these effects from those due to pathological aging as it occurs in dementia. ERP research has been no exception. Overall, the results of most ERP studies of aging have been interpreted in terms of either slowed cognitive processing or a decline in processing resources with advancing age. Other factors that might be considered, however, include loss of synapses and neurons leading to changes in the orientation and/or size of ERP generators, an altered balance among the different transmitter systems, and changes in cognitive strategies with advancing age. In the following, we will summarize some of the most consistent and important results from the different cognitive domains.

Auditory processing and the MMN

The link between the negativity and echoic (sensory) memory has rendered paradigms wherein the MMN is elicited the primary vehicle for studying the effects of aging on preattentive auditory processing. Pekkonen, Rinne, Reinikainen et al. (1996) examined the MMNs elicited by deviants in frequency and duration dimensions at different inter-stimulus intervals in normal young and elderly individuals. At short ISIs (0.5 and 1.5 s) members of the two age groups were characterized by equivalent-sized MMNs indicating that automatic auditory stimulus discrimination is intact in the elderly. However, at a longer ISI (~4.5 s), the MMN was significantly attenuated in the older participants, thus indicating faster decay of the auditory trace with advancing age. Gaeta, Friedman, Ritter and Cheng (1998) focussed

on the effects of aging on MMNs deviants that differed only slightly (50 Hz) or substantially (300 Hz) in frequency from that of the standards. They found a stable MMN for both levels of deviance in their younger subjects, which was significantly reduced to the large (300 Hz) frequency difference and absent to the smaller frequency (50 Hz) difference in the elderly subjects. Moreover, while all deviants also elicited a P3 component in the younger participants, in the elderly only novel environmental sounds did, suggesting a decreased sensitivity to stimulus deviance with aging.

P300 and stimulus categorization

As previously noted peak P300 latency has been interpreted as indexing some aspect of the duration of stimulus evaluation (Kutas et al., 1977) although this is still a matter of debate (Verleger, 1997). Consequently, many groups have examined the effect of age on P300 latency mostly using simple oddball tasks that can be performed even by cognitively impaired individuals. Indeed, over 30 studies in this area, expertly reviewed in Polich (1996), have found a correlation between P300 latency and age, with latencies prolonged with age. By computing regression lines along with standard deviations it is possible to define the normal limits of P300 latency variation statistically and thus compare any (intact or brain-damaged) individual's latency with the norm. Several laboratories have attempted to use these data to assess the sensitivity and specificity of P300 latency measurements with regard to the diagnosis of dementia (Filipovic and Kostic, 1995; Sara, Kraiuhin, Gordon et al., 1988). While these results appear promising, little use is currently being made of the P300 in clinical practice as it neither makes careful neuropsychological testing obsolete nor provides essential new information for the clinician.

Another observation that has received some attention is an apparent change in the distribution of the P3b topography across the scalp with advancing age. Specifically, over a handful of studies have consistently reported that the P3b has a more frontal distribution in the elderly. Fabiani and Friedman (1995), for example, contrasted the effects of normal aging on the P3a and P3b components in an oddball paradigm comprising, standard, target, and novel stimuli. Recall that novel stimuli typically

elicit an early frontal positivity (P3a) that has been linked to orienting. Consistent with previous reports they observed a posterior P3b to targets and a frontal P3a to novel stimuli but only in their younger subjects. In their older subjects, both classes of stimuli elicited a frontally-distributed positivity. Moreover, while in the younger subjects, target stimuli elicited a frontally distributed positivity at the beginning of the experiment and a posterior P3 at the end, no such topographical change over time was seen in the elderly. These findings indicate that elderly individuals seem to treat target and novel stimuli similarly, and further suggest that elderly individuals may be less able to maintain the templates needed for stimulus categorization (presumably in working memory). In a subsequent study, Fabiani, Friedman and Cheng (1998) found that this shift in the topography of the P3 with advancing age was systematically related to frontal lobe dysfunction assessed with standard neuropsychological tests. Findings with source localization methods suggest that the more frontal P3 distribution in the elderly reflects decreased activity of superior parietal and right prefrontal sources (Anderer, Pascual-Marqui, Semlitsch and Saletu, 1998).

Memory

As the decline of explicit memory is a hallmark of both normal aging and — to a much larger extent — dementia, age-related ERP changes in memory experiments are of particular interest. Several investigators have used the repetition priming paradigm (as an indirect test of memory) to assess effects of normal aging on memory processes. Hamberger and Friedman (1992), for instance, found no differences in reaction time or ERP measures of repetition priming between young and elderly subjects for words that were repeated with a lag of 2, 8, and 32 intervening items. Both age groups showed a more positive ERP for repeated items regardless of inter-item lag. Rugg et al. (1994), observed a similar ERP repetition effect in elderly and young subjects, which was somewhat (~80 ms) delayed in the older subjects. In fact, Friedman et al. (1992) and Rugg et al. (1994) both obtained similar albeit slightly smaller ERP repetition effects even in groups of individuals with probable Alzheimer's dementia. Such data provide clear evidence of relatively spared implicit memory in the face of gross impairments of explicit mem-

ory, consistent with the proposed distinction between implicit and explicit memory processes.

These findings on the effects of aging in indirect memory tasks stand in sharp contrast to results from studies wherein memory is tested directly via recognition tasks. For example, Rugg, Mark, Gilchrist and Roberts (1997) found equivalent ERP recognition memory effects in young and elderly subjects only when one item intervened between first and second presentations; at a lag of 10 items between repetitions, elderly subjects displayed no ERP recognition effect. Similar results were obtained by Swick and Knight (1999).

As discussed in the section on memory, several new paradigms have emerged recently that have supported a further fractionation of the memory ERP effects. On the whole, there are little data from older individuals in most of these new paradigms. One notable exception is the study of Trott, Friedman, Ritter and Fabiani (1997) comparing and contrasting item and source memory in young and elderly subjects. Briefly, during the study phase subjects were exposed to two lists of words that could be distinguished in when they were presented (i.e., temporal source). In the recognition phase subjects were asked to decide first whether a given item had or had not been presented during the study phase, and then whether it came from the early or the late list. While item memory ERP effects were similar in both subject groups, only the younger subjects had a frontally-distributed late onset positivity that varied as a function of source attribution. These promising results underscore the need for further studies that include more precise manipulations of memory parameters.

Language

As discussed in the section on language, a negative component with a peak latency around 400 ms (N400) can be recorded in a multitude of language tasks. One of the key findings in N400 research has been that its latency, unlike that of the P300, is relatively stable across tasks. In a study of the age effects on N400 across the decades from 20 through 80 years of age, Kutas and Iragui (1998) found N400 latency significantly increased linearly by ~2 ms/year and linearly decreased in amplitude by ~0.07 $\mu\text{V}/\text{year}$. In a further study using a similar

paradigm, Iragui, Kutas and Salmon (1996) compared young, old and demented patients and found that the N400 was further delayed and reduced in amplitude in the Alzheimer patients. These data sets were interpreted as indicating less efficient integration of lexical items with semantic context in normal aging, which is further exacerbated in dementia. Corroborating evidence comes from studies of Gunter, Jackson and Mulder (1995, 1996). In one study, Gunter et al. (1995) manipulated working memory load of sentences. Besides a slowed and smaller N400 component, these researchers also described two components that appeared to differ with the individual working memory capacity of the subjects rather than with their age.

The next section will introduce the methodology of standard cognitive electrophysiology.

Overview: from scalp potentials to plots

To conduct a cognitive ERP experiment, one must be able to present stimuli of the desired types while simultaneously acquiring EEG data from several sites on the scalp, along with behavioral data as needed. The time course of the stimulus presentation or response and EEG data acquisition must be synchronized to an accuracy on the order of a millisecond and registered with the stimulus sequence so that the EEG data can be sorted according to the event or event type to which it is temporally registered.

Following acquisition, the EEG data for each subject must be screened for artifacts, either by an automated procedure or manually (usually some combination of both). When scalp potentials are of interest, bioelectric artifacts include potentials generated by eye-movements, blinking, heartbeats, and muscles. Technical artifacts include the saturation or 'blocking' that occurs when the dynamic range of the amplifier is exceeded, intermittent signals caused by loose electrode connections, and interference due to electrical sources in the environment, e.g., nearby electrical equipment. The damage done by some types of artifacts, e.g., ocular artifacts and high frequency electrical interference can be mitigated after the fact whereas that of other types, e.g., large myoelectric potentials and amplifier blocking are irreparable, necessitating dropping the data from further analyses. The remaining data may be processed

further by a variety of techniques including digital filtering, re-referencing the electrode derivation, normalizing, or computing a Laplacian transform. The choices here are dictated in part by the character of the data and in part by the type of signal that is to be extracted from the continuous EEG. When the data have been appropriately processed, the desired experimental measure is calculated (e.g., time domain average potentials, frequency band power, or estimates of neural electrical sources), a selected feature (e.g., peak or mean amplitude, root mean square amplitude) for each participant is measured, and then subjected to a statistical analysis and tabulated. The EEG data are visualized at each stage of this process. As in non-EEG experiments, behavioral data acquired in the course of the experiment are treated in a similar fashion with the proviso that the behavioral and EEG data often need to be coordinated to allow the inferences researchers are wont to make.

General methods

Contemporary ERP research systems are typically built around a multichannel electroencephalograph (EEG) and two or more personal computers (PCs) dedicated to stimulus presentation, digitization and storage of EEG data, and data analysis.

Stimulus presentation

The PC has become the stimulus presentation device of choice in cognitive ERP research because it is relatively easy to use and a cost effective way to present a useful range of auditory and visual stimuli. There are some important limitations, however, some of which are inherent to typical PC hardware and some of which involve the software.

For example, stimulus presentation in real time requires millisecond accurate timing information for stimulus duration, and inter-stimulus intervals. Yet, the system clock in a PC is only accurate to about 50 ms. The solution is to temporarily reprogram the system clock for millisecond accuracy or to install an add-on card that has a clock/counter circuit.

Another family of considerations is related to the video display system. The image on a conventional computer monitor is drawn by sweeping an electron beam back and forth across the phosphors on the back of the glass screen from the top to the bottom.

After the pass of the beam, the phosphor luminance begins to decay and the image will fade away if the image is not refreshed. Until recently, the standard computer CRT in the United States was refreshed at 60 Hz, i.e., once about every 16.67 ms (50 Hz in Europe), although some combinations of newer monitors and video display adapters can be configured for refresh rates above 100 Hz. This way of doing things in the computer hardware has some important consequences for the presentation and synchronization of visual stimuli.

First, the nominal duration of a visual stimulus presentation must be an integer multiple of the duration of the refresh cycle, subject to the qualification in the next paragraph. Second, the integer multiple of the refresh rate is only a nominal figure because the amount of time the CRT phosphor remains visible can vary from practically zero to hundreds of milliseconds depending on the materials and viewing conditions (Bridgeman, 1998; Di Lollo, Seiffert, Burchett et al., 1997). These considerations have critical implications for stimulus durations in the 0 to 100 ms range, e.g., for subliminal presentations, or in which the details of retinal illumination are important.

Finally, in the conventional PC, the internal timing of the monitor refresh is not directly coordinated with the internal timing for shuttling information into and out of the video buffers. Thus a software instruction to place an image in the video buffer for display at time t will do so without regard to the current location of the electron beam in the refresh cycle. It is up to the programmer to synchronize stimulus presentation with the monitor refresh cycle, and avoid latency jitter of ± 8.4 ms for 60 Hz refresh.

Auditory stimuli can be presented in a variety of ways. Simple tones and tone sequences can be generated by programmable tone generators with the timing of the stimuli tracked by a time-locked reference signal. Speech, music, and the like can be presented using tape or the analog-to-digital sound cards now common in 'multi-media' PCs. For some applications, the stimuli can be recorded, stored digitally on the computer hard drive, and edited for subsequent presentation. Using the sound card with digitized stimuli, the EEG recording can be synchronized with stimulus onset by embedding reference signals at known points in the stimulus or by calibrating the playback properties of the presentation

computer. Note that it can take a non-negligible amount of time for a PC to execute a command to pipe a digitized acoustic signal out the line-out jack of the sound card, with (nonlinear) delays likely in reading the signal from the hard drives or introduced by the playback algorithm reading signals from memory, if it was not designed with real-time millisecond accuracy in mind. Even if the playback rate is well behaved, there may be hidden startup delays associated with the execution of the playback algorithm. As with visual stimuli, it is worthwhile ensuring that the time course of auditory stimulus presentation is in fact as assumed.

Recording scalp potentials

The general techniques for recording EEG data for a cognitive ERP experiment are much the same as for clinical EEG recordings. At present, the most common systems for cognitive ERP research digitize continuous EEG and process it off-line. In such systems, scalp potentials are amplified by the electroencephalograph, the analog output of the electroencephalograph is converted to a digital representation by an analog-to-digital converter and stored on a computer hard disk for subsequent processing.

Electrodes: material, positions, placement. Many different types of electrodes are available for recording from the scalp, including surface cup or disk electrodes (4–10 mm in diameter) and subdural needle electrodes (Geddes, 1972; Regan, 1989; Spehlmann, 1985).

Ideally, electrodes would be placed over precisely the same areas of cortex for each subject in an experiment but differences between individual brains make this impossible. Solutions involving brain imaging are usually impractical, and as an approximation, placement of electrodes are calculated with reference to the location of bony landmarks of the skull with interelectrode distances scaled by head size (American EEG Society, 1994; Jasper, 1958). Electrodes may be positioned and affixed to the scalp individually but a common alternative is to use elasticized caps or nets wherein multiple electrodes (tin, silver chloride) are mounted.

With the electrode locations determined, the scalp is prepared by parting the hair, cleaning, and/or lightly abrading the area that will be under the elec-

trode. The aim of cleaning and abrading is to reduce the electrical resistance of the electrode–scalp junction since the ability of the differential amplifier circuits in the typical electroencephalograph to reject common mode noise, e.g., ambient electrical noise from electrical mains, varies inversely with the electrical impedance of the circuit. Breaking the skin also eliminates the skin potential, another source of artifact especially when the components of interest are of very low frequency.

An electrode–scalp junction is formed by applying a small amount of electrolytic gel between the scalp and the electrode. Whether gel or paste is used, the scalp–electrolyte–electrode junction has an intrinsic resistance (R) and capacitance (C), which together act as a high-pass filter that attenuates lower frequency fluctuations in the scalp potentials. The specific frequency response is determined by the electrical properties of the materials used. Surface electrodes are commonly made of gold (Au), silver (Ag), chlorided silver (Ag–AgCl) and tin (Sn). Because of their resistance to artifacts, ease of use and economy, tin electrodes are now widely used for ERP research in which the potentials of interest are generally above 2 Hz. However, the time constant of the electrode–gel–scalp junction for tin is sufficiently low that for recording DC shifts or potentials that evolve over the course of several seconds or more, chlorided-silver electrodes are preferred. Bias and polarization potentials can result in standing potentials between electrodes and between electrodes and scalp if electrodes consisting of dissimilar metals are used or direct current is passed through the junction as when testing impedance with a DC ohm meter. Thus, it is inadvisable to use electrodes of different materials.

In addition to the placement of the electrodes, the type of montage must be determined, and this includes selecting an appropriate reference electrode(s). See, e.g., Nunez (1981, pp. 178 ff.) for discussion. In principle, electrical potentials are measured against an electrically neutral reference; but there is no such spot on the human body — not even the big toe, and certainly not the most commonly used cephalic references such as the nose tip, earlobe, or mastoid process(es).

In general the choice of a single electrode or linked pairs of electrodes results in EEG data whose

properties, i.e., the distribution of potentials across the scalp, depend on the choice of reference position. However, reference free EEG data, i.e., data that are insensitive to the particular choice of the reference electrode can be obtained by mathematically transforming the data after it has been acquired (see discussion of electrode derivations below). Multi-electrode references can be obtained by combining individual electrodes, for instance, by electrically linking the mastoids or by linking electrodes on the sternum and vertebrae near the base of the neck. Simple electrical linkages between the mastoids or earlobes create an electrical shunt that can distort the distribution of scalp potentials but this can be avoided by adding resistors of sufficiently high resistance to ensure that the current flow between the linked electrodes is negligible.

The electroencephalograph. The electroencephalograph (EEG) is an electronic amplifier optimized for bioelectric scalp potentials. It amplifies the tiny scalp potentials from their naturally occurring levels of about $\pm 50 \mu\text{V}$ to a level that matches the input voltage range of the analog to digital converter. It also provides some initial signal conditioning of the scalp potentials, attenuating high-frequencies in the amplifier output signal to prevent aliasing artifacts (see discussion of analog to digital conversion below). Simply applying the leads of a sufficiently sensitive voltmeter to two electrodes affixed to the scalp would not reveal what we recognize as characteristic background EEG because of high amplitude interference from ambient electromagnetic fields. Since scalp electrodes are in fairly close proximity, this interference tends to be fairly constant across recording sites, and can be subtracted out via common mode rejection built into conventional differential amplifiers. There is typically one amplifier channel for each position on the scalp that data will be acquired from, with the number of channels varying from a few for recording of BERs to the more common number around 32, all the way up to 128 for high density arrays in cognitive ERP studies.

Spontaneous EEG potentials recorded at the scalp of healthy awake subjects generally fall in the 50 to 100 μV range varying with cortical folding and skull thickness. The potentials are much larger on the scalp of non-human primates and human infants.

The amplifier ‘gain’ is the factor by which these input signals are multiplied. For EEG signals on the order of 50 μV , gain factors of 5 K or 10 K are common. The optimum gain depends the amplitude of the input scalp potentials and the output voltage range of the amplifier (often in the ± 2.5 to 10 V range). It is important not to have gain so low as to lose precision nor so high that large signals will exceed the output voltage range of the amplifier (i.e., block) causing parts of the signal to be irretrievably lost.

The main function of the amplifier filters is to attenuate certain ranges of frequencies in the changing scalp potentials. Although the decision to deliberately throw away some of the EEG ‘data’ may seem initially alarming, at least some signal conditioning is necessary if the analog data are being digitized. Aliasing, for instance, can be avoided by bandlimiting the frequency content of the amplifier output, in particular, by ensuring that high frequencies are adequately attenuated. Also, filtering can be used to remove artifacts as long as their frequency content does not overlap with that of the signal of interest. Cortical potentials can range from very slowly changing potentials, essentially DC shifts that evolve over the course of several seconds, to BAEPs which, in addition to lower frequency components, have significant energy at frequencies over 500 Hz. The question of exactly what passband to select depends crucially on the frequency characteristics of the signal one wishes to observe.

Analog filters do not exhibit ideal behavior in the sense that they do not completely eliminate energy above or below a specified frequency and pass remaining frequencies through unchanged. In the first place, the extent to which frequencies are attenuated varies as a function of frequency. The frequency response of a filter is typically characterized by (1) the 3-dB corner frequency, i.e., the frequency at which the gain is -3dB , and (2) the ‘rolloff’ or rate at which gain changes as a function of frequency, which can be expressed as change in dB per octave, i.e., per doubling of the frequency. In addition to changing the amplitude at a given frequency, analog filters also change the phase. Although this change is greatest outside the pass band, phase lead or lag can also extend into the pass band and distort the timing of peaks and troughs in the waveform.

There are many different types of analog filter designs, and they make different types of tradeoffs. For instance, some have particularly flat pass bands, or particularly steep rolloffs, or linear phase vs. frequency characteristics.

Analog to digital conversion. Using the same sort of digital technology that allows the analog (continuous) acoustic signal produced by an entire symphony to be represented as a sequence of (discrete) numbers on a CD, the continuous analog output of the electroencephalograph can also be digitized. The basic technique is to ‘sample’ the analog signal, i.e., to measure to within some finite numerical precision at periodic intervals. Both the rate at which the signal is sampled and the precision of the numeric representation are critical for accurately representing the data.

Choosing an appropriate sampling rate is a trade-off. Higher sample rates allow higher frequencies present in the signal to be accurately represented but generate larger data sets which require more computer storage and take longer to process. In addition, beyond a certain point, higher sample rates do not lead to any better representation of the signal. If the signal varies sufficiently smoothly from sample to sample, sampling the intermediate values adds no additional information. The minimum degree of ‘smoothness’ required is given by the Nyquist frequency which is $\frac{1}{2}$ of the sample rate, although in practice, data are typically oversampled at 2.5 to 5 times the Nyquist frequency. At a given sampling rate, frequencies above half this sample rate will appear in the digital record as spurious low frequency components, i.e., aliasing.

The second factor is the degree of numerical precision used to represent the continuously varying analog amplified output. The analog-to-digital (A–D) converter divides up the range of input voltages into however many distinct values it has available and maps non-overlapping ranges of voltages into these numeric values. In general, n bits permit 2^n distinct values to be represented. So for instance, if the input voltage can vary between 0 and $+2\text{ V}$ and the A–D converter uses four bits to represent these voltages, it might treat voltages in the range 0–0.5 as 0, 0.5–1 as 1, 1–1.5 as 1.5, and 1.5–2 as 2. The error introduced by treating 1 V and 1.25 V signals as

the same is the ‘quantization error’. Clearly, having more bits available for the numeric representation of the signal permits the input range to be divided into smaller ranges, and this allows smaller differences in the input voltages to be distinguished. Twelve bits with 4096 distinct values are now common and in some instances 14 or 16 bit A–D converters are used.

Data analysis

There are a wide variety of techniques for analyzing EEG data and professional standards for reporting the results of cognitive ERP research are articulated in Heinze, Münte, Kutas et al. (1999) and Picton et al. (2000). This section will outline some of the filtering and time domain averaging techniques one is most likely to encounter in a cognitive electrophysiology research report. A selection of newer techniques will be sketched in subsequent sections.

EEG data. Schematically the data in an ERP experiment can be classified hierarchically as follows:

Each experiment	= a set of subject groups
Each subject group	= a set of subjects
Each subject	= a set of within subject experimental conditions and levels
Each within subject condition and level	= a set of trials
Each trial	= a set of electrode positions (EEG channels)
Each channel	= a set of data samples recorded at regular intervals
Each sample	= the digitized version of an analog scale potential value

Conceptually then, the data from a typical cognitive electrophysiology experiment consist of a six-dimensional array of digital EEG samples, with the dimensions of the array as follows: Groups (for between subject variables) \times Subjects \times Condition (for within subject variables) \times trial \times channel \times timepoint. The following will outline some common procedures for visualizing and quantitatively analyzing these large data sets. Of primary interest in cognitive experiments are comparisons between groups and between within subject conditions.

The peak-to-peak amplitude of background EEG recorded at the scalp is typically in the 25 to 100 μV range whereas the amplitude modulations of the potential elicited by a stimulus event are typically much smaller ($\sim 5\text{--}10 \mu\text{V}$). Furthermore, the differ-

ence in event-related amplitude modulation by an experimental manipulation can be smaller still. It is not uncommon to expect an experimental manipulation to produce only a 1–2 μV difference between ERPs. In general, the small amplitude ERP signals of experimental interest are buried in relatively higher amplitude background EEG noise. The signal-to-noise ratio can be improved in a variety of ways including selectively filtering in the frequency domain and time-domain averaging.

Frequency filtering. One technique to improve the signal-to-noise ratio is to empirically or theoretically identify the frequency characteristics of the signal of interest and then selectively filter the data to pass these frequencies while stopping the others. In addition to passing energy carried by the ERP of interest, if the frequency characteristics of the noise are known, it can be selectively filtered out.

Frequency filtering is the process of selectively removing or altering parts of the frequency content of a signal to create a new signal. Filters, both in continuous and discrete time, can be grouped loosely into one of four categories: lowpass, highpass, bandpass, and notch. A lowpass filter passes low frequencies, but stops high frequencies above the cutoff frequency; it is useful for noise removal, interpolation, and data smoothing. A highpass filter passes high frequencies, but stops low frequencies below the cutoff frequency; it is useful for removing DC or low frequency drift. A bandpass filter passes a band of frequencies, stopping all others. A notch filter removes all frequencies between the cutoff frequencies; it is useful for removing noise at a particular frequency, e.g., 60 Hz.

Filtering can be done either with analog filters typically built into circuitry of the bioamplifier or with a variety of digital signal processing techniques after the data are digitized. Some analog filtering is necessary to avoid aliasing artifacts, and the rest should be undertaken with caution for several reasons. Filters typically attenuate rather than eliminate energy at various frequencies and the extent of the attenuation can vary from filter to filter. Certain sorts of analog filters significantly phase shift frequencies in the pass band and digital filters often corrupt the signal at the beginning and end of the digital record. Finally, a difficulty with all frequency-based filtering is that some ERPs may have may have significant energy in the

same frequency range as artifacts. Specific examples include the potentials in the first 200 ms post stimulus which often have significant energy at the higher frequencies characteristic of myoelectric artifact and the slower ‘cognitive’ ERPs such as the P300 and the N400 that have significant energy in the 10–12 Hz band characteristic of background alpha activity. Filtering to attenuate frequencies in these ranges would throw out the ERP baby with the noise bathwater. See Nitschke, Miller and Cook (1998) for a tutorial review of digitally filtering EEG data.

Time-domain averaging. The most common technique for improving the ERP signal-to-noise ratio is signal averaging in the time domain. In this technique, the data points from each of the trials in an

experimental condition are aligned with respect to the onset of the stimulus. Then for each moment in time, the arithmetic mean of the recorded samples is calculated. The result is the time-domain average of all the ERPs in the experimental condition.

The time domain averaging process is illustrated schematically in Fig. 18. (Fig. 18A shows an ERP-like signal embedded in epochs of simulated background EEG [$n = 4, 16, 32, 64$]. Fig. 18B shows the result of averaging these epochs in the time domain, illustrating the extent to which the stationary signal emerges as a function of the number of trials being averaged.)

In principle, the numbers of trials that must be averaged to get a meaningful estimate of an average

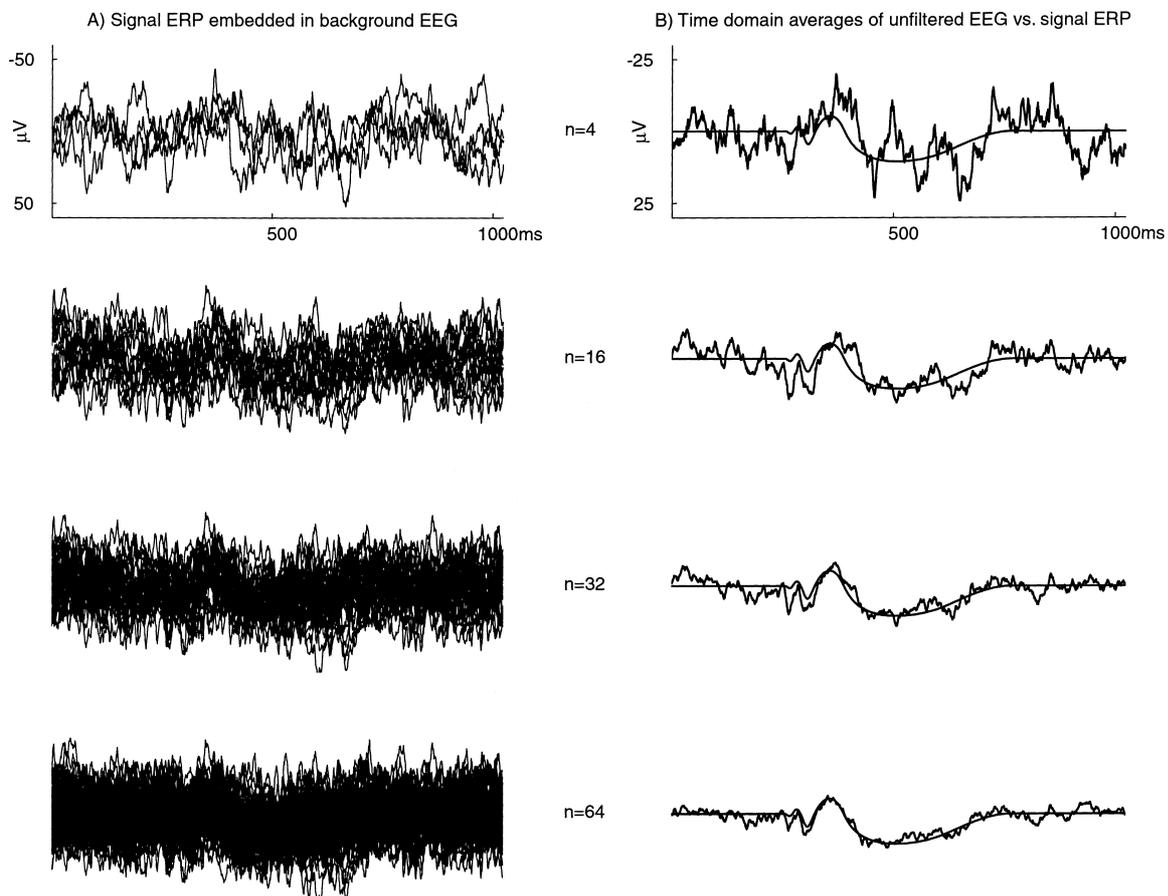


Fig. 18. Time domain averaging. (A) shows 4, 16, 32, and 64 epochs of an ERP-like signal embedded in simulated background EEG. In the ideal case, improvements in the signal to noise ratio vary with the square root of the number of epochs/trials, n , being averaged. (B) illustrates the difference between the time domain average and the embedded signal for different numbers of trials.

ERP or the difference between two ERPs depends on the characteristics of the ERP and the background noise. In practice, for very small signals such as BAEPs, very large numbers of trials (~ 1000) are used. For cognitive experiments in which a difference between experimental conditions of $2\text{--}3\ \mu\text{V}$ is expected, averaging 30 stimuli in each condition for each of 16 subjects is a good working number. Good results can still be obtained with fewer trials if the difference between experimental conditions is larger, or there is little variability across trials and subjects. The number also depends on the question under study. Much fewer trials are needed to establish that two conditions reliably differ at some point than to measure the onset latency of the difference.

Time domain averaging assumes that the ERP signal in each trial is identical, and that the background EEG varies randomly. Hence as the number of trials that are averaged together, increases, the mean of the random EEG tends toward zero. Averaging offers an improvement in the signal-to-noise ratio of \sqrt{n} where n is the number of trials being averaged together (Regan, 1989, Appendix 1.1). Both the assumptions of a stationary signal and random noise are violated to some degree in EEG data. Like any other calculation of an arithmetic mean, the time domain average is sensitive to outliers.

The process of time domain signal averaging collapses the data recorded at each scalp location in each trial of a given subject into an average ERP for each experimental condition of interest. These waveforms are a time series of data points that generally are reduced to the values of the dependent variables for subsequent statistical analysis.

Data reduction. The three most common dependent measures used in cognitive experiments are peak waveform amplitude, peak waveform latency, and mean waveform amplitude in some time window. These measures are often computed for a specific pre- or post stimulus interval after the average waveform has been normalized by subtracting the mean amplitude of a specified prestimulus window. This 'baseline' adjustment ensures that the ERP waveforms all start from the same, on average, prestimulus voltage. One alternative to calculating amplitude relative to a prestimulus baseline is the calculation of amplitude relative to another specified peak, i.e., a peak-to-

Selected ERP data reduction measures

- (i) 100ms prestimulus baseline
- (ii) peak latency 75-150ms = 110ms
- (iii) peak amplitude 150 - 300ms = $4.50\ \mu\text{V}$
- (iv) area 300 - 500ms = $-848\ \mu\text{Vms}$
- (v) mean amplitude 300 - 500ms = $\text{area}/\text{interval} = -4.24\ \mu\text{V}$

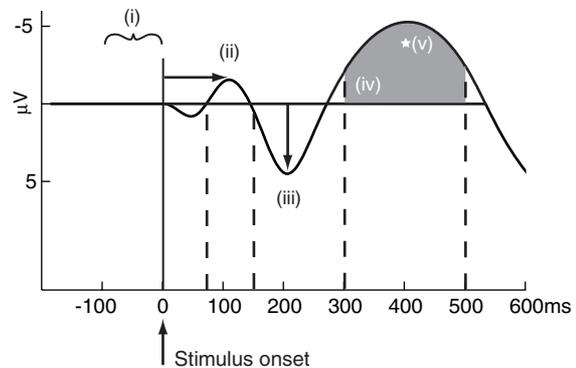


Fig. 19. ERP data reduction measures. (i) is the 100 ms prestimulus interval. The mean voltage over this interval is commonly used as a baseline voltage for the measurement of post-stimulus potential amplitudes. (ii) is the latency of the maximum negative peak amplitude in the interval 75–150 ms post stimulus; (iii) is the peak amplitude in the interval 150–300 ms post stimulus; (iv) the shaded region indicates the area obtained when amplitude is integrated (summed) over the interval 300–500 ms post stimulus; (v) is the mean amplitude in the interval 300–500 ms post stimulus calculated by dividing the integrated amplitude over the interval by the length of the interval.

peak amplitude measure. Alternatively, the peak can be identified by its relative position in a wave train, e.g., the first negative, or second positive peak, and its amplitude or latency calculated. In this case, the peak is not constrained to occur in some specific interval. Fig. 19 illustrates with a cartoon waveform how some of these measures are calculated.

Choosing a given measure to use a dependent variable for a specific experiment can be guided by the question at hand, theory, previous experimental work, the usual and customary procedures found in the literature, and practical factors like ease of calculation. If the relative timing of cognitive processes is of interest, the latency of a particular peak might be an appropriate choice. Peak amplitude and latency measures are only suitable when the waveforms at issue have clearly defined peaks, otherwise mean amplitude measures are preferable. Mean amplitude in an interval of interest can be used to smooth out

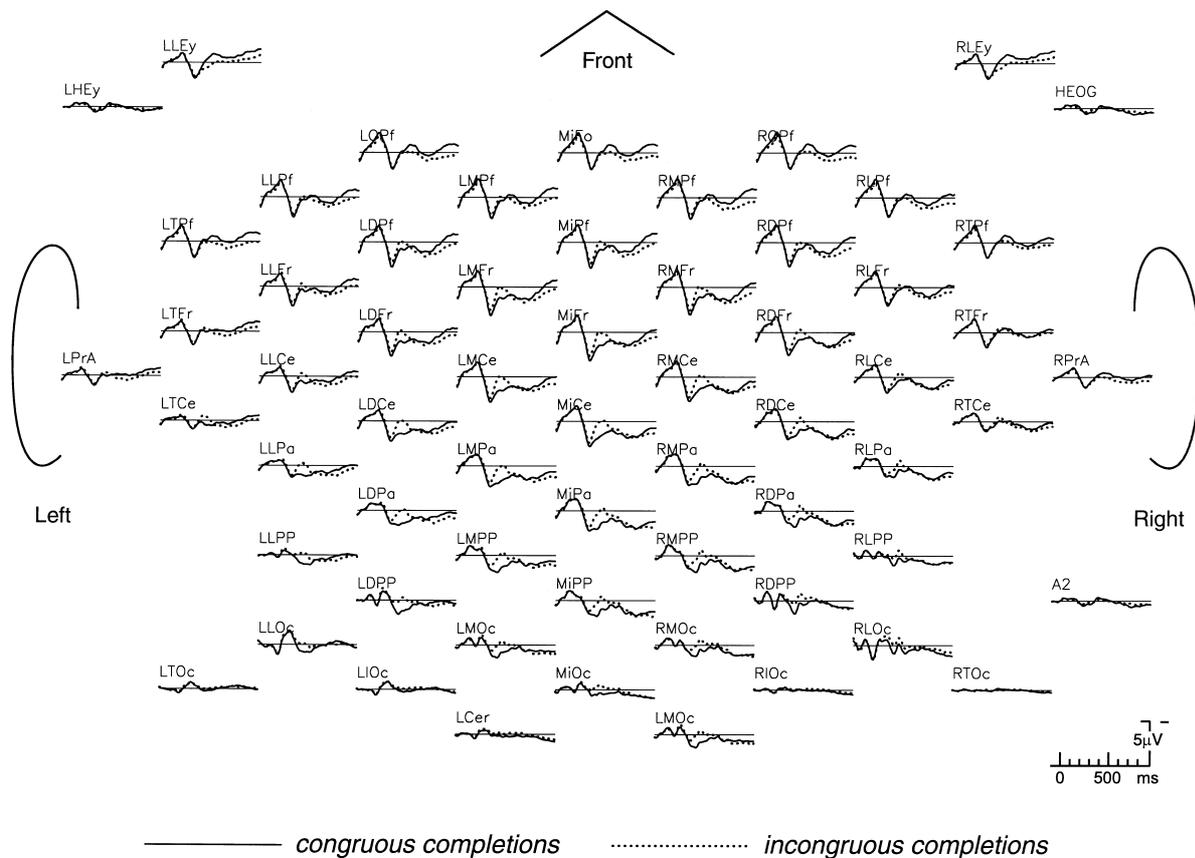


Fig. 20. Grand average time domain N400 ERPs elicited by semantically congruous and semantically incongruous sentence final words at 62 electrode positions. This view is looking down on the top of the head with the ears to the sides and the nose at the top of the figure.

smaller variations and characterize the central tendency of the potential at that latency. Some alternatives to these simple time domain voltage measures are reviewed below.

Visualization: know thy data. Key to understanding the vast quantities of EEG data acquired in an experiment is to be able to visualize it at different levels. Of particular value are the ability to visualize (1) single trial ERPs; (2) condition average waveforms for individual subjects (collapsing across trials); and (3) condition average waveforms for groups of subjects (collapsing across subjects, so-called grand average). These waveform data can be represented in a variety of ways, with the most common being time-series plots (voltage over time), surface (potential or current source density) maps, and 3-D rendering.

Fig. 20 illustrates how grand averages for two experimental conditions for 64 channels can be overlotted. The relative locations of the electrode positions in three-dimensions are projected into two-dimensions. Although interelectrode distances are not accurately represented, the relative positions of the electrodes lateral to the midline and from front to back are preserved. This plot makes it easy to compare the time course of the waveforms in the two conditions at different post stimulus latencies. For example, the responses to congruous and incongruous completions do not differ until about 250 ms, at which point incongruous completions elicit much greater posteriorly distributed negativity (N400).

At the level of individual trials, time series plots can be used as computer renderings of conventional pen-and-paper EEG strip charts. The two main con-

texts for visualizing single trial data are monitoring the data for various problems (artifacts, equipment problems) during acquisition, and reviewing the data for artifacts and integrity after it has been collected and before it is analyzed. The visualization of single trial time series at this stage is important since these are the basic EEG data and the results of all subsequent analyses are strictly determined by their properties. Like any time-series data, a range of statistical properties can be quantified including their range and standard deviation. This kind of information can be instructive, but does not obviate inspecting the raw data.

As noted above, time-domain averaging takes a given subject's individual experimental trials, aligns them with respect to stimulus onset, sorts them into the different (within subject) experimental conditions, and then computes a single waveform that is the mathematical average of the individual trials in each condition. These single subject condition averages are waveforms with the same structure as single trials, i.e., some number of channels with some number of samples per channel. The same resources used to visualize single trial data should be able to accommodate single subject condition averages with at most minor modification. These condition averages for each subject are then reduced according to the measure of interest, and the inferential statistics that support hypothesis testing are conducted on these individual subject measures.

After the data are reduced to a single measure for each subject and each experimental condition, the EEG measures are like the mean reaction time or error rate of a behavioral response paradigm. Line and bar graphs serve the same purpose in ERP research as they do in behavioral research, representing the main effects or interactions of the experimental variables.

Other techniques and measures

The standard ERP signal processing procedures discussed above are a combination of analog filtering, digital filtering, and time domain averaging. A wide variety of other techniques have been used to address issues such as low signal-to-noise ratio, trial-by-trial latency jitter in the time course of the ERPs, and identification of the neuroelectric generators of

the scalp potentials. With the advent of ever more powerful computers, the division of labor in signal processing has shifted more and more to the digital domain, and the techniques reviewed below use software algorithms to post-process digitized EEG data. Briefly reviewed are additional techniques for sifting information content out of the EEG data and for looking for different types of information.

Scalp topography and electrode derivations

As discussed above, conventional EEG recordings use differential amplifiers to suppress common-mode noise. As a result the potential attributed to 'an electrode' at a given scalp site is in reality, the voltage difference between that scalp site and some other reference electrode. The manner in which electrode pairs are connected to the differential amplifier is the 'derivation'. Traditionally, derivations in which pairs of difference potentials are measured between nearby electrodes are termed 'bipolar', whereas those in which difference potentials are measured between electrodes at locations of interest and some relatively distant electrode (of no particular theoretical interest) are termed 'monopolar'. This terminology is harmless as long as it does not obscure the facts that (1) all derivations measure voltage differences between pairs of electrodes, and (2) there are no 'inactive' reference sites on the body. Since the difference potential between a pair of electrodes is a function of the electrical field at both, an observed difference can be driven by either one or both in combination.

Fig. 21 uses hypothetical low frequency sinusoidal data at four scalp sites (Fz, Cz, P3, P4) and a higher frequency signal at the reference electrode A1 to schematically illustrate how potentials at the 'theoretically uninteresting' reference electrode can contaminate the observed scalp potentials. Fig. 21A shows the hypothetical 'true' slow sinusoidal potentials at the three scalp sites and the high frequency potential at the reference site, each relative to an infinitely distant reference. Fig. 21B shows the same data referenced to A1 as the shared or 'common' reference electrode, i.e., ($V_{Fz}-V_{A1}$, $V_{P3}-V_{A1}$, $V_{P4}-V_{A1}$). The contamination of each recording by the high frequency potential of the reference electrode is patent.

This sort of contamination by the reference site can be eliminated by re-referencing each site to the common average reference. The common average

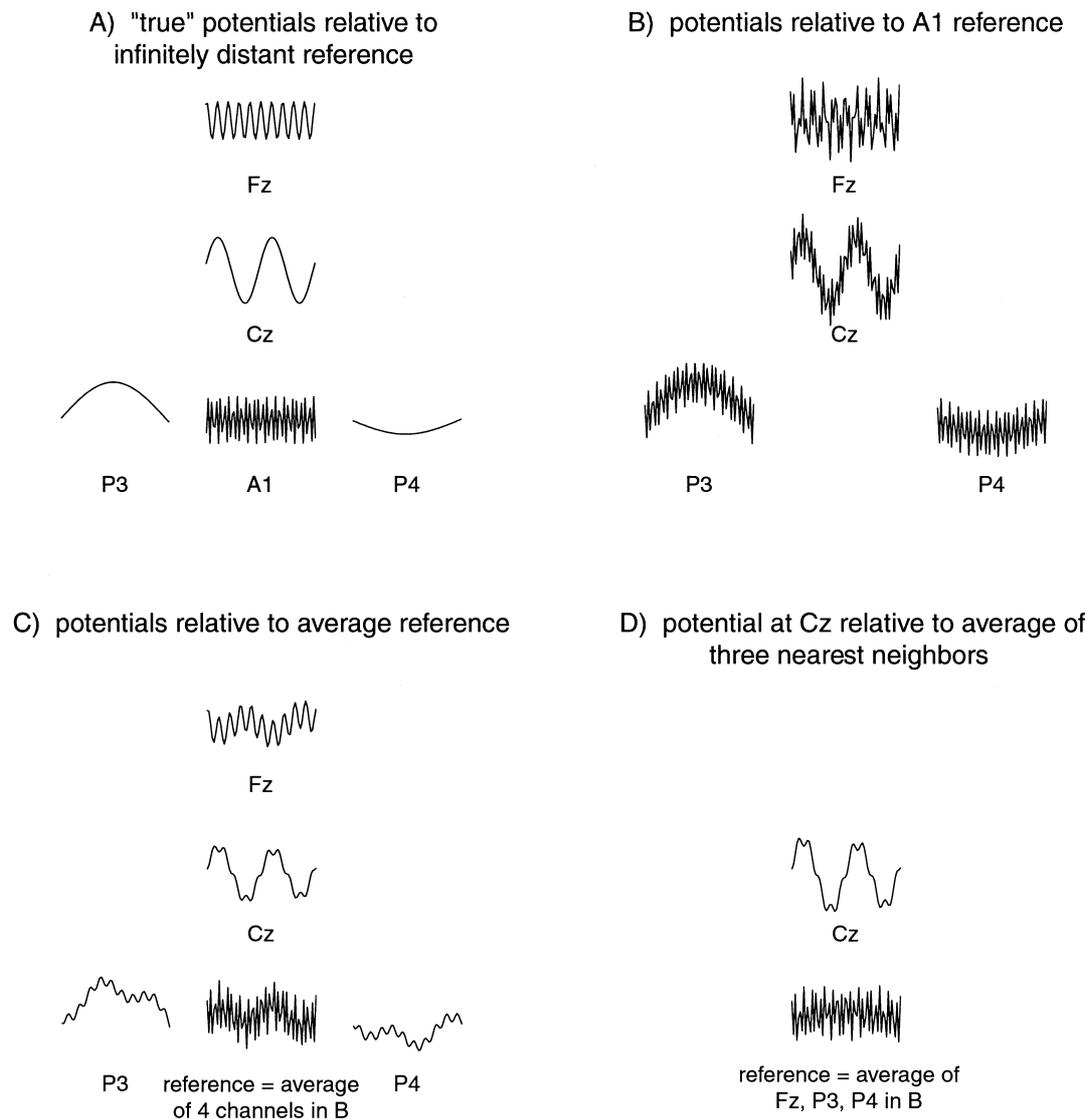


Fig. 21. Different choices of reference. (A) illustrates the 'true' potentials that cannot be directly observed. (B) illustrates the widely used common reference and the impact that noise at the reference site has on all the sites which are referred to it. (C) illustrates how the common average reference eliminates the noise at the reference site but introduces unwanted potentials from the other sites. (D) illustrates an alternative average reference in which the average of Cz's three nearest neighbors is used as the reference potential. Note that the potential at Cz is somewhat different in (C) and (D).

reference is the average at each point in time of all the sites. Fig. 21(C) illustrates this common average reference for the data in Fig. 21(B) and the potentials at each site referenced to this common average. Note that the high frequency contamination by A1 has indeed been eliminated. Fig. 21(D) illustrates an

alternative presentation of the same data at Cz, in this case, referenced to the average of its three nearest neighbors (Fz, P3, P4). Note that this derivation is also reference free, and also provides an estimate of the local rate of change of the potential field, i.e., current source density (see below).

Some comments are in order. Since selecting the location for the reference electrode can be difficult, if not arbitrary, it can be a virtue to have measurable potentials that do not depend on the initial choice. For instance, if there is unwanted variability at a common reference electrode, calculation of the common average reference can eliminate a source of noise. That said, however, even an average reference ‘contaminates’ the data at an individual site by the contribution of all the channels that go into the average, and rarely do these cover the head completely; i.e., a reference free recording at some site is still not a pure measure of activity at that location and that location only. This is clear from Fig. 21C in which the potentials at the electrodes deviate from the ‘true’ potentials in Fig. 21A by a blend of the ‘true’ Fz, Cz, P3, and P4 waveforms. Even ‘reference free’ derivations still involve the difference between the potential at the site of interest and some quantity or other. The fewer the number of electrodes overall, the more an average reference is like any particular single reference. The common average reference is also liable to a bias that results from conventional electrode montages that sample above but not below the sources of the potentials (Junghöfer, Elbert, Tucker and Braun, 1999). Discussions of the common reference and common average reference can be found in Desmedt, Chalklin and Tomberg (1990) and Dien (1998a).

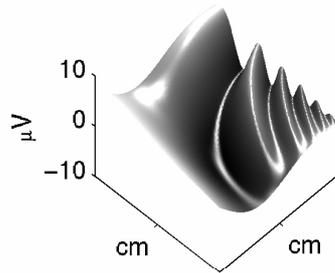
Another type of derivation that has enjoyed application in the analysis of scalp potentials is used to estimate the ‘current source density’ (CSD), based on the spatial distribution of potentials across the scalp. The CSD is a reference free quantity in the same sense as the common average reference, and also has a physical interpretation in terms of the quantity of current flowing from sources in the brain, in this case through the skull normal to the scalp. This physical interpretation is based on the fact that the source density of a potential field distribution is proportional to the Laplacian transform of the field. A variety of techniques for estimating the surface Laplacian have been studied, often in connection with models of head geometry, volume conductance, and estimates of the cortical sources of scalp potentials (Babiloni, Babiloni, Fattorini et al., 1995; Hjorth, 1975; Huiskamp, 1991; Law, Nunez, Wijesinghe et al., 1993; Oostendorp and Van Oosterom,

1996; Perrin, Bertrand and Pernier, 1987; Perrin, Pernier, Bertrand and Echallier, 1989). Informally, the CSD quantifies the difference between the potential at a given scalp site and its surrounding neighbors. This means that in areas of the scalp where the potentials are of similar amplitudes, the CSD is smaller, and in areas where there are abrupt changes in potential from electrode to electrode, the CSD is larger.

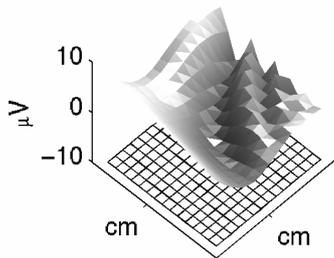
Fig. 22A illustrates a two dimensional potential field in which the spatial frequency of the potential varies by region. The magnitude of the potential is represented by the height of the surface, so regions with large peaks and troughs correspond to regions of large positive and negative potentials respectively, and regions with closely spaced peaks are regions with higher spatial frequency, as in the far right. Fig. 22B illustrates the potential field sampled at 256 points on a regular 16×16 grid. Although the representation of the field is less smooth than the underlying field, the major features of the potential distribution are preserved. Fig. 22C plots the four-point nearest neighbor approximation of the Laplacian using data from the 16×16 point grid. Fig. 22C illustrates how the transform selectively preserves information about the higher spatial frequencies. Fig. 22D illustrates the original potential field sampled at only 36 points on a regular 6×6 grid. Although some features of the slower spatial frequencies are preserved, the higher frequencies are not accurately represented and, in fact, aliasing is evident in the form of the low spatial frequency peaks and troughs running orthogonal to the ripples in original potential field. Fig. 22E illustrates the four-point nearest neighbor approximation of the Laplacian based on the 6×6 grid. Since this approximation is based on data that contain aliasing artifacts, it is not surprising that this estimate badly misrepresents the current source density of the underlying field. The flat edges of Fig. 22C,E are a consequence of the fact that simple ‘nearest neighbor’ approximations of the CSD can only be calculated for electrodes that are surrounded by other electrodes, thereby excluding electrodes around the perimeter.

The potential field at the scalp is continuous and the Laplacian must be approximated from the activity recorded. Just as more closely spaced samples are required to accurately represent higher

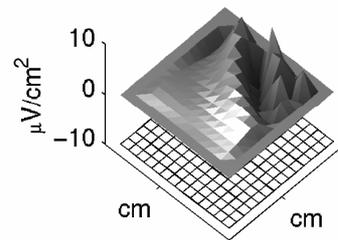
A) Spatial distribution of potentials on a 2-D surface



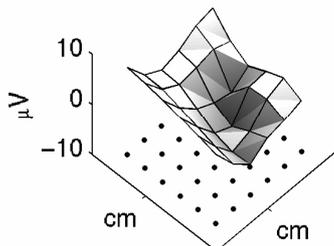
B) Distribution of surface potentials spatially sampled on a high density 256 point grid (16 x 16)



C) Nearest 4 neighbor CSD estimate sampled on a high density 256 point grid (16 x 16)



D) Distribution of surface potentials spatially sampled on a low density 36 point grid (6 x 6)



E) Nearest 4 neighbor CSD estimate sampled on a low density 36 point grid (6 x 6)

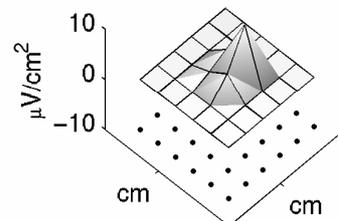


Fig. 22. Surface potentials (A, B, D) and nearest 4 neighbor CSD estimates (C, E) based on higher and lower spatial sampling frequencies. The high density CSD in (C) has large values at regions where there are larger local changes in the potential field in (A), i.e., at the peaks and valleys. The values of the CSD are smaller in regions where there are smaller local changes in the potential, e.g., (A), left, despite the overall higher amplitude of the potentials in this region. Note the pronounced aliasing for both the potential map and the CSD when the potentials are spatially sampled on the low density grid.

frequencies in a time varying waveform, closely spaced electrodes are required to accurately represent high spatial frequencies in the potential field (Srinivasan, Tucker and Murias, 1998). The number of electrodes required to adequately sample the

spatial frequencies observed in scalp potentials has been estimated to be between about 100 and 250 (Junghöfer, Elbert, Leiderer et al., 1997; Srinivasan, Nunez, Tucker et al., 1996; Srinivasan et al., 1998). The choice of the reference electrode is relevant

as well (Gencer, Williamson, Gueziec and Hummel, 1996).

The CSD transform has implications for inferences about the location of underlying neuronal generators. As the field due to volume conductance from a set of current sources (current exiting) and sinks (current entering) that are far from the scalp will tend not to change much between closely spaced electrodes, their contribution to the surface Laplacian will be small. On the other hand, the field due to a set of sources and sinks closer to the electrodes may show more variation at the scale of interelectrode distances. Accordingly, the likely generators for the current sources identified by a surface Laplacian transform are in the surface of the cortical sheath near the recording electrodes. An exception to this is a tangentially-oriented dipole because the projection at the scalp of the polarity shift along the plane perpendicular to the axis of the dipole can result in an abrupt local change in the potential field. Whether this bias is a liability or an asset depends on whether one is primarily interested in measuring the activity of electrical sources deep in the brain or the activity of superficial sources.

Analytic techniques

The standard technique of time-domain averaging followed by reducing the average potential waveforms to peak or mean amplitude or peak latency measures extracts information about phase-locked voltage amplitude changes. This is just one sort of information contained in such recordings.

This section will outline some other analytic techniques based on Fourier transforms, wavelets, and linear components. There are variations within each type of analysis and many theoretical and practical considerations involved in the selection of a particular analytic technique. There is, to our knowledge, no one analysis technique that is superior to alternatives in every regard and all are controversial in one way or another, e.g., with respect to assumptions that are not satisfied, artifacts they produce, or inability to support the desired inferences. The aim should be to select an analysis best suited to the support the inferences to be drawn based on the design and experimental predictions (see references below).

In moving beyond simple time domain averaging, a central thrust in analysis of the EEG data is to split

the time domain waveform into constituent parts of one sort or another and then treat these parts as the units of subsequent analyses. Three important classes of these analytic techniques are gaining in popularity:

Fourier analysis. The Fourier transform is a mathematical transformation that maps the time domain potential waveform $x(t)$ onto a corresponding representation in the frequency domain $X(f)$ by treating the time domain waveform as the weighted sum (integral) of sinusoidal waveforms whose amplitude and phase varies as a function of frequency. The Fourier transform determines the strength of the signal at each frequency.

Wavelet analysis. A signal approximation theory that describes the frequency content of a signal in time. The time domain potential waveform is split into representations that characterize amplitude variations at different time scales, e.g., one level of wavelet analysis will characterize features of the waveform that change gradually over time while ignoring small scale changes; another level will characterize fine-grained changes that occur over small intervals while ignoring the gradual changes.

Component analyses. The time domain waveform is treated as the linear sum of components which satisfy specific mathematical conditions, e.g., being uncorrelated or linearly independent. This class of analyses includes principal component analyses (PCA) and independent component analyses (ICA).

Each of these techniques breaks the time domain waveform into particular sorts of pieces and permits further processing or analyses that are impossible or impractical in the time domain. Furthermore, these analyses are often reversible. This permits the time domain waveform to be decomposed, and then recombined into a new time domain waveform after one or more parts are modified and/or discarded.

These techniques can also be used to investigate the neurophysiological and cognitive significance of the component parts. For instance, the manner in which the frequency content or power spectrum of the EEG changes in response to events has been attracting an increasing amount of attention. Reduction in the amplitude of occipital alpha following visual stimulation was among the earliest event-related effects observed in human EEG (Berger, 1929). Event-related modulations of EEG power in

specific frequency bands have been observed and interpreted in terms of information processes such as perceptual feature binding, attention, motor preparation, and memory (see the edited volumes by Andreassi and Gruzelier, 1996; Basar and Bullock, 1992; Pantev, Elbert and Lütkenhöner, 1994). Recent event-related time–frequency experiments have investigated a wide range of cognitive processes including visual sensory processes (Nalcaci, Basar-Eroglu and Stadler, 1999), selective attention (Gomez, Vazquez, Vaquero et al., 1998), visual object processing (Hermann, Mecklinger and Pfeifer, 1999; Iesoaglu-Alkac, Basar-Eroglu, Ademoaglu et al., 1998), memory (Tallon-Baudry, Bertrand, Peronnet and Pernier, 1998; see Klimesch, 1999 for a review), lexical processing (Klimesch, Doppelmayr, Pachinger and Russeger, 1997; Pulvermueller, Lutzenberger and Preissl, 1999), real and imagined movements (Neuper, Schlögl and Pfurtscheller, 1999; Van Burik and Pfurtscheller, 1999), and cognitive aging (Yordanova, Kolev and Basar, 1998). The following sections outline Fourier and wavelet analyses, with an emphasis on applications to frequency domain analyses.

Fourier analysis and the frequency domain. Intuitively, the idea behind Fourier analysis is to treat a time domain waveform as composed of sinusoidal waveforms that, when added together, give the pattern of peaks and troughs in the original waveform. Fourier's interesting mathematical result is that any infinite periodic waveform of period T can be decomposed into a unique linear combination of sinusoids of period T characterized by their amplitude, frequency and phase. In other words, such a function $x(t)$ can be represented as the weighted sum (integral) of many different sinusoids with weight function $X(f)$ for each different frequency sinusoid.

It is also possible to take the Fourier transform of a discrete signal (e.g., digitized EEG data) which is a continuous function of frequency (discrete time Fourier transform or DTFT). However, it is more common to use the discrete Fourier transform (DFT), which is equally spaced samples of the DTFT, and can be implemented on a computer. The fast Fourier transform (FFT) is a computationally efficient algorithm designed to speed the DFT. The FFT of a sequence of N data points produces N complex

numbers (encoding amplitude and phase), each of which corresponds to the center of one of $N - 1$ evenly spaced frequency bins in the range between 0 Hz and $\frac{1}{2}$ the frequency of the data sampling rate, i.e., the Nyquist frequency. FFTs on longer stretches of data improve the frequency resolution within the bandwidth determined by the sampling rate. It is impossible to define a signal that is arbitrarily small in both the time and frequency domains. As EEG data are neither infinite nor periodic, applying the FFT without care may lead to distortions in estimating how much of what frequencies are in the time domain waveform. However, a great deal of effort in digital signal processing has been expended to reduce the distortions in FFT analyses of EEG data by preprocessing the waveform in various ways. If used with care, FFT methods are important analytic tools in ERP research data processing. Rigorous treatments of Fourier transforms and FFT algorithms can be found in standard digital signal processing textbooks (Marple, 1987; Percival and Walden, 1993), and computer program source code for the FFT is widely available, e.g., in Press, Teukolsky, Vetterling and Flannery, 1994). For a tutorial review of FFT applications to EEG data see Nitschke et al. (1998).

Although time domain averaging is an appropriate technique for recovering event-related potential fluctuations that are both time- and phase-locked from trial to trial, it is inadequate if the potentials of interest do not have the same phase relation to the onset of the stimulus. There are a number of analytic techniques that can be used to measure event-related changes in non-phase-locked potentials. Although the general ideas and implementation of the techniques described below are fairly straightforward, digital signal processing techniques for real data tend to be exercises in compromises and tradeoffs. The properties of the particular techniques outlined below should be thoroughly understood before they are used to draw inferences about the information content of EEG data. Fig. 23A illustrates different types of alpha activity embedded in simulated background EEG: no alpha, constant alpha, a pair of early spindles out of phase by 180° , and a late spindle.

The anti-phase early alpha spindles are of particular interest. Although two trials of real data would not be expected to cancel out perfectly, to the extent that the phase of the alpha spindles are dissimilar

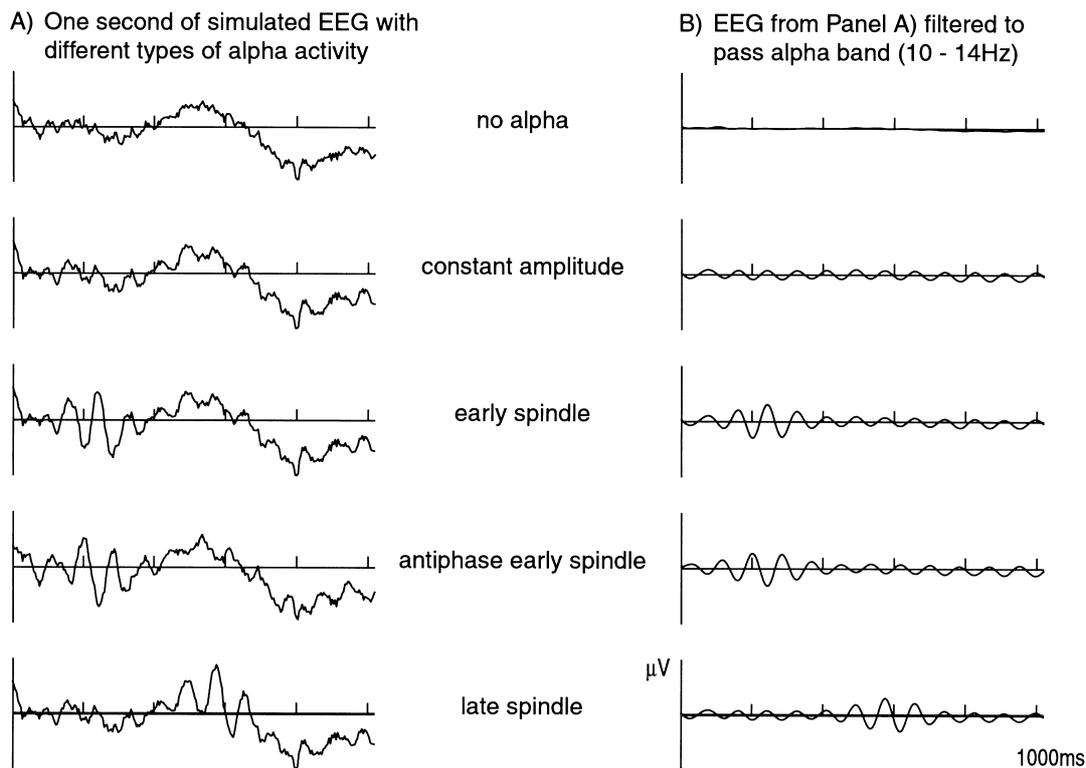


Fig. 23. (A) shows five epochs of simulated EEG activity containing different types of ‘alpha’ activity, i.e., a 12 Hz sinusoid: no alpha, constant amplitude, an early spindle, an early spindle of opposite phase, and a late spindle. (B) shows these same five epochs after digital band-pass filtering between 10–14 Hz.

from trial to trial, even if time locked, this modulation of alpha activity will be treated as noise and tend to be reduced in the time domain average. One approach to measuring such non-phase-locked potentials is to estimate the energy in the different frequencies contained in the time domain waveform, i.e., estimate of the power spectral density (PSD). A crude estimate of the PSD is the simple periodogram. The periodogram for a sequence of data points can be obtained by calculating the FFT, then multiplying each complex number in the result by its complex conjugate (inverts the sign of the imaginary component without affecting the real component) and normalizing by number of data points. Where $X(f)$ is the FFT of the N point epoch at frequency f , the PSD is as follows:

$$G(f) = \frac{X(f)X^*(f)}{N^2}$$

Here the asterisk indicates complex conjugate. The

resulting sequence of positive real numbers is mapped to bins of frequencies ranging from 0 to the Nyquist frequency of $\frac{1}{2}$ the data sampling rate. Frequencies carrying more energy in the time domain data show up as higher peaks in the periodogram.

Fig. 24A illustrates Welch method periodograms (Hanning window) for the waveforms in Fig. 23. The plots give the single trial and selected average PSDs for the data in Fig. 23. The PSDs in Fig. 24A show that the unfiltered EEG data have energy distributed over a broad band of frequencies. The single trial PSD for the epoch with no alpha shows the expected low energy around 12 Hz and the four epochs containing alpha activity all show an energy spike around 12 Hz. This spike is more of a hump because of energy leakage into nearby frequency bands. The PSDs in Fig. 24B show that bandpass filtering the data concentrates the energy in the alpha band 10–14 Hz.

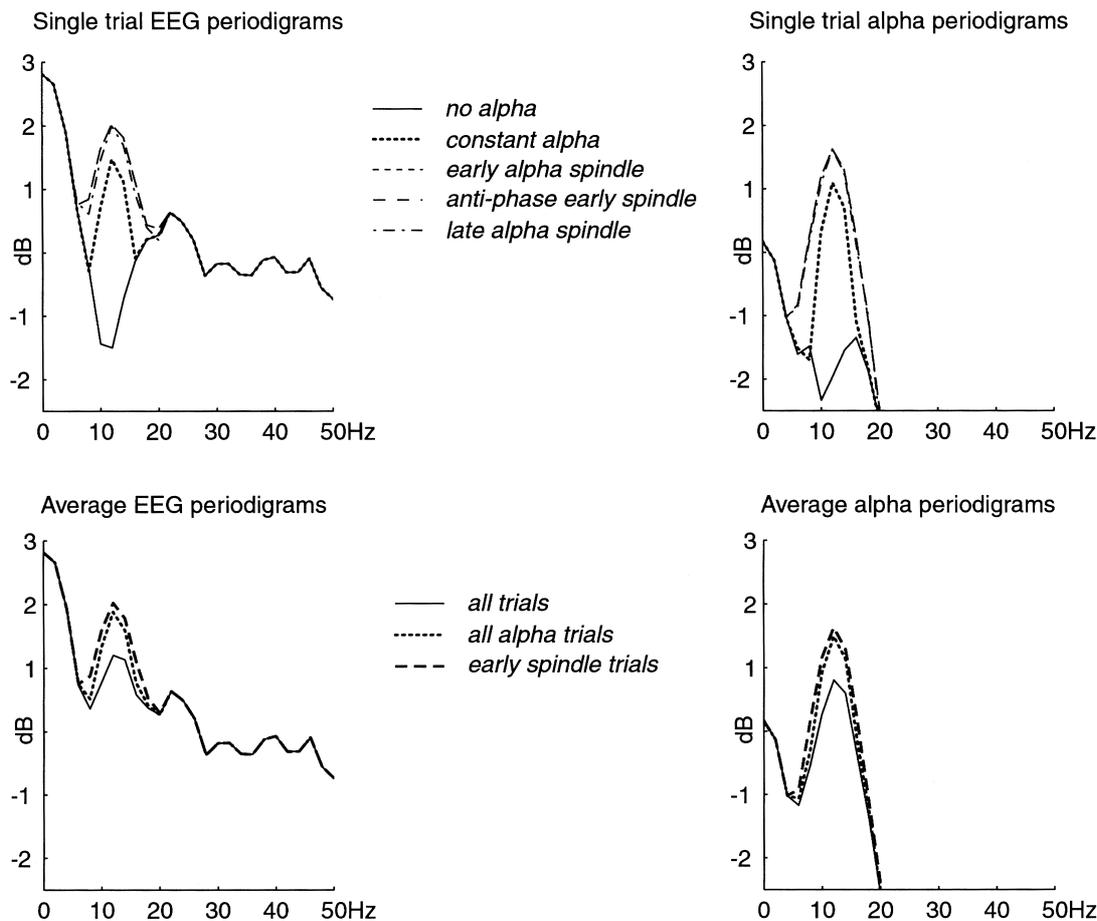


Fig. 24. Welch method periodograms use FFT to estimate energy at different frequencies for the epochs of data in Fig. 23. The periodograms for both the unfiltered and the filtered individual trials show the difference between the no alpha trial and the trials containing alpha at frequencies around 12 Hz. To a lesser extent they show the difference between the constant alpha and the epochs with spindles, with the spindles showing up as more energy around 12 Hz. Average periodograms for selected subsets of the epochs are illustrated in the bottom two plots. The individual periodograms, and hence the average periodograms, do not distinguish the epochs with the early spindles from the epoch with the late spindle, and this illustrates the insensitivity of the simple periodogram to the time course of frequency band power changes, i.e., transients with a time course that is short relative to the length of the epoch.

A primary point of interest here is that although the two anti-phase early spindles would tend to cancel each other out in the time domain leaving just background noise in the conventional ERP, their individual PSDs do not cancel out. If an experimental manipulation evokes event-related changes in alpha band activity without phase locking the alpha oscillations to the event, this may be evident in the post stimulus PSDs, but not the conventional time domain ERP average. Note also that the individual alpha band PSDs in Fig. 24B show a slight increase in alpha power for the three epochs with spindles in

comparison with the constant alpha epoch. This is as expected since the spindles have more energy at the alpha frequency. These figures illustrate one way in which frequency domain analyses provide a different perspective on the time domain data.

Periodograms and related estimates of the power spectral density can reveal relatively fine-grained differences in the frequency components of the time-domain waveform as well as preserve differences that might have been cancelled out in the averaging process due to phase differences. What is lost in this type of analysis is the way the frequency

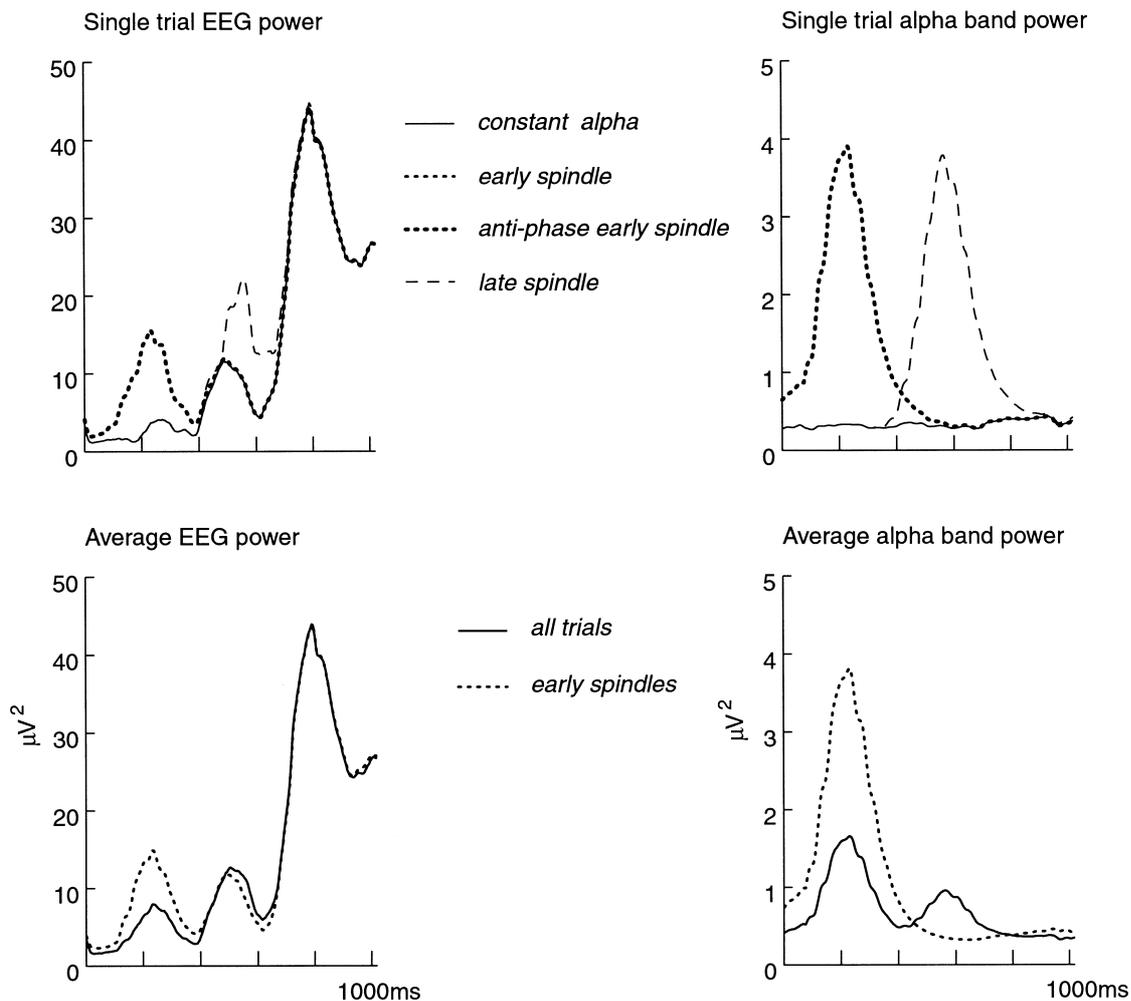


Fig. 25. EEG power for the individual epochs in Fig. 23 and average power for selected subsets of epochs. The power over time is calculated as V^2 and the resulting power waveform digitally smoothed. The first two prominent peaks in the time–power plots for the unfiltered epochs correspond to the early and late alpha spindles, the third and largest peak corresponds to the large slow wave that occurs late in all of the epochs and it partially obscures the time course of the late spindle. The time–power plots for the epochs that were bandpass filtered illustrate how this filtering isolates the power changes associated with the early and late spindles in the alpha band. The time–power estimates for individual epochs can be averaged as illustrated in the two lower plots. Unlike the periodograms, this technique clearly distinguishes the early from the late spindles in individual epochs and, hence, in the averages.

energy changes as a function of time. This can be seen by comparing the virtually indistinguishable individual PSDs for the early and late alpha spindles in Fig. 24B. One approach to quantifying time-varying event-related effects that are restricted to a particular range of frequencies is to bandpass filter the continuous EEG using Fourier, time domain, or wavelet filtering methods to reduce energy outside the frequency band of interest. What remains after

bandpass filtering is a more or less sinusoidal waveform with the bulk of its energy at frequencies in the passband. The amplitude of this waveform can vary over time and the changes can evolve gradually or abruptly in the form of spindles as illustrated in Fig. 23B. Quantifying how the energy in the pass band changes over time, can be done in various ways (see the papers collected by Andreassi and Gruzelier, 1996 for a representative selection of these meth-

ods). The power (V^2) can be calculated by squaring the voltage at each time point in the single trial waveforms. Fig. 25(left top) illustrates a digitally smoothed time–power waveform for the unfiltered EEG in Fig. 23A.

Fig. 25(right top) illustrates the same type of time–power waveform for the bandpass filtered EEG in Fig. 23B. These alpha band power measures clearly show the different time courses of the early and late spindles for both single trials and averages. Event-related power changes can be obtained by comparing post stimulus power against prestimulus baseline power. For instance, root mean square voltage (RMS) is computed by calculating the square root of the mean of the power in the interval of interest. Other power measures have been adopted that involve additional transformations such as smoothing the time-domain averaged power and normalizing by expressing it as a percentage of baseline power (Pfurtscheller and Aranibar, 1977). This type of normalization has the effect of making small post stimulus power changes that are relative to low prestimulus baseline power comparable to large post stimulus power changes that are relative to high prestimulus power. Many variations on the power analysis are possible and with each come a set of assumptions and allowable inferences.

A limitation of pass band power techniques is that they restrict attention to a particular frequency band and to analyze the time course of the entire EEG power spectrum, a variety of techniques is used (Lin and Chen, 1996; Muthuswamy and Thakor, 1998). An approach based on Fourier methods is to divide the epoch of EEG data into smaller segments and calculate the PSD for each segment. The result is a series of PSDs, each based on a short time Fourier transform (STFT) (Allen and Rabiner, 1977; Nawab and Quatieri, 1988). Each PSD in the series is a ‘snapshot’ of the power spectrum during that interval and the series indicates how the power spectrum changes over time. The STFT technique is limited by a tradeoff between time and frequency resolution. As the FFT is applied to longer sequences of data, the frequency resolution improves, providing a better estimate of small differences between frequencies. However, using longer sequences reduces the ability to resolve the time course of power changes as we saw above for the early and late alpha spindles in

Fig. 24. Better temporal resolution can be achieved by shortening the segments, but this reduces the number of available frequency bins, hence frequency resolution. Another difficulty is that since the Fourier transform is forced to treat all signals as composed of underlying sinusoids, if there are no underlying periodicities, the PSD based on the Fourier transform will say there is energy in the signal at frequencies where there really isn’t. This misallocation of energy can be a particular problem when the changes in the event-related potentials of interest occur over a brief period, i.e., are ‘transients’. In this case, the discontinuous nature of the signal in conjunction with incautious application of the FFT can lead to seriously erroneous estimates of the power spectrum (Harris, 1998; Nitschke et al., 1998). The problem of misallocation of energy in the power spectrum can have practical consequences in experimental applications because it undermines inferences about the event-related changes in particular frequency bands and meaningful comparison of the power spectra obtained in different experimental conditions.

Wavelet analysis. To analyze events at both the large scales corresponding to lower frequencies and small scales corresponding to higher frequencies in a single analysis, recent developments in wavelet analysis are attracting increasing attention. Seminal work in the modern development of wavelets can be found in Daubechies (1988), Grossman and Morlet (1984) and Mallat (1989). The historical development of wavelet analysis is discussed in Meyer and Ryan (1993) and helpful reviews of wavelet analyses in application to physiological data are given by Lin and Chen (1996) and Samar, Bopardikar, Rao and Swartz (1999). Although wavelet and Fourier analyses are similar to the extent that both can analyze a time domain signal into component oscillating waveforms, in wavelet analyses, the component waveforms are not infinitely extended sinusoids, but can be non-sinusoidal snippets of time–amplitude waveforms whose frequency content is band-limited and whose non-zero values are restricted to a particular region of time (see Strang and Nguyen, 1996 for a thorough comparison of Fourier and wavelet transforms). Accordingly, wavelets are said to be localized in both frequency and time. Wavelets can be ‘scaled’, which is to say stretched out or compressed

Wavelet at different scales and translations

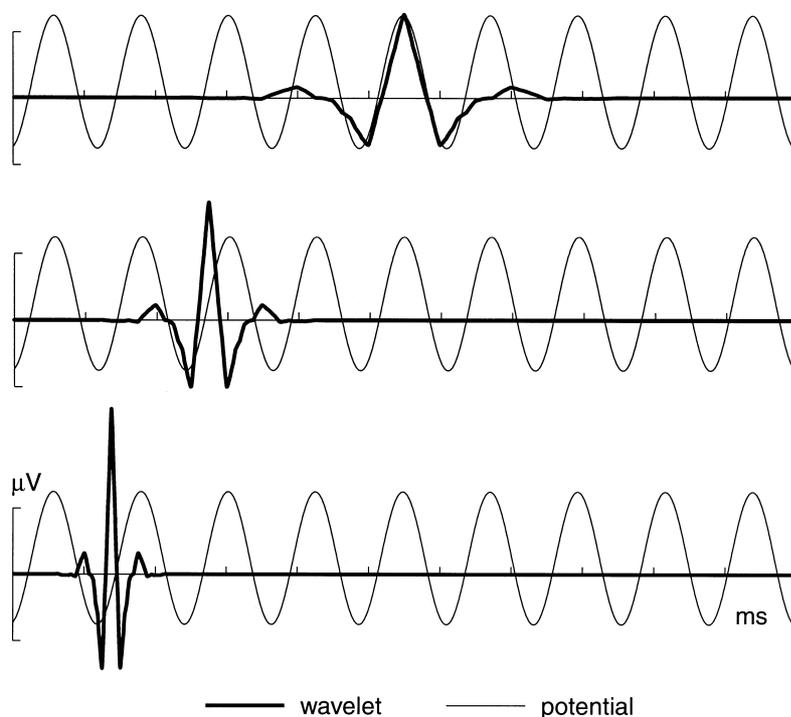


Fig. 26. Illustration of a biorthogonal spline wavelet (5,5) at different scales and translations relative to a sinusoidal time-potential waveform. The plot at the top shows a combination of scale and translation for which the wavelet and the potential waveform exhibit a good point wise match and a correspondingly high large wavelet coefficient.

in time as well as ‘translated’, i.e., shifted left or right in time. Fig. 26 illustrates a wavelet at different scales and translations superimposed on a sinusoid.

The idea behind the continuous wavelet transform analysis is to decompose a time domain waveform into a set of coefficients that characterizes the goodness of fit between a stretch of the time domain data and a particular wavelet at a given scale and translation. If the point by point match is good, i.e., the wavelet and time domain waveform are highly correlated (Fig. 26, top panel), then the wavelet coefficient is large. At small scales, the compressed wavelet will tend to match best any rapidly changing amplitude patterns in the time domain waveform, i.e., high frequencies. At large scales, the stretched wavelet will tend to match best the slow changes in amplitude, i.e., lower frequencies. The extent to which the wavelet matches at each scale can vary with the

translation which enables the wavelet transform to pick out transients.

Calculating the continuous wavelet transform is a matter of determining the wavelet coefficients at all scales and translations; in the mathematical definition of the wavelet transform, the translations and scales can vary continuously. There are, in principle, an infinite number of scales for each translation, an infinite number of translations for each scale, and an infinite number of wavelet coefficients. However, numerical approximations of the wavelet coefficients can be calculated for specified ranges of wavelet scales and translations. The result is a finite set of wavelet coefficients for each scale and each point in time and these wavelet coefficients can be visualized as a time-scale plot as illustrated in the center column of Fig. 27.

By selecting different wavelet shapes, wavelet

analysis can decompose the data in different ways and, in principle, can tune the analysis to the task at hand. The balance of this section is a brief look at the discrete wavelet transform and wavelet packet analysis and how these can be applied to EEG data.

The coefficients of the *continuous* wavelet transform are based on calculating coefficients for as many scales and translations as possible within the constraints imposed by digitally sampled data. This results in large numbers of coefficients and translations, and coefficients in small neighborhoods of time scales and translations that tend to be correlated. The *discrete* wavelet transform (DWT) is an alternative that uses a small set of orthogonal, i.e., uncorrelated, scaled and translated wavelets; they do not contain redundant information and are a more parsimonious representation of the data than the full set of coefficients from the continuous wavelet transform.

The DWT is computed iteratively, by using the wavelets to high and low pass filter the time domain waveform. The original waveform is initially split into ‘detail’ coefficients containing the high frequency information and an ‘approximation’ function containing the low frequency information. The process is then repeated on the approximation function (see Fig. 27C). Each iteration strips roughly the top half of the frequency band from the previous approximation and encodes it in the detail coefficients. At each split, the approximation function and detail coefficients can be downsampled by a factor of two without loss of information, and by so doing, the number of data points after the high and low pass split is the same as the number of data points in the original waveform. For appropriately selected wavelets, the DWT is reversible and the original time domain waveform can be reconstructed from the approximation functions and detail coefficients. Also, time domain waveforms of the same length as the original can be reconstructed from any approximation function, detail coefficients or combination of these. This makes it possible to isolate the contribution that any given approximation or detail coefficients makes to the original waveform. Signal processing, e.g., attenuating the coefficients that encode undesirable noise, can also be performed at the different levels of wavelet analysis and the corresponding time domain waveform reconstructed.

This process of iteratively pulling the detail coefficients out of each successive low frequency approximation function is not the only possible wavelet decomposition. In the wavelet packet method, each level of detail coefficients as well as the approximations can be split in the same manner.

Fig. 28 (adapted from Samar et al., 1999) illustrates a complete wavelet decomposition tree and the nominal high and low pass frequency bands associated with the decomposition of a 0–128 Hz bandlimited signal at each level. The standard DWT wavelet analysis selects the path through this tree indicated by the dashed line. However, it is possible to choose other paths through the tree to split the original signal into other frequency bands. The approximation coefficients A1 contain most of the energy in the bottom half of the original data, i.e., 0 to 64 Hz. At the next level, the detail coefficients, DA2 encode the preponderance of energy in the top half of the A1 frequency band, i.e., centered between 32 and 64 Hz. If frequencies in the gamma band around 40 Hz are of experimental interest, then one might wish to further split the detail coefficients for the decomposition of A1 into the 32–48 Hz and 48–64 Hz bands. The appropriate coefficients are calculated as ADA3 in the wavelet packet analysis and would not be calculated in the standard DWT.

Although the DWT provides a computationally efficient way to compute a wavelet representation of the time domain waveform, some of the potentially nice wavelet matching behavior of the continuous wavelet transform can be lost. This is illustrated in the DWT in Fig. 27C. The low frequency oscillation that is evident in the time domain waveform and that shows up as the wide bands in the CWT in Fig. 27B is distributed across two of the seven levels in the wavelet decomposition rather than corresponding neatly to a single level and this kind of smearing between levels in the DWT can happen for transients as well. Some of the applications of wavelets in electrophysiology include preprocessing data for input to neural networks, data compression, spike and transient detection, component decomposition, and time–scale or time–frequency analysis (see Samar et al., 1999 for an overview).

Component analyses. Visual inspection of a multi-channel EEG strip chart or time-domain averaged

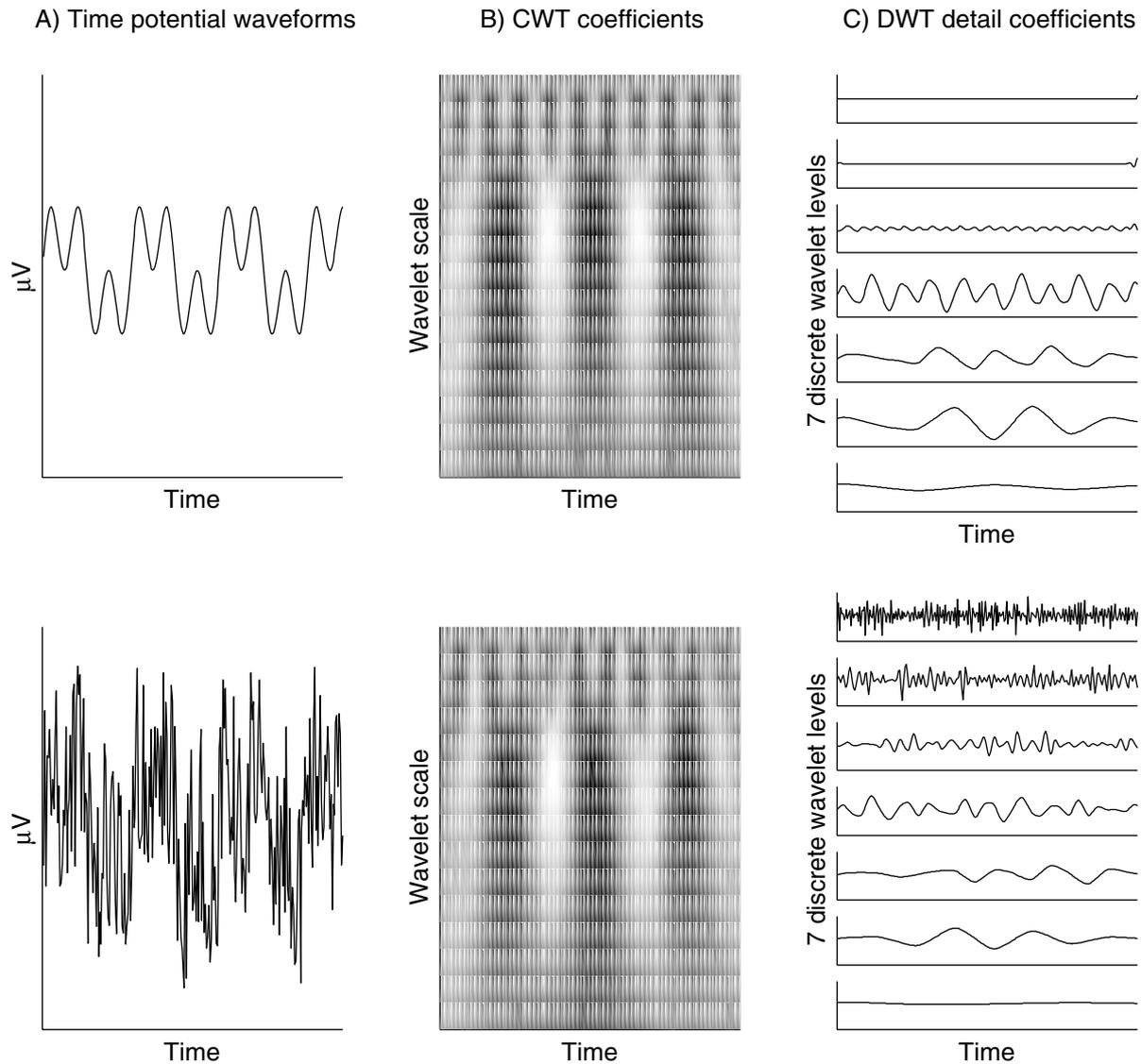


Fig. 27. Time domain waveforms consisting of two constant amplitude sinusoidal components with and without high frequency noise are compared with their continuous wavelet transforms (CWT) and discrete wavelet transforms (DWT) using the biorthogonal spline wavelet (5,5). (A) shows the time domain waveform. (B) shows the CWT and the two frequencies present in the time-potential show up as banding in the plot of the CWT. This banding reflects periodicities in the magnitude of the wavelet coefficient at different scales and translations. (C) shows a DWT with seven levels. Comparison of the upper and lower DWT plots shows that the high frequency noise is corresponds largely to the top two levels of the DWT and that the remaining levels capture the information about the lower frequency sinusoids. This ability of the DWT to split a time-domain waveform into different levels makes it useful for signal processing. Note that using other types of wavelets would result in quite different CWTs and DWTs which may or may not have desirable properties.

potentials generally shows that there are both similarities and differences between the potentials over time between channels, conditions, and subjects. A

particular feature such as a pronounced amplitude deflection that evolves over several hundred milliseconds, may be manifest at some scalp sites in some

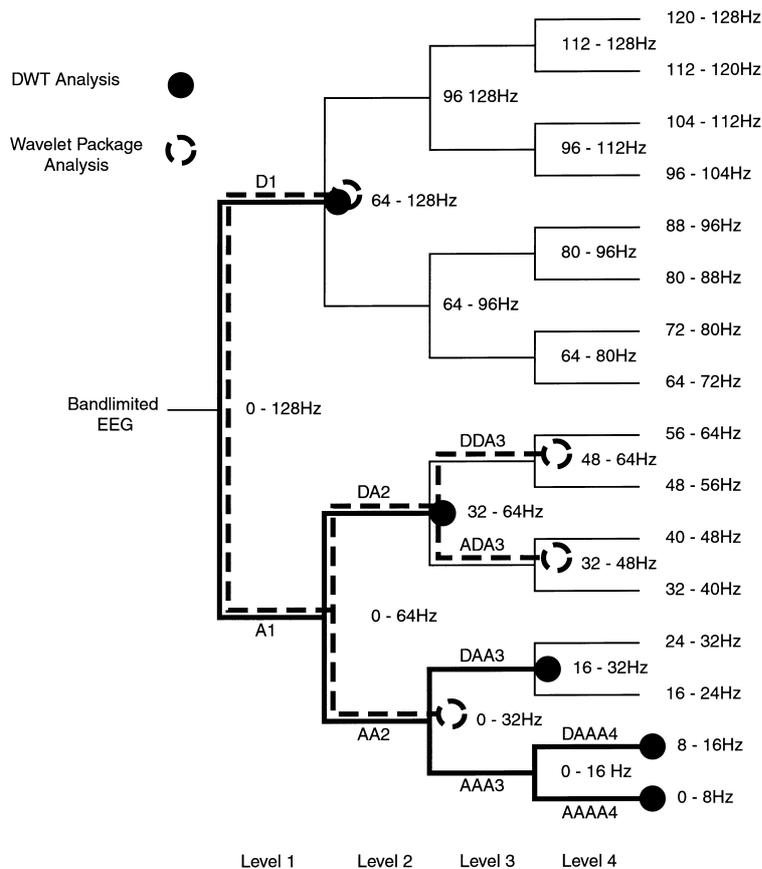


Fig. 28. Four level discrete wavelet transform (DWT) and wavelet packet analysis. In both cases, the basic process is to split a time series into detail coefficients and approximations. The standard DWT, illustrated by the solid line; does this iteratively on the approximations generated at the previous level. Wavelet packet analysis allows both the approximations and the detail coefficients from previous levels to be split. This makes it possible to tune the wavelet packet analysis to isolate specific frequency bands, e.g., the gamma band at 32–48 Hz. Adapted from Samar et al., 1999.

experimental conditions, but not in others. For instance, in addition to the background activity unique to each electrode, several adjacent electrodes might all show the effects of a large nearby current source. The suggestion that different channels have something in common and something different leads to the idea that the potential at each recording site consists of a combination of 'components' some of which may also contribute to the potential at other sites and others of which are unique to that particular recording site.

The component analyses outlined below have two parts: (1) a definition of the mathematical properties and relations a component must have and (2) an algorithm for decomposing a set of potential waveforms

into components that satisfy these conditions. Typically, the original waveforms must be the linear sum of the appropriately weighted components. The analyses are distinguished by the additional constraints they place on the components, e.g., that each is statistically uncorrelated with the others or the entire set of components is statistically independent. After defining the properties of a component, algorithms for finding the components, thus defined, are applied to a given set of waveforms. Of the different component analyses, three are enjoying use in cognitive ERP analyses: principal components analysis (PCA), spatial principal components analysis (SPCA), and independent component analysis (ICA).

Principal component analysis (PCA) is a well

known type of factor analysis that has been systematically applied to event-related potentials since the mid-1960s (Donchin, 1966; Ruchkin, Villegas and John, 1964). The goal is to decompose ERP data into components corresponding to distinct cognitive or physiological functions. To the extent that a time domain waveform varies smoothly over time, nearby points can be reasonably good predictors of one another. This means that the time domain waveform can contain a good deal of redundant information. By analyzing the waveform into the linear sum of a small number of uncorrelated components, the PCA can parsimoniously represent the bulk of the information in the data.

For 'temporal' PCA, the variables are the time points, and the cases are typically the data points from a set of time domain averaged potentials from several subjects, multiple experimental conditions, and one or more scalp electrode locations. The voltage $V(t)$ at a moment in time is assumed to be the weighted linear combination of a small (about 4–8) number of components (C). For each component, k , there is a time-invariant 'score' S_k and a time-variant 'loading' $L_k(t)$. The product of the score and loading, $S_k L_k(t)$, characterizes the contribution of the k -th component to the original waveform at each point in time. Adding contributions of all K components gives the original time-varying waveform. The components identified by PCA are orthogonal, hence uncorrelated, and extracted from the data sequentially in a such a way that each successive component accounts for a maximal amount of variance in the data that is not correlated with previous components. The PCA is not conducted directly on the voltage data points but on measures of their associations such as the covariance, cross-product, or correlation matrices. With the components extracted, they are typically rotated according to the Varimax criterion (Kaiser, 1958) which simplifies the factors so that each has only a minimum number of large loadings. In the case of temporal PCA, this has the effect of minimizing the temporal overlap of the principal components. Following rotation, analysis of variance is often conducted on the component scores and the loadings for each component can be plotted over time (for more details see Chapman and McCrary, 1995; Donchin and Heffley, 1978; Glaser and Ruchkin, 1976; Van Boxtel, 1998).

Construed as entities with interesting mathematical relations to the data set, the components identified by PCA are unproblematic. However, the aim of analytic techniques in ERP research is to separate the functionally significant cognitive or physiological wheat from the bioelectric chaff and interpretations of the functional significance of the components extracted by PCA have been something of a lightning rod for controversy. Some points appear to be generally recognized. A chronic limitation of temporal PCA in this form is that it does not distinguish between variability that arises from amplitude differences and variability that arises from latency differences. Donchin and Heffley (1978) showed that PCA on 200 half sine waves jittered at different latencies produced a biphasic loading vector, and in simulations, Wood and McCarthy (1984) found that PCA combined with Varimax rotation misallocated variance particularly when components overlapped. Of course, other analysis techniques, such as peak picking also suffer from the problem of component overlap and whether latency jitter or component overlap is a problem may vary from experiment to experiment. In any case, used in conjunction with judicious designs, PCA is an informative analytic technique (Donchin, 1969).

A recent 'spatial' variant of PCA addresses a different version of the question, namely, determining the principal components of the spatial distribution of the potentials (Dien, 1998b; Spencer, Dien and Donchin, 1999; Van Boxtel, 1998). Rather than treating the time points as the variables, and the data from the electrodes, conditions and subjects as the observations, spatial PCA treats the electrodes as variables and the data points from a given experimental condition as the observations. The resulting component scores indicate the time course of activity. Whereas the loadings in temporal PCA indicate the temporal intervals in the recording epoch that are associated with the activity of each component, the loadings in spatial PCA indicate the spatial interval, i.e., the location on the scalp, associated with the activity of each component. Spatial and temporal PCA can be used in combination, for instance, by conducting a temporal PCA to identify intervals of high variability and then conducting a spatial PCA on those intervals.

A third type of component analysis that has attracted considerable attention recently is independent

component analysis (ICA). ICA is conceptually similar to PCA in as much as the aim is to decompose a signal into linear components, and the components must satisfy certain mathematical conditions. In this case, however, the condition is statistical independence, which is a stronger condition than being uncorrelated. In general ICA aims to find components that are as independent as possible relative to some measure of independence. A variety of measures of independence have been studied and algorithms proposed (for reviews, see Cardoso, 1998; Hyvärinen, 1999; Lee, Griolami, Bell and Sejnowski, 2000). Although, schematically, the project in PCA and ICA is similar, the types of analyses differ in important ways. ICA assumes that the components are non-Gaussian whereas PCA assumes they are Gaussian. Whereas the components extracted by PCA are ordered by the amount of variance accounted for, ICA components need not be, although some kind of ordering can usually be obtained that is specific to the analysis. And whereas PCA is often used to reduce the dimension of the data, the emphasis in ICA is on finding independent components and this may or may not reduce the dimensions (Hyvärinen, 1999).

ICA has been applied to both EEG and biomagnetic data. For instance, Vigario (1997) used ICA to identify and remove components of the scalp potential corresponding to ocular artifacts. Recently, Makeig, Westerfield, Jung et al. (1999) used ICA in a spatial attention task to identify three independent components of the late positive complex (LPC), including a frontal component, the equivalent of the parietal P3b component, and a motor component. Their analysis includes a discussion of the ICA methods and a comparison of the ICA with PCA. ICA, like each of the other analytic techniques, accounts for the variability in scalp potentials in a somewhat different way, and in so doing, offers yet another perspective on the data. What this new perspective shows and how it compares with other techniques are ongoing issues.

Other analyses. Although considerable attention has been given to transforming time domain potentials into other domains in order to get different perspectives on the data, there are techniques in addition to averaging that operate on time-domain potentials.

Difference potentials. Calculating difference potentials is a simple but useful technique. Difference potentials are calculated by subtracting one waveform from another, time point by time point. The result is a single waveform that represents the difference in potential between the two original waveforms. This technique has the effect of canceling out amplitude deflections (which may or may not be due to the activity of the same generators) that the waveforms share and it is particularly useful for comparing time domain averaged waveforms in different experimental conditions. Difference ERPs are not without their problems and are no panacea to complexity; they should never be interpreted without recourse to the original waveforms. Both amplitude and latency variation between two conditions will lead to a difference, although they obviously have different implications for processing. Moreover, if the two ERPs that go into the subtraction are fundamentally different, then the difference ERP would be at best descriptive of the difference.

Single trials and latency correction. Latency jitter poses a problem not only for component analyses but also for conventional time domain averaging. If the same waveform is jittered in time, the amplitude of the average peak will underestimate the value of the true peak of the original waveform. If the peak is asymmetrical, latency jitter will also shift peak latency. An adaptive filtering approach to latency correction has been proposed by Woody (1967). The procedure starts with a template waveform and in each single trial determines the latency at which the template best fits the waveform. The signals are then lined up according to these latencies and averaged, and the process repeated. If started with an appropriate template, this technique can converge on latency corrected average waveforms. However, since there is always a 'best' match even if it is not very good, the procedure can line up random noise in a way that looks most like the template and through a series of iterations, eventually extract a something from nothing if the signal-to-noise ratio is too low, i.e., below about 0.5 RMS (Ruchkin, 1987). Woldorff (1993) presents a set of algorithms, collectively termed adjacent response technique (ADJAR) for estimating and removing distortion due to response overlap; the distortion is modeled in terms of mathematical convolutions of the ERP waveform

elicited by each type of adjacent stimulus with the corresponding distribution in time of those stimuli relative to the averaging epoch. Dale and colleagues (Burock, Buckner, Woldorff et al., 1998; Dale, 1999; Dale and Buckner, 1997) have developed and tested a more general method for teasing apart overlapping responses that is useful for analyses of fMRI as well as ERP data. This method makes methodological suggestions about the best inter-stimulus intervals for eventual correction of overlapping components.

Component latency is just one feature of single trials and new methods continue to be brought to bear in the analysis of single trial event-related potentials (cf., Demiralp, Yordanova, Kolev et al., 1999; Gupta, Molfese, Tammana and Simos, 1996; Hansson, Gänslar and Salomonsson, 1996; Heinrich, Dickhaus, Rothenberger et al., 1999; Jaskowski and Verleger, 1999; Karjalainen, Kaipio, Koistinen and Vauhkonen, 1999; Kong and Qiu, 1999; Kong and Thakor, 1996; Lange and Inbar, 1996; Lange, Pratt and Inbar, 1997).

Inter-electrode measures. Different regions of the cortex, if not specialized, are at least differentially engaged during different types of cognitive processing. The patterns of activity of populations of neurons in functionally significant cortical networks are likely to be correlated, albeit at a range of lags because of differences in timing of information transactions. Accordingly, there are reasons to expect systematic relationships between activity in different regions of the scalp as cognitive processes evolve during the response to a stimulus.

To analyze the time course of these relationships, an evoked potential covariance (EPC) or event-related covariance (ERC) technique has been developed by Gevins and his colleagues (Gevins, 1989; Gevins, Bressler, Morgan et al., 1989). This technique computes the covariance between all pairs of non-peripheral electrodes. The effects of volume conduction are mitigated, if not eliminated, by transforming the common reference potentials to a Laplacian derivation, after which, windows based on the width of the ERP peaks are specified and the covariance between all pairs of non-peripheral electrodes is calculated for lags up to half the period of the highest frequency in the EEG data. These EPCs are compared to non-event-related values computed in the same manner but for sequences of data that are

selected at random with respect to the onset of the stimulus. Significant relationships between electrode pairs are visualized as arrows. As a measure, EPCs are sensitive to a range of experimental manipulations involving visuo-motor and memory processes (see Gevins and Cutillio, 1995 for an overview) although interpretation of the source of the correlations must be made with caution.

EPCs measure time domain covariation between pairs of recording electrodes and measures of the coordinated activation of neuronal ensembles can be obtained in the frequency domain. By using the FFT, it is possible to calculate the manner in which phase varies by frequency in the data for a given electrode, and thus, to determine the extent to which these phase values are associated at two electrodes. The phase associations between two electrodes can be quantified as 'cross spectral density' which is a non-normalized quantity analogous to covariance, or 'coherence' which is a normalized unitless quantity analogous to the correlation coefficient. Using an FFT, both cross spectral density and coherence are straightforward to calculate (see Andrew and Pfurtscheller, 1995 and Nunez, Srinivasan, Westdorp et al., 1997).

Naturally, not all correlations between electrodes are equally interesting, see Nunez et al. (1997) for discussion of the methodological issues. A single large current source is likely to contribute systematically to the potential at several electrodes because of volume conductance. Furthermore, potentials at a common reference electrode will result in correlated activity at all non-reference scalp electrodes. These concerns can be addressed with appropriate spatial filtering techniques, but even if relatively focal current sources in different areas are found to be coordinated with respect to some measure, the coordinating mechanism remains an open question. Again, care must be taken when interpreting measures of correlated interelectrode activity.

Neuroelectric source analysis. The task of identifying the neural current sources of the observed patterns of scalp potentials has attracted considerable attention since the advent of electroencephalography (for recent reviews see Cuffin, 1998 and Koles, 1998). The relation between scalp potentials and the neuroelectric sources involves two related problems.

The so-called 'forward problem' is a matter of calculating the electrical field generated by a particular configuration of electrical sources in the conducting media of the head. The 'inverse problem' is a matter of calculating the locations of electrical sources given the values of the scalp potentials measured at a set of electrodes. Solving the inverse problem is often referred to as source or dipole localization. The forward and inverse problems are related when source localization techniques incorporate forward models. EEG source localization is a special case of the general problem of source localization in biological media and related work includes localizing the source of magnetic fields in the brain and the sources of non-cephalic biofields such as the electrical and magnetic fields of the heart. Recent research in EEG source localization has pushed toward improving the accuracy of source localization algorithms and developing more anatomically detailed models of the head (Cuffin, 1995, 1996; De Munck, 1992; Fuchs, Drenckhahn, Wischmann and Wagner, 1998; George, Aine, Mosher et al., 1995; Gorodnitsky, George and Rao, 1995; Gorodnitsky and Rao, 1997; Hämäläinen and Ilmoniemi, 1994; Haueisen, Ramon, Eiselt et al., 1997; Huiskamp, Vroeijsstijn, Van Dijk et al., 1999; Koles and Soong, 1998; Mosher and Leahy, 1998; Oostendorp and Van Oosterom, 1989; Pohlmeier, Buchner, Knoll et al., 1997; Rosenfeld, Tanami and Abboud, 1996; Scherg and Berg, 1996; Srebro, 1996; Yan, Nunez and Hart, 1991; Yvert, Bertrand, Echallier and Pernier, 1996; Zanow and Peters, 1995). Given the details of intracranial tissue geometries, e.g., from MRI data, estimated current sources can be projected back onto the cortical surface (e.g., Babiloni, Babiloni, Carducci et al., 1996; Dale and Sereno, 1993; Gevins, Le, Brickett et al., 1991; He et al., 1999).

The forward problem can, in principle, be solved if the location and strength of the current sources, the spatial geometry and conductances of the media are specified. In practice, however, these details are unknown and approximations must be used. Early head models were based on spherical volume conductors and the simplest of these treats the head as single spherical homogeneous volume conductor, e.g., Geisler and Gerstein (1961). Subsequent refinements modeled the geometry of the media in the head as three or more concentric shells (Cuffin and Cohen,

1979; Rush and Driscoll, 1969). The different shells have conductances based on estimates of the conductances of the brain, cerebro-spinal fluid, skull, and scalp (Baumann, Wozny, Kelly and Meno, 1997; Geddes and Baker, 1967; Law, 1993, 1984; Robillard and Poussart, 1977). Given electrical sources located in concentric homogeneous volume conductors with known conductances, the forward solution for the electrical field at the surface of the outermost layer, i.e., the scalp potential, can be calculated analytically. However, the head is only approximately spherical and other forward solutions based on more realistic head geometries have been developed in conjunction with magnetic resonance images that provide detailed information about the cranial geometry.

One type of technique, the boundary element method (BEM), specifies the boundaries between the main types of different tissues using a surface consisting of a mesh of small geometric elements, typically a few thousand triangles. The volumes enclosed by these surfaces are treated as homogeneous conductors and the potentials are calculated for the boundary elements, including those corresponding to the surface of the scalp. Mosher, Leahy and Lewis (1999) give a recent analysis of different boundary element methods. The finite element method (FEM) divides up the entire volume of the head into small geometric volumes each with a specified conductance and again, the potential at each such element is calculated. Although computationally intensive, these approaches provide fine-grained models of head properties that can take into consideration factors such as differences in skull thickness and anisotropic conductances (Ollikainen, Vauhkonen, Karjalainen and Kaipio, 1999; Haueisen et al., 1997; Marin, Guerin, Baillet et al., 1998).

The aim of source localization is to start with scalp potentials and produce models of neuroelectric sources that have properties, i.e., location, orientation, and magnitude, that make them good approximations of the real electrical sources responsible for the scalp potentials. The unconstrained version of the inverse problem is unsolvable in principle since for any given pattern of potentials at the surface of the scalp, there is no unique pattern of electrical sources that can generate this and only this pattern. The asymmetry between the forward and inverse

problems is analogous to the asymmetry between ‘forward problem’ of addition and the ‘inverse problem’ of subtraction. Although it is easy enough to calculate the unique value of the sum of a pair of known numbers 12 and 24, there is no unique answer to the question: what numbers sum to give 36? However, by putting constraints on the problem, the number of possible solutions can be narrowed down. If, for instance, one is looking for any two numbers or any three or any four that sum to 36, or if two are constant and the other two can be allowed to vary, or the range of the numbers cannot exceed some value, then the range of possible solutions can be narrowed down, perhaps to uniqueness, if the constraints are sufficiently restrictive. In an analogous manner, the inverse problem of determining electrical sources from scalp potentials proceeds by adding constraints of one sort or another to try to narrow the range of possible solutions. Constraints may include a model of head geometry and conductances, restrictions on the number of sources to be located, or specifications of the properties and relations that the sources are assumed to have.

Source localization methods can be divided into two main types: parametric and non-parametric. Parametric methods employ an explicit model for the sources in the problem formulation, e.g., assuming that there are exactly three electric dipole sources that generated the scalp potentials, and then attempting to estimate the properties of these three sources. The equations for these dipoles are incorporated into the forward model of the EEG and each dipole has five or six unknown parameters that specify its strength and orientation. The result is a non-linear system of equations and solving the inverse problem involves estimating the unknown dipole parameters in this non-linear system. Non-parametric methods, on the other hand, solve linear sets of equations.

Parametric source localization methods. Well known parametric localization methods include the brain electrical source analysis (BESA) algorithms developed by Scherg and colleagues (see Scherg and Berg, 1996), and the multiple signal classification (MUSIC) algorithms that Mosher and colleagues have applied to biological data, e.g., Mosher and Leahy (1998). Setting aside important implementational details, BESA for instance takes a dipole or dipoles and searches among the possible combi-

nations of locations, orientations, and magnitudes, looking for the configuration that generates surface potentials most similar to the actual data. Candidate source configurations are evaluated by computing the forward solution and calculating the difference between the surface potential generated by the sources and the actual data. The best source configuration is the one that minimizes this error difference. Early versions of BESA found best fits for a specified number of dipoles at each time point. This allowed the source locations to change over the entire time course of the data, i.e., ‘moving dipoles’. Applied to data recorded with typical numbers of scalp electrode, i.e., 32–64, both methods are limited to a few dipoles since 32 or 64 divided by 6 freely varying parameters for each dipole gives about 5–10 dipoles. Furthermore, this algorithm is liable to getting stuck in local error minima, so the solutions depend on how the algorithm is initialized. The single time point version of BESA has been superseded by the spatiotemporal version of the algorithm (Scherg and Ebersole, 1993) which holds the location and orientation of the dipoles fixed and looks for time varying magnitudes of the dipoles that give the best fit for all the data points in the epoch.

In restricted domains, where the character of underlying sources is understood, parametric methods can be used to good advantage. For instance, the real sources of early VEPs are likely to be few in number and located in limited areas of visual cortex. For these data, a parametric algorithm could be constrained to postulate a small number of dipoles in posterior areas only. The parametric method is also well suited to localizing the source of epileptic seizures that can be modeled as single dipoles. In another type of application, the technique can be used to remove ocular potential artifacts from the EEG record (Berg and Scherg, 1991). In this case, again, the electrical sources are better understood. Each eyeball generates a large dipolar field. Rotation of the eyeballs changes the orientation of the field and blinks shunt current from the positive pole at the cornea through the eyelids to primarily pre-frontal and frontal scalp. The BESA algorithm can be used to determine a best estimate of how much of the scalp potential at each scalp electrode can be attributed to these ocular dipoles and, on the basis of

this estimate, their contribution to the scalp sites of interest can be selectively removed.

Parametric methods have certain limitations and in cases where the neural activity is more distributed, or where the number and type of sources are not clear, the accuracy of the sources identified by parametric methods cannot be ensured. A general difficulty with parametric methods is that one must specify in advance how many sources are generating the data, and what kind they are, i.e., dipole or something else. The sources need not be limited to dipoles, one can specify electric quadrupoles for example, but this must be done in advance of the estimate of the sources. Parametric models are also restricted in the number of parameters they can accommodate. It takes a minimum of five parameters to model a single dipole and this number rises geometrically with the increased complexity of electrical source, i.e., from dipole to a quadrupole. A large number of parameters are needed to describe a single complex source but the number of unknown parameters in the model cannot exceed the number of sensors in order to solve the equations uniquely and find the values for the parameters. This restriction imposes an upper bound on the complexity of the model that can be solved parametrically. As the number of postulated dipoles increases there is a combinatorial explosion of possible configurations, and algorithms that compute forward solutions for candidate source configurations are limited in practice to about five or six, but if quadrupoles are included, then the limit is one to three. Generally, a small number of dipoles may be inadequate if the real sources generating scalp potentials are broadly distributed, e.g., neurons in a patch of cortex a few square centimeters in area. In this case, a dipole layer is a better model of the source and the electric field near the center of such a dipole layer falls off more slowly than a single dipole at distances comparable to the width of the patch (see Fig. 1). Since scalp electrodes can be placed a centimeter or so above the cortex, they may fall within this region of the field and modeling this potential with a single large dipole will result in the estimate of the location of the dipole being farther from the surface of the scalp, i.e., deeper, than the actual source. To summarize, parametric methods offer fine resolution, i.e., relatively high accuracy in estimating location, and they are useful if there

are a small number of compact sources. The chief reasons parametric methods are not always suited to describe brain activity in the general case is because it is impossible to specify in advance the appropriate dipole model for unevenly shaped distributed electrically active regions and because such parametric modeling is 'expensive' in terms of the number of unknown parameters that must be fitted. If the number or type of sources initially postulated is incorrect, then even though the algorithm will obtain the best fit of these sources to the scalp potential, they will not necessarily correspond to the electrically active brain regions.

Non parametric methods. Methods that do not explicitly specify an equation for the signal, in this case neuroelectric sources, are non-parametric. Specific types of non-parametric methods for EEG source localization include low resolution electromagnetic tomography (LORETA) (Pascual-Marqui, Michel and Lehmann, 1994), minimum norm methods, e.g., Hämäläinen and Ilmoniemi (1994), and different types of weighted minimum norm methods such as the focal underdetermined system solution (FOCUSS; Gorodnitsky et al., 1995; Gorodnitsky and Rao, 1997). For comparisons of different types of minimum norm methods see Fuchs, Wagner, Köhler and Wischmann (1999) and Taylor, Ioannides and Müller-Gärtner (1999).

Non-parametric formulations of the source localization problem divide the head shape into small volume elements (voxels). Associated with each voxel is a dipole whose strength and direction is given as a vector specified by components in the x , y , and z directions. Current distributions in the volume are specified by non-zero values of the dipole vectors. If a dipole vector is set to zero, there is no current at that location. This approach specifies in advance the entire range of possible EEG currents that comprise the solution, and does so in such a way that a continuous current can be represented by a discrete set of these dipoles. Since the EEG signal is the sum of all the dipole contributions, putting the problem in this way leads to linear equations which can be written as a linear system, $\mathbf{Ax} = \mathbf{b}$ where \mathbf{b} is a vector consisting of the scalp potentials, \mathbf{x} specifies the dipole values for each voxel and the matrix \mathbf{A} is a spatial weighting matrix which specifies, for each voxel and each electrode, the contribution that a dipole

component of unit strength at that voxel makes to that electrode. These contributions can be a simple function of distance or a more complicated function that takes into account the effect of tissue geometry and conductances. Given the matrix \mathbf{A} , the aim is to solve for the potentials \mathbf{b} in terms of the current sources \mathbf{x} . The number of sources in \mathbf{x} may be orders of magnitude greater than the number of electrodes in \mathbf{b} so the system is underdetermined. Accordingly, additional assumptions are made about the properties of the solution, \mathbf{x} , which will allow the selection of a specific solution out of the infinite set of candidates. For instance, the minimum 2-norm solution of Hämäläinen and Ilmoniemi (1994) constrains the solution so that the overall current density inside the head is a minimum. This approach has been criticized for being biased toward solutions close to the scalp electrodes. The bias can be mitigated by down-weighting sources close to the scalp but the result still tends to be blurry current sources and the spatial resolution of these approaches is limited.

For many types of brain activity it is plausible to assume that sources of activity, although irregularly shaped and spatially distributed are compact, in which case, most of the dipoles in the solution are zeros. The FOCUSS algorithm of Gorodnitsky et al. (1995) takes advantage of this assumption to improve the spatial resolution of the source estimate. FOCUSS initially calculates a weighted minimum-norm solution and then uses this solution to weight the next iteration of the minimum norm calculation in such a way that voxels with the lowest current densities are de-weighted. This process is repeated until the algorithm converges on a solution. In addition to identifying dipolar sources, FOCUSS can find solutions consisting of spatially distributed irregularly shaped current distributions.

As a class of methods, non-parametric approaches have some attractive features. In the first place, the form of the solution, i.e., the number and type of source, e.g., dipole or quadrupole, need not be specified in advance. Second, in principle it is possible to solve for very distributed current sources if one can find the solution that describes that current distribution, so there is no limit on the type of sources that could figure in the solution. Third, the number of parameters that describe sources grows linearly with the complexity of a distributed cur-

rent source. Hence, non-parametric methods require fewer parameters than parametric methods to describe sources that have complex distributed shapes. Equivalently, non-parametric methods require fewer data points to resolve a set of sources that are more complex than dipoles.

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