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# High Density Event-Related Potentials: Current Theories and Practice

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Event-Related Potentials (ERPs) are changes in the ongoing electrical activity of the brain (Electroencephalograms, or EEGs) which are caused by the specific occurrence of a cognitive, motor or perceptual event. Any changes in EEG due to the demands of the task are amplified, averaged and extracted as ERP waveforms (see Figure 1). These wave-forms are measured as the difference between the electrical activity of a baseline reference electrode attached to an electrically inactive site, such as the mastoid bone below the ear or the naison on the nose, and the electrical activity of the areas of the brain covered by the electrodes. These changes allow neuroscientists to determine what areas of brain are being stimulated at a given time (and therefore which brain areas are involved in a given process), precisely when these areas become activated and what happens in these areas when people make an error.

***Historical Background of ERPs***

Caton (1875) described the first sensory evoked electrical responses from the surface of the brains of rabbits and monkeys using single electrode recording. Beck (1890) furthered the work of Caton by studying the electrical brain responses of rabbits and dogs to presentation of sensory stimuli. Within 40 years, recordings of electrical brain potentials had moved from animals to humans, and in 1938 Hans Berger published the first recorded study of scalp recordings of human EEGs, in which he first used the term "Elektrenkephalogramm". A year later, Davis (1939) published a paper in which he extracted the changes in EEG due to a sensory stimulus, naming it an Evoked Potential (EP). Renshaw, Forbes and Morison proposed the possible relationship between the slow potentials of neurons and the oscillations of the EEG in 1940, leading to the foundation of the American EEG Society. Up until the 1950s there was no set method of electrode placement on the scalp, leading to a committee headed by Jasper developing the international 10-20 placement system. Dawson (1954) extended the EP extraction techniques introduced by Davis (1939), by averaging large numbers of EPs to increase signal-to-noise ratio, beginning the study of Event Related Potentials (ERPs). By the 1970s, ERPs were being widely applied in clinical diagnosis.

***Physiological basis of ERPs***

Communication in the central nervous system takes place through the transmission of electrochemical signals between nerve cells, or neurons (see Figure 2). Messages to either excite or inhibit activity in other neurons are passed via the release of neurotransmitter substances from the axon of the efferent (or pre-synaptic) cell to the dendritic tree or cell body of the afferent (or post-synaptic) neuron.

The neurotransmitters influence the activity of the neuron by binding to receptors which alter the electrical potential across the membrane of the cell. Due to the constant influx and outflow of both positively and negatively charged ions across this membrane, the equilibrium state, or resting potential, of a neuron is approximately –70 mV. Any deviation from this state will make the cell either more or less likely to generate an action potential. An excitatory signal from a presynaptic cell will cause certain ion channels to open or close, with the result that the membrane potential rises from –70 mV to 0 mV and possibly higher. Such excitatory impulses are termed Excitatory Post-Synaptic Potentials (EPSPs). If the membrane potential rises above a particular threshold level, approximately +30 mV, then an action potential is generated in the neuron, and neurotransmitter is released onto another cell. The rise in membrane potential due to an EPSP is called depolarisation.

In contrast, Inhibitory Post-Synaptic Potentials (IPSPs) make cell firing less likely by lowering the membrane potential, thereby pushing it further from the threshold level for action potential propagation. This lowering of the potential across the membrane is called hyperpolarisation. It is the summated effects of these depolarisations and hyperpolarisations (which may collectively be termed Neural Current Sources), rather than the action potentials themselves, that are recorded by EEG and ERPs.

Neural Current Sources originate at the cell membrane and represent a deviation from the equilibrium state or resting potential. During an EPSP, a local current *sink* is produced, which sucks positive ions into the cell, thereby moving the potential closer to 0 mV. A sink may be thought of as a negative source. Local sinks are balanced by distant passive sources; as the sink draws ions into the cell, thus depolarising the membrane, these ions move through the neuron and are ejected at some other location, known as a (positive) *source*. For example, if a sink existed at a branch of the cell's dentritic tree, the distant source might occur at the cell body, or near the axon hillock. The co-occurrence of the positive source at one location and the negative sink at another means that the cell may effectively be viewed as a dipole.

In an IPSP, the opposite situation occurs. A local source is produced, which emits positive ions, thereby lowering the membrane potential. This source is balanced by a distant sink, which takes in ions at another location on the cell. Again, this may be considered as a dipole. The EEG gives a macroscopic view of the activity of these sinks and sources. Although we can only provide a brief overview here, a detailed account of the workings of this technique is provided by Nunez (1990).

EEG and ERPs record from the scalp the electrical activity (produced by sinks and sources) of populations of pyramidal cells which form the grey matter of the cortical surface. If a scalp potential recorded activity due to current sources over an area of less than 1 $cm^2$, then the large number of sources may be considered as a *single dipole source*. Usually, however, scalp potentials are due to larger areas of activity. When a large number of dipoles fire with synchronous activity, and their polarities are the same (i.e. all their positive terminals or sources are adjacent to other positives), as can happen with the densely interconnected pyramidal neurons of the cortical surface, then the group could be considered to form a *homogenous dipole layer*. However, dipole layers rarely occur with completely homogenous polarities of sinks and sources. The more common occurrence is for the layer to consist of a mixture of polarities of dipoles, in which case the overall potential will reflect the majority of dipole polarities.

It has been repeatedly demonstrated by correlating scalp recorded EEG with intracranial neuronal discharges in the monkey and the cat that the polarity of ERPs are related to either excitation or inhibition of cells. Comparison of evoked potentials and neuronal spiking activity reveals that neuronal discharges/firing in thalamocortical cells seem to result in negative ERP components, while cellular inhibition underlies positive potentials. Thus EPSPs/depolarisations appear responsible for negative ERP deflections, while IPSPs/hyperpolarisations are the cause of scalp-recorded positivities. Specifically, the scalp recorded negative shifts seem to be due to the depolarisation of pyramidal cell dendrites, which results in an extracellular surface current sink, with the opposite situation the case for scalp recorded positives. The relationship between neuronal activity and scalp-recorded potentials is shown in Figures 3 and 4, from Coenen (1995). Although this polarity reversal between intracranial and scalp recorded activity is true in most cases, the opposite relationship, where scalp positives are due to neuronal excitation and negatives to inhibition, has also been found on occasion.

***Utilities of ERPs***

ERPs are especially useful due to their temporal resolution. Temporal resolution is the ability of a recording method to provide an accurate picture of the timing and sequence of the occurrence of cognitive events. Electrical potentials travel through the bone and skin of the skull and scalp at high speed leading to almost instantaneous recording of the electrical activity of the brain, thus providing very high temporal resolution. The time-course of processing in the cortex

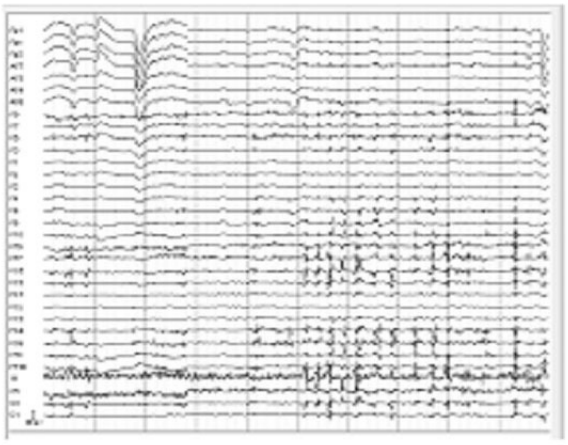


**Figure 1:** EEG waveforms following amplification and extracted ERP waveforms from the FCZ electrode following averaging.

may be seen with millisecond accuracy. In this facet of functional brain activity recording, ERPs is considerably superior to the other major options available, Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI). Both of these imaging techniques rely on the idea that increased cognitive processing in an area of cortex requires increased regional cerebral blood flow (rCBF) to support the local energetic demands of the tissue for nutrients and oxygen. There is a significant time-lag involved in such approaches, due to the relatively slow speed at which blood flows through the brain (in comparison to electrical impulses). Also, a blocked design must be used in most imaging studies, so a real-time record of processing cannot be obtained.

The major stumbling block encountered in the use of ERPs is the relatively poor spatial resolution it affords both experimenters and clinicians. Electrical fields are significantly distorted by skull and scalp tissue, so the pattern of activity recorded on the scalp may bear little resemblance to the regions of cortex responsible for such activity. As such, it is difficult to assert that a potential recorded by a dorsolateral prefrontal electrode emanated from the dorsolateral prefrontal cortex. PET and fMRI allow for very high spatial resolution, because the anatomical structures receiving increased blood flow can be represented in three dimensions. Also, because they do not rely on mere scalp recordings, activity in deep sub-cortical regions may also be seen. This disadvantage limits the use of ERPs in experimental study, and many laboratories have conducted much research on methods to overcome this apparent deficit.

Two major ways in which neuroscientists have attempted to counter this problem are through source localization analysis and co-registration procedures. Source localization algorithms attempt to mathematically solve the problem known as *the Inverse Problem*. Given an EEG scalp distribution of activity observed at given scalp electrodes, any number of brain source distributions can be found that would produce the given distribution. Therefore, solving the inverse problem requires making additional assumptions about the nature of the source distributions. Unfortunately, the problem of finding the locations of more than one simultaneously active equivalent dipole does not have a single unique solution, and *Best Fit* solutions will differ depending on the observed scalp distribution(s) that are given to the source inversion algorithm. To combat this problem, source analysis software packages have been developed (e.g. BESA; MEGIS software) that attempt to maximize spatial resolution through the use of multiple source algorithms, creating source montages (see Figure 5). This has been found to allow the location of ERP potentials to be displayed at a much higher spatial resolution (Scherg, Bast & Berg, 1999).

Co-registration involves bringing two brain images into alignment, specifically aligning two images of different modalities, such as ERP and fMRI. Ideally, the point represented by a given voxel in the ERP analysis represents the same point in the fMRI image. This allows neuroscientists to compare rCBF to electrical activity, forming an educated estimate as to the relationship between brain energy use (measured by rCBF) and brain electrical output (measured by scalp potentials). The development of realistic head models rather than the more commonly used spherical model has greatly increased the efficacy of this model (Vanrumste, Van Hoey, Van de Walle, D'Havé, Lemahieu & Boon, 2002). This method has been utilized with great success by John Foxe and colleagues from the Nathan Kline Institute, in the areas of multi-sensory integration (Gonzalez Andino, Murray, Foxe & Grave de Peralta Menendez, 2005), executive control (Kelly, Hester, Murphy, Javitt, Foxe & Garavan, 2004) and in the clinical study of schizophrenia (Foxe, Doniger & Javitt, 2001).

***Utilities of high density ERP Arrays***

Recently, there has been much discussion as to the efficacy of High-Density ERPs systems, of 64, 128 or 256 electrodes, rather than the traditional 32 (See Figure 6). Lantz, de Peralta, Spinelli, Seeck and Michel (2003) conducted a study to examine the efficacy of different electrode densities in the measurement of EEGs of epileptic patients. Three electrode array sizes were used in this study, 31, 63 and 123. Each participant was subjected to an MRI scan to create a realistic model of the brain by which source localization could take place through the use of source analysis software. The EPIFOCUS source localization algorithm was utilized to interpret the results and find the accuracy of each ERP density in localizing interictal discharges in the 14 epileptic patients. In 9 participants, there was a significant increase in accuracy between 31 and 63 electrodes, and significantly improved results were found in 11 of the 14 participants when 123 electrodes were used. Michel, Lantz, Spinelli, Thut, Perrig, Ducommun, Blanke and Seeck (2001) carried out a comparison of the accuracy of a 128-channel system versus a conventional clinical array of 29 channels in localizing the source of electrical dipolar activity involved in epilepsy. To do so, 17 epileptic patients, whose epileptic zones were known from presurgical workup or subsequent operation, were tested to a standard clinical protocol of eyes-open, eyes-closed, and hyperventilation periods. In all patients, a highly significant result was found of smaller variance in source localization accuracy in the 128-channel system compared to the conventional system.

Michel et al (2001) state unequivocally that *"localization precision largely depends on the number of recording channels"*. Magnetoencephalography (MEG) users have also demonstrated the increased efficacy of high density, whole head recording, but slow preparation times have curtailed the widespread use of high density ERP recording systems. Recent developments, such as the Geodesic Sensor Net (Electrical Geodesics inc.) and Active Electrodes (Biosemi inc.), which do not require scalp abrasion, have significantly cut down on the time it takes to prepare participants for neuropsychological experiments, allowing for a far more widespread use of this technology. The evidence seems to clearly show that a dense array of electrodes over the entire head is preferable to any other method, such as low density or irregularly placed electrodes, if the equipment is available and there are no methodological difficulties involved, as it is the only method that allows for accurate use of source analysis software and algorithms, without which it is impossible to assess the neural generators of the scalp potentials found during ERP recording.

***Current ERPs research in Ireland***

Currently in Ireland, a number of Universities, research institutions and clinical settings make use of ERPs to further their research. Researchers at both the National University of Ireland, Maynooth (NUIM) and Trinity College Institute of Neuroscience (TCIN) are currently using the method in studying memory and source memory processes, attentional memory (Roche, Garavan, Foxe, & O'Mara, 2005), and visuo-motor learning (Roche & O'Mara, 2003). Other ERPs based research being carried out in TCIN includes that of

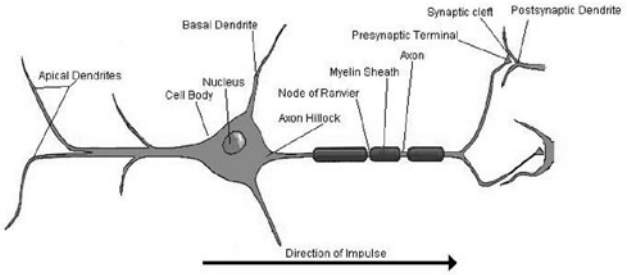


**Figure 2:** Neural communication in the central nervous system. The diagram depicts the anatomical structure and connectivity of neurons in the brain (adapted from Kandel, Schwartz & Jessell, 1995).

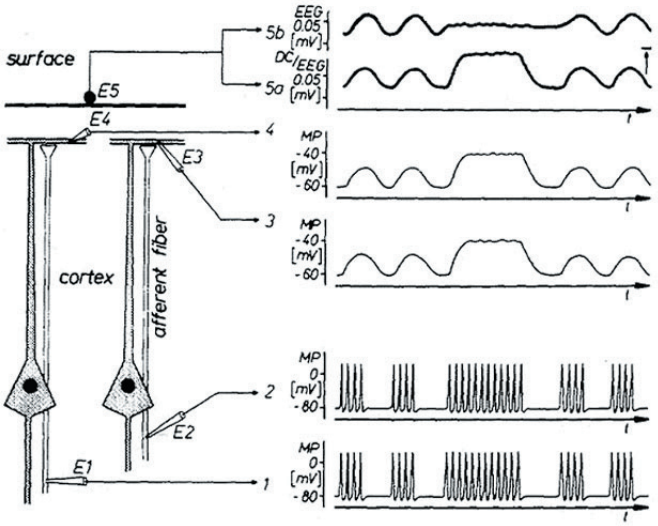


**Figure 3:** A model showing the principles of EEG wave generation. Note that the electrical potentials recorded from the two large pyramidal cells have the opposite polarity at the cortical surface (upper right waveforms) compared to those recorded at E1 and E2 (lower waveforms; from Coenen, 1995). Reproduced with permission of the author.

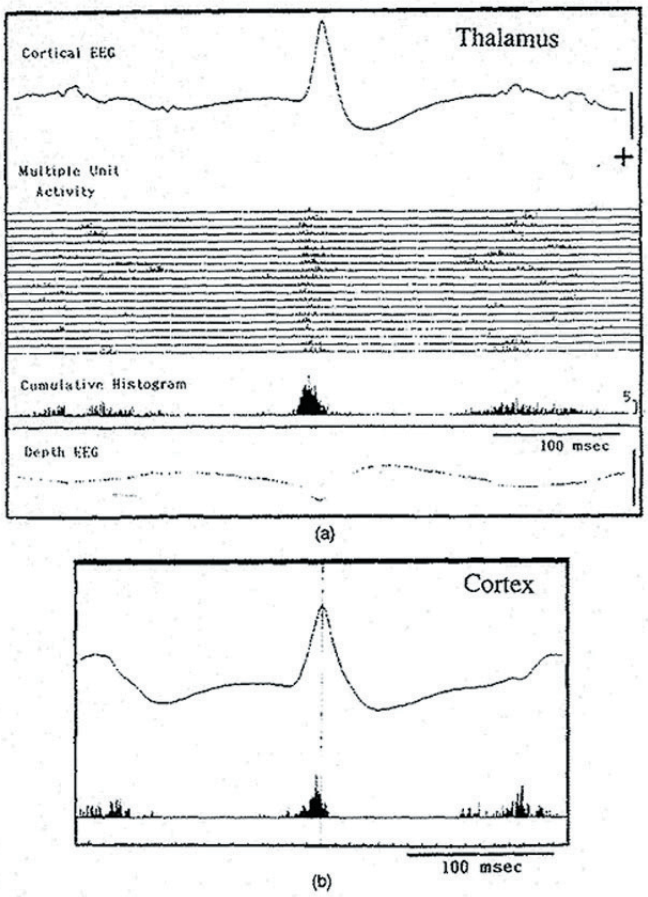


**Figure 4:** Correlation of cortically recorded spike-wave discharges with "multiple unit activity" of (a) thalamic and (b) cortical neurons. Note again the polarity reversal between depth and surface recorded potentials. (from Coenen, 1995). Reproduced with permission of the author.

Ian Robertson, Paul Dockree, Redmond O'Connell and colleagues on sustained attention, ADD/ADHD sufferers and brain injury patients and that of Hugh Garavan and colleagues with response inhibition and executive function. Researchers at the National University of Ireland, Galway (NUIG), NUIM and the University of Ulster (UU) are currently collaborating on work involving the monitoring of ERPs as part of ongoing research on behavioural analysis and derived stimulus relations (Barnes-Holmes et al., 2004). In University College Dublin (UCD) work is ongoing on the effect of driving on visual attention using ERPs (Keyes, Maguire, Brady & Moran, 2004). On the clinical front, the Mercier Institute of Research into ageing (MIRA), in St. James's Hospital, Dublin, employs researchers to study, among other areas, the effects of Alzheimer's Disease on memory using ERPs (Hogan, Swanwick, & Kaiser, 2003), while the St. Vincent's Hospital Cognitive Neurophysiology lab, Dublin, in conjunction with John Foxe's Cognitive Neurophysiology Laboratory in the Nathan Kline Institute (NKI), New York, is engaged in much ERPs-based work, including that of Sherlyn Yeap, who is studying ERP endophenotypes (genetic markers) in patients with schizophrenia and Edward Lawlor, who is examining EEG alpha modulations during selective attention and developing new measurement and analysis techniques for EEG.

The uses of ERPs in the field of cognitive neuroscience and in psychology as a discipline are myriad, and have allowed increasing understanding of such varied interests as human language and cognition, memory and visuo-spatial ability. The method has greatly increased our understanding of the workings of the human brain in a functional manner and has allowed for great leaps to be made in research. High-density ERPs recorders, using 128 electrodes (see Figure 6), when combined with source analysis software can allow for extrapolation of the neural correlates of scalp potentials and when co-registered with fMRI data can meld the excellent temporal resolution of ERPs recording with the spatial resolution of fMRI brain imaging, giving a 3D map of the brain that can accurately estimate the areas of the cortex active during certain tasks. These developments show a promising future for the use of ERPs data in both neuroscientific studies and in clinical settings.

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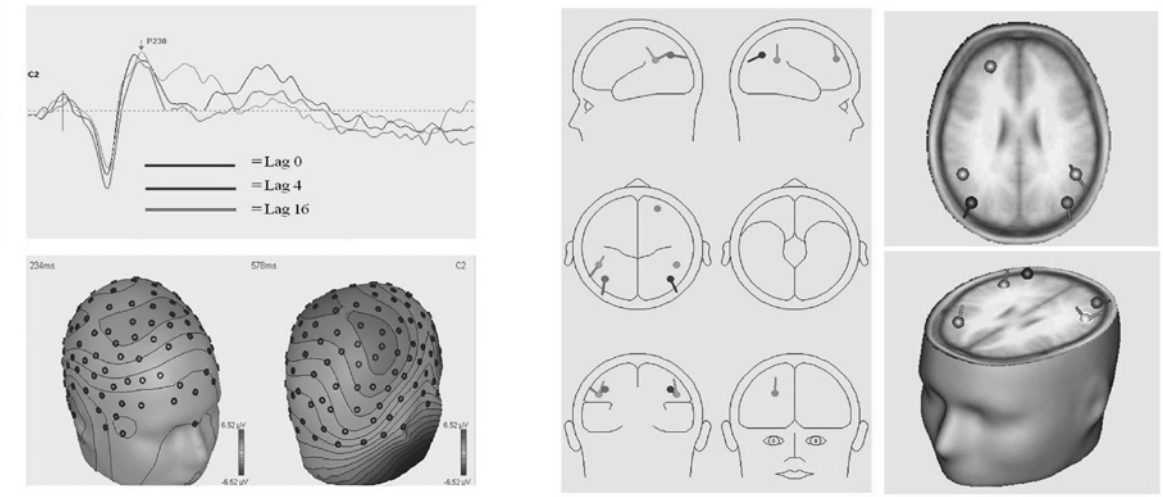


**Figure 5:** BESA source analysis software displaying ERP waveforms and scalp topographies (left), dipole solutions and anatomical locations of brain sources (right)

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**Figure 6:** An example of a High-Density ERPs Array, as used by researchers in NUIM during the 1st 128-channel ERPs based study completed in Ireland (Nov, 2005).