Introduction to the application of event-related potentials in cognitive rehabilitation research

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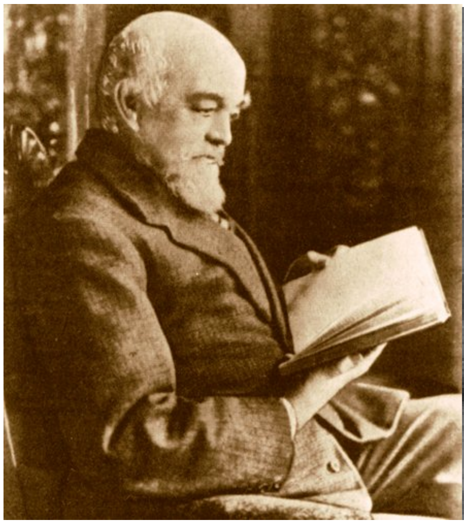
In 1875, Richard Caton, a physician and medical lecturer from Liverpool, discovered that brain electrical signals could be recorded directly from the surface of the exposed cortex using a reflecting galvanometer. A half century later, Hans Berger (1929) was able to detect these brain waves with electrodes placed on scalp. He, like Caton, noted that these voltages could be influenced by external events that stimulated the senses.


Richard Caton (1842-1926)


Hans Berger (1873-1941)

These "event-related potentials" became particularly accessible to noninvasive study in humans when methods were developed in the 1940's that allowed researchers to separate out the small potentials evoked by sensory stimuli from the larger voltage oscillations present in the spontaneous electroencephalogram (EEG). George D. Dawson (1947) discerned that sensory-evoked electrical potentials in the order of a few microvolts in magnitude could be recorded from the scalp of humans by using a technique where a large number of responses to similar stimuli were averaged, thus canceling out random variation in background noise of the EEG. The advent of electronic averagers, and then subsequently the use of digital computers (Galambos & Sheatz, 1962), promoted a rapid expansion in the application of event-related potential techniques. Currently, it is one of the most widely used methods in cognitive neuroscience research to study the physiological correlates of sensory, perceptual and cognitive activity associated with processing information (Handy, 2005).

Electrophysiology & Functional Interpretation of ERPs

Event-related potentials can be elicited by a wide variety of sensory, cognitive or motor events. They are thought to reflect the summed activity of postsynaptic potentials produced when a large number of similarly oriented cortical pyramidal neurons (in the order of thousands or millions) fire in synchrony while processing information (Peterson, Schroeder, & Arezzo, 1995). Pyramidal cells are critical cortical computational elements involved in deciphering information relayed to cortex via thalamocortical pathways or from long distance cortico-cortical connections. Far field potentials can also be recorded, which reflect activity generated in subcortical structures such as the brain stem nuclei (Hari, Sulkava, & Haltia, 1982; Musiek, *et al.*, 2004; Stern, *et al.*, 1982).

This approach to studying neural processing has several advantages over purely behavioral measures. Reaction time, for example, reflects the output of a number of different cognitive processes and consequently, variations in response latency or accuracy are difficult to attribute to a specific cognitive operation. By contrast, event-related potentials constitute a millisecond-by-millisecond record of neural information processing that occurs between presentation of a discrete stimulus and the production of the motor response. This level of temporal resolution is vastly greater than other functional neuroimaging techniques. By comparison, the temporal resolution of functional magnetic resonance imaging (fMRI) or Positron Emission Tomography (PET) is on the order of seconds to tens of seconds. ERPs are therefore regarded as an excellent complementary technique to measures such as fMRI, which has exquisite spatial resolution. The spatial resolution of the ERP is difficult to establish but is may be as much as an order magnitude more than fMRI.

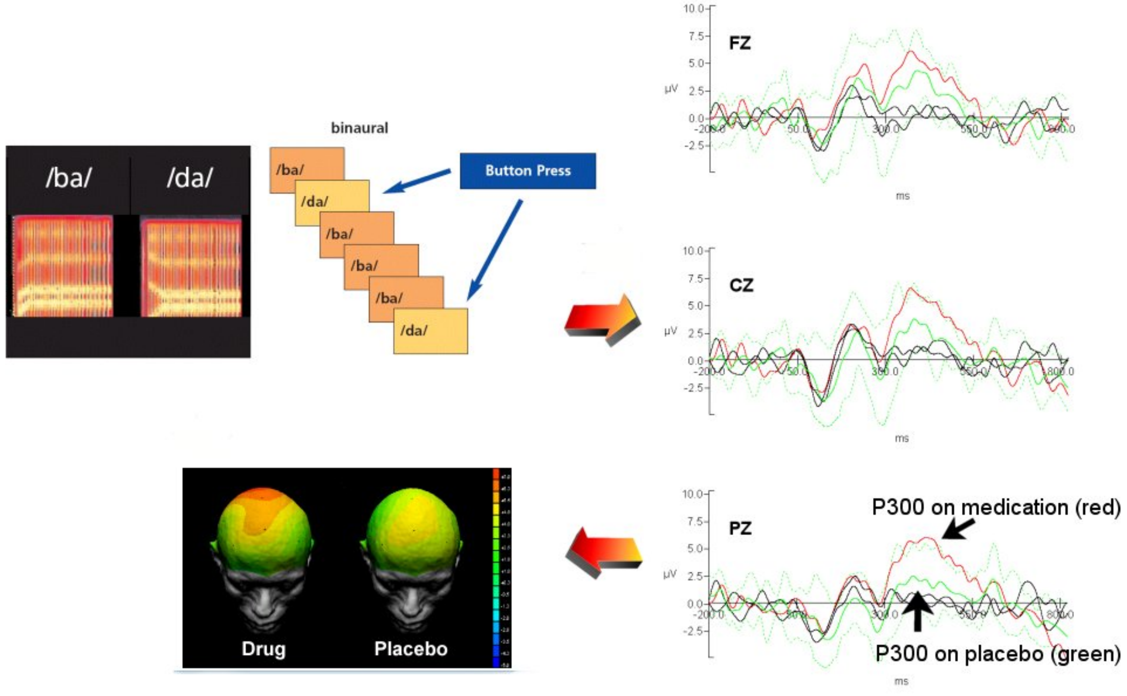
Through systematic examination of the amplitude and latency of numerous deflections in the electrical potentials that comprise the ERP, it has been possible to link particular components of a response to specific psychological processes. The examination of these components can provide information regarding the sequence of perceptual and cognitive operations involved in processing a stimulus or generating a response. For example, in processing an auditory event, early components of the ERP (e.g., N1) represent activity in the first cortical areas to receive sensory input (e.g., auditory cortex) and subsequent deflections such as P2 reflect early stimulus evaluation and feature detection (Luck & Hillyard, 1994) in temporal cortex. The N2 wave is thought to index inhibitory processes and is probably generated in medial prefrontal cortex (Bekker, Kenemans, & Verbaten, 2005). Still later components of the ERP (e.g., P300 or P3) are representative of processing of information at more advanced cognitive levels, reflecting operations such as shifting attention or updating mental representations in working memory (Donchin, Miller, & Farwell, 1986; Picton, 1992). The P300 is thought to be generated by a distributed network with frontal and parietal contributions, possibly also involving hippocampus (for reviews, see Bashore & van der Molen, 1991; Polich & Criado, 2006; Tarkka, *et al.*, 1995). Still later components can reflect responses to violations of semantic (N400) or syntactic (P600) expectancy (Osterhout, Holcomb, & Swinney, 1994).

Clinical Application of ERPs

Clinical studies have revealed abnormalities in ERP components resulting from neurological conditions such as dementia (Boutros, *et al.*, 1995), Parkinson's disease (Prabhakar, Syal, & Srivastava, 2000; Wang, *et al.*, 2002), multiple sclerosis (Boose & Cranford, 1996), head injury (Duncan, Kosmidis, & Mirsky, 2003; Reinvang, Nordby, & Nielsen, 2000; Segalowitz, Bernstein, & Lawson, 2001; von Bierbrauer & Weissenborn, 1998) and stroke (D'Arcy, *et al.*, 2003; Korpelainen, *et al.*, 2000; Pulvermuller, Mohr, & Lutzenberger, 2004). The within-subject reliability, stability and sensitivity (Lewis, 1984; Neylan, *et al.*, 2003; Polich & Criado, 2006; Turetsky, Colbath, & Gur, 1998) of many ERP components is sufficient to allow the technique to be used to evaluate changes in function that occur in response to treatment. For example, several studies have shown that the amplitude of the P3 component is diminished in Attention Deficit Hyperactivity Disorder (ADHD) but can normalize in response to treatment with psychostimulant medications (McPherson & Salamat, 2004; Ozdag, *et al.*, 2004; Sangal & Sangal, 2006).

ERPs in Cognitive Rehabilitation

In recent years, ERP techniques have gained popularity in studying responses to cognitive rehabilitation and adjuvant pharmacologic treatment. Several authors have proposed that ERPs are well-suited for monitoring recovery of neural mechanisms responsible for language in patients with post-stroke aphasia (Cobianchi & Giaquinto, 2000; Pulvermuller, *et al.*, 2005). It has been argued that behavioral changes observed in chronic patients over therapeutic intervals lasting several months may be inappropriately attributed to cortical reorganization. Pulvermueller et al. (2005) suggest that, in order to relate behavioral and neuronal changes to the treatment program, rather than changes in strategy or habits, it is necessary to examine both changes in performance and in their physiological responses, preferably over short intervals of therapy. They used ERPs to demonstrate neuronal changes underlying accumulated improvements associated with constraint induced aphasia therapy in individuals with chronic aphasia. The figure below reflects our own work that has examined the effects of single-dose psychostimulant medications in subjects with aphasia. Note the difference in the P300 component.



P300 in aphasia on medication vs placebo

Several studies have also suggested that ERP components may be sensitive to neuroplastic changes in the brain that accompany new learning (Gottselig, *et al.*, 2004; Reinke, *et al.*, 2003) and can index failures in learning mechanisms associated with neurological disease or damage (Olichney, *et al.*, 2006). The technique may also be useful in assessing functions in a passive manner in patients who are unable or have difficulty producing overt responses (Connolly, *et al.*, 2000; D'Arcy, *et al.*, 2003; Marchand, D'Arcy, & Connolly, 2002). Moreover, the procedure may allow a determination of processing at the unconscious level (Eimer, *et al.*, 2002) and may be particularly useful in distinguishing the stage of processing information where problems may be apparent (see Eimer, 2000 for example).

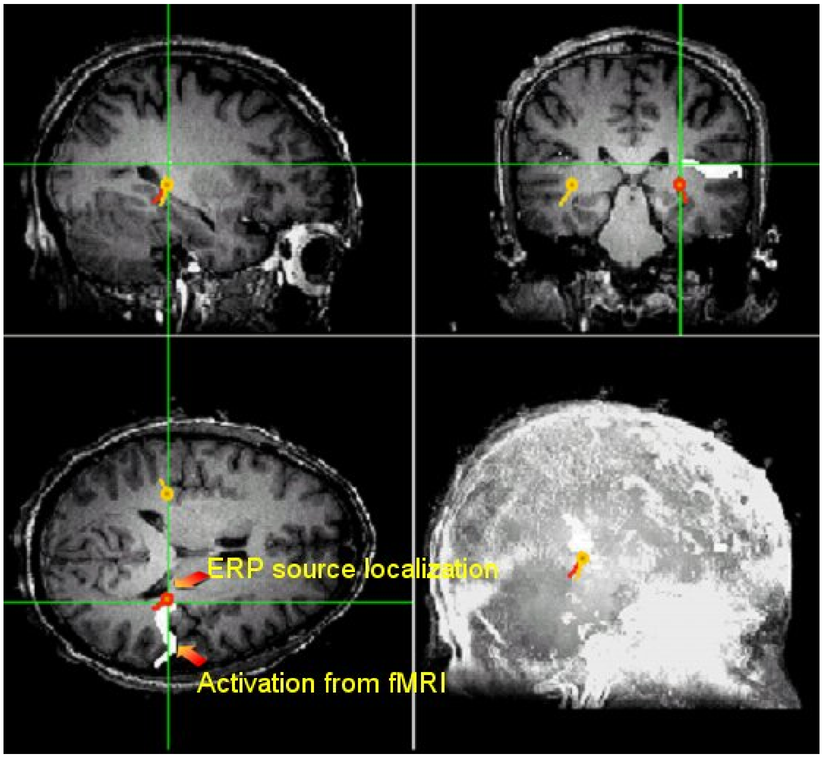
Other advantages of ERP as a neuroimaging technique are that it is associated with relatively low cost for setup and maintenance. In addition, the instrumentation is potentially portable so studies can be obtained in a variety of settings. Moreover, while fMRI cannot be performed on some individuals (e.g., if they have implanted metal devices, fear enclosed spaces), the ERP technique is generally well tolerated and subject to fewer constraints.

Problems, Pitfalls, & Limitations

One of the primary drawbacks of ERP methods concerns problems inherent in discerning the location of cortical generators (cortical dipoles) that account for observed scalp topographical distributions. Resolution of this issue has been limited by a basic indeterminancy - many possible solutions can potentially account for a given scalp potential topography (the “inverse problem”, see Riera, *et al.*, 2006 for a discussion). Currently, there are no algorithms for choosing a mathematically-definitive unique solution.

However, several recent developments have enhanced the applicability of ERP recording for cognitive neuroscience and cognitive rehabilitation research. First, the use of high-density electrode arrays (Johnson, *et al.*, 2001) during ERP recording may partially overcome the problem of spatial localization. Secondly, frameworks for combining information from EEG/ERP with structural data from MRI have been established. This makes possible the identification of plausible multiple cortical sources with a spatial resolution as good as PET but with a much finer temporal resolution (Dale & Sereno, 1993). In addition, improved analytic techniques (e.g., Low Resolution Electromagnetic Tomography- LORETA), which utilize biological information to constrain solutions, have substantially enhanced the quantitative estimation of source dipoles (Dien, Spencer, & Donchin, 2003; Ding, Lai, & He, 2005; Fuchs, *et al.*, 2004; Hegerl & Frodl-Bauch, 1997; Pascual-Marqui, *et al.*, 2002). These advances have permitted the calculation of unique solutions to the inverse problem.

Recognizing that a unique solution may not necessarily be the correct one, several studies have sought to validate these approaches by comparing source estimates of ERPs with other functional neuroimaging procedures. In general, there has been good concordance in source localization of EEG results with results of magnetoencephalography (Tarkka, *et al.*, 1995), and PET (Gamma, *et al.*, 2004). Cohen et al. (1990), for example, created an artificial source by passing subthreshold current through depth electrodes implanted in three seizure patients undergoing intracranial monitoring. The precise location of these electrodes, determined from roentgenographs, was compared to the estimated location of dipoles calculated from MEG and EEG recordings. The average error of 10 mm from EEG recordings was not significantly different from the error associated with MEG (8 mm). Either method appeared comparable to the best ${}_{15}$O positron emission tomography (PET) resolution (6 to 100 mm). The results of a recent study comparing source localization of an auditory ERP with concurrent fMRI are depicted below.(Personal communication, C. Ponton 2003, see also Scarff, *et al.*, 2004). Others have also demonstrated concordances on language tasks (Vitacco, *et al.*, 2002).



Auditory ERP Source localization vs fMRI

Future Prospects

ERPs have an established track record in the study of alterations in neural information processing in humans. In some domains of investigation, their sensitivity to pathology, combined with their reproducibility and robustness, has resulted in their utilization as a mainstream diagnostic procedure. In neurology, for example, brainstem auditory evoked potentials have excellent sensitivity in diagnosing cerebellopontine angle tumors, with a false-negative rate of less than 3% (Goodin, 1990). In other contexts, ERPs have been considered an excellent means to investigate cognitive or biological differences between already-diagnosed patients and controls or to assess response to treatment. Although there are often significant variations in the amplitude of these responses between individuals, they are highly stable within individuals from session to session, whether recorded hours or months apart. This temporal stability appears sufficient to allow the use of the technique to monitor changes in cognitive and neural functioning in patients undergoing cognitive remediation.

One of the main limitations that has held back progress in utilizing ERPs in this manner has been the lack of precise correlation of scalp data to underlying generators or sources. However, recent advances in source localization techniques have made substantial progress towards mitigating these concerns. In addition, the growing integration of ERPs with fMRI will allow further specification of the underlying brain activations associated with late ERP components. Combining these techniques may provide the best of two worlds: precise spatial localization and a high-temporal resolution of the underlying brain activity (McCarthy, 1999; Mulert, *et al.*, 2002; Opitz, *et al.*, 1999). While fMRI can precisely localize regions of activation during performance of a cognitive task, the simultaneously recorded ERPs may help define the time course of processing associated with these activations.

SUMMARY

In summary, ERPs are voltage potentials that can be recorded from the scalp that reflect time-locked electrical activity generated in the brain in response to sensory, motor, or cognitive events. The study of these responses provides a means to noninvasively evaluate brain functioning in patients with cognitive disorders. This approach to examining neural processing has several advantages relevant to its application in cognitive rehabilitation research. Whereas behavioral indices such as reaction time do not allow one to link variations to specific cognitive operations, ERPs constitute a millisecond by millisecond record of neural information processing that can be associated with particular operations such as sensory encoding, inhibitory responses, and updating working memory. In some cases, responses have been linked to activity generated in particular neural structures or brain regions. Moreover, responses can be recorded passively and are therefore useful in patients who may have limitations in their ability to generate motor or verbal responses. Indeed, the technique can be sensitive to processing information at the unconscious level and can be used in unresponsive patients. The stability and reproducibility of ERPs is sufficient to allow their use to assess changes in function overtime. As a consequence, ERPs can be useful in assessing neuroplastic changes that occur in normal course of recovery or to monitor changes induced by behavioral or pharmacological treatments. Finally, an advantage of ERP techniques over other neuroimaging methods is that it is associated with relatively low cost for setup and maintenance.

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