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Best Practices for Event-Related Potential Research in Clinical Populations

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ABSTRACT

The event-related potential (ERP) technique has been used for decades to answer important questions about sensory, cognitive, motor, and emotion-related processes in clinical disorders. However, ERP research with clinical populations often involves unique challenges above and beyond the general issues involved in conducting ERP studies in typical research participants. The goal of this article is to provide an overview of the common challenges that arise in ERP research with clinical populations, including issues in experimental design and recording, analysis, and interpretation of ERPs. In addition, we provide strategies that have proven effective in each of these areas for maximizing the potential of the ERP technique to provide important insights about clinical disorders.

Keywords: Clinical disorders, EEG, ERPs, Psychiatric disorders, Psychological disorders, Schizophrenia

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The event-related potential (ERP) technique has been used for decades to assess sensory, cognitive, motor, and emotion-related processes in individuals with clinical disorders, and it has great promise for yielding new insights in the future. However, many complex methodological challenges arise in applying this technique to clinical populations, and these challenges must be overcome for the ERP technique to live up to its potential. The goal of this article is to describe some of the most salient challenges and provide effective strategies for dealing with them. Our own experience has been mainly in schizophrenia, but much of the information presented here applies to any clinical population. We focus our discussion on traditional approaches to ERPs, for which methods have been refined over many decades. Information about newer approaches, such as time-frequency analysis, can be found elsewhere (1,2).

We begin with a brief overview of the ERP technique, followed by a discussion of the challenges in designing experiments, practical considerations in recording and analysis, and issues in interpreting ERP effects. The present article is necessarily brief and focused, but broader reviews are available elsewhere (3–11). In addition, we strongly recommend the ERP publication guidelines of the Society for Psychophysiological Research as a supplement to the recommendations in this article (12).

OVERVIEW OF EVENT-RELATED POTENTIALS

ERPs are voltage fluctuations in the electroencephalogram (EEG) that occur as a result of an external or internal event (e.g., the presentation of a visual stimulus or the preparation of a movement). ERPs arise from postsynaptic potentials in cortical pyramidal neurons, which produce opposite polarities on either side of the active tissue [the specific polarity depending on whether the postsynaptic potential is excitatory or inhibitory; see (13) for a more detailed account]. If a large number of neurons (on the order of thousands to millions) are active together in time and spatially aligned, their electric fields summate, and the summed voltage can be recorded on the surface of the head. Importantly, this means that not all brain activity can be measured with scalp-recorded EEG, and ordinarily ERPs do not directly reflect action potentials, interneuron activity, or subcortical activity (although their influence on cortical postsynaptic potentials may indirectly affect ERPs).

ERPs are conducted through the brain, skull, and scalp virtually instantaneously (at nearly the speed of light). Therefore, scalp-recorded voltages reflect neural activity happening at exactly that point in time. This is what gives the ERP technique such excellent temporal resolution. Postsynaptic potentials last tens to hundreds of milliseconds and may be occurring in dozens of areas of the brain at the same time. Because the potentials generated in a given region of the brain spread widely across the scalp, the voltages recorded at a given electrode site typically reflect activity from multiple brain areas (discussed further below). Note that the spreading of voltages in ERP recordings makes it generally difficult to localize ERPs to specific regions of the brain with confidence [for more information on source localization, see (3,14–16)].

ERPs have several properties that make them especially useful for understanding key aspects of psychiatric disorders. The fact that ERPs provide an instantaneous, continuous, millisecond-resolution measure of processing means that they can be used to isolate the dozens of individual sensory, cognitive, affective, and motor processes that occur between a stimulus and a response, making it possible to unpack the many different factors that contribute to overt behavior. All of these processes are typically collapsed into a single time slice

in functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) experiments because of the sluggish nature of the hemodynamic response. Thus, ERPs are particularly useful for unpacking processes that occur rapidly over a period of 1 to 2 seconds, whereas fMRI and PET are useful for unpacking processes that operate on slower time scales or for which relationships with distinct neuroanatomical substrates are important to resolve or confirm. In addition, many disorders are characterized by a change in the timing of one or more neural processes, and this can be measured much more readily with ERPs than with fMRI or PET. Practically speaking, ERPs are inexpensive compared with other neuroscience techniques (including the magnetic cousin of EEG, magnetoencephalography), with typical equipment costs of $15,000 to $100,000 and disposable supply costs of $1 to $3 per recording session. Whereas some individuals cannot easily tolerate fMRI and PET, EEG recordings are safe and well tolerated by infants, children, adults, and the elderly (17,18), as well as individuals with clinical disorders, including autism, schizophrenia, depression, and Parkinson's disease, among others (19–21). Recent developments in equipment have also made it easier to record the EEG in well-controlled environments outside the laboratory, such as clinics, schools, and hospitals. Moreover, although there are differences in wave shape, size, and timing of ERPs between individuals, ERPs tend to be highly stable within an individual. Indeed, high internal consistency and high test-retest reliability of ERPs have been demonstrated in typical research participants and individuals with psychiatric disorders (22–25). This high reliability, coupled with the fact that ERPs can be recorded many times from the same individual, means that ERPs can be used to examine changes in brain activity resulting from treatment intervention or disease progression. Furthermore, animal models exist for some ERP components, which can be particularly useful in the early stages of drug development (26,27). Collectively, these features make ERPs promising candidates for biomarkers of psychiatric disorders (24,28).

DESIGNING AN ERP EXPERIMENT

Although the temporal resolution of the ERP technique makes it possible to see the many processes that occur between a stimulus and a response, many processes operate simultaneously, and the voltages from these processes are summed together in the ERP waveform. Thus, one major challenge in conducting ERP research is to isolate a single operation from the many other operations the brain is performing at the same time. A single operation is typically what ERP researchers are referring to when they use the term ERP component. We will use the terms operation and component interchangeably in the remainder of the article. Isolating a component from the ERP waveform is necessary to make conclusions about the presence, size, or timing of a specific mental operation (as opposed to conclusions about brain activity, more generally). Given that individuals with clinical disorders often exhibit deficits in more than one operation, isolating a single ERP component can be especially important for drawing clear conclusions from ERPs in clinical research. Importantly, the conclusions that can be drawn from an ERP study also depend on how well the ERP component has been linked to a specific mental operation in previous research, which may or may not be well determined [discussed further below; see also (11,29,30)].

One factor that plays a significant role in how well an ERP component can be isolated is the design of the experiment. Although it is certainly possible to take any experiment, put electrodes on participants, record the EEG, and extract ERPs, this approach is very likely to yield ERP waveforms that collapse multiple operations, making it difficult (or impossible) to tell which operation (or operations) varied among conditions or groups. One effective design strategy is to focus the experiment on a single ERP component, holding all factors unrelated to that component consistent across the experiment. For example, we were interested in whether people with schizophrenia exhibit delays in stimulus evaluation time (31). To do this, we focused on the P3 wave, which is larger for stimuli from a rare category versus a frequent category and whose latency reflects the time needed to perceive and categorize stimuli [see (32) for a review]. To ensure that the P3 could be isolated from all other brain activity that might differ between people with schizophrenia and control subjects, all factors were balanced across the experiment, except for probability. Specifically, the assignment of stimuli to categories, the stimulus-response mapping, and the category-response mapping were all matched across the rare and frequent trial types (see Figure 1 for more details). As a result, this paradigm could isolate the small subset of operations that

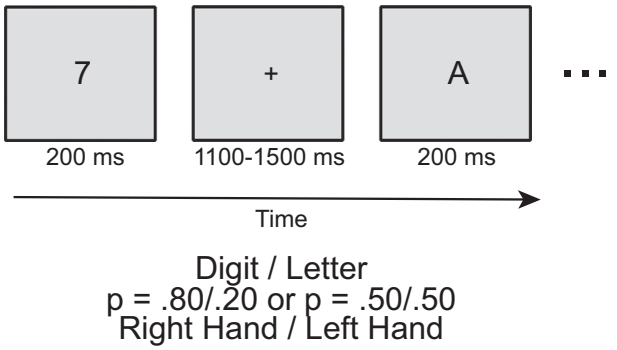

Figure 1. Example stimuli from the study of 31. In this task, participants categorized stimuli as letters or digits. In half the experiment, letters were mapped to a left-hand button response and digits to a right-hand button response; in the other half of the experiment, the category-response mapping was reversed. The probability of letters and digits was manipulated within each half of the experiment, such that letters were 80% probable and digits were 20% probable in one block, digits were 80% probable and letters were 20% probable in one block, and letters and digits were each 50% probable in the remaining block. The order of blocks was counterbalanced across participants. This factorial manipulation of response mapping and probability meant that across the experiment, each possible combination of response mapping (two levels) and category probability (three levels) occurred, for a total of six trial blocks. The probability-sensitive P3 component was isolated from the four trial blocks in which one category was 80% probable and the other was 20% probable, collapsing across the category that was more probable and the response mapping that was used. The response-sensitive lateralized readiness potential component was isolated from the two trial blocks in which the category response mapping was manipulated but the probability was 50% for each category.