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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 paper is to provide an overview of the common challenges that arise in ERP research with clinical populations, including issues in experimental design, 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.

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 paper 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 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 paper (12).

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Keywords

clinical disorders; EEG; ERPs; psychiatric disorders; psychological disorders; schizophrenia

Overview of ERPs

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 PSPs 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 1–2 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 to other neuroscience techniques (including the magnetic cousin of EEG, magnetoencephalography [MEG]), with typical equipment costs of $15,000–$100,000 and disposable supply costs of $1–$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 EEG in well-controlled environments outside the laboratory, such as clinics, schools, and hospitals. Moreover, although there are differences in waveshape, 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 paper. 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 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 controls, 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 are sensitive to the probability of the task-defined stimulus category. The results of this study are discussed below.

In many cases, it may be desirable to examine multiple operations within a single EEG recording session. For instance, there may be multiple operations that are hypothesized to be affected in a clinical population, or it may be useful to include an operation that does not differ between patients and controls as a way of demonstrating specificity. There are many ways to combine multiple operations within a single session, while maintaining the ability to isolate each individual component. For example, multiple tasks may be performed serially in a single recording session. Alternatively, a single task may include separate trial blocks that each focus on a different component, or trial types focused on different components may be intermixed within a block of trials. As an example, the study of the P3 in schizophrenia described above was designed to also isolate the lateralized readiness potential (LRP), an index of response preparation. To combine the P3 and LRP in a single experiment, some trial blocks focused on the P3 (by manipulating stimulus probability) whereas other trial blocks focused on the LRP (by manipulating response hand). The P3 was then isolated from one group of trials, and the LRP was isolated from a different group of trials. An extended version of this approach, known as the MONSTER technique, involves using multiple orthogonal manipulations to isolate several ERP components from a single experiment (see 33 for a description of this approach). In rare cases, it may be possible to examine multiple ERP components using the same trials if the components are present at completely non-overlapping time points.

Another useful strategy for isolating a component is to use *difference waves*. Creating a difference wave simply involves subtracting the ERP waveform for one condition from the ERP waveform for another condition, effectively eliminating the operations in common to the two conditions. For example, to further isolate the P3 effect in the study described above (31), we created a rare-minus-frequent difference wave to remove all non-probability-related brain activity. Whereas the amplitude of the P3 was reduced in people with schizophrenia in both the rare and frequent non-difference (*parent*) waveforms, the difference wave showed no difference in P3 amplitude between the schizophrenia and control groups (see Figure 2). In other words, there was an overall reduction in P3 amplitude in people with schizophrenia, but this was the same for the rare and frequent categories (see similar results from 34). Thus, the difference wave showed that the P3 amplitude reduction in schizophrenia was not related to probability, but rather reflected a probability-insensitive process that was active during that same time. These conclusions would have been much more difficult to draw without the difference waves.

One potential problem with difference waves is that it is easy to make incorrect assumptions about which parent waveform was responsible for the difference. It is therefore important to examine the parent waveforms to see which condition is driving the effect. Moreover, publications should typically include figures showing the parent waveforms as well as the

difference waveforms (12). Other limitations to the difference wave approach are discussed extensively in Luck (2014).

Practical Issues in Recording and Analysis

Task and Recording Parameters

Although EEG recordings are well tolerated in patient groups, it is sometimes necessary to modify the standard recording procedures in research with clinical populations. In some patient groups, it may be advisable to shorten the amount of time participants spend in the lab. One way to accomplish this is by limiting the amount of time spent on task by focusing on a small number of conditions. It also may be advisable to decrease electrode application time by using a smaller number of EEG electrodes. Although there are differing opinions on how many electrode sites are optimal, the majority of ERP studies conduct statistical analyses on a relatively small number of electrode sites (or clusters of sites), even in cases in which a large number of channels were recorded. In addition to decreasing electrode application time, a smaller number of channels are easier to monitor during the recording session, resulting in increased data quality. In our opinion, it is preferable to record cleaner data from fewer electrode sites rather than noisier data from a larger number of electrode sites. We typically find that 32 electrode sites are sufficient for most ERP studies, although the optimal number and location of electrode sites varies somewhat across studies.

Individuals with clinical disorders may exhibit more artifacts than typical participants during EEG recordings. Therefore, it may be useful to provide instructions for how to minimize artifacts. Demonstrating the effect of artifacts on the EEG in real time prior to recording can be especially instructive (this simply involves having a monitor on which the participant can view his/her EEG). It also may be helpful to provide instructions about the most acceptable times for artifacts, such as moving during break periods or blinking after a response. However, it should be noted that instructing participants to monitor or withhold artifacts creates a dual-task situation, requiring the participant to think about artifacts in addition to performing the task. This may have unintended consequences on task performance and on ERPs (35). For example, the clinical group may perform worse than controls as a result of difficulty handling the dual-task load, not as a direct result of poorer performance on the primary task. Therefore, it may be advisable to provide minimal instructions about artifacts, or to skip artifact instruction entirely and rely on artifact correction (described in the next section). It also may be useful to provide more frequent rest breaks, or to increase the intertrial interval to accommodate for artifacts (and in some cases, slower response times).

Analysis Procedures

Artifact Removal—Some offline procedures for artifact removal are almost always necessary in ERP studies. The two methods for removing artifacts are *artifact rejection*, which involves eliminating artifact-contaminated segments of EEG, and *artifact correction*, which involves subtracting the estimated contribution of the artifact; often a combination of both methods is used. Removing segments of EEG that contain artifacts is most effective if artifacts are present on only a modest proportion of trials. The removal of artifacts should be factored into the design of the experiment to ensure that enough EEG segments are retained

to construct a reliable ERP waveform. In some cases, it may be preferable or necessary to correct for artifacts. There are many different algorithms available for artifact correction but, in general, they work best at removing artifacts that are large and consistent, such as eyeblinks. Smaller or less consistent artifacts may not be completely removed, and some neural activity may also be removed along with the artifacts. If there are differences in artifacts across groups, artifact correction procedures could produce artificial differences in the ERPs. It should also be noted that correction methods cannot account for changes in sensory input related to how a visual stimulus hits the retina, such as when the eyes are closed at the time of the stimulus (3; 12).

Measurement—Accurately measuring ERP components is one of the most challenging aspects of conducting ERP research. It can be especially difficult in clinical studies, in which the timing of the components may vary substantially within a group and/or between groups. ERP components are typically quantified by measuring the amplitude or latency of the ERP waveform within a specified time range. The most common methods for measuring amplitudes and latencies are peak-based methods, which measure the size or time of the most positive or most negative point within a time window, and mean/area-based measures, which measure the aggregated size or time of the average activity across the time window. Mean/area measures are typically (but not always) superior to peak-based measures, especially in cases in which the number of trials contributing to the ERP or the signal-to-noise ratio of the data differs between groups, which can occur in clinical research (3; 11; 12).

It can be difficult to select a time window for measuring an ERP component that accurately captures the component in all participants but does not overlap with preceding or subsequent components. Implementing the experimental design strategies described above can significantly mitigate these issues. For example, if a single component has been isolated with a difference wave, it may be possible to choose a very large time window that captures the broad timing of the component across participants. Alternatively, it may be useful to measure the ERP component across many small time windows (e.g., in 50 or 100 ms increments across a broad time range), and to include time as a within-subjects factor in the ANOVA. This can help to capture differences in an ERP between groups of participants who vary substantially in the timing of the component. Another approach is to combine the peak- and mean-based measures, first identifying the peak and measuring the mean value in a time window around the peak (although simply applying a low-pass filter prior to peak measurement may be superior; see Luck, 2014).

One primary concern in measurement is to avoid biasing the results in favor of a statistically significant result (i.e., increasing the probability of a false positive). This is often done unintentionally by choosing a time window that shows the largest difference between groups in the *grand average* waveforms (averaged across participants separately for each group). One unbiased method is to use the same time window from previous studies; however, this can be difficult for experiments involving new tasks or experimental manipulations, or for experiments involving populations or age groups that have not been studied in the same context. An alternative that can work well in these situations is to make what is called a *grand-grand average*, collapsing the data from all groups, and choosing the time window

that best captures the ERP component in the collapsed average. This method allows the selection of a time window that captures the ERP component, without biasing the selection to the part of the waveform that shows the biggest difference between groups (which is not visible in the collapsed average).

A related issue is the need to select the electrodes that are used for measurement and analysis. If the electrodes are chosen on the basis of the observed effect, this will bias the results to be significant. To avoid this problem, one can use previous research or grand-grand averages to guide the choice of electrode sites. Another increasingly common approach is to simply average across all the electrodes within a region prior to measuring the amplitudes and latencies. Another approach, which can be used to deal with both the selection of time windows and electrode sites, is to do separate statistical tests for each time point at each electrode site, combined with an intelligent correction for multiple comparisons (36–38).

Interpreting ERP Effects

Interpreting ERP effects in clinical research can be challenging, even in cases in which a single ERP component has been isolated. The conclusions that can be drawn from an ERP study depend in large part on how well previous research has linked the ERP component with a specific operation (i.e., the *construct validity* of the ERP measure), which varies significantly among ERP components. For example, despite hundreds of studies over many decades, it is still unclear what process is reflected by the P3 (32), which greatly limits the conclusions that can be drawn from differences in P3 amplitude between groups. By contrast, some components, such as the LRP, have much better construct validity, allowing stronger conclusions to be drawn from the results (39).

The psychometric properties of an ERP component may be influenced by a variety of factors, which can further complicate the interpretation of ERP results. One such factor is the task or experimental manipulation. For example, the ERN from a flanker task has been shown to have higher internal reliability than the ERN from Stroop, go/no-go, and picture/word tasks (24; 25). In addition, the choice of task can influence the external validity of an ERP measure. For instance, the ERN derived from a flanker task has been shown to better relate to clinical characteristics than the ERN from a picture/word task (24). Similarly, although the amplitude of the mismatch negativity (a response to deviant auditory stimuli) is reduced in schizophrenia for pitch, intensity, and duration deviants, these stimulus types show independent correlations with outcome measures, and therefore do not reflect the same neural process (40). An ERP component also may be highly influenced by the operations that came before it, such that a deficit in one process may influence a downstream process that relies on its input. A good example of this is the study of Haenschel et al. (41), in which abnormal working memory performance in schizophrenia could be explained, in part, by deficient visual encoding of stimuli, indexed by reduced P1 amplitude.

A consequence of these varied influences on ERPs is that a given ERP effect can be caused by many different factors. In the context of clinical research, this means that the same ERP effect may be found in multiple disorders, but this does not mean this effect reflects the

same underlying deficit. For example, a reduction in P3 amplitude could be caused by impaired sensory coding, impaired perceptual categorization, or impaired attention. Thus, a component by itself should not be considered a measure of a specific neural or psychological process; instead, it is necessary to consider an ERP effect in the context of the experimental paradigm and broader class of deficits exhibited in the population.

It is important in interpreting ERP effects in clinical studies to consider how differences in behavior between patients and controls may be influencing the ERPs. In some cases, understanding behavioral deficits in the clinical group is the goal of the study, and differences in behavior are therefore a necessary consequence of the experiment. In these circumstances, it is important to ensure that the behavioral differences are not caused by deficits in motivation or comprehension, and that the ERP measurement procedures can accommodate for any differences in trial count and timing of the components between groups (see section on measurement above). It can be useful to examine differences in ERPs between groups in the absence of behavioral differences, for example, by examining ERPs in a subset of trials or subgroup of participants who are matched on behavioral performance (42).

It is also important in ERP research to consider the potential influence of medications and other psychotropic substances. If the effect of a specific medication or substance on an ERP component is known, it may be possible to determine whether the pharmacological agent may have driven the results. However, in many cases, the effect of a specific medication on a given ERP component is unknown. In these situations, it can be useful to interpret the results in relation to unmedicated patients, individuals with sub-clinical versions of the disorder, or unaffected family members. In some cases, ERPs may be used to test the effects of a medication (or other treatment approach. For example, Umbricht et al. (43) used ERPs to examine the cognitive effects of Clozapine, an antipsychotic sometimes prescribed to individuals with schizophrenia. They found that Clozapine—in contrast to other antipsychotics, such as—Haloperidol normalized P3 amplitude in people with schizophrenia, without influencing early preattentive processes, including the mismatch negativity (MMN) or P2 (43). Using ERPs in this way can be an effective approach for determining the influence of medication on underlying disease state.

Conclusions

The ERP technique is a useful tool in the study of clinical disorders; however, additional factors often must be taken into consideration in designing ERP experiments, recording EEG, analyzing data, and interpreting results in clinical science. In this paper, we have attempted to highlight the most common issues that arise in ERP research with clinical populations. By employing the relatively simple strategies outlined above, ERPs can provide a wealth of information about neural processing in clinical disorders.

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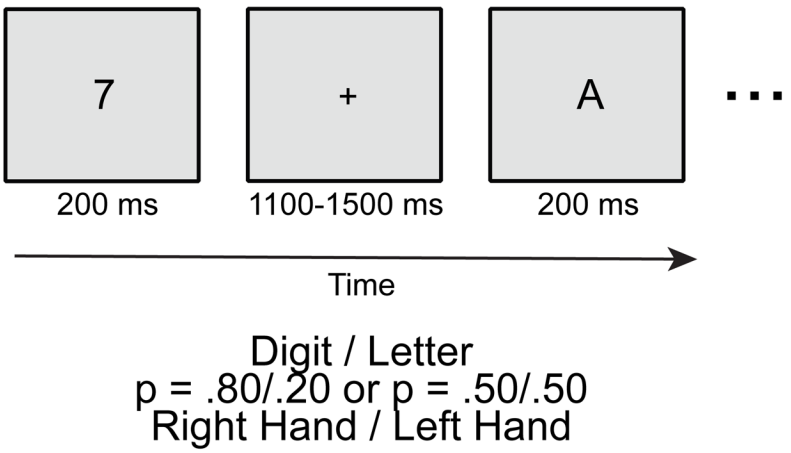

Figure 1.

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 (2 levels) and category probability (3 levels) occurred, for a total of 6 trial blocks. The probability-sensitive P3 component was isolated from the 4 trial blocks in which one category was 80% probable and the other was 20% probable, collapsing across which category was more probable and which response mapping was used. The response-sensitive LRP component was isolated from the 2 trial blocks in which the category response mapping was manipulated but the probability was 50% for each category.

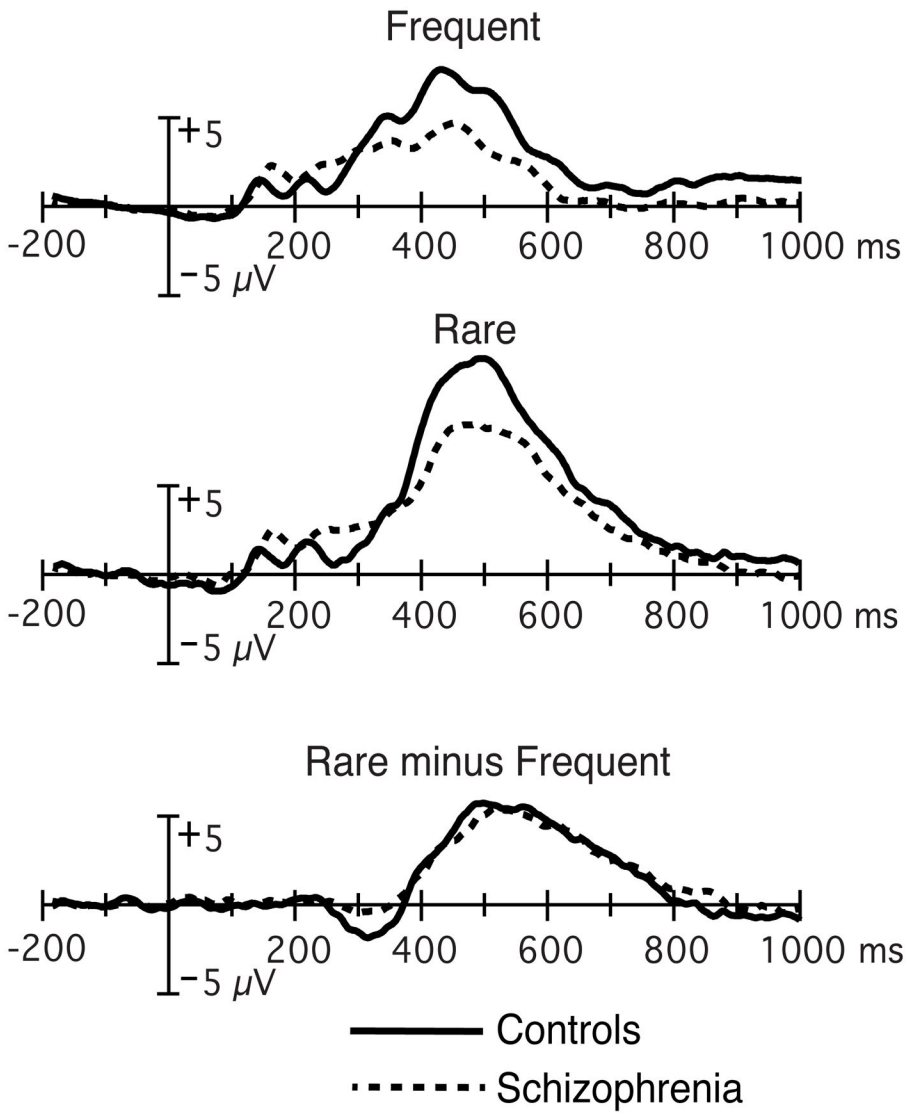

Figure 2.

Grand average ERP waveforms recorded at the Pz electrode site from people with schizophrenia and controls (from the study of 31). The patient and control waveforms are overlaid for stimuli from the frequent category, stimuli from the rare category, and the rare-minus-frequent difference wave.