

Direct and Indirect Integration of Event-Related Potentials, Functional Magnetic Resonance Images, and Single-Unit Recordings

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Abstract: Cognitive neuroimaging techniques vary along three primary dimensions: invasiveness, temporal resolution, and spatial resolution. Several of the major techniques excel on two of these three dimensions, but none of them excels on all three. In principle, multiple techniques with different strengths and weaknesses could be combined to obtain high temporal and spatial resolution data about human neural activity, and this article compares two approaches to combining microelectrode, hemodynamic, and electromagnetic measures of neural activity. The first approach involves using structural magnetic resonance images to provide a common reference frame for the mathematical estimation of neural activity, and the second approach involves parallel experimental manipulations and converging evidence. At present, neither approach is entirely satisfactory, and the integration of different measures of neural activity, therefore, requires a combination of direct and indirect approaches. *Hum. Brain Mapping 8:115–120, 1999.* © 1999 Wiley-Liss, Inc.

Key words: evoked potentials; ERPs; positron emission tomography; functional magnetic resonance imaging

INTRODUCTION

If you ask any cognitive neuroscientist to describe the “perfect” neuroimaging technique, the reply will almost certainly involve a spatial resolution that can measure the activity of individual neurons as well as large populations, a temporal resolution on the same order of magnitude as individual action potentials, and a measurement device that can be used easily and

ethically with normal humans. For many investigators, a technique that combines these three characteristics—high spatial resolution, high temporal resolution, and noninvasiveness—are the “holy grail” of cognitive neuroscience (i.e., highly sought after but not yet found).

As illustrated in Table I, there is no single mainstream technique that currently combines all three of these characteristics. However, given that each of these types of measures is good or excellent along a different set of two of the three dimensions, it seems plausible that any two of these measures could be combined to achieve good or excellent properties along all three dimensions. For example, it seems plausible that the time course of activation in a Positron Emission Tomography (PET) “hot spot” could be determined by combining Event-Related Potential (ERP) recordings and PET scans from the same subjects performing the same

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TABLE I. Extent to which criteria of noninvasiveness, high spatial resolution, and high temporal resolution are met by microelectrode measures (single-unit and local field-potential recordings), hemodynamic measures (PET and fMRI), and electromagnetic measures (ERPs and ERFs)

	Micro-electrode measures	Hemo-dynamic measures	Electro-magnetic measures
Noninvasive	Poor	Good (PET) Excellent (fMRI)	Excellent
Spatial resolution	Excellent	Good	Undefined
Temporal resolution	Excellent	Poor	Excellent

tasks [see e.g., Heinze et al., 1994; Mangun et al., 1997]. Of course, it is not enough just to measure an ERP response and a PET response and assume that they reflect the same neural activity, because many ERP components and many PET hot spots are typically present in a given task. Thus some "intermodality integration technique" is necessary to determine whether measures obtained with different imaging modalities actually correspond to the same underlying neural activity.

The purpose of this article is to describe and evaluate two different approaches to inter-modality integration, focusing on electromagnetic measures (event-related potentials, ERPs, and event-related magnetic fields, ERFs), hemodynamic measures (PET and fMRI), and microelectrode measures (single-unit and local field-potential recordings). One approach, here called the direct approach, involves the mathematical combination of different sources of data via a common spatial reference frame (usually a structural MRI scan). The other approach, here called the indirect approach, involves conducting parallel experiments with different measurement techniques and looking for corresponding results across multiple experimental manipulations. Because both approaches have significant limitations, it can be argued that neither approach is satisfactory in isolation and that the two approaches should be combined.

DIRECT APPROACHES TO INTEGRATION

Direct approaches to intermodality integration have been described in detail elsewhere [e.g., Dale and Sereno 1993; George et al., 1995]. Here, we present only a brief sketch of this class of techniques, focusing on the integration of electromagnetic and hemodynamic

measures. To combine these measures, cortical surface reconstructions (derived from structural MRI scans) are typically used to provide a common reference frame. That is, the electromagnetic data are assumed to arise from electrical activity in the gray matter with a dipolar orientation perpendicular to the cortical surface, and the goal of direct intermodality integration procedures is to estimate the magnitude of the electrical activity at each point along the cortical surface.¹ Because the number of points along the cortical surface is very large and the data are always somewhat noisy, measurements of ERP or ERF activity alone do not provide enough information to determine the distribution of neural activity on the cortical surface. In other words, there are many different distributions of voltage over the cortical surface that can adequately explain an observed surface distribution of ERP or ERF signals. Additional evidence about the likely distribution of neural activity across the cortical surface is therefore necessary, and this information can be provided by PET or fMRI data. However, it is not reasonable to assume that the cortical distribution of hemodynamic and electromagnetic signals will always be identical, and the hemodynamic data, therefore, provide a probabilistic constraint on the cortical distribution of electromagnetic activity [see Liu et al., 1998].

INDIRECT APPROACHES TO INTEGRATION

As an alternative to direct mathematical integration, it is possible to build indirect bridges across methodologies by means of parallel experimentation. That is, by conducting a set of parallel experimental manipulations in two different imaging modalities, it is possible to link the modalities by demonstrating that both exhibit the same pattern of experimental effects. For example, consider how one might use fMRI data to assist in localizing an (imaginary) ERP component called the Z-wave that is observed in memory experiments. If the Z-wave is found to be larger for words that are later remembered than for words that are later forgotten, the first step might be to conduct a parallel fMRI experiment and determine which regions of cortex show greater signal strength for words that are later remembered. Using a rather liberal statistical criterion, one might find 10 candidate areas of cortex that show such an effect. At this point, it would be difficult to know which of these areas, if any, is the

¹Not all electromagnetic localization procedures work in this manner, but techniques that take advantage of cortical surface reconstructions have many advantages and this article is, therefore, limited to such techniques.

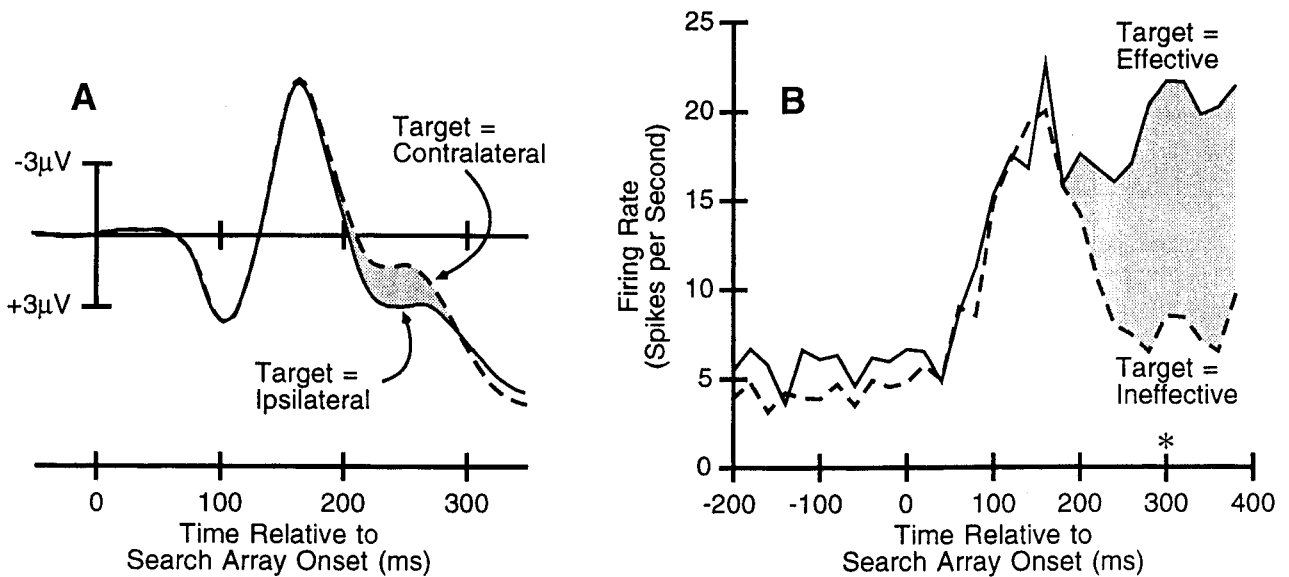


Figure 1.

A. Example of an N2pc component elicited by a target during a visual search task in which subjects reported the presence or absence of a predefined target object. Note that negative is plotted upward. The data were recorded at lateral occipital scalp sites and collapsed across the left and right hemisphere electrodes to show the difference between the response to ipsilateral and contralateral targets. That is, the contralateral waveform is an average of the left hemisphere response to right hemifield targets and the right hemisphere response to left hemifield targets, and the ipsilateral

waveform is an average of the left hemisphere response to left hemifield targets and the right hemisphere response to right hemifield targets. **B.** Single-unit responses averaged over 22 inferotemporal neurons during a visual search task. In this version of the task, the monkeys were required to make a saccade to the target stimulus, which was sometimes an effective stimulus and sometimes an ineffective stimulus for the neuron being recorded (mean saccade latency is indicated by the asterisk). This figure adapted by permission from Luck et al. [1997b].

generator source of the Z-wave, so additional experiments would be necessary. Imagine, e.g., that the Z-wave is also known to be larger for concrete nouns than for abstract nouns. A parallel fMRI experiment could then be conducted, using the 10 areas identified in the first fMRI experiment as regions of interest. Of these 10 areas, perhaps three might exhibit a statistically significant effect of concreteness. Additional parallel experiments would be conducted until a single area of cortex is found that shows a perfect or near-perfect correspondence with the Z-wave in terms of the effects of experimental manipulations (or until it is clear that there is no corresponding area that is visible with fMRI). As each new manipulation is tested and found to have corresponding effects across imaging modalities, the confidence in the linkage between them will grow.

We have recently used this approach to assess the relationship between an attention-related ERP component called the N2pc wave [Luck et al., 1997b] and an attentional modulation of single-unit activity in monkey visual cortex [Chelazzi et al., 1993]. These two electrophysiological attention effects are illustrated in

Figure 1. Both the N2pc and the single-unit effects appear to reflect an attention-related suppression of the nontarget stimuli beginning around 175 ms post-stimulus, and we therefore hypothesized that the N2pc is an ERP manifestation of the same neural activity that is responsible for the modulations of single-unit responses.

To test this hypothesis, we took advantage of several experimental manipulations that had previously been shown to influence the size of the single-unit attention effect, and we conducted a set of parallel manipulations with ERP recordings [Luck et al., 1997b]. Several correspondences were observed. First, the single-unit attention effects in area V4 are larger when multiple stimuli are presented inside the neuron's receptive field, and we similarly found that the N2pc is larger when a nontarget stimulus is presented close to the target stimulus. Second, the single-unit effects are larger when the targets are complex multidimensional patterns rather than simple colored squares, and we similarly found that the N2pc is larger when the target is defined by a conjunction of color and form than when the target is a simple colored square. Third, the

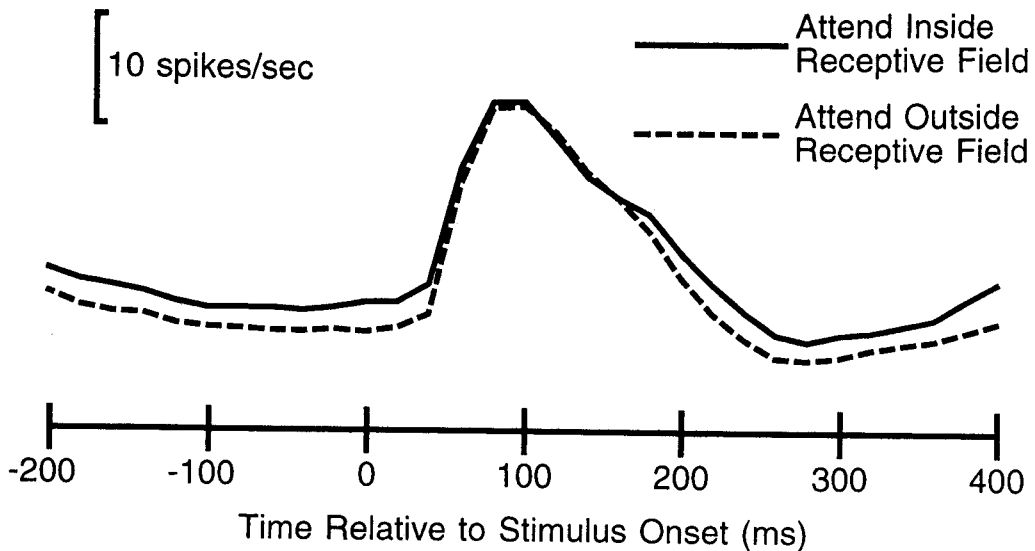


Figure 2.

Data from the single-unit recording study of Luck et al. [1997a]. These firing rates were averaged over a set of 74 neurons in area V4 while the monkey attended to a location that was either inside or outside of the receptive field of the neuron being recorded.

single-unit effects are larger when the monkey must make a saccade to the target rather than making a manual target present/absent response, and we also found that the N2pc component was larger in a saccade task than in a manual response task. Together, these experiments provide converging evidence in support of the hypothesis that the N2pc wave reflects the same neural activity that is responsible for the single-unit attention effects. A similar approach was used by Mangun et al. [1997] to integrate ERP and PET attention effects.

The known topographic mapping of sensory and motor systems has also been used to provide an indirect means of localizing certain ERP components. For example, the upper and lower visual fields are represented in area V1 on the lower and upper banks of the calcarine fissure, respectively, and this is paralleled by a polarity inversion of the visual C1 wave for upper versus lower field stimuli [Clark et al., 1995]. These results imply that the C1 wave is generated in area V1, because no other area of visual cortex would be expected to show this polarity inversion. Similarly, the lateralized readiness potential, a response-related ERP response, is inverted in polarity for foot responses relative to hand responses [Brunia and Vingerhoets, 1980], and this finding is consistent with the opposing orientations of the hand and foot representations in motor cortex.

OBSTACLES TO INTEGRATION

Both direct and indirect approaches to intermodality integration face a common problem, namely, that the three classes of techniques shown in Table I measure different and imperfectly correlated aspects of neural function. For example, single-unit recordings measure action potentials, whereas ERP and ERF recordings measure postsynaptic potentials. Similarly, ERPs and ERFs primarily reflect transient neural responses (due to the common use of high-pass filters to eliminate artifacts), whereas PET and fMRI scans tend to emphasize tonic responses (due to the fact that they integrate information over long periods of time). As an example of the potential for discordant results among these measures, consider the single-unit responses from area V4 that are shown in Figure 2 [from the study of Luck et al., 197a]. In this experiment, monkeys fixated centrally while rapid sequences of stimuli were presented at two peripheral locations, one that was inside the neuron's receptive field and one that was outside. The monkeys were trained to attend to one of these locations and respond to occasional targets at the attended location. Under these conditions, the neurons exhibited an elevated spontaneous firing rate when attention was directed inside the receptive field, even before the onset of the stimulus (as shown in the period -200-0 ms in Fig. 2). However, there was no

response and a hemodynamic response, it would be possible to provide an even more detailed test of this link by determining whether individual differences in the location of the hemodynamic effect can explain individual differences in the distribution of electromagnetic signals. This combination of direct and indirect approaches is clearly expensive and time-consuming, but at present it is the only general-purpose means of noninvasively measuring neural activity with both high spatial and temporal resolution.

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