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Convergent Approaches to Electrophysiological and Hemodynamic Investigations of Memory

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Abstract: The strengths and weaknesses of electrophysiological and hemodynamic methods for investigating neural activity associated with mnemonic processes are discussed, and an example is given of how the two classes of methods can be employed to provide complementary information about the neural basis of memory. The advantages of event-related fMRI over conventional functional neuroimaging approaches are illustrated in the context of a study of recognition memory. Finally, some of the issues that must be confronted by efforts to integrate electrophysiological and hemodynamic data in a formal sense are outlined. *Hum. Brain Mapping 6:394–398, 1998.* © 1998 Wiley-Liss, Inc.

Key words: fMRI; Event related potential; PET; recognition memory

INTRODUCTION

Methods that permit brain activity to be measured noninvasively while subjects engage in experimental tasks play a central role in understanding the functional and neural bases of memory. The available methodologies fall into two main classes: electrophysiological methods (ERP and MEG) for recording event-related, time-varying electromagnetic scalp fields, and hemodynamic methods (PET and fMRI), based upon the measurement of regional cerebral blood flow (rCBF) and oxygenation [for recent reviews of memory studies employing electrophysiological and hemodynamic measures, see Rugg, 1995; Fletcher et al., 1997].

Table I lists the principal advantages and disadvantages of electrophysiological and hemodynamic methods. Several of the points listed in Table I have been discussed previously, notably those relating to the trade-off between the two classes of measurement in respect of temporal and spatial resolution, and the difficulties of interpretation arising from the insensitivity of ERP / MEG to activity in neural populations with ''closed-field'' configurations [Rugg, 1995]. Other points, however, have received less attention. One of these concerns the advantage that hemodynamic measures enjoy over electrophysiological measures through their capacity to detect activity with roughly equal sensitivity in all brain regions, regardless of depth or geometric configuration (cf. points 4 and 6 in Table I). In the case of fMRI, this capacity is limited to regions which are not subject to magnetic susceptibility artifact. Susceptibility artifact degrades signal quality in two brain regions, the basal temporal and orbitofrontal cortex, that are of interest to memory researchers. In experiments in which these regions are of primary interest, PET may be the optimal methodology.

A deeper issue is raised by point 10 of Table I. Conventionally (and, in the case of PET, of necessity), hemodynamic studies have employed blocked designs, in which measurement is made over a succession of trials constituting a single experimental condition. Such designs have three undesirable

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TABLE I. Strengths and weaknesses of electrophysiological and haemodynamic measures

Electrophysiological	
Strengths	Weaknesses
1. Direct measure of neural activity	4. Samples only a partial and unknown fraction of activity
2. High temporal resolution	5. Poor spatial resolution
3. Easy to obtain data contingent on performance	
Hemodynamic	
Strengths	Weaknesses
6. Homogeneous (PET) or near-homogeneous (fMRI) sampling of task-related activation	8. Indirect measure of neural activity
7. High spatial resolution	9. Poor temporal resolution
	10. Difficult (until recently) to obtain data contingent on performance
	11. Difficult (until recently) to distinguish state- and stimulus-related effects

consequences. First, it is difficult, if not impossible, to assess which differences between experimental conditions are stimulus-related (i.e., reflect changes in the neural activity associated with the processing of the experimental stimuli), and which reflect state-related changes in activity (i.e., activity unrelated to the processing of specific stimuli which is tonically maintained across a block of trials). In the case of memory research, this is a crucial distinction: one generally wants to know about the neural activity associated with the processing of specific classes of items (e.g., old items vs. new items in a recognition task) rather than (or in addition to) changes in state-related activity.

Second, blocked designs maximize the opportunity for subjects to adopt condition-specific ''sets'' or strategies. The adoption of condition-specific sets is likely to both contribute to state-related differences between conditions, and to modify stimulus-related effects relative to those that would be found in a randomized design. An example of the latter was provided by Johnson et al. [1997], who compared the ERP correlates of veridical and ''false'' recollection under blocked and randomized conditions, and found that ERPs at frontal electrode sites differentiated true and false recollection only when the two kinds of memory retrieval were blocked.

A third difficulty (cf. points 3 and 11 in Table I) with blocked designs as conventionally employed in functional neuroimaging studies is that they do not allow data from different experimental trials to be sorted and analyzed post hoc. This difficulty is especially restrictive in studies of memory, when the neural correlates of behavioral variability (e.g., accurate vs. inaccurate retrieval) are often the focus of experimental interest. By contrast, post hoc sorting and averaging of data have long been standard practice in electrophysiological studies of memory. Indeed, the most important ERP findings in relation to memory could not have been obtained without the capacity to create classes of ERP waveform associated with different behavioral responses [Rugg, 1995].

ERP AND PET STUDIES OF MEMORY RETRIEVAL: AN EXAMPLE OF CONVERGENCE

In light of the issues discussed above, it is not obvious how best to bring together data from conventional neuroimaging studies with electrophysiological findings; not only are the experimental procedures employed to obtain the two kinds of data dissimilar, but it is difficult to establish which neuroimaging effects are stimulus- rather than state-related, and thus have a potential stimulus-locked electrophysiological counterpart. Because of these problems, our strategy until recently has involved interrelating the two kinds of data through a common theoretical framework, within which findings obtained with one method (ERPs in the example below) are employed to predict and interpret findings with another (PET), rather than by attempting to ''coregister'' the data in any formal sense.

The ERP findings in question come from studies employing a variety of memory tests, ranging from fairly complex procedures such as source memory [Wilding and Rugg, 1996] to simple ''old/new'' recognition judgments [Allan and Rugg, 1997]. Relative to unstudied items, ERPs elicited in these tests by correctly classified old items elicit a characteristic pattern of effects. One of these effects, a phasic positivity maximal over the left temporo-parietal scalp, was first identified some time ago and has been linked to episodic retrieval [Rugg, 1995]. In more recent studies it has become apparent that a second ERP effect can frequently be observed in ERPs to recollected old items, which takes the form of a late-onset positive wave which is maximal over right frontal regions of the scalp [Allan and Rugg, 1997; Wilding and Rugg, 1996].

The functional significance of the right frontal ERP effect is unclear. It is hypothesized [Wilding and Rugg, 1996] to reflect cognitive operations carried out on the products of episodic memory retrieval, but the nature of these ''postretrieval'' operations is uncertain. A further outstanding question concerns the brain regions responsible for the generation of the effect. Given its scalp distribution, it is tempting to hypothesize that it reflects stimulus-related neural activity in the right prefrontal cortex.

To test this hypothesis, we sought converging evidence from functional neuroimaging data. Numerous studies have found that, relative to a range of control conditions, engagement in tasks requiring episodic memory retrieval gives rise to activation of the right anterior prefrontal cortex [Fletcher et al., 1997]. These findings are encouraging, since they indicate that the right prefrontal cortex is indeed implicated in episodic memory retrieval. However, the ERP findings give rise to a further, crucial prediction: activity in the right prefrontal cortex should vary with whether a retrieval cue elicits successful or unsuccessful retrieval. This prediction follows from the fact that the right frontal ERP effect is manifest as a difference between test items (new and old words) that vary solely with respect to whether they elicit retrieval of a study episode.

To test this prediction with PET it is necessary, within the constraints of a blocked design, to vary the probability of successful retrieval while holding other factors constant. Rugg et al. [1996] obtained PET images while subjects performed tests of recognition memory for visually presented words. The ratio of old to new words in the lists employed for these tests was held at 50:50 for the first 20 and last 10 items. For the intervening 20 items, corresponding to the period during which PET images were acquired, the old:new ratio varied: 0:100 for two of the lists, 20:80 for two others, and 80:20 for the final two. Thus, it was possible to determine whether right prefrontal activity was sensitive to retrieval success by searching for regions in which rCBF covaried with old:new ratio.

The only regions in which rCBF covaried with old:new ratio were in the prefrontal cortex, most prominently in right anterior and dorsolateral regions. These findings are consistent with the hypothesis, formulated on the basis of the ERP results discussed earlier, that the right prefrontal cortex is sensitive to retrieval success. We therefore view the ERP and PET data as providing converging evidence in support of the proposals that right prefrontal activity is sensitive to whether a memory test item elicits retrieval of a prior episode, and that this activity supports cognitive processes that operate on the products of memory retrieval.

The convergence of ERP and PET findings with regard to the role of the right prefrontal cortex in memory retrieval provides a good example of how the two methodologies can be integrated in what might be termed an informal fashion. However, the congruence of these findings should not detract from the fact that the interpretation of the PET findings is predicated on two related assumptions: that the manipulation of the old:new ratio affected stimulus- and not state-related processing, and that the findings do not reflect changes in retrieval strategy brought about by this manipulation. Although these assumptions can be defended [Rugg et al., 1996], they cannot be proven.

EVENT-RELATED FMRI: PRELIMINARY DATA

It is clear that the use of blocked experimental designs to obtain hemodynamic data places constraints both on the utility of these data for studying memory, and on the degree to which they can be integrated with electrophysiological findings. What is required is a method that permits hemodynamic data to be obtained on a trial-by-trial basis. Such a method, i.e., event-related fMRI, is currently undergoing rapid development, and along with others [e.g., Schacter et al., 1997], we have begun to evaluate its potential for the study of memory retrieval.

As part of this evaluation, we recently investigated recognition memory in 3 subjects. We employed a series of five study-test cycles, in each of which subjects first learned 10 sequentially presented words and then, after a short break, discriminated between these words and an equal number of new ones [for details, see Friston et al., 1998]. The interstimulus interval (ISI) during the test runs was 16 sec. The data were pooled over the five runs and analyzed for regions in which there were significant differences in signal as a function of the words' study status. Data analysis was performed according to the method described by Friston et al. [1998], in which basis functions were employed to identify regions in which event-related signals differed significantly. We employed a single basis function, corresponding to an idealized hemodynamic response function and its temporal derivative, to analyze the data obtained from each subject. Regions reliably activated across subjects were identified by performing a conjunction analysis [Price and Friston, 1997] to eliminate those regions in which differential event-related activity was either unreliable, or differed between subjects in magnitude at a significance level of $P < .001$ or lower.

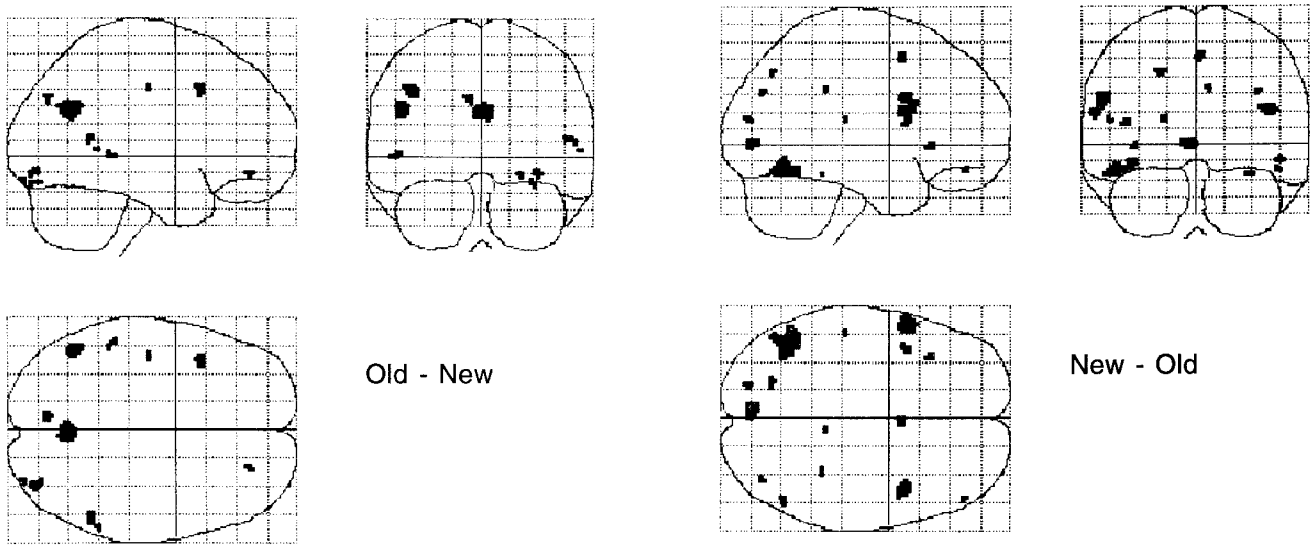

Figure 1.
Maximum intensity SPM projections (threshold, $P < .001$, uncorrected), showing regions in which the event-related fMRI signal obtained in a recognition memory task varied consistently across subjects as a function of the study status (old vs. new) of test items. **Left:** Regions where signal intensity was greater for old words. **Right:** Regions where signal intensity was greater for new words.

Figure 1 shows maximum intensity SPM projections identifying regions in which there were reliable across-subject old / new differences. Areas showing relatively greater activity (after correction for multiple comparisons) for old words included a region of the left middle frontal gyrus (x, y, z = −42, 14, 38, Z = 5.63), and the posterior cingulate (x, y, z = 2, −64, 26, Z = 5.06). Areas showing relatively greater activation for new words included a left ventral occipital region (x, y, z = −46, −56, −16, Z = 5.18), and the left inferior frontal gyrus (x, y, z = −56, 10, 28, Z = 4.87).

For present purposes, the important point about these data is that they demonstrate that event-related fMRI is sufficiently sensitive to reveal retrieval-related differences in brain activity that are of potential functional and biological interest. As already noted, the ISI employed to obtain these data was 16 sec. The choice of this interval was prompted by a concern to minimize overlap between successive event-related responses. However, it appears that this concern was misplaced: event-related changes in fMRI signals appear to interact almost linearly, permitting quite short ISIs to be employed without loss of sensitivity [Dale and Buckner, 1997]. Together with our findings from the recognition memory task, these observations give strong grounds for optimism about the potential of the event-related fMRI method for the study of memory retrieval.

One final issue is worth mentioning. In the kind of experiment described above, the focus of interest lies in the *difference* between two (or more) sets of event-related responses, and not the responses themselves. In the absence of a suitable control condition, it is not possible to give a functional interpretation to responses from regions in which event-related responses to, say, old and new words do not differ. While such responses may index memory-related processing engaged to an equivalent extent by each class of item, they may just as well index more general aspects of item processing, unrelated to their role as retrieval cues [cf. Schacter et al., 1997].

CONCLUDING COMMENTS

The event-related fMRI method is quickly evolving to the stage where it is possible to conduct truly convergent electrophysiological and hemodynamic studies, offering the prospect of integrating the two classes of data in the knowledge that they were obtained under identical experimental conditions.

However, it is important to note that even under such favorable circumstances, one cannot assume that the data obtained with each method will be isomorphic. As summarized in Table II, the preconditions for detecting electrophysiological and hemodynamic signals are different, and hence there are likely to be

TABLE II. Preconditions for detecting electrophysiological and hemodynamic signals

Electrophysiological
1. Activation of a neural population must be synchronous
2. Activity must be time-locked to some reference event
3. Elements must be configured so as to produce an "open field"
But
1. Critical neural activity need not be extended in time
2. Signal will be sensitive to changes in relative *timing* of activity in two or more neuronal populations as well as in relative *magnitude*
Hemodynamic
1. Neural activity need neither be synchronous nor time-locked
2. Geometrical orientation of the activated neural system is irrelevant
But
1. Signal amplitude influenced by the duration as well as the magnitude of change in neural activity; more difficult to detect transient changes in activity than sustained changes
2. Changes in activity of a neural population can only be detected if they alter its net metabolic demand

circumstances in which only one of the methods is sensitive to experimentally induced changes in neural activity. Among the most important of these differences are the insensitivity of electrophysiological methods to activity in neural populations that do not generate an open electromagnetic field, and the insensitivity of hemodynamic measures to changes in neural activity which have little or no net metabolic consequence.

These and the other points summarized in Table II do not lessen the importance of attempting to integrate electrophysiological and hemodynamic data sets. However, they do emphasize the difficulty of predicting the overlap that will be found between the task-sensitive brain regions identified by the two methodologies.

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