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Event-Related fMRI and the Hemodynamic Response

Randy L. Buckner[1,2,3]*

[1]*Departments of Psychology, Anatomy and Neurobiology, and Radiology, Washington University, St. Louis, Missouri*
[2]*Massachusetts General Hospital–Nuclear Magnetic Resonance Center, Boston, Massachusettes*
[3]*Department of Radiology, Harvard Medical School, Cambridge, Massachusettes*

Abstract: Event-related functional magnetic resonance imaging (ER-fMRI) methods are allowing a new spectrum of task designs to be explored with brain imaging techniques. Individual trial events can be presented rapidly, in randomly intermixed order, and the hemodynamic responses associated with individual trial events appreciated. The basis of ER-fMRI is that the hemodynamic response tracks neuronal activity on the order of seconds and, in many situations, summates over trials in a manner well predicted by a linear model—even for trials spaced as briefly as 2 sec apart. These properties are discussed, as well as certain basic characteristics of the hemodynamic response in the context of ER-fMRI. *Hum. Brain Mapping 6:373–377, 1998.*

Key words: single trial; neuroimaging; MRI; fMRI; imaging

INTRODUCTION

The spectrum of task designs that can be examined with functional magnetic resonance imaging (fMRI) has been broadly expanded by the development of event-related (ER-fMRI) procedures. ER-fMRI allows paradigms to depart from ''blocked'' testing procedures in which long periods of task performance are integrated to paradigms that isolate individual trial events or subcomponents of trial events (Fig. 1A). ER-fMRI is based on the observation that changes in hemodynamics are rapid and occur within seconds after a neuronal event. Blamire et al. [1992], for example, noted that brief visual stimuli (2-sec) produce detectable hemodynamic responses when measured using blood oxygenation level-dependent (BOLD) contrast fMRI. Savoy and colleagues have shown that visual stimulation as brief as 34 msec in duration is sufficient to elicit a detectable BOLD hemodynamic response [see Rosen et al., 1998]. In the realm of cognitive task paradigms, Buckner et al. [1996] observed that subtle signal changes in visual and prefrontal brain areas can be detected during isolated trials of a word generation task. Taken collectively, these and other observations make clear that fMRI is sensitive to transient signal change to brief neuronal events [see Rosen et al., 1998, for review].

The observation that fMRI is sensitive to transient signal change is important for several reasons. First, behavioral and evoked response potential (ERP) studies typically use paradigms where individual trial events are the focus. fMRI, by detecting signals to individual trial events, can parallel behavioral studies by examining responses to individual trial events rather than blocks of trials. Second, classification of events often cannot be determined apriori—such as

*Correspondence to: Dr. Randy L. Buckner, Department of Psychology, Box 1125, Washington University, One Brookings Drive, St. Louis, MO 63130.

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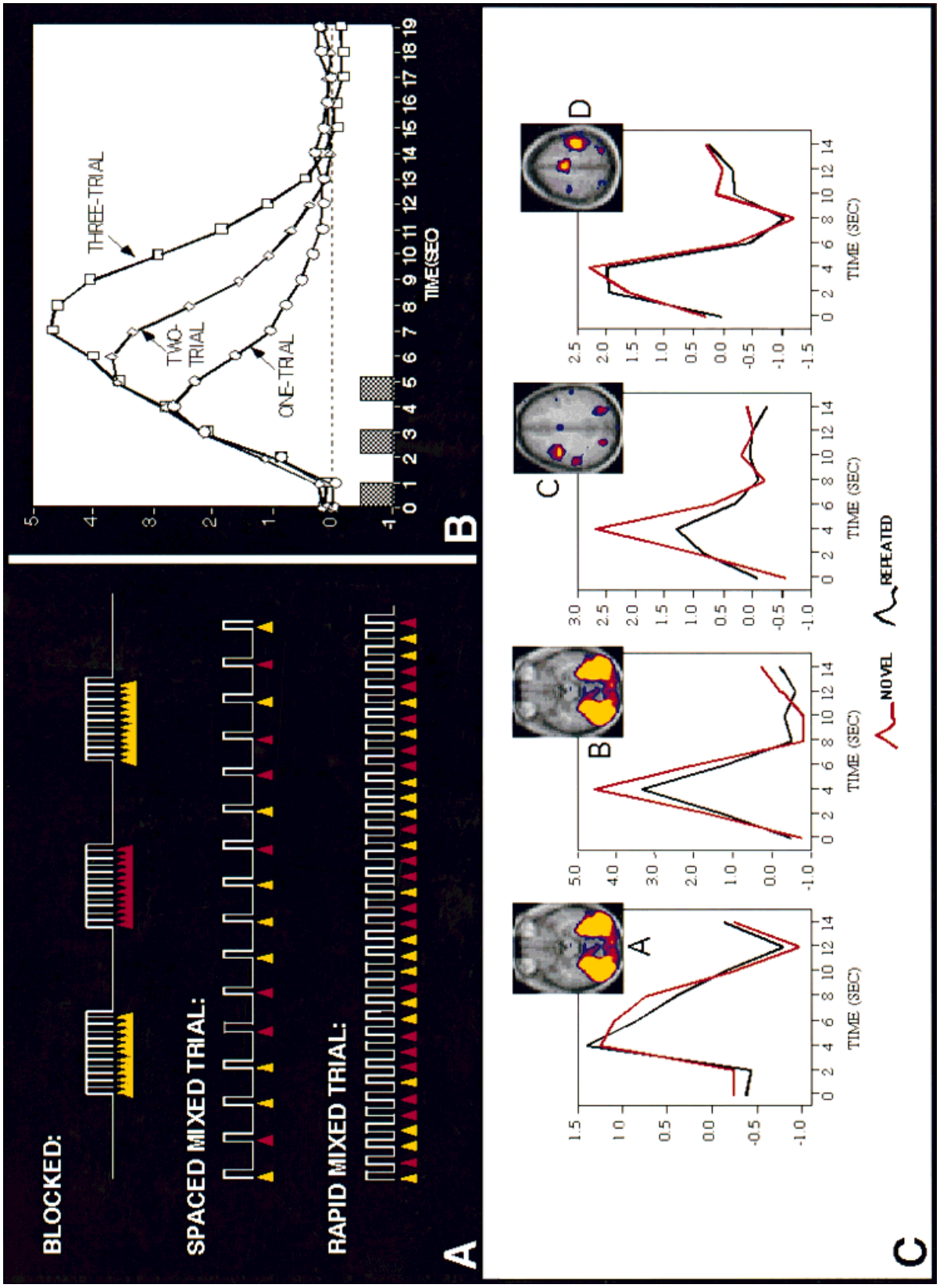
A
BLOCKED:
SPACED MIXED TRIAL:
RAPID MIXED TRIAL:
B
THREE-TRIAL
TWO-TRIAL
ONE-TRIAL
TIME(SEC)
C
A
B
C
D
TIME (SEC)
NOVEL
REPEATED

Figure 1.

when the subject's response to the event is a factor. Being able to isolate fMRI signals allows the BOLD response to be sorted by subject performance (e.g., by whether an event is performed correctly or not, or based on how long an event takes to complete). Finally, there are certain kinds of events that are not stable and are therefore best addressed by dynamic measurement. Paradigms exploring novelty effects and learning paradigms provide prime examples. Thus, the benefit of ER-fMRI is that the flexibility afforded to paradigm design allows new classes of behavioral paradigms to be tested. The manner in which we can perform such tests is constrained by the nature of the hemodynamic response.

The hemodynamic response

In order to map brain activity based on the transient fMRI signal, it is important to understand the basic nature of the BOLD-contrast hemodynamic response. For a brief sensory event, the hemodynamic response is delayed in onset occurring about 2 sec after neuronal activity, and is prolonged in duration [Blamire et al., 1992] (see Fig. 1B). For a neural event that lasts a second, the robust positive deflection of the BOLD-contrast response will evolve over a 10–12-sec period while certain, more subtle, components of the response will have considerably longer recovery periods. On first appearance, this would suggest that hemodynamic events—to be determined—must be well separated in time. Fortunately, this is not the case; ER-fMRI can measure the separate contributions of rapidly occurring neuronal events even when the hemodynamic responses they elicit overlap.

The reason for this is that, on first approximation, the hemodynamic response summates in a roughly linear fashion over time [Boynton et al., 1996; Dale and Buckner, 1997]; the hemodynamic response of one *neural* event adds on top of the preceding events. Figure 1B shows linear summation for multiple presentations of a 1-sec visual stimulus. Reliable departures from linear summation can be observed but may be subtle enough, in certain situations, to be considered approximately linear. Situations in which stimulus events occur extremely rapidly (e.g., $<$1 sec apart), can show marked departures from linearity [e.g., Friston et al., 1997]. Although the sources of such departures are incompletely understood, a tentative explanation may be that the basic coupling between net neuronal activity and hemodynamic response is roughly linear, but the relation between neuronal response and stimulus/task parameters is often nonlinear [Rosen et al., 1998]. The upshot is that separate sensory and higher-level cognitive events can be elicited in rapid succession ($\sim$1 event per 2 sec), and their response contributions separated and analyzed [Dale and Buckner, 1997; Buckner et al., 1998a; Clark et al., 1998] (Fig. 1C).

Variance

A central issue in analyzing ER-fMRI data is variance of the hemodynamic response. As would be expected in any real-world system, variation is present; the relevant issues are: 1) the magnitude and

Figure 1.

A: Schematic diagrams illustrate the difference between two forms of ER-fMRI paradigms and a more traditional blocked trial paradigm. Each schematic shows two trial types indicated by either yellow or red arrows. In blocked trial paradigms (labeled blocked), the trial types are clustered together in succession so that the same trial type or condition occurs for an extended period of time. ER-fMRI, by contrast, allows paradigms that randomly intermix different trial types either by spacing them widely apart to allow the hemodynamic response from one trial to decay before the next trial occurs (labeled spaced mixed trial), or by presenting them rapidly (labeled rapid mixed trial) and using analysis methods to account for the overlap of the hemodynamic response across trials. **B:** Data are displayed that support the critical feature (linear summation), which allows the BOLD response to be estimated by signal deconvolution—even in situations where trial responses overlap considerably [Dale and Buckner, 1997]. The hemodynamic response is plotted for 3 separate conditions that either contained a single trial (labeled one-trial), 2 separate trials each spaced 2 sec apart (labeled two-trial), or three separate trials each spaced 2 sec apart (labeled three-trial). Each trial consisted of a 1-sec full-field flickering checkerboard. The relative positions of the three trials are shown by shaded rectangles on the x-axis. Linear summation over trials is apparent as each additional trial adds on top of the preceding trials. The basic shape of the hemodynamic response can be appreciated by examining the one-trial condition; it does not start until about 2 sec after the stimulus onset, and lasts for about 10–12 sec. **C:** Rapid ER-fMRI procedures were applied to the examination of repetition priming [adapted from Buckner et al., 1998a]. Novel and repeated objects were randomly intermixed, one object per 2 sec. ER-fMRI procedures were used to extract the time-course of activation for multiple regions throughout the brain (labeled A, B, C, **D**). Differential signal change was observed between novel and repeated objects for certain extrastriate visual (B) and left prefrontal regions (C); while other regions, such as early visual cortex (A) and motor cortex (D), showed similar responses to novel and repeated objects.

practical implications of the variance, and 2) what the sources of variance can tell us about and / or do to limit our exploration of brain function. While only preliminary analyses have been conducted, it appears that the hemodynamic response is reasonably stable across subjects. In one analysis, the hemodynamic responses in two cortical regions (SMA and extrastriate visual cortex) were examined across 13 subjects during a memory recognition task [Buckner et al., 1998b]. Each response was derived from many observations within a subject so that stable within-subject estimates of the responses could be obtained. The question then asked was: if the timing and shape of one subject's hemodynamic response was known, how well could it predict the other subjects' hemodynamic responses? The answer was clear: the basic shape and timing of the hemodynamic was stable across subjects. 72% of the variance of the shape of one subject's response could be predicted—on average—by any other subject. Moreover, the absolute range of the timing of the response was a few seconds, indicating that the standard error estimate of the mean response time was fractions of a second for the group of 13 subjects. As a further empirical demonstration, the response of one group of 6 subjects was compared to a second independent group of 7 subjects. They nearly overlapped.

Despite the stability of the response for similar regions of cortex across subjects, marked variation in the timing and shape of responses has been observed across regions, even within the same subjects. Schacter et al. [1997] and Buckner et al. [1998b] have noted delays across separate prefrontal regions on the order of seconds. The source of such variance in hemodynamic response timing is presently unclear, but may originate from differential sampling of vessels across regions [Lee et al., 1995], or from delays in underlying neuronal activity [see Rosen et al., 1998, for discussion]. Further investigation will be necessary to distinguish among these and other possibilities.

One practical implication of variance in the hemodynamic response across regions is that present methods are unlikely to inform us about the cascades of neural activity that occur between regions on the timescale of msec. Bandettini, O'Craven, and Savoy performed a procedure for normalization of hemodynamic delay across regions and showed that a 500 msec offset in stimulus-induced neuronal activity could be appreciated [see Rosen et al., 1998]. It seems likely that significantly better temporal resolution, on the order of tens of msec, will require integration with techniques that are sensitive to signals timelocked to neural activity on the order of msec such as EEG, MEG, and optical imaging. A further implication of hemodynamic variance across brain regions is that statistical methods used to identify areas of signal change will need to allow for variance in the timing and / or shape of the hemodynamic response to be sensitive to all forms of signal change. Several currently available statistical methods possess this feature [e.g., Friston et al., 1997; Schacter et al., 1997]. ER-fMRI may further benefit from analysis procedures that make no or minimal assumptions about the shape and timing of the hemodynamic response.

Future Directions

ER-fMRI procedures promise to expand the array of paradigms that can be explored with functional neuroimaging techniques. As with any methodological advancement, the utility of ER-fMRI will be evaluated by the new scientific questions that are asked and informed by their application. A number of studies already presented in the literature foreshadow the impact these research techniques may eventually have. Courtney et al. [1997], for example, used a variant of ER-fMRI to separate subcomponents of trial events in relation to working memory. They noted that a distributed network of brain areas were active during a working memory task; certain areas differentially contributed to processes related to perception and others to maintenance of information over time. Posterior visual areas showed mostly transient stimulus-locked activity which links them most directly with perceiving the stimulus; while anterior areas, particularly regions in prefrontal cortex, demonstrated sustained activity as would be expected of regions contributing to the maintenance of information over time. In standard blocked trial procedures, these processes would be blurred together and the differential contributions across regions difficult to appreciate. McCarthy et al. [1997] examined the classical odd-ball paradigm by observing stimulus-locked activity to infrequent target events, again a procedure best addressed by ER-fMRI techniques. In their study, target events elicited transient increases in prefrontal and parietal cortex activity. Going forward, these kinds of applications are likely to become routine in functional neuroimaging studies.

A number of central issues are still in debate. Statistical analyses for mapping event-related hemodynamic responses are just beginning to evolve. Methods that make few or no assumptions about the shape of the hemodynamic response as well as those that consider the possibility of nonlinear summation of the hemodynamic response are on the horizon. In addition, we have yet to come to fully understand the relative signal-to-noise tradeoffs between blocked trial

and event-related paradigms, and for event-related paradigms that space or position trials in fundamentally different ways. Empirically, we know that randomly intermixed trial events spaced just a few seconds apart can be used to generate activity maps and time-course information for the hemodynamic responses associated with the intermixed event types [Dale and Buckner, 1997; Buckner et al., 1998a; Clark et al., 1998]. Such demonstrations make clear the potential of ER-fMRI methods.

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