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Multiple Movement Representations in the Human Brain: An Event-Related fMRI Study

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Abstract

■ Neurovascular correlates of response preparation have been investigated in human neuroimaging studies. However, conventional neuroimaging cannot distinguish, within the same trial, between areas involved in response selection and/or response execution and areas specifically involved in response preparation. The specific contribution of parietal and frontal areas to motor preparation has been explored in electrophysiological studies in monkey. However, the associative nature of sensorimotor tasks calls for the additional contributions of other cortical regions. In this article, we have investigated the functional anatomy of movement representations in the context of an associative visuomotor task with instructed delays. Neural correlates of movement representations have been assessed by isolating preparatory activity that is independent from the performance of an actual motor act, or from the presence of a response's target. Movement instruction (specified by visual cues) and motor performance (specified by an auditory cue) were separated by a variable

delay period. We have used whole-brain event-related fMRI to measure human brain activity during the performance of such a task. We have focused our analysis on specific preparatory activity, defined as a sustained response over *variable* delay periods between a transient visual instruction cue and a brief motor response, temporally independent from the transient events. Behavioral and electrophysiological controls ensured that preparatory activity was not contaminated by overt motor responses or working memory processes. We report suggestive evidence for multiple movement representations in the human brain. Specific sustained activity in preparation for an action was found not only in parieto-frontal regions but also in extrastriate areas and in the posterior portion of the superior temporal sulcus. We suggest that goal-directed preparatory activity relies on both visuomotor and visuo-perceptual areas. These findings point to a functional-anatomical basis for the integration of perceptual and executive processes. ■

INTRODUCTION

Sustained patterns of neural discharge can be elicited by the transient presentation of an instruction cue (IC) and by the expectation of a motor response in the near future. Under these circumstances, it is possible to isolate neural activity that is temporally independent from the performance of an actual motor act, or from the presence of a response's target (Fuster, 1973). Such preparatory activity has been considered a neural correlate of the cognitive representation of movement (Jeanerod, 1997), since it opens a window into internal states of an agent that are not tied to a particular sensory or effector system (Markman & Dietrich, 2000).

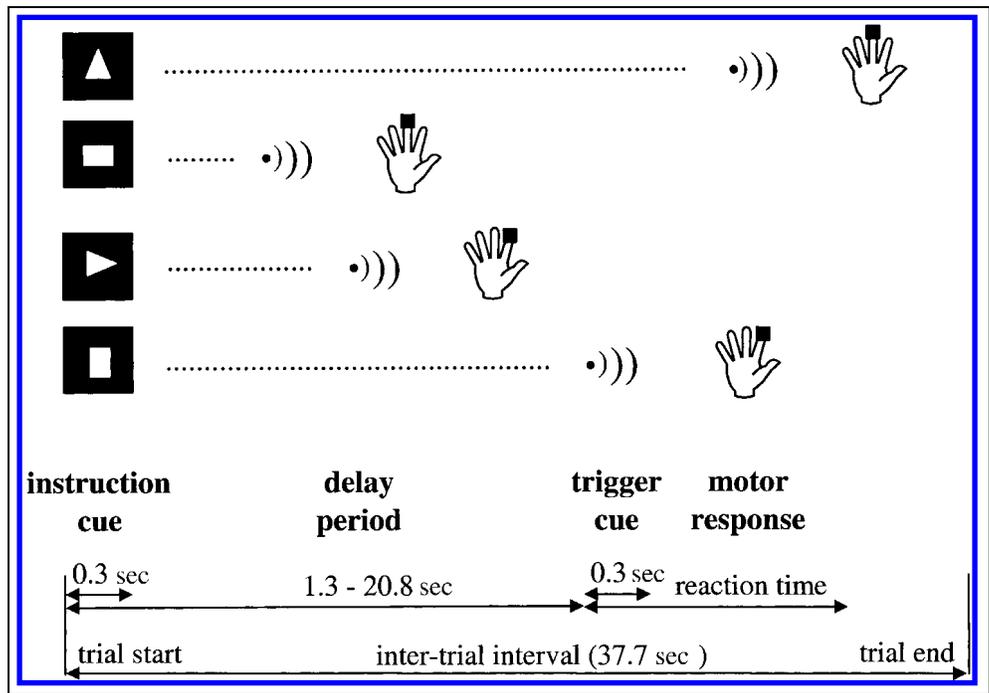
This article investigates the functional anatomy of movement representations in the context of an associative visuomotor task with instructed delays. This class of visuomotor transformations is not constrained

in spatial or temporal frameworks (Wise & Murray, 2000). Therefore, this particular category of stimulus-response relationships is likely to rely on integrative and dynamic processes occurring over a distributed cerebral network.

Brain imaging is well suited to address the spatially distributed nature of visuomotor transformations (Krams, Rushworth, Deiber, Frackowiak, & Passingham, 1998; Deiber, Ibanez, Sadato, & Hallett, 1996; Stephan et al., 1995; Kawashima, Roland, & O'Sullivan, 1994). However, previous studies on motor preparation and movement representation have usually relied on the assumption of pure insertion of cognitive processes (Friston et al., 1996; Steinberg, 1969). In the present context, this assumption implies that preparing to move does not affect the selection and execution stages of the sensorimotor transformation. This assumption has been shown to be invalid, at the level of both the single unit (Crammond & Kalaska, 2000) and the neuronal population (Zarahn, Aguirre, & D'Esposito, 1999). Other imaging studies have directly assessed delay-related activity, but with constant

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Figure 1. Trial timecourse. Diagram of the time course of a trial. One of four shapes (IC) was presented for 300 msec. Two shapes instructed the subjects to flex the index finger; the other two shapes instructed the flexion of the middle finger. After a variable delay (DP: pseudorandomly varied between 1.3 and 20.8 sec in steps of 1.3 sec), a tone (TC) was presented for 300 msec. The subjects were asked to respond as quickly as possible after the auditory TC. The intertrial interval, that is, the time between two successive presentations of the IC, was held constant at 37.7 sec.



temporal gaps between stimulus presentation and behavioral response (D'Esposito, Ballard, Zarahn, & Aguirre, 2000; Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000; Chawla, Rees, & Friston, 1999; Postle & D'Esposito, 1999; Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998; Petit, Courtney, Ungerleider, & Haxby, 1998). This approach is appropriate for studying working memory or sustained attentional processes, where a long delay is necessary to establish the cognitive set at the basis of the phenomena under investigation. However, in a motor context, delay unpredictability is more important than delay itself. When IC and TC are separated by a *variable* delay period (DP), the transformation of a stimulus into a motor response can be partitioned into temporally distinct components, since the subject needs to be ready to respond at any time but the timing of the response cannot be predicted (Moody & Wise, 2000; Klemmer, 1957). Under these circumstances, selection of the appropriate movement is likely to occur at the presentation of the IC. In contrast, the implementation of the executive motor commands can occur only after the trigger presentation. Accordingly, the goal of the movement is likely to be held during the DP (Moody & Wise, 2000; Bastian, Riehle, Erlhagen, & Schoner, 1998; Requin, Brener, & Ring, 1991). Therefore, specific preparatory activity (i.e., dissociable from transient stimulus-locked responses and robust to the assumption of pure insertion of cognitive processes) is not related to the enactment of a movement, but rather to its representation (Jeannerod, 1997) and it is likely to reflect higher cognitive aspects of the motor planning process (Wise, di Pellegrino, & Boussaoud, 1996).

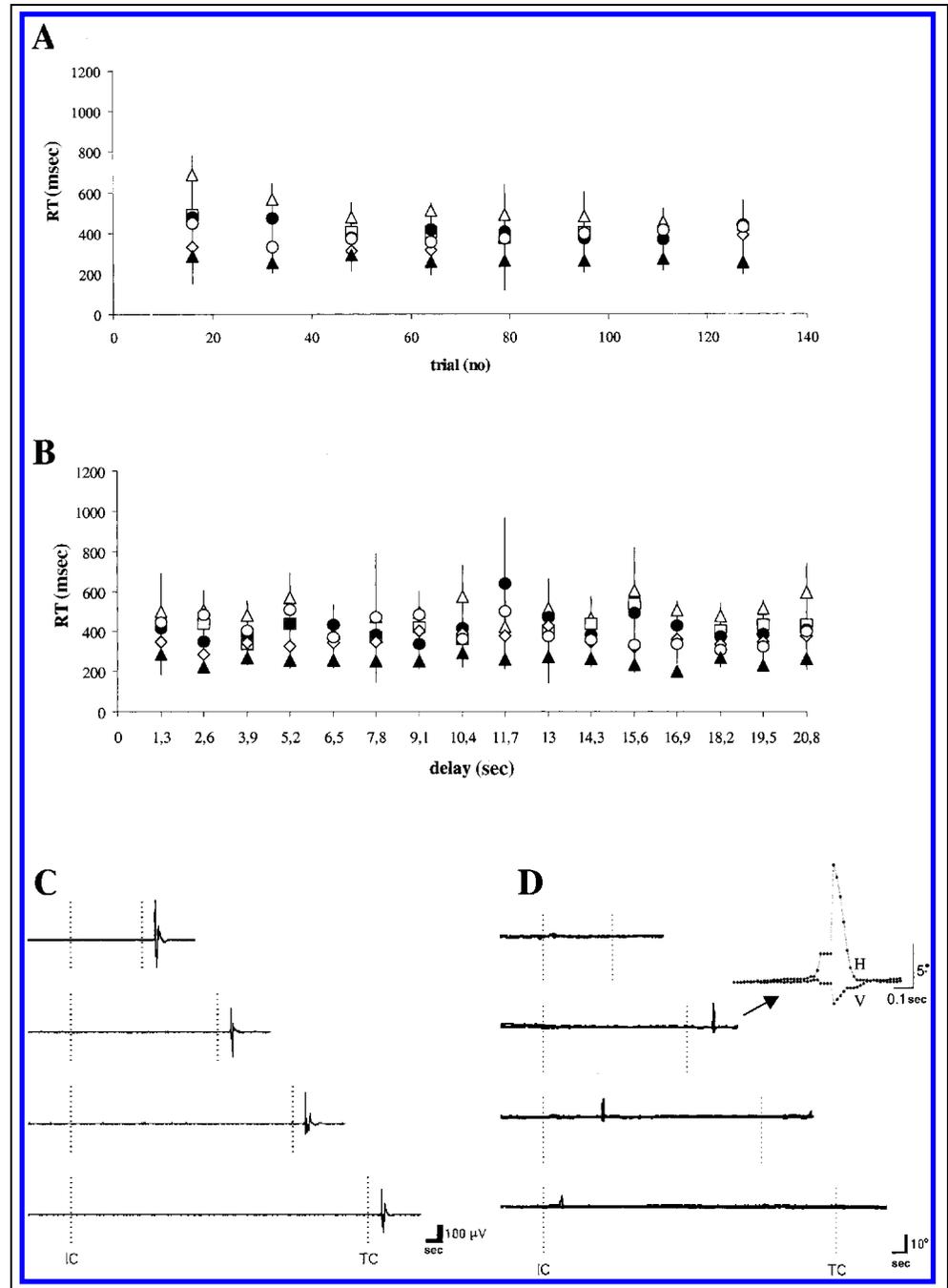
Here we exploit a particular application of whole-brain, event-related fMRI that has proved effective in dissociating between transient responses time-locked to sensory or motor events in the context of a visuo-motor associative task (Toni, Schluter, Josephs, Friston, & Passingham, 1999). We focus on the neural correlates of "specific preparatory activity" in humans during such a task, in order to gain insights into the functional anatomy of movement representations. Preparatory activity has been defined as sustained responses over *variable* DPs between a transient visual IC and a brief motor response. The specificity of preparatory activity has been ensured by taking into account and removing the contribution of transient events to the overall response. Compared with the study by Toni et al. (1999), a wider range of instructed delays and a refined set of basis functions have allowed us to define each task component as an independent partition of our statistical model. Here we provide suggestive evidence that parts of the ventral visual stream contribute to the preparatory activity preceding a motor response.

RESULTS

Task Performance

The extensive training ensured a steady-state performance during the scanning. Subjects' performance was almost free of errors. The mean error rate across subjects was $1.4 \pm 2.4\%$. The response time (RT), averaged over each session for each subject (Figure 2A), did not show any consistent trend as a function

Figure 2. Behavioral data. RT, EMG, and eye position traces measured during task performance in the scanner. (A) RT (mean \pm standard deviations) for each of the six subjects as a function of experimental time. (B) RT as a function of length of delay. (C) Representative EMG and (D) eye position recordings from four individual trials in a single subject. Vertical dotted lines represent the onset of the visual IC and the onset of the auditory TC. The inset in (D) shows an enlarged view of the eye position record for horizontal (H) and vertical (V) movements.



of trial number, neither for the group nor for each individual subject. Four subjects did not show any significant effect of trial number, one subject showed a trend to increase [RT = 13.3*Session + 295; $F(1,6) = 11.87$; $p < .05$], and another subject showed a decrease [RT = -28.1*Session + 638; $F(1,6) = 14.67$; $p < .05$].

The unpredictable timing of the TC avoided response anticipation and effectively triggered motor preparation. The RT, averaged over each delay for each subject, showed no significant trend as a function of the delay, either for the group or for each individual subject (Figure 2B).

EMG measurements (Figure 2C) confirmed that the subject performed the task according to the instructions, providing an overt response only after the presentation of the trigger cue (TC). There were significant differences in EMG amplitude [$F(2,4) = 29.54$; $p < .05$] and variability [$F(2,4) = 9.03$; $p < .05$] between different epochs of task performance. EMG activity recorded at the time of response execution (Response: $1.34 \pm 0.43 \mu$ V [mean amplitude \pm SD]; $87.13 \pm 59.64 \mu$ V [mean variability \pm SD]) was higher and more variable (Tukey's post hoc test, $p < .05$) than EMG activity recorded during the other task epochs (baseline: $0.24 \pm$

0.10 μV ; 24 ± 24 ; delay: $0.25 \pm 0.10 \mu\text{V}$; $25 \pm 24 \mu\text{V}$). Conversely, no significant differences emerged between baseline and delay epochs.

Eye position measurements (Figure 2D) confirmed that task performance did not affect the pattern of gaze displacements across experimental epochs. In particular, there were no differential tonic shifts of the gaze or differential numbers of saccades between epochs (baseline: $1.7, -0.5 \pm 0.9, 2.2^\circ$ [mean x coordinate, mean y coordinate $\pm SDx, SDy$]; $3.3, 2.5 \pm 1.2, 1.3^\circ$ [mean x variability, mean y variability $\pm SDx, SDy$]; delay: $0.7, -0.9 \pm 0.6, 1.3^\circ$; $3.1, 2.1 \pm 1.3, 1.2^\circ$; response: $1.6, -0.8 \pm 0.4, 1.3^\circ$; $3.2, 2.0 \pm 1.2, 0.8^\circ$).

Statistical Parametric Maps

The following section describes the SPM{F}s associated with each of the three behavioral components of the task (IC, DP, TC). These SPM{F}s have been obtained from the group analyses and compared with the SPM{F}s of single-subject analyses. The list of significant activations is presented in Tables 1, 2, and 3 and is illustrated in Figure 3. We also report the number of subjects showing maxima that fell within a sphere centered on the maxima obtained from the group analyses, with a radius equal to the FWHM of the relative SPM{F}. This measure (labeled as “occurrence” in Tables 1–3) provides an index of the reproducibility of the activations across subjects.

Activity time-locked to the presentation of the visual IC (Figure 3A–B; Table 1) was observed in the occipital, parietal, and posterior temporal cortices, as well as in the anterior portion of the left premotor cortex. The IC evoked responses bilaterally in the calcarine fissure, lunate sulcus, occipito-parietal fissure and along the intraparietal sulcus. There was also IC-related activity in the left superior parietal lobule and in the precentral gyrus. The responses obtained in the group analysis were consistent with those observed in each single subject (Table 1). The activations elicited around the calcarine fissure fall within a variability map of Brodmann’s area (BA) 17 in the human brain (Amunts, Malikovic, Mohlberg, Schormann, & Zilles, 2000).

Sustained activity occurring during the DP between the IC and the TC (Figure 3C–D; Table 2) was found in the extrastriate, parietal, and premotor cortices. The DP evoked responses in the superior occipital sulcus, superior temporal sulcus (STS), superior occipito-parietal fissure, along the intraparietal sulcus, and in the convexity of the superior parietal lobule, as well as in the precentral gyrus and in the anterior cingulate sulcus. These activities were also observed in single-subjects analyses (Table 2), although with a smaller degree of consistency than for sensory- or movement-related responses.

Activity time-locked to the presentation of the acoustic TC and to the subsequent movement (Figure 3E–F;

Table 1. Coordinates of Local Maxima Associated with the Instruction Cue

<i>Anatomical Region</i>	<i>Stereotactic Coordinates</i>	<i>F Value</i>	<i>Occurrence</i>
Calcarine fissure	6, -74, 18	3.71	6/6
	-6, -70, 18	3.13	6/6
Lunate sulcus	36, -92, 20	2.89	4/6
Occipito-temporal fissure	-48, -60, -24	2.15	5/6
Superior temporal sulcus			
Posterior segment	50, -42, 22	2.86	5/6
	62, -42, 28	2.61	4/6
Occipito-parietal fissure			
Rostral bank	10, -74, 46	3.51	5/6
	20, -72, 26	2.55	6/6
Intraparietal sulcus			
Anterior third	-26, -56, 62	4.67	6/6
	36, -54, 54	3.75	5/6
Middle third	-30, -68, 52	3.17	6/6
	40, -50, 44	2.87	5/6
Posterior third	-18, -70, 52	3.14	6/6
Superior parietal lobule			
Dorsal convexity	-16, -48, 74	2.85	5/6
	-12, -58, 70	2.66	5/6
Precentral gyrus			
Anterior bank	-26, -2, 54	3.16	5/6
	-48, 4, 40	3.16	5/6
Dorsal convexity	-38, -14, 56	3.11	5/6
	-26, -20, 68	2.99	6/6
Medial convexity	-4, 0, 52	2.58	5/6
	-14, 8, 70	2.58	3/6

Coordinates of local maxima for specific event-related activations. The voxels presented here are significantly ($p < .05$ corrected for multiple comparisons) associated with the IC only. The components of the fMRI signal associated with the other task components have been removed as covariates of no-interest (see Methods). “Occurrence” refers to the number of subjects showing maxima that fell within a sphere centered on the local maximum obtained from the group analysis, with a radius equal to the FWHM (7.9, 8.0, 7.1) of the relative SPM{F}.

Table 3) is evident in the temporal, anterior parietal, and motor cortices. The TC evoked responses bilaterally in the transverse gyrus and the perisylvian temporal cortex, contralaterally in the left superior temporal gyrus, superior parietal lobule, postcentral and precentral gyri. These responses were highly consistent across subjects (Table 3). The stereotactic coordinates of the activations elicited around the

Table 2. Coordinates of Local Maxima Associated with the Delay Period

<i>Anatomical Region</i>	<i>Stereotactic Coordinates</i>	<i>F Value</i>	<i>Occurrence</i>
Superior occipital sulcus	-4, -74, 48	1.82	4/6
	30, -92, 24	1.87	2/6
Superior temporal sulcus			
Posterior segment	62, -40, 24	1.76	5/6
Lateral convexity	68, -26, 8	1.74	4/6
Occipito-parietal fissure			
Rostral bank	8, -74, 48	1.88	3/6
Superior parietal lobule			
Marginal sulcus	16, -40, 60	2.03	2/6
Dorsal convexity	-18, -46, 74	1.71	4/6
Intraparietal sulcus			
Anterior third	-26, -56, 62	2.39	6/6
	-52, -34, 56	2.00	6/6
Middle third	-30, -62, 46	2.07	6/6
	-38, -50, 58	1.98	6/6
Posterior third	-8, -76, 56	1.95	3/6
	-18, -70, 52	1.82	6/6
Parietal operculum	44, -8, 12	1.78	2/6
Precentral gyrus			
Anterior bank	-38, -14, 64	2.11	6/6
Dorsal convexity	-26, -22, 72	2.02	6/6
	-42, -8, 54	1.78	5/6
Lateral convexity	64, -2, 8	1.72	2/6
	-48, 4, 42	1.71	5/6
Posterior bank	44, -12, 62	2.33	3/6
	50, -24, 58	2.03	3/6
Cingulate sulcus	0, -8, 48	1.90	3/6
	-6, 2, 46	1.77	5/6

Coordinates of local maxima for specific event-related activations. Voxels significantly associated with the DP only. Other conventions as in Table 1.

transverse gyrus fall on the border of human BA 21 (Rademacher et al., 2001).

Evoked Hemodynamic Responses (EHRs)

This section characterizes the EHRs of some relevant areas to each of the three behavioral components of the task (IC, DP, TC). The EHRs have been plotted as estimated from Analysis 1 (activity time-locked to the

IC), Analysis 2 (activity time-locked to the DP), and Analysis 3 (activity time-locked to the TC).

EHRs Associated with the IC

Figure 4A illustrates the EHRs for a local maximum in the occipito-temporal fissure. This area shows a significant hemodynamic response to the IC, but not to the DP or to the TC (see Tables 1–3). The IC-related activity shows a sharp increase of the EHR, although delayed with respect to the occurrence of the visual IC. This result closely resembles that obtained in a previous study from the same anatomical region (Toni et al., 1999).

Figure 4B displays the EHRs for a local maximum in the left superior parietal lobule. This area shows a significant hemodynamic response to the IC. There is a remarkable prepeak undershoot of the EHR not observed on this scale in other maxima. This area also shows a response time-locked to the TC, although just below the significance threshold. As it will be seen for another cluster in the posterior parietal cortex (Figure 5B), the TC-related response is delayed with respect to the onset of the acoustic TC.

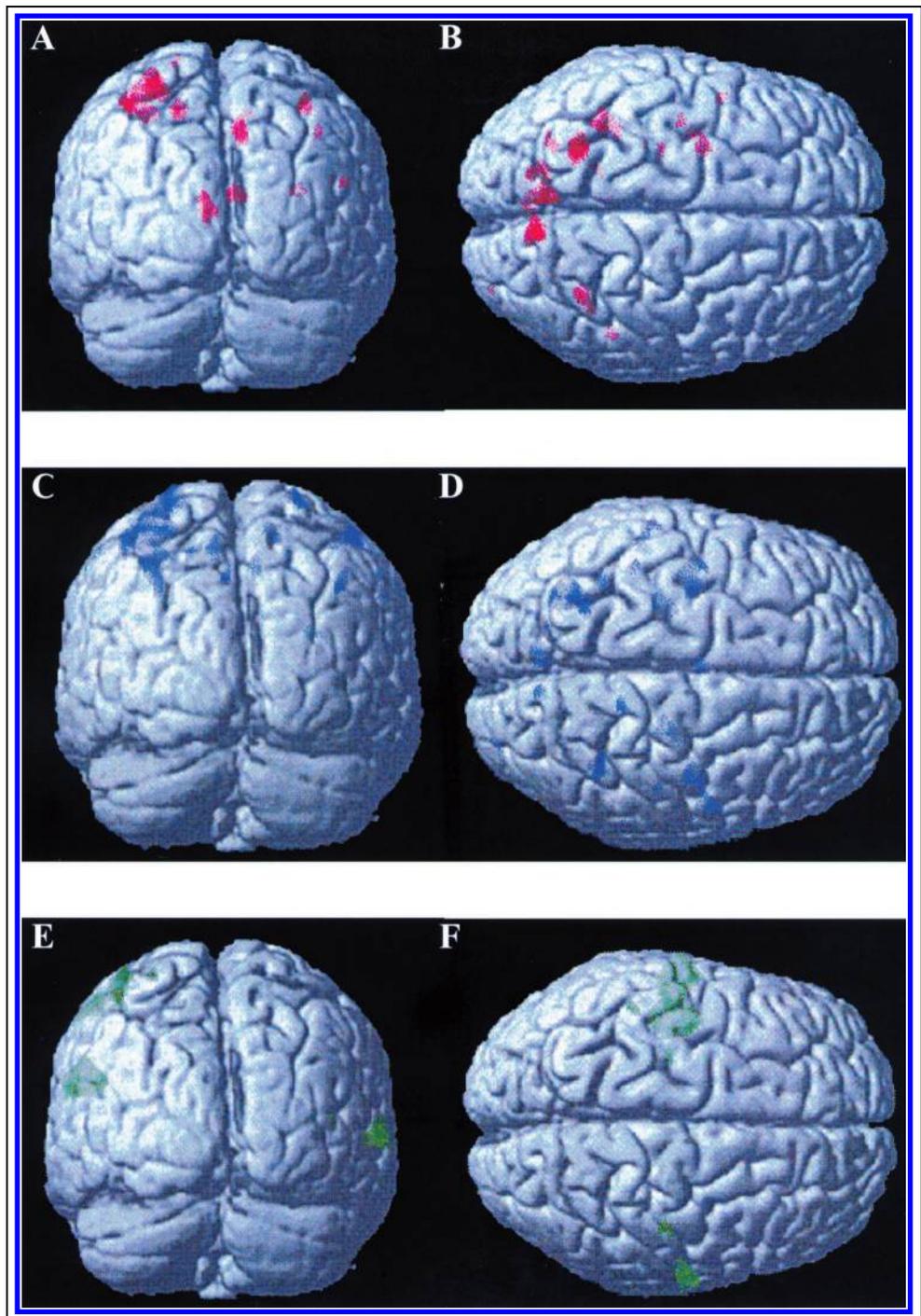
Figure 4C shows the EHRs for a local maximum on the dorsal convexity of the left precentral gyrus. In this area, there are significant hemodynamic responses to both

Table 3. Coordinates of Local Maxima Associated with the Trigger Cue

<i>Anatomical Region</i>	<i>Stereotactic Coordinates</i>	<i>F Value</i>	<i>Occurrence</i>
Transverse gyrus	66, -14, 4	3.93	6/6
	-56, -14, 8	2.66	6/6
Superior temporal gyrus			
Medial bank	-42, -28, 6	2.57	5/6
Superior parietal lobule			
Dorsal convexity	-18, -32, 76	2.60	4/6
Postcentral gyrus			
Anterior bank	-46, -20, 56	3.00	6/6
	-50, -30, 38	2.71	6/6
Precentral gyrus			
Dorsal convexity	-26, -22, 66	3.00	6/6
Posterior bank	-58, -12, 22	3.53	6/6
	-36, -18, 68	3.17	6/6
Inferior frontal gyrus	48, 24, -12	2.33	5/6
Parietal operculum	-46, -36, 26	3.15	5/6

Coordinates of local maxima for specific event-related activations. Voxels significantly associated with the TC. Other conventions as in Table 1.

Figure 3. Anatomical rendering of the significant activations. SPM{F}s projected onto a representative brain from the MNI series. Left column: posterior view; right column: top view. (A, B) Activity associated with the visual IC. (C, D) Activity associated with the DP. (E, F) Activity associated with the auditory TC and the subsequent motor response. Significant clusters are displayed as the integral of all transformed F values, exponentially decayed according to their depth with respect to the cortical surface. Voxels that are 10 mm behind the surface have half the intensity of those at the surface.



the IC and the TC, but not to the DP (Tables 1 and 3). The IC-related activity increases shortly after the presentation of the visual IC, followed by a prolonged postpeak undershoot. The TC-related signal also shows a well-timed response to the movement, followed by a slow return to baseline.

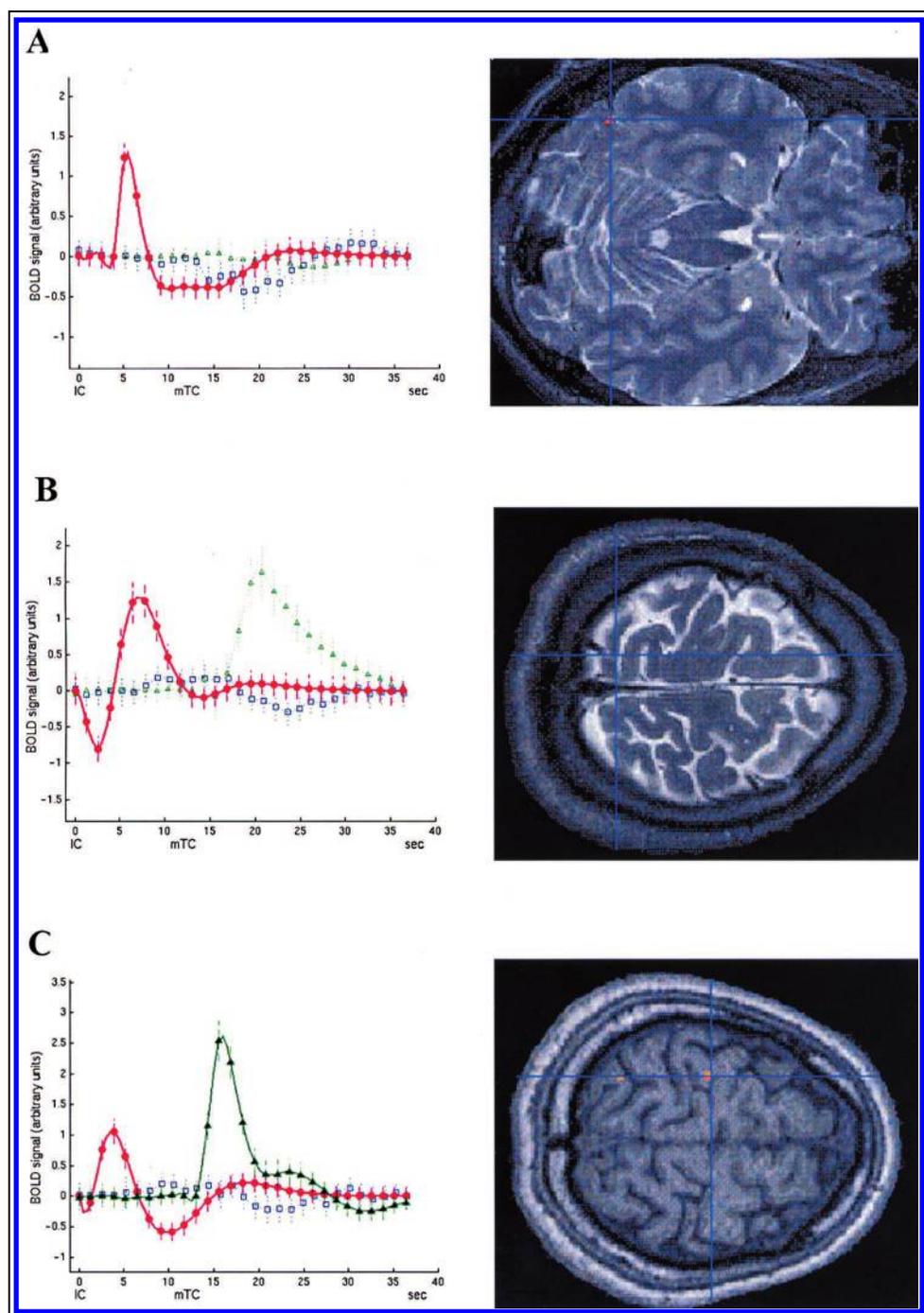
EHRs Associated with Sustained Activity

Figure 5A shows the EHRs measured in a local maximum in the right STS. There are significant hemody-

amic responses to the IC and the DP, but not to the TC (Tables 1 and 2). The DP-related activity shows a slow and gradual increase from the presentation of the IC until the mean occurrence of the TC, followed by an equally slow and gradual decrease towards baseline. The IC-related signal shows an unusual pattern, with a sustained response appearing just after the IC presentation, followed by a slow drift towards baseline.

Figure 5B illustrates the EHRs for a local maximum in the dorsal bank of the left intraparietal sulcus.

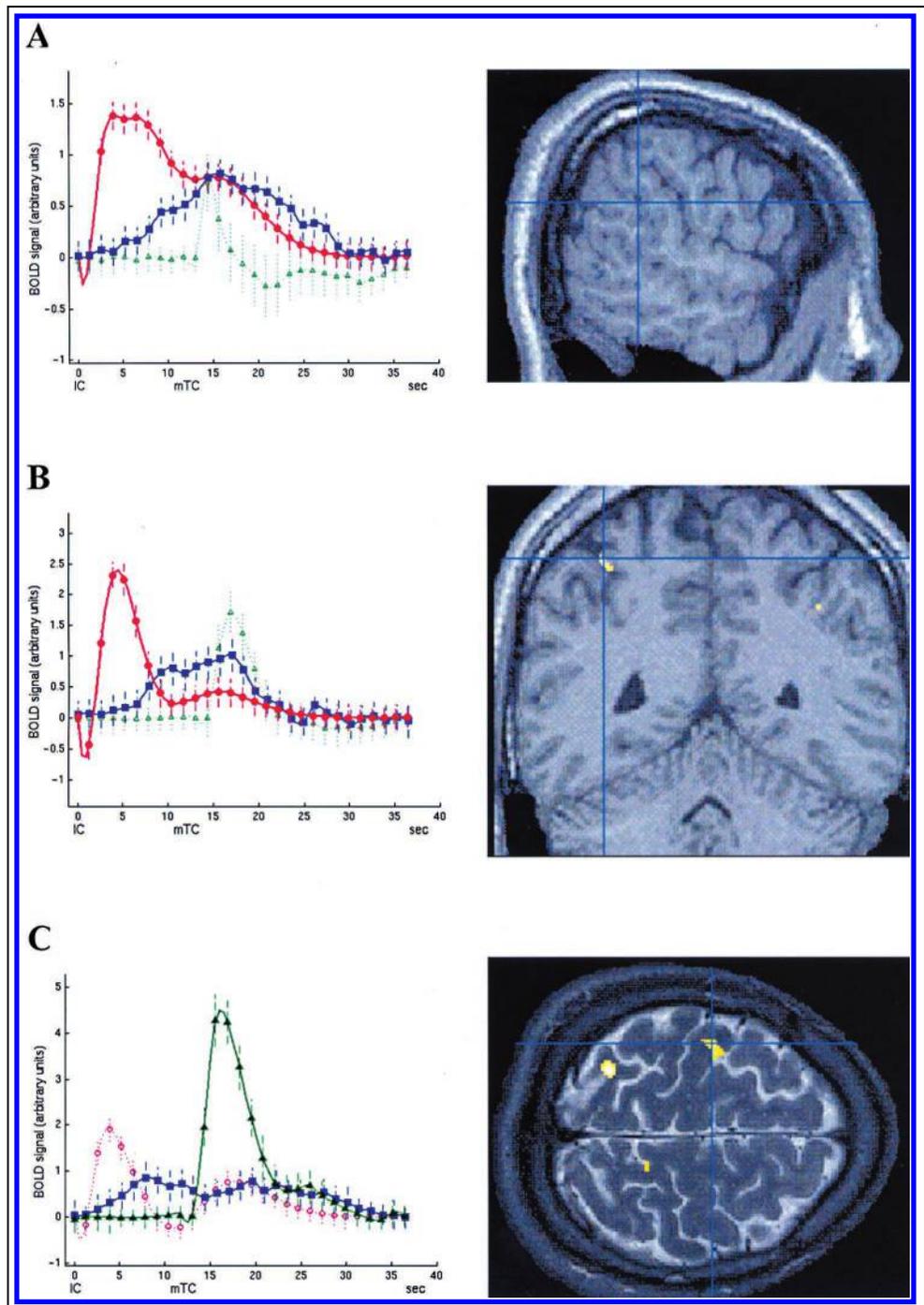
Figure 4. Time course and anatomical localization of the EHRs associated with the IC. Left: Plots representing the mean (\pm standard error) of the adjusted group data obtained from Analysis 1 (red circles), Analysis 2 (blue squares), and Analysis 3 (green triangles). The three analyses test models representing responses time-locked to the IC, the DP, or the TC (see Methods—statistical model and inference). Responses above or below the significance threshold are displayed with continuous or dotted lines, respectively. The curves are obtained from the cubic spline interpolation of the means at each time point. mTC = mean stimulus onset asynchrony (11.7 sec). Signal from local maxima in (A) left occipito-temporal fissure ($-48, -60, -24$); (B) left superior parietal lobule ($-12, -58, 70$); (C) left precentral gyrus ($-26, -20, 68$). Right: Anatomical rendering of significant voxels. The SPM{F} relative to responses time-locked to the IC has been superimposed on normalized structural images of the subjects.



This area shows hemodynamic responses to all three behavioral events of the task, although only the IC- and DP-related activities were above statistical significance. The DP-related activity raises above baseline just after the peak of the IC-related response and it shows a sustained signal for most of the DP. The onset of the TC-related response shows a substantial temporal offset that is absent in the IC-related response. This result closely resembles that obtained in a previous study from the same anatomical region, in a different group of subjects (Toni et al., 1999).

Figure 5C presents the EHRs for a local maximum in the caudal bank of the left superior precentral sulcus, at the convergence with the superior frontal sulcus. This area shows hemodynamic responses to all three behavioral events, although only the DP- and TC-related activities were above statistical significance. The DP-related activity increases above baseline just after the presentation of the IC. However, the signal increases at a lower rate than the IC-related hemodynamic response and it shows a prolonged sustained phase that extends until the end of the trial.

Figure 5. Time course and anatomical localization of the EHRs associated with the DP. Left: Plots representing the mean (\pm standard error) of the adjusted group data. Other conventions as in Figure 4. Signal from local maxima in (A) right superior temporal sulcus (62, -40, 24); (B) left intraparietal sulcus (-38, -50, 58); (C) left precentral gyrus (-38, -14, 64). Right: Anatomical rendering of significant voxels. The SPM{F} relative to responses occurring during the DP has been superimposed on normalized structural images of the subjects.

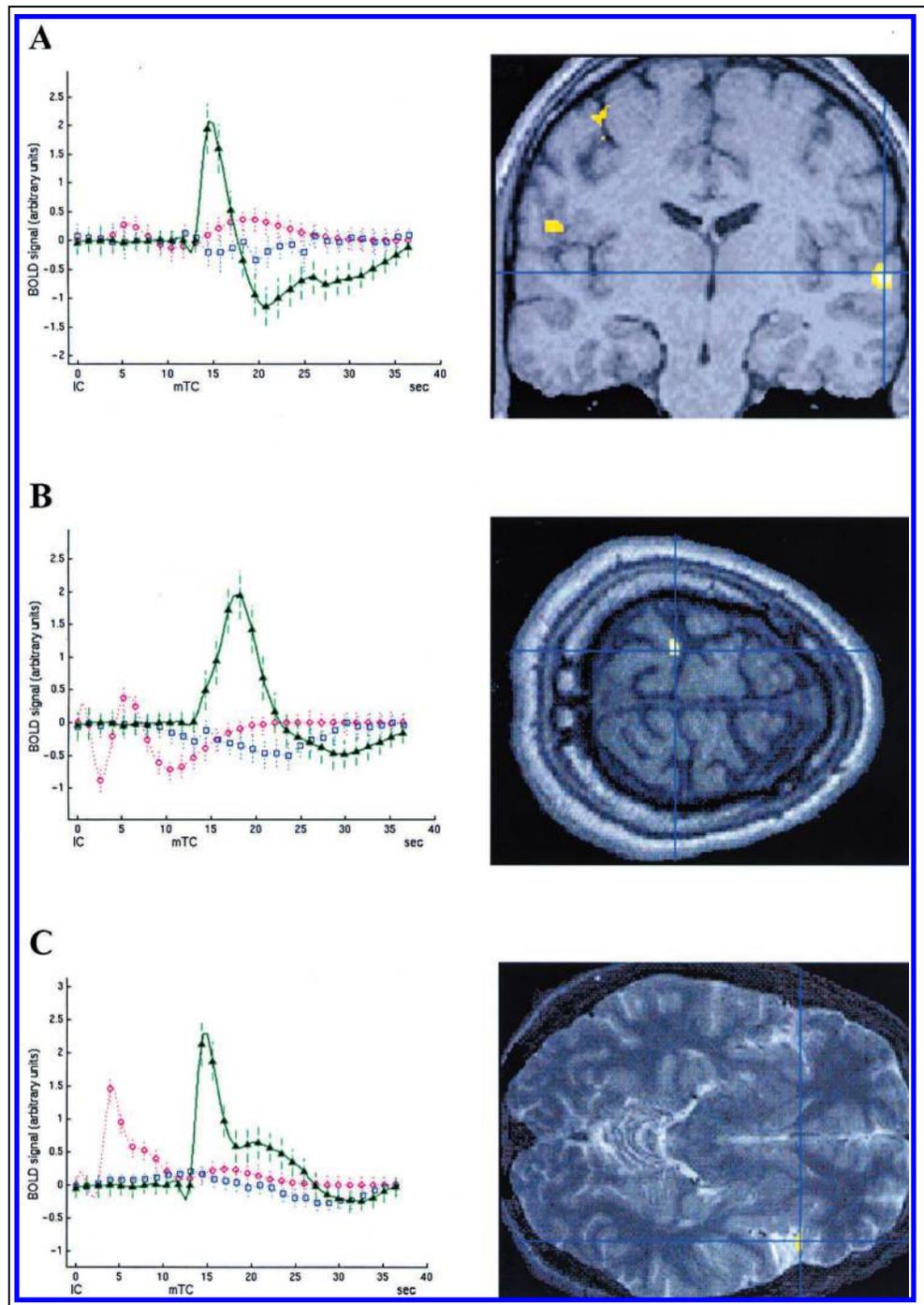


EHRs Associated with the TC

Figure 6A shows the EHRs for a local maximum in the transverse gyrus of the right temporal lobe. In this area, there was a significant hemodynamic response to the TC, but not to the IC or the DP (Tables 1–3). The TC-related activity sharply increases in synchrony with the occurrence of the acoustic TC. The EHR for this maximum shows a conspicuous postpeak undershoot, differing in this respect from other EHRs.

Figure 6B illustrates the EHRs for a local maximum in the dorsal convexity of the superior parietal lobule, just posterior to the postcentral sulcus. This area shows a significant hemodynamic response to the TC, but not to the IC or the DP (Tables 1–3). The TC-related activity increases relatively slowly, in synchrony with the occurrence of the motor response, and it is followed by a postpeak undershoot. This response can be compared with the EHR of Figure 4B. Although both EHRs arise from the same anatomical region, they

Figure 6. Time course of the EHRs associated with the TC. Left: Plots representing the mean (\pm standard error) of the adjusted group data. Other conventions as in Figure 4. Signal from local maxima in (A) right transverse gyrus (66, -14, 4); (B) superior parietal lobule (-18, -32, 76); (C) inferior frontal gyrus (48, 24, -12). Right: Anatomical rendering of significant voxels. The SPM{F} relative to responses time-locked to the TC has been superimposed on normalized structural images of the subjects.



reveal drastically different properties, both in terms of event specificity and response time course. The short delay of the TC-related EHR obtained in this area provides evidence that the delayed responses detected in other parietal maxima are not a generalized phenomenon or a sampling artifact.

Figure 6C displays the EHRs for a local maximum in the opercular convexity of the inferior frontal gyrus, just posterior to the precentral sulcus. This area shows a significant hemodynamic response to the TC, but not to the IC or the DP (Tables 1–3). The TC-related activity sharply increases in synchrony with the occur-

rence of the acoustic TC and the subsequent motor response, and is followed by a slow drift towards baseline. This is reminiscent of the pattern observed for the IC-related response in Figure 5A. Note that the IC-related response, although below significance, is not entirely absent.

DISCUSSION

In this experiment, we have imaged a distributed network underlying movement preparation in the context

of an associative visuomotor task with instructed delays. Our results suggest that, apart from the established contribution of the dorsal visuomotor stream (Milner & Goodale, 1995), portions of the ventral visual stream also take part in the goal-related activity that *precedes* a motor response. These results raise the possibility that preparing an action involves multiple cerebral representations, centered not only on parieto-frontal circuitry (Snyder, Batista, & Andersen, 1997; Riehle, Kornblum, & Requin, 1994), but also in ventral occipito-temporal regions.

In the following sections, we discuss the behavioral and neural correlates of preparatory activity isolated in this experiment, and their relationship with stimulus- and response-related activities. Finally, we interpret these findings in the context of integration between perceptual and executive processes.

Behavioral Performance

This experiment concerns motor preparation in the context of arbitrary visuomotor associations. The experimental task required speeded performance of precued responses following the presentation of an auditory TC. The error-free performance indicates that the information on the movement to be performed was carried over the DP interposed between the IC and the TC. It might be argued that the process of carrying an item over a short delay might represent a basic form of working memory, independently from the nature of the item, the presence of distractors, the need to update the memory content, or the manipulations to be performed on such item. However, temporary storage of sensory information for prospective behavior (“working memory”; Fuster, 1997; Baddeley, 1992) and motor preparation are usually seen as complementary, rather than functionally overlapping, processes (Constantinidis, Franowicz, & Goldman-Rakic, 2001; Quintana & Fuster, 1999; Goldman-Rakic, 1998; Rushworth, Nixon, Eacott, & Passingham, 1997).

The absence of effects of delay on the mean RT (Figure 2B) suggests that the motor preparation process was homogenous across the whole range of DPs. It might be argued that such delay-independent performance (Figure 2B) is a floor-effect reflecting the minimal load of the task. However, we have previously shown that holding in memory sensory items (the visual ICs) induces a delay-dependent performance, whereas preparing to move is independent from the length of the delay (Toni, Thoenissen, Zilles, & Niedeggen, 2001). While the generality of those results needs to be assessed, they suffice to infer that, under the present circumstances, the responses measured during the DP are likely to reflect motor preparatory activity rather than working memory processes. However, the present study cannot exclude that other incidental cognitive processes, although unrelated to task performance,

might have occurred in individual brain regions and might have contributed to the delay-related activities. As suggested by one reviewer, selective attention to the upcoming acoustic TC or idle imaging of the visual stimuli might have played a role in the sustained activities observed in posterior regions. Further experiments are under way to assess the significance of these potential confounds. However, we would like to emphasize that the TC was an abrupt, isolated sensory transient event, with an intensity well above the attenuated background noise of the MR scanner and a different spectral distribution. Under these conditions, transient stimulus-driven attentional capture is likely to dominate over goal-directed sustained attention, in particular, over posterior areas (Schubo, Meinecke, & Schroger, 2001; Egeth & Yantis, 1997).

Finally, motor preparatory activity might have been affected by overt movements. Subjects’ responses required the displacement of a button press, and the task was performed in free vision. However, electrophysiological and behavioral controls allowed us to exclude that delay-related activity was contaminated by overt finger or eye movements.

Fronto-Parietal Interactions

Figure 3A–B reveals a distributed system activated by the brief presentation of a visual stimulus instructing subjects to simply flex a finger. Activity temporally associated with the IC spreads from the primary visual cortex towards the ventral extrastriate areas and, dorsally, towards the posterior parietal and premotor areas. A similar fronto-parietal network was also responsive during the DP interposed between the IC and the TC (Figures 3C–D, 5B–C). These sustained activities are specific since the transient components of the response (i.e., IC- or TC-related activities) have been taken into account and removed. Therefore, these neurovascular activities reflect the selection and the preparation of the movement independently from sensory afference and motor output, even though triggered by an IC and in expectation of a movement in the near future.

It might be argued that the sustained activities detailed in Figure 5 are related to the expectation of the auditory TC. Clearly, fMRI studies cannot distinguish between the expectation of a sensory event and the preparation of a movement on the basis of the neurons’ discriminatory abilities for stimuli or responses (Snyder et al., 1997; Kalaska & Crammond, 1995). However, the subthreshold TC-related activities found at the parietal and occipito-temporal sites suggest that the sustained activity of these regions are not *primarily* related to a sensory event like the auditory TC (Figure 5A–B). Finally, although the premotor cluster showed both DP- and TC-related activities (Figure 5C), it is parsimonious to interpret this pattern of activity in terms of preparation and execution of a motor response, rather

than in terms of expectation of an auditory event. Nevertheless, the sustained activity evoked in different cerebral regions might reflect different combinations of preparatory processes with other cognitive phenomena. For instance, motor planning might dominate premotor signals, while encoding potential targets of movement might be the main drive behind parietal responses (Toni, Thoenissen, & Zilles, 2002; Kalaska & Crammond, 1995).

Temporo-Prefrontal Interactions

The present study confirms and extends our previous findings regarding the involvement of ventral visual areas in the performance of visuomotor associative tasks (Toni & Passingham, 1999; Toni et al., 1999; Toni, Ramnani, Josephs, Ashburner, & Passingham, 2001). Neurovascular activity associated with the presentation of the visual IC was not limited to striate and peristriate areas (Table 1, Figure 3A–B), but it extended towards the occipito-temporal sulcus and the posterior segment of the STS (Table 1, Figures 4A, 5A). This latter region also showed sustained activity during motor preparation. Anatomically, much of the cortex in the caudal STS of the macaque has visual functions (Yaginuma, Osawa, Yamaguchi, & Iwai, 1993; Desimone & Ungerleider, 1986), and it receives convergent input from areas of both the dorsal and the ventral visual stream (Distler, Boussaoud, Desimone, & Ungerleider, 1993; Baizer, Ungerleider, & Desimone, 1991; Morel & Bullier, 1990). Our results suggest a functional role for this anatomical bridge between inferotemporal visuoperceptual areas and fronto-parietal visuomotor areas. Behavioral analyses have shown subtle perceptual effects on motor output in normals (Jackson & Shaw, 2000). These effects become particularly evident after lesions of the posterior parietal region (Jeannerod, Decety, & Michel, 1994) and in the absence of on-line access to the target of the action (Fischer, 2001; Gentilucci, Chieffi, Departi, Saetti, & Toni, 1996). Here we have shown a possible functional–anatomical basis for the integration of perceptual and executive processes in the context of delayed performance of visuomotor associations.

This hypothesis does not contradict our previous suggestions on the involvement of the ventral prefrontal cortex in *establishing* the appropriate association between a particular sensory cue and an arbitrary motor response (Passingham, Toni, & Rushworth, 2000; Passingham & Toni, 2001; Toni & Passingham, 1999; Toni, Rushworth, & Passingham, 2001). Figure 6C not only confirms the involvement of a caudal portion of the inferior frontal gyrus in the control of finger movements (Ehrsson et al., 2000; Ehrsson, Fagergren, & Forssberg, 2001; Iacoboni et al., 1999; Krams et al., 1998), but it also reveals that IC-related responses are not completely absent in this region. On the basis of a related study (Toni, Ramnani, et al., 2001), it is tempting to speculate

that the involvement of the ventral prefrontal cortex in the initial stages of the sensorimotor transformation might decrease in favor of other areas as the visuomotor associations become automatic.

Sustained Activity in Sensory Areas

It might appear surprising that specific preparatory activity was found in occipital visual areas (Table 2). However, a series of neuroimaging and electrophysiological studies have reported attentional (or contextual) modulation of activity in primary visual areas (Gilbert, Ito, Kapadia, & Westheimer, 2000; Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999; Kosslyn et al., 1999; Watanabe et al., 1998; Fuster, 1990). More specifically, the occipital area involved in the current study (30, –92, 24) has been implicated, in humans, in the perception of kinetic boundaries (Dupont et al., 1997; Van Oostende, Sunaert, Van Hecke, Marchal, & Orban, 1997) (34, –88, 0)¹ and of biological motion (Grezes, Costes, & Decety, 1999) (24, –84, 28). Our results confirm that the visual cortex can show sustained responses even in the absence of visual stimulation. Furthermore, such contextual modulation can be observed not only during the expectation of visual stimulation (Kastner et al., 1999), but also during the expectation of a visually instructed movement. As suggested by one reviewer, it is possible to speculate that these posterior sustained activities might represent a way of anticipating the sensory consequences of an intended action. It remains to be seen if these extrastriate activities are necessary to the preparatory process.

Conclusions

We have exploited neuroimaging to gain access to human cerebral activity underlying cognitive representations of movement, independently from overt behavior. We have confirmed that in humans, as in other primates, portions of the parietal and premotor areas contribute to holding the goal of the movement during a DP, that is, they are involved in implementing a rule guiding behavior. Furthermore, we have provided suggestive evidence for the involvement of the ventral visuo-associative areas in movement representation. These results might indicate that visually instructed actions rely not only on visuomotor guidance and spatial reference frames (impinging on the fronto-parietal circuitry), but also on representations stored in the occipito-temporal regions.

METHODS

Experimental and Imaging Set-Up

We studied 6 neurologically normal, right-handed, male volunteers (20–34 years of age) after obtaining informed

consent. The subjects lay supine in the scanner. Head movements were minimized by an adjustable padded head-holder. Visual stimuli were projected onto a screen above the subjects' heads. The visual stimuli (white shapes on a black background, centrally presented) subtended an angle of about 20° on the retina. The acoustic stimuli (300 Hz tones) were presented binaurally via MRI-compatible piezoelectric headphones, which also protected the subjects from the scanner noise. Motor responses were monitored via a keypad with two buttons positioned on the subject's abdomen. Stimulus presentation and response collection were controlled by and synchronized with the scanner through a second computer.

Anatomical (i) MP-RAGE; TE/TR = 4.5/11.4 msec; voxel size = 0.9 × 0.9 × 1.2 mm; and (ii) Turbo Spin-Echo; TE/TR = 90/7000 msec; voxel size = 0.9 × 0.9 × 2.2 mm) and BOLD-sensitive functional images (T2*-weighted EPI; TE/TR = 66 msec/5.2 sec; FOV = 200 × 200 mm; voxel size = 3.1 × 3.1 × 3.3 mm; 30 slices; 960 images in eight consecutive sessions) were acquired using a VISION scanner operating at 1.5 T (Siemens, Erlangen, Germany). These imaging parameters ensured full brain coverage, apart from the inferior part of the cerebellum.

On a separate occasion, three subjects underwent a further scanning session in order to assess skeleto- and oculomotor activities during task performance. Bipolar surface EMGs were recorded (1 kHz) from the flexor digitorum superficialis of the right forearm (band-pass filter 1–200 Hz, notch filter 50 Hz). Eye position was recorded (60 Hz) with an infrared video-oculographic system (<http://www.a-s-l.com/>; Gitelman, Parrish, LaBar, & Mesulam, 2000). In order to collect meaningful EMG data, the MR gradients were turned off during the EMG measurements.

Task

The subjects were trained to perform a visuomotor conditional task with instructed delays (Figure 1). One of four shapes (IC) was presented for 300 msec. Two shapes instructed the subjects to flex the right index finger; the other two shapes instructed the flexion of the right middle finger. After a variable DP (1.3–20.8 sec in steps of 1.3 sec), a tone (TC) was presented for 300 msec. The subjects were asked to prepare the response during the delay, but not to tense or move their right hand until the TC. The movement was to be performed as quickly as possible after the TC.

The task rules were learned by trial and error by the subjects during a prescanning training session, during which they practiced the task for 360 trials. The task was the same as that used in the scanning session, apart from the presence of feedback on performance (a green tick for correct responses, a red cross for wrong responses), the range of delays (0.1–1.0 sec in steps

of 0.1 sec), and the presence of a reaction time cutoff (0.7 sec). The feedback allowed the subjects to learn the task. The different range of delays allowed the subjects to complete the training phase in a short time. The reaction time cutoff was introduced to stress the speed of the responses.

The subjects were given 10 further training trials in the scanner, just before the beginning of the scanning session. This allowed them to experience the range of delays and the experimental set-up used during the scanning procedure.

The subjects were allowed free vision during the whole scanning procedure and task performance. The visual IC was centrally presented and it covered a conspicuous portion of the subjects' visual field. Special care was taken in order to position the central portion of the screen into the resting line of gaze of each subject. These procedures minimized potential interaction between the neural systems controlling eye and finger movements.

Experimental Timing

The intertrial interval (ITI, 37.7 sec) was chosen so that successive trials started progressively later (1.3 sec, i.e., TR/4) in the scanning sequence. This mismatch between trial occurrence and volume acquisition allowed a characterization of the EHRs at a finer temporal resolution than the actual TR, while preserving coverage of the whole brain (Josephs, Turner, & Friston, 1997). The long ITI allowed the estimation of the whole time course of the EHR to each experimental event and not only the differential component of the responses to each event (Josephs & Henson, 1999).

The delays between the IC and the TC were selected from a uniform distribution of intervals (1.3–20.8 sec in steps of 1.3 sec). This range of delays allowed us to partition the EHR model into three independent components; one aligned with the IC, one aligned with the TC, and one extending over the DP. The pseudorandom variation in the DP between the IC and the TC ensured that the subjects could not anticipate the occurrence of the TC. The extensive range of delays ensured that the subjects were ready to respond at any time after the presentation of the IC.

Image Analysis

The data were analyzed with SPM97 (www.fil.ion.ucl.ac.uk/spm; Friston, Holmes, Worsley, et al., 1995). After standard preprocessing procedures (Toni, Krams, Turner, & Passingham, 1998; Toni et al., 1999), functional images smoothed with an isotropic Gaussian kernel of 4 mm were submitted to statistical analysis. Note that this spatial filter preserved the native anatomical resolution, emphasizing cerebral structures of comparable spatial extent (cortical mantle), but penalizing structures

with a different spatial organization (basal ganglia, cerebellum; Hopfinger, Buchel, Holmes, & Friston, 2000).

One hundred and twenty-eight trials were analyzed for each subject. The EHRs to each of the 3 behavioral components of the task (IC, DP, TC) were modeled independently in the same model with different sets of temporal basis functions. The sustained EHRs (i.e., DP component) were modeled with a set of Fourier series temporal basis functions (up to the sixth harmonic), having the DP at each trial (plus a decay time of 6 sec) as the fundamental period. Furthermore, these temporal basis functions were smoothed at the extremes of the fundamental period. The assumption embodied by this model is that the neural activity occurring during the DP is sustained and the rise and fall of the hemodynamic response is smooth. DP-related activity is thus defined by a time interval, rather than by a specific time point. Fourier series temporal basis functions allowed us to characterize EHRs without specifying their exact form or timing, that is the phase and amplitude of the basis functions. We consider it important to use a very flexible model for this component of the response, since sustained responses represent cognitive processes of unknown timing and intensity that are not necessarily time-locked to a particular time point.

The transient EHRs (i.e., IC and TC components) were modeled with a set of gamma functions and their temporal derivative (Friston, Josephs, Rees, & Turner, 1998), time-locked to the occurrence of the IC and the TC. These temporal basis functions allowed unconstrained characterization of the transient responses while avoiding collinearity with the partition of the model representing the sustained responses. Residual correlations between these two partitions of the statistical model (representing transient and sustained components of the response) were removed by orthogonalizing the gamma functions with respect to the smoothed Fourier set.

The 3 partitions of the model, representing transient responses time-locked to the IC, the TC, or sustained responses during the DP, were considered alternately as effects of interest and no-interest (or confounds), in order to distinguish the EHRs associated with each behavioral component of the task. In Analysis 1, we tested for the presence of transient responses time-locked to the IC, having accounted for and removed the contribution of the DP and TC components. In Analysis 2, we tested for the presence of sustained responses occurring during the DP, having accounted for and removed the contribution of IC and TC components. Finally, in Analysis 3, we tested for the presence of transient responses time-locked to the TC, having accounted for and removed the contribution of the IC and DP components.

Low-frequency drifts over time, residual head movement-related effects, changes in mean signal over the whole brain, and overall differences across runs were

considered as effects of no-interest. Low-frequency changes in signal were modeled with a set of discrete cosine basis functions. The highest frequency modeled was twice the longest experimental period (two trials), that is, 75.4 sec; the lowest frequency modeled was a whole scanning run. Head movement-related effects were modeled using the first-, second-, and third-order polynomial expansions of the movement estimates obtained from the realignment procedure.

The statistical significance of the estimated EHRs was assessed using F statistics in the context of a multiple regression analysis. The null hypothesis was that the variance explained by the effects of interest was consistent with the residual error, once the variance explained by the effects of no-interest was removed. F ratios for each voxel in the image were computed. SPM{F}s were generated to indicate the spatial distribution of significant event-related activations associated with either IC (Analysis 1), DP (Analysis 2), or TC (Analysis 3). Gaussian field theory allowed us to make inferences corrected for the number of nonindependent comparisons (Friston, Holmes, Worsley, et al., 1995). The effective degrees of freedom of the error term took into account the temporal autocorrelation of the data (Friston, Holmes, & Poline, et al., 1995).

We report the results of single-subject analyses and of a fixed-effect group analysis. This approach allowed us to preserve the advantages of both single-subject analyses (precise identification of the anatomical location of the activation foci, evaluation of the consistency of the results across subjects) and of fixed-effect group analyses (high signal-to-noise ratio, concise overview of the activation patterns). The limitation of this approach is that the inferences are about the presence of an effect in these subjects during these scanning sessions and not about the average size of the effect in the population from which the subjects were drawn (Friston, Holmes, Price, Buchel, & Worsley, 1999; Friston, Holmes, & Worsley, 1999). In order to appropriately estimate intersubject variability and thus extend the inferences to the population, it would be necessary to collapse the data over replications within subjects. However, the analyses used in the present paper make use of multiple regressors to describe each event and they cannot be handled by the univariate statistics available in SPM97.

The statistical thresholds used in the single-subject analysis were $F(48.0, 591.7) > 2.56$ (for Analyses 1 and 3), and $F(56.0, 591.7) > 2.43$ (for Analysis 2), corresponding to $p < .05$ (corrected for multiple comparisons). The corrected F thresholds used in the group analyses were 1.77 and 1.61, respectively. These thresholds ensured a low incidence of Type I errors, at the expenses of decreased sensitivity (increased Type II errors). This implies that regions with robust preparatory activity (e.g., cerebellum, basal ganglia, cingulate motor areas, presupplementary motor area, SMA

proper) might nevertheless have failed to reach our statistical threshold. Due to computational limitations (see www.mailbase.ac.uk/lists/spm/1998-12/0000.html for a discussion of this issue), the group analyses were performed on three of the six subjects. Note that this procedure is statistically conservative, since it decreases the subject pool, and hence, the degrees of freedom of the analyses.

Anatomical details of significant signal changes were obtained by superimposing the SPM{F}s on both the structural and the mean functional images of each subject. The atlas of Duvernoy, Cabanis, & Vannson (1991) was used to identify relevant anatomical landmarks. The time course of the EHRs is shown for some significant areas of activation. The signal estimated from each slice has been reordered according to its latency with respect to either IC or TC. Note that this allows one to take into account the delay occurring between the beginning of the acquisition of each volume and the actual time of acquisition of each slice.

Behavioral Analysis

The mean RT and the number of errors were measured. The RT data were linearly regressed over two different explanatory variables: trial number (Sessions 1–8) and length of the DP (1.3–20.8 sec in 20 steps of 1.3 sec). Each of these regressions was performed for the whole group ($n = 6$) and for each subject individually. Analysis of regression assessed the significance of the slope ($p < .05$).

EMG and eye position recordings were examined offline. Means and standard deviations of 16 artifact-free trials were measured for each subject across three epochs (baseline: 3 sec immediately preceding the onset of the visual IC; delay: time interval between the onset of the visual IC and the onset of the auditory TC; response: 3 sec immediately following the onset of the auditory TC). Analysis of variance (ANOVA) assessed the significance of the experimental manipulation ($p < .05$; one-way ANOVA for repeated measures with one factor [epoch] over three levels [baseline, delay, response]). Tukey's t test was used for post hoc pairwise comparisons ($p < .05$).

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The data reported in this experiment have been deposited in The fMRI Data Center (<http://www.fmridc.org>). The accession number is 2-2001-112E9.

Note

1. Note that the latter experiments have been analyzed with SPM95, whereas the current study used SPM97. Different default frames of stereotactic normalization (bounding boxes) are used in SPM95/97, differing mainly along the z -axis (SPM95: -28 to $+72$; SPM97: -50 to $+85$).

REFERENCES

- Amunts, K., Malikovic, A., Mohlberg, H., Schormann, T., & Zilles, K. (2000). Brodmann's areas 17 and 18 brought into stereotaxic space—where and how variable? *Neuroimage*, *11*, 66–84.
- Baddeley, A. (1992). Working memory. *Science*, *255*, 556–559.
- Baizer, J. S., Ungerleider, L. G., & Desimone, R. (1991). Organization of visual inputs to the inferior temporal and posterior parietal cortex in macaques. *Journal of Neuroscience*, *11*, 168–190.
- Bastian, A., Riehle, A., Erhagen, W., & Schoner, G. (1998). Prior information preshapes the population representation of movement direction in motor cortex. *NeuroReport*, *9*, 315–319.
- Chawla, D., Rees, G., & Friston, K. J. (1999). The physiological basis of attentional modulation in extrastriate visual areas. *Nature Neuroscience*, *2*, 671–676.
- Constantinidis, C., Franowicz, M. N., & Goldman-Rakic, P. S. (2001). The sensory nature of mnemonic representation in the primate prefrontal cortex. *Nature Neuroscience*, *4*, 311–316.
- Courtney, S. M., Petit, L., Maisog, J. M., Ungerleider, L. G., & Haxby, J. V. (1998). An area specialized for spatial working memory in human frontal cortex. *Science*, *279*, 1347–1351.
- Crammond, D. J., & Kalaska, J. F. (2000). Prior information in motor and premotor cortex: Activity during the delay period and effect on pre-movement activity. *Journal of Neurophysiology*, *84*, 986–1005.
- Deiber, M. P., Ibanez, V., Sadato, N., & Hallett, M. (1996). Cerebral structures participating in motor preparation in humans: A positron emission tomography study. *Journal of Neurophysiology*, *75*, 233–247.
- D'Esposito, M., Ballard, D., Zarahn, E., & Aguirre, G. K. (2000). The role of prefrontal cortex in sensory memory and motor preparation: An event-related fMRI study. *Neuroimage*, *11*, 400–408.
- Desimone, R., & Ungerleider, L. G. (1986). Multiple visual areas in the caudal superior temporal sulcus of the macaque. *Journal of Comparative Neurology*, *248*, 164–189.
- Distler, C., Boussaoud, D., Desimone, R., & Ungerleider, L. G. (1993). Cortical connections of inferior temporal area TEO in macaque monkeys. *Journal of Comparative Neurology*, *334*, 125–150.
- Dupont, P., DeBruyn, B., Vandenberghe, R., Rosier, A., Michiels, J., Marchal, G., Mortelmans, L., & Orban, G. (1997). The kinetic occipital region in human visual cortex. *Cerebral Cortex*, *7*, 283–292.
- Duvernoy, H. M., Cabanis, E. A., & Vannson, J. L. (1991).

- The human brain: Surface, three-dimensional sectional anatomy and MRI*. Wien: Springer-Verlag.
- Egeth, H. E., & Yantis, S. (1997). Visual attention: Control, representation, and time course. *Annual Review of Psychology*, *48*, 269–297.
- Ehrsson, H., Fagergren, A., Jonsson, T., Westling, G., Johansson, R., & Forssberg, H. (2000). Cortical activity in precision-versus power-grip tasks: An fMRI study. *Journal of Neurophysiology*, *83*, 528–536.
- Ehrsson, H., Fagergren, E., & Forssberg, H. (2001). Differential fronto-parietal activation depending on force used in a precision grip task: fMRI study. *Journal of Neurophysiology*, *85*, 2613–2623.
- Fischer, M. H. (2001). How sensitive is hand transport to illusory context effects? *Experimental Brain Research*, *136*, 224–230.
- Friston, K. J., Holmes, A. P., Poline, J. B., Grasby, P. J., Williams, S. C., Frackowiak, R. S., & Turner, R. (1995). Analysis of fMRI time-series revisited. *Neuroimage*, *2*, 45–53.
- Friston, K. J., Holmes, A. P., Price, C. J., Buchel, C., & Worsley, K. J. (1999). Multisubject fMRI studies and conjunction analyses. *Neuroimage*, *10*, 385–396.
- Friston, K. J., Holmes, A. P., & Worsley, K. J. (1999). How many subjects constitute a study? *Neuroimage*, *10*, 1–5.
- Friston, K. J., Holmes, A. P., Worsley, K. J., Poline, J. B., Frith, C., & Frackowiak, R. S. (1995). Statistical parametric maps in functional imaging: A general linear approach. *Human Brain Mapping*, *2*, 189–210.
- Friston, K. J., Josephs, O., Rees, G., & Turner, R. (1998). Nonlinear event-related responses in fMRI. *Magnetic Resonance in Medicine*, *39*, 41–52.
- Friston, K. J., Price, C. J., Fletcher, P., Moore, C., Frackowiak, R. S., & Dolan, R. J. (1996). The trouble with cognitive subtraction. *Neuroimage*, *4*, 97–104.
- Fuster, J. M. (1973). Unit activity in prefrontal cortex during delayed-response performance: Neuronal correlates of transient memory. *Journal of Neurophysiology*, *36*, 61–78.
- Fuster, J. M. (1990). Inferotemporal units in selective visual attention and short-term memory. *Journal of Neurophysiology*, *64*, 681–697.
- Fuster, J. M. (1997). *The prefrontal cortex: Anatomy, physiology, and neuropsychology of the frontal lobe*. New York: Lippincott-Raven.
- Gentilucci, M., Chieffi, S., Deprati, E., Saetti, M. C., & Toni, I. (1996). Visual illusion and action. *Neuropsychologia*, *34*, 369–376.
- Gilbert, C., Ito, M., Kapadia, M., & Westheimer, G. (2000). Interactions between attention, context and learning in primary visual cortex. *Vision Research*, *40*, 1217–1226.
- Gitelman, D. R., Parrish, T. B., LaBar, K. S., & Mesulam, M. M. (2000). Real-time monitoring of eye movements using infrared video-oculography during functional magnetic resonance imaging of the frontal eye fields. *Neuroimage*, *11*, 58–65.
- Goldman-Rakic, P. S. (1998). The prefrontal landscape: Implications of functional architecture for understanding human mentation and the central executive. In A. C. Roberts, T. W. Robbins, & L. Weiskrantz (Eds.), *The prefrontal cortex: Executive and cognitive functions* (pp. 87–102). Oxford: Oxford University Press.
- Grezes, J., Costes, N., & Decety, J. (1999). The effects of learning and intention on the neural network involved in the perception of meaningless actions. *Brain*, *122*, 1875–1887.
- Hopfinger, J. B., Buchel, C., Holmes, A. P., & Friston, K. J. (2000). A study of analysis parameters that influence the sensitivity of event-related fMRI analyses. *Neuroimage*, *11*, 326–333.
- Iacoboni, M., Woods, R. P., Brass, M., Bekkering, H., Mazziotta, J. C., & Rizzolatti, G. (1999). Cortical mechanisms of human imitation. *Science*, *286*, 2526–2528.
- Jackson, S. R., & Shaw, A. (2000). The Ponzo illusion affects grip-force but not grip-aperture scaling during prehension movements. *Journal of Experimental Psychology, Human Perception and Performance*, *26*, 418–423.
- Jeannerod, M. (1997). *The cognitive neuroscience of action*. Oxford: Blackwell.
- Jeannerod, M., Decety, J., & Michel, F. (1994). Impairment of grasping movements following a bilateral posterior parietal lesion. *Neuropsychologia*, *32*, 369–380.
- Josephs, O., & Henson, R. N. (1999). Event-related functional magnetic resonance imaging: Modelling, inference and optimization. *Philosophical Transactions of the Royal Society of London, Series B: Biological Sciences*, *354*, 1215–1228.
- Josephs, O., Turner, R., & Friston, K. J. (1997). Event-related fMRI. *Human Brain Mapping*, *5*, 243–248.
- Kalaska, J. F., & Crammond, D. J. (1995). Deciding not to GO: Neuronal correlates of response selection in a GO/NOGO task in primate premotor and parietal cortex. *Cerebral Cortex*, *5*, 410–428.
- Kastner, S., Pinsk, M. A., De Weerd, P., Desimone, R., & Ungerleider, L. G. (1999). Increased activity in human visual cortex during directed attention in the absence of visual stimulation. *Neuron*, *22*, 751–761.
- Kawashima, R., Roland, P. E., & O'Sullivan, B. T. (1994). Fields in human motor areas involved in preparation for reaching, actual reaching, and visuomotor learning: A positron emission tomography study. *Journal of Neuroscience*, *14*, 3462–3474.
- Klemmer, E. T. (1957). Simple reaction time as a function of time uncertainty. *Journal of Experimental Psychology*, *54*, 195–200.
- Kosslyn, S. M., Pascual-Leone, A., Felician, O., Camposano, S., Keenan, J. P., Thompson, W. L., Ganis, G., Sukel, K. E., & Alpert, N. M. (1999). The role of area 17 in visual imagery: Convergent evidence from PET and rTMS. *Science*, *284*, 167–170.
- Krams, M., Rushworth, M. F., Deiber, M. P., Frackowiak, R. S., & Passingham, R. E. (1998). The preparation, execution and suppression of copied movements in the human brain. *Experimental Brain Research*, *120*, 386–398.
- Markman, A. B., & Dietrich, E. (2000). In defense of representation. *Cognitive Psychology*, *40*, 138–171.
- Milner, A. D., & Goodale, M. A. (1995). *The visual brain in action*. Oxford: Oxford University Press.
- Moody, S. L., & Wise, S. P. (2000). A model that accounts for activity prior to sensory inputs and responses during matching-to-sample tasks. *Journal of Cognitive Neuroscience*, *12*, 429–448.
- Morel, A., & Bullier, J. (1990). Anatomical segregation of two cortical visual pathways in the macaque monkey. *Vision Neuroscience*, *4*, 555–578.
- Passingham, R. E., & Toni, I. (2001). Contrasting the dorsal and ventral visual systems: Guidance of movement versus decision making. *Neuroimage*, *14*, S125–S131.
- Passingham, R. E., Toni, I., & Rushworth, M. F. (2000). Specialisation within the prefrontal cortex: The ventral prefrontal cortex and associative learning. *Experimental Brain Research*, *133*, 103–113.
- Petit, L., Courtney, S. M., Ungerleider, L. G., & Haxby, J. V. (1998). Sustained activity in the medial wall during working memory delays. *Journal of Neuroscience*, *18*, 9429–9437.
- Postle, B. R., & D'Esposito, M. (1999). “What”-Then-“Where” in visual working memory: An event-related fMRI study. *Journal of Cognitive Neuroscience*, *11*, 585–597.

- Quintana, J., & Fuster, J. M. (1999). From perception to action: Temporal integrative functions of prefrontal and parietal neurons. *Cerebral Cortex*, *9*, 213–221.
- Rademacher, J., Morosan, P., Schormann, T., Schleicher, A., Werner, C., Freund, H. J., & Zilles, K. (2001). Probabilistic mapping and volume measurement of human primary auditory cortex. *Neuroimage*, *13*, 669–683.
- Requin, J., Brener, J., & Ring, C. (1991). Preparation for action. In J. R. Jennings & M. G. Coles (Eds.), *Handbook of cognitive psychophysiology* (pp. 357–448). New York: Wiley.
- Riehle, A., Kornblum, S., & Requin, J. (1994). Neuronal coding of stimulus–response association rules in the motor cortex. *NeuroReport*, *5*, 2462–2464.
- Rowe, J. B., Toni, I., Josephs, O., Frackowiak, R. S., & Passingham, R. E. (2000). The prefrontal cortex: Response selection or maintenance within working memory? *Science*, *288*, 1656–1660.
- Rushworth, M. F., Nixon, P. D., Eacott, M. J., & Passingham, R. E. (1997). Ventral prefrontal cortex is not essential for working memory. *Journal of Neuroscience*, *17*, 4829–4838.
- Schubo, A., Meinecke, C., & Schroger, E. (2001). Automaticity and attention: Investigating automatic processing in texture segmentation with event-related brain potentials. *Brain Research, Cognitive Brain Research*, *11*, 341–361.
- Snyder, L. H., Batista, A. P., & Andersen, R. A. (1997). Coding of intention in the posterior parietal cortex. *Nature*, *386*, 167–170.
- Steinberg, S. (1969). The discovery of processing stages: Extensions of Donder's method. *Acta Psychologica*, *30*, 276–315.
- Stephan, K. M., Fink, G. R., Passingham, R. E., Silbersweig, D., Ceballos-Baumann, A. O., Frith, C. D., & Frackowiak, R. S. (1995). Functional anatomy of the mental representation of upper extremity movements in healthy subjects. *Journal of Neurophysiology*, *73*, 373–386.
- Toni, I., Krams, M., Turner, R., & Passingham, R. E. (1998). The time course of changes during motor sequence learning: A whole-brain fMRI study. *Neuroimage*, *8*, 50–61.
- Toni, I., & Passingham, R. E. (1999). Prefrontal–basal ganglia pathways are involved in the learning of arbitrary visuomotor associations: A PET study. *Experimental Brain Research*, *127*, 19–32.
- Toni, I., Ramnani, N., Josephs, O., Ashburner, J., & Passingham, R. E. (2001). Learning arbitrary visuo-motor associations: Temporal dynamic of brain activity. *Neuroimage*, *14*, 1048–1057.
- Toni, I., Rushworth, M. F. S., & Passingham, R. E. (2001). Neural correlates of visuomotor associations: Spatial rules compared with arbitrary rules. *Experimental Brain Research*, *141*, 359–369.
- Toni, I., Schluter, N. D., Josephs, O., Friston, K., & Passingham, R. E. (1999). Signal-, set- and movement-related activity in the human brain: An event-related fMRI study [published erratum appears in *Cerebral Cortex* 1999 Mar;9(2):196]. *Cereb Cortex*, *9*, 35–49.
- Toni, I., Thoenissen, D., & Zilles, K. (2002). Movement preparation and motor intention. *Neuroimage*, *14*, S110–S117.
- Toni, I., Thoenissen, D., Zilles, K., & Niedeggen, M. (2001). Movement preparation and working memory: A behavioural dissociation. *Experimental Brain Research*, *142*, 158–162.
- Van Oostende, S., Sunaert, S., Van Hecke, P., Marchal, G., & Orban, G. A. (1997). The kinetic occipital (KO) region in man: An fMRI study. *Cerebral Cortex*, *7*, 690–701.
- Watanabe, T., Harner, A. M., Miyauchi, S., Sasaki, Y., Nielsen, M., Palomo, D., & Mukai, I. (1998). Task-dependent influences of attention on the activation of human primary visual cortex. *Proceedings of the National Academy of Sciences, U.S.A.*, *95*, 11489–11492.
- Wise, S. P., di Pellegrino, G., & Boussaoud, D. (1996). The premotor cortex and nonstandard sensorimotor mapping. *Canadian Journal of Physiology and Pharmacology*, *74*, 469–482.
- Wise, S. P., & Murray, E. A. (2000). Arbitrary associations between antecedents and actions. *Trends in Neurosciences*, *23*, 271–276.
- Yaginuma, S., Osawa, Y., Yamaguchi, K., & Iwai, E. (1993). Differential functions of central and peripheral visual field representations in monkey prestriate cortex. In T. Ono, L. R. Squire, M. E. Raichle, D. I. Perrett, & M. Fukuda (Eds.), *Brain mechanisms of perception and memory* (pp. 3–15). Oxford: Oxford University Press.
- Zarahn, E., Aguirre, G. K., & D'Esposito, M. (1999). Temporal isolation of the neural correlates of spatial mnemonic processing with fMRI. *Brain Research, Cognitive Brain Research*, *7*, 255–268.

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1. Simone Kühn, Anika Werner, Ulman Lindenberger, Julius Verrel. 2014. Acute immobilisation facilitates premotor preparatory activity for the non-restrained hand when facing grasp affordances. *NeuroImage* **92**, 69-73. [[CrossRef](#)]
2. Jill Campbell Stewart, Xuan Tran, Steven C. Cramer. 2013. Age-related variability in performance of a motor action selection task is related to differences in brain function and structure among older adults. *NeuroImage* . [[CrossRef](#)]
3. N. Sadeh, J. M. Spielberg, W. Heller, J. D. Herrington, A. S. Engels, S. L. Warren, L. D. Crocker, B. P. Sutton, G. A. Miller. 2013. Emotion disrupts neural activity during selective attention in psychopathy. *Social Cognitive and Affective Neuroscience* **8**, 235-246. [[CrossRef](#)]
4. Magnus-Sebastian Vry, Dorothee Saur, Michel Rijntjes, Roza Umarova, Philipp Kellmeyer, Susanne Schnell, Volkmar Glauche, Farsin Hamzei, Cornelius Weiller. 2012. Ventral and dorsal fiber systems for imagined and executed movement. *Experimental Brain Research* **219**, 203-216. [[CrossRef](#)]
5. Oliver Jakobs, Robert Langner, Svenja Caspers, Christian Roski, Edna C. Cieslik, Karl Zilles, Angela R. Laird, Peter T. Fox, Simon B. Eickhoff. 2012. Across-study and within-subject functional connectivity of a right temporo-parietal junction subregion involved in stimulus-context integration. *NeuroImage* **60**, 2389-2398. [[CrossRef](#)]
6. István Ákos Mórocz, Firdaus Janoos, Peter van Gelderen, David Manor, Avi Karni, Zvia Breznitz, Michael von Aster, Tammar Kushnir, Ruth Shalev. 2012. Time-resolved and spatio-temporal analysis of complex cognitive processes and their role in disorders like developmental dyscalculia. *International Journal of Imaging Systems and Technology* **22**:10.1002/ima.v22.1, 81-96. [[CrossRef](#)]
7. E. A. Cartmill, S. Beilock, S. Goldin-Meadow. 2012. A word in the hand: action, gesture and mental representation in humans and non-human primates. *Philosophical Transactions of the Royal Society B: Biological Sciences* **367**, 129-143. [[CrossRef](#)]
8. Cathérine C.S. Delnooz, Rick C. Helmich, W.P. Medendorp, Bart P.C. Van de Warrenburg, Ivan Toni. 2012. Writer's cramp: Increased dorsal premotor activity during intended writing. *Human Brain Mapping* 00-00. [[CrossRef](#)]
9. Gaspare Galati, Giorgia Committeri, Sabrina Pitzalis, Gina Pelle, Fabiana Patria, Patrizia Fattori, Claudio Galletti. 2011. Intentional signals during saccadic and reaching delays in the human posterior parietal cortex. *European Journal of Neuroscience* no-no. [[CrossRef](#)]
10. Paige E. Scalf, Paul E. Dux, René Marois. 2011. Working Memory Encoding Delays Top-Down Attention to Visual Cortex. *Journal of Cognitive Neuroscience* **23**:9, 2593-2604. [[Abstract](#)] [[Full Text](#)] [[PDF](#)] [[PDF Plus](#)]
11. R. Ronsse, V. Puttemans, J. P. Coxon, D. J. Goble, J. Wagemans, N. Wenderoth, S. P. Swinnen. 2011. Motor Learning with Augmented Feedback: Modality-Dependent Behavioral and Neural Consequences. *Cerebral Cortex* **21**, 1283-1294. [[CrossRef](#)]
12. John-Dylan Haynes. 2011. Decoding and predicting intentions : Predicting intentions. *Annals of the New York Academy of Sciences* **1224**:1, 9. [[CrossRef](#)]
13. Antonio Cerasa, Demetrio Messina, Pierfrancesco Pugliese, Maurizio Morelli, Pierluigi Lanza, Maria Salsone, Fabiana Novellino, Giuseppe Nicoletti, Gennarina Arabia, Aldo Quattrone. 2011. Increased prefrontal volume in PD with levodopa-induced dyskinesias: A voxel-based morphometry study. *Movement Disorders* n/a-n/a. [[CrossRef](#)]
14. Simone Kühn, Nils Christian Bodammer, Marcel Brass. 2010. Dissociating mental states related to doing nothing by means of fMRI pattern classification. *NeuroImage* **53**, 1294-1300. [[CrossRef](#)]
15. Chen-Gia Tsai, Chien-Chung Chen, Tai-Li Chou, Jyh-Horng Chen. 2010. Neural mechanisms involved in the oral representation of percussion music: An fMRI study. *Brain and Cognition* **74**, 123-131. [[CrossRef](#)]
16. Ian M. Lyons, Andrew Mattarella-Micke, Matthew Cieslak, Howard C. Nusbaum, Steven L. Small, Sian L. Beilock. 2010. The role of personal experience in the neural processing of action-related language. *Brain and Language* **112**, 214-222. [[CrossRef](#)]
17. Uta Wolfensteller, D. Yves von Cramon. 2010. Bending the Rules: Strategic Behavioral Differences Are Reflected in the Brain. *Journal of Cognitive Neuroscience* **22**:2, 278-291. [[Abstract](#)] [[Full Text](#)] [[PDF](#)] [[PDF Plus](#)]
18. Philippe A. Chouinard, Melvyn A. Goodale. 2009. fMRI adaptation during performance of learned arbitrary visuomotor conditional associations. *NeuroImage* **48**, 696-706. [[CrossRef](#)]
19. Mareike M. Menz, Adam McNamara, Jane Klemen, Ferdinand Binkofski. 2009. Dissociating networks of imitation. *Human Brain Mapping* **30**:10.1002/hbm.v30:10, 3339-3350. [[CrossRef](#)]
20. Hannes Ruge, Thomas Goschke, Todd S. Braver. 2009. Separating event-related BOLD components within trials: The partial-trial design revisited. *NeuroImage* **47**, 501-513. [[CrossRef](#)]
21. Oliver Jakobs, Ling E. Wang, Manuel Dafotakis, Christian Grefkes, Karl Zilles, Simon B. Eickhoff. 2009. Effects of timing and movement uncertainty implicate the temporo-parietal junction in the prediction of forthcoming motor actions. *NeuroImage* **47**, 667-677. [[CrossRef](#)]

22. Jozina B. de Graaf, Alexey Frolov, Michel Fiocchi, Bruno Nazarian, Jean-Luc Anton, Jean Pailhous, Mireille Bonnard. 2009. Preparing for a motor perturbation: Early implication of primary motor and somatosensory cortices. *Human Brain Mapping* **30**, 575-587. [[CrossRef](#)]
23. Jennifer K. Dionne, Sean K. Meehan, Wynn Legon, W. Richard Staines. 2009. Crossmodal influences in somatosensory cortex: Interaction of vision and touch. *Human Brain Mapping* NA-NA. [[CrossRef](#)]
24. Sian L. Beilock Grounding cognition in action: expertise, comprehension, and judgment 3-11. [[CrossRef](#)]
25. S. L. Beilock, I. M. Lyons, A. Mattarella-Micke, H. C. Nusbaum, S. L. Small. 2008. Sports experience changes the neural processing of action language. *Proceedings of the National Academy of Sciences* **105**, 13269-13273. [[CrossRef](#)]
26. M. Bakker, F.P. De Lange, R.C. Helmich, R. Scheeringa, B.R. Bloem, I. Toni. 2008. Cerebral correlates of motor imagery of normal and precision gait. *NeuroImage* **41**, 998-1010. [[CrossRef](#)]
27. Hiske van Duinen, Remco Renken, Natasha M. Maurits, Inge Zijdwind. 2008. Relation between muscle and brain activity during isometric contractions of the first dorsal interosseus muscle. *Human Brain Mapping* **29**:10.1002/hbm.v29:3, 281-299. [[CrossRef](#)]
28. Vaia Lestou, Frank E. Pollick, Zoe Kourtzi. 2008. Neural Substrates for Action Understanding at Different Description Levels in the Human Brain. *Journal of Cognitive Neuroscience* **20**:2, 324-341. [[Abstract](#)] [[PDF](#)] [[PDF Plus](#)]
29. R. B. Mars, C. Piekema, M. G. H. Coles, W. Hulstijn, I. Toni. 2007. On the Programming and Reprogramming of Actions. *Cerebral Cortex* **17**, 2972-2979. [[CrossRef](#)]
30. Lewis A. Wheaton, Mark Hallett. 2007. Ideomotor apraxia: A review. *Journal of the Neurological Sciences* **260**, 1-10. [[CrossRef](#)]
31. Juha Salmi, Teemu Rinne, Alexander Degerman, Oili Salonen, Kimmo Alho. 2007. Orienting and maintenance of spatial attention in audition and vision: multimodal and modality-specific brain activations. *Brain Structure and Function* **212**, 181-194. [[CrossRef](#)]
32. Jacinta O'Shea, Heidi Johansen-Berg, Danielle Trief, Silke Göbel, Matthew F.S. Rushworth. 2007. Functionally Specific Reorganization in Human Premotor Cortex. *Neuron* **54**, 479-490. [[CrossRef](#)]
33. M MILLER, J VANHORN. 2007. Individual variability in brain activations associated with episodic retrieval: A role for large-scale databases. *International Journal of Psychophysiology* **63**, 205-213. [[CrossRef](#)]
34. K OGAWA, T INUI, T SUGIO. 2007. Neural Correlates of State Estimation in Visually Guided Movements: an Event-Related fMRI Study. *Cortex* **43**, 289-300. [[CrossRef](#)]
35. Elke Praeg, Michaela Esslen, Kai Lutz, Lutz Jancke. 2006. Neuronal Modifications During Visuomotor Association Learning Assessed by Electric Brain Tomography. *Brain Topography* **19**, 61-75. [[CrossRef](#)]
36. Beatriz Calvo-Merino, Julie Grèzes, Daniel E. Glaser, Richard E. Passingham, Patrick Haggard. 2006. Seeing or Doing? Influence of Visual and Motor Familiarity in Action Observation. *Current Biology* **16**, 1905-1910. [[CrossRef](#)]
37. Mary A. Mayka, Daniel M. Corcos, Sue E. Leurgans, David E. Vaillancourt. 2006. Three-dimensional locations and boundaries of motor and premotor cortices as defined by functional brain imaging: A meta-analysis. *NeuroImage* **31**, 1453-1474. [[CrossRef](#)]
38. N SAHIN, S PINKER, E HALGREN. 2006. Abstract Grammatical Processing of Nouns and Verbs in Broca's Area: Evidence from fMRI. *Cortex* **42**, 540-562. [[CrossRef](#)]
39. M.D. Hesse, C.M. Thiel, K.E. Stephan, G.R. Fink. 2006. The left parietal cortex and motor intention: An event-related functional magnetic resonance imaging study. *Neuroscience* **140**, 1209-1221. [[CrossRef](#)]
40. Agatha Lenartowicz, Anthony R. McIntosh. 2005. The Role of Anterior Cingulate Cortex in Working Memory is Shaped by Functional Connectivity. *Journal of Cognitive Neuroscience* **17**:7, 1026-1042. [[Abstract](#)] [[PDF](#)] [[PDF Plus](#)]
41. Gaëtan Garraux, Mark Hallett, S. Lalith Talagala. 2005. CASL fMRI of subcortico-cortical perfusion changes during memory-guided finger sequences. *NeuroImage* **25**, 122-132. [[CrossRef](#)]
42. Floris P. de Lange, Peter Hagoort, Ivan Toni. 2005. Neural Topography and Content of Movement Representations. *Journal of Cognitive Neuroscience* **17**:1, 97-112. [[Abstract](#)] [[PDF](#)] [[PDF Plus](#)]
43. J. Richard Jennings, Maurits W. van der Molen. 2005. Preparation for Speeded Action as a Psychophysiological Concept. *Psychological Bulletin* **131**, 434-459. [[CrossRef](#)]
44. Andreas Kleinschmidt, Ivan Toni Functional Magnetic Resonance Imaging of the Human Motor Cortex . [[CrossRef](#)]
45. D GORBET, W RICHARDSTAINES, L SERGIO. 2004. Brain mechanisms for preparing increasingly complex sensory to motor transformations. *NeuroImage* **23**, 1100-1111. [[CrossRef](#)]
46. K KANSAKU, T HANAKAWA, T WU, M HALLETT. 2004. A shared neural network for simple reaction time. *NeuroImage* **22**, 904-911. [[CrossRef](#)]
47. F Binkofski. 2004. Motor functions of the Broca's region. *Brain and Language* **89**, 362-369. [[CrossRef](#)]

48. Anna B. Smith, Eric Taylor, Mick Brammer, Katya Rubia. 2004. Neural correlates of switching set as measured in fast, event-related functional magnetic resonance imaging. *Human Brain Mapping* **21**:10.1002/hbm.v21:4, 247-256. [[CrossRef](#)]
49. The Motor System 5-32. [[CrossRef](#)]
50. Alexander M. Gorbach, John Heiss, Conrad Kufta, Susumo Sato, Paul Fedio, William A. Kammerer, Jeffrey Solomon, Edward H. Oldfield. 2003. Intraoperative infrared functional imaging of human brain. *Annals of Neurology* **54**:10.1002/ana.v54:3, 297-309. [[CrossRef](#)]
51. J Grèzes. 2003. Activations related to “mirror” and “canonical” neurones in the human brain: an fMRI study. *NeuroImage* **18**, 928-937. [[CrossRef](#)]
52. 2003. Current Awareness in NMR in Biomedicine. *NMR in Biomedicine* **16**:10.1002/nbm.v16:1, 56-65. [[CrossRef](#)]