

The Effect of Stimulus–Response Compatibility on Cortical Motor Activation

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Stimulus-response compatibility (SRC) is a general term describing the relationship between a triggering stimulus and its associated motor response. The relationship between stimulus and response can be manipulated at the level of the set of stimulus and response characteristics (set-level) or at the level of the mapping between the individual elements of the stimulus and response sets (element-level). We used functional magnetic resonance imaging (fMRI) to investigate the effects of SRC on functional activation in cortical motor areas. Using behavioral tasks to separately evaluate set- and element-level compatibility, and their interaction, we measured the volume of functional activation in 11 cortical motor areas, in the anterior frontal cortex, and in the superior temporal lobe. Element-level compatibility effects were associated with significant activation in the pre-supplementary motor area (preSMA), the dorsal (PMd) and ventral (PMv) premotor areas, and the parietal areas (inferior, superior, intraparietal sulcus, precuneus). The activation was lateralized to the right hemisphere for most of the areas. Set-level compatibility effects resulted in significant activation in the inferior frontal gyri, anterior cingulate and cingulate motor areas, the PMd, PMv, preSMA, the parietal areas (inferior, superior, intraparietal sulcus, precuneus), and in the superior temporal lobe. Activation in the majority of these areas was lateralized to the left hemisphere. Finally, there was an interaction between set and element-level compatibility in the middle and superior frontal gyri, in an area co-extensive with the dorsolateral prefrontal cortex, suggesting that this area provided the neural substrate for common processing stages, such as working memory and attention, which are engaged when both levels of SRC are manipulated at once. © 2001

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INTRODUCTION

The time required to evoke a motor response to a stimulus is determined in part by the relation between

stimulus and response, referred to as stimulus-response compatibility (SRC; Fitts and Seeger, 1953; Fitts and Deininger, 1954). This SRC is dependent on relations at the *set level*—that is, the general relation between the characteristics of the stimulus and response sets, also described as congruence (Fitts and Seeger, 1953) or dimensional overlap (Kornblum *et al.*, 1990)—and at the *element level*—that is, the pairing between the individual elements of the sets (or mapping). Conceptually, one can imagine that the determinants of SRC are part of the sensorimotor transformation which must be effected before a motor response to a visual stimulus is executed. In dealing with SRC we have adopted the terminology and model of Kornblum and others (Kornblum *et al.*, 1990; Zhang and Kornblum, 1998). This approach treats the issue of SRC not as a collection of properties specific to particular tasks but in terms of a number of basic common cognitive mechanisms.

SRC has robust effects on response time. In general, the shortest response time is for sets of stimuli and responses which have a high degree of dimensional overlap (or congruence) at the set-level, and for which the individual elements of the sets are directly mapped to one another. For example, during direct movements to spatial targets, both the stimulus and the response are within the spatial domain and the response is directly mapped onto the stimulus (target). An increase in response time occurs when stimulus and response have lower degrees of dimensional overlap (Fitts and Seeger, 1953; Brainard *et al.*, 1962), such as a symbolic cue that evokes a motor response, or when the mapping between the stimulus and response sets is other than direct (Fitts and Deininger, 1954; Sanders, 1967; Sternberg, 1969). Furthermore, response time effects can be analyzed according to Sternberg's additive-factors method (Sternberg, 1969) to provide information about the stages of mental processing associated with the different SRC dimensions. The results of one such analysis suggest that there is at least one stage of

processing that is involved in decoding both set- and element-level SRC relationships (Dassonville *et al.*, 1999).

Manipulating the level of SRC has been shown to be associated with changes in brain activation in humans (Pardo *et al.*, 1990; Iacoboni *et al.*, 1996; Taylor *et al.*, 1994; Tagaris *et al.*, 1998). The majority of studies have examined the functional correlates of manipulating SRC at the element-level (i.e. using different mapping rules), rather than at the set-level. In general, changes in the relation between elements which decrease the level of SRC have resulted in increased activation in the superior parietal lobule bilaterally (Iacoboni *et al.*, 1996; Tagaris *et al.*, 1997; Kosslyn *et al.*, 1998), and in a network of areas including the precentral gyrus and parietal cortex (Tagaris *et al.*, 1998; Kosslyn *et al.*, 1998). These areas are known to be involved in visuo-motor transformations (Johnson *et al.*, 1996; Andersen *et al.*, 1997; Wise *et al.*, 1997). By contrast, there is less information about the neural substrate of manipulating SRC at the set-level. Several studies have examined the neural substrate of learning arbitrary visuo-motor associations (Hazeltine *et al.*, 1997; Grafton *et al.*, 1998; Deiber *et al.*, 1997; Sakai *et al.*, 1999) for which the dorsal premotor cortex appears to be particularly important. Our focus is somewhat different in that we use an over-learned symbolic stimulus rather than an arbitrary association to manipulate set level compatibility.

In the current study we hypothesized that a core network of cortical motor areas involved in visuomotor transformations would be activated irrespective of the level at which the SRC was manipulated and that additional areas would be activated specifically for each of the individual levels. We further hypothesized that the interaction between different types of SRC, which we have documented behaviorally (Dassonville *et al.*, 1999), would be reflected in an interaction in the activation of areas in the frontal cortex known to be involved in visuospatial memory and attention, as these processes are likely to be engaged when both levels of SRC are manipulated at once. To test these hypotheses, we performed functional MR imaging while subjects used a joystick to control movement of a cursor to spatial targets in conditions in which SRC was manipulated either at the set level (spatial ν symbolic visual instruction), the element level (direct ν counter-clockwise movement to targets) or both.

MATERIALS AND METHODS

Behavioral task. Eight subjects (7 women and 1 man; aged 21 to 32 years, mean 27.75) gave their informed consent to participate in the study, which was approved by the University of Minnesota Institutional Review Board. All subjects were right-handed as determined by the Edinburgh inventory (Oldfield,

1971). Subjects moved a joystick (Measurement Systems Inc., Norwalk, CT) with the right hand to control a cursor on a computer screen visible via a small mirror positioned in the magnet directly in front of the eyes. To begin each trial, the subject moved the cursor into a small annulus at the center of the screen. After a random delay of 100 to 300 ms, a visual cue was presented, instructing the subject to move to one of eight annuli distributed about a larger circle (Fig. 1). In separate blocks of trials, the cue was either spatial (the filling of one of the outer annuli) or symbolic (a one or two letter abbreviation indicating a compass direction; e.g., N = up, NE = up/right, E = right, etc.). In addition, the relationship between the cued direction and the appropriate motor response was varied between blocks. This relationship was either a direct mapping between stimulus and response (i.e., subject was to move toward the annulus indicated by the cue) or a counter-clockwise mapping (ccw; i.e., toward the annulus positioned 90 degrees counter-clockwise from the direction indicated by the cue). For a given trial to be considered correct, the cursor was required to pass through the ring of target annuli with a directional error of less than 22.5 degrees. Trials were presented at 3-s intervals.

Experimental design. Before each subject was placed in the magnet, he or she performed short practice blocks with each of the 4 task combinations (spatial/direct, spatial/ccw, symbolic/direct and symbolic/ccw). Each practice block was continued until the subject had responded correctly in 16 trials. Each of 3 scanning periods comprised five 60-s blocks of trials. Trials in the first (fMRI images 1-20), third (images 41-60) and fifth (images 81-100) blocks of each scanning period were of the spatial/direct type. Trials in the second (images 21-40) and fourth (images 61-80) blocks were of the spatial/ccw, symbolic/direct or symbolic/ccw types. Each block was prefaced by a 2-s text instruction indicating the upcoming type of trials (e.g. SPATIAL DIRECT). Scanning periods were separated by rest periods of 3 to 4 min. (Additional experimental tasks were performed by each subject; preliminary results from these tasks have been described elsewhere; Dassonville *et al.*, 1997).

Magnetic resonance imaging. We obtained magnetic resonance images in a 4 Tesla whole-body system (SIS Co., Palo Alto, CA, and Siemens, Erlangen, Germany) with an actively shielded head gradient coil insert and a quadrature head coil. T_1 -weighted anatomic images [multislice turboFLASH, echo time (TE) = 3 ms, repetition time (TR) = 7 ms, 128×128 pixels, field of view (FOV) = 24×24 cm², 5 mm slice thickness] were collected to determine the appropriate volume for the subsequent images. To allow an accurate overlay of the functional images (Kim *et al.*, 1996), T_1 -weighted anatomic images were also collected in the

transverse plane with echo planar imaging (4 segment EPI, TE = 8 ms, TR = 42 ms/segment and 3 s/image, inversion time = 1.2 s, 128×128 pixels, FOV = 24×24 cm², 5 mm slice thickness). Three-dimensional anatomic images were acquired with a fast segmented 3-D Modified Driven Equilibrium Fourier Transform (MDEFT) gradient-recalled echo sequence [TE = 3 s, TR = 5 s, tau = 1.1 s, 6 segments (Ugurbil *et al.*, 1993; Lee *et al.*, 1995), with an isotropic resolution of $0.9375 \times 0.9375 \times 0.9375$ mm³]. Blood oxygen level dependent (BOLD) based functional images (TE = 25 ms, TR = 50 ms and 3 s/image, 64×64 pixels, FOV = 24×24 cm², 5 mm thickness) were obtained with blipped EPI.

Functional image processing for all analyses. Functional images were screened for motion artifact by plotting the location of the center of mass in 3 dimensions, and by visually inspecting the images using a Cine movie playback. Images found to contain excessive motion were not analyzed further; in such cases the whole data set was discarded. Of the 24 scans collected (8 subjects \times 3 scans), 3 were discarded due to excessive motion. Corrections for physiologic fluctuations were performed (Hu *et al.*, 1995; Le and Hu, 1996) using waveforms of respiration and cardiac cycles collected and digitized during the functional scans. The functional data were zero-filled to 128×128 pixels and then Fourier-transformed, resulting in a nominal in-plane resolution of 1.875×1.875 mm². To eliminate large vessel contributions, we masked voxels with signal intensities having a coefficient of variation greater than 3% during the control periods (Kim *et al.*, 1994). Baseline drifts were eliminated for each voxel by determining the linear relationship of the intensity over time during the spatial/direct control periods, and subtracting this trend from the entire time course of activation.

Analysis based upon anatomic regions of interest. Signal intensities were smoothed in the spatial domain using a gaussian filter (FWHM = 2 mm). Activated voxels were determined by t-tests that compared the intensity of the BOLD signal during the task (spatial/ccw, symbolic/direct or symbolic/ccw) periods and the spatial/direct control periods. Specifically, this was accomplished with two t-tests which compared i) the activation during the second block of trials (first task period, images 33-40) with those from the first block (first control period, images 3-20 of the 100 image scanning period) and the first half of the third block (middle control period, images 43-50), and ii) the activation during the fourth block (second task period, images 63-80) with those from the last half of the third block (middle control period, images 51-60) and the fifth block (final control period, images 83-100). The first two images from each block were ignored to prevent transition effects from distorting the maps. To be

considered significantly active, a voxel was required to have a resultant t-value that exceeded a threshold of 4.0, and to be a member of a contiguous cluster of 8 or more similarly activated voxels. Voxels determined to be active using these criteria ($P < 0.005$, after correction for multiple comparisons; Xiong *et al.*, 1995) formed a functional activation map that was overlaid onto the EPI anatomic images. The functional maps created in this way can be interpreted as showing those voxels that have a significantly greater level of activation associated with a S-R incompatibility at the set congruency (symbolic/direct) or mapping level (spatial/ccw), or both (symbolic/ccw), in comparison to the compatible spatial/direct control task.

For the ANOVA examining the main effects of set congruence and mapping and their interaction we required four sets of variables, one associated with the performance of each task. However, in the case of three of the tasks the activation maps we produced were in relation to the spatial/direct task which was essentially subtracted as a control. Therefore, we created an activation map for the spatial/direct condition in a manner identical to that for the other task conditions (i.e., by subtracting the activation of spatial/direct "control" periods from that of spatial/direct "task" periods). By using this task as its own control, we created a map that reflected the inherent variability in the functional activation; in statistical terms, this variability mirrors the Type 1 errors that are present in the activation maps of the other tasks. This map was not intended to reflect the total activation in the spatial/direct task, but it did allow for a two-factor ANOVA to test the effects of set congruency and mapping over and above the activation of the spatial/direct control task. Using this self-difference in the ANOVA still yielded *unbiased estimates* of all factorial effects.

Specifically, the spatial/direct map we used in the ANOVA was created using t-tests comparing the activation during the third block of trials (middle control period, images 43-60) with the activation during the first block (first control period) and the fifth block (final control period) during two (randomly selected) of the three scanning sessions from each subject. To equalize the degrees of freedom involved in the creation of this map and those of the spatial/ccw, symbolic/direct and symbolic/ccw tasks, only the last half of the first control period (images 11-20), or the first half of the final control period (images 83-90), were used. We then thresholded (t-value > 4.0) the voxels and applied a spatial contiguity criterion (spatial extent > 8 voxels), to derive the final activation map for this condition.

Regions of interest were delineated in the EPI anatomic images using anatomic landmarks in individual subjects. Motor cortex was defined as the volume of cortex that included the posterior half of the precentral gyrus (including the anterior bank of the central sulcus). Premotor cortex was defined by an anterior bor-

Set-level SRC

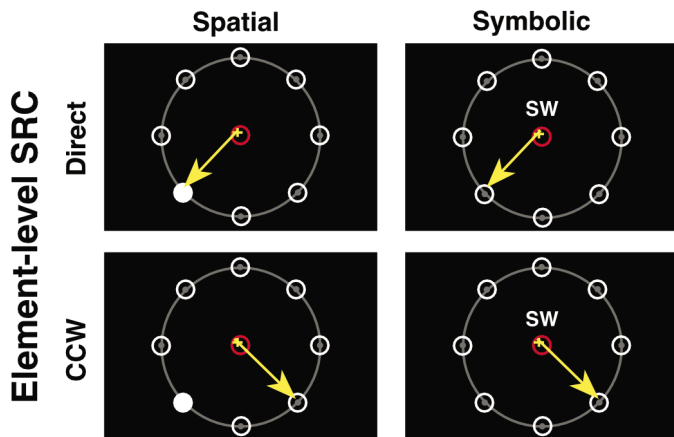


FIG. 1. Examples of the four experimental tasks using the two stimulus sets (spatial and symbolic) and the two types of mapping (direct and 90° counterclockwise rotation, ccw). Arrow denotes the appropriate response direction for the stimulus depicted in the different task conditions. *Note:* the arrow was not seen by the subjects during the task.

der half way between the frontal pole and the central sulcus terminating ventrally in the intersection of the precentral sulcus and the sylvian fissure and a posterior border defined by the anterior border of the motor cortex. Premotor cortex was further separated into dorsal and ventral premotor areas, using as a dividing line the Talairach coordinate ($Z = 41$) that fell halfway between the centers of mass for the dorsal and ventral premotor areas seen in the spatially-congruent activation maps (see below). Supplementary motor area (SMA) was limited to the cortex on the medial wall of the hemisphere, extending from the superior pole to the cingulate sulcus, excluding the dorsal bank of the cingulate sulcus. The posterior boundary was halfway between the extension of the central and precentral sulci onto the medial surface and the anterior boundary was defined by vertical line drawn through the anterior commissure (VCA line). Cingulate was defined as the ventral and dorsal bank of the cingulate sulcus and the cingulate gyrus ventral to the SMA. Pre-supplementary motor area (preSMA) was the extension of the SMA rostral to the VCA line to include sectors C and D in Talairach space (Talairach and Tournoux, 1988), from the superior pole to the cingulate sulcus, excluding the dorsal bank of the cingulate sulcus. Anterior cingulate was defined as the ventral and dorsal bank of the cingulate sulcus and the cingulate gyrus ventral to the preSMA. The parietal lobe was divided into 4 regions of interest. On the medial wall, the precuneus extended from the cingulate sulcus to the parieto-occipital sulcus, and ventrally to the subparietal sulcus. On the lateral surface, the superior parietal lobule extended anteriorly to the postcentral sulcus, ventrally to the lip of the intraparietal sulcus,

posteriorly to the parieto-occipital sulcus. Intraparietal sulcus included both the lateral and medial walls of the sulcus. Inferior parietal was the portion of the parietal cortex inferior to the intraparietal sulcus and superior to the sylvian fissure. In addition to these areas which are most likely to be related to motor and visuomotor function, we also defined a number of other regions of interest in the frontal and temporal lobes. In the frontal lobe, the superior, middle and inferior frontal gyri were delineated, each extending rostrally from the premotor regions of interest to the frontal pole. In the temporal lobe, we examined the activation in the superior temporal gyrus.

We determined the number of voxels activated within each region of interest for each of the scanning periods. For statistical tests, these values were transformed using a square root transformation for counts to stabilize the variance and normalize the distribution, and outliers were removed (Snedecor and Cochran, 1989). Comparisons of set-level (spatial vs. symbolic) and element-level (direct vs. ccw transformation) SRC effects were tested with a full-factorial analysis of variance (ANOVA, $P < 0.01$).

Analysis based upon spatially congruent activation maps. In order to determine the spatial congruence of activation across the subjects, we performed a secondary analysis by warping the activation maps from each subject onto a standardized anatomic image of the brain. An additional advantage of this approach is that it allowed us to define the focus of activation in areas for which we had not drawn detailed regions of interest (e.g., extrastriate areas).

To allow for a better spatial congruence in spite of subtle subject-to-subject anatomic differences, a more extensive spatial filter was employed (Gaussian, FWHM = 6 mm). For this analysis, activated voxels were determined by a cross-correlation of the functional time course with a reference waveform (modified boxcar design) modeled after the time course of the experimental task. To be considered significantly activated, a voxel was required to have a correlation coefficient that exceeded 0.4, and to be a member of a contiguous cluster of 8 or more similarly activated voxels. Voxels determined to be activated using these criteria ($P < 10^{-7}$, after correction for multiple comparisons; Xiong *et al.*, 1995), formed a functional activation map that was subsequently warped into Talairach space (Strupp, 1996). Warped maps were combined across subjects, forming a single map in which a voxel was considered active only if the corresponding voxels were active in the maps of at least 4 of the 8 subjects. The three resulting maps (symbolic/direct, spatial/ccw and symbolic/ccw, with the common activation of the spatial/direct control effectively subtracted) were overlaid onto the 3-D MDEFT anatomic image (also warped to Talairach coordinates) of a typical subject.

RESULTS

Behavior. The reaction time for the spatial/direct control tasks was 420 ± 10 ms (mean \pm s.e.). The reaction times for the experimental tasks were as follows: symbolic/direct (869 ± 86 ms), spatial/ccw (786 ± 34 ms), and symbolic/ccw (1481 ± 108 ms). This pattern of reaction times, increasing with more complex stimulus-response relationships, is in agreement with the results of a behavioral study performed using identical tasks (Dassonville *et al.*, 1999).

Element-level compatibility effects. Using a 2×2 factorial design, there was a significant ($P < 0.01$) main effect of element-level compatibility (i.e., mapping) in the following areas: inferior parietal, intraparietal sulcus, superior parietal, precuneus, dorsal (PMd) and ventral (PMv) premotor areas, and preSMA. In each of these areas, there was a greater activation when the subjects were required to respond in a clockwise direction, as compared to a direct response. None of the other areas that were also examined showed any effect of element-level compatibility: inferior, middle and superior frontal cortex, anterior cingulate, cingulate, motor cortex, SMA and superior temporal gyrus.

Set-level compatibility effects. There was a significant ($P < 0.01$) main effect of set-level compatibility in inferior frontal cortex, anterior cingulate, cingulate, PMv, PMd, preSMA, inferior and superior parietal cortex, intraparietal sulcus, precuneus, and superior temporal gyrus. The locus of activation in the inferior frontal cortex was predominantly in Brodman area (BA) 44 and 45. In each of these areas, there was a greater activation when the subjects responded to symbolic cues, as compared to spatial cues. The remaining areas showed no effect of set-level compatibility: superior frontal cortex, motor cortex, or SMA.

Interaction between set- and element-level effects. Only two areas showed a significant ($P < 0.01$) interaction between element and set level compatibility: middle and superior frontal gyri. In both gyri, this interaction was manifest as a large activation when both levels of SRC were manipulated (symbolic/ccw), with little or no activation when set- (symbolic/direct) or element-level SRC (spatial/ccw) were manipulated independently. The locus of activation in the middle and superior gyri was primarily in BA 9 with little involvement of BA 46 or 8.

Spatially congruent activation at the element level. The averaged maps of activation across subjects (see Methods) were constructed so that we could define the center of mass of the spatially congruent pixels in those areas found to be activated on the basis of the ANOVA, determine the hemispheric distribution of the activated areas, and examine activation in areas not originally defined in our region of interest analysis (e.g. extrastriate areas). For element-level manipulations of

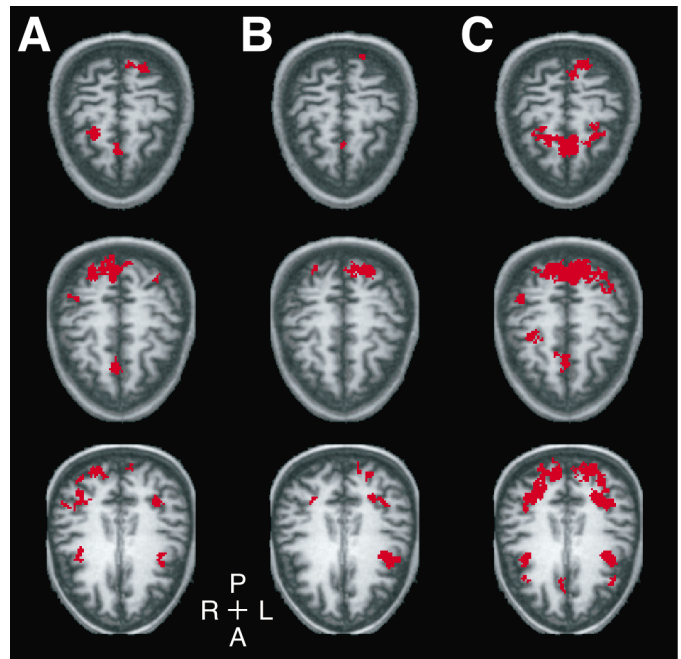


FIG. 2. Spatially congruent activation at three different anatomic levels in the (A) spatial/ccw, (B) symbolic/direct, and (C) symbolic/ccw tasks. For the volume of activation in specific areas, see Tables 1–3.

SRC, the preponderance of activation was in the right hemisphere (Fig. 2A and Table 1); this is particularly evident in the intraparietal sulcus, PMd, and preSMA. Table 1 also summarizes other areas of activation, in extrastriate cortex, that lay outside of the anatomically defined regions of interest that were the main focus of this investigation.

Spatially congruent activation at the set level. For set-level manipulations of SRC, the preponderance of spatially congruent activation is in the left hemisphere; this is particularly true for the PMv and to a lesser extent for the superior parietal and intraparietal sulcus (See Fig. 2B and Table 2). Table 2 also lists areas of activation in extrastriate and insular cortex that were affected by manipulations of set-level SRC.

Spatially congruent activation during the combined task. When element- and set-level incompatibilities were combined in the symbolic/ccw task, there was a general increase in activation in the areas already identified as being involved in either set- or element-level compatibility alone (see Fig. 2C and Table 3). In addition, the insula and several extrastriate areas, which were not included in the initial regions of interest, showed activation when the task involved incompatibility at both the set and element levels (Table 3).

Spatial overlap between set and element-level activations. The voxels activated with manipulations of set- and element-level compatibility tended to be quite spatially distinct, with a segregation best appreciated on

TABLE 1

A. Regions of interest affected by element-level compatibility						
Region of interest	Left hemisphere			Right hemisphere		
	Talairach (<i>x, y, z</i> ; mm)	Anatomic Location (Brodmann Area)	Volume (voxels)	Talairach (<i>x, y, z</i> ; mm)	Anatomic Location (Brodmann Area)	Volume (voxels)
Dorsal premotor				-25, -5, 51	BA6	140
Ventral premotor	36, 1, 33	BA6	73	-39, 0, 28	BA6	147
Superior parietal	12, -72, 43	BA7	296	-17, -73, 40	BA7	452
Intraparietal sulcus	32, -53, 37	BA39	169	-30, -62, 37	BA39	849
	32, -70, 35	BA19	19			
Precuneus	6, -71, 42	BA7	191	-10, -70, 41	BA7	296
Pre-SMA				-6, 15, 46	BA6	149
B. Other regions affected by element-level compatibility						
Extrastriate				-25, -77, 29	BA19	113
				-37, -80, 21	BA19	10
				-30, -84,		
				-10	BA18	23

the basis of hemisphere (Figs. 3A and B). The voxels activated in the different conditions are color coded: those activated only in the element-level compatibility task are red, only in the set-level compatibility are green, and those active in both tasks are yellow. The amount of overlap (yellow) is minimal, with some shared voxels in both parietal areas and in the left ventral premotor cortex. Even within individual areas in the same hemisphere (e.g., PMv) the voxels activated in the different conditions tend to be spatially segregated (Fig. 3B).

DISCUSSION

The factorial experimental design used in this study enabled us to determine the cortical areas activated as main effects of set- and element-level compatibility,

and their interaction. The principal findings were as follows: (i) both types of SRC led to the activation of a core network of areas in the parietal and frontal cortex; (ii) additional areas (inferior frontal, superior temporal, anterior cingulate and cingulate) were activated only during the set-level SRC; (iii) element-level SRC was associated with lateralization of activation to the right hemisphere while set-level SRC was lateralized to the left; and (iv) an interaction effect between both types of SRC was seen in the middle and superior frontal gyri, and in the insula.

Methodological issues. In the present investigation, we determined the areas affected by each of the SRC factors in two ways. In the region-of-interest analysis, the volume of activation in the different conditions was compared using an ANOVA model within

TABLE 2

A. Regions of interest affected by set-level compatibility						
Region of interest	Left hemisphere			Right hemisphere		
	Talairach (<i>x, y, z</i> ; mm)	Anatomic Location (Brodmann Area)	Volume (voxels)	Talairach (<i>x, y, z</i> ; mm)	Anatomic Location (Brodmann Area)	Volume (voxels)
Ventral premotor	38, 1, 30	BA6	293			
Superior parietal	16, -69, 44	BA7	170	-18, -78, 36	BA7	61
Intraparietal sulcus	29, -56, 35	BA39	309	-29, -61, 38	BA39	119
Precuneus	8, -69, 42	BA7	79			
Pre-SMA				-4, 10, 49	BA6	9
B. Other regions affected by set-level compatibility						
Extrastriate	23, -76, 24	BA18	402	-35, -88, -4	BA18	133
	27, -83, -5	BA18	147			
Insula	42, 7, 12	BA13	16			

TABLE 3

A. Regions of interest affected when set- and element-level compatibility are varied simultaneously						
Region of interest	Left hemisphere			Right hemisphere		
	Talairach (x, y, z; mm)	Anatomic location (Brodmann Area)	Volume (voxels)	Talairach (x, y, z; mm)	Anatomic location (Brodmann Area)	Volume (voxels)
Dorsal premotor	23, -2, 51	BA6	223	-28, -4, 49	BA6	265
Ventral premotor	36, 0, 33	BA6	237	-41, 4, 31	BA9	193
	41, 4, 20	BA9	21			
Superior parietal	13, -72, 41	BA7	701	-19, -72, 39	BA7	483
Intraparietal sulcus	27, -63, 36	BA7	1050	-31, -60, 35	BA39	891
Precuneus	3, -68, 42	BA7	533	-11, -71, 38	BA7	432
Pre-SMA/anterior cingulate	3, 10, 48	BA6	216	-6, 12, 44	BA6	487
Middle frontal gyrus	39, 22, 29	BA9	75	-39, 25, 34	BA9	77
				-31, 33, 28	BA9	10
				-43, 22, 24	BA46	25
				-38, 35, 19	BA10	11
B. Other regions affected when set- and element-level compatibility are varied simultaneously						
Extrastriate	25, -78, 26	BA18	116	-28, -77, 26	BA19	68
	28, -80, 06	BA18	46	-32, -81, 14	BA18	67
	29, -82, -5	BA18	19	-32, -90, 5	BA18	74
	35, -65, -12	BA19	36	-25, -77, -12	BA19	38
Insula	44, 08, 13	BA13	8	-48, 7, 11	BA13	8
	30, 18, 9	BA13	89	-32, 17, 6	BA13	217

regions of interest defined with respect to the anatomical landmarks of individual subjects. In the second analysis, data from individual subjects were warped into Talairach space and combined, yielding a map showing the spatially-congruent activation across subjects for each of the separate task conditions. Although there was a general agreement in the findings with these two analyses, there was not an exact concordance; in a few cases, areas found to be activated using the ANOVA did not show congruent activation across subjects. Because the factorial design of the experiment was particularly suited for an analysis by ANOVA, and because the determination of activation within regions of interest is less dependent on spatial filtering and more forgiving of idiosyncrasies in the anatomy of individual subjects, we feel that the region-of-interest analysis was the most suitable method to determine the pattern of activation associated with each of the SRC factors.

The method of analysis based on spatial congruence in the activation across subjects enabled us to address a different but related set of issues. This secondary analysis was performed so that we could determine the spatial location of activated regions in terms of the Talairach coordinate system to allow for an easy comparison with the published results from other laboratories. It allowed us to comment on the hemispheric distribution of the activation. Finally, it also provided us with the opportunity to examine areas of activation that cannot be easily segregated into regions of interest using anatomical landmarks (e.g., extrastriate areas).

Common frontoparietal network subserves both types of SRC. There is a wealth of evidence in both the monkey (Johnson *et al.*, 1996; Wise *et al.*, 1997) and in the human (Lacquaniti *et al.*, 1997) that suggests that a network of cortical areas in the parietal and frontal lobes is intimately involved in visual-spatial operations. In essence, to perform any movement to a visual target or under visual guidance, the relevant visual information needs to be accessed by the motor areas in the frontal lobe. The visual information from the primary visual areas reaches the premotor areas of the frontal lobe via a complicated relay which first involves areas PO and MT/MST which project in turn to areas surrounding the intraparietal sulcus (MIP, LIP, VIP, 7a, 7b) before forming synapses with neurons in PMd and PMv (Johnson *et al.*, 1993, 1996) and to a lesser extent with primary motor cortex. The extensive nature of this network is related, in part, to the fact that visual signals need to be transformed into the appropriate frame of reference for motor action (for review see Andersen, 1997; Lacquaniti *et al.*, 1997).

As regards the activation of subareas within the frontal and parietal cortex in the present investigation, all areas of the parietal cortex were activated during performance of tasks involving each level of SRC. Lesions of the posterior parietal cortex in humans are known to lead to deficits during the performance of tasks involving spatial operations (Critchley, 1953; Perenin and Vighetto, 1988). The posterior parietal cortex, which contains a multi-modal representation of space, is essential for visuomotor integration, and may

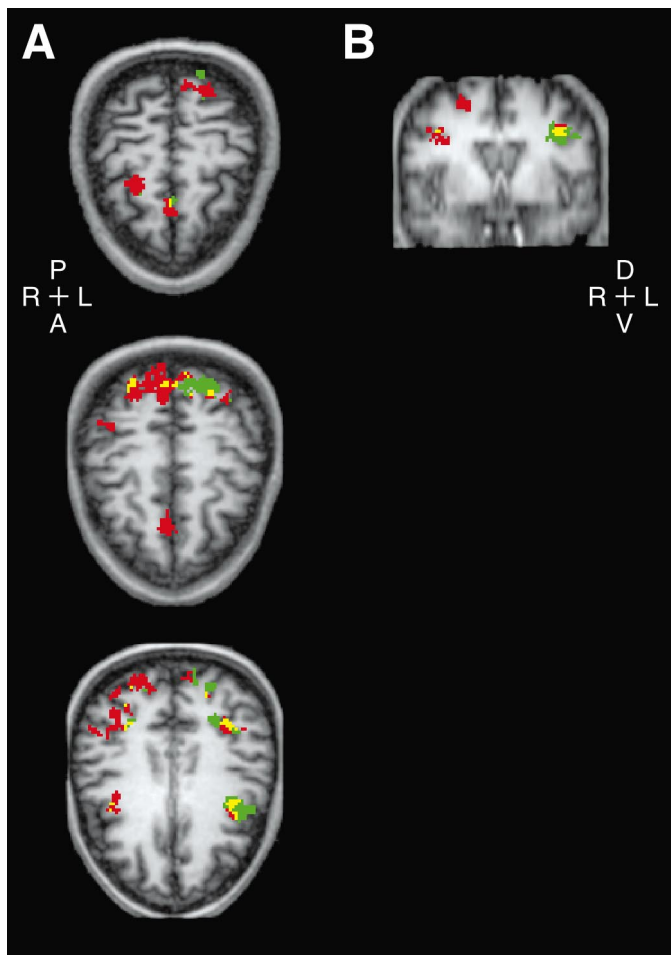


FIG. 3. (A) Spatial overlap in areas activated when either set-level (green voxels) or element-level (red voxels) SRC are manipulated separately, plotted in the same transverse sections depicted in Fig. 2. Voxels activated with both manipulations are shown in yellow. (B) Activation plotted in a coronal section through PMv and PMd. Distinct subregions within areas were activated in the different tasks; this is particularly evident in the left ventral premotor area which is primarily active for the set level SRC task.

be activated during relatively simple visually guided movement (Andersen *et al.*, 1997; Nishitani *et al.*, 1999). It is not surprising, therefore, that the posterior parietal cortex is activated when the relation between the stimulus and response was rendered more complex as it was during manipulation of either level of SRC.

We also found prominent activation in the PMv and PMd. Both of these areas receive visual input from different parts of the parietal lobe and the type of visual information conveyed in each of these channels may be different (see Wise *et al.*, 1997). These areas also receive sensory input about the state of the limb which are then integrated with the visual signals to produce an appropriate motor output. Despite the similarities between the areas, there are distinct functional and even structural differences. The functional differences between the two areas may be determined,

at least in part, by the type of somatosensory information they receive. In PMd, cells are modulated by proprioceptive input and by the behavioral significance of visual stimuli (see Wise *et al.*, 1997). In PMv, many cells are bimodal in that they have both tactile and visual receptive fields which move with the body part (Graziano *et al.*, 1994, 1997; Fogassi *et al.*, 1996). Such apparent functional differences have led to the suggestion that PMd is primarily involved in sensorimotor mapping (Graziano and Gross, 1998; Wise *et al.*, 1997) while PMv is engaged during visually controlled movements in space (Graziano and Gross, 1998). Our results do not support a specific role for PMd in sensorimotor mapping as both the premotor areas were activated during our tasks. Rather, the results suggest that both areas are engaged during the process of visuomotor mapping. Nevertheless, it may be difficult to extrapolate our findings to those documented in the monkey as the homology between monkey and human premotor areas is still not clear, although putative boundaries between subareas have been suggested (Fink *et al.*, 1997).

The preSMA, although not commonly thought of as being part of the frontoparietal network referred to above, was consistently activated when SRC was manipulated at either level. The preSMA (Matsuzaka *et al.*, 1992; Tanji, 1994) is activated during more complex forms of motor output, such as during online changes to the motor plan (Matsuzaka and Tanji, 1996), the free selection of movements (Deiber *et al.*, 1991; Rao *et al.*, 1997) and during sequence learning (Hikosaka *et al.*, 1996). A recent study has shown that it is invariably activated during tasks which involve learning simple visuomotor associations (Sakai *et al.*, 1999); this property may underlie its engagement during sequence learning. Our results suggest that preSMA continues to be active during tasks which use novel visuomotor associations even when there is little behavioral evidence of learning as was the case in our subjects.

Functional substrates of element-level compatibility. Several imaging studies have explicitly addressed the issue of SRC at the level of the mapping between the individual stimulus and response elements (Iacoboni *et al.*, 1996, 1998; Taylor *et al.*, 1994). Perhaps the most common forms of SRC studied using functional imaging have been mental rotation (Kosslyn, 1980) and the Stroop effect (Stroop, 1935), although the effects of these processes on brain activation have been examined in their own right and not explicitly in the context of SRC. The Stroop task has been studied with functional imaging (Pardo *et al.*, 1990; Taylor *et al.*, 1994, 1997; Bush *et al.*, 1998) and while it does represent a form of stimulus-response incompatibility at the element level, it has been used primarily to study selective attention and response selection. The results of

these studies are difficult to interpret from the viewpoint of SRC because of an inherent interference between relevant and irrelevant stimulus factors in the task (Pardo *et al.*, 1990; Taylor *et al.*, 1994). Mental rotation, whether it be of visual objects (Shepard and Metzler, 1971; Kosslyn, 1980), or stimuli indicating directions (Georgopoulos *et al.*, 1986), is a form of element-level SRC as the stimulus needs to be transformed by rotation before a response is possible. The mental rotation of stimulus direction, such as that in the current study, has been associated with activation bilaterally in the parietal cortex, extrastriate cortex, cerebellum, anterior cingulate, and unilaterally contralateral to the responding hand in the precentral gyrus, and the middle frontal gyrus (Tagaris *et al.*, 1998). Our results are consistent with these findings and also with the pattern of functional activation seen during the mental rotation of complex objects (Cohen *et al.*, 1996; Tagaris *et al.*, 1998). Other forms of SRC in which subjects respond to lateralized visual or auditory targets with the contralateral hand (Iacoboni *et al.*, 1996, 1998) have been associated with activation in two regions of the posterior parietal cortex (superior parietal lobule and intraparietal sulcus) and in the rostral portion of the dorsal premotor area (Iacoboni *et al.*, 1996, 1998) which were also active in the current study.

A striking feature of the current experiment was the extent to which activation was lateralized to the right hemisphere in the conditions manipulating element-level compatibility. This lateralization was especially evident in the PMd, the intraparietal sulcus, and the preSMA. Although present it was less marked for the superior parietal cortex. The right sided predominance in the parietal areas is consistent with the role of the right parietal cortex in the more cognitive aspects of visuospatial function (Hecaen *et al.*, 1956; Jeannerod, 1988; McFie *et al.*, 1950). The direction of the asymmetry, however, is at variance with the finding of Iacoboni and colleagues using a different SRC task (Iacoboni *et al.*, 1996, 1998), in which the subjects did not perform visuomotor transformation as such but merely assigned a responding hand to the lateralized stimulus; perhaps, the left parietal cortex may be more important for "motor" assignments (Perenin and Vighetto, 1988). The lateralization of activation in the intraparietal sulcus in our study may relate to its role in mediating both spatial and non spatial attention (Coull and Frith, 1998), although there is no reason to expect that the attentional demands of the element-level compatibility should differ significantly from that at the set-level in which the activation was lateralized to the left. The lateralization in the PMd has received less attention than that of the parietal areas, but consistent activation lateralized to the right PMd has been seen during the explicit acquisition of visuomotor sequences (Grafton *et al.*, 1995; Hazeltine *et al.*, 1997). Our find-

ing in which activation in the right PMd was seen exclusively during element-level compatibility tasks suggest that this area is indeed a substrate for visuomotor mapping (Graziano and Gross, 1998; Wise *et al.*, 1997) at the level of the individual stimulus-response elements, and that this property is lateralized to the right in humans. Little or no information is available about lateralization in the pre-SMA as the majority of studies in human subjects involved task performance with one hand only as in the current study.

Functional substrates of set-level compatibility. There is a fundamental difference between re-mapping a response into a different coordinate frame—in other words, a visuomotor transformation as in the element-level compatibility task—and translating a symbolic stimulus into a spatial frame of reference that is congruent with the response frame. We have no way of determining exactly how the translation was effected by the subjects, but it presumably first involved the translation of the symbol into the appropriate word (e.g., "North" for "N"), the interpretation of the word, and the transformation of this information into the spatially appropriate motor output. Although there is a vast literature on the functional correlates of semantic processing in the context of language, and a sizable body of work dealing with the learning of arbitrary visuomotor associations (Hazeltine *et al.*, 1997; Grafton *et al.*, 1998; Deiber *et al.*, 1997; Sakai *et al.*, 1998, Sakai *et al.*, 1999) there are no functional imaging studies which directly address the issue of the activation associated with the interpretation of symbols similar to those used in the current task. There is, however, a case report of a pianist who became unable to interpret the meaning of musical notation, and translate it into appropriate motor output after a lesion in the left parieto-occipital area (Horikoshi *et al.*, 1997) and it is interesting to note that in the current study the predominant activation in the parietal lobe was also on the left side.

The following areas were engaged in the set-level compatibility tasks but not in the element-level compatibility: inferior frontal gyri, superior temporal gyrus, cingulate, and anterior cingulate cortex. We would have predicted that language-related brain areas, particularly those involved in semantic decoding, would be recruited during the set-level compatibility task. The inferior frontal gyrus encompasses Broca's area and, based on the classic understanding of language areas, it is not entirely expected that it would be activated during a task that did not involve the overt production of language but rather the interpretation of a symbol. However, since the advent of functional imaging studies it has become clear that large portions of the anterior frontal lobe are involved in language processing (see Binder *et al.*, 1997; Fiez and Petersen, 1998). The results of these studies suggest that many areas, in-

cluding the classic Broca's area in the inferior frontal gyrus may be engaged during language tasks which are predominantly "receptive" or involving the interpretation of semantic/lexical content (Binder *et al.*, 1997; Demonet *et al.*, 1992; Bottini *et al.*, 1994; Price *et al.*, 1996). The involvement of the superior temporal gyrus, locus of the classic Wernicke's area, is perhaps less surprising as lesions of this area generally lead to deficits in semantic processing of speech (Barrett, 1910; Tanaka *et al.*, 1987). In addition, difficulties in the interpretation of written material may be seen following lesions to surrounding cortex such as angular, supramarginal and middle temporal gyri (Penfield and Roberts, 1959; Geschwind, 1965); these findings have been corroborated by the results of many imaging studies on semantic processing (see Cabeza and Nyberg, 1997 for review). Our results suggest that the superior temporal gyrus is involved in the interpretation of symbols and therefore may have an important role in the semantic processing of written material. The contribution of functional imaging studies to our understanding of the neural substrate of language is that they indicate that the classic language areas are much less rigidly associated with specific aspects of language processing (see Binder *et al.*, 1997; Fiez and Petersen, 1998). The results of the current study extend these findings by suggesting that both classic areas are engaged in the interpretation of symbols.

Both major functional divisions of the human cingulate cortex, the caudal and rostral cingulate zones (see Picard and Strick, 1996; Koski and Paus, 2000), were activated exclusively during the set-level SRC task. The caudal area straddles the VCA line, is mostly in BA 24, and is activated during simple motor (Paus *et al.*, 1993) and somatosensory (Coghill *et al.*, 1994) tasks; this area has generally been regarded as a primordial motor area similar to the motor cortex (Dum and Strick, 1991; Braak, 1976). The more rostral area is located predominantly in BA 32, and may be subdivided into anterior and posterior portions which appear to have different functional properties (Picard and Strick, 1996), although both have been referred to in the literature as belonging to "anterior cingulate." The functions ascribed to the anterior cingulate have been quite various and include spatial attention, working memory, semantic and episodic memory, silent word reading, and word listening (see Cabeza and Nyberg, 1997; Paus *et al.*, 1998). Recent studies suggest that the anterior cingulate detects and monitors conflicts in information processing (Botvinick *et al.*, 1998; Carter *et al.*, 1998). The incompatibility between the symbolic stimulus and the motor response may represent such a conflict and account for the activation we observed. One might argue, on the basis of the response time data, that the conflict might be similar for the subjects during the element-level compatibility condition; how-

ever, the symbolic stimulus was subjectively more difficult for the subjects.

Voxels showing spatially congruent activation were lateralized to the left hemisphere in many of the areas, particularly in the parietal cortex. Whereas the right parietal cortex is thought to be dominant for spatial attention, the left is more involved in motor function (Perenin and Vighetto, 1988; Auerbach and Alexander, 1981). However, what is distinct about the set-level compatibility task is not the motor output per se but the translation of an abstract stimulus and its subsequent mapping onto a spatial domain appropriate for movement. There is ample evidence from animal experiments that an important function of the posterior parietal cortex is the translation of stimuli from different frames of references into one suitable for action or movement (Andersen *et al.*, 1997), and in the case of spatial visual stimuli this function seems to be lateralized to the right parietal cortex as suggested by this and other imaging studies (Lacquaniti *et al.*, 1997). It is possible that nonspatial visual stimuli are linked to movement primarily in the left parietal cortex but other work using nonspatial stimuli documented activation in the right parietal cortex (Deiber *et al.*, 1997). The only plausible explanation for our findings is that the left posterior parietal cortex may be involved particularly when the nonvisual stimuli have semantic properties. The semantic nature of the instruction may also account for the lateralization in PMv, which although clearly important for conditional visuomotor associations in humans and animals (see Wise *et al.*, 1997 for review) has not been found to be strongly lateralized in other studies.

Interaction between set- and element-level incompatibility. Sternberg (1969) has dealt with the general question of how one should interpret interaction effects in SRC experiments. He noted that the existence of an interaction allowed one to reject the proposition that the factors in the interaction were processed in separate stages but not that they were the reflection of separate processes. In the context of the current experiment the presence of an interaction effect in a number of brain areas does not necessarily mean that these areas are involved in some unique cognitive process common to both set- and element-level compatibility effects; it is just as likely that independent processes specific to each of the SRC effects are executed in parallel in these brain areas.

One of the more interesting findings in the current study was that three cortical areas (insula, middle and superior frontal gyri) were engaged primarily when SRC was manipulated at both the set and element level (dual task condition). The activation of the insula is somewhat puzzling given our current information about the functions of this area. The insula has been implicated in a number of functions from autonomic

and gustatory processes to somatosensory processing and emotional behavior (Buchel *et al.*, 1998). Within the somatomotor system its putative functions include the appreciation of painful stimuli (Lenz *et al.*, 1998), and acting as a funnel for the processing of somatosensory information (Hadjikhani and Roland, 1998; and see Augustine, 1996 for review). A more general view of its function suggests that it has a role in modifying the affective response to the motor and multimodal sensory systems from which it receives inputs (Mesulam, 1985). The insula, in association with the surrounding frontal cortex, has also been implicated in orthographical to phonological transformations in studies of language production (Fiez and Petersen, 1997). Such a transformation is not the type of visuomotor transformation examined in the current study, nevertheless we do deal with the transformation from symbol to movement which is perhaps an analogous process. There is little evidence that the insula is engaged during more simple visuomotor transformation although it has been activated during tasks which involve mental navigation along memorized routes (Ghaem *et al.*, 1997).

The interaction effect in the superior and middle frontal gyri is more easily understood in the context of our experiment. Portions of both the middle and superior frontal gyri, which contain BA 46 and 9, may be included in the dorsolateral prefrontal cortex (DLPFC; Rajkowska and Goldman-Rakic, 1995). The DLPFC is recognized as the locus of working memory for both spatial (Goldman-Rakic, 1988; Smith and Jonides, 1999) and non spatial processes (Goldman-Rakic, 1988; Wilson *et al.*, 1993). It is possible that both types of working memory are engaged in the performance of the dual task condition: both the spatial and the symbolic rule must be kept in mind for successful performance. One might legitimately argue that working memory related to the symbolic rule would be located more ventrally in the speech areas (Smith and Jonides, 1999). However, most of the processing in one task (spatial) and part of it in the other (symbolic) relate to spatial aspects of motor behavior. Therefore the common aspects of the tasks which relate to working memory are explicitly spatial in character. In the same vein, one can imagine that the combined performance of the tasks places a greater load on working memory in general; working memory load has been shown to correlate with activation in the DLPFC (Klingberg *et al.*, 1997).

The prefrontal cortex is also important as a substrate for the distribution of attention or "executive processes" (Smith and Jonides, 1999). The DLPFC is activated when subjects are required to perform dual tasks in which they presumably continuously switch attention from one task process to the other (D'Esposito *et al.*, 1995). This then is another plausible explanation for the frontal activation we see in the dual task condition in the current experiment. Returning to

Sternberg's (1969) consideration of interaction effects mentioned above we suggest that the interaction effects we document in the DLPFC are the result of both tasks using a common working memory process which share the same neural substrate. In addition, the interaction may also reflect a unique process, one of divided attention, which is only present in the dual task condition. Finally, we recognize that the exact processes underlying interaction effects cannot be definitively determined in our study but may form the basis for further work.

Generalization of the results. The question of whether the results may be applied to all stimulus-response manipulations that involve movements to targets or only to the specific manipulations we tested remains an open one. In all conditions in the current experiment, the stimulus was presented visually and the response involved movements to a spatial target. It was that which intervened between the stimulus and response which defined the nature of the SRC. Our results suggest that there is a core network of areas in the frontal and parietal lobes, which is activated during visuomotor tasks irrespective of the level of the SRC. It is possible that the specific nature of the set- and element-level compatibility determines the activation of additional areas.

Whether there exists a common cognitive mechanism in the brain for all forms of SRC, modulated by the extent of dimensional overlap between stimulus and response sets, as conceptualized by Kornblum, is also an open question. To approach such a problem experimentally there would need to be a consensus as how one might quantify dimensional overlap across all possible stimulus/response sets.

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