Title

Specialized Neural Systems Underlying Representations of Sequential Movements

Journal

Journal of Cognitive Neuroscience, 12(1)

ISSN

0898-929X

Authors

Harrington, Deborah L
Rao, Stephen M
Haaland, Kathleen Y
et al.

Publication Date

2000

DOI

10.1162/08989290051137602

Peer reviewed

Specialized Neural Systems Underlying Representations of Sequential Movements

Deborah L. Harrington
Albuquerque Veterans Affairs Medical Center and University of New Mexico

Stephen M. Rao
Medical College of Wisconsin

Kathleen Y. Haaland
Albuquerque Veterans Affairs Medical Center and University of New Mexico

Julie A. Bobholz, Andrew R. Mayer, Jeffrey R. Binder, and Robert W. Cox
Medical College of Wisconsin

Abstract

■ The ease by which movements are combined into skilled actions depends on many factors, including the complexity of movement sequences. Complexity can be defined by the surface structure of a sequence, including motoric properties such as the types of effectors, and by the abstract or sequence-specific structure, which is apparent in the relations amongst movements, such as repetitions. It is not known whether different neural systems support the cognitive and the sensorimotor processes underlying different structural properties of sequential actions. We investigated this question using whole-brain functional magnetic resonance imaging (fMRI) in healthy adults as they performed sequences of five key presses involving up to three fingers. The structure of sequences was defined by two factors that independently lengthen the time to plan sequences before movement: the number of different fingers (1–3; surface structure) and the number of finger transitions (0–4; sequence-specific structure). The results showed that systems involved in visual processing (extrastriate cortex) and the preparation of sensory aspects of movement (rostral inferior parietal and ventral premotor cortex (PMv)) correlated with both properties of sequence structure. The number of different fingers positively correlated with activation intensity in the cerebellum and superior parietal cortex (anterior), systems associated with sensorimotor, and kinematic representations of movement, respectively. The number of finger transitions correlated with activation in systems previously associated with sequence-specific processing, including the inferior parietal and the dorsal premotor cortex (PMd), and in interconnecting superior temporal–middle frontal gyrus networks. Different patterns of activation in the left and right inferior parietal cortex were associated with different sequences, consistent with the speculation that sequences are encoded using different mnemonics, depending on the sequence-specific structure. In contrast, PMd activation correlated positively with increases in the number of transitions, consistent with the role of this area in the retrieval or preparation of abstract action plans. These findings suggest that the surface and the sequence-specific structure of sequential movements can be distinguished by distinct distributed systems that support their underlying mental operations. ■

INTRODUCTION

Everyday activities, like driving a car, draw upon diverse sensory and cognitive processes involved in assembling a series of movements into an action. The ease by which this is accomplished depends upon many factors, including the complexity of the underlying sensory and cognitive processes. For instance, behavioral investigations into the representation of sequential movements have shown that increases in sequence complexity prolong reaction time (RT), or the time it takes to plan a series of events prior to movement (Kerr, 1978). This presumably reflects the greater amount of programming, encoding, or retrieval time required for each response in the sequence (Rosenbaum, Inhoff, & Gordon, 1984; Sternberg, Monsell, Knoll, & Wright, 1978). The latency of individual movements also depends on the complexity of sequences in which they are contained (Povel & Collard, 1982; Restle, 1973), because mental operations are ongoing during movement. Table 1 shows that these behavioral observations

are compatible with functional imaging studies, in which the neural representation of sequential movements also depends on the complexity of sequences. This table shows that most functional imaging studies have manipulated sequence complexity by varying the length or the type of sequences (that is, repeated and heterogeneous sequential movements are contrasted), yet similar complexity manipulations have produced a number of discrepant findings.

The complexity of an action can be understood in many ways, including the surface and the abstract structures of a sequence. Surface structure is exemplified by perceptual or motoric properties of sequences such as the number of movements or the types of effectors. Abstract or sequence-specific structure is manifested in the relations between movements, such as repetitions or alternations (Povel & Collard, 1982; Restle, 1973; Rosenbaum et al., 1984), because these relations permit the encoding of sequential movements into integrated chunks that facilitate learning and memory. Many different manipulations of structural complexity produce anticipatory effects on RT and alter response latency, but the underlying cognitive and neural mechanisms are not entirely understood. Information-processing models imply that similar mental operations underlie many of these effects (Rosenbaum et al., 1984; Sternberg et al., 1978), because they depend on common programming, encoding, decoding, or retrieval operations. However, this view overlooks that actions are represented in multiple ways by their perceptual, motoric, and abstract structural properties (MacKay, 1985). In fact, the acquisition of abstract, but not surface, structure (that is, types of effectors), appears to depend on attention (Keele, Jennings, Jones, Caulton, & Cohen, 1995). Likewise, the prospect that different neural systems participate in sequencing at different levels is suggested by findings from single-cell studies showing that, prior to movement, different sets of neurons fire in response to spatial (for example, direction) and sequence-specific (for example, temporal order) properties of movements (Barone & Joseph, 1989; Kettner, Marcario, & Clark-Phelps, 1996).

The present study used whole-brain functional magnetic resonance imaging (fMRI) to investigate whether different forms of sequence structure are handled by distinct neural systems by comparing independent manipulations of surface and sequence-specific structure. Previous functional imaging studies in healthy adults have not addressed this issue. These studies have investigated the neural systems that support mental operations involved in sequencing finger movements by increasing sequence length or varying sequence type. Table 1 shows that these studies differ considerably in terms of the structure of the sequences, such that other potentially important variables (for example, number of repetitions and different fingers, finger orderings, sequence length) covaried with the experimental manipulation. In all of these studies, structural complexity was defined by manipulating a single attribute (sequence length or type), so that it was not possible to test whether different distributed neural systems represent different structural aspects of sequential movements.

In the present study, subjects performed sequences consisting of five key-press responses using their index (1), middle (2), and ring (3) fingers. Digit sequences were displayed on a screen and, unlike previous studies, remained in view throughout the movement to minimize memory demands, which might correlate with sequence complexity. This procedure does not rule out, however, the possibility that subjects still utilize working memory (for example, phonological loop) to sustain digit sequences while implementing them. We varied two fundamental features of sequential movements that have frequently covaried with sequence complexity manipulations in previous functional imaging studies. The number of different responses (1–3 different fingers) was manipulated to examine the neural representation of one aspect of surface structure. The assumption that this factor describes the surface structure of sequential events is suggested by findings showing that the representation of a sequence (that is, the latency of individual movements) is independent of the fingers used to execute the movements, when a sequence contains a definable abstract structure (Povel & Collard, 1982). In contrast, to investigate the neural systems that support the processing of abstract or sequence-specific structure, the number of transitions among different responses (0–4 finger transitions; Table 2) was varied, because this changes the relationship among movements, including the number of repetitions (for example, 12222 vs. 12111 vs. 12122 vs. 12121; 12333 vs. 12133 vs. 12131). When sequence length is controlled, RT increases independently with the number of different responses or the number of transitions (Harrington & Haaland, 1987), demonstrating that both manipulations lengthen the time to plan sequences prior to movement. However, it is not known if different neural systems support these structural aspects of sequential movements. It is possible that a common representation underlies both if, for instance, they require the same perceptual, programming, retrieval, or encoding operations. If this is the case, increasing the complexity of both properties of sequences should be associated with activation in common neural systems. Alternatively, if each property depends upon different representational systems, each should contribute a unique component to the activation pattern. One possibility is that greater demands are placed on systems involved in sensorimotor processing (for example, primary motor and sensory cortices, cerebellum), when there are more fingers involved in sequencing. This outcome would point to a sensorimotor representation under-

Table 1. Summary of Functional Imaging Studies of Sequence Complexity

Citation (Method)	*Task*	*Areas Associated with Complexity*[a]				
		Motor	*Prefrontal*	*Parietal*	*Basal Ganglia*	*Cerebellum*
Manipulations of Sequence Length						
Boecker et al. (1998) [PET]	4 to 8 element sequences	↑ i. M1, c. PMC, SMA		↑ i. Precuneus	↑ b. GP	
	Number of repetitions and interposed movements covaried		↓ b. BA 10	↓ i. BA 39		
Catalan et al. (1998) [PET]	1 and 12 element sequences Number of different fingers and finger orderings covaried	↑ b. PMd		↑ c. S1, b. p. BA 7, b. Precuneus		↑ Vermis
Sadato et al. (1996) [PET]	4, 8, 12, and 16 element sequences Number of different finger orderings covaried	↑ i. PMC		↑ i. Precuneus ↓ c. BA 40		↑ Vermis
Manipulations of Sequence Type						
Chen et al. (1997) [rTMS to M1]	Simple (4312 repeated 4 times) vs. Complex (16 nonrepeated elements) Right and left hands tested; Number of finger transitions and orderings covaried	↓ left M1	*NA*	*NA*	*NA*	*NA*
Colebatch et al. (1991) [PET]	Repetitive (index finger) vs. Heterogeneous (1234 repeated) Number of different fingers covaried	↑ c. M1, i. PMC	↑ c. BA 44	↑ c. S1		
Dassonville et al. (1998) [fMRI][b]	Fixed order (1234) vs. Random orders Right and left hands tested; Number of finger orderings covaried	↑ b. SMA	↑ b. PMC	↑ b. BA 7	*NA*	*NA*
Gerloff et al. (1997) [rTMS to SMA, M1, parietal and frontal cortex]	Repetitive (index finger) vs. Scale (4321) vs. Heterogeneous (non-adjacent finger sequences) Number of different fingers covaried	↓ SMA			*NA*	*NA*

(continued)

Table 1. *(continued)*

Citation (Method)	*Task*	*Areas Associated with Complexity*[a]				
		Motor	*Prefrontal*	*Parietal*	*Basal Ganglia*	*Cerebellum*
Gordon et al. (1998) [fMRI][c]	Repetitive (JJJJ) vs. Uni-digit (JUYH) and multi-digit typing task (JKJK, JFIELSPQ) Number of different fingers, finger transitions, hands, spatial positioning requirements, and sequence length covaried	↑ b. M1, b. SMA	*NI*	↑ b. S1, b. BA 7, b. BA 40	↑ c. lentif	*NI*
Rao et al. (1993) [fMRI][d]	Repetitive (4 fingers simultaneously) vs. Heterogeneous (2431 repeated) Number of active muscle groups and different fingers covaried	↑ i. M1, b. PMC, SMA	*NI*	↑ b. S1	*NI*	*NI*
Van Oostende et al. (1997) [fMRI]	Fixed order (for example, 1234) vs. Random order (for example, 2431) Number of finger orderings covaried	↑ b. PMC, SMA	↑ b. SFS	↑ b. BA 5, b. p. BA 7		
Wexler et al. (1997) [fMRI]	Repetitive (1 or 4 fingers simultaneously) vs. Heterogeneous (1234 or 113224) Sequence length, number of active muscle groups, and finger repetitions covaried	↑ i. M1, i. PMC, SMA	*NI*	↑ b. BA 7, b. BA 40	*NI*	*NI*

Notes: The table lists studies representative of the methods used in functional imaging and repetitive transcranial magnetic stimulation [rTMS] experiments to investigate the neural systems involved in controlling simple and complex sequential finger movements (that is, finger opposition or key presses) in humans. Only directly relevant portions of the tasks and results are described. In most studies, sequences were performed using the right hand, except for two in which both hands were tested. Sequences were practiced to varying degrees prior to imaging and performed from memory during imaging. An exception is the Van Oostende et al. (1997) study in which auditory digit-sequences were presented on each trial, and the Dassonville et al. (1998) study, which used a serial reaction time procedure wherein visual stimuli designating a digit were presented sequentially, cueing subjects to move the appropriate finger as quickly as possible. Finger movements were paced (externally or self-paced) at rates varying between 0.5 to 2.5 Hz. An exception is the Gordon et al. (1998) study in which self-paced typing rates ranged between approximately 5 to 8 Hz. The control condition was rest and the statistical tests of complexity varied among studies. The numbers 1, 2, 3, and 4 refer to index, middle, ring, and little finger movements, respectively. The ↑ symbol indicates that activation increased and the ↓ symbol indicates that activation decreased in relationship to sequence complexity. For the rTMS studies, the ↓ symbol signifies that sequencing performance was increasingly disrupted as sequences became more complex. *NA* denotes "not applicable" for (1) rTMS studies, which apply stimulation to specific brain areas and, (2) region of interest studies, in which some brain regions were not investigated. *NI* denotes "not imaged" for studies that did not conduct whole brain imaging, however, several other studies did not image the entire cerebellum or frontal cortex. BA=Brodmann Area, c=contralateral, GP=globus pallidus, i=ipsilateral, lentif.=lentiform nucleus, M1=primary sensorimotor cortex, p.=posterior, PMC=premotor cortex, PMd=dorsal premotor cortex, PRE=precentral gyrus, POST=postcentral gyrus, S1=somatosensory cortex, SFS=superior frontal sulcus, SMA=supplementary motor area.

[a]The table summarizes the principal findings. Other areas of increased or decreased activation (for example, thalamus, insula, cingulate motor area) were reported in some studies.

[b]The data were first subtracted from a visual control condition (that is, subjects attended to the same visual stimuli, but did not respond) and then the fixed and random conditions were compared. Activation in the inferior parietal cortex (area 40) was not studied.

[c]The findings are presented from the descriptive comparisons between repetitive and all other conditions. Statistical tests were not conducted to validate these observations.

[d]The findings presented are from the self–paced condition.

Table 2. Experimental Design and Sequence Conditions

	Number of Transitions				
Number of Fingers	*0*	*1*	*2*	*3*	*4*
1	Condition 1				
	11111				
	22222				
	33333				
2		Condition 2	Condition 3	Condition 5	Condition 7
		12222	12111	12122	12121
		23333	23222	23233	23232
		31111	32333	32322	32323
3			Condition 4	Condition 6	Condition 8
			12333	12133	12131
			23111	23211	23231
			32111	32311	32321

Note: Numbers beneath each condition represent the sequences of finger key presses where "1" denotes the index, "2" the middle, and "3" the ring finger.

lying this aspect of sequential movements. In contrast, variations in the number of finger transitions might activate neural systems that support mental operations involved in processing specific aspects of the sequence structure, independent of the number of fingers involved in executing them. The neural underpinnings of sequence-specific processing have not been widely studied. Investigations of sequence learning in humans suggest that the inferior parietal cortex plays a key role encoding sequence-specific information (Honda et al., 1998; Jenkins et al., 1994; Sakai et al., 1998), and sequence-specific neural activity has been reported in the dorsal premotor cortex (PMd) of monkeys (Kettner et al., 1996; Kurata, 1994; Mushiake, Inase, & Tanji, 1991). Additionally, the basal ganglia and supplementary motor area (SMA) have been associated with the encoding of serial order in animals (Aldridge & Berridge, 1998; Berridge & Whishaw, 1992; Clower & Alexander, 1998; Kermadi & Joseph, 1995). Hence, if changing the number of transitions alters some aspect of sequence-specific processing, it should correlate with activation in one or more of these areas.

RESULTS

Behavioral Data

The RT, MT, and accuracy data were first analyzed using an analysis of variance (ANOVA) with repeated measures to determine if there was an interaction between the number of fingers and the number of transitions for each dependent measure. Conditions 3, 4, 5, 6, 7 and 8 were included in these analyses (Table 2), and no significant interaction was found for any of the measures. Next, the independent effects of each factor were fully analyzed by including all levels on each factor. To test the effect of a number of different fingers (1–3), means were collapsed across the number of transitions. Similarly, to test the effect of a number of transitions

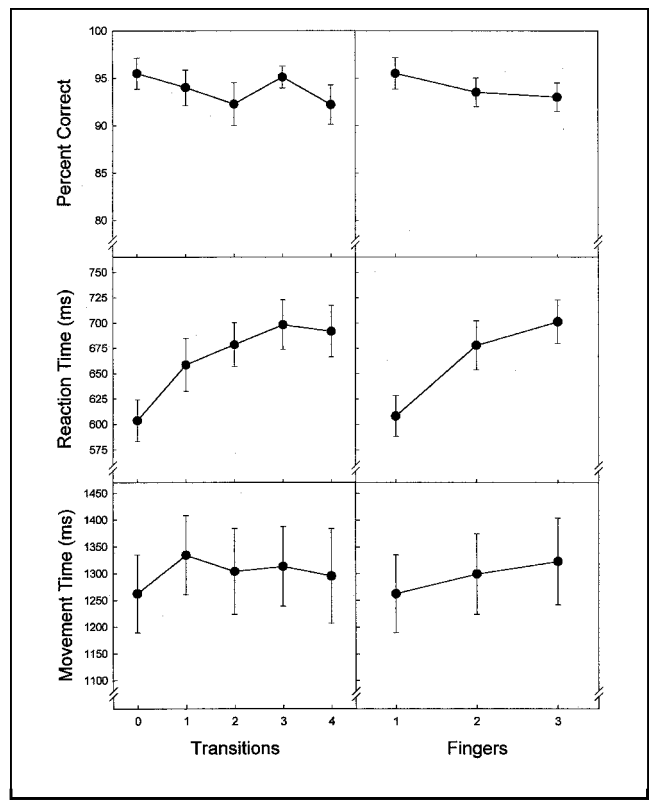

Figure 1. Mean accuracy (top panel), preparatory reaction time (RT; middle panel), and movement time (MT; bottom panel) as a function of number of transitions (left side) and fingers (right side). Bars represent standard error of the mean.

(0–4), means were collapsed across the number of different fingers. The linear and quadratic components of the RT, MT, and accuracy functions were tested.

Figure 1 presents the mean and standard error of the mean for accuracy (top panel), RT (middle), and MT (bottom) as a function of the number of transitions (left side) and fingers (right side). Repeated measures ANOVAs indicated no significant linear or quadratic components for the number of transitions or fingers for mean accuracy ($p > .20$), which ranged from 93 to 96% correct across all conditions, or for mean MT ($p > .18$). In contrast, mean RT, the measure of advance programming of the motor sequence, significantly increased as a function of the number of transitions (Linear: $F(1,14) = 37.5$, $p < .0001$; Quadratic: $F(1,14) = 19.5$, $p < .001$) and fingers (Linear: $F(1,14) = 45.8$, $p < .0001$), consistent with previous findings (Harrington & Haaland, 1987). These results showed that the sequences differed in terms of the speed of advance planning, but not motor implementation.

To determine if the findings were due entirely to the faster RTs for repetitive sequences, the same analyses were carried out, eliminating the repeated condition. The results were similar, showing RT significantly increased as a function of the number of transitions (that is, 1–4) (Linear: $F(1,14) = 6.7$, $p < .025$) and fingers (that is, 2–3) (Linear: $F(1,14) = 5.5$, $p < .05$). Hence, advance planning took longer as the number of transitions or fingers increased, even when the repetitive condition was eliminated from the analyses. Only the main effects of these factors were tested in the analyses applied to the functional imaging data, because the number of fingers and transitions had independent effects on RT.

Functional Imaging Data

Repetitive Sequences

Table 3 shows the center of mass, volume, and peak intensity (maximum t) of the activation foci for the t-tests that compared the repetitive sequence condition with rest. The activation foci are also displayed in Figure 2. These data show that repetitive sequences activated striate cortex and regions of ventral extrastriate cortex. Repetitive sequences also activated the left sensory (S1) and motor cortex (M1), the right vermis, and bilateral

Table 3. Activation Foci: Comparison of Repetitive Sequences With Rest

		Talairach Coordinates				
Region (Brodmann's Area)	*L/R*	*x*	*y*	*z*	*Volume (cm^3)*	*Max. t*
Condition 1>Rest						
Striate and extrastriate cortex						
[1] Striate cortex (17)	R	18	– 100	– 10	0.3	2.2
[2] Lingual gyrus (18)	L	– 10	– 98	– 8	0.3	2.0
[3] Fusiform gyrus (18)	L	– 26	– 95	– 13	1.6	2.8
Sensorimotor cortex						
[4] Motor cortex (4)	L	– 37	– 27	58	7.6	3.6
[5] Postcentral gyrus (2)	L	– 56	– 23	43	0.4	2.5
Cerebellum						
[6] Hemisphere (superior, posterior)	L	– 39	– 74	– 18	2.3	2.3
[7] Hemisphere (superior, anterior)	L	– 26	– 49	– 23	0.3	1.9
[8] Vermis	R	4	– 55	– 9	1.4	2.4
[9] Hemisphere (superior, anterior)	R	19	– 45	– 22	0.9	2.2
[10] Hemisphere (superior, anterior)	R	33	– 57	– 23	0.6	2.0
Rest>Condition 1						
Basal ganglia						
[11] Putamen	R	25	0	2	0.6	2.6

Notes: Region is defined as center of mass. The second column refers to left (L) and right (R) hemisphere activations. Coordinates represent distance in mm from anterior commissure: x right (+)/left (–); y anterior (+)/posterior(–); z superior (+)/inferior(–). Maximum t-value defines the intensity of activation. Numbers in brackets refer to locations demarcated in Figure 2.

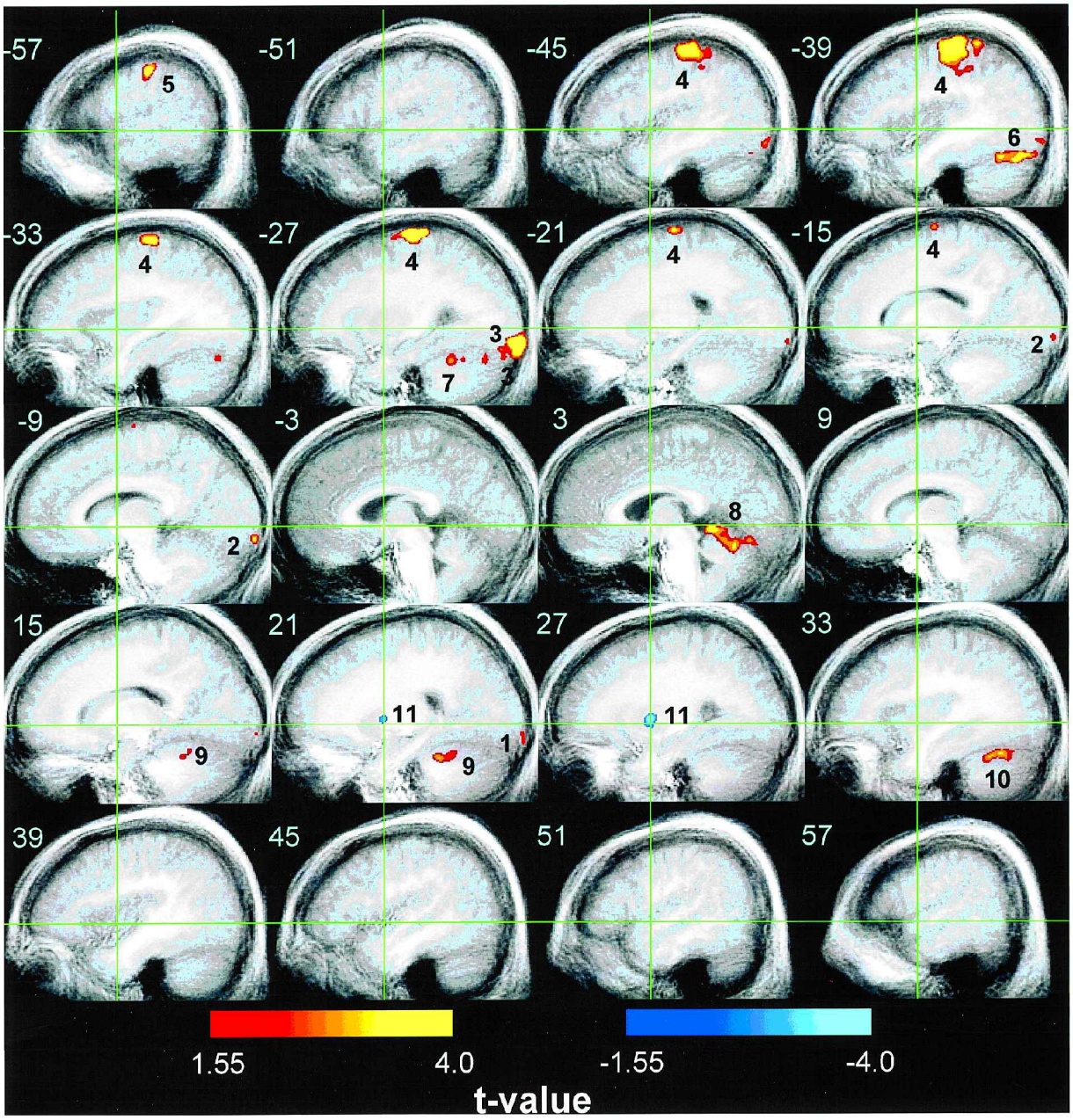

Figure 2. Areas of increased (red–yellow scale) and decreased (blue scale) MR signal intensity from *t*-tests comparing the repetitive sequence condition with rest. Numbers in the upper left of each slice represent mm from the interhemispheric fissure (–, left; +, right). Numbers adjacent to the activated foci correspond to numbers in brackets listed in Table 3.

cerebellar hemispheres. Additionally, activation was greater during rest than repetitive sequencing in the right putamen, an unexpected result. SMA activation was not observed in these analyses.

Effects of Sequence Complexity

Table 4 shows the center of mass, volume, and peak intensity (maximum *F*) of the activation foci for the ANOVAs that tested for changes in functional activity associated with variations in sequence complexity. The table presents the common regions of activation associated with increasing the complexity of both factors and the regions that were activated only by variations in number of fingers or transitions. The activation foci are also displayed in Figure 3 in terms of the regions activated by variations in the number of fingers (yellow), transitions (red), or both factors (green). In addition,

graphs of activation intensity (see Methods Section) are displayed in Figure 4 for regions that characterized the relationships between sequence complexity and change in activation intensity. Regions that are not displayed showed similar patterns of activation as those in Figure 4 for nearby areas within or between the two hemispheres.

Both experimental manipulations were associated with increased activation primarily in the left, but some right, extrastriate cortex, bilateral superior parietal cortex (area 7), left anterior supramarginal gyrus (SMG; area 40) near the post central gyrus, left PMd (area 6), and ventral premotor cortex (PMv; area 6). Figure 4 suggests that some of these effects, especially for extrastriate cortex and rostral SMG, were largely due to the greater change in activation intensity for heterogeneous than repeated sequences. Activation intensity of the cerebellum is not graphed for regions commonly activated by both sequence complexity manipulations, but followed a similar pattern: greater activation for heterogeneous than repeated sequences, but little difference among heterogeneous sequences. Neither of the experimental manipulations correlated with basal ganglia or SMA activation.

The number of different fingers was uniquely and positively associated with activation of the left superior frontal gyrus (area 10), the left cerebellar vermis, and the right cerebellar hemispheres (superior and inferior). The activation focus in area 10 was close to the middle frontal gyrus. Activation intensity in the left precuneus region of the superior parietal cortex (area 7) also correlated with variations in the number of fingers, although it was below baseline levels, especially for repetitive sequences.

The number of transitions positively correlated with activation of the right PMd and had a nonlinear effect on right SMG activation, increasing between repetitive and 1 transition sequences, decreasing for the 2 and 3 transition sequences, and then increasing again for 4 transition sequences. Left caudal SMG activation was above baseline only for simpler sequences (0 and 1 transitions). Similarly, while left angular gyrus (area 39) activation correlated with the number of transitions, activation was below baseline resting levels for all but the 1 transition sequences (Figure 4).

Effects of Complexity Excluding Repetitive Sequences

The above results showed areas commonly activated by variations in both parameters of sequences and activity unique to variations in a specific sequence parameter. However, activation of common areas could be due to including the repeated condition as a level in both analyses. Therefore, ANOVAs were conducted, eliminating condition 1. Table 5 and Figures 5 and 6 display the results from the ANOVAs that tested for changes in functional activity associated with increasing programming complexity when the repeated condition was omitted from the analyses. Table 5 shows there were no common areas of activation, indicating that inclusion of the repeated sequences was responsible for the overlap between the two factors. Importantly, inclusion of repeated sequences was entirely responsible for the transition and finger effects in extrastriate cortex, rostral SMG, and PMv (Figure 4), which were not uniquely activated by either factor alone when this condition was omitted from the analyses.

Statistical power was substantially reduced for the tests of the finger effect due to the inclusion of only two levels. Despite this restriction, significantly greater activation intensity was found for three than two finger sequences in the right superior parietal (rostral) and left cerebellar hemisphere (superior, anterior) (Table 5 and Figures 5 and 6). Although significant activations in other areas were not found, this may be due in part to the restricted number of levels on the finger factor. This possibility is suggested by Figure 4, wherein there was a trend for changes in activation to increase between two and three finger sequences in left vermis and left superior frontal gyrus.

The statistical power for tests of the transition effect was evidently not affected by excluding the repeated condition. Similar to the previous ANOVAs, variations in the number of transitions correlated with activation of the left angular gyrus, bilateral SMG (caudal), left superior parietal cortex (caudal), and a region of the left PMd (– 25,– 9,49), which was caudal to the other two left hemisphere PMd activations (Table 5 and Figure 6). The patterns of activation intensity were also similar to those displayed for comparable regions in Figure 4.

Unlike the previous ANOVAs, a negative relationship was found between number of finger transitions and activity in two additional left PMd foci (– 19,18,58; – 43,3,47), which were rostral to the other PMd focus. The change in activation intensity in the rostral PMd sites was above baseline for 1 transition sequences and near or below resting level for sequences containing two or more transitions (Figure 6). Likewise, the number of transitions negatively correlated with activation in the left middle frontal gyrus, left insula (medial and beneath the precentral gyrus; not shown in Figure 6), and left superior temporal gyrus. These effects were also due to the relatively greater activation intensity for the 1 transition sequences than the other sequences. These regions were not uncovered by the previous ANOVAs, likely because the effect was mitigated by the repeated condition (not shown in Figure 6), in which activation intensity was similar to sequences consisting of 2, 3, and 4 transitions.

DISCUSSION

Both attributes of sequence structure positively correlated with activation in areas associated with visual

Table 4. Activation Foci: ANOVA Results for Transitions and Fingers

Region (Brodmann's Area)	*F/T*	*L/R*	*Talairach Coordinates*			*Volume (cm^3)*	*Max. F*[a]
			x	*y*	*z*		
Common Regions of Activation							
Extrastriate cortex							
[1] Inferior occipital gyrus (18)	F	L	– 34	– 88	– 1	0.9	15.7
	T	L	– 32	– 91	– 5	0.2	8.1
	T	L	– 32	– 88	4	0.4	8.1
[2] Inferior occipital gyrus (18)	F	L	– 38	– 85	– 11	0.3	14.4
	T	L	– 36	– 84	– 10	0.3	8.1
[3] Fusiform gyrus (19)	F	L	– 48	– 67	– 12	0.2	10.9
	T	L	– 47	– 67	– 11	0.3	6.3
[4] Superior occipital gyrus (19)	F	R	35	– 74	29	0.9	21.6
	T	R	36	– 76	31	0.2	9.3
Parietal cortex							
[5] Superior parietal (caudal) (7)	F	L	– 24	– 64	44	4.7	21.2
	T	L	– 23	– 66	47	4.0	16.1
[6] Superior parietal (caudal) (7)	F	R	24	– 61	54	2.6	23.3
	T	R	22	– 61	54	2.0	14.5
[7] SMG (rostral) (40)	F	L	– 45	– 29	44	0.5	14.7
	T	L	– 49	– 29	44	0.3	9.3
Frontal cortex							
[8] Premotor (dorsal) (6)	F	L	– 27	– 7	48	0.9	19.9
	T	L	– 25	– 7	49	1.2	10.5
[9] Premotor (ventral) (6)	F	L	– 45	– 3	32	0.6	11.3
	T	L	– 45	– 3	32	0.8	7.0
Cerebellum							
[10] Hemisphere (superior, anterior)	F	L	– 29	– 49	– 20	1.9	17.4
	T	L	– 35	– 49	– 17	0.5	8.2
	T	L	– 19	– 42	– 21	0.3	6.8
[11] Hemisphere (superior, anterior)	F	R	22	– 45	– 23	0.4	25.5
	T	R	23	– 45	– 24	0.2	7.9
Regions Activated by Fingers							
Parietal cortex							
[12] Precuneus (7)	F	L	– 6	– 58	43	0.3	14.4
Frontal cortex							
[13] Superior frontal gyrus (10)	F	L	– 14	56	5	0.3	11.3
Cerebellum							
[14] Vermis	F	L	– 3	– 43	– 11		11.8
[15] Hemisphere (inferior, anterior)	F	R	15	– 47	– 47		16.2
[16] Hemisphere (superior, posterior)	F	R	17	– 67	– 21	0.3	14.1

(continued)

Table 4. *(continued)*

Region (Brodmann's Area)	F/T	L/R	Talairach Coordinates			Volume (cm^3)	Max. F^a
			x	*y*	*z*		
Regions Activated by Transitions							
Parietal cortex							
[17] Angular gyrus (39)	T	L	– 49	– 61	32	0.2	8.3
[18] SMG (caudal) (40)	T	L	– 52	– 45	30		8.1
[19] SMG (caudal) (40)	T	L	– 57	– 41	38	0.6	7.2
[20] SMG (caudal) (40)	T	R	42	– 50	40	0.5	6.7
Frontal cortex							
[21] Premotor (dorsal) (6)	T	R	31	– 6	52	0.3	7.1

Notes: Numbers in brackets refer to locations demarcated in Figure 3. The second column refers to the ANOVAs testing the main effect of the number of fingers (F) and the number of transitions (T). The third column refers to left (L) and right (R) hemisphere activation. SMG refers to the supramarginal gyrus.

[a]Tabled values represent the maximum *F*. Transitions *df*=(4, 56) and cutoff *F*– value=4.17; Fingers *df*=(2, 28) and cutoff *F*– value=6.44. All statistical tests included repetitive sequences in the analyses.

processing and somatosensory aspects of movement. However, each was also correlated with activation in distinct distributed neural systems. The activation patterns were consistent with the proposal that increasing the number of different fingers heightens the processing demands on systems that compute sensorimotor operations. In contrast, changing the number of finger transitions altered activation in distributed systems that have been associated with abstract or sequence-specific processing. These results are considered next in the context of previous studies.

Neural Systems Underlying Both Aspects of Sequence Complexity

Both manipulations of sequence complexity activated common brain regions only when the analyses included repetitive sequences. First, we observed differences in the visual processing of repetitive and heterogeneous sequences. Left extrastriate cortical activation was greater for heterogeneous than repetitive sequences, and was found in inferior areas associated with the visual processing of objects, including numbers (Bly & Kosslyn, 1997; Ungerleider & Haxby, 1994). Additionally, activation of *superior* area 19 in the right hemisphere was below resting level for repetitive sequences, possibly due to perceptual priming generated by the high redundancy of repetitive digits, which may be enhanced by the blocking of the sequence condition in the present study. Redundant stimulus information may weaken connections among nonessential neurons, resulting in more rapid object discrimination (Wiggs & Martin, 1998). Although perceptual priming of words produces activation suppression in *inferior* extrastriate cortex (Schacter, Alpert, Savage, Rauch, & Albert, 1996; Squire et al., 1992), suppression of *superior* area 19 in our study may reflect the significance of the stimulus for goal-directed movement (Goodale & Milner, 1992). Importantly, extrastriate cortical activation was similar for all heterogeneous sequences, suggesting that attentional demands associated with the early stages of visual analysis (Motter, 1993; Schiller, 1994) did not differ among heterogeneous sequences.

Activation was also greater for heterogeneous than repetitive sequences in the left rostral SMG and PMv, with little difference observed amongst heterogeneous sequences (Figure 4). The rostral SMG has been closely associated with the use of visual information to prepare movement (Deiber, Ibanez, Sadato, & Hallett, 1996), perhaps by integrating higher-level somatosensory and spatial representations from other parietal areas (Rizzolatti, Luppino, & Matelli, 1998). This is compatible with the predominance of somatosensory inputs into the rostral-inferior parietal cortex in monkeys and its significant projections to PMv (Cavada & Goldman-Rakic, 1989), an area which responds to visual or tactile information that is anchored to a particular body part, and is independent of eye or head movements (Graziano & Gross, 1998). Previous studies have failed to find a relationship between sequence type and anterior (rostral) SMG activation (Table 1), possibly because the sequences used were highly predictable, which behavioral studies show reduces response preparation processing (Rosenbaum, 1980). Specifically, two or three different sequences were used in most studies (Table 1), and during imaging, each was performed repeatedly from memory. This procedure likely minimizes the regular need for some mental operations (for example, encoding, retrieval), in contrast to our methods, which

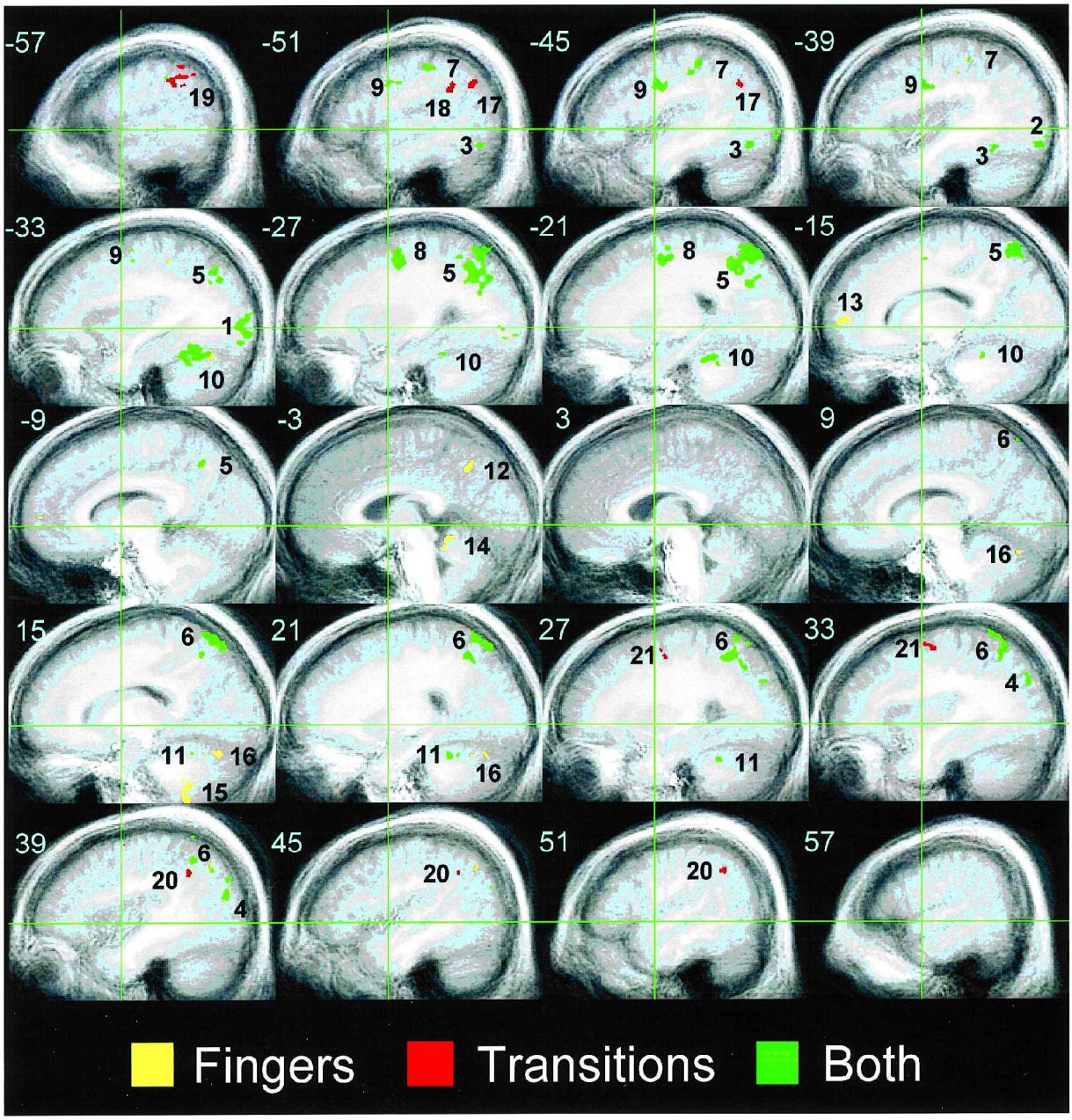

Figure 3. Areas of increased MR signal intensity associated with increases in programming complexity. Activated foci are based on ANOVAs that separately tested for changes in functional activity associated with increasing the number of fingers or transitions. Activation foci are based on the analyses which included repeated sequences. Regions uniquely activated by fingers and transitions are shown in yellow and red, respectively. Regions of common activation, defined as foci located within a 10-mm radius of each other, are displayed in green. Numbers in the upper left of each slice represent mm from the interhemispheric fissure (–, left; +, right). Numbers adjacent to activated foci correspond to numbers in brackets listed in Table 4.

placed greater demands on the preparation process because a different sequence was presented on each trial. The role of the rostral SMG in anticipatory processing is further suggested by the increasing activation of this region during implicit learning, irrespective of the motor effector being used (Grafton, Hazeltine, & Ivry, 1998).

Neural Underpinnings of Surface and Sequence-Specific Properties of Sequences

The above findings suggest that repetitive and heterogeneous sequences differed in essential ways that impacted visual processing and integrating or preparing somatosensory and spatial information for movement.

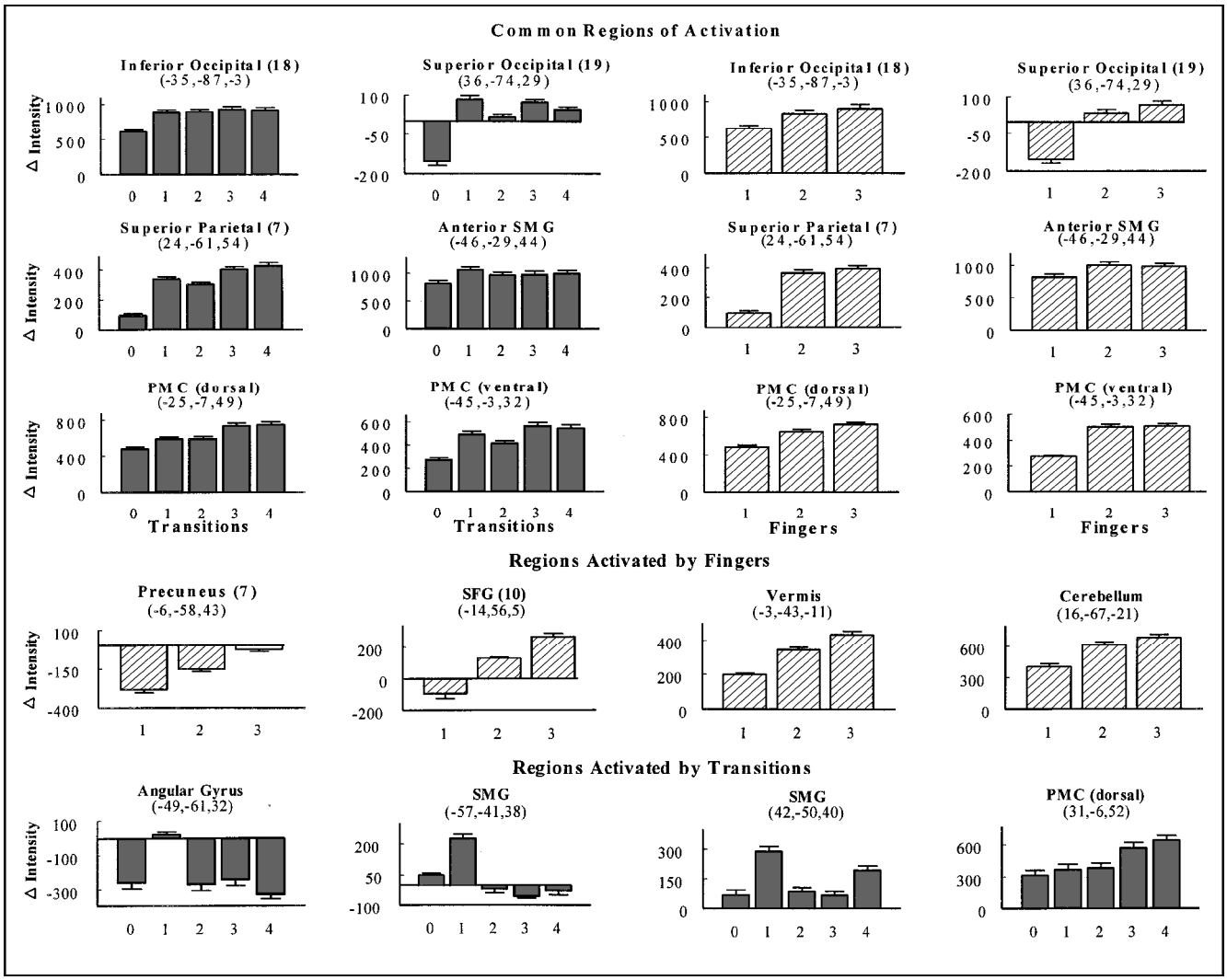

Figure 4. Change in activation intensity for repetitive and heterogeneous sequences. The change in activation intensity is displayed for common regions of activation, regions activated by fingers, and regions activated by transitions. See Methods for calculation of activation intensity from cross-correlation analysis and note that intensity values have been scaled by a factor of 1000. Solid and striped bars represent significant activation foci ($p<.005$) defined by ANOVAs performed on the number of transitions (0–4) and the number of fingers (1–3), respectively. PMC=premotor cortex; SMG=supramarginal gyrus; SFG=superior frontal gyrus. Error bars=s.e.m.

However, RT increased significantly with variations in both properties of sequence structure, even when repetitive sequences were removed from the analyses, which suggested differences amongst heterogeneous sequences in the complexity of underlying mental operations. The results for heterogeneous sequences further indicated that each aspect of sequence structure activated different distributed neural systems, some of which have been previously associated with sensorimotor representations and others with sequence-specific processing.

Neural Representations of Surface Structure

The number of different fingers contained in a sequence positively correlated with activation in the right superior parietal cortex (rostral area 7; Figure 6), consistent with other findings (Grafton, Mazziotta, Woods, & Phelps, 1992; Kawashima et al., 1996; Matsumura et al., 1996). The rostral region of area 7 is commonly associated with somatosensory processing (Rizzolatti et al., 1998), and there is mounting evidence that it represents kinematic information about movements (for example, velocity, spatial position, spatiotemporal coupling) (Ashe & Georgopoulos, 1994; Ferraina & Bianchi, 1994; Kalaska, Cohen, Prudhomme, & Hyde, 1990; Scott, Sergio, & Kalaska, 1997). This latter proposal concurs with studies showing impaired finger positioning after lesions of the superior occipitoparietal pathway in humans (Goodale, Jakobson, & Servos, 1996; Jeannerod, 1986) and after muscimol injections in the intraparietal sulcus in monkeys (Gallese, Murata, Kasede, Niki, & Sakata, 1994). It is also consistent with a recent study indicating that damage to area 7 is strongly associated with ideomotor

Table 5. Activation Foci: ANOVA Results for Transitions and Fingers After Excluding Repeated Sequences

Region (Brodmann's Area)	F/T	L/R	Talairach Coordinates			Volume (cm^3)	Max. F[a]
			x	*y*	*z*		
Common Regions of Activation							
None							
Regions Activated by Fingers							
Parietal cortex							
[1] Superior parietal (rostral) (7)	F	R	26	– 41	51	0.2	37.9
Cerebellum							
[2] Hemisphere (superior, anterior)	F	L	– 26	– 41	– 19	0.3	38.7
Regions Activated by Transitions							
Parietal cortex							
[3] Angular gyrus (39)	T	L	– 49	– 60	33	0.2	9.6
[4] SMG (caudal) (40)	T	L	– 56	– 42	36	1.7	12.7
[5] SMG (caudal) (40)	T	R	50	– 35	53	0.3	15.0
[6] Superior parietal (caudal) (7)	T	L	– 20	– 65	53	0.3	9.1
Frontal cortex							
[7] Premotor (dorsal) (6)	T	L	– 25	– 9	49	0.5	9.9
[8] Premotor (dorsal) (6)	T	L	– 19	18	58	0.2	8.6
[9] Premotor (dorsal) (6)	T	L	– 43	3	47	0.3	7.9
[10] Middle frontal gyrus (9)	T	L	– 48	18	29	1.1	10.8
[11] Middle frontal gyrus (46)	T	L	– 47	32	15	0.3	12.1
[12] Middle frontal gyrus (10)	T	L	– 36	45	25	0.2	7.1
[13] Insula/white matter	T	L	– 32	– 10	24	0.2	9.4
Temporal cortex							
[14] Superior temporal gyrus (22)	T	L	– 47	– 48	12	0.2	10.0
[15] Superior temporal gyrus (22)	T	L	– 53	11	– 2	0.3	9.4

Numbers in brackets refer to locations demarcated in Figure 5. The second column refers to the ANOVAs testing the main effect of the number of fingers (F) and the number of transitions (T). The third column refers to left (L) and right (R) hemisphere activation. SMG refers to the supramarginal gyrus.

[a]Tabled values represent the maximum *F*. Transitions $df=(3, 42)$ and cutoff *F*-value=4.94; Fingers $df=(1, 14)$ and cutoff *F*-value=11.06.

limb apraxia (Haaland, Harrington, & Knight, 1999), which disrupts the positioning, spatiotemporal coupling, and sequencing of hand and arm movements (Harrington & Haaland, 1992; Poizner et al., 1995), possibly due to an inability to specify kinematic properties of movement.

Changes in intensity within the anterior cerebellum bilaterally were greater for heterogeneous than repetitive sequences (Table 4). Additionally, activation intensity in the vermis and the cerebellar hemispheres bilaterally positively correlated with the number of fingers, particularly when all levels of this factor were included in the analyses (Figures 4 and 6). These results are consistent with the cerebellum's traditional role in motor control, particularly when there are more fingers involved in sequential actions. However, this cannot explain activation of the left cerebellar hemisphere (Table 5) in the absence of activation within the right sensorimotor cortex.

Left primary motor and sensory areas were activated while performing repetitive sequences; however, activation did not correlate with variations in the number of

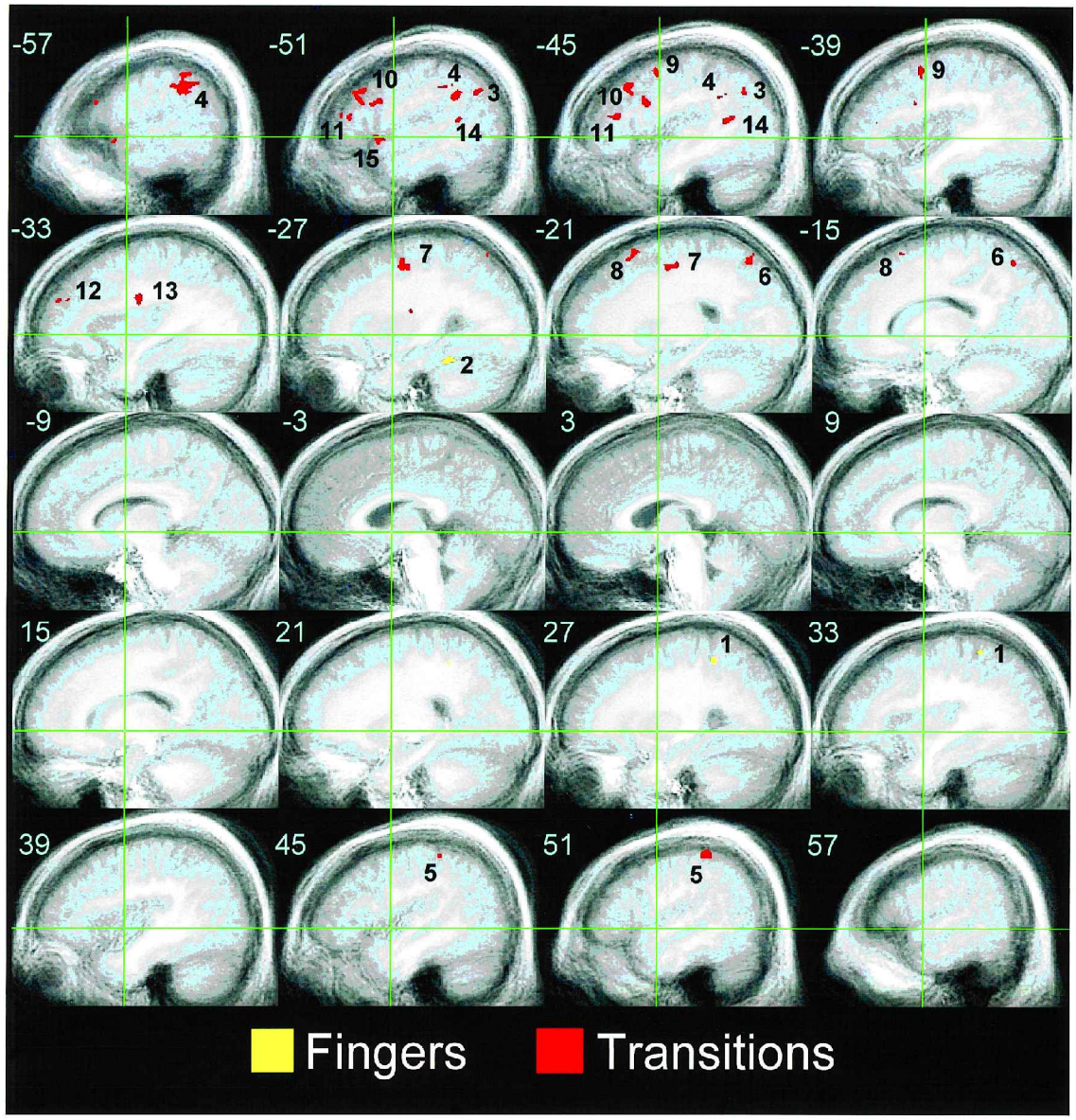

Figure 5. Areas of increased MR signal intensity associated with increases in programming complexity for heterogeneous sequences. Activated foci are based on ANOVAs that separately tested for changes in functional activity associated with increasing the number of fingers or transitions. Activation foci are from the analyses that excluded repeated sequences. Regions uniquely activated by fingers and transitions are shown in yellow and red, respectively. Numbers in the upper left of each slice represent mm from the interhemispheric fissure (–, left; +, right). Numbers adjacent to activated foci correspond to numbers in brackets listed in Table 5.

different fingers, contrary to our predictions. Most studies have reported a positive relationship between sequence complexity and activation in M1 and S1 (Table 1), especially when the number of different fingers or active muscle groups covaried with complexity (Colebatch, Deiber, Passingham, Friston, & Frackowiak, 1991; Gordon, Lee, Flament, & Ugurbil, 1998; Rao et al., 1993; Roland, Larsen, Lasses, & Skinhoj, 1980; Shibasaki et al., 1993). One potential explanation for the discrepant results may relate to differences among studies in the familiarity of sequences, because representations in the sensorimotor cortex become expanded with practice (Karni et al., 1995) and seem to reflect experience-specific knowledge related to the effectors (Grafton et al., 1998; Nudo, Milliken, Jenkins, & Merzenich, 1996). Previous studies have used only two to six different sequences, which were well-practiced or highly familiar (for example, finger-opposition tasks, typing) and performed cyclically during scanning. By comparison, in the present study, subjects performed 24 different se-

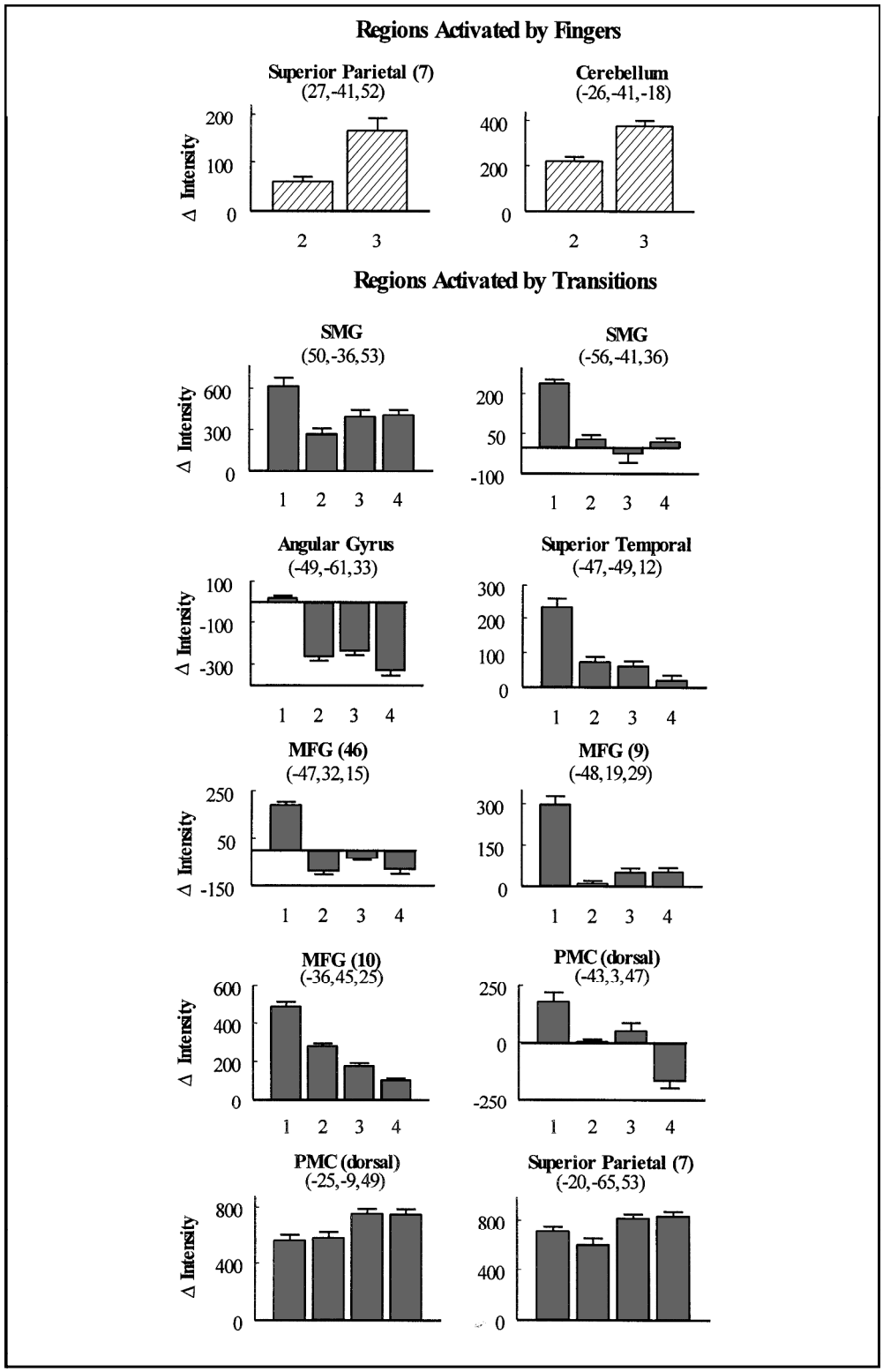

Figure 6. Change in activation intensity for heterogeneous sequences, excluding the repetitive condition. The change in activation intensity is displayed for regions activated by fingers (striped bars) and regions activated by transitions (solid bars), with the repetitive sequence condition excluded from the analyses. See Methods section for calculation of activation intensity from cross-correlation analysis and note that intensity values have been scaled by a factor of 1,000. Significant activation foci ($p < .005$) were defined by ANOVAs performed on the number of transitions (1–4) and the number of fingers (2–3). PMC=premotor cortex; SMG=supramarginal gyrus; SFG=superior frontal gyrus; MFG=middle frontal gyrus. Error bars=s.e.m.

quences, a different one in each trial, and received relatively little practice in each one prior to or during scanning. One speculation is that more extended practice may be required to establish differentiated sensorimotor representations of the sequences under the conditions of our experiment.

Neural Representations of Sequence-Specific Structure

The patterns of activation associated with variations in the number of fingers were complex, sometimes relating to the structure of individual sequences in ways that were not anticipated. First, activation of the left angular

gyrus, caudal SMG, superior temporal cortex, insula, and middle frontal gyrus covaried *negatively* with the number of transitions, such that it was greatest for 1 transition sequence and then significantly decreased for the other sequences. Others have reported a negative relationship with sequence complexity and inferior parietal cortex activation when sequence length was manipulated (Boecker et al., 1998; Sadato, Campbell, Ibanez, Deiber, & Hallett, 1996), but not sequence type (Table 1). There is mounting evidence that the inferior parietal cortex plays a role in encoding abstract or sequence-specific information, because activation increases in caudal area 40 with practice (Honda et al., 1998; Jenkins et al., 1994; Rauch et al., 1995; Sakai et al., 1998). This raises the possibility that the negative covariation in activation of area 40 with sequence length or the complexity of the abstract structure may be due to the greater practice required for building an abstract representation of more complex sequences. However, the precise nature of the encoding remains speculative in our study, and in others, because it is usually difficult to determine a priori how subjects will organize a series of movements. Sequential events can be encoded in many different ways, for example, by using associations between adjacent movements or developing more abstract organizations that integrate salient properties (for example, temporal, spatial) of movement patterns. Additionally, encoding may be mediated by language. This latter possibility is raised by the pattern of activation in the left hemisphere in interconnecting pathways associated with an articulatory loop of working memory, including the superior temporal cortex and the middle frontal gyrus (Figure 6) (Goldman-Rakic, 1987; Paulesu, Frith, & Frackowiak, 1993). One speculation is that the negative correlation between increases in finger transitions and activation of the left posterior parietal cortex was due to reduced phonological encoding of more structurally complex sequences. This account is compatible with the role of the left angular gyrus in acalculia (Levin & Spiers, 1985), the left posterior SMG in phonological storage (Paulesu et al., 1993; Smith, Jonides, & Koeppe, 1996), and the left superior temporal cortex, insula, and middle frontal gyrus network (Figure 6) in verbal working memory (Goldman-Rakic, 1987; Manoach et al., 1997; Paulesu et al., 1993; Smith et al., 1996). Activation suppression in two rostral PMd foci (– 19,18,58; – 43,3,47) for sequences containing two or more transitions (Table 5 and Figure 6) may be linked to suppression in area 46 for these same sequences, as area 46 projects to rostral PMd in monkeys (Ghosh & Gattera, 1995). This explanation is problematic, however, because a phonological encoding hypothesis would also predict increased activation in these same areas for repetitive sequences, which was not found.

Decreasing activation with sequence complexity might also reflect the reallocation of a system's attentional resources to other systems devoted to processing information in other modalities. This hypothesis might relate to the different patterns of activation found in the right SMG, which showed a *nonlinear* relationship with the number of transitions (Figure 6). While activation intensity in this region was also greatest for sequences involving one transition, it increased systematically from two to four transition sequences. This area has been widely associated with spatial attention (Posner & Dehaene, 1994), encoding spatial coordinates (Jonides et al., 1993; Smith et al., 1996), and more recently, it has been implicated in attentional mechanisms of temporal processing (Harrington, Haaland, & Knight, 1998). The timing of successive finger movements is partially determined by the pattern of finger repetitions and alternations (Povel & Collard, 1982; Restle, 1973). Simple sequences, like those containing 1 transition, may readily activate bilateral SMG because spatial, temporal, or phonological encodings are highly salient. However, encoding abstract structural properties of more complex sequences may require more practice and attentional resources (Cohen, Ivry, & Keele, 1990), because spatial and temporal cues for organizing sequential movements are less salient.

In contrast to the above findings, activation of the caudal PMd *positively* correlated with the number of finger transitions in both analyses. The PMd, which has reciprocal projections with the inferior and the superior parietal lobes (Boussaoud, Pellegrino, & Wise, 1996; Dum & Strick, 1991; Petrides & Pandya, 1984), appears to be involved in the retrieval of abstract action plans computed in the parietal lobe (Shadmehr & Holcomb, 1997). This is consistent with the greater sequence-specific activation of PMd than PMv in monkeys (Kettner et al., 1996; Kurata, 1994; Mushiake et al., 1991), and may suggest that this area is involved in the retrieval and the programming of sequential actions for movement execution. Other investigations of sequence complexity in humans have reported similar results (Table 1), but ours is the first to demonstrate that PMd activation specifically correlates with sequence structure, controlling for sequence length, and the number of different effectors.

Both structural properties of sequences also *positively* correlated with activation of left caudal area 7, near area 19, largely due to the greater activation intensity of heterogeneous than repetitive sequences (Table 4 and Figure 4). Although this effect was found for increases in transitions but not fingers, only when repeated sequences were omitted from the analyses (Table 5 and Figure 5), the power of the finger-effect test was substantially reduced. These results are consistent with some (Catalan, Honda, Weeks, Cohen, & Hallett, 1998; Van Oostende, Hecke, Sunaert, Nuttin, & Marchal, 1997), but not all studies (Table 1), whereas others have not analyzed the precise focus of activation within area 7 that correlates with sequence complexity (Dassonville

et al., 1998; Gordon et al., 1998; Wexler et al., 1997). The caudal–superior parietal area is traditionally thought to be involved in early visual processing of extrapersonal spatial coordinates (Ungerleider, Courtney, & Haxby, 1998). This view would predict that both properties of sequence complexity should correlate with activation within this area, because variations in both should increase the difficulty of translating a visual stimulus into a spatial code specifying the placement of fingers on the keypad. This traditional notion has been challenged by recent findings showing that activation in area 7 (anterior and posterior combined) was similar for finger sequences performed in intra- or extrapersonal space (Gordon et al., 1998), and correlated positively with sequence complexity when auditory digit-sequences were performed (Van Oostende et al., 1997). The caudal portion of the superior parietal cortex presumably translates a stimulus event (for example, auditory, visual, imagined) into the goal of the action. For finger sequences, this form of early processing might specify global, spatial, or temporal patterns of a sequential event, which should be easier to realize for more structurally simple than complex sequences. This speculation would suggest that the relationship between sequence complexity and area 7 activation should diminish with extended practice, because decoding should become more automatic. In fact, activation in area 7 decreases with practice (Dassonville et al., 1998; Hazeltine, Grafton, & Ivry, 1997; Schlaug, Knorr, & Seitz, 1994), which may explain why sequence complexity does not typically correlate with activation in posterior area 7, when sequences are highly familiar or well practiced.

Neither manipulation of complexity correlated with basal ganglia activation, despite the apparent role of the striatum in temporal ordering (Aldridge & Berridge, 1998; Berridge & Whishaw, 1992; Kermadi & Joseph, 1995). Nevertheless, our findings are consistent with most, but not all, functional imaging studies (Boecker et al., 1998; Gordon et al., 1998). Although our results appear at odds with the sequential-planning disturbances in PD (Benecke, Rothwell, Dick, Day, & Marsden, 1987; Harrington & Haaland, 1991; Jennings, 1995; Stelmach, Worringham, & Strand, 1987), these impairments are typically due to a decreased ability to plan ahead as sequence length increases. The SMA, which has reciprocal pathways to the basal ganglia (Alexander, DeLong, & Strick, 1986), has also been associated with the encoding of temporal order (Clower & Alexander, 1998). SMA activation was not found for repetitive sequences, a finding consistent with some (Gordon et al., 1998; Rao et al., 1993), but not all studies (Shibasaki et al., 1993). However, SMA activation also did not correlate with sequence complexity, contrary to most investigations (Table 1). A potentially crucial difference exists between our experimental methods and those of others: our subjects did not have to rely on internally generated models of a stimulus sequence, which correlates with SMA activation (Tanji, 1996), because on each trial a new sequence was displayed until the completion of the movement. This may also minimize the need for temporal ordering, unlike other studies in which sequences were performed from memory.

Summary

The identification of the neural underpinnings of properties of sequence structure is a first step toward understanding the different levels at which sequential movements are represented in the brain. The present study demonstrated that some neural systems mediate the sequencing of movements regardless of their structural properties, whereas others uniquely represent the surface and the abstract structure of sequential movements. A theoretical framework was put forth based on previous investigations, in which these issues have been studied using different approaches. Both properties of sequence structure correlated with activation in systems related to visual processing (extrastriate cortex) and preparing and retrieving somatosensory information (rostral SMG, PMv). Although increasing activation in the caudal superior parietal cortex was slightly more associated with abstract than surface complexity, existing theory would suggest that both aspects of sequence structure should influence early processes related to the identification of an action goal. The number of different fingers contained within a sequence positively correlated with activation in the anterior area 7 and the cerebellum, systems that have been associated with kinematic (Ashe & Georgopoulos, 1994; Ferraina & Bianchi, 1994; Kalaska et al., 1990; Scott et al., 1997) and sensorimotor representations (Bower, 1997), respectively. Conversely, increases in the number of finger transitions correlated with activation in distributed systems, including the angular gyrus, caudal area 40, the superior temporal cortex, the middle frontal gyrus, and the PMd. The patterns of activation in the inferior parietal cortex and interconnecting temporal-frontal pathways, and the hemispheric biases depended on the specific structure of sequences, but not the number of fingers used to perform the sequences. These results were consistent with the purported role of the inferior parietal cortex in encoding sequence-specific information (Honda et al., 1998; Jenkins et al., 1994; Sakai et al., 1998), although the specific nature of the encoding is speculative. Sequence-specific computations in the parietal cortex may be retrieved and programmed for execution in the PMd (Kettner et al., 1996; Kurata, 1994; Mushiake et al., 1991; Shadmehr & Holcomb, 1997). The finding that greater PMC activation (that is, volume) is found for response times to unpredictable than predictable finger movements (Dassonville et al., 1998) further suggests that both PMd and PMv support retrieval or preparatory processes, but perhaps for different forms of sensory information (Kettner et al., 1996; Kurata, 1994; Mushiake

et al., 1991). The overall results are consistent with the view that sequential events are represented at different levels that reflect their perceptual, sensorimotor, and abstract structural properties.

METHODS

Subjects

Fifteen normal volunteers (six males and nine females; 18 to 31 years of age with a mean of 23.9 years) participated in the study. All subjects were strongly right-handed [mean Laterality Quotient=94.3 on the Edinburgh Handedness Inventory (Oldfield, 1971)]. Potential subjects were excluded if they had a history of neurological or medical disease or were taking psychoactive medications. Written informed consent was obtained from each subject in accordance with institutional guidelines approved by the Medical College of Wisconsin. Two additional subjects were excluded because their accuracy rate fell below 70% correct on one or more of the experimental conditions.

Task Procedures

Subjects performed finger-key presses in response to numerical sequences that were presented visually on a screen. The subject rested his or her index (''1''), middle (''2''), and ring (''3'') fingers of the right hand on response keys that were arranged horizontally on a box, which was taped to the subject's right thigh and occluded from sight. There was a one-to-one mapping between a digit and a key. The digits 1, 2, and 3 corresponded to the left, middle, and right keys, respectively. Likewise, the left, middle, and right keys were always pressed using the index, middle, and ring fingers, respectively. Subjects were instructed not to move their left hand. Prior to each trial, subjects looked at the center of a blank screen. A trial began with a 5-digit number sequence appearing on the screen, cueing subjects to immediately perform the sequence as quickly and accurately as possible. The sequence remained on the screen for 2.5 sec, thereby minimizing memory demands, because the duration of the stimulus display was typically as long as the total time to execute the sequence (that is, RT+movement time [MT]). Specifically, conditions 7 and 8 (see below), which took the longest to execute, were completed, on the average, within 2023 msec (*SD*=±320 msec). Even if total execution time fell within 2 *SD* of the mean, the display would have terminated while the subject was initiating the last finger key press. Hence, it is unlikely that stimulus duration covaried with sequence complexity in a way that would have affected memory for the visual stimulus. The inter-trial interval was 3.0 sec. Subjects briefly practiced the sequencing conditions prior to scanning.

The dependent measures consisted of percent correct trials, RT, and MT. A correct trial was defined as all five key presses performed in the specified order. If subjects pressed the wrong key or pressed two or more keys simultaneously, the computer program registered an error, and these trials were excluded from the RT and MT data analyses. RT was measured from the time of stimulus onset to the first key press, and MT was the time from the end of the RT interval to the last key press. RT reflects the amount of time it takes to plan a sequence prior to movement, although response implementation time for the first key press is also included in this interval. MT reflects ongoing planning, motor control and implementation processes, and the influence of biomechanical factors associated with different effectors.

Table 2 depicts the experimental design and the sequences that were used. Sequence condition was blocked and within a block, one of three sequences was randomly presented on each trial. For example, in condition 1 (Table 2), one of three repetitive sequences (''11111'', ''22222'', or ''33333'') was randomly presented on each trial. Conditions 2–8 consisted of heterogeneous sequences which varied systematically in the number of transitions (0–4) and fingers (1–3). The order of the conditions was counterbalanced across subjects.

Functional Imaging

In the scanner, visual stimuli were computer-generated and rear-projected onto an opaque screen located at the subject's feet. Subjects viewed the screen through prism glasses and corrective lenses, if necessary. The viewing distance was 230 cm. fMRI was conducted on a 1.5 T General Electric Signa scanner equipped with a prototype 30.5 cm i.d. 3-axis local gradient head coil and an elliptical endcapped quadrature radio frequency coil allowing whole-brain functional imaging. Echo-planar (EP) images were collected using a single-shot, blipped, gradient-echo EP pulse sequence: echo time (TE)=40 msec; data acquisition time=40 msec, field of view (FOV)=24 cm, resolution=64×64. Sixteen contiguous sagittal 7-mm thick slices were selected to provide coverage of the entire brain (voxel size: 3.75×3.75×7 mm). Prior to functional imaging, high resolution 3-D spoiled gradient-recalled at steady-state (GRASS) anatomic images were collected: TE=5 msec, repetition time (TR)=24 msec, 40° flip angle, number of excitations (NEX)=1, slice thickness=1.2 or 1.3 mm, FOV=24 cm, resolution=256×128. Foam padding was used to limit head motion within the coil. Each image time series was spatially registered in-plane to reduce the effects of head motion using an iterative, linear, least squares method (Keren, Peleg, & Brada, 1988). Linear drift in each time series was removed using a regression analysis (Bandettini, Jesmanowicz, Wong, & Hyde, 1993).

An imaging series consisted of 64 sequential EP images collected with an interscan interval of 4 sec (total scanning duration=256 sec). The first two images of

each imaging series were removed from further analysis to allow the MR signal to reach steady state. Each series consisted of 10 cycles of a sequencing condition alternating with rest. During rest periods, subjects were instructed to remain still and look at the blank screen. The sequencing condition and rest periods were three images each (12 sec) in duration. Each activation cycle contained four 3-sec sequence trials for a total of 40 trials per imaging series. Subjects underwent eight consecutive series, one for each of the sequence conditions (Table 2). Order of the conditions was counterbalanced across subjects.

Functional Image Generation

Two methods were employed for generating functional images from an imaging time course. The first method was used to compare the repetitive (condition 1) and rest conditions within an imaging series by generating statistical parametric maps (SPMs). The second method, using cross-correlation analysis, enabled the use of analysis of variance statistics to make comparisons across imaging series to analyze the effects of varying the number of fingers and transitions.

For the first method, functional images were created by generating statistical SPMs of t-deviates reflecting differences between the repetitive condition and rest states at each voxel location for each subject (Rao et al., 1997a, b). This analysis was conducted to examine the regions that were activated by sequencing a simple repetitive movement. Specifically, *t*-tests were conducted at each voxel to measure changes in signal intensity between each of the 10-task epochs in an imaging series and a local baseline (that is, rest). The first image (4 sec) in the repetitive condition and rest periods was discarded from analysis due to the rise and fall time of the hemodynamic response (Bandettini et al., 1993). The first stage of the analysis involved averaging the final two images in each of the 10-task epochs. Next, the final two images of the rest periods preceding and following each task (four images in all) were averaged. A difference image was created by subtracting the average rest image from the corresponding average repetitive condition image. Each repetitive condition was compared to the neutral, rest image so that all areas involved in each repetitive condition could be localized. In all, 10 difference images were generated per subject. Finally, these mean difference values were compared on a voxel-by-voxel basis against a hypothetical mean of zero using pooled-variance student *t*-tests.

For the second method, functional images were generated using a cross-correlation technique (Bandettini et al., 1993; Rao et al., 1997a,b) to identify regions showing changes in activity as a function of the experimental manipulations. A series of phase-shifted sinusoids were used as reference waveforms. A least-squares fit between the reference waveforms and the time course series was performed on a voxel-by-voxel basis. The magnitude of the best fit (defined as the amplitude of the sinusoid generating the highest correlation with the time course) served as the functional image intensity. If $x(t)$ is a vector representing the acquired data in a single voxel, and $r(t)$ is a vector representing the selected reference waveform for that voxel (that is, the phase-shifted waveform with the best least-squares fit), then the magnitude of the least squares fit is a number a, such that a makes $x(t)=a*r(t)$ a least squares fit. In statistical terms, it can be shown that $a=r_{x(t)*r(t)}*(\sigma_{x(t)}/\sigma_{r(t)})$ where $r_{x(t)*r(t)}$ is the product–moment correlation between $x(t)$ and $r(t)$ and $\sigma_{x(t)}$ is the standard deviation of $x(t)$ and $\sigma_{r(t)}$ is the standard deviation of $r(t)$. Since $\sigma_{x(t)}$ is a measure of the amplitude of $x(t)$, and $1/\sigma_{r(t)}$ can be thought of as a constant applied to each voxel, a can be conceived of as containing information about the goodness of the least squares fit of the acquired time series with the selected reference wave form and the amplitude of the acquired time series.

Anatomical Standardization and Statistical Evaluation

For both functional image generation methods, high-resolution anatomical and functional images were linearly interpolated to volumes with 1 mm^3 voxels, co-registered, and converted to stereotaxic coordinate space (Talairach & Tournoux, 1988). Functional images were blurred using a 4-mm Gaussian full-width half-maximum filter to compensate for intersubject variability in anatomic and functional anatomy.

For the within-imaging series analysis (method 1), SPMs were averaged across the 15 subjects on a voxel-by-voxel basis to identify all foci demonstrating significant changes in image intensity within a single image series (that is, sequence condition). Thus, each voxel in the resulting averaged SPM contains an averaged *t*-statistic. The procedure of averaging statistics was chosen to guard against nonequal MR signal variances between subjects. A threshold was then applied to the averaged *t*-statistics to identify voxels in which the mean change in MR signal between rest and task was unlikely to be zero. The average of a set of *t*-deviates is not a tabulated distribution. Therefore, the Cornish–Fisher expansion of the inverse distribution of a sum of random deviates (Fisher & Cornish, 1960) was used to select a threshold ($t=1.55$, $p<10^{-e\ 6}$) for rejection of the null hypothesis. This threshold effectively eliminates false positive voxels from the functional maps.

For the between-imaging series analysis (method 2), repeated measures ANOVA was applied on a voxel-by-voxel basis across the 15 subjects. This analysis method identified regions demonstrating changes in functional activity associated with increasing sequence complexity. The functional image intensity generated from the

cross-correlation analysis was the dependent measure (see above). Two ANOVAs were performed, one for transitions and the other for fingers. The interaction between the two factors was not examined because, in the analyses of the behavioral data (see Results Section), the finger *X* transition interaction was not significant for RT, MT, or accuracy. To assess the effects of transitions, functional intensity maps for conditions 3 and 4 (two transitions), 5 and 6 (three transitions) and 7 and 8 (four transitions) were averaged (see Table 2) so that the transition factor consisted of five levels (0–4). The effect of transitions was compared using a cutoff *F*-value of 4.17 ($p<.005$, $df=4, 56$). The fingers effect was assessed by averaging maps from conditions 2, 3, 5, and 7 (two fingers) and 4, 6, and 8 (three fingers) so that the finger factor consisted of three levels (1–3). A cutoff *F*-value of 6.44 ($p<.005$, $df=2, 28$) was applied to test the effect of the number of fingers. The $p<.005$ cutoff was selected based on a reanalysis of the data using randomized (aperiodic) reference waveforms (Rao et al., 1997a,b). Using this procedure, no false positive clusters were identified using this cutoff value.

For both methods, a cluster-size threshold of 0.2 ml was applied as an additional procedure for removing false positive activation foci from the brain maps (Forman et al., 1995). Individual 3-D SPGR data from the 15 subjects were merged to produce an ''average brain'' for anatomical reference.

Acknowledgments

This research was funded by a grant from the Medical Merit Review, Department of Veterans Affairs (DLH, KYH) and a Program Project Grant (P01 MH51358) from the National Institute of Mental Health (SMR). We thank J. Cunningham, S. Fuller, T. Hammeke, G. Mallory, R. Reynolds, A. Rosen, D. Ward, and S. Woodley for their assistance.

REFERENCES

Aldridge, J. W., & Berridge, K. C. (1998). Coding of serial order by neostriatal neurons: A ''natural action'' approach-to-movement sequence. *Journal of Neuroscience*, *18*, 2777–2798.

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally-segregated circuits linking basal ganglia and cortex. In W. M. Cowan (Ed.), *Annual review of neuroscience* (pp. 357–381). Washington, DC: Society for Neuroscience.

Ashe, J., & Georgopoulos, A. (1994). Movement parameters and neural activity in motor cortex and area 5. *Cerebral Cortex*, *6*, 590–600.

Bandettini, P. A., Jesmanowicz, A., Wong, E. C., & Hyde, J. S. (1993). Processing strategies for timecourse data sets in functional MRI of the human brain. *Magnetic Resonance Medicine*, *30*, 161–173.

Barone, P., & Joseph, J. P. (1989). Prefrontal cortex and spatial sequencing in macaque monkey. *Experimental Brain Research*, *78*, 447–464.

Benecke, R., Rothwell, J. C., Dick, J. P. R., Day, B. L., & Marsden, C. D. (1987). Disturbance of sequential movements in patients with Parkinson's disease. *Brain*, *110*, 361–379.

Berridge, K. C., & Whishaw, I. Q. (1992). Cortex, striatum and cerebellum: Control of serial order in a grooming sequence. *Experimental Brain Research*, *90*, 275–290.

Bly, B. M., & Kosslyn, S. M. (1997). Functional anatomy of object recognition in humans: Evidence from positron emission tomography and functional magnetic resonance imaging. *Current Opinion in Neurobiology*, *10*, 5–9.

Boecker, H., Dagher, A., Ceballos-Baumann, O., Passingham, R. E., Samuel, M., Friston, K. J., Poline, J. -B., Dettmers, C., Conrad, B., & B'rooks, D. J. (1998). Role of the human rostral supplementary motor area and the basal ganglia in motor sequence control: Investigations with $H^2\ ^{15}O$ PET. *Journal of Neurophysiology*, *79*, 1070–1080.

Boussaoud, D., Pellegrino, G., & Wise, S. P. (1996). Frontal lobe mechanisms subserving vision-for-action vs. vision-for-perception. *Behavioural Brain Research*, *72*, 1–15.

Bower, J. M. (1997). Control of sensory data acquisition. In J. D. Schmahmann (Ed.), *The Cerebellum and cognition (pp. 489–513). San Diego: Academic Press.*

Catalan, M. J., Honda, M., Weeks, R. A., Cohen, L. G., & Hallett, M. (1998). The functional neuroanatomy of simple and complex sequential finger movements: A PET study. *Brain*, *121*, 253–264.

Cavada, C., & Goldman-Rakic, P. S. (1989). Posterior parietal cortex in rhesus monkey: II. Evidence for segregated corticocortical networks linking sensory and limbic areas with the frontal lobe. *Journal of Comparative Neurology*, *287*, 422–445.

Chen, R., Gerloff, C., Hallett, M., & Cohen, L. G. (1997). Involvement of the ipsilateral motor cortex in finger movements of different compexities. *Annals of Neurology*, *41*, 247–254.

Clower, W. T., & Alexander, G. E. (1998). Movement sequence-related activity reflecting numerical order of components in supplementary and presupplementary motor areas. *Journal of Neurophysiology*, *80*, 1562–1566.

Cohen, A., Ivry, R., & Keele, S. W. (1990). Attention and structure in sequence learning. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *16*, 17–30.

Colebatch, J. G., Deiber, M. -P., Passingham, R., Friston, K. J., & Frackowiak, R. S. (1991). Regional cerebral blood flow during voluntary arm and hand movements in human subjects. *Journal of Neurophysiology*, *65*, 1392–1401.

Dassonville, P., Lewis, S., Zhu, X., Ugurbil, K., Kim, S., & Ashe, J. (1998). Effects of movement predictability on cortical motor activation. *Neuroscience Research*, *32*, 65–74.

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.

Dum, R. P., & Strick, P. L. (1991). The origin of corticospinal projections from the premotor areas in the frontal lobe. *Journal of Neuroscience*, *11*, 667–689.

Ferraina, S., & Bianchi, L. (1994). Posterior parietal cortex: Functional properties of neurons in area 5 during an instructed-delay reaching task within different parts of space. *Experimental Brain Research*, *99*, 175–178.

Fisher, R. A., & Cornish, E. A. (1960). The percentile points of distributions having known cumulants. *Technometrics*, *2*, 209–226.

Forman, S. D., Cohen, J. D., Fitzgerald, M., Eddy, W. F., Mintun, M. A., & Knoll, D. C. (1995). Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): Use of a cluster-size threshold. *Magnetic Resonance in Medicine*, *33*, 639–647.

Gallese, V., Murata, A., Kasede, M., Niki, N., & Sakata, H. (1994). Deficit of hand preshaping after muscimol injection in monkey parietal cortex. *NeuroReport*, *5*, 1525–1529.

Gerloff, C., Corwell, B., Chen, R., Hallett, M., & Cohen, L. G. (1997). Stimulation over the human supplementary motor area interferes with the organization of future elements in complex motor sequences. *Brain*, *120*, 1587–1602.

Ghosh, S., & Gattera, R. (1995). A comparison of the ipsilateral cortical projections to the dorsal and ventral subdivisions of the macaque premotor cortex. *Somatosensory and Motor Research*, *12*, 359–378.

Goldman-Rakic, P. S. (1987). Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In V. Mountcastle & F. Plum (Eds.), *The nervous system, higher functions of the brain, Vol. 5, Handbook of physiology (pp. 373–417). Washington, DC: American Physiological Society.*

Goodale, M. A., Jakobson, L. S., & Servos, P. (1996). The visual pathways mediating perception and prehension. In A. M. Wing, P. Haggard, J. R. Flanagan (Eds.), *Hand and brain: The neurophysiology and psychology of hand movements (pp. 15–31). San Diego: Academic Press.*

Goodale, M. A., & Milner, A. D. (1992). Separate visual pathways for perception and action. *Trends in Neuroscience*, *15*, 35–62.

Gordon, A. M., Lee, J. H., Flament, D., & Ugurbil, K. (1998). Functional magnetic resonance imaging of motor, sensory, and posterior parietal cortical areas during performance of sequential typing movements. *Experimental Brain Research*, *121*, 153–166.

Grafton, S. T., Hazeltine, E., & Ivry, R. (1998). Abstract and effector-specific representations of motor sequences identified with PET. *Journal of Neuroscience*, *18*, 9420–9428.

Grafton, S. T., Mazziotta, J. C., Woods, R. P., & Phelps, M. E. (1992). Human functional anatomy of visually-guided finger movements. *Brain*, *115*, 565–587.

Graziano, M. S. A., & Gross, C. G. (1998). Spatial maps for the control of movement. *Current Opinion in Neurobiology*, *8*, 195–201.

Haaland, K. Y., Harrington, D. L., & Knight, R. T. (1999). Spatial deficits in ideomotor limb apraxia: A kinematic analysis of aiming movement. *Brain*, *122*, 1169–1182.

Harrington, D. L., & Haaland, K. Y. (1987). Programming sequences of hand postures. *Journal of Motor Behavior*, *19*, 77–95.

Harrington, D. L., & Haaland, K. Y. (1991). Sequencing in Parkinson's disease: Abnormalities in programming and controlling movement. *Brain*, *114*, 99–115.

Harrington, D. L., & Haaland, K. Y. (1992). Motor sequencing with left hemisphere damage: Are some cognitive deficits specific to limb apraxia? *Brain*, *115*, 857–874.

Harrington, D. L., Haaland, K. Y., & Knight, R. T. (1998). Cortical networks underlying mechanisms of time perception. *The Journal of Neuroscience*, *18*, 1085–1095.

Hazeltine, E., Grafton, S. T., & Ivry, R. (1997). Attention and stimulus characteristics determine the locus of motor-sequence encoding a PET study. *Brain*, *120*, 123–140.

Honda, M., Deiber, M. -P., Ibanez, V., Pascual-Leone, A., Zhuang, P., & Hallett, M. (1998). Dynamic cortical involvement in impicit and explicit motor-sequence learning — A PET study. *Brain*, *121*, 2159–2173.

Jeannerod, M. (1986). The formation of finger grip during prehension: A cortically-mediated visuomotor pattern. *Behavioural Brain Research*, *19*, 99–116.

Jenkins, I. H., Jahanshahi, M., Brown, R., Frackowiak, R. S. J., Marsden, C. D., Passingham, R. E., & Brooks, D. J. (1994). Impaired activation of mesial frontal cortex during self-paced movements in Parkinson's disease. *Neurology*, *44*, A352

Jennings, P. J. (1995). Evidence of incomplete motor programming in Parkinson's disease. *Journal of Motor Behavior*, *27*, 310–324.

Jonides, J., Smith, E., Koeppe, R. A., Awh, E., Minoshima, S., & Mintun, M. A. (1993). Spatial-working memory in humans as revealed by PET. *Nature*, *363*, 623–625.

Kalaska, J. F., Cohen, D. A. D., Prudhomme, M., & Hyde, M. L. (1990). Parietal area 5 neuronal activity encodes movement kinematics, not movement dynamics. *Experimental Brain Research*, *80*, 351–364.

Karni, A., Meyer, G., Jezzard, P., Adams, M. M., Turner, R., & Ungerleider, L. G. (1995). Functional MRI evidence for adult motor cortex plasticity during motor-skill learning. *Nature*, *377*, 155–158.

Kawashima, R., Naitoh, E., Matsumura, M., Itoh, H., Ono, S., Satoh, K., Gotoh, R., Koyama, M., Inoue, K., Yoshioka, S., & Fukuda, H. (1996). Topographic representation in human intraparietal sulcus of reaching and saccade. *NeuroReport*, *7*, 1253–1256.

Keele, S. W., Jennings, P. J., Jones, S., Caulton, D., & Cohen, A. (1995). On the modularity of sequence representation. *Journal of Motor Behavior*, *27*, 17–30.

Keren, D., Peleg, S., & Brada, R. (1988). Image sequence enhancement using sub-pixel displacements. *IEEE Conference on Computer Vision and Pattern Recognition*, 742–746.

Kermadi, I., & Joseph, J. P. (1995). Activity in the caudate nucleus of monkeys during spatial sequencing. *Journal of Neurophysiology*, *74*, 911–933.

Kerr, B. (1978). Task factors that influence selection and preparation for voluntary movements. In G. Stelmach (Ed.), *Information processing in motor control and learning* (pp. 55–69). New York: Academic Press.

Kettner, R. E., Marcario, J. K., & Clark–Phelps, M. C. (1996). Control of remembered-reaching sequences in monkeys: I. Activity during movement in motor and premotor cortex. *Experimental Brain Research*, *112*, 335–346.

Kurata, K. (1994). Information processing for motor control in primate premotor cortex. *Behavioural Brain Research*, *61*, 135–142.

Levin, H., & Spiers, P. A. (1985). Aculculia. In K. Heilman and E. Valenstein (Eds.), *Clinical Neuropsychology* (pp. 97–114). New York: Oxford University Press.

MacKay, D. G. (1985). A theory of the representation, organization, and timing of action with implications for sequencing disorders. In E.A. Roy (Ed.), *Neuropsychological Studies of Apraxia and Related Disorders* (pp. 267–308). Amsterdam: North-Holland.

Manoach, D. S., Schlaug, G., Siewert, B., Darby, D. G., Bly, B. M., Benfield, A., Edelman, R. R., & Warach, S. (1997). Prefrontal cortex fMRI signal changes are correlated with working-memory load. *Cognitive Neuroscience and Neuropsychology, 8,* 545–549.

Matsumura, M., Kawashima, R., Naito, E., Satoh, K., Takahashi, T., Yanagisawa, T., & Fukuda, H. (1996). Changes in rCBF during grasping in humans examined by PET. *NeuroReport*, *7*, 749–752.

Motter, B. C. (1993). Focal attention produces spatially selective processing in visual cortical areas V1, V2, and V4 in the presence of competing stimuli. *Journal of Neurophysiology*, *70*, 909–919.

Mushiake, H., Inase, M., & Tanji, J. (1991). Neuronal activity in the primate premotor, supplementary, and precentral motor cortex during visually-guided and internally-determined sequential movements. *Journal of Neurophysiology*, *66*, 705–718.

Nudo, R. J., Milliken, G. W., Jenkins, W. M., & Merzenich, M. M. (1996). Use-dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys. *Journal of Neuroscience*, *16*, 785–807.

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh Inventory. *Neuropsychologia*, *9*, 97–113.

Paulesu, E., Frith, C. D., & Frackowiak, R. S. (1993). The neural correlates of the verbal component of working memory. *Nature*, *362*, 342–345.

Petrides, M., & Pandya, D. N. (1984). Projections to the frontal cortex from the posterior parietal region in the rhesus monkey. *Journal of Comparative Neurology*, *228*, 105–116.

Poizner, H., Clark, M., Merians, A. S., Macauley, B., Rothi, L., & Heilman, K. (1995). Joint coordination deficits in limb apraxia. *Brain*, *118*, 227–242.

Posner, M. I., & Dehaene, S. (1994). Attentional networks. *Trends in Neuroscience*, *17*, 75–79.

Povel, D. -J., & Collard, R. (1982). Structural factors in patterned finger tapping. *Acta Psychologica*, *52*, 107–123.

Rao, S. M., Binder, J. R., Bandettini, P. A., Hammeke, T. A., Yetkin, F. Z., Jesmanowicz, A., Lisk, L. M., Morris, G. L., Mueller, W. M., Estkowski, L. D., Wong, E. C., Haughton, V. M., & Hyde, J. S. (1993). Functional magnetic resonance imaging of complex human movements. *Neurology*, *43*, 2311–2318.

Rao, S. M., Bobholz, J. A., Hammeke, T. A., Rosen, A. C., Woodley, S. J., Cunningham, J. M., Cox, R. W., Stein, E. A., & Binder, J. R. (1997a). Functional MRI evidence for subcortical participation in conceptual reasoning skills. *NeuroReport*, *8*, 1987–1993.

Rao, S. M., Harrington, D. L., Haaland, K. Y., Bobholz, J. A., Cox, R. W., & Binder, J. R. (1997b). Distributed neural systems underlying the timing of movements. *Journal of Neuroscience*, *17*, 5528–5535.

Rauch, S. L., Savage, C. R., Brown, H. D., Curran, T., Alpert, N. M., Kendrick, A., Fischman, A. J., & Kosslyn, S. M. (1995). A PET investigation of implicit and explicit sequence learning. *Human Brain Mapping*, *3*, 271–286.

Restle, F. (1973). Serial pattern learning: Higher order transitions. *Journal of Experimental Psychology*, *99*, 61–69.

Rizzolatti, G., Luppino, M., & Matelli, M. (1998). The organization of the cortical motor system: New concepts. *Electroencephalography and Clinical Neurophysiology*, *106*, 283–296.

Roland, P. E., Larsen, B., Lasses, N. A., & Skinhoj, E. (1980). Supplementary motor area and other cortical areas in organization of voluntary movements in man. *Journal of Neurophysiology*, *43*, 118–136.

Rosenbaum, D. A. (1980). Human movement initiation: Specification of arm, direction, and extent. *Journal of Experimental Psychology: General*, *109*, 444–474.

Rosenbaum, D. A., Inhoff, A. W., & Gordon, A. M. (1984). Choosing between movement sequences: A hierarchical editor model. *Journal of Experimental Psychology: General*, *113*, 372–393.

Sadato, N., Campbell, G., Ibanez, V., Deiber, M. P., & Hallett, M. (1996). Complexity affects regional cerebral blood flow change during sequential finger movements. *Journal of Neuroscience*, *16*, 2693–2700.

Sakai, K., Hikosaka, O., Miyauchi, S., Takino, R., Sasaki, Y., & Putz, B. (1998). Transition of brain activation from frontal to parietal areas in visuomotor sequence learning. *Journal of Neuroscience*, *18*, 1827–1840.

Schacter, D., Alpert, N. M., Savage, C. R., Rauch, S. L., & Albert, M. S. (1996). Conscious recollection and the human hippocampal formation: Evidence from positron emission tomography. *Proceedings of the National Academy of Science (USA)*, *93*, 321–325.

Schiller, P. H. (1994). Area V4 of the primate visual cortex. *Current Directions in Psychological Science*, *3*, 89–92.

Schlaug, G., Knorr, U., & Seitz, R. J. (1994). Inter-subject variability of cerebral activations in acquiring a motor skill: A study with positron emission tomography. *Experimental Brain Research*, *98*, 523–534.

Scott, S., Sergio, L. E., & Kalaska, J. F. (1997). Reaching movements with similar hand paths but different arm orientations. II. Activity of individual cells in dorsal premotor cortex and parietal area 5. *Journal of Neuroscience*, *78*, 2413–2426.

Shadmehr, R., & Holcomb, H. H. (1997). Neural correlates of motor memory consolidation. *Science*, *277*, 821–825.

Shibasaki, H., Sadato, N., Lyshkow, H., Yonekura, Y., Honda, M., Nagamine, T., Suwazono, S., Mageta, Y., Ikeda, A., Miyazaki, M., Fukuyama, H., Asato, R., & Konishi, J. (1993). Both primary motor cortex and supplementary motor area play an important role in complex finger movement. *Brain*, *116*, 1387–1398.

Smith, E. E., Jonides, J., & Koeppe, R. A. (1996). Dissociating verbal and spatial working memory using PET. *Cerebral Cortex*, *6*, 11–20.

Squire, L. R., Ojemann, J. G., Miezin, F. M., Petersen, S. E., Videen, T. O., & Raichle, M. E. (1992). Activation of the hippocampus in normal humans: A functional anatomical study of memory. *Proceedings of the National Academy of Science (USA)*, *89*, 1837–1841.

Stelmach, G. E., Worringham, C. J., & Strand, E. A. (1987). The programming and execution of movement sequences in Parkinson's disease. *International Journal of Neuroscience*, *36*, 55–65.

Sternberg, S., Monsell, S., Knoll, R. L., & Wright, C. E. (1978). The latency and duration of rapid movement sequences: comparisons of speech and typewriting. In G. E. Stelmach (Ed.), *Information processing in motor control and learning* (pp. 117–152). New York: Academic Press.

Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain.* New York: Thieme.

Tanji, T. (1996). New concepts of the supplementary motor area. *Current Opinion in Neurobiology*, *6*, 782–787.

Ungerleider, L. G., Courtney, S. M., & Haxby, J. V. (1998). A neural system for human visual-working memory. *Proceedings of the National Academy of Science (USA)*, *95*, 883–890.

Ungerleider, L. G., & Haxby, J. V. (1994). ''What'' and ''where'' in the human brain. *Current Opinion in Neurobiology*, *4*, 157–165.

Van Oostende, S., Hecke, P. V., Sunaert, S., Nuttin, B., & Marchal, G. (1997). FMRI studies of the supplementary motor area and the premotor cortex. *Neuroimage*, *6*, 181–190.

Wexler, B. E., Fulbright, R. K., Lacadie, C. M., Skudlarski, P., Kelz, M. B., Constable, R. T., & Gore, J. C. (1997). An fMRI study of the human cortical motor system response to increasing functional demands. *Magnetic Resonance Imaging*, *15*, 385–396.

Wiggs, C. L., & Martin, A. (1998). Properties and mechanics of perceptual priming. *Current Opinion in Neurobiology*, *8*, 227–233.