

Interconnected Large-Scale Systems for Three Fundamental Cognitive Tasks Revealed by Functional MRI

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Abstract

■ The specific brain areas required to execute each of three fundamental cognitive tasks—object naming, same–different discrimination, and integer computation—are determined by whole-brain functional magnetic resonance imaging (fMRI) using a novel technique optimized for the isolation of neurocognitive systems. This technique (1) conjoins the activity associated with identical or nearly identical tasks performed in multiple sensory modalities (conjunction) and (2) isolates the activity conserved across multiple subjects (conservation). Cortical regions isolated by this technique are, thus, presumed associated with cognitive functions that are both distinguished from primary sensory processes and from individual differences. The object-naming system consisted of four brain areas: left inferior frontal gyrus, Brodmann's areas (BAs) 45 and 44; left superior temporal gyrus, BA 22; and left medial frontal gyrus, BA 6. The same–different discrimination system consisted of three brain areas: right inferior parietal

lobule, BA 40; right precentral gyrus, BA 6; and left medial frontal gyrus, BA 6. The integer computation system consisted of five brain areas: right middle frontal gyrus, BA 6; right precentral gyrus, BA 6; left inferior parietal lobule, BA 40; left inferior frontal gyrus, BA 44; and left medial frontal gyrus, BA 6. All three neurocognitive systems shared one common cortical region, the left medial frontal gyrus, the object-naming and integer computation systems shared the left inferior frontal gyrus, and the integer computation and same–different discrimination systems shared the right precentral gyrus. These results are consistent with connectionist models of cognitive processes where specific sets of remote brain areas are assumed to be transiently bound together as functional units to enable these functions, and further suggest a superorganization of neurocognitive systems where single brain areas serve as elements of multiple functional systems. ■

INTRODUCTION

The neuroanatomy of human cortex consists of multiple cytoarchitectonic regions originally described by Brodmann (1994) and characterized according to functional specificity by direct cortical stimulations (Penfield, 1975) and by neurological investigations (Damasio, Grabowski, Tranel, Hichwa, & Damasio, 1996; Mesulam, 1990, 1994). These discrete cytoarchitectural regions are richly interconnected by a complex array of neuronal fibers in nonhuman primates (Fellerman & Van Essen, 1991; Goldman-Rakic, 1988; Pandya & Kuypers, 1969) and support the emerging view that complex brain function relies not only on the activity of specific structural areas but also on coordinated linkages between multiple brain areas (Mesulam, 1998; Bressler, 1995; Van Essen, Anderson, & Olshausen, 1994).

An empirical foundation for this notion has emerged from observations such as the ventral and dorsal stream segmentation of signals during visual tasks that involve object identification and localization respectively (Haxby et al., 1991; Mishkin & Ungerleider, 1982; Ungerleider &

Mishkin, 1982), and the covariance of signals observed during complex visual, attention, memory, and learning tasks that occur between regions of brain connected by known or assumed anatomical pathways (Buchel & Friston, 1997; Buchel, Coull, & Friston, 1999; Nyberg et al., 1996; McIntosh et al., 1994). Both anatomically distributed, as well as regionally specialized, processes have been proposed to account for a wide range of these cognitive tasks (Bullier & Nowak, 1995; Seek et al., 1995; Parks et al., 1991; Jennings, McIntosh, & Kapur, 1988). Collectively, these observations suggest that complex mental events are mediated by integrated assemblages of cortical areas. However, in part due to the difficulty in distinguishing a signal that primarily reflects cognitive activity from a signal that primarily reflects input sensory activity, and in part due to individual variations in cortical evoked responses, the essential neural substrates specialized for many neurocognitive tasks have not been determined.

We selected three tasks: object naming, same–different discrimination, and integer computations, to represent a set of cognitive actions corresponding to building blocks of cognition. These tasks are representative of

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early developmental milestones consistent with the hypothesis that a predisposition for language, categorization, and computational skills are partially biologically determined. Object naming, for example, represents the initial stages of language acquisition and is a well-studied cornerstone of linguistic processes. Neuroimaging studies reveal multiple brain areas associated with various aspects of object-naming tasks (Johnson, Paivio, & Clark, 1996; Price, Moore, Humphreys, Frackowiak, & Friston, 1996; Vandenberghe, Price, Wise, Hoesephs, & Frackowiak, 1996), and deficits in object-naming performance have been associated with damage to some of those particular areas (Mesulam, 1990; Carthy & Warrington, 1984; Damasio & Damasio, 1980; Geschwind, 1970). Nonetheless, isolation of the minimal set of cortical

areas that specifically drive object-naming operations in neurologically intact brains has challenged current neuroimaging techniques.

Similarly, judgments that involve comparisons of two objects by determination of whether they are “same” or “different” are also fundamental to the appreciation and classification of multiple objects, and serve as a representative elementary task for categorical processes. Neuroimaging studies of shape discrimination based on tactile presentations reveal an extensive array of brain areas active during this task (Roland, 1993) but do not further partition the active regions by sensory or cognitive contributions. Recordings from isolated neurons in intraparietal cortex of macaque monkeys during shape discrimination tasks reveal neural activity assumed to be

Table 1. Subject Information and Total Response Volume Per Task and Hemisphere

Subject	Age	Gender	Handedness	Laterality Quotient ^a	Object Naming		Same/Different Discrimination		Integer Computations	
					Percent Left	Percent Right	Percent Left	Percent Right	Percent Left	Percent Right
DM	29	F	Right	+89.47	59.8	40.2	37.4	62.6		
TBD	33	F	Ambidextrous	-66.00			52.2	47.8		
YM	30	F	Right	+100.00			26.6	73.4		
ST	24	F	Right	+100.00			46.8	53.2		
SG	29	F	Right	+100.00	58.2	41.8				
IR	28	F	Right	+55.55	48.4	51.6				
HP	31	F	Right	+81.81	49.9	50.2				
VM	23	F	Right	+69.23					63.6	36.4
JX	31	F	Ambidextrous	-20.00					52.0	48.0
Females' average percentage					54.0	46.0	40.8	59.2	57.8	42.2
HB	24	M	Right	+100.00	70.4	29.6	38.6	61.4		
KK	31	M	Right	+100.00	40.0	60.0	40.2	59.8	60.8	39.2
AK	29	M	Right	+50.00	54.4	45.6				
BK	29	M	Right	+90.48	40.7	59.3				
JP	28	M	Right	+46.66	52.8	47.3				
RV	35	M	Right	+100.00					62.8	37.2
CJ	19	M	Right	+100.00					72.7	27.3
MS	19	M	Right	+81.82					60.1	39.9
KA	22	M	Right	+100.00					58.5	41.5
BK	27	M	Right	+100.00					81.9	18.1
Males' average percentage					51.7	48.3	39.4	60.6	66.1	33.9
Total average percentage					52.8	47.2	40.1	59.9	62.0	38.0

^aEdinburgh handedness inventory (Oldfield, 1971).

associated with cognitive aspects of the shape discrimination task including attending to and recognizing shape features (Sereno & Maunsell, 1998). However, the minimal set of cortical areas that are required for same-different categorizations has not been established.

Finally, the ability to mentally perform calculations on positive integers requires a fundamental understanding of objects, magnitudes, and simple arithmetic operations, and the mastery of these operations precedes subsequent mastery of more complex quantitative operations. The notion of a biological basis for these numerical tasks is advanced by recent evidence that rhesus monkeys demonstrate the capacity to appreciate numerosity (Brannon & Terrace, 1998), and that human infants are endowed with abilities to appreciate quantity and numerosity (Dehaene, Dehaene-Lambertz, & Cohen, 1998). In some cases, lesion studies also suggest a disassociation between the ability to perform mathematical and verbal tasks (Dehaene & Cohen, 1997; Dehaene, Spelke, Pinel, Stanescu, & Tsivkin, 1999). Neuroimaging studies of cortical activity observed during mental multiplication (Dehaene, 1996; Dehaene & Akhavein, 1995; Dehaene et al., 1999) and counting backwards by sevens (Rueckert et al., 1996) confirm a high degree of cortical specificity for some mathematical operations. However, as with object naming and same-different discrimination, the minimal set of cortical areas required for integer computations excluding sensory processes is not determined.

These particular tasks also offer the advantage of incorporating a rationale based on previously organized philosophical notions and the expectation that these cognitive actions may be related by virtue of underlying fundamental neural operations. For instance, the foundations of cognitive processes thought to be essential for logic and reasoning were the focus of a classical school of philosophy founded by Bertrand Russell (Russell, 1938, 1960), and according to this school of thought, the assignment of proper names to objects was assumed to (1) predicate the cognate notion of the object, (2) form a basis for more complex notions of differences between objects, and (3) form the basis for the appreciation of numbers and quantities of objects (Johnson-Laird, 1983; Russell, 1938, 1960). These notions suggest a relationship that might be reflected in the underlying neurophysiology for each of these tasks.

In this study, we aim to isolate the cortical structures critically associated with object naming, object discrimination, and integer computations, and identify possible shared areas between the putative systems. Motivated to isolate and relate elements of cognition to specific neurological processes, we employed functional magnetic resonance imaging (fMRI) and a novel technique to isolate the cognitive-related activity that was conserved over all subjects. This approach assumes that these targeted higher cognitive elements of the task are not dependent upon the input modality (Chee, O'Craven,

Bergida, Rosen, & Savoy, 1999), and that the fundamental neural substrate will be conserved over all subjects (Friston, Holmes, Perice, Büchel, & Worsley, 1999). Task-related cortical areas activated by multiple sensory modalities are assumed to be primarily cognitive related, and areas conserved across all subjects are assumed to be associated with generalizable patterns rather than individually specific evoked responses.

RESULTS

Twenty subjects (9 females and 11 males) participated in fMRI studies during the performance of three tasks (Table 1). Each task was performed in three separate sensory modalities and the activity common to all three performances was assumed to represent the cortical "machinery" that serves the cognitive aspects of the task beyond the input- and sensory-related activity for each individual subject.

All conjunctive activity was labeled according to the anatomy, Brodmann's area (BA), and stereotactic coordinates based on the Human Brain Atlas (Talairach & Tournoux, 1988). Finally, the activity that was conserved for all subjects was isolated from the activity that was specific to individual subjects in order to yield the cortical substrate, either a single area or a system of areas, representative of the most fundamental machinery for the task (see Methods).

Conjunction: Brain Areas Active Across Multiple Sensory Presentations of the Task

In the case of the object-naming task, we assume that the neurological substrates associated with the cognition of object naming are active during naming when objects are seen or heard or felt. Therefore, these cognitive aspects of the tasks are assumed to be isolated from the sensory aspects of the tasks by the activity in common to all modalities. This "crossmodality" technique is illustrated in Figure 1 where the activity associated with seeing, hearing, and touching objects is shown by the red areas in the three left columns, respectively. The common activity among the three modalities (conjunction) operationally represents aspects of the object-naming events that are not sensory specific (shown in the right column by the yellow areas with the assigned anatomical labels).

For the same-different discrimination task, the activity in common across all tasks included judgments of whether two objects were the "same" or "different" irrespective of either the sensory modality employed to appreciate pairs of objects (visual or tactile) or specific physical features (shapes or colors). Thus, the resultant activity is assumed to represent the cognition of same-different discriminations for objects exclusive of the sensory-related activity.

The activity associated with integer computations including addition and multiplication was isolated by

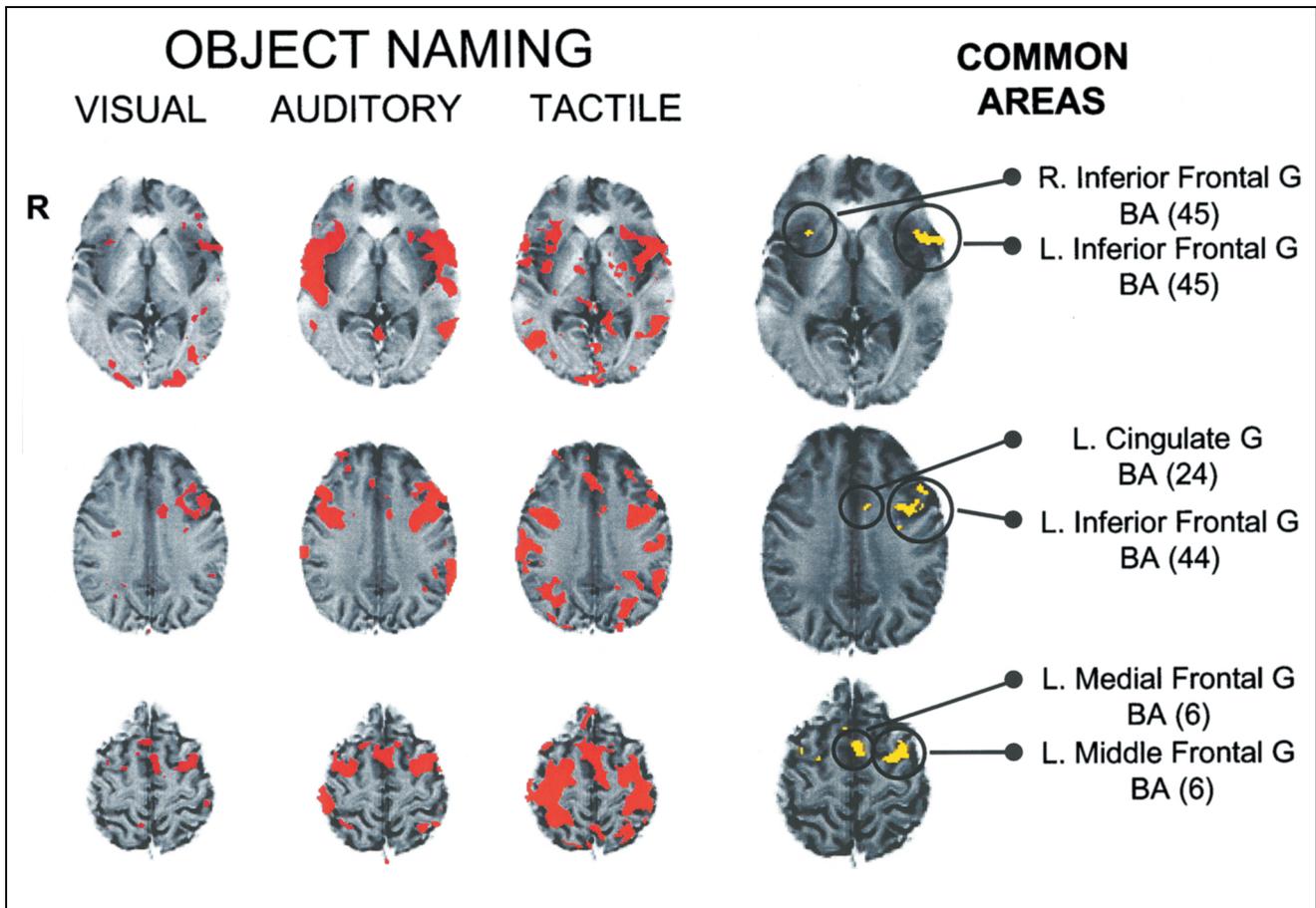


Figure 1. Method of conjunction across sensory modalities. Three representative brain slices (rows) are shown to illustrate the general method employed to isolate supramodal brain activity for one subject, HB. Active voxels are indicated as red for the object-naming task during visual presentations of pictures (column 1), auditory presentations of sounds (column 2), and tactile presentations of objects (column 3). The yellow voxels in column 4 indicate the activity in common to all three modalities following a Boolean AND operation and are assumed to include the representation of the aspects of object naming that are observed in common across the sensory modalities and to exclude processes not observed in common that are assumed to be primarily associated with the specific sensory modalities. The probability, p , of a false positive result for the common areas based on the conjunction of six runs (two for each modality) is $p \leq 4 \times 10^{-7}$.

presenting numbers visually, tactilely, and aurally. The conjunctive activity is assumed to yield brain areas called upon for the basic appreciation of numbers and computations reflected in these positive integer calculations.

In the event that no conjoint activity is observed, it is concluded either that the tasks are not the same, therefore do not share the same neural substrates, or that some cognitive functions are executed within the sensory cortices. Conversely, in the event that crossmodal cortical activity is observed, it is concluded that these regions perform some aspect of a common cognitive process (Bookheimer et al., 1998).

Conservation: Crossmodal Brain Areas Observed Across All Subjects

In the event that fewer than all (of a sufficient number of) subjects demonstrate activity within a given brain region, it is concluded that the region is not universally

required to execute the task; rather, the activity is assumed to be more likely due to individual variations. Conversely, in those cases where a brain region is active across all subjects, we conclude that it reflects a fundamental functional specialization that is characteristic of the population of normal subjects. This inference is based upon a random effects model with repeated observations across multiple subjects where simulations of individual case probabilities and true population characteristics (Friston et al., 1999) demonstrate that consistent activations in specific brain areas over six subjects provide a firm basis for inference to the population of subjects represented by the subjects engaged in the study. Assignment of a precise p value to this inference, however, requires the benefit of currently ongoing theoretical work in this area. However, empirically, six thresholded activations per area per subject in this study yields a false positive rate of $p \leq 4 \times 10^{-7}$ (see Methods) and the additional criteria that 100% of at least six subjects observe the same effect (conservation) sets a

Table 2. Proportion of Subjects for all Active Regions

<i>Anatomical Area</i>	<i>Object Naming (Percentage of Subjects) (N = 9)</i>	<i>Discrimination (Percentage of Subjects) (N = 6)</i>	<i>Integer Computation (Percentage of Subjects) (N = 8)</i>
Medial frontal gyrus	100.00	100.00	100.00
Middle frontal gyrus	100.00	100.00	100.00
Inferior frontal gyrus	100.00	100.00	100.00
Precentral sulcus	88.89	100.00	100.00
Inferior parietal lobule	77.78	100.00	100.00
Superior temporal gyrus	100.00	100.00	75.00
Middle temporal gyrus	100.00	83.33	87.50
Anterior cingulate gyrus	88.89	66.67	100.00
Superior parietal lobule	55.56	100.00	87.50
Inferior temporal gyrus	77.78	100.00	50.00
Occipital gyrus	66.67	100.00	25.00
Lingual gyrus	77.78	66.67	87.50
Precuneus	77.78	83.33	62.50
Angular gyrus	44.44	83.33	75.00
Supramarginal gyrus	44.44	83.33	75.00
Fusiform gyrus	77.78	66.67	50.00
Cuneus	55.56	66.67	75.00
Cerebellum	88.89	50.00	50.00
Postcentral gyrus	55.56	66.67	62.50
Calcarine sulcus	66.67	66.67	50.00
Superior frontal gyrus	66.67	50.00	50.00
Middle occipital gyrus	66.67	0.00	75.00
Caudate	77.78	16.67	25.00
Thalamus	55.56	16.67	50.00
Superior occipital gyrus	44.44	0.00	50.00
Inferior occipital gyrus	55.56	0.00	25.00
Hippocampus	33.33	16.67	25.00
Posterior cingulate gyrus	0.00	33.33	25.00
Insula	11.11	0.00	37.50
Putamen	44.44	0.00	0.00
Paracentral lobule	22.22	16.67	0.00

very high standard that is consistent with population inferences.

The crossmodal activity observed across all tasks is presented in Table 2. The left-hand column lists all active anatomical areas. The proportion of subjects with activity in each region is shown on the right three columns for each task. The cortical activity that was conserved

across all subjects (indicated as 100%) was further subdivided into left and right hemispheres and Brodmann's areas for each subject (Table 3a–c).

The individual variation across subjects illustrated in Tables 2 and 3 for the brain regions that were active over all modalities is also illustrated in Table 1 (right-hand columns) where the percent of total brain

Table 3. Cortical Activity Conserved Across all Subjects

a. Object Naming, Anatomical and Brodmann's Areas Per Subject and Hemisphere

Anatomical Area	Subjects											Conserved Brodmann's Areas	
	DM	HP	SG	IR	HB	AK	BK	JP	KK				
	<i>Left hemisphere</i>												
Medial frontal gyrus	6, 8	6	6, 8	6	6	6, 8, 9	6	6	6	6	6	6	6
Inferior frontal gyrus	44, 45, 47	44, 45	44, 45	44, 45	44, 45, 46, 47	44, 45, 47	44, 45, 46	44, 45, 47	44, 45	44, 45, 47	44, 45	44, 45	45 and 44
Superior temporal gyrus	22, 42	22, 42	22	22	22	21, 22	22	22	22, 42	22	22, 42	22, 42	22
Middle frontal gyrus	9, 46	6, 8, 9, 21, 46	-	9	6, 8, 9	9, 10, 22, 46	9, 6	6, 9, 10, 46	-	6, 9, 10, 46	-	-	-
Middle temporal gyrus	19, 21, 37, 39	21	-	39	21	37	39	21, 39	21	21, 39	21	21	-
	<i>Right hemisphere</i>												
Medial frontal gyrus	6, 8, 10	6	6, 8	6	6	6, 8, 9	6, 8	6, 8	-	6, 8	-	-	-
Inferior frontal gyrus	44, 45, 47	44, 45, 46	44, 45, 46	-	44, 45	44, 45, 47	44, 45	44, 45, 47	44, 45	44, 45, 47	44, 45	44, 45	-
Superior temporal gyrus	22, 38, 42	22	22	22	22, 42	22	22	22	42	22	42	42	-
Middle frontal gyrus	8, 9	6, 8, 9, 10, 21	6, 9	6, 9, 10, 46	6, 9, 21	4, 6, 9, 10	9, 10, 46	6, 9, 10, 46	6	6, 9, 10, 46	6	6	-
Middle temporal gyrus	19, 21, 22, 37	21, 39	21	21, 37	21, 39	21, 37	21, 39	21, 39	-	21, 39	21	-	-

<i>b. Same-Different Discrimination. Anatomical and Brodmann's Areas Per Subject and Hemisphere</i>										
<i>Anatomical Area</i>	<i>Subjects</i>									<i>Conserved Brodmann's Areas</i>
	<i>DM</i>	<i>TBD</i>	<i>YM</i>	<i>ST</i>	<i>HB</i>	<i>KK</i>				
	<i>Left hemisphere</i>									
Medial frontal gyrus	6	6	6	6, 8	6	6	6	6	6	6
Inferior parietal lobule	7, 40	40	-	7, 40	40	7, 40	-	7, 40	-	-
Precentral gyrus	4, 6	6	4	6	6	-	-	-	-	-
Superior temporal gyrus	22	-	22	22	-	-	-	-	-	-
Inferior temporal gyrus	37	-	37	-	19, 37	19	-	19	-	-
Superior parietal lobule	7	7	-	7	7	7	-	7	-	-
Occipital gyrus	18, 19, 37	18, 19	19	18, 19, 37	19	18	-	18	-	-
Inferior frontal gyrus	44	44	45	44, 45	45, 46	44	-	44	-	-
Middle frontal gyrus	9	6, 9	-	6	6	6, 46	-	6, 46	-	-
	<i>Right hemisphere</i>									
Medial frontal gyrus	6	6	6	6	6	-	-	-	-	-
Inferior parietal lobule	7, 40	40	40	40	40	40	-	40	-	40
Precentral gyrus	6	6	4, 6	6	6	6	-	6	-	6
Superior temporal gyrus	22, 42	22	-	22	22	22	-	22	-	-
Inferior temporal gyrus	37	37	37	37	19	-	-	-	-	-
Superior parietal lobule	7, 40	-	7	7	7	7	-	7	-	-
Occipital gyrus	19	18, 19	19	18, 19	19	-	-	-	-	-
Inferior frontal gyrus	44, 45	44	-	44, 45	44, 45	44, 45	-	44, 45	-	-
Middle frontal gyrus	6, 9	-	6	6, 9	6	6, 9, 46	-	6, 9, 46	-	-

<i>c. Integer Computation. Anatomical and Brodmann's Areas Per Subject and Hemisphere</i>												
<i>Anatomical Area</i>	<i>Subjects</i>										<i>Conserved Brodmann's Areas</i>	
	<i>VM</i>	<i>JX</i>	<i>RV</i>	<i>CJ</i>	<i>MS</i>	<i>KA</i>	<i>KK</i>	<i>BK</i>				
	<i>Left hemisphere</i>											
Medial frontal gyrus	6	6	6	6	6	6	6	6	6	6	6	6
Inferior parietal lobule	40	40	40	40	40	40	40	40	40	40	40	40
Inferior frontal gyrus	44, 45	44, 45	44	44, 45	44, 45	44, 45	44, 45	44, 45	44, 45	44, 45	44, 45, 47	44
Middle frontal gyrus	6, 9	6, 9, 10	6, 9, 46	6, 9	6, 9	6, 9, 46	6, 9, 46	6, 9, 46	6, 9, 46	6, 9, 46	6, 8, 9, 46	-
Precentral gyrus	4, 6	6	4, 6	6	4, 6	-	-	-	-	-	6	-
Anterior cingulate gyrus	24, 32	32	24	32	24, 32	24	24	24	24	24	24	-
	<i>Right hemisphere</i>											
Medial frontal gyrus	6	6	6	6	6	6	6	6	6	6	8, 9	-
Inferior parietal lobule	40	40	40	-	-	40	40	40	40	40	40	-
Inferior frontal gyrus	44, 45	44	44, 45	-	44, 45	44, 45	44, 45	44, 45	44, 45	44, 45	44, 47	-
Middle frontal gyrus	6, 9, 46	6, 8, 9	6, 9	6, 9, 46	6, 9	6, 9	6, 9	6, 9	6, 9	6, 9	6, 8, 9	6
Precentral gyrus	4, 6	6	4, 6	6	6	4, 6	4, 6	4, 6	4, 6	4, 6	6	6
Anterior cingulate gyrus	24, 32	-	24	-	24, 32	24	24	24	24, 32	32	24	-

Table 4. Network Coordinates

<i>Task</i>	<i>Anatomical Region</i>	<i>Area</i>	<i>Center-of-Mass^a</i>		
			<i>x</i>	<i>y</i>	<i>z</i>
Object Naming	Medial frontal gyrus (GFd)	6	9	-6	53
	Superior temporal gyrus (GTs)	22	57	-26	9
	Inferior frontal gyrus (GFi)	44	49	10	25
	Inferior frontal gyrus (GFi)	45	40	25	8
Same-Different Discrimination	Medial frontal gyrus (GFd)	6	9	-7	52
	Inferior parietal lobule (LPi)	40	-46	-45	40
	Precentral gyrus (GPrC)	6	-43	-11	36
Integer Computations	Medial frontal gyrus (GFd)	6	9	-4	54
	Inferior parietal lobule (LPi)	40	45	-39	40
	Inferior frontal gyrus (GFi)	44	49	9	20
	Middle frontal gyrus (GFm)	6	-33	-2	50
	Precentral gyrus (GPrC)	6	-42	-8	47

^aTalairach and Tourneau coordinates (Talairach & Tournoux, 1988).

volume activated within each hemisphere for each subject and task shows profound subject-to-subject variation. For example, in the object-naming task, the extreme left-right distribution of activated brain area ranges from approximately 70–30% (HB) to 40–60% (KK) respectively; in the same-different discrimination task the left-right distributions range from approximately 27–73% (YM) to 52–48% (TBD); and the distributions in the integer computation task range from approximately 82–18% (BK) to 52–48% (JX). Gender has been suggested as one possible source of individual variation in hemispheric dominance for some language-related tasks (Shaywitz et al., 1995). However, as illustrated in Table 1, the hemispheric asymmetries observed for the three specific tasks employed in this study do not suggest that the effects are gender-related.

Crossmodality and Conserved Neurocognitive Systems

In the case of object naming, four regions were conserved across all subjects: left medial frontal gyrus (BA 6), left inferior frontal gyrus (BA 44 and BA 45), and left superior temporal gyrus (BA 22) (Table 3a, right column). Three regions were conserved across all subjects for the same-different discrimination tasks: left medial frontal gyrus (BA 6), right precentral gyrus (BA 6), and right inferior parietal lobule (BA 40) (Table 3b, right column). Finally, five regions were conserved across all subjects in the positive integer computation tasks: left

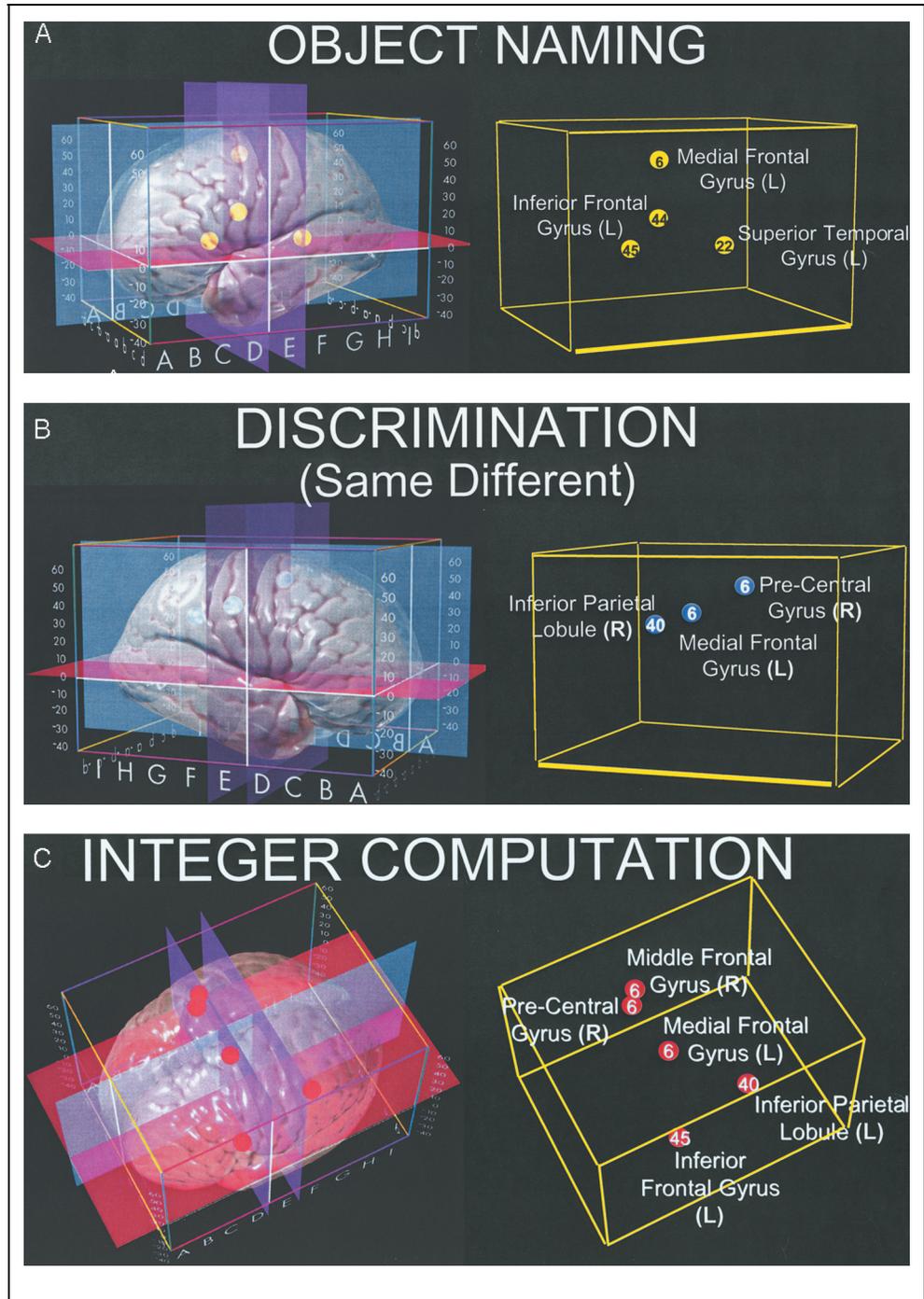
medial frontal gyrus (BA 6), left inferior frontal gyrus (BA 44), left inferior parietal lobule (BA 40), right middle frontal gyrus (BA 6), and right precentral gyrus (BA 6) (Table 3c, right column). A three-dimensional center-of-mass averaged over all subjects for each of the conserved regions provides the best estimate of these locations in standardized stereotactic space (Table 4), and these locations are presented on three-dimensional views of a standard brain atlas for each task (Figure 2). These observations are consistent with the hypothesis that these cognitive tasks are the purviews of specific and transiently bound constellations of multiple brain areas, which we refer to as large-scale neurocognitive systems.

DISCUSSION

Object Naming

The observed elements of the object-naming system are consistent with expectations based on clinical observations: including putative Broca's Area (BA 44 and BA 45), putative Wernicke's Area (BA 22), and putative supplementary motor area (BA 6) (Roland, 1993) on the dominant hemisphere (Figure 2a). The anatomical connections between these areas are well described (Seltzer & Pandya, 1989; Petrides & Pandya, 1988) and characteristic aphasias are reported for lesions in each of the three general areas (Mesulam, 1990; Carthy & Warrington, 1984; Damasio & Damasio, 1980). The hypothesis that these areas are bound together as a unified functional

Figure 2. The large-scale neurocognitive systems. The locations of each of the components that are coactive and presumed bound together in the service of object naming (A), same–different discriminations (B), and integer computations (C) are illustrated by “balls” located within the three-dimensional “glass” brain based upon the Talairach and Tournoux Human Brain Atlas stereotactic coordinate system (left). These regions are extracted in the wire-frame space (right) to clarify the anatomical labels and Brodmann’s areas. The coordinates for the components (listed in Table 4) have been converted to the mm scale whereas the standard transparent brains are shown on the sector scale. (A) is shown from the left side view with anterior brain toward image left. (B) is shown from the right side view with anterior brain toward the figure right. (C) is shown from a rotated top-down view to illustrate the cross-hemisphere locations of active brain regions. Anterior brain faces the lower left page. Each of these systems was determined by a “super conjunction” where all (at least six) subjects showed these active areas following the cross-modality conjunction illustrated in Figure 1. Based on a model of independent observations across subjects, the probability of a false positive finding for each area would be estimated as $n(4 \times 10^{-7})$ where n is the number of subjects who participated: nine for object naming, six for same–different discrimination, and eight for integer computation.



entity during object-naming tasks is also consistent with recent findings of both functional and temporal cooperation between the anterior and posterior language-sensitive regions (Posner & Pavese, 1998). We take this consistency between the findings of this study and these prior observations as further support for the hypothesis that the function of object naming depends upon this basic framework of multiple brain areas.

Based on the inference that these findings appropriately describe the population of similar normal sub-

jects, it also follows that object naming performed in any modality should require the activity of these four regions in a similar group of subjects in addition to activity associated with a specific sensory input system, and other individually specific patterns of activity. We evaluated this prediction retroactively on a population of 16 right-handed adult volunteers who participated in fMRI studies where visual object-naming tasks were performed. In all cases, these four regions were present within the individual responses, as well as the

expected visual areas consistent with the predictions of this study.

Same-Different Discrimination

In the same-different discrimination system, two out of the three regions were represented on the right hemisphere, inferior parietal lobule (BA 40) and precentral gyrus (BA 6) (Figure 2b). This finding is consistent with previous observations that the right inferior parietal lobule is associated with cognitive manipulations of spatial information, and that the ability to judge whether rotated objects are same or different is particularly vulnerable to right posterior brain damage (Milner & Goodale, 1995; Butters, Barton, & Brody, 1970). To our knowledge, the right precentral gyrus and left medial frontal gyrus have not previously been implicated for this task, although both are active during cognitive tasks, which may share some cognitive operations with same-different discriminations (Fiez & Peterson, 1998).

Integer Computation

The integer computation system also extends across both hemispheres (Figure 2c). Of particular note is the left inferior parietal lobule (BA 40), which is consistent with deficits in number processing observed in patients with focal injury to the left inferior parietal regions, and also developmental dyscalculia in children with damage to the same area (Dehaene et al., 1996, 1998). Results of the integer computation study also implicate the involvement of left hemisphere inferior frontal regions active during object-naming tasks as has been also suggested by exact arithmetic operations (Dehaene et al., 1999). Beyond the language-related regions, the activity in precentral sulcus has also been previously observed with a greater response for computational approximation than for exact calculation (Dehaene et al., 1999), and is consistent with the interpretation that subjects in this study performed the operations using combinations of exact and approximate strategies, which involved components of the language systems (GFi, BA 44; Dehaene et al., 1999), as well as areas unique to computation (LPi, BA 40, and GFm, BA 6), and shared by the same-different system (GPrC, BA 6). In this study, subjects were not instructed to differentiate between computational styles, so both may be represented. The observations of this study are also aligned with these previous findings in that the neural substrate called upon for mathematical operations is not synonymous with that called upon for language-related tasks although some common regions may be involved for some strategies. Thus, the observed regions coactive during positive integer computation, as well as object-naming and discrimination tasks, are, in general, in accordance with previous findings.

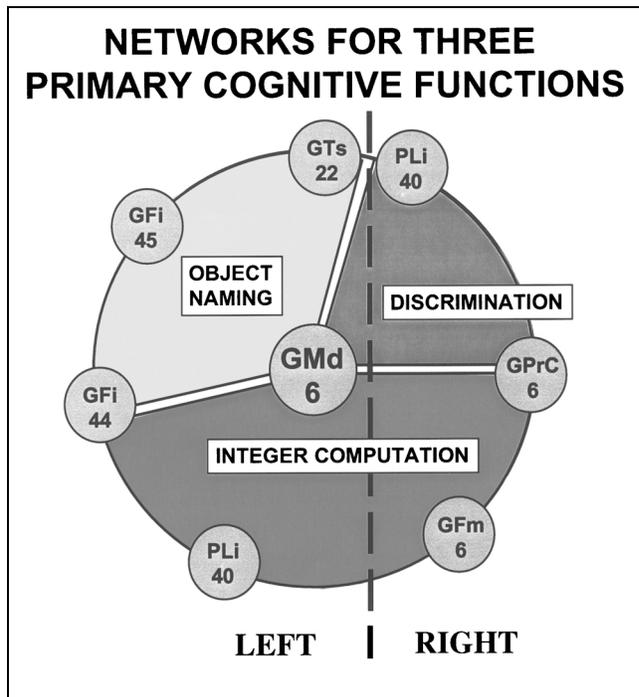


Figure 3. A system of large-scale neurocognitive systems. A schematic diagram of the interrelationships between systems for object naming, same-different discrimination, and integer computations. Abbreviations for brain areas are defined in Table 4. The left medial frontal gyrus (GFi, BA 6) is common to all three systems, the left inferior frontal gyrus (GFi, BA 45) is common to object naming and integer computations, and right precentral gyrus (GPrC, BA 6) is common to integer computations and same-different discrimination.

Interrelated Large-scale Neurocognitive Systems

The interrelationships between the three neurocognitive systems determined in this study (Figure 3) suggest an interconnected global scaffold of systems that serve these primary cognitive functions. The yellow field includes the object-naming system; the blue field includes the discrimination system; and the red field includes the integer computation system. This schematic draws attention to the common left medial frontal gyrus (center).

The medial frontal gyrus has been previously implicated in language (Roland, 1993; Mesulam, 1990), in the motor system (Picard & Strick, 1996), in inductive reasoning (Goel, Gold, Kapur, & Houle, 1997), in thinking (Roland & Friberg, 1985), in attention (Ishi et al., 1999; Nagahama et al., 1999), in memory (Carlson et al., 1998; Petit et al., 1998), and in the activation of appropriate procedures for the execution of mathematical computations (Lucchelli & DeRenzi, 1993). The finding that it is engaged during all three of the tasks employed in this study is consistent with a multifunctional role of this area, and suggests that functions such as object naming, same-different discriminations, and integer computations either share some basic neural operations

or that the medial frontal gyrus is functionally diverse. Either notion is supported by the close proximity of all three activity centroids in the left medial frontal gyrus (Table 4). In particular, the three-dimensional center-of-mass coordinates for object-naming, discrimination, and computation tasks are nearly overlapping in the medial frontal gyrus: object naming ($x = 9, y = -6, z = 53$), discrimination ($x = 9, y = -7, z = 52$), and computation ($x = 9, y = -4, z = 54$).

Other shared areas include the left inferior frontal gyrus (employed for both object naming and integer computations) and the right precentral gyrus (employed for both discrimination and integer computation tasks). In the case of the regions shared for two of the systems, the averaged centroids were slightly displaced for each of the regions (see Table 4), possibly adding task-specific subspecializations within these areas to the above possible interpretations of either common operations between the two tasks or functional diversity within the brain regions.

Summary

A novel and stringent fMRI neuroimaging strategy (with-in-subjects conjunction of activity associated with multiple sensory modalities, followed by across-subjects conservation of active brain areas) was directed toward the problem of isolating basic cortical working parts that enable three fundamental cognitive tasks: object naming, same-different discrimination, and integer computation. These findings contribute specific hypotheses for more direct investigation of connectivity such as path analysis (Buchel & Friston, 1997; Buchel et al., 1999), covariation of EEG recordings (Rodriguez et al., 1999; Posner & Pavese, 1998), and covariation of event-related fMRI signals (Nagahama et al., 1999). The conjunction and conservation technique described in this study does not rely upon prior knowledge of functional specificity and is uniquely suited for the investigation of human systems involved in high-level cognitions that often challenge the capabilities of animal subjects.

Three tasks were selected as representative of foundations for advanced cognitive and problem solving ability: object naming, same-different discrimination, and integer computation. A specific constellation of distributed brain regions (referred to as a neurocognitive system) was found for each of these tasks, with component elements that are consistent with previous clinical observations, neuroimaging findings, and inferences to a population of normal subjects. All three systems shared one common cortical area, left medial frontal gyrus. In addition, the integer computation system shared one area with the same-different discrimination system, right precentral gyrus, and one area with object naming, inferior frontal gyrus, suggesting either common neural processes for these cognitions or functional diversity of the shared brain areas.

These findings are consistent with the hypothesis that multiple brain regions cooperate as elements of a working unit to execute these cognitive tasks, and that a single brain area can be integral to multiple cognitive tasks as previously suggested for memory functions (McIntosh, 1998). These findings also offer the first determinations of specific systems that serve naming, discrimination, and simple computations, and suggest a biological determination for these large-scale neurocognitive systems.

METHODS

Imaging

A 1.5-T magnetic resonance scanner and a standard head coil (General Electric) located in the Department of Radiology at Memorial Sloan-Kettering Cancer Center was used to obtain T2*-weighted images with a gradient echo pulse sequence (echo time, 60 msec; repetition time, 4000 msec; flip angle, 60°), which was sensitive to magnetic resonance signal changes induced by alteration in the proportion of deoxyhaemoglobin in the local vasculature accompanying neuronal activation (Ogawa, Lee, Nayak, & Glynn, 1990). The cubic size of each volume element, voxel, was approximately 10 mm³ where the in-plane resolution was approximately 1.5 × 1.5 mm and slice thickness was 4.5 mm. Twenty-one contiguous slices of brain were obtained parallel to the AC/PC line, a standard reference line that intersected the superior edge of the anterior commissure and the inferior edge of the posterior commissure. This orientation allowed direct comparison of the acquired images with the Talairach and Tournoux Human Brain Atlas (Talairach & Tournoux, 1988). The 21 slices covered the entire cortex for all subjects. Conventional high-resolution (T1 weighted) images were also acquired along sagittal planes and at the same axial plane locations as the T2*-weighted images during each imaging session and served as a reference for subsequent labeling of the anatomical and Brodmann's areas, as well as the atlas sectors.

Thirty-six images of the whole brain were acquired during each run, which lasted 2 min, 24 sec. The initial three images of each run were not retained in order to assure that all acquisitions were acquired at a common level of magnetic susceptibility. A repeated block design was employed where 10 images (40 sec) were acquired during a baseline epoch, which was followed by a stimulation or task epoch of 11 images (44 sec) and a recovery baseline epoch. The first image of the stimulation epoch was not retained to allow the signal to reach a steady state, and the first two images acquired after the stimulation epoch were also not retained in order to allow the signal to return to a stable recovery baseline acquired during the final 10-image (40 sec) epoch. Images for all tasks were acquired on two separate runs (see Kim, Relkin, Lee, & Hirsch, 1997 and Hirsch et al., 1995 for further methodological details).

Analysis

All brain images for each subject were computationally aligned to allow direct comparisons between all conditions using a common coordinate (Woods, Mazziotta, & Cherry, 1993) and a two-dimensional Gaussian filter (approximately two to three voxels at half-height) was applied. Significant signal changes for each run were identified by a multistage statistical analysis, which compared average signals acquired during baseline and stimulation epochs. Signal averages were required to be statistically different on each of the two same-condition runs (Kim et al., 1997; Hirsch et al., 1995). An “active” voxel was, therefore, defined as any voxel in which the average magnetic resonance signal acquired during the period of the stimulation was significantly different from both the average initial and average recovery baseline levels on two separate occasions.

This “coincidence” requirement is based on the assumption that signals originating from noise sources are distinguished from signals originating from real events by the probability of a repeat occurrence at the same location. The criterion for significance, p , of two replicated runs (coincidence) was set at $p \leq .007$ (empirically determined from the analyses of images acquired on individuals during resting conditions). This relatively lenient level served to reduce the possible problem of a thresholding artifact where meaningful results might not be appreciated due to an inappropriately high criterion for threshold.

Voxels that passed all statistical criteria for each of three tasks and, therefore, were reliably activated on six separate occasions (conjunction between three modalities) resulted in a vanishingly small false positive rate based on both response consistency and on the signal-to-noise characteristics of the signal. Empirical determinations of false positive occurrences based on images acquired during resting states indicated that the probability of a false positive result using this conjunction method was approximately $p \leq 4 \times 10^{-7}$. Similar determinations based on images acquired on a spherical container of copper sulfate solution (General Electric) revealed similar rates.

This analysis strategy based on “logical inclusion” (which we have previously referred to as “coincidence” in the case of two runs) achieves a rigorous level of confidence while minimizing the risk of a threshold artifact. Further, the specific assumptions of response linearity that are applied to subtractive analyses (Jennings, McIntosh, Lapur, Tulving, & Houle, 1997) do not apply to this logical inclusion technique. All data were obtained at the same level of statistical stringency applied uniformly across all subjects.

Subjects were recruited according to institutional guidelines and were all right-handed as assessed by the Edinburgh handedness inventory (Oldfield, 1971) except for TBD who was ambidextrous (Table 1). The

mean age of subjects was 28.4 ± 4.4 years. Subjects were randomly assigned to the imaging tasks and were not required to participate in all studies due to the large numbers of runs. However, KK participated in each on separate experimental sessions, and subjects DM and HB participated in two of the three tasks. Other subjects participated in only one task.

A modified “forward-transform” method was developed to assign labels to the active brain areas where brain topology was employed as an index to labels on the Human Brain Atlas (Lancaster et al., 1997). The stages of assignment included: (1) identification of the brain slice passing through the AC/PC line and location of respective commissures on the axial view; (2) assignment of an atlas plate to each brain slice; (3) location of the vertical AC/PC plane on all brain slices; (4) location of the central sulcus on all T2*-weighted slices where it was represented and confirmation of those landmarks on all T1*-weighted images; (5) assignment of the anatomical labels, Brodmann’s areas, and atlas sectors for each active cluster; and (6) determination of the active cluster volume based on the voxel count for each area. Brain images with “colored” voxels indicating brain activity following all Boolean AND operations were displayed slice by slice on the original T2*-weighted images with a grid indicating actual voxel location. The corresponding set of 21 high-resolution T1 images acquired on the same plane lines was employed to clarify all anatomical landmarks on the T2*-weighted images, and, in particular, all representations of the central sulcus. All of the above information were incorporated in the assignment of Talairach and Tournoux plates to each of the brain slices. This process was achieved in the same manner for all subjects. Initially, the axial atlas plate no. 6 at +24 cm was assigned to the brain slice at the top of the ventricles. Since some atlas slices vary in thickness by 1–2 mm both above and below the ventricle line, the plate-to-slice assignments were made based on the anatomy as represented on the corresponding T1-weighted images, and were reconciled between two independent experienced readers. Further, the anterior and posterior commissures visible on the axial slice passing through the AC/PC line marked the coordinates of the vertical anterior and posterior commissure planes. These coordinates were noted on each slice using the brain coordinates and incorporated into the labeling procedure. Individual regions of active brain were separated by outlining the boundaries of each active area and a count of all active voxels within each regional cluster was obtained. Finally, the specific “active” areas were assigned anatomical names, Brodmann’s areas, and atlas sectors based on judgments of brain and atlas correspondence. This process yielded a summary tabulation containing anatomical region, volume of activity, and the transformed atlas sectors for each task. All judgments were made by at least two independent investigators and all uncertainties were reconciled by efforts to max-

imize internal consistency based on reference to high-resolution sagittal and axial slices. The Talairach coordinates were further crosschecked where possible by comparison with the corresponding listing of brain labels provided by the preliminary database label server (Talairach Daemon, <http://ric.uthscsa.edu/projects>) under development by the Human Brain Project P20MH/DA52176, and were determined to be consistent. Since these standard coordinate referencing systems are currently under development and tighter atlas-to-brain relationships will be further refined in the future, the coordinates and assignments reported here will be made available on the web: <http://fMRI.org> for any possible future “fine tuning” as new technologies emerge.

Brain regions that were consistently activated (conserved) across all subjects were taken as the system elements (Table 3). This is the most conservative approach and more lenient criteria could also be set. For example, brain regions active during a particular task in, say, 90% of subjects would indicate the most likely “nearest ring” of involved structures. This information is presented in Table 2. The epicenter of activity averaged across all subjects for each conserved region (100%) was determined as the three-dimensional center-of-mass (shown in Table 4 and Figure 2). The minimum number of subjects for each task was set at six prior to the data acquisition, and was based in part on determinations of centroid stability as a function of sample size during pilot stages of this study. For a representative set of system regions, the centroid positions were found to be asymptotically stable at four to five subjects. Further, arguments described in Friston et al., 1999 suggest that consistent activation in a specific brain area over six subjects is sufficient for inference to the population.

Object Naming

The object-naming task was performed silently (internal speech) to minimize head movements and was similar to tasks previously employed in neuroimaging studies of language (Kim et al., 1997). Objects were presented in three modalities: visual, auditory, and tactile, and each modality was run twice. During all stimulation epochs (all modalities) 10 objects were presented at 4-sec intervals. Each of the two runs for each modality was similar except that all objects were novel. Therefore, a total of 20 individual objects was presented for each modality. All objects were ordinary “every day” items that were readily identifiable, and all subjects confirmed that each item was named as it appeared. The subject was instructed to name the object using the sentence, “This is a . . .” The visual objects were black and white line drawings of familiar items that were back-projected onto a screen located in front of the subject as viewed through the slanted mirror located above the head coil. The drawings subtended approximately $7^\circ \times 7^\circ$ of visual

angle. The auditory stimuli were recorded sounds of familiar objects that were heard through headphones designed to reduce background scanner noise (Resonance Technology), and the tactile objects were familiar items that were both magnetically inert and conveniently presented and retrieved to and from the subjects hands at 4-sec intervals. Subjects employed both hands placed in front of them to sense the objects, and were blindfolded both during the auditory and tactile conditions in order to prevent visual stimulation during these runs. The order of runs and conditions was counter balanced and interleaved over the entire session. A Boolean AND operation (conjunction) across all three modalities (six runs) for each subject revealed the system of brain operations involved in the task of object naming irrespective of the operations of the sensory modality employed to appreciate the objects.

Same or Different Discriminations

Similar to the object-naming task, “same” or “different” judgments were performed silently by internal speech on two objects presented simultaneously. Discriminations were made using pairs of stimuli presented visually and tactilely that were composed of three shapes: squares, triangles, and circles. In the case of the visual presentations, the subject judged “same” or “different” with respect to either the shape of the paired objects or the color of the paired objects (red, green, or blue) presented every 4 sec on two runs each. In the case of the tactile presentations, each hand was presented a wooden block of one of the three shapes, which was changed every 4 sec. The subject judged whether the two simultaneous shapes were “same” or “different.” A blindfold was applied for these runs to eliminate all visual input, and all subjects confirmed that each pair of items was discriminated as it appeared. A Boolean AND (conjunction) operation across all three tasks (six runs)—visual shape, visual color, and tactile shape—revealed the system of brain operations involved in judgments of whether two simultaneous objects were the same or different irrespective of either the sensory modality employed to appreciate the object or the specific features of the object.

Integer Computations

Subjects performed two types of mathematical computations: addition and multiplication on pairs of integer numbers presented visually, tactilely and aurally. The method of visual presentations was similar to the visual methods previously described for the object naming and same-different discriminations. Although the orders of number pairs were counter-balanced for each run, the numbers were identical for all three tasks. Each visual panel included three pairs of single digit integers and remained displayed for

approximately 4 sec. Subjects were instructed to do as many computations as possible but were under no pressure to complete all. However, if all computations were completed prior to a new display, subjects were instructed to repeat the computations. In the case of the tactile presentations, subjects (who were blindfolded) received a pair of plastic numbers to each hand every 4 sec. Subjects practiced the number identification prior to the experiment and were instructed to focus on the numerical operation. In the case of the auditory presentations, subjects (who were blindfolded) performed the instructed operation on pairs of numbers presented by recorded voice and heard through the head phones employed in the object-naming tasks. All subjects reported that each computational task was performed as it appeared. As in the previous tasks, the integer computation task consisted of six runs (two runs for each modality). Each of the paired runs for each modality included one addition run and one multiplication run. A Boolean AND operation (conjunction) across all three modalities revealed the system of brain operations involved in integer computations.

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The data reported in this experiment have been deposited in the National fMRI Data Center (<http://www.fmridc.org>). The accession number is 2-2001-111G6.

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