Top-down Modulation of Early Sensory Cortex

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Data from nine previous studies of human visual information processing using positron emission tomography were reanalyzed to contrast blood flow responses during passive viewing and active discriminations of the same stimulus array. The analysis examined whether active visual processing (i) increases blood flow in medial visual regions early in the visual hierarchy and (ii) decreases blood flow in auditory and somatosensory cortex. Significant modulation of medial visual regions was observed in six of nine studies, indicating that top-down processes can affect early visual cortex. Modulations showed several task dependencies, suggesting that in some cases the underlying mechanism was selective (e.g. analysis- or feature-specific) rather than non-selective. Replicable decreases at or near auditory Brodmann area (BA) left 41/42 were observed in two of five studies, but in different locations. Analyses that combined data across studies yielded modest but significant decreases. Replicable decreases were not found in primary somatosensory cortex but were observed in an insular region that may be a somatosensory association area. Decreases were also noted in the parietal operculum (perhaps SII) and BA 40. These results are inconsistent with a model in which the precortical input to task-irrelevant sensory cortical areas is broadly suppressed.

The sensory activity produced by a visual stimulus can be modulated by the manner in which that stimulus is processed (Mountcastle *et al.*, 1975; Robinson *et al.*, 1978; Bushnell *et al.*, 1981; Moran and Desimone, 1985; Haenny and Schiller, 1988; Corbetta *et al.*, 1991a; Dupont *et al.*, 1993; Motter, 1993; Haxby *et al.*, 1994; Simpson *et al.*, 1995). Top-down modulations can be separated into two general cases, selective and non-selective. In the selective case, performance of a task modulates a set of neurons concerned with a task-relevant feature, spatial region, object or modality. Selective modulations are generally thought to reflect the effects of selective attention. In the non-selective case, performance of a task modulates all sensory responses, irrespective of their task relevance. Non-selective modulations are often thought to reflect effects of tonic or phasic arousal.

Single cell studies in behaving monkeys consistently show selective modulations of cell activity in extrastriate regions such as V4, but have yielded conflicting results with respect to V1 (Wurtz and Mohler, 1976; Moran and Desimone, 1985; Haenny and Schiller, 1988; Motter, 1993). Non-selective modulations in striate and extrastriate cortex have been less extensively examined. Wurtz and Mohler (1976) reported that only a small percentage of V1 cells showed spatially nonselective modulations. These cells increased their activity, relative to a no-task control, when monkeys either made a saccade or released a bar to the dimming of a stimulus outside the cell's receptive field. Mountcastle *et al.* (1987) measured the responses of V4 neurons to peripheral stimuli during three conditions: attentive fixation of a light whose dimming must be detected, the intertrial interval and a quiescent state in which no task was given. Cells showed equivalent activity during attentive fixation and the intertrial interval, but less activity during the quiescent state. This latter effect presumably reflects non-specific arousal.

Many studies of visual perception in humans have now been conducted with neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). These studies provide a new source of evidence concerning top-down modulations of early visual areas (Corbetta *et al.*, 1991a; Dupont *et al.*, 1993; Haxby *et al.*, 1994; DeYoe *et al.*, 1995; Simpson *et al.*, 1995). Corbetta *et al.* (1991a) reported medial blood flow increases along or near the calcarine sulcus when subjects judged the shape, color or speed of a stimulus array as compared with a passive condition in which the same array was presented but subjects simply maintained fixation. Modulations in early medial areas from an active task, relative to a passive baseline, have also been reported by Dupont *et al.* (1993), Haxby *et al.* (1994), DeYoe *et al.* (1995) and Simpson *et al.* (1995).

Although modulations can be caused by selective or non-selective mechanisms, they indicate that early visual areas can be modulated by top-down processes. In this paper, we present a reanalysis of nine PET studies involving visual processing in order to determine the generality of these modulations across a wide variety of visual tasks.

While performance of a visual task can increase blood flow in early visual cortex, it may also produce decreases in primary and association sensory cortical areas of task-irrelevant modalities such as audition and somesthesis. If blood flow decreases reflect decreased neural activity in the corresponding cortex, they might increase selectivity for visual stimulation by suppressing the effects of auditory or somatosensory transients that might compete for attention and interfere with the performance of the primary visual task. Haxby *et al.* (1994) reported large blood flow decreases during visual processing in primary auditory cortex, an auditory association region (the posterior region of the superior temporal gyrus), primary somatosensory cortex and the posterior insula, a region that has been activated by passive vibrotactile stimulation (Burton *et al.*, 1993; Coghill *et al.*, 1994; Drevets *et al.*, 1995).

Blood flow decreases in primary or association cortex of task-irrelevant sensory modalities have also been reported during non-visual tasks. Fiez *et al.* (1995) observed blood flow decreases in primary somatosensory cortex during performance of auditory discriminations, while Kawashima *et al.* (1995) found that performance of a tactile discrimination task produced significant blood flow decreases in lateral areas of extrastriate cortex and the inferior parietal lobe, although not in primary visual cortex. Since decreases in auditory or somatosensory cortex were not found in an earlier study of visual processing (Corbetta *et al.*, 1991a), the generality of this phenomenon was examined through a reanalysis of a large set of previously collected data.

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Table 1
Sample sizes for all experiments

Study	Generate		Test		Total		Auditory	Somatosensory
	Subjects	Scan pairs	Subjects	Scan pairs	Subjects	Scan pairs		
1. Same–Different Discrimination	10	22	10	21	10	43	x	x
2. Visual Search 1	10	17	12	24	13	41	x	x
3. Visual Search 2	14	27	14	40	14	67	x	x
4. Visual Search 3	15	35	15	37	15	72	x	x
5. Spatial Attention	14	17	14	20	18	37	x	
6. Language	6	6	7	17	13	23		
7. Practice Language	12	32	13	39	13	71		
8. Memory	10	16	13	32	23	48		
9. Cross-modal Imagery	6	10	7	14	13	24	x	x
Total	97	182	105	244	132	426		

For those experiments in which subjects contributed scan pairs to both the generate and test groups, the sum of the number of subjects in the generate and test groups exceeded the total number of subjects in the experiment (Total). The last two columns indicate the experiments included in the analysis of blood flow decreases in auditory and somatosensory areas. Although auditory blood flow decreases were analyzed for the cross-modal imagery study, this study was not included in the analyses that combined data across experiments (see text for details).

Materials and Methods

The analysis was conducted on a set of 10 experiments, all of which have previously been published. Two experiments were virtually identical and were therefore combined. All nine studies (Tables 1 and 2) involved comparisons between active tasks in which subjects made judgements based on a visual stimulus while maintaining fixation on a central cross, and passive tasks in which the same or a very similar stimulus was presented but subjects were simply instructed to remain fixated on the cross. In some passive conditions, subjects also made a motor response (e.g. pressing a key) on each trial. The term 'passive' therefore refers to the fact that subjects did not make a discrimination based on the displayed stimulus. The nine studies differed primarily in the nature of the stimulus displays and the tasks performed on those displays (Table 2). Informed consent for subjects in all studies was obtained prior to participation following guidelines approved by the Human Studies Committee (IRB) and the Radioactive Drug Research Committee of Washington University.

PET Methodology

The general PET methodology for all experiments was similar. Experiments were conducted on a PETT VI tomograph (Ter-Pogossian *et al.*, 1982; Yamamoto *et al.*, 1982), which provides seven transverse slices with a 14.4 mm interslice distance. During PET scans, earplugs were inserted to dampen background noise and a molded plastic facial mask was fitted to each subject's head to reduce movement (Fox *et al.*, 1985). Stimuli were presented on a color monitor positioned ~40–50 cm from the subject and black cloth was placed around the monitor to reduce extraneous visual input. The experimental room lights were dimmed during scans. Cooling fans and the scanner itself provided low-level background noise. All displays involved a central fixation cross and EOG was monitored in most conditions.

^{15}O-labeled water (half-life of 123 s) was used as a blood flow tracer and administered as an i.v. bolus injection. The number of scans varied across studies, but in each case there was a delay of at least 10 min between scans to allow decay of ^{15}O. The PETT VI system was used in the low-resolution mode. Images were reconstructed to 17 mm full width at half-maximum using filtered back-projection (Yamamoto *et al.*, 1982). As blood flow increases are known to be a linear function of radiation counts for scans of <1 min duration, measurements of arterial blood radioactivity following ^{15}O injection were not made (Herscovitch *et al.*, 1983; Fox *et al.*, 1984).

All PET images were normalized by linear scaling for global blood flow so that fluctuations in the flow would not obscure local changes induced by task manipulations (Fox *et al.*, 1987b). A lateral skull X-ray, taken during the PET session to verify head alignment, was used to identify the glabella and inion as markers to locate the position of the transverse plane intersecting the anterior and posterior commissures (Talairach *et al.*, 1967; Fox *et al.*, 1985). Each image was then transformed into a standardized stereotaxic space (Talairach and Tournoux, 1988) and the voxels in the transformed images measured 2.0 × 2.0 × 2.0 mm.

Studies

Although each experiment differed in many characteristics, they fell into broadly defined categories. Experiments 1–4 did not involve any linguistic processes and motor demands were similar in both the active and passive conditions (e.g. either both or neither active and passive conditions involved a keypress response), while experiments 6–8 involved language-related processing with vocal responses in the active tasks and no responses in the passive tasks. The term language-related is purposely vague. While the input (a letter string) and output (a vocal response) characteristics of experiments 6–8 were similar, the intermediate processes related to the selection of an appropriate response were very different. Experiments 5 and 9 mixed the motor and language factors. Experiment 5 did not involve language and did not require a response in the passive condition. Experiment 9 involved language and required a keypress in both the active and passive conditions.

The same procedures were applied for the analysis of blood flow increases in early visual cortex and blood flow decreases in auditory and somatosensory cortex. The analysis of decreases in auditory areas, however, was mainly restricted to experiments 1–5, which included tasks that did not involve language or vocal responses (see Table 1). Subjects in experiments 6–8 produced vocal responses in the active, but not passive tasks, producing confounding effects of auditory feedback. The conditions of experiment 9 (Cross-modal Imagery) required only manual responses but involved linguistic judgements, including judgements of phonology, that might obscure blood flow decreases in auditory cortex. This experiment was therefore not included in the analyses that combined data across experiments but was analyzed separately. The analysis of blood flow decreases in somatosensory cortex was restricted to the five experiments in which the response requirements of the active and passive conditions were the same (experiments 1–4 and 9).

Overview of Analyses

Several analyses, described in detail below (see Specific Analysis Procedures), were conducted to address different questions. The reliability of observed regional blood flow changes was determined by a replication analysis. An area was first identified in a hypothesis-generating group of active minus passive scan pairs (called the *generate group*) and was then tested for replication via a one-tailed *t*-test in a separate hypothesis-testing group of active minus passive scan pairs (called the *test group*). The location of the replicated change was given by the corresponding focus in the union of the scan pairs from the generate and test group (called the *generate plus test group*), and the *z*-score for this change was computed. Within-experiment analyses were then conducted at the replicated foci to determine whether reliable active minus passive changes differed according to the active task within an experiment (e.g. the read and verb-generation tasks of the Language experiment). Since the replication analysis might miss small or moderate blood flow changes, a secondary analysis involving a lenient *z*-score/

Table 2
Display characteristics and task descriptions for individual experiments

Experiment	Display	Task
Successive Same–Different Discrimination (Corbetta *et al.*, 1991a,b)	two 400 ms arrays of moving, colored rectangles, separated by 200 ms	1. Color: Do colors in two arrays match? 2. Motion: do speeds in two arrays match? 3. Shape: do rectangles in two arrrays match? 4. Divided: do colors, speeds and rectangles in two arrays match? (note: two-choice manual unspeeded response in active tasks; alternating keypress on successive trials in the passive condition)
Visual Search 1 (Corbetta *et al.*, 1990, 1991a,b)	four colored squares, each at 17°, 100 ms duration four colored rectangles, each at 17°, 100 ms duration	1, 2. Color: does array contain particular color? Target color present on 5 or 50% of trials 3, 4. Color-form: does array contain oriented rectangle of particular color? Target rectangle present on 5 or 50% of trials (note: no overt response during either active or passive condition. In active tasks, subjects report approximate target percentage after scan)
Visual Search 2 (Corbetta *et al.*, 1990, 1991a,b)	same as Visual Search 1 but eccentricity = 5°	1, 2. Color: same as Visual Search 1. Target frequency 5, 45% 3, 4. Color-form: same as Visual Search 1. Target frequency 5, 45% (note: two-choice manual unspeeded response in active tasks; alternating keypress on successive trials in passive condition)
Visual Search 3 (Corbetta *et al.*, 1995)	four windows of moving, colored dots. Each window at 2 deg, 500 ms duration	1, 2. Color: is particular color present? Target frequency 20, 80% 3, 4. Motion: is particular speed present? Target frequency 20, 80% 5, 6. Conjunction: is conjunction of of color and speed present? Target frequency 20, 80% (note: two-choice manual speeded response in active tasks; alternating keypress on successive trials in passive condition)
Spatial Attention (Corbetta *et al.*, 1993)	bilateral horizontal array of ten boxes. Asterisk appears for 150 ms in each box, in a predictable sequence	1. Left field/left direction: detect asterisk moving in left field and dir. 2. Left field/right direction: detect asterisk moving in left field, right dir. 3. Right field/left direction: detect asterisk moving in right field, left dir. 4. Right field/right direction:detect asterisk moving in right field and dir. (note: simple speeded manual response in active tasks; no response in passive condition)
Language (Petersen *et al.*, 1989)	noun printed in upper case letters, 1° below fixation, 150 ms duration	1. Read: subject reads the noun 2. Verb-generation: subject names a verb appropriate to the noun (note: speeded vocal response in active tasks; no response in passive condition)
Practice Language (Raichle *et al.*, 1994)	noun printed in upper case letters, 1° below fixation, 150 ms duration	1. Read naive: subject sees list of nouns for first time 2. Verb-generation naive: subject sees list of nouns for first time 3. Verb-generation practice: noun list has been practiced ten times 4. Read practice: noun list has been practiced ten times 5. Verb-generation novel: task conducted with new list 6. Read novel: task conducted with new list (note: speeded vocal response in active tasks; no response in passive condition)
Memory (Buckner *et al.*, 1995)	three letter word stem presented in upper case letters 1° below fixation, 3 s duration	subjects see study list of words prior to each condition and indicate how much they liked each word 1. Baseline: subjects complete word stems 2. Priming: subjects complete word stems. 50% of words from study list 3. Cued-recall: subjects recall words from study list. 50% of words from study list (note: speeded vocal response in active tasks; no response in passive condition)
Cross-modal Imagery (Fiez *et al.*, 1995)	word presented in upper case letters 1° below fixation, 150 ms duration	1. Orthographic: does word contain lower case ascender (i.e. 'd')? 2. Phonological: does word contain long vowel? (note: two-choice manual speeded response in active tasks; alternating keypress on successive trials in passive condition).

magnitude threshold was also conducted (see Analyses of Additional Blood Flow Changes).

Averaging of Scan Pairs

The analyses in this paper combined data from the different conditions and subjects within an experiment and, in some cases, combined data from different experiments. These averaging procedures are described below.

Averaging of Scan Pairs within an Experiment

All active conditions within an experiment generally involved identical or very similar stimuli but differed in how the stimuli were processed. The various conditions of an experiment were therefore combined (e.g. active minus passive blood flow changes were summed across the active conditions) in order to increase the stability and sensitivity of the analyses.

Since scan pairs from subjects were sometimes missing or not analyzed for technical reasons, the total number of scan pairs from each subject generally differed, and the total number of scan pairs from each active condition of an experiment also generally differed. Scan pairs were therefore weighted to satisfy two constraints that eliminated these differences. (i) The active minus passive scan pairs from the different active conditions for a subject were weighted so that, when summed across condition, each subject contributed equally to the generate, test and generate plus test groups, irrespective of the number of scan pairs obtained for that subject. (ii) The active minus passive scan pairs from the different active conditions for a subject were weighted so that, when summed across subject, each active condition contributed equally to the generate, test and generate plus test groups, irrespective of the number of scan pairs obtained for that condition.

The rationale for constraint (i) was the following. During the test phase of the replication analysis, each subject contributed a single observation which was based on a weighted sum of the test scan pairs from that subject (see Replication Analyses: Replication in Test Group). Since each subject contributed equally to this test phase, it was thought that blood flow changes determined during the generate phase would be more likely to replicate if they reflected each subject equally and were not biased towards subjects who contributed more scan pairs to the generate group. Constraint (ii) insured that the replication of foci in the test group reflected all active conditions equally. It also insured that the computed location of a blood flow change in the generate plus test group from an experiment was not biased towards particular conditions within the experiment. This prevented any corresponding bias in the within-experiment analyses (see below), which determined whether those changes significantly varied across conditions.

Differential weighting of scan pairs was achieved by multiplying the normalization factors used to factor out global blood flow differences between scans. For example, by doubling the normalization factors for both scans in an active minus passive subtraction pair, the contribution of that scan pair to the total image could be halved relative to a scan pair whose normalization factors were unchanged.

Averaging of Scan Pairs across Experiments

Stimulus displays across experiments were quite varied, involving different features (i.e. motion, color, word form, etc.) at different eccentricities. Since the exact coordinates and magnitudes of early visual modulations presumably depended on the visual display, averaging across experiments was problematic. It seemed possible, however, that blood flow decreases in auditory or somatosensory cortex during visual processing might not depend on the characteristics of the visual stimulus. Analyses of decreases in task-irrelevant modalities therefore involved images that combined data across experiments to increase sensitivity, as well as images of individual experiments. Any image that combined data across experiments was called a *megaimage*.

Specific Analysis Procedures

Replication Analyses: Construction of Generate and Test Groups

The generate group of scans provided candidate blood flow changes for replication in the test group. Within each experiment, active minus passive scan pairs were pseudorandomly assigned to a generate group with the weighting constraints noted above.

The test group was constructed in a similar manner. Experiments 1–5 and 7 contained multiple passive conditions so that all subjects (or at least most subjects) could contribute independent active minus passive subtraction pairs to both the generate and test groups. This procedure carried two advantages: (i) the degrees of freedom in the test group were increased (doubled for the case in which all subjects contributed scan pairs to the generate and test group); and (ii) variance between the generate and test groups due to anatomical variability across subjects was minimized. For experiments involving multiple passive scans, the total number of subjects in Table 1 is therefore less than the sum of the number of subjects in the generate and test groups (for the case in which all subjects contributed to both generate and test groups, generate = test = total). For experiments 6, 8 and 9, in which each subject only received a single passive scan, subjects contributed scan pairs to either the generate or the test group, but not both. For these experiments, the total number of subjects in Table 1 equals the sum of the subjects in the generate and test groups. For all experiments (1–9), the active and passive scans in the generate group were entirely separate from those in the test group.

In order to increase the stability of the test data, more scan pairs were generally assigned to the test group than to the generate group (Table 1). Megaimages that combined data across experiments were constructed by summing generate or test groups from individual experiments. In both the generate and test groups, all scan pairs were screened for head movement and pairs with movement artifact were eliminated. The behavioral performance for each subject was also reviewed. Data from an active task were eliminated if the subject performed very poorly on that task. The sample sizes for each experiment in Table 1 may differ from those in the published papers, since some papers only included subjects that contributed data to all active task conditions, while this restriction was not necessary for the present analysis.

Replication Analyses: Selection of Generate Foci

Using a center-of-mass search algorithm (Mintun *et al.*, 1989), all peaks of blood flow change >20 PET counts were localized within the generate image. Since the megaimages used to analyze decreases in auditory and somatosensory cortex had a sample size 4–5 times larger than that of individual experiments, a threshold of 10 counts was applied.

The analysis of blood flow increases in visual cortex was restricted to medial cortex near the calcarine sulcus. The analysis of blood flow decreases in auditory cortex was conducted in Brodmann area (BA) 41, containing primary auditory cortex, and the surrounding auditory BA 42. Since Haxby *et al.* (1994) reported large blood flow decreases in the posterior part of the superior temporal gyrus (posterior BA 22), decreases were also analyzed if they plotted in BA 22 within 15 mm of the published coordinates (Haxby *et al.*, 1994). Analyses of decreases in somatosensory cortex were conducted in BAs 3, 1 and 2, corresponding to primary somatosensory cortex. Since Haxby *et al.* (1994) reported large decreases in an insular region that has been activated by passive vibrotactile stimulation (Burton *et al.*, 1993; Coghill *et al.*, 1994; Drevets *et al.*, 1995), insular decreases within 15 mm of the published coordinates (Haxby *et al.*, 1994) were also analyzed.

In all cases, the assignment of blood flow changes to particular Brodmann areas was based on the atlas of Talairach and Tournoux (1988). These assignments are necessarily approximate, since they are based on a standardized atlas, but the Brodmann system provides a convenient means of anatomical description.

Replication Analyses: Replication in Test Group

The generate foci were then tested for reliability. For each focus, a region of interest (ROI) was defined that included all pixels contained within a 7 mm radius sphere. The mean magnitude of blood flow change was calculated within each ROI for each scan pair in the test group. The magnitudes for the different scan pairs from a single subject were summed (since the sum of the weights for each subject was identical) so that each subject contributed a single observation to the statistical analysis (i.e. for all statistical analyses the degrees of freedom depended on the number of subjects, not the number of scan pairs). Because of the weighting procedure, all conditions within an experiment were represented equally in the test observations. A one-tailed *t*-test was then conducted on these observations to determine which blood flow changes were significantly greater than zero in the test group. A one-tailed test was appropriate since the generate group data specified the expected sign of the blood flow change in the test group.

Replication Analyses: Computation of Location and z-score of Replicated Foci

For each replicated focus, the best estimate of location was determined from the generate plus test group. Using the center-of-mass search algorithm (Mintun *et al.*, 1989), all peaks of blood flow change were localized within the generate plus test image. The focus in the generate plus test group nearest the designated focus in the generate group was then determined. A *t*-score was computed for this focus, based on the average magnitude for each subject within a sphere (7 mm radius) centered on the focus, and converted to a *z*-score.

Replication Analyses: Computation of Test Statistic that Aggregates over Experiment

In addition to computing the significance of blood flow increases for individual experiments, an aggregate statistic was computed that tested the null hypothesis that a significant change in a general area (e.g. early visual cortex, auditory BAs 41/42) did not occur in any experiment (Hedges and Olkin, 1985). For each experiment, the *t*-score for each test statistic from the replication analysis for an area was first converted to a *z*-score. If more than one generate focus was isolated for an experiment (e.g. a left and a right hemisphere focus in early visual cortex) and therefore tested during the replication analysis, an aggregate *t*-score was computed for that experiment by averaging for each test subject the magnitudes in the relevant foci and conducting the *t*-test on these average magnitudes. A single *z*-score was therefore obtained for each experiment that contributed to the replication analysis. The sum of these *z*-scores was then divided by the square root of the number of scores. The resulting statistic has the standard normal distribution (Hedges and Olkin, 1985). Significance levels were assigned to this statistic using a one-tailed criterion, since the sign of the expected change in the test group was specified by the sign of the change in the generate group. Since this statistic aggregates over experiments, it can reach significance even if no individual experiment is significant but enough experiments show a sufficient trend. Conversely, if one experiment shows a significant effect, but some of the other experiments show a reverse or 'negative' effect, the resulting test statistic may not be significant.

Table 3
Active minus passive increases in early visual areas

Study	Generate coordinate			Test		Generate plus test data					
	X	*Y*	*Z*	Mag	*P*-value	*X*	*Y*	*Z*	*n*	Mag	*z*-score
Same–Different	–15	–87	0	42	<0.005	–13	–89	4	10	39	2.42
Discrimination	13	–81	8	19	<0.05	9	–81	8	10	35	3.12
Visual Search 1	7	–77	8	1	NS						
Visual Search 2	–3	–81	8	47	<0.0001	–3	–87	16	14	63	4.17
Visual Search 3	–13	–81	8	21	<0.05	–13	–79	8	15	30	3.76
Spatial Attention											
Language	–1	–83	6	17	<0.05	–9	–96	8	13	30	2.41
Language Practice	–3	–83	14	29	<0.0005	–9	–85	6	13	37	3.17
Memory	–9	–91	10	19	<0.05	–5	–93	6	23	25	3.29
	11	–89	8	17	=0.05	11	–87	6	23	27	3.38
	–3	–75	12	14	NS						
Cross-modal Imagery	1	–83	16	23	NS	–1	–81	16	13	36	2.52

The left columns show the coordinates from the generate group and the magnitude ('Mag') and one-tailed *P*-value for replication of those coordinates in the test group. The right columns show the coordinates from the generate plus test group that were nearest the foci in the generate group, and the sample size, magnitude and *z*-score associated with those coordinates. Coordinates represent the location of the peak of each increase in stereotaxic space (Talairach and Tournoux, 1988), with the origin located on the midline at the bisection of the anterior and posterior commissures. *X*: (+ = left, – = right). *Y*: (+ = anterior, – = posterior). *Z*: (+ = superior, – = posterior). 'NS' refers to statistical tests that were not significant ($P > 0.05$).

Within-experiment Analyses
For each focus that replicated, analyses were conducted to determine if the active minus passive magnitudes at that focus (from the generate plus test group) differed for the various conditions of the experiment. For example, an analysis compared the blood flow changes in the read and verb-generation tasks of the Language experiment. For each task in the experiment, the magnitude at the focus was determined for each subject and entered into an ANOVA or *t*-test. All analyses were within-subject, except for Visual Search 2, which involved a between-subject factor. Since the weighting procedure guaranteed that each active task in an experiment contributed equally to the image used to determine the selected foci, the analysis procedure was not biased toward any particular task within an experiment.

Analyses of Additional Blood Flow Changes
Since the replication procedure might miss small or moderate blood flow changes, a more liberal analysis procedure was also used. The tables list all blood flow changes in the generate plus test group that exceeded a magnitude threshold of 12 (10 for the megaimage) and a *z*-score threshold of 2.05, corresponding to an uncorrected one-tailed probability of 0.02. We emphasize that this is a lenient screen and does not constitute a statistical test. Blood flow changes from the generate plus test image which did not pass the replication procedure are of uncertain reliability.

Results

Blood Flow Increases in Early Visual Areas

Replication Analyses
Medial blood flow increases near the calcarine sulcus were observed in the generate images for eight of nine experiments. These foci were significantly replicated in the test groups for six of the eight experiments (Table 3). The aggregate *z*-score that combined the test statistics from these eight experiments was highly significant ($z = 5.82$, $P < 0.0001$).

The coordinates from the generate plus test groups provide the best estimate of the location of the replicated foci (Table 3). Generate plus test foci in four experiments (Same–Different Discrimination, Visual Search 3, Memory and Language Practice) were located along the calcarine sulcus [as determined from the atlas of Talairach and Tournoux (1988)], while foci in the Language experiment and Visual Search 2 plotted above the sulcus (see Fig. 1). For the Language experiment, the nearest focus in the generate plus test group was 15 mm distant from the focus in the generate image and may represent a separate change. The generate group focus was obscured in the generate plus test group by a large cerebellar change. A focus from the Cross-modal Imagery study did not replicate but a moderate increase was present in the generate plus test group. This discrepancy may reflect the small sample size for that study (six of seven test subjects showed an increase at the coordinate from the generate image).

Within-experiment Analyses
Three experiments showed significant differences in the magnitude of replicated blood flow increases across conditions. The Language Practice experiment showed an interaction of Task (verb-generation, read) and Practice (naive, practiced, novel) [$F(2,14) = 5.92$, $P < 0.05$]. The increase was larger during the practiced state than during the naive or novel state, but this practice effect was significantly more pronounced for the verb-generation than read task. Separate one-factor ANOVAs confirmed that the practice effect was significant for the verb -generation task [$F(2,16) = 7.79$, $P < 0.005$] but not for the read task [$F(2,22) = 0.73$]. Individual contrasts for the verb-generation task indicated that the increase in the practiced condition was significantly greater than the increase in either the naive [practice magnitude = 72, naive magnitude = 3; $F(1,16) = 15.5$, $P < 0.005$] or the novel condition [practiced magnitude = 72, novel magnitude = 34; $F(1,16) = 4.63$, $P < 0.05$]. Figure 2 shows the blood flow increases in the verb-generation task as a function of practice.

The Memory experiment showed a significant effect of Condition [$F(2,16) = 6.78$, $P < 0.01$] at the right hemisphere focus, with a larger increase in the priming than in the baseline condition [priming magnitude = 30, baseline magnitude = 0; $F(1,16) = 13.5$, $P < 0.005$] and a marginally larger increase in the cued recall than in the baseline condition [cued recall magnitude = 16, baseline magnitude = 0; $F(1,16) = 4.06$, p = 0.06]. A similar but non-significant trend was observed at the left focus. In Visual Search 2, a larger increase was found in the color-form than in the color condition [color-form magnitude = 89, color magnitude = 45; $t(12) = 2.62$, $P < 0.05$].

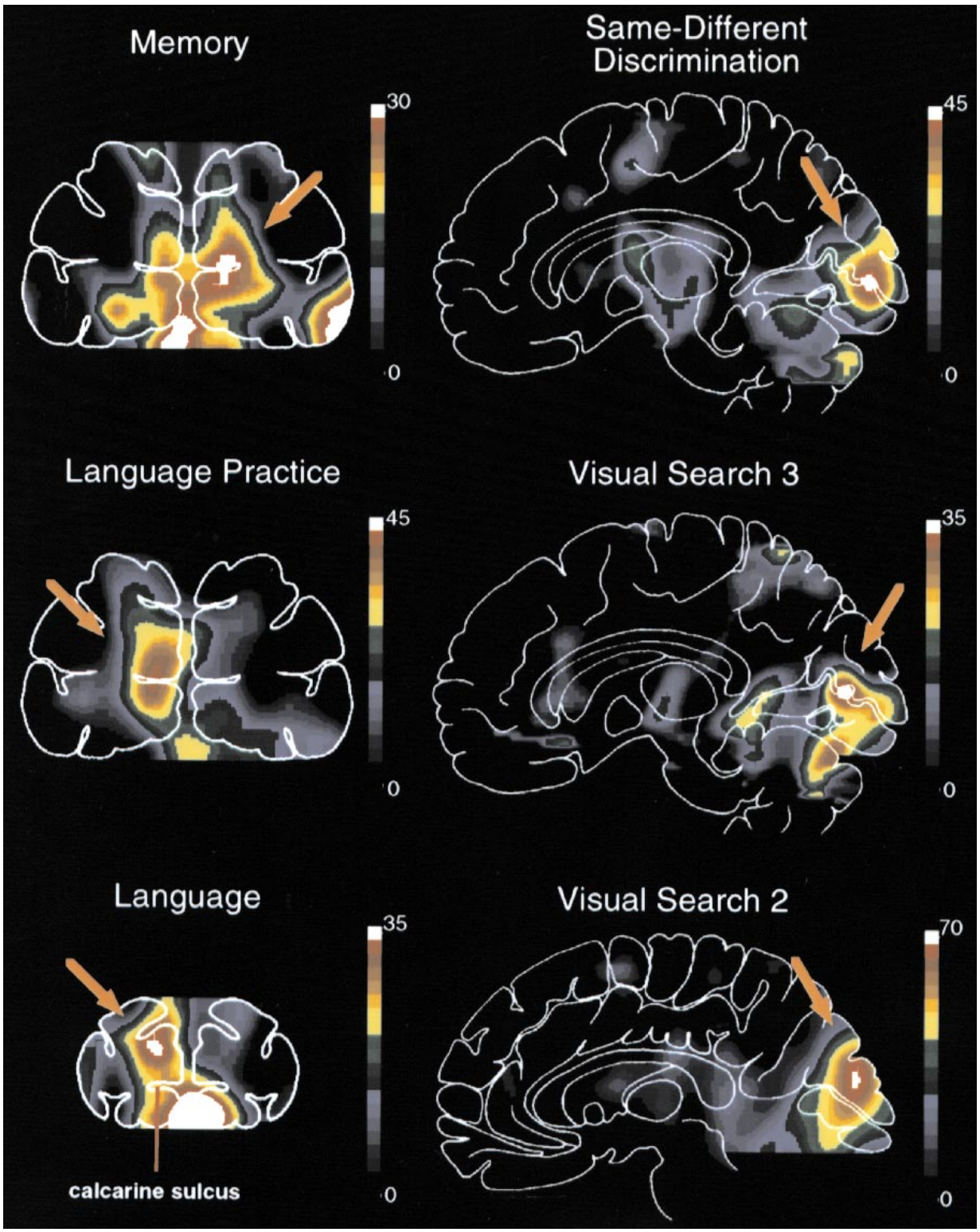

Figure 1. Medial blood flow responses near the calcarine sulcus for each experiment in which an active minus passive modulation was replicated. Images are based on the generate plus test data and each section is centered on the coordinate yielding the peak of the increase (see Table 3 for coordinates). Sagittal sections are shown for the three experiments in which a response was made in both the active and passive conditions. For the three experiments in which no response was made in the passive, coronal sections are shown to eliminate the large cerebellar blood flow increases related to the motor response during the active task. These coronal sections also show that the early visual blood flow changes in the Language and Practice Language experiments were confined to the left hemisphere. The arrow in each panel points to the early visual modulation. This modulation is located on the calcarine sulcus for the top four panels, and located above the sulcus for the bottom two panels.

Blood Flow Decreases in Auditory Brodmann Areas 41 and 42

Replication Analyses

Decreases were observed in the generate images for each experiment within BA 41 or 42 (Table 4; the only decrease in Visual Search 3 had a magnitude of 14 counts, less than the criterion threshold, but it was included for completeness). The generate megaimage yielded a right hemisphere focus at the junction of BAs 41 and 42, a focus slightly posterior to left BA 41, a focus more medial to BA 41 in the right insula, and a focus just superior to left BA 42 in BA 40.

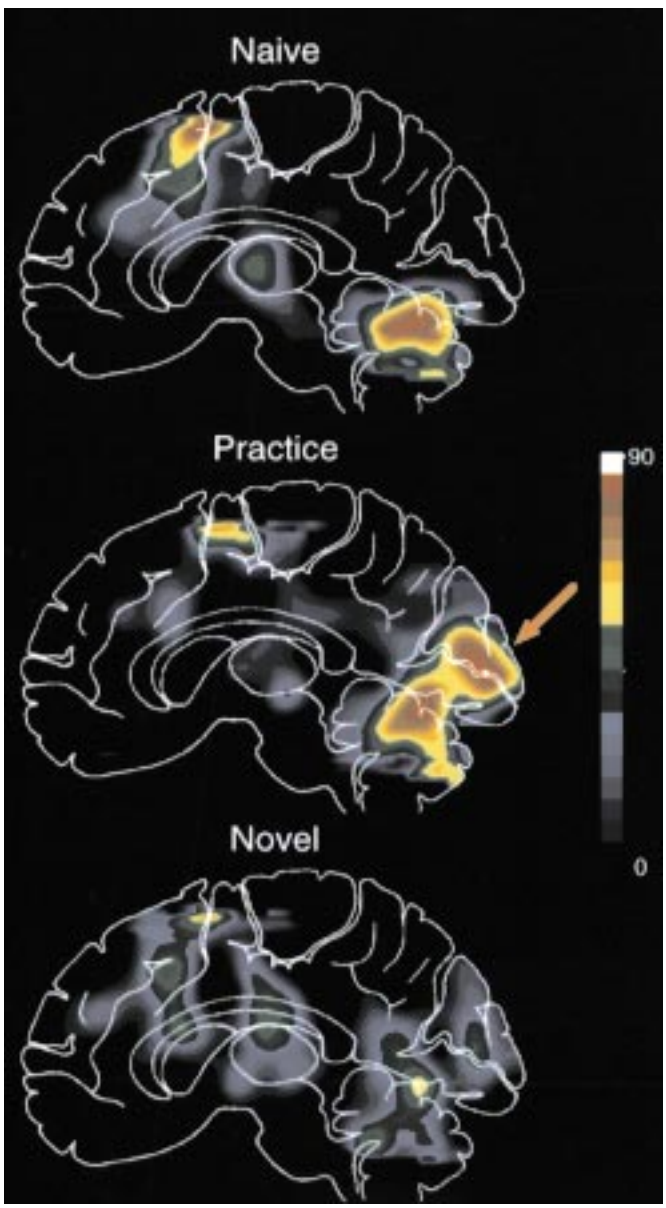

Figure 2. Sagittal sections showing the effect of practice on the size of the active minus passive modulation during the verb-generation task of the Practice Language experiment. Modulations were significantly larger during scans involving a practiced word list (Practice, middle panel) than during scans with a new word list that either preceded (Naive, top panel) or followed (Novel, bottom panel) the practice condition. Sections are centered on the coordinate for the Practice Language experiment listed in Table 3.

Decreases were replicated for two individual experiments (Visual Search 1 and Spatial Attention) and for the megaimage, all in the left hemisphere. The aggregate statistic that combined the test statistics from the five non-language experiments yielding foci in the generate group was also significant (z = 2.48, P < 0.01). The Visual Search 1 focus was just posterior to left BA 41, the Spatial Attention focus was in left BA 42 (24 mm distant from the Visual Search 1 focus) and the megaimage focus was in left BA 41. These decreases were considerably weaker than those observed by Haxby *et al.* (1994) (they reported z-scores of 6.31 and 5.30 for the left BA 41 decreases in their face and location matching tasks). The magnitudes and z-scores of the decrease at the megaimage coordinate were computed separately for each experiment (Table 5). Although the z-scores in some experiments were small, the decreases were moderately consistent across experiments.

Within-experiment Analyses

Neither replicated focus from the Visual Search 1 and Spatial Attention experiments differed across conditions.

Analyses of Additional Decreases

Each experiment produced decreases in BA 41 or 42 of the generate plus test image that passed the z-score/magnitude criterion, with the strongest decreases in left BA 41 for Visual Search 2 and right BA 41 for Cross-modal Imagery (Table 4). Most of the generate plus test foci in Table 4 were near a corresponding focus from the generate group that had passed the selection criterion (and which appear on the same row in the table). 'Additional' generate plus test foci (i.e. foci in addition to the replicated foci discussed above) therefore usually reflected blood flow changes that did not replicate. Sometimes, however, a generate plus test focus did not have a corresponding generate focus (e.g. Cross-modal Imagery).

Blood Flow Decreases in Posterior Brodmann Area 22

Replication Analyses

Only the Cross-modal Imagery study yielded a replicable decrease, located in right BA 22 (Table 6). The aggregate test statistic from the two non-language experiments that yielded generate foci was not significant (z = 0.28). The generate megaimage contained two foci, one of which replicated but was located in BA 21, just posterior to BA 22.

Within-experiment Analyses

The replicated focus from the Cross-modal Imagery study did not vary in magnitude with condition.

Analyses of Additional Decreases

Modest left hemisphere decreases were noted in the generate plus test image for two experiments (Table 6).

Blood Flow Decreases in Primary Somatosensory Cortex

Replication Analyses

Decreases in or bordering on BAs 3, 1 and 2 were observed in the generate images for several experiments (Table 7; the right hemisphere focus for Visual Search 1 was slightly below the magnitude threshold). Significant replication occurred in Visual Search 2, but while the generate focus plotted between BA 40 and BA 2, the generate plus test focus was located more

Table 4.
Blood flow decreases in Brodmann areas 41 and 42 during active tasks involving a visual discrimination

Study	Hemisphere	Generate coordinate			Test		Generate plus test data					
		X	*Y*	Z	Mag	P-value	X	Y	Z	*n*	Mag	z-score
Megaimage	R	53	–29	14	–3	NS						
	L	–41	–39	12	–2	NS						
	R	39	–11	12	–5	NS						
	L	–57	–25	20	–10	<0.001	–57	–17	12	70	–10	–3.45
Same–Different Discrimination	L	–39	–33	10	–11	NS	–43	–25	4	10	–20	–2.18
	R	43	–11	14	–8	NS	53	–9	12	10	–20	–2.34
Visual Search 1	L	–39	–33	14	–19	<0.05	–41	–35	14	13	–33	–3.29
	R	39	–15	16	–9	NS	45	–21	14	13	–21	–2.15
	R	53	–31	14	–8	NS						
Visual Search 2	L	–45	–17	12	2	NS	–49	–19	10	14	–16	–3.31
Visual Search 3	R	53	–29	14	–6	NS	45	–23	14	15	–14	–2.40
Spatial Attention	L	–61	–23	12	–16	<0.05	–63	–25	12	18	–29	–3.72
Cross-modal Imagery	R	33	–31	18	–15	NS	31	–23	20	13	–31	–3.44
	L						–35	–23	20	13	–25	–2.46

See Table 3 footnote for details. The megaimage combines data from the experiments listed in the table (except Cross-modal Imagery). The generate plus test columns list all coordinates passing a *z*-score/magnitude threshold rather than only coordinates that replicated. The generate plus test coordinate corresponding to a generate coordinate is listed in the same row.

posteriorly in BA 40. No generate foci were observed for the megaimage, with the nearest focus plotting in BA 40, posterior to BA 2. The corresponding generate plus test focus, however, was even more posterior in BA 40. The aggregate test statistic combining the four experiments that contributed foci to the replication analysis was significant (z = 1.99, P < 0.05). This statistic, however, included the focus in Visual Search 2 that probably reflected blood flow changes in BA 40. When this focus was excluded, the test statistic was marginal (z = 1.57, P = 0.058).

Analyses of Additional Decreases
Several decreases in or bordering on somatosensory cortex were observed in the generate plus test images for individual experiments, including a robust right hemisphere focus in the Cross-modal Imagery study. These decreases were compared with the somatotopic maps that were derived from passive vibrotactile stimulation of the toe, finger or lip (Table 7) (Fox *et al.*, 1987a; Drevets *et al.*, 1995). No megaimage decreases were localized in primary cortex, with the nearest decrease in the parietal operculum (coordinate = 51, –27, 20; magnitude = 13; z = 4.23), which may correspond to SII (Burton *et al.*, 1993).

Blood Flow Decreases in the Insula

Replication Analyses
Replicable active minus passive decreases (Table 8) were observed in the right insula for Cross-modal Imagery, the left insula for Visual Search 1 and the right insula for the active minus passive megaimage (although the generate plus test focus plotted medial to the insula, between the claustrum and putamen). The aggregate test statistic from the four experiments contributing foci to the replication analysis was significant (z = 1.80, P < 0.05).

Within-experiment Analyses
The replicated foci from the Cross-modal Imagery and Visual Search 1 studies did not vary in magnitude with condition.

Table 5.
Blood flow decreases for each experiment at the megaimage coordinate in the left Brodmann areas 41/42 that replicated

	n	Mag	*z*-score
Same–Different Discrimination	10	–10	–1.36
Visual Search 1	13	–9	–1.25
Visual Search 2	14	–3	–0.56
Visual Search 3	15	–10	–2.99
Spatial Attention	18	–17	–2.06

Analyses of Additional Decreases
Modest decreases were observed in Visual Search 1 and 2, with more robust changes in the megaimage.

Discussion

Modulations in Early Visual Areas
Increases replicated in six of the nine studies, and the test statistic aggregating over studies was highly significant, indicating that active tasks can induce modulations in early stages of the cortical visual pathway. Bilateral increases were often not isolated. Foci were sometimes near the midline (e.g. Visual Search 2), perhaps reflecting the merger of two or more lateralized foci, but in other cases (e.g. Language Practice, Visual Search 3) the increase appeared to be confined to a single hemisphere. It is interesting, for example, that both the Language and Language Practice foci in the generate plus test data were located in the left hemisphere.

Increases in four experiments (Successive Same–Different Discrimination, Visual Search 3, Language Practice, Memory) were localized along the calcarine sulcus (see Fig. 1). Although these increases probably included BA 17, there is some uncertainty since the observations were based on summed images that were referenced to a standard atlas (Talairach and Tournoux, 1988), and there is individual variability in the location of the calcarine sulcus. As a conservative measure, we refer to the location of the active minus passive increases as BA

Table 6
Blood flow decreases in posterior Brodmann area 22

Study	Hemisphere	Generate coordinate			Test		Generate plus test data						
		X	*Y*	*Z*	Mag	*P*-value	*X*	*Y*	*Z*	*n*	Mag	*z*-score	Distance (mm)
Megaimage	L	–51	–53	10	–11	<0.05	–51	–53	10	70	–11	–3.20	14
	L	–41	–39	12	–2	NS							
Same–Different Discrimination													
Visual Search 1	L	–53	–51	14	–2	NS							
Visual Search 2	L						–53	–55	22	14	–19	–2.33	11
Visual Search 3	L						–49	–51	20	15	–13	–2.05	9
Spatial Attention	L	–43	–39	8	–2	NS							
Cross-modal Imagery	L	–53	–35	12	–1	NS							
	R	55	–43	14	–40	<0.05	53	–43	16	13	–40	–3.80	5

See Table 3 caption for details. The megaimage combines data from the experiments listed in the table (excluding Cross-modal Imagery). The last column shows the vector distance between the generate plus test coordinate and the nearest Brodmann area 22 coordinate reported by Haxby *et al.* (1994).

Table 7
Blood flow decreases in Brodmann areas 3, 1 and 2

Study	Hemisphere	Generate coordinate			Test		Generate plus test data						
		X	*Y*	*Z*	Mag	*P*-value	*X*	*Y*	*Z*	*n*	Mag	*z*-score	Body part
Megaimage													
Same–Different Discrimination													
Visual Search 1	R	63	–21	40	–14	NS	63	–23	38	13	–20	–2.63	lip–finger
	L	–47	–13	24	–7	NS							
Visual Search 2	R	49	–33	54	–10	<0.05							
							45	–17	38	14	–12	–3.14	lip–finger
Visual Search 3	L	–57	–15	36	0	NS							
	L	–13	–29	56	–1	NS	–13	–27	56	15	–16	–2.42	toe
							–61	–15	20	15	–16	–3.43	
Cross-modal Imagery	R	57	–17	20	–5	NS	53	–15	30	13	–31	–4.25	lip

See Table 3 caption for details. The megaimages combine data from the experiments included in the table. Although the generate coordinate from Visual Search 2 replicated, the corresponding generate plus test coordinate did not plot in primary somatosensory cortex. The last column indicates whether the generate plus test coordinate was within 1 cm of the blood flow change produced by passive vibrotactile stimulation of the lip, finger or toe as determined from the data of Fox *et al.* (1987a,b) and Drevets *et al.* (1995). Foci with distances >1 cm from any body part were described by the body parts bracketing the coordinate. The unlabeled decrease in Visual Search 3 occurred inferior to the lip region in an area of the body map that Drevets *et al.* (1995) have described as intraoral, based on an extrapolation from monkey data.

Table 8
Blood flow decreases in the insula

Study	Hemisphere	Generate coordinate			Test		Generate plus test data						
		X	*Y*	*Z*	Mag	*P*-value	*X*	*Y*	*Z*	*n*	Mag	*z*-score	Distance (mm)
Megaimage	R	37	–13	12	–9	<0.05	31	–15	10	65	–14	–3.83	13
	R	43	–13	–6	–6	NS	41	–7	–4	62	–14	–3.70	9
	L	–37	9	4	–5	NS	–37	5	4	64	–12	–3.28	9
	L						–33	–13	2	64	–13	–3.72	8
Same–Different Discrimination	L	–35	–7	2	6	NS							
Visual Search 1	L	–33	–13	2	–32	<0.05	–35	–13	2	12	–30	–2.36	8
	R						–37	3	6	12	–26	–2.47	7
Visual Search 2	R	37	–11	10	–3	NS	39	–13	4	14	–16	–2.31	7
Visual Search 3													
Cross-modal Imagery	R	39	–3	–4	–21	<0.05	37	1	–4	13	–37	–3.65	9

See Table 3 caption for details. The megaimages combine data from the experiments listed in the table. The last column shows the vector distance between the generate plus test coordinate and the nearest insular coordinate reported by Haxby *et al.* (1994).

17/18. The replicated increases from two other experiments, Visual Search 2 and Language, were localized above the calcarine sulcus, probably in BA 18 (Sereno *et al.*, 1995).

Possible Artifacts

Blood flow increases in more ventral cerebellar regions could artificially produce increases in BA 17/18. Cerebellar increases

are of some concern in those studies without a motor control, and may have obscured active minus passive modulations in the Language experiment. A distinct increase along the calcarine sulcus, however, was evident in the practiced verb-generation condition of the Language Practice experiment (see Fig. 2) as well as the Memory experiment (Fig. 1). Significant increases were also found in several studies (Successive Same–Different Discrimination, Visual Search 2 and Visual Search 3) in which the motor response was controlled, limiting cerebellar spread.

More eye movements might have occurred during the active conditions. It is unclear if eye movements *per se* would directly produce blood flow increases in BA 17/18. Eye movements could indirectly produce increases, however, by making the task-relevant stimuli more foveal. Eye movements were usually monitored with EOG. Although this control does not rule out the presence of small eye movements below the resolution of the equipment, it does indicate that differences were not caused by moderate-to-large eye movements. Furthermore, significant modulations were found in several experiments (Visual Search 2, Language, Language Practice) that involved stimulus durations too brief for an eye movement (150 ms or less). Eye movements also do not explain the significant effects of practice on the size of the modulation during the verb-generation task of the Language Practice experiment.

Mechanisms Underlying the Modulations

The absence of active minus passive increases in the Spatial Attention and Visual Search 1 experiments suggest an interesting property of the modulation. In both experiments, the stimuli presumably produced weak sensory responses, either because the stimulus was extremely impoverished (for example, in the Spatial Attention experiment, although a fair amount of visual stimulation was tonically present, the only transients were provided by small, briefly presented stars at peripheral locations) or was located in the periphery (in Visual Search 1, the stimuli were presented at an eccentricity of 17°). The weak increase in Visual Search 1 was particularly interesting since a robust modulation was found in Visual Search 2, which was similar in procedure except that the stimuli were less peripheral. This contrast suggests that the strength of the modulation may be related to the size of the phasic sensory response produced by the task-relevant stimulus.

As noted in the introduction, modulations may reflect selective or non-selective mechanisms. Spatially selective modulations could be produced by topographically organized feedback connections from extrastriate visual areas (see Felleman and Van Essen, 1991). In addition, since extrastriate areas encode different kinds of information (Ungerleider and Mishkin, 1982; Maunsell and Newsome, 1987; Van Essen and DeYoe, 1995), modulations produced by a feedback mechanism may vary with the nature of the analysis performed on the stimulus (e.g. the modulations can be feature-selective). Nonselective modulations could reflect activation of brainstem monoaminergic systems (Morrison and Foote, 1986; Robbins and Everitt, 1995) or the reticular formation (Moruzzi and Magoun, 1949). Either type of mechanism could account for a dependence of the modulation on the degree of sensory activation.

The variation of the active minus passive magnitudes with condition in several experiments, however – particularly the interaction of practice and task in the Language Practice experiment – provides strong evidence that selective mechanisms are involved in at least some of the modulations (i.e. there may be multiple mechanisms). Modulations in the verb-generation task of the Language Practice experiment were significantly greater after subjects had practiced that task with the same word list, but this practice effect did not transfer to the read task. This task dependency is very difficult to explain through nonselective mechanisms. The practiced verb- generation task was considerably easier than the naive or novel verb-generation task (reaction times were several hundred milliseconds faster after practice), ruling out arousal effects that might be caused by increases in task difficulty. Petersen *et al.* (1990) observed a left medial extrastriate area along the collateral sulcus that was sensitive to word form and the early modulation may reflect feedback connections from this area. Irrespective of the exact mechanism of the practice effect, however, the task specificity of the effect indicates that an early visual modulation may depend on the nature of the analysis demanded by the task, as opposed to a non-specific process.

The greater modulation in the color-form condition than color condition of Visual Search 2 is also consistent with the involvement of selective mechanisms. Since the color-form task required an analysis of orientation and many cells in primate V1 and V2 are orientation selective (Hubel and Wiesel, 1968; Haenny and Schiller, 1988), the modulation might reflect feedback onto earlier analyzers from extrastriate regions coding orientation. Since the color-form condition was more difficult than the color condition, however, the greater modulation during the former condition might also have reflected non-specific arousal.

The source of the early visual modulations is unclear. To the extent that the modulations were produced by selective feedback from extrastriate areas, the immediate source may differ across experiments. The control signals for the modulations, however, were presumably produced in extravisual areas. An analysis of the extravisual increases that were common across all experiments in the present dataset (Shulman *et al.*, 1997) revealed a right thalamic focus that could plausibly be related to attentional engagement of a stimulus. Blood flow changes at this focus did not correlate with the magnitude of the observed modulation (e.g. it was present in both the Spatial Attention experiment and Visual Search 1), but since the modulation appeared to depend partly on stimulus efficacy, perhaps a correlation should not be expected (e.g. the same control signal may have been sent during Visual Search 1 and Visual Search 2, even though only the latter produced a large modulation).

Additional Observations

The greater active minus passive increase in the priming and cued recall conditions than in the baseline condition of the Memory experiment was a surprising result. The response of early visual areas to letter strings was affected by their similarity to letter strings presented minutes earlier. Since the word stems in the passive and baseline conditions never matched the study words while half the stems in the priming and cued recall condition matched the study words, the active minus passive modulation in the latter conditions may have reflected a stimulus driven process (Schacter, 1994). Blood flow differences between the priming, cued recall and baseline condition might have been observed even if subjects had viewed the stimuli passively instead of completing the stems. It is also possible, however, that the modulation depended on the active nature of the priming and cued recall tasks. For example, the modulation might have been caused by the explicit recognition that the word stem was related to a previously presented word [Buckner

et al. (1995) noted that subjects in the priming condition were aware of the study–test relationship].

Buckner *et al.* (1995) have reported that the priming condition in these studies produced a blood flow *reduction* in lateral extrastriate cortex, the opposite of the effect in early visual cortex. These two effects may be causally related: augmentation of the response to the letter string in early visual cortex may facilitate the analysis of that stimulus by later extrastriate areas, resulting in faster processing and a reduced extrastriate blood flow response (i.e. processing in extrastriate cortex can be terminated more quickly because of the enhanced BA 17/18 response). This hypothesis is less plausible if the early augmentation reflected explicit recognition of the primed stimulus.

Blood Flow Decreases in Task-irrelevant Modalities

Auditory BAs 41 and 42

The results indicate that performing a visual task can produce blood flow decreases in auditory areas. Two of the five individual experiments yielded significant replications in BAs 41 or 42, while the test statistic aggregating over all studies was significant. Although decreases in the other three experiments did not replicate, small-to-moderate decreases that may reflect real responses were seen in their generate plus test images. Large decreases in BA 41, however, were not routinely or invariably produced, with the *z*-scores for all blood flow decreases in the generate plus test images being considerably smaller than those reported by Haxby *et al.* (1994). Furthermore, the location of the strongest decreases varied with the experiment. As a result, the megaimage yielded only a weak (although statistically significant) decrease in left BA 41.

Auditory Posterior BA 22

Modest decreases were found in BA 22. The megaimage contained a replicable focus more posterior in left BA 21, while the Cross-modal Imagery study yielded a replicable focus in right BA 22. The test statistic aggregating over the two non-language studies that contributed foci to the replication analysis was nonsignificant.

Primary Somatosensory Cortex

The results for primary somatosensory cortex were weaker than those for primary auditory cortex. Individual experiments did not yield replicable decreases, and the aggregate test statistic was marginal. Some decreases in the generate plus test images, however, may have reflected real responses (e.g. Cross-modal Imagery and Visual Search 3; see Table 7). These latter decreases were inconsistently localized. Correspondingly, the megaimage analysis did not yield replicated decreases or generate plus test decreases within primary cortex. The generate plus test megaimage did, however, yield a robust decrease in the parietal operculum (possibly SII) (Burton *et al.*, 1993).

Insular Cortex

More consistent blood flow decreases were found in an insular region which was activated by passive vibrotactile stimuli (Burton *et al.*, 1993; Coghill *et al.*, 1994; Drevets *et al.*, 1995). Replicable decreases were observed in two individual experiments and in the megaimage, while the test statistic aggregating over experiments was also significant.

Mechanisms Underlying Blood Flow Decreases in Sensory Areas

Haxby *et al.* (1994) suggested that blood flow decreases in primary auditory or somatosensory cortex during a visual task reflected the suppression of neural activity in task-irrelevant modalities. They noted that this suppression could be mediated by precortical sites, decreasing the input to primary sensory cortex and damping an entire modality. This hypothesis suggests that different visual tasks should inhibit the same regions of auditory or somatosensory cortex, and this inhibition should be extensive. Furthermore, if decreased blood flow in association areas results from the suppression of activity in primary areas, then decreases in association areas should be contingent on decreases in primary areas.

The inconsistently localized (and weak) blood flow decreases in the present dataset do not fit with this functional explanation. To the extent that blood flow decreases in BAs 41 or 42 of the present dataset reflected a suppression of auditory cortex, different tasks primarily suppressed different regions. Furthermore, the region of common suppression involved a small decrease in left BA 41. It is not clear what determines this variation with task nor how suppression of activity in one part of the auditory cortex would diminish interference from the entire modality. Similarly, it is not clear how blood flow decreases in a restricted region of primary somatosensory cortex, corresponding to a particular body part, might play a functionally important role in decreasing interference from somesthesis.

There were intriguing hemispheric differences in the auditory cortex decreases produced by language and non-language-related studies. Significant BA 41/42 decreases in the non-language studies (both the individual studies and the megaimage) were confined to the left hemisphere.

The non-language studies produced blood flow decreases in left BA 22, while the Cross-modal Imagery study produced a replicable decrease in right BA 22. These hemispheric differences, if reliable, indicate that blood flow decreases in auditory cortex depend on the nature of the task conducted with the visual stimuli (as noted above, the inconsistent localization of the decreases across experiments suggests a similar conclusion). Task dependencies implicate mechanisms involving intracortical pathways rather than non-specific inhibition from precortical sites.

Replicable decreases were observed in the insula but not in primary somatosensory cortex, indicating that decreases in association areas may not be a consequence of reduced activity in the corresponding primary area [although in monkey the posterior insula receives projections from both somatosensory and auditory areas (Mesulam and Mufson, 1985)]. Kawashima *et al.* (1995) also reported blood flow decreases in lateral extrastriate areas during a tactile discrimination task in the absence of significant changes in primary visual cortex.

Dissociations between blood flow decreases in primary and association cortex may be more common in the current dataset. Although the current analyses principally examined the two association areas that showed large blood flow decreases in Haxby *et al.* (1994), decreases were also observed in other association or non-primary areas. Replicable decreases in the somatosensory megaimage were found bilaterally in BA 40, posterior to primary somatosensory cortex (left BA 40, coordinate = –53, –39, 40; magnitude = 13; z = 4.27; right BA 40, coordinate = 45, –41, 34; magnitude = 12; z = 3.62), and a robust focus was observed in the parietal operculum, which may

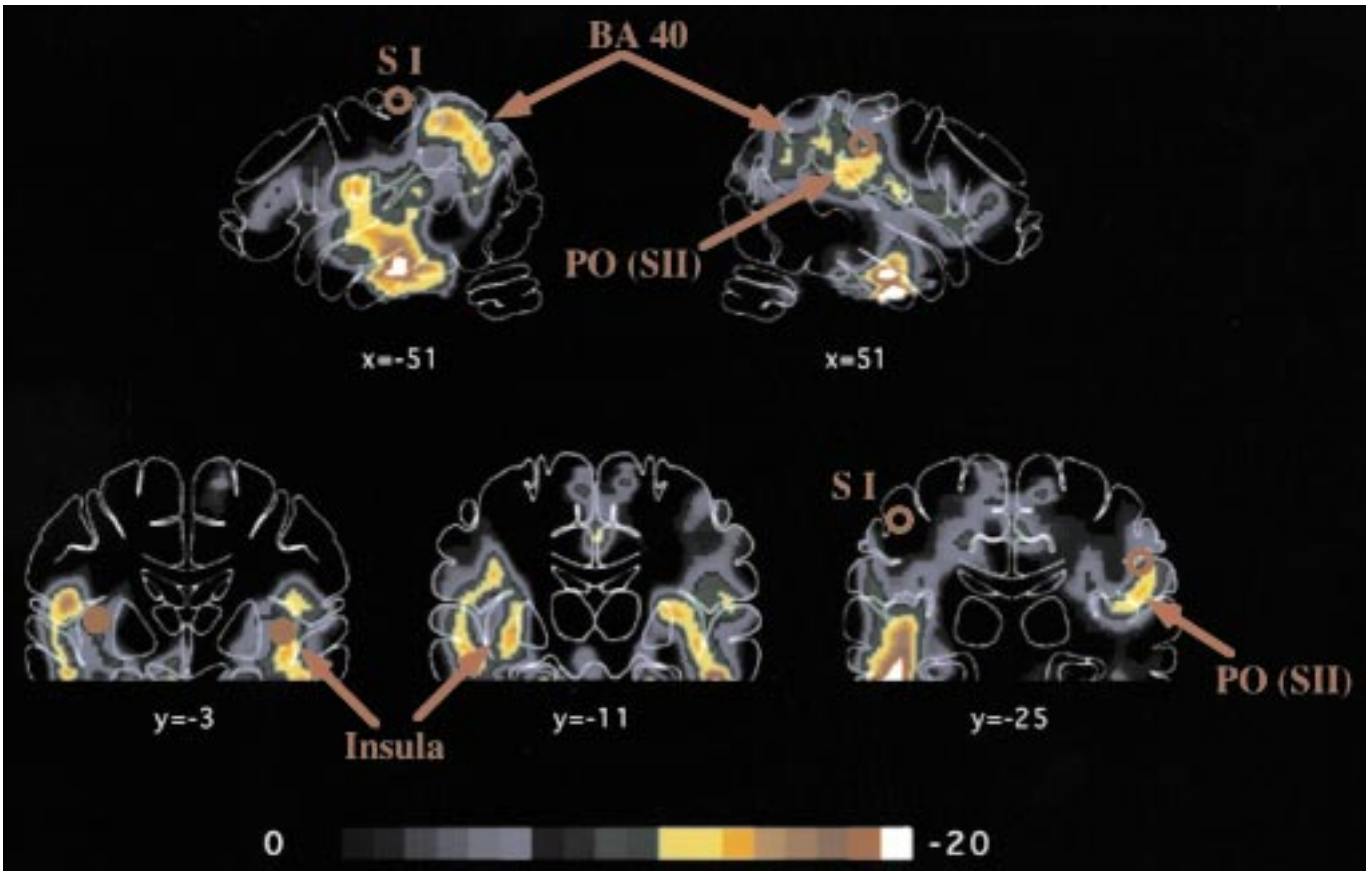

Figure 3. Blood flow decreases in the insula, parietal operculum (PO, perhaps corresponding to SII) and BA 40 in the megaimage used to assess decreases within the somatosensory system. The open red circles show the approximate locations of the decreases in left and right S1 reported by Haxby *et al.* (1994), while the filled red circles show the approximate locations of the decreases they reported in the left and right insula. The top panel shows sagittal sections while the bottom panel shows coronal sections.

correspond to SII (Burton *et al.*, 1993). These blood flow changes are shown in Figure 3.

An alternative explanation of the blood flow decreases is that subjects partly attended to the irrelevant modality during the passive conditions. The observed blood flow decreases during the active tasks (i.e. increases during the passive condition) could therefore reflect the same type of excitatory processes that occurred in the task-relevant modality during the active tasks (i.e. the same processes that produced modulations in early visual cortex) rather than a suppression of neural activity.

This hypothesis does not explain the inconsistency in the location of the replicated decreases in auditory BAs 41 and 42, but it does explain the reliable decreases in the insula. Prior experiments with passive vibrotactile stimulation have not demonstrated somatotopy in this region (Burton *et al.*, 1993; Drevets *et al.*, 1995). Consistent insular decreases may have occurred because the same region can be activated by a shift of attention to any body region during the passive condition (e.g. the insular response is not attenuated by inconsistency in the attended body region). Alternatively, gating of input from a modality may be more effective in areas that are not somatotopic.

Factors That May Affect Blood Flow Decreases in Auditory and Somatosensory Areas during Visual Tasks

Several factors may account for the fact that decreases were smaller and more variable in the current dataset than in Haxby *et al.* (1994).

1. While the passive condition of Haxby *et al.* (1994) did not involve a fixation point, the fixation requirement of the present passive conditions may have increased attention to the visual modality. Several results, however, suggest that the passive conditions in the present experiments involved minimal processing demands. Passive conditions often show increased blood flow, relative to active conditions, in a variety of cortical areas. Haxby *et al.* (1994), for example, report that the posterior cingulate/precuneus region showed greater blood flow in their passive than active conditions. The present experiments also revealed an extensive set of areas, including the posterior cingulate/precuneus, that showed greater blood flow during the passive condition (Shulman *et al.*, 1997). Secondly, reliable active minus passive increases in the present dataset were found in early visual areas (many of the present tasks also generated large extrastriate changes), indicating that the

visual demands of the passive condition did not match those of the active tasks.

2. Blood flow decreases may only occur with very demanding visual tasks. The tasks in the Haxby *et al.* (1994) study seemed more difficult than those in the present study, while their visual stimuli may also have been more complex. Reaction times in all conditions of their study exceeded 2 s, while reaction times for the relevant experiments in the current data set involving a speeded response (Visual Search 3, Spatial Attention) were generally <1 s.
3. Stimulation of the irrelevant modalities during the present experiments may have differed from that in Haxby *et al.* (1994). Control of the sensory environment is important, since suppression of task-irrelevant modalities may be functionally important in the presence of transients that might compete for attention and interfere with the performance of the primary visual task. Shifts of attention to the irrelevant modality during the passive condition may also produce different blood flow patterns depending on the ambient stimulation. Auditory input in the present studies was mainly provided by noise from the cooling fans and the scanner itself. Somatosensory input was mainly provided by the motor response.

Admittedly, these three factors do not distinguish the two experiments in the current data set that showed reliable blood flow decreases in BAs 41 and 42 from those that did not. Both Visual Search 1 and Spatial Attention involved passive conditions with a fixation requirement, did not appear more difficult than the other experiments, and involved the same ambient noise environment. It is probably only a coincidence that these two experiments also did not show enhancement of early visual areas, but it is also possible that blood flow decreases in auditory areas are generated by active processes that cannot simultaneously be used for visual enhancement. Haxby *et al.* (1994) report both phenomenon, although as they note, their enhancement phenomenon is difficult to interpret because of the possible confounding effects of eye movements.

Conclusions

1. Cortical areas early in the visual hierarchy, probably including BA 17, were modulated by top-down mechanisms during the processing of visual stimuli. Reliable modulations were found in six of nine studies, with four studies showing modulations that plotted along the calcarine sulcus in the Talairach and Tournoux (1988) atlas.
2. Modulations were task dependent in several experiments, indicating that in some cases the underlying mechanism was selective. The most convincing evidence was the strong practice-related dependence of the modulation in the verb-generation task of the Language Practice experiment. Modulations may also depend on the strength of the sensory response evoked by a stimulus.
3. Replicable blood flow decreases in auditory BA 41 or 42 were observed in two of five non-language studies, with the other studies showing modest decreases of uncertain reliability. A test statistic that aggregated over experiments was significant. Although decreases in individual studies were inconsistenty localized, a megaimage that combined data across studies contained a weak but replicable decrease in left BA 41. There was a tendency for blood flow decreases in auditory areas to be localized in the left hemisphere during non-language tasks, and in the right hemisphere for language-related tasks. Replicable blood flow decreases were not observed in primary somatosensory cortex, although individual experiments yielded decreases that may reflect real responses. These decreases were inconsistently localized and were not observed in a megaimage. Reliable decreases were found in an insular region which may be a somatosensory association area, while decreases were also noted in the parietal operculum (SII) and BA 40.

These results are not consistent with a model in which the precortical input to task-irrelevant sensory cortical areas is broadly suppressed. Cross modal blood flow changes are an important phenomenon but the rules governing their appearance and localization are not well understood.

Notes

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