Functional MRI Studies of Word-Stem Completion: Reliability Across Laboratories and Comparison to Blood Flow Imaging With PET

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Abstract: Functional magnetic resonance imaging (fMRI) based on blood oxygen level-dependent (BOLD) contrast has become an increasingly popular technique for mapping the brain. The relationship between BOLD-fMRI imaging and imaging of blood flow activation with positron emission tomography (PET) remains unclear. Moreover, BOLD imaging strategies and analysis procedures vary widely across laboratories. To examine the relationship between these different methods, we compared brain activation maps of a word-stem completion task obtained both using PET and using fMRI across two separate institutions (Washington University and Massachusetts General Hospital) with different acquisitions (gradient-refocused echo and asymmetric spin echo) and different analysis techniques. Overall, activation maps were highly similar across both fMRI methods and PET. A set of activated brain areas, in consistent locations in Talairach atlas space, were identified across all three studies, including visual striate and extrastriate, left prefrontal, supplementary motor area (SMA), and right cerebellar areas. Decreases in activation were also consistently observed in medial parietal, posterior insular, and medial inferior frontal

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areas. Some differences were noted that may be related to the silent performance of the task with fMRI. The largely consistent results suggest that comparisons can be made appropriately across imaging modalities and laboratory methods. A further implication of the consistencies, which extended to both increases and decreases in signal, is that the underlying brain physiology leading to BOLD contrast may be more similar to blood flow than originally appreciated. *Hum. Brain Mapping* 6:203–215, 1998. © 1998 Wiley-Liss, Inc.

Key words: BOLD; cerebral blood flow; cerebral oxygen metabolism; cognition; imaging methods

INTRODUCTION

Functional neuroimaging with positron emission tomography (PET) has been used to study blood flow and metabolism changes associated with cognitive activation [e.g., Raichle 1987]. Recent developments in magnetic resonance imaging (MRI) have permitted evaluation of changes in blood oxygenation associated with functional activation of the brain [Fox and Raichle, 1986; Fox et al., 1988; Kwong et al., 1992; Ogawa et al., 1990, 1992]. Functional MRI (fMRI) has been used to study the relatively small (~1% signal change) activations during behavioral tasks, including studies of visual, sensory, language, and memory systems. The implicit assumption in using fMRI is that the responses are comparable to those found using other, direct measures of cerebral blood flow (CBF), such as PET using H₂¹⁵O. However, few direct comparisons exist and the similarities and differences between the two methods are not fully established.

Benefits of fMRI techniques include the absence of radiation exposure, availability of machines, and improved spatial and temporal resolution. However, measurement of the blood oxygen level-dependent (BOLD) signal may not be comparable to blood flow changes measured with PET. The location of signal relative to particular structures, such as venules or capillaries, may differ between PET and fMRI [Boxerman et al., 1995; Frahm et al., 1994]. Additionally, reproduction of decreases in blood flow with BOLD-fMRI has not been demonstrated.

Previous correlations of PET and fMRI have used robust activations, such as visual stimulation [Clark et al., 1996; Fried et al., 1995; Kraut et al., 1995] or somatosensory stimulation [Ramsey et al., 1996]. Several of these comparisons have used small numbers of slices and, in one study of cognitive activations, found different results between PET and fMRI [Paulesu et al., 1995]. Here, we evaluate several of these questions regarding PET and fMRI comparisons, using a cognitive paradigm that has been previously reported for a large number of subjects studied with PET [Buckner et

al., 1995; Squire et al., 1992]. This paradigm, involving word-stem completion, activates several regions, giving smaller but very reliable flow changes. Activation maps generated using this paradigm allow comparison of PET and fMRI for smaller activations often seen in studies of cognitive activation. The reliability of the activations was tested using two different BOLD-sensitive sequences at two different institutions. A gradient-refocused echo (GRE) echo-planar imaging (EPI) sequence was used at Washington University in St. Louis, and an asymmetric spin echo (ASE) EPI sequence was used at Massachusetts General Hospital. Finding reliable activations with BOLD imaging, using different machines, sequences, analysis strategies, and subject groups, would demonstrate the consistency of BOLD imaging and the sensitivity of BOLD imaging to the small activations seen in cognitive paradigms. Further, a consistent map between PET and fMRI studies would give additional confidence in the BOLD technique and support comparisons of PET and fMRI activation studies in the literature.

MATERIALS AND METHODS

PET

The PET study has been previously reported [Buckner et al., 1995; Squire et al., 1992]. In brief, three-letter strings (0.8° per letter) were presented below a central cross-hair every 3.5 sec for a duration of 3.0 sec. Each letter string, or “stem,” could be completed to form at least five different words excluding proper nouns, each with greater than one per million frequency [Kucera and Francis, 1967]. Subjects were instructed to say aloud the first word that came to mind and completed the stem presented. Images were acquired with the PETT VI system following a labeled bolus intravenous injection during both the word-stem completion task and during visual fixation on a central cross-hair. Skull X-rays were obtained for transformation into stereotactic coordinates [Fox et al., 1985].

Whole brain counts were normalized to 1,000, and images obtained during fixation were subtracted from those obtained during word-stem completion. After individual transformation into stereotactic space, these subtraction images were averaged across subjects ($N = 32$). These subtractions were previously reported as the “baseline minus fixation” comparison in Buckner et al. [1995]. Published regions of PET activation were used to evaluate replication of responses in fMRI. The coordinates used in the current report differ slightly from those previously published, as newer versions of the same processing steps are now used which directly transform the data to the atlas of Talairach and Tournoux [1988] (the previous report [Buckner et al., 1995] transformed the data to the older atlas of Talairach et al. [1967] and then converted the coordinates). All coordinates are reported as x (right of midline is positive), y (anterior is positive), and z (superior to the AC-PC plane is positive).

fMRI: Gradient-refocused echo (GRE) EPI

Eight right-handed subjects (3 male, 5 female, ages 19–28, mean 24 years) were imaged with whole brain contiguous multislice echo-planar imaging. Informed consent was obtained after approval by the Washington University Human Studies Committee. Subjects were reimbursed \$25 for each hour of participation. When tolerated by the subject ($n = 2$), dental impression mouthpieces were fashioned out of standard dental epoxy (Henry Schein, Port Washington, NY) and fastened to the head coil to control subject movement. In the other subjects, surgical tape and cushions were used around the head to minimize movement. Images were obtained using the Siemens MAGNETOM Vision 1.5 T system (Siemens, Erlangen, Germany) using the standard circularly polarized head coil and imaging gradients operating with a capacity of a rise time of 300 μ sec to a maximum strength of 25 mT/m. Anatomical images were obtained, after automatic shimming, using a sagittal MP-RAGE [Mugler and Brookeman, 1990] sequence (echo time $TE = 4$ msec, repetition time $TR = 9$ msec, inversion time $TI = 300$ msec, flip angle $\alpha = 12^\circ$, 80 slices, and $2 \times 2 \times 2$ mm voxels). From this image, the anterior commissure-posterior commissure (AC-PC) plane was determined and functional imaging was performed parallel to this plane. Single-shot gradient-refocused echo-planar images were obtained ($TE = 50$ msec, $TR = 2200$ msec, $\alpha = 90^\circ$, in-plane resolution 3.1×3.1 mm, contiguous 8-mm slices). The voxel size was chosen to have high BOLD signal-to-noise ratio [Conturo et al., 1996]. Each of these fMRI runs consisted of 120 whole brain EPI

acquisitions (frames). The first frame of each study was used for the preserved anatomical information present in this purely T_2^* -weighted frame, while each frame from the fourth on was considered steady-state and used for functional imaging.

Stimuli were presented through a Power Macintosh 7100 computer (Apple Computer), projected through a Sharp LCD projector (640×480 pixel resolution) and directed to a mirror placed over the head coil. All word stems were presented in the center of the field of view with a size of 0.8° visual angle per letter and presented every 3.3 sec for a duration of 2.0 sec. When stems were not presented, a cross-hair was shown in the center of the field of view. At the start of each run, subjects maintained visual fixation on a centrally placed cross-hair. After an initial 12-frame fixation period, the stimuli alternated between 18 frames of word-stem presentation and 18 frames of visual fixation. Subjects were instructed to silently complete the word stems without articulation, with emphasis on avoiding movement of the head or jaw. A total of three cycles of stem completion was performed in the 120 frames of a run. Each run (3–4 per subject) used a different list of word stems. In one subject, runs (3 total) had only 90 frames, as artifacts involved later frames in each run.

Each 120-frame run (hereafter referred to as a “time-series”) underwent several automated processing steps. First, a central single-pixel spike caused by signal offset was detected as the pixel with the largest timeseries variance and replaced by the local pixel average. Next, signal was corrected for contiguous slice effects. Using contiguous slice acquisition with interleaved excitation leads to attenuation of signal from alternating slices due to the effect of the RF pulses of neighboring slices. This effect was corrected by empirically determining a correction factor which, when added to even-numbered slices and subtracted from odd-numbered slices, minimized differences in slice intensities. Realignment using a rigid-body rotation and translation correction [Friston et al., 1994; Snyder, 1996] was applied to all frames, both within runs and across runs. To minimize artifacts at this step from interpolation [Hajnal et al., 1995], a computationally efficient, three-dimensional cubic spline interpolation [Friston et al., 1994] was employed. Subsequently, slice-based normalization was performed to address artifactual fluctuations in signal intensity. To permit comparison across subjects, the mode brain voxel value was normalized to 1,000 [see also Ojemann et al., 1997].

The transformation of images into a standard reference space was accomplished in several steps. For each subject, the timeseries was registered to the subject’s

own MP-RAGE image using an eight-parameter transformation. In addition to the six rigid body parameters [Woods et al., 1993], two floating in-plane voxel size parameters were used to allow compensation for artifactual distortions characteristic of EPI. Next, the subject's MP-RAGE image was mapped by a 12-parameter affine transformation (similar to the method of Collins et al. [1994]) to a target, atlas-representative [Talairach and Tournoux, 1988] MP-RAGE image. This target MRI was previously obtained by coregistration of the MP-RAGE images of 12 normal young adults from another study group. This average MP-RAGE was computed and then spatially normalized [Lancaster et al., 1995] to create the target, atlas-representative MP-RAGE. In the present study, the transformation that brought a subject's MP-RAGE onto the atlas MP-RAGE was then applied to the fMRI timeseries (after coregistration with the MP-RAGE), thus bringing the timeseries into stereotactic space. In the final transformation of the timeseries to atlas space, the data were resampled (using linear interpolation) with 3.0-mm cubic voxels.

Subtraction of linear trends within the timeseries was performed on a pixel-by-pixel basis. For each subject, timeseries were averaged across runs. A cross-subject difference image was created from the averaged timeseries by simple subtraction of frames acquired during fixation from those acquired during word-stem completion. Time points were shifted by two frames (approximately 4 sec) to account for the delay in the physiologic response relative to the onset of a stimuli [Bandettini et al., 1992; Frostig et al., 1990; Malonek and Grinvald, 1996]. This image corresponds conceptually to a normalized PET subtraction image in stereotactic space [Fox et al., 1987].

In individual subjects, prior to atlas transformation, a two-tailed Wilcoxon rank sum statistic was applied to each voxel. Each voxel was assigned a Z value given by the Wilcoxon test. This Z image was then transformed to stereotactic space using the same transformation determined for the timeseries data above. These Z images were averaged, in stereotactic space, across subjects. A threshold was then applied to correct for multiple comparisons [Ollinger, 1997]. Voxels were included such that the overall significance was $P < .05$. A search routine identified peaks of positive and negative Z values, requiring peaks be separated by at least 8 mm.

fMRI: Asymmetric spin echo (ASE)

Eight right-handed subjects (2 female, 6 male, ages 24–32, mean age 27 years) volunteered and received

\$50 for a 2-hr session. The study was approved by the Human Studies Committee of Massachusetts General Hospital and informed consent was obtained prior to scanning. Imaging was performed on a 1.5 T General Electric Signa scanner (Milwaukee, WI) with an EPI upgrade (Advanced NMR Systems, Wilmington, MA), using the standard General Electric quadrature head coil. Visual stimuli were presented using a Power Macintosh 7100 (Apple Computer) system projected through a Sharp 2000 projector, through a collimating lens, onto a screen attached to the head coil. Subjects were snugly fit into the head coil, using pillows and cushions as a means of reducing motion.

For each subject, high-resolution anatomic images were acquired using an RF-spoiled GRASS (SPGR) sequence (60 sagittal slices, 2.8 mm thickness). An automated EPI shim procedure improved B_0 magnetic field homogeneity [Reese et al., 1995]. Functional images were acquired using an asymmetric spin echo (ASE) sequence [Baker et al., 1993] sensitive to BOLD contrast (TE = 50 msec, RF pulse offset = -25 msec, TR = 2,000 msec).

Functional images were acquired in runs of 110 frames (i.e., time points), with whole-brain acquisition in each frame (17 slices, in-plane resolution 3.1×3.1 mm, 7-mm slice thickness with 1-mm gap between slices). Each slice was aligned to the AC-PC plane. The first five time points were discarded to retain only data acquired at steady-state magnetization. The remaining 105 time points were divided into seven blocks of 15 time points each, with each block collected during either the word-stem completion or fixation conditions. Each run started with a fixation block and alternated with stem completion blocks, thereafter yielding 45 frames (in three blocks) of stem completion and 60 frames of fixation per run. Stems were presented in the center of the field of view every 2.5 sec for a duration of 1.5 sec. Eight runs were performed for each subject. Subjects were instructed to complete the stems into words silently without head or jaw movement.

Data from one subject were lost due to failed acquisition of the SPGR image, leaving 7 subjects for all further analysis. Data from each subject were transformed into the stereotactic space of the atlas of Talairach and Tournoux [1988]. The anterior and posterior commissures were manually identified, along with the highest point in the midsagittal plane and the edges of the brain as viewed in the SPGR images. These points defined a linear transformation of the SPGR images into the stereotactic space of the atlas of Talairach and Tournoux [1988] (using linear interpolation).

The functional images were realigned to the SPGR images. These additional transformations were derived from the image header information along with y-axis realignment from a contour-tracing algorithm. The transformation matrix of the acquired SPGR images to the atlas space was separately applied to each of the images in the functional runs, placing the functional runs (using linear interpolation) into atlas space with 3.125-mm cubic voxels. Once in atlas space, both the interpolated SPGR images and the functional runs were averaged across subjects. Linear trends were subtracted for each voxel prior to statistical calculations. Spatial smoothing with a one-voxel-wide Hanning filter was applied. A statistical activation map was constructed, using the nonparametric Kolmogorov-Smirnov (K-S) statistic [Press et al., 1988] to compare the stem completion condition to the fixation reference condition. A search algorithm identified peaks of maximal statistical significance (at least $P < 10^{-5}$) for both increases and decreases in signal, requiring peaks to be separated by at least 8-mm distance, and be part of a cluster of eight contiguous activated voxels.

Comparison across studies

Along with qualitative inspection of the images (PET and both fMRI studies), the reliability of activations across studies was assessed using two methods. First, the *replication* of activations was assessed by determining the coordinates of peak activations in all three studies. This step evaluated the degree to which activations agreed across the imaging techniques and different postacquisition analyses. Thus, to the degree that similar activations were determined, the different methods would be equally valid for the purposes of studying cognitive activation.

Second, the *reproducibility* of activations was assessed by generating a region of interest (ROI) in one study and determining whether the activation could be demonstrated within the ROI in another study. This strategy has been used in PET studies to validate activations across subjects [Buckner et al., 1995; Hunton et al., 1996; Squire et al., 1992]. To demonstrate the reproducibility of PET results with fMRI, spherical ROIs generated from the PET study were analyzed in the GRE-fMRI study. To assess the reproducibility across fMRI studies, the GRE-fMRI study was again tested, this time using the ASE-fMRI study to generate ROIs.

The focus of both analyses was on regions outside of primary motor and visual cortical areas. The visual presentation of word stems activates a variety of regions in the striate and extrastriate cortex in all three

TABLE I. Reproducibility of PET activations in GRE-fMRI data†

Region (coordinate)	t-value	P (one-tailed)
Regions of PET increases		
Left frontal (−37, 21, 12)	5.07	<.001*
(−43, 7, 30)	8.83	<.0001*
SMA (−3, 11, 52)	8.08	<.0001*
Right cerebellum (31, −63, −18)	4.98	<.001*
Regions of PET decreases		
Medial parietal (7, −53, 42)	−7.45	<.0001*
(−5, −65, 44)	−4.75	<.001*
Right lateral parietal (53, −35, 38)	−2.99	.01
(41, −67, 26)	−5.33	.0005*
Right insula (39, −7, 6)	−8.58	<.0001*
Right prefrontal (33, 15, 42)	−2.77	.014
Left postcentral (−31, −35, 52)	−2.10	.07
Left lateral parietal (−53, −33, 36)	−0.56	.30
Right anterior prefrontal (35, 47, 14)	−0.41	.35

† T-values (and associated *P* values) are based on application of the region to GRE data. SMA, supplementary motor area.

* Significant at $P < .05$ after correction for multiple comparisons.

studies. These regions, which were not the focus of the study, were excluded from further detailed analysis and are not reported in search routines, nor are they included in regions of interest. Primary motor responses were also excluded from detailed analysis, as the fMRI experiments did not have an overt motor response.

To evaluate the reproducibility of PET results with BOLD imaging, select ROIs (Table I), identified in Buckner et al. [1995], were measured in individual difference images of subjects in the GRE-fMRI study. PET regions were selected from published points that were originally reported as significant. The coordinates for one region, in the right cerebellum, differed somewhat from those in the earlier report [Buckner et al., 1995]. A more permissive search routine of the PET data identified a large peak in the right cerebellum previously excluded because of its proximity to a larger “right fusiform/cerebellar” response [Buckner et al., 1995], and this cerebellar region was added to the ROI analysis. For ROI analysis of the GRE-fMRI study, a difference image was calculated for each GRE-fMRI subject, transformed into atlas coordinates, and Butterworth-filtered at 14-mm full-width half-maximum. For each PET-derived region, the magnitude of signal change was measured within a sphere of 7-mm radius, centered at the coordinates of the region of interest. A one-tailed t-test was applied to the regional values measured across all 8 subjects to test for fMRI re-

TABLE II. Reproducibility of ASE-fMRI results in GRE-fMRI data†

Region (coordinate)	–Log <i>P</i>	t-value for GRE data	<i>P</i>
ASE-fMRI regions—Positive			
Left frontal (–50, 19, 28)	47.4	3.39	.006
Left frontal (–43, 0, 31)	45.7	9.78	<.0001*
Left frontal (–53, 6, 9)	45.7	3.26	.007
SMA (–3, 3, 50)	46.8	5.69	.0004*
Left cerebellum/fusiform (–40, –52, –21)	39.9	5.40	.0005*
Right cerebellum/fusiform (46, –49, –25)	26.6	1.31	.12
Right inferior cerebellum (18, –62, –43)	38.9	0.15	.48
Left superior parietal (–15, –68, 53)	43.6	1.85	.054
Left superior parietal (–25, –65, 40)	42.5	5.68	.0004*
Right superior parietal (28, –65, 40)	44.1	4.41	.0016*
Right inferior frontal (37, 25, 3)	31.8	1.24	.13
Right superior frontal (50, 0, 34)	30.9	2.33	.026
Left putamen (–21, 6, 0)	30.0	2.99	.01
Left thalamus (–9, –12, 9)	21.8	3.92	<.003*
ASE-fMRI regions—Negative			
Medial parietal (3, –62, 34)	40.5	–7.95	<.0001*
Right parietal (12, –55, 21)	34.6	–8.51	<.0001*
Left parietal (–12, –62, 21)	34.6	–5.37	.0005*
Inferior medial frontal (6, 50, –3)	29.1	–2.85	.01

† Regions found in the ASE search routine are given along with the coordinates and K-S significance (given as $-\log(P)$) for the region. T-values were determined on the GRE-fMRI data. SMA, supplementary motor area.

* Significant at $P < .05$ after correction for multiple comparisons.

sponses in the same direction (positive or negative) as the PET responses. Significance values were calculated (StatView, Abacus Concepts, Berkeley, CA), and those significant after correction for the number of regions sampled were identified.

To demonstrate reproducibility across institutions and modalities of fMRI, ROIs were identified from the ASE peak-search routine (Table II) with peaks of the highest significance reported for a given cortical domain (e.g., left parietal). Additional regions with lower peak significance were also selected if they represented separate anatomical structures (e.g., left thalamus) not represented in peaks with higher significance; all

peaks had K-S values such that $-\log(P) > 20$. As above, regions in the visual cortex were excluded from analysis. Spheres of 7-mm radius, centered on these regions, were then applied to the filtered difference images for each of the 8 GRE-fMRI subjects. One-tailed t-tests were applied to the difference signal values from the 8 subjects.

RESULTS

A qualitative, graphic comparison of the fMRI and PET data revealed a similar pattern of activation. Figure 1 demonstrates positive changes between stem completion and visual fixation for the PET study (top row), the fMRI Z-image using GRE (middle row), and the fMRI K-S map using ASE (bottom row). Peak activations across different regions of the brain are given for PET (Table I), ASE-fMRI (Table II), and GRE-fMRI (Table III).

Certain activations are clearly evident in all three studies, including extensive bilateral visual cortex increases, extending anteriorly and inferiorly. Left frontal activation was also seen in all three studies. The PET images show two left frontal activations (one superior and one inferior, $z = 26$ mm and 11 mm, respectively, in the original coordinates of Buckner et al. [1995]). In the fMRI studies, these regions appear to contain at least three activations, consistent across GRE and ASE: left inferior frontal ($z = 0$ mm of Fig. 1), left superior frontal ($z = 32$ mm), and an activation anterior to the left superior frontal activation ($z = 16$ mm and 32 mm) are seen in both fMRI studies. In PET and both fMRI studies, bilateral cerebellar activation ($z = -32$ mm) is present with a greater spatial extent on the right. Activation in left SMA (including pre-SMA as defined by Picard and Strick [1996]) was also seen in PET and both fMRI studies ($z = 48$ mm). A smaller right opercular activation (homologous to the larger left inferior frontal activation at $z = 0$ mm) was seen across studies but was better-defined in the two fMRI studies than in PET. Left thalamic activation is small in PET but evident in all three studies. Basal ganglia activation on the left was primarily seen with ASE-fMRI, although also suggested in the GRE-fMRI data. Additionally, bilateral parietal activation (predominantly left-sided) was evident in both fMRI studies, and absent in the PET study ($z = 32$ mm and 48 mm).

The regions showing a negative activation (regions with greater signal in fixation than in stem completion) are also highly similar across the three techniques (Fig. 2). Robust decreases in medial parietal ($z = 32$ mm and 48 mm), inferior medial frontal ($z = 0$ mm), and lateral

Figure 1.

Positive responses (stem completion > fixation). Comparison in stereotactic space of PET (top row), GRE-fMRI (middle row), and ASE-fMRI (bottom row) activation maps averaged across subjects. All three modalities reveal similar functional anatomy. Activation maps are overlaid on the cross-subject average anatomical MRI, except for the PET data which are overlaid on a standardized MRI

placed into stereotactic space. Each column of images corresponds to the same transverse cut (except for $Z = 64$ mm, which in PET is the highest slice in the data set at $Z = 60$ mm). Color bars at right indicate the scale for either PET counts (top row), Z scores (middle row), or significance (K-S statistic given as $-\log_{10}(P)$). The anatomical right side is on the image right.

parietal ($z = 32$ mm) were seen across all three studies. Bilateral insular decreases ($z = 0$ mm) were also seen across studies, although the right insular negative is more prominent than the left in PET, whereas the decreases are more symmetric in both fMRI studies, and stronger in the GRE-fMRI study.

Representative timeseries from the GRE-fMRI study are given in Figure 3 for two regions. A left frontal region has a signal time course that matches the presentation of stimuli. A region (medial parietal cortex) with negative changes is also demonstrated. The medial parietal area is seen to decrease with onset of the stem-completion task and to return to baseline at the end of stem completion.

The reproducibility of activation for multiple regions identified in the PET study is reported in Table I, for both positive and negative changes. All regions of increase were significant, even after correction for multiple comparisons. Of the nine negative regions identified in PET, the six with the largest magnitudes (as reported in Buckner et al. [1995]) showed significant decreases in the GRE-fMRI data.

The reproducibility of the ASE-fMRI regions is reported in Table II. Each region chosen from nonvisual peaks of significance in the ASE-fMRI study is reported with coordinates and peak statistical significance (given as the absolute value of the natural logarithm of the K-S significance value). In this analysis, three separate left frontal increases were identified, all of which reached significance. Other regions, including bilateral parietal, supplementary motor area (SMA), and subcortical (thalamus and putamen), were also reproducible, along with decreases in the medial parietal and inferior medial frontal cortex.

The search routine for the GRE-fMRI data identified multiple regions of peak significance, including regions identified in the reproducibility analysis above (Table III). Additionally, peaks were identified that were in the vicinity of ASE-fMRI regions that did not reach significance in the ROI analysis, including increases in the right cerebellum (37, -61, -22; homologous to the replicating left cerebellum region), right inferior cerebellum (11, -79, -34), and right lateral inferior frontal cortex (51, 15, -2 and 33, 21, 2). Peak

TABLE III. Results of peak search routine for GRE-fMRI data*

Region (coordinate)	Z
Positive	
Left frontal (−49, 7, 32)	13.9
(−45, 25, 22)	10.1
(−45, 15, −2)	9.7
(−53, 9, 6)	8.6
SMA (−3, 11, 48)	12.4
Left cerebellum (−41, −57, −24)	9.3
Right cerebellum (37, −61, −22)	8.9
Right inferior cerebellum (11, −79, −34)	5.3
Left parietal (−25, −65, 40)	11.4
(−39, −55, 50)	8.8
Right parietal (27, −63, 42)	8.1
Right inferior frontal (51, 15, −2)	5.7
(33, 21, 2)	5.6
Left putamen (−21, −3, 4)	4.0
Left thalamus (DM) (−7, −19, 10)	5.9
Negative	
Medial parietal (1, −57, 42)	−10.9
(1, −45, 44)	−9.4
Inferior medial parietal (1, −63, 26)	−8.3
Right parietal (11, −59, 16)	−8.4
Left parietal (−15, −61, 16)	−7.4
Right insula (41, −7, −4)	−7.3
(39, −15, −2)	−7.2
Left insula/STG (−47, −9, 2)	−6.9
Inferior medial frontal (5, 47, 0)	−8.1

* Peaks are grouped by brain region and given with corresponding coordinates. The Z value for each peak is given in the second column. DM, dorsomedial nucleus; SMA, supplementary motor area; STG, superior temporal gyrus.

decreases were also seen in the bilateral insular cortex, whereas only the right insula was included in the analysis of PET regions above.

DISCUSSION

Many areas of activation were the same in PET and fMRI. In both modalities, visual, left prefrontal, superior medial frontal (pre-SMA), and right cerebellar activations were demonstrated. Regions of decrease were seen in the medial and lateral parietal cortex and right insula. The similarities across studies occurred despite different modalities of blood flow imaging, different fMRI techniques, and different image analysis methods. A more specific analysis showed that some activations were virtually identical, while others differed in ways that may demonstrate important advantages, and disadvantages, of functional MRI.

Similarities across studies: Increases

In the left frontal region, two large PET responses, found at (−37, 21, 12) and (−43, 7, 30), separated into more responses when viewed with fMRI. The presence of a left inferior frontal (opercular), left superior premotor, and an additional activation in the next most anterior frontal gyrus (e.g., anterior superior frontal at −50, 19, 28) were demonstrated with both ASE and GRE. The central tendency of these regions approximated the PET response. The improved resolution of fMRI demonstrated subregions within the left frontal lobe in this task. Contrary to earlier reports that articulation is required for left inferior frontal activation [McCarthy et al., 1993], the presence of such activation (e.g., −53, 6, 9 in Table II and −53, 9, 6 in Table III) in the silent performance of the stem-completion task (in the fMRI studies) indicates that the role of this region is independent of overt speech, confirming the findings of others [Binder et al., 1995; Buckner et al., 1995; Cuenod et al., 1995; Desmond et al., 1995; Wise et al., 1991].

Also of significance was the presence of a *right* frontal response, more isolated than the left-sided responses and of less magnitude. This was not noted in the earlier PET studies but may be present as a weaker activation (Fig. 1, top row). This response was clearly evident in both fMRI studies here. The posterior-superior right frontal activation (50, 0, 34; Table II) did replicate, although the anterior right frontal activation (37, 25, 3) did not statistically replicate, despite the presence of a Z-image peak nearby (33, 21, 2; Table III). The presence of bilateral frontal responses during language tasks in right-handed subjects has been seen in several studies [Binder et al., 1995; Cuenod et al., 1995; Desmond et al., 1995]. The concept of left-lateralization of language function in right-handers appears to be a relative, rather than an absolute, phenomenon, at least in functional imaging.

Several other regions active in the PET study are part of a network which has been seen in a variety of language and memory tasks [Buckner et al., 1995, 1996b; Petersen et al., 1988, 1989; Raichle et al., 1994]. Along with the left inferior frontal cortex, this system includes the right cerebellum and anterior SMA regions. All three of these regions were also seen in both fMRI studies, and all three regions formally replicated in the GRE analysis. Both GRE and ASE studies lateralized the pre-SMA responses to the left. The precise location of this superior medial frontal response (PET coordinates −3, 11, 52), often seen with cognitive tasks [Buckner et al., 1996b; Picard and Strick, 1996], fell anteriorly to the response in SMA-

Figure 2.

Negative responses (stem completion < fixation). The format is the same as in Figure 1. As seen with increases, decreases associated with activation give similar maps across PET (top row) and both fMRI studies (GRE, middle row; ASE, bottom row).

proper seen for motor-related tasks, including studies involving simple repetition [Buckner et al., 1996b; Petersen et al., 1988, 1989; Raichle et al., 1994].

Bilateral cerebellar activation was seen in both fMRI studies, along with a replicating right cerebellar region in PET and GRE-fMRI. Cerebellar activation was also seen more inferiorly, on the right, in GRE and ASE (Fig. 1, $z = -32$ mm), although the difference in localization (18, -62, -43, Table II vs. 11, -79, -34, Table III) prevented replication of this region. Cerebellar activation persisted, despite the absence of motor output in the silent fMRI tasks. This provides further evidence for a nonmotor role for the cerebellum in at least some aspects of cognitive function. The importance of right cerebellar activation during certain language tasks has been discussed [Fiez et al., 1992, 1995], with special emphasis on frontocerebellar connections. The somewhat less extensive left cerebellar activation paralleled the presence of a weaker right frontal activation, suggesting that the crossed frontocerebellar relationship is present in both the left frontal-right cerebellar

and the right frontal-left cerebellar networks during this task.

Increases in subcortical structures were also consistent across studies. Both fMRI studies demonstrated left thalamic activation, consistent with suggestions from the PET data (Fig. 1) [Buckner et al., 1995] and the described role of the thalamus in language and verbal memory [e.g., Ojemann, 1975]. The precise localization of the activation to the lateral aspect of the dorsal medial (DM) nucleus in both studies was less expected, although the medial aspects of ventrolateral (VL) or ventroanterior (VA) nuclei are only millimeters away, closer than the spatial resolution of any of the studies. Additionally, left basal ganglia activation was seen, localizing to the putamen in both fMRI studies. ASE-fMRI activations in both the left thalamus and left putamen replicated in the GRE-fMRI study (Table II).

The similarity between the PET and fMRI studies has been demonstrated only for this particular cognitive task. It remains to be seen if other areas of the

Figure 3.

Representative timeseries for regions of increased and decreased signal from the GRE-fMRI data. Signal change relative to the fixation state is plotted against time (in seconds, ~ 2 sec per measurement). The paradigm is graphically represented (thin line), with stem completion (Stem) represented by the larger value and fixation (Fix) represented by the lower value. Left frontal region increases (bold solid line) and medial parietal decreases (dashed line) both correlate with the behavioral state but in opposite directions. Each time course was obtained from a $10 \times 10 \times 3$ mm region of interest centered on the given activation. Time courses were not temporally smoothed.

brain, not activated by word-stem completion, show equivalent activations in PET and fMRI during different tasks. This may be of particular importance in areas of high susceptibility artifact, such as the inferior temporal cortex [Frahm et al., 1988; Ojemann et al., 1997], that were not activated by this task, but that might be difficult to detect with some fMRI techniques.

Similarities across studies: Decreases

Several areas demonstrated decreases across all three studies. The medial parietal cortex was found to decrease during stem completion relative to fixation. The more superior medial parietal regions (Fig. 2, $z = 48$ mm) matched quite closely across fMRI and PET, whereas more inferior medial parietal regions were less prominent in PET ($z = 16$ mm). However, the more inferior regions did generalize across fMRI studies. Similar superior and inferior medial parietal regions demonstrated decreases across multiple PET studies that involved language or nonlanguage visual stimuli and that used fixation points as the control task [Shulman et al., 1997].

Another region found to be negative across many stimulation paradigms was the inferior medial frontal region, including orbital frontal gyrus and gyrus rectus [Shulman et al., 1997]. Although this area was not fully sampled in the PET study, PET decreases were evident in all three studies (Fig. 2, top row), with reproducible decreases in the ASE and GRE studies (Table II). Negatives have also been reported near this area in fMRI and PET studies of somatosensory stimuli [Coghill et al., 1994] and in an fMRI study of auditory stimuli [Maldjian et al., 1996]. The full sampling of this region may be limited posteriorly because of the close proximity of susceptibility artifacts [Frahm et al., 1988; Ojemann et al., 1997].

The PET and fMRI studies have additional areas of matching decreases, including the bilateral insula (more right-lateralized in the PET) and replicating areas in bilateral parietal regions (anterior and lateral to the parietal regions of increase). Combined with the regions discussed above, the map of decreases acquired with the direct blood flow measure of PET matches that obtained from BOLD measurements with either GRE or ASE-fMRI. Timeseries (e.g., Fig. 3) demonstrate that the signal in such regions correlates with the stimulus blocks, with decreases in signal occurring with the onset of the stem completion. The correlation with stimulus is highly similar to the curves seen for the left frontal region (Fig. 3) [Buckner et al., 1996a], but with signal change in the opposite direction.

The reproducibility of negative responses from PET to fMRI may have implications for models of blood flow and metabolism. Although some negative responses may be due to regional increases in CBF and BOLD signal during the fixation control task, other negative responses could represent regions in which, during the active task, CBF and BOLD signals drop below resting, baseline values. In the latter case, to produce a negative BOLD signal, rCBF would decrease more than regional oxygen metabolism (rCMRO₂). This differential response between rCBF and rCMRO₂ has only been directly demonstrated during functionally induced *increases* of blood flow [Fox and Raichle 1986; Fox et al., 1988]. In the case of functionally induced *decreases*, if rCBF decreases more than rCMRO₂ (to give a negative BOLD signal), then oxygen extraction would actually increase relative to the resting state where rCBF and rCMRO₂ are tightly coupled [Raichle et al., 1976; see related discussions in Buxton and Frank, 1997].

Differences across studies

Any interpretation of differences across studies is limited by the use of different subject groups. How-

ever, certain differences exist that may be due to varying methods in the three studies. First, motor regions present in the PET studies were not seen in the fMRI studies, as expected given the silent performance of the task in fMRI. However, such differences were limited to the Rolandic motor cortex and anterior cerebellum (regions that were a priori excluded from the ROI analysis). Notably consistent, despite the absence of an overt motor response in the fMRI subjects, was the presence of left inferior frontal and anterior SMA responses. The premotor increases seen in fMRI studies may not be identical to the PET activations in nearby regions (Fig. 1, $z = 32$ mm). It has been suggested that performing a language task silently, as in these fMRI studies, may affect the distribution of activations, especially the left precentral responses in language tasks [Rosen et al., 1997]. Alternatively, differences in these premotor regions may simply be due to different subject groups contributing to each study.

Superior parietal activations, which were more extensive on the left, replicated across fMRI studies but were not present in the PET study (Fig. 1, $z = 32$ mm and 48 mm). On the left side, this seemed to represent several parietal regions: one homologous to the right-sided response, the other two more anterior without a corresponding right-sided activation. Several differences in the experiments may contribute to this discrepancy. First, only one third of the PET subjects were scanned in a position that allowed imaging of these more superior regions, thus limiting the sensitivity of the PET study to changes in these regions. Second, throughout the fMRI study, the echo-planar imaging resulted in a loud, repetitive noise, evident even despite headphones using active noise-suppression techniques. Decreases in activation in these superior parietal regions have been seen during various auditory tasks [Fiez et al., 1995], especially when a task demands attention to auditory features. During the fixation part of the fMRI studies, in the absence of an active task such as word-stem completion, more attention may be given to the loud surrounding noises. This could lead to a *relative* decrease in activation of the parietal areas during fixation, thus appearing as an activation during the stem completion minus fixation subtraction.

A third explanation is suggested by the finding of increased activity in the lateral parietal regions during internal speech compared to overt speech [Rosen et al., 1997]. For now, attempts to use fMRI with overt speech have met with difficulty due to direct and indirect effects of movement [Birn et al., 1997; Yetkin et al., 1995]. The significance of internal vs. overt speech, and

the importance of this manipulation in the face of the other findings for these parietal areas relative to attention mechanisms, remain to be explored with future studies. For both left frontal and parietal regions, language tasks may give different activations, beyond traditional motor-related structures, when performed silently instead of aloud.

Some cerebellar regions did not replicate across fMRI studies, despite the presence of cerebellar activations in both studies. These activations appear to be more diffuse, without clear peaks (Fig. 1, $z = -32$ mm). It is also possible that signals from the posterior fossa are weaker or have slightly different locations, leading to error in precise peak locations.

CONCLUSIONS

In these studies, BOLD imaging of a word-stem completion task gave highly similar results across different institutions. Despite different machines, different sequence acquisitions, and different postacquisition processing strategies, very similar activation maps were obtained. Both fMRI studies gave maps consistent with rCBF-PET studies of a similar task, for both increases and decreases in signals, despite the different physiologic mechanisms underlying each imaging modality. The reproducibility of BOLD and CBF responses should permit comparison of results across institutions and across imaging modalities for similarly designed experiments.

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