Magnetic Resonance in Medicine 54:569–576 (2005)

Resolution and Reproducibility of BOLD and Perfusion Functional MRI at 3.0 Tesla

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Visual and somatosensory activation studies were performed on normal subjects to compare the spatial discrimination and reproducibility between functional MRI (fMRI) methods based on blood oxygen level-dependent (BOLD) and perfusion contrast. To allow simultaneous measurement of BOLD and perfusion contrast, a dedicated MRI acquisition technique was developed. Repeated experiments of sensory stimulation of single digits of the right hand showed an average variability of activation amplitude of 25% for BOLD data, and a significantly lower variability of 21% for perfusion data. No significant difference in the variability of the locus of activity was observed between the BOLD and perfusion data. In somatotopy experiments, digits II and V were subjected to passive sensory stimulation. Both the BOLD and perfusion data showed substantial overlap in the activation patterns from the two digits. In a retinotopy study, two stimuli were alternated to excite different patches of V1. Again there was substantial overlap between the activation patterns from both stimuli, although the perfusion performed somewhat better than the BOLD method. Particularly for the visual studies, the overlap in activation patterns was more than expected based on the fine-scale retinotopic mapping of cortical activity, suggesting that both BOLD and perfusion contrast mechanisms contribute substantially to the point-spread function (PSF). Magn Reson Med 54:569–576, 2005. Published 2005 Wiley-Liss, Inc.†

Key words: MRI; functional imaging; localization; brain imaging; fMRI; BOLD

Changes in tissue perfusion with brain activation can be measured with MRI methods sensitized to perfusion contrast (1) or blood oxygenation level-dependent (BOLD) contrast (2). Since perfusion changes are the source of and potentially precede blood oxygenation changes, it can be argued that perfusion MRI is a more direct method for detecting brain activity. This can lead to distinct differences between perfusion and BOLD measures of activity, with potentially important implications for functional activation studies.

One potential difference between perfusion and BOLD functional MRI (fMRI) is in the accuracy of localization (3). Perfusion fMRI is thought to be primarily sensitized to the arterial side of the capillary bed, with a potential contribution from the arterioles and larger arteries. BOLD fMRI, on the other hand, has a bias toward the venous side of the capillary bed and can include venules and the larger veins, as well as their surrounding tissue. This sensitivity to venous or arterial effects can result in localization errors of a few to several millimeters depending on the contribution of signals from outside the capillary bed (i.e., the macrovascular contribution).

The difference in contrast mechanisms between BOLD and perfusion MRI can also lead to differences in the reproducibility of the localization and the amplitude of the activation. Since BOLD fMRI relies on an imbalance between changes in vascular oxygen extraction and perfusion, one could argue that perfusion contrast, which does not rely on this imbalance, might be a more robust and reproducible measure.

Despite the potential problems related to localization, a number of studies have shown that under certain conditions BOLD fMRI can be used to accurately discriminate between functional areas in the brain. Studies in humans have shown that BOLD fMRI can reveal the precise retinotopic mapping in the early visual areas, such as V1 (4–6), and furthermore can discriminate features on the submillimeter scale, such as ocular dominance columns (7,8). Several BOLD fMRI studies of the primary somatosensory system (S1) have confirmed the existence of a fine-scale somatotopic mapping (9–15), and detected differences in finger-representations on the order of a few millimeters. In those studies, spatial overlap of activated regions introduced by vascular artifacts was reduced by a number of strategies, including thresholding and subtraction of activation patterns. Under certain conditions, perfusion fMRI also allows high functional resolution. A study on cats at 4.7 T suggested that perfusion fMRI was able to discriminate ocular dominance columns (16).

In the following, the potentially improved localization accuracy and reliability of perfusion imaging is investigated. An attempt is made to quantitatively compare the localization accuracy of BOLD and perfusion fMRI by comparing activated areas in tasks that target distinct cortical areas in the visual and somatosensory systems. For this purpose, a fMRI method was used that measures BOLD and perfusion changes within the same functional run simultaneously. In addition, the reproducibility of the measured activation amplitude and location was evaluated with repeated experiments in the somatosensory and sensorimotor systems.

MATERIALS AND METHODS

Study Design

Three fMRI experiments (studies A–C) were performed to evaluate the scan-to-scan reproducibility and localization

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Received 1 June 2004; revised 29 December 2004; accepted 8 March 2005.
DOI 10.1002/mrm.20577
Published online 5 August 2005 in Wiley InterScience (www.interscience.wiley.com).

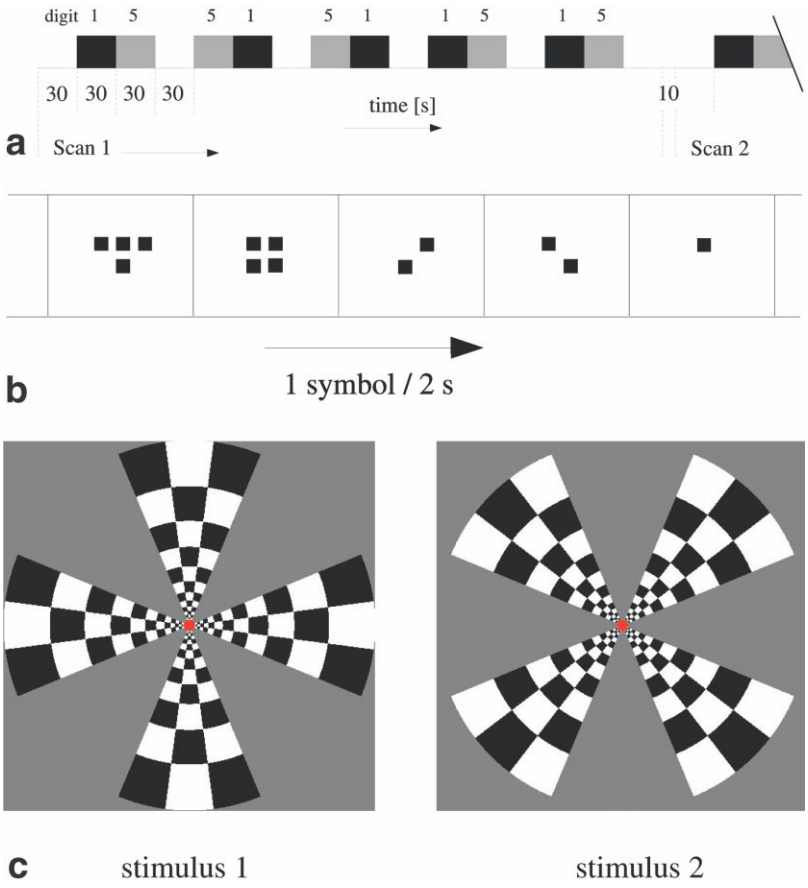

FIG. 1. Stimuli used in the three studies. **a:** Sequence of finger tapping used in study A. Each segment lasted 30 s, and the order of the digits was randomized. **b:** Example of the patterns used for tactile stimulation in study B. The black squares represent the dots embossed in the paper tape, which was moved about at about one symbol every 2 s during the 30-s stimulus time. The patterns were repeated in random order. **c:** Pattern of the two visual stimuli used in study C. Each stimulus period consisted of 30 s of one of these patterns with contrast reversals at a 4 Hz rate (eight images per second).

accuracy of BOLD and perfusion-based fMRI. BOLD and perfusion were measured simultaneously using a dedicated pulse sequence (see MRI Scanning section). All studies were performed under an IRB-approved protocol for experiments involving human subjects. Normal volunteers were scanned after they provided written informed consent.

The reproducibility study (A) was performed with a task known to activate the sensorimotor system robustly, whereas the localization studies (B and C) were performed with tasks that activate distinct cortical areas in the early somatosensory (B) and visual systems (C).

Study A

To evaluate reproducibility, we performed 38 experiments using a visually paced finger-tapping paradigm that was designed to activate the primary sensory (S1) and motor (M1) cortices. Within a scan session, the identical paradigm was repeated six times. A short delay of around 10 s was used between successive repeats (runs) of the paradigm to reduce the effects of fatigue. Each run lasted 8 min, during which time the subjects went through successive stages of resting, tapping with the first digit (thumb), and tapping with the fifth digit (little finger). Each stage lasted 30 s. A visual cue was used to pace the tapping rhythm at one tap per second. Execution of the task was visually monitored. The timing of the paradigm is presented in Fig. 1a. To minimize the effects of learning across functional runs, the task was practiced prior to scanning. A total of 23 volunteers (10 females and 13 males, 23–50 years old, average age = 35.7 years) participated, some in two or three experiments several weeks apart (analyzed independently). All of the subjects were right-handed and tapped with the dominant hand.

Study B

To evaluate localization accuracy in the somatosensory system, seven normal volunteers (four females and three males, 24–37 years old, average age = 30.7 years) performed a tactile task with two fingers. The task was designed to activate the separate patches corresponding to digits II and V of the dominant hand, while minimally engaging the motor system. The rationale for this was to minimize confounding signals from the nearby motor cortex, which is likely to have substantial overlap in finger representation (17). The subjects were asked to recognize and count patterns embossed on paper tape. Each pattern, similar to a Braille character, consisted of one to four dots arranged on the grid points of a rectangular 2×3 matrix (Fig. 1b). The subjects were instructed to count one target pattern among four distractors, and to not move their fingers during the experiments. The patterns were presented to the subject by a device that allowed the tip of the subject's index and little fingers to be positioned on separate tapes, and the tape to be slid through a guide. The right hand of the volunteers was positioned such that they could feel both paper strips without moving their fingers. The task was designed to be sufficiently difficult that the

volunteers would keep paying attention to the task, which appears to be important for producing reliable activation with tactile stimuli. The volunteers briefly practiced the tasks before they entered the scanner, to familiarize themselves with the various symbols. The activation paradigm consisted of two active stages and one rest stage, each of which lasted 30 s. During each of the active stages, one of the paper tapes was manually moved to present a series of patterns at a rate of approximately one symbol every 2 s. One run consisted of four repetitions of 30 s rest, 30 s index finger, and 30 s little finger stimulus, for a total time of 6 min. These runs were repeated three times, each time with a different target pattern.

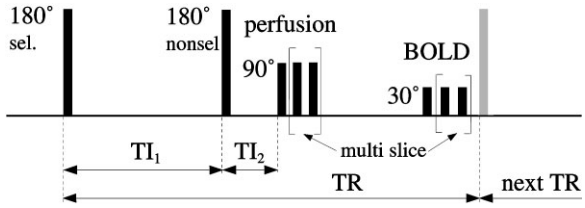

FIG. 2. SSPL pulse sequence used in the experiments. The double inversion results in perfusion images with background suppression, while the extra 30° excitation at the end allows for near simultaneous BOLD measurements. The labeling time is the sum of TI_1 and TI_2.

Study C

To evaluate localization accuracy in the visual system, eight normal subjects (five females and three males, 23–37 years old, average age = 30.7 years) were presented with a contrast reversing (eight reversals per second) checkerboard. As in study B, two different stimuli were used, each of which involved a number of separate sections of the visual field (Fig. 1c). The stimuli were presented to the volunteers with video goggles (Silent Vision 4000; Avotec). The activation paradigm again consisted of two active stages and one rest stage, each of which lasted 30 s. A uniform gray stimulus was used during rest stages. One run consisted of four repetitions of the three stages, for a total time of 6 min (Fig. 1c). The subjects were asked to attend to a small dot in the center of each visual field, which changed color periodically. To reduce saccades and ensure that the volunteers paid persistent attention to the center of the screen, the subjects were asked to count the number of color changes. Six volunteers completed two runs, and two completed three runs.

MRI Scanning

All of the imaging studies were performed on a 3 T GE MRI scanner, equipped with a CRM gradient coil (40 mT/m maximum gradient, 150 T/m/s slew rate). A detunable transmit-receive head coil (model NM-001A; Nova Medical) was used for RF excitation, and quadrature combined dual surface coils were used for MR signal reception focused to the relevant cortical areas (model NMSC-003A; Nova Medical). To facilitate prescription of the slices for the fMRI acquisition, anatomical localizers were acquired using the product inversion recovery 3D FSPGR pulse sequence.

The fMRI pulse sequence was based on single-shot perfusion labeling (SSPL) using two inversion pulses (18), and included a BOLD acquisition (see Fig. 2). The first (selective) inversion created perfusion sensitivity, while the second (nonselective) inversion provided background suppression and minimized BOLD contamination of the perfusion signal. The effective labeling time corresponded to the delay between the first inversion and the image acquisition. The BOLD acquisition was inserted just before the first inversion pulse. A low (30°) flip angle was used to ensure that the perfusion signal would be minimally affected. The estimated reduction in the perfusion signal due to the insertion of a BOLD acquisition was 13%. To evaluate the potential pitfalls of the lack of a perfusion reference scan in the single-shot perfusion technique, in 12 of the experiments in study A (forming group 1) a perfusion reference with two nonselective inversion pulses was incorporated in alternating repetitions, similarly to the fluid-attenuated inversion recovery (FAIR) technique (19). The remainder of the experiments in study A (the 26 in group 2) were performed without a reference acquisition.

Image acquisition for BOLD and perfusion signals was performed using an EPI readout (20), with ramp sampling (50% of the ramp time) and a 250 kHz acquisition bandwidth (4 μs dwell time). Four 3.0-mm slices were acquired with 1.0-mm gap, going sequentially from superior to inferior. The echo times (TEs) were 18 ms and 38 ms for the perfusion and BOLD acquisitions, respectively. The corresponding slice-to-slice repetition times (TRs) were 38 ms and 58 ms, respectively. The timing of the two inversion pulses was chosen to provide a labeling time of around 1.5 s, while making sure that the perfusion acquisition was performed just before the zero crossing of the magnetization of the tissue components. This resulted in a delay time (TI_1) of 1086 ms after the first inversion pulse, and a delay time (TI_2) ranging from 250 to 364 ms over all acquired slices after the second pulse (see Fig. 2). The overall TR was 3.0 s for all experiments. The effective TR for the experiments with perfusion reference (see above) was 6.0 s. To suppress intravascular contribution from the larger vessels, a flow suppression crusher was applied in both the perfusion and BOLD acquisitions. The crusher was applied in the direction of the slice-select gradient and immediately followed the slice selection (a bipolar pulse with 2 ms pulse width, 25 mT/m amplitude, and 1.5 ms separation). The delay from the perfusion to the BOLD acquisition was about 1.6 s.

For study A, the field of view (FOV) was 240 × 120 mm, and the voxel matrix size was 64 × 32, resulting in a nominal in-plane image resolution of 3.8 mm.

For study B, the FOV was 192 × 144 mm, the voxel matrix size was 64 × 48, and the nominal in-plane image resolution was 3.0 mm. The TEs were 23 ms and 43 ms for the perfusion and BOLD acquisitions, respectively, and the slice TRs were 60 ms and 80 ms, respectively. The inversion delays TI1 and TI2 were 1082 and 220–460 ms, respectively.

For study C, the FOV was set to 256 × 72 mm, and the matrix size was 128 × 36, resulting in a nominal 2.0-mm

resolution. The slice thickness and gap were reduced to 2.0 mm and 0.5 mm, respectively. A spatial saturation pulse was added to the sequence to suppress the anterior part of the brain, which in combination with the coil sensitivity profile allowed the reduced phase-encoding FOV. The TI's, TEs, and TRs were the same as in study B.

Image Analysis

All data analyses were performed with in-house-developed software written in IDL (RSI, Boulder, CO, USA). For EPI image reconstruction, the ramp-sampled data were transformed using a direct matrix multiplication with the inverse of the encoding matrix containing the appropriate Fourier coefficients. A phase correction to compensate for the differences between odd and even echoes was calculated from a reference echo from the center of *k*-space after temporal low-pass filtering was applied (21). For the perfusion scans with a reference, the reference signal was subtracted from the perfusion-weighted data. The time-series image data were then analyzed by curve-fitting using multilinear regression, which incorporated the activation function convolved with a model response function (a delayed Gaussian with $\sigma = 3.5$ s, delay = 5 s), as well as two drift terms (22). This resulted in activation *t*-score and amplitude maps. Anatomically based regions of interest (ROIs) were chosen in the relevant areas, and masks to discriminate subregions of activated voxels were generated based on a *t*-threshold ($P < 0.05$, Bonferroni corrected).

For the reproducibility study (A), a single (combined) mask was generated from all runs, which contained all voxels that exceeded the statistical threshold in any of the runs. The activation amplitude and *t*-scores were averaged per run over this mask. Based on these averages, the relative standard deviation (SD/mean) over the runs was calculated for the average *t*-score and activation amplitude for each volunteer. Also, the root sum of squares of the SD of the *x*, *y*, and *z* coordinates of the center of gravity (CG) of activation was calculated as a measure of spatial stability. Volunteers with less than an average of four activated voxels in either the perfusion or the BOLD data were excluded from further analysis, to exclude meaningless relative SD measures. The calculated parameters were than averaged over the remaining volunteers.

For studies B and C, the same procedure was followed as for study A, with the addition that to calculate spatial differences in activated areas, a mask that combined activated voxels across tasks was also generated to compare localization between tasks. From the CG, the difference between the areas activated with the two tasks and the difference between modalities (perfusion and BOLD) was calculated. As a measure of spatial separation of areas activated with the two tasks performed within each study, a similarity *S* between areas was calculated from:

$$S = \frac{\sum(P \cdot Q)}{\sqrt{\sum(P \cdot P)\sum(Q \cdot Q)}}$$

where *P* and *Q* are the maps of activation amplitude associated with the two tasks performed. For this calculation all voxels with a *t*-score above 1.3 ($P < 0.1$) in either task were included. The similarity measure can be interpreted as a correlation with zero mean or as a normalized vector in-product. Very similar overlapping regions produce *S*-values close to unity, whereas $S = 0$ signifies complete separation between regions. Finally, for study B a quantitative measure for the spatial distance between the areas activated with the different tasks was calculated from the CG, and from this the average and SD over the runs were taken.

RESULTS

Study A: Reproducibility

The reproducibility studies were analyzed in two separate groups, based on the type of perfusion measurement that was performed (see Materials and Methods): group 1 studies were performed with a perfusion reference scan, and group 2 studies were performed without a perfusion reference scan. Due to lack of activation in one or more of the runs, a total of nine subject studies were excluded from further analysis, leaving 12 subjects in group 1, and 26 subjects in group 2. Seven of the excluded subjects had higher than normal instability (two times higher on average). One subject in group 2 failed to tap in two of the runs (data from these runs were excluded from analysis), two others only completed five runs, and the remaining volunteers completed six runs successfully. An example of the activation maps is shown in Fig. 3.

The average *t*-scores in group 1 were 2.60, 2.33, and 2.21 for perfusion, perfusion-reference, and BOLD, respectively, and for group 2 they were 3.01 and 2.33 for perfusion and BOLD, respectively. The *t*-scores were significantly higher for perfusion than for BOLD, for both groups 1 and 2.

The variation in activation amplitude was substantial and ranged from 18% to 28%, depending on the task and scan technique used. A paired *t*-test showed a significantly higher relative variation in the BOLD activation amplitude compared to the perfusion data for both groups 1 and 2 (difference between BOLD and perfusion variability: 4.8%, $P = 0.039$, and 4.5%, $P = 0.012$, respectively). There was no significant difference between the stability of the perfusion data of groups 1 and 2, or between perfusion data with or without inclusion of the reference data in group 1. For the *t*-score and CG, no significant difference was found in any comparison, either between tasks or between scan modalities. Table 1 summarizes the reproducibility results. The average over all volunteers of the linear correlation coefficient of the BOLD and perfusion amplitude over the runs was 0.74 (SD over volunteers = 0.22).

Study B: Somatotopy

In study B, one subject showed insufficient BOLD activation and was excluded from further analysis. The results from the remaining six subjects are listed in Table 2. The average distance between the activation patterns of digits II and V was 2.9 mm for perfusion and 1.9 mm for BOLD. Although neither measurement is significantly different from zero, a paired *t*-test showed a significant difference between perfusion and BOLD ($P < 0.02$). The average

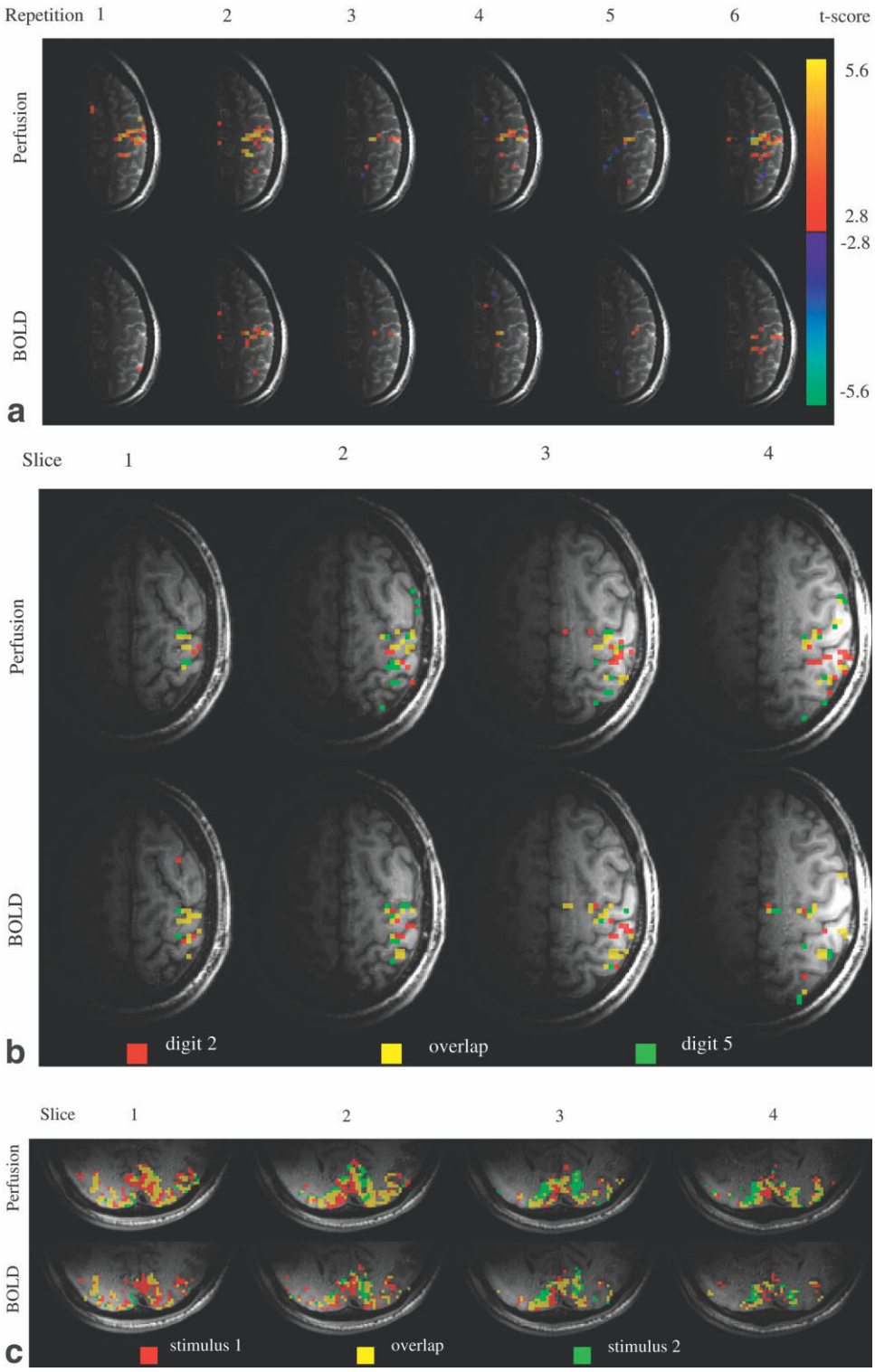

FIG. 3. Examples of the resulting activation in the three studies. **a:** Example of reproducibility (study A), showing one slice over six repeated trials with activated voxels in color overlay. Colors correspond to *t*-values, indicated on the bar on the right. **b:** Example of tactile study B. Shown are four slices with active voxels (based on *t*-score) for either one of the two stimuli, or both. Only the voxels directly posterior to the central sulcus were used in the analysis. **c:** Example of results from visual study C, showing the area activated by either one of the two stimuli, or both.

similarity between the activation pattern of digits II and V was 0.8, with no significant difference between BOLD and perfusion. Figure 3b shows an example of the activation map for both methods.

Study C: Retinotopy

All subjects in the retinotopic study showed robust activation, and none were excluded from further analysis. Table 3 lists the similarity of activation patterns between the two tasks, each of which stimulated a distinctly different area in the visual field. As with study B, a large similarity was found between activation patterns of the two stimuli in both the perfusion and BOLD data (average = 0.79 and 0.84, respectively). The similarity was smaller for the perfusion data, suggesting a somewhat improved localization, but the difference was not significant.

Table 1
Reproducibility of BOLD and Perfusion Measures in Sensorimotor Cortex*

	Perfusion		Perfusion-reference		BOLD	
	Digit I	Digit V	Digit I	Digit V	Digit I	Digit V
Group 1						
AA	0.22 (0.09)	0.24 (0.16)	0.27 (0.18)	0.22 (0.13)	0.27 (0.15)	0.28 (0.13)
TS	0.25 (0.12)	0.25 (0.16)	0.24 (0.10)	0.24 (0.15)	0.27 (0.13)	0.27 (0.13)
CG	1.42 (0.89)	1.70 (1.81)	1.68 (0.94)	1.74 (1.26)	1.73 (1.31)	1.34 (0.72)
Group 2						
AA	0.20 (0.17)	0.18 (0.08)			0.23 (0.12)	0.24 (0.10)
TS	0.23 (0.16)	0.21 (0.09)			0.24 (0.10)	0.24 (0.10)
CG	1.15 (0.92)	1.30 (0.56)			1.23 (0.57)	1.71 (0.89)

*Average of the standard deviation of activation amplitude (AA), t-score (TS), and center of gravity (CG) are listed for the two groups of experiments (see text). AA and TS are normalized to the average, the CG is in millimeters. Numbers in parenthesis represent the SD of the reported parameters over the volunteers.

DISCUSSION

General Remarks

The applied MRI pulse sequence, in combination with surface coils at 3.0 T, allowed the simultaneous detection of both BOLD and perfusion changes in visual and somatosensory experiments. The number of acquired slices in a single experiment was limited, as imposed by the particular methodology used for suppression of background signal. To achieve optimal perfusion sensitivity, the excitation flip angle for the BOLD acquisition had to be reduced to 30°, which led to an estimated 50% reduction in BOLD signal. In addition, there was some loss due to the limited recovery time (1.6 s) between the perfusion and BOLD acquisitions. However, because of the high SNR of the BOLD images for experiments A and B (SNR ~ 100 and 75, respectively), those experiments remained physiologic noise limited (and not thermal noise limited), and the flip angle reduction did not adversely affect the contrast-to-noise ratio (CNR). Preliminary comparisons with a conventional BOLD scan (90°) showed no significant difference (data not shown). Second, the activation amplitude was averaged over all active voxels, further reducing the influence of scanner noise. The higher-resolution visual experiment had an SNR of about 40, so a higher flip angle could improve the BOLD results in that case. However, it should be noted the addition of more noise results in less similarity between scans (noise images are dissimilar), and in that sense the reduced flip angle works in favor of BOLD compared to perfusion.

The exclusion of results with insufficient activation from the analysis could have created a bias toward higher stability; however, the bias would have been similar for both the perfusion and BOLD data, and therefore would not have led to a bias in the comparison. The exclusion was based on the average number of voxels activated, not on the stability, and lack of activation in either perfusion or BOLD was used as the criterion. The excluded data had low *t*-scores in both perfusion and BOLD measurements, due to either low signal stability or the overall performance of the volunteer. Therefore, we do not believe the exclusion led to a bias in the comparison. The exclusion was necessary in order to calculate a meaningful activation stability expressed as a percentage of the average activation amplitude.

As was pointed out previously (23), the *t*-score is not the best measure of reproducibility (since the uncertainty in the SD adds to the variance), which is why our main comparison was based on the relative amplitude of activation. The *t*-score results are reported here as well, because in most experiments only one run is used and the *t*-score is effectively the measure of activation. The bias introduced by taking the average of the *t*-scores is very small, as with higher degrees of freedom the probability distribution becomes close to symmetric.

The perfusion measurements have some BOLD contribution as well, since the background suppression is not perfect, mostly due to the timing differences over the multislice acquisition. Based on the relative baseline amplitude and the TEs, the BOLD contribution to the activation measured in the perfusion acquisition is estimated to range from 7% in the most suppressed slice to 25% in the least suppressed slice (as a percentage of the total measured activation). These effects are likely small enough that the results are not dominated by the BOLD contribution to the perfusion measurements. This is supported by the observation that the perfusion-with-reference scan, in which the BOLD contribution was canceled out, was not significantly more stable than the measurements without a reference.

Table 2
Difference in Location Between Sensory Activity of Digit II and V, Expressed by Distance (in mm) and Similarity of Activation Patterns (See Text)

Volunteer	Perfusion		BOLD	
	Distance	Similarity	Distance	Similarity
1	5.76	0.65	4.49	0.52
2	0.95	0.93	0.44	0.90
3	3.08	0.81	2.07	0.77
4	2.54	0.88	0.86	0.87
5	1.93	0.87	1.06	0.91
6	2.91	0.87	2.25	0.86
Average	2.86	0.83	1.86	0.80
SD	1.61	0.098	1.47	0.15

Table 3
Similarity of Activation Patterns of the Two Visual Stimuli

Volunteer	Perfusion	BOLD
1	0.91	0.94
2	0.80	0.80
3	0.75	0.83
4	0.77	0.83
5	0.65	0.83
6	0.83	0.86
7	0.86	0.85
8	0.83	0.78
Average	0.80	0.84
SD	0.08	0.05

Reproducibility

The use of a perfusion reference scan in our measurements resulted in reduced *t*-scores for the perfusion data. This is explained by the reduced efficiency (fewer averages) and the increased noise level associated with experiments that incorporate a reference scan. A scheme with a reference scan does have the potential advantage to result in a more absolute measure of perfusion and activation.

The improved stability of the activation amplitude observed in the perfusion experiments as compared to BOLD may be related to the different mechanism of the perfusion signal, and confirms the hypothesis that perfusion is a more direct and therefore more stable measure of activation than BOLD. It should be noted, however, that the difference between the methods is small (20% vs. 25% instability), and that in most applications this advantage of the perfusion method is negated by the inherent disadvantages of the technique, such as the lower time resolution and the complications involved in acquiring a large number of slices. It is also interesting to note that the variations in the BOLD and perfusion activation amplitudes appear to be partly correlated (0.74). This suggests a common source for at least a part of the variability, which in turn means that the stability of both methods will always be similar. Part of the variability may be caused by physiology unrelated to activity (such as breathing), or the hemodynamic response to the neuronal activity may not be completely stable.

The results appear to be similar to those obtained in previous BOLD reproducibility studies (24–26) in the sense that there is a substantial variation in activation amplitude but the localization (as CG) is relatively stable, with an SD of 1.2–1.7 mm.

Accuracy of Localization

In the light of the expected distinctly localized mapping within S1 and V1, the somatotopy and retinotopy experiments showed a surprisingly large similarity (i.e., overlap) between presumably separately activated regions. This was true for both the BOLD and perfusion data, although the latter showed a somewhat reduced overlap in V1. Similarly to the arguments noted above, it is questionable whether this small advantage of perfusion measurements outweighs the extra complications of the technique.

In the visual experiments, the activation task was designed to stimulate separate cortical regions. Previously reported data on the cat visual system suggest a point-spread function (PSF) on the order of 1 mm for neuronal activity (27). With each hemifield covering about 4 cm in cortical distance (28), the estimated cortical distance spanned by the radial extend of each wedge was 5 mm. With an image resolution of 2 mm, this should be resolved, although folding of the cortex may reduce the separation substantially. Another factor that potentially affects the PSF is small eye movements. Although the experiments were designed to reduce saccades, they can not be completely avoided.

The large overlap of digit representations in S1 seems to contradict a number of earlier BOLD fMRI (9,11–14,29,30) and magnetoencephalography (MEG) measurements (31–33) that showed an orderly and often separable representation, covering a cortical distance ranging from 2.5–20 mm. However, a number of those studies reported multiple clusters per digit or substantial overlap between digits (12–14,29,30). Furthermore, most retinotopy studies do not quantify overlap (as was the case in the above-cited studies), and are often designed to suppress potential overlap in the data by thresholding the activation maps and/or taking the difference in activation of two stimuli, instead of comparing both to the rest state. Conversely, a large similarity, as defined in this study, does not necessarily mean that the separation between task areas is impossible—it just leads to a reduced task difference.

One explanation for the substantial overlap observed in both the retinotopy and somatotopy experiments is vascular pooling. Since blood from topographically distinct regions may drain into the same vessels, macrovascular signal in BOLD data could lead to substantial overlap. This is consistent with data from Engel et al. (4), who found a PSF full width at half maximum (FWHM) of 3.5 mm in V1. An increase in the activation area due to large vessel contributions was also found in Ref. 34. A similar explanation may account for the overlap observed in the perfusion data, where incomplete flow suppression may lead to contributions from arteries. On the other hand, no significant difference in location was found in the somatotopy experiments between perfusion and BOLD data, which would be expected if larger arteries and veins shift the location in different directions.

Another explanation for the observed overlap is the limited spatial resolution of vascular control required to increase capillary perfusion in response to neuronal activation. On the other hand, BOLD fMRI measurements of ocular dominance columns in humans (7,8), and fMRI and optical imaging experiments involving orientation columns in cats (35,36) and monkeys (37) indicate that this resolution is on a much finer scale than the scale of overlap observed in the current study, which suggests that neurovascular control is not a limiting factor.

ACKNOWLEDGMENT

The authors thank Patrick Ledden of Nova Medical Inc. for helpful discussions and for supplying the hardware.

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