Original Research

fMRI Activation Mapping as a Percentage of Local Excitation: Consistent Presurgical Motor Maps Without Threshold Adjustment

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Purpose: To evaluate the performance of a relative activation amplitude algorithm, versus standard t-value thresholding, for reliably establishing the location, amplitude, and spatial extent of functional magnetic resonance imaging (fMRI) brain activation for presurgical planning.

Materials and Methods: Diagnostic fMRI maps from 42 neurosurgical patients performing a simple hand movement task were analyzed. Relative activation maps were made by normalizing statistical t-value maps to the local peak activation amplitude within each functional brain region. The spatial distribution of activation was quantified and compared across mapping algorithms, subjects, and scan duration.

Results: Whereas the spatial distribution of blood oxygenation level-dependent (BOLD) t-value statistical activation maps was highly variable across subjects and scan duration, the spatial distribution of relative activation maps was highly reproducible both within individual subjects and across different subjects. In every case the 40% most active voxels in the cortical hand region were consistently localized to the pre- and postcentral gyri of the sensorimotor cortex.

Conclusion: The reproducibility and anatomical specificity of the spatiotemporal pattern of BOLD activation makes relative amplitude fMRI mapping a useful tool for clinical imaging, where accuracy, reproducibility, and quality control are critical concerns.

Key Words: fMRI; reproducibility; presurgical mapping; motor cortex
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FUNCTIONAL MAGNETIC RESONANCE IMAGING (fMRI) detects brain regions with task-dependent signal fluctuations, but is currently not very consistent at quantifying the spatial extent of those regions, nor is it able to discriminate whether a task-correlated region is directly involved in the observed behavior. The first problem, determining spatial extent, arises because fMRI active areas are usually defined using a statistical significance threshold; image voxels are defined as "active" if their task-dependent signal fluctuations exceed the threshold criterion (1). Spatial extent can be highly variable, therefore, because it depends on the quality and quantity of signal acquired, rather than on intrinsic boundaries of brain function itself (1,2). The second problem, determining whether a task-correlated region is essential for a particular function, arises because most fMRI is based on a blood oxygen level-dependent (BOLD) signal, which is an indirect indicator of neuronal function. BOLD signals can change in nonessential active brain regions and in nonactive regions with vascular connections to active regions (3).

Despite being an indirect statistical measure of brain activity, however, fMRI could be a more reliable mapping tool if conditions could be found empirically under which fMRI consistently and accurately identifies regions of behaviorally important brain function. Identifying such conditions and measuring their reliability is particularly important when fMRI is being used in a clinical context. In diagnostic localization of function for neurosurgical planning, for example, fMRI is increasingly being used to identify essential speech and sensorimotor regions of the brain for treatment planning. Numerous feasibility studies have reported that functional areas identified by presurgical fMRI generally agree with areas identified by intraoperative functional mapping (4–17). However, such reports also show considerable variability, with no clear guidelines for how to assess the reliability of any particular fMRI map.

The issue of variability in fMRI mapping has been assessed directly in control studies in which normal healthy volunteers underwent multiple scans, each time performing a consistent simple task (2,18–23). For example, Liu et al (19) showed considerable variability in fMRI activation even when comparing repeated scans

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of a single subject performing identical motor tasks under controlled performance conditions. In general, the central locations of brain activation tend to be consistent across repeated scans, but the amplitude and spatial extent of activation is highly variable. Such variability in spatial extent can be partially compensated by adjusting the statistical threshold criterion, but there are as yet no clear guidelines for what activation threshold should be used for any particular fMRI scan. Defining active voxels by a minimum significance threshold makes the spatial extent of activation highly dependent on scan duration and the stability of the least active voxels, rather than on any intrinsic boundaries of the activation signal itself. This uncertainty about spatial extent is especially troubling for diagnostic fMRI scans, where determining proximity of a tumor to a functional brain region is an important clinical goal.

To address this issue we used an automated adaptive method for assessing statistical threshold levels that greatly improves the consistency of fMRI activation maps (2). This method, activation mapping as a percentage of local excitation (AMPLE), combines standard statistical significance testing with a relative analysis of the spatiotemporal distribution of all brain voxels within a local region of brain activity. AMPLE analysis generates standard parametric maps for assessing statistical significance, as well as temporal consistency measures for assessing the reproducibility of the activation pattern, and relative signal amplitude maps for assessing the spatial extent of activation. An important advantage of this approach is that it provides consistent normalized assessments of the spatial extent of brain activity without the confound of changing absolute significance levels. A previous study (2) demonstrated that AMPLE analysis resulted in consistent activation maps when healthy individual subjects repeated the same behavioral task under a variety of scanning conditions; it also improved the accuracy of detection of active voxels as assessed by simulated fMRI scans.

In the current study we empirically tested whether this AMPLE approach can consistently and accurately identify regions of behaviorally important brain function in patients undergoing fMRI mapping for presurgical planning. For this we focused on diagnostic localization of the motor cortex and used the known functional anatomy of the hand region of cortex in the pre- and postcentral gyri in order to assess the accuracy of fMRI maps during a hand sensorimotor task. To ensure normal anatomical localization of the hand area, only patients whose pathology was found to be remote from the sensorimotor cortex were included in the study. Our goal was to test whether the relative spatial distribution of the BOLD signal can provide a consistent description of the spatial extent of brain activity, and whether the AMPLE approach can provide objective and empirically validated metrics for assessing the reliability of fMRI data. The results indicate that for presurgical motor mapping, at least, the AMPLE analysis approach establishes conditions under which fMRI may be considered a consistent and reliable mapping tool.

MATERIALS AND METHODS

Subjects

This study involved retrospective analysis of fMRI motor mapping data from patients who underwent presurgical diagnostic fMRI mapping at our medical center over a 22-month period (July 2006 to May 2008). Subjects were included if they had complete structural and functional datasets and no visible pathology within 5 cm of the hand sensorimotor cortex. Subject selection was blind to the fMRI results obtained for any patient. All patients gave written Institutional Review Board (IRB)-approved informed consent to be included in this research.

MR Image Acquisition

Scanning was performed on a 3.0 T GE Signa LX scanner (Milwaukee, WI) using standard clinical pulse sequences. The three-scan series used in the current analysis were: a whole brain high-resolution T1-weighted series (fast spoiled gradient echo [FSPGR] TR/TE/TI/flip = 8/3/450 msec/12°, field of view [FOV] 25.6 cm, 1 mm slices, 256 × 256 × 166 voxels) for 3D reconstruction of the cortical surface; a gradient echo echo-planar series (TR/TE/flip = 1500/35 msec/90°, FOV 24 cm, 5 mm thick, 64 × 64 × 22 voxels, 256 timepoints) for BOLD fMRI analysis; and a spin echo echo-planar series (TR/TE/flip = 10,000/92 msec/90°, FOV 24 cm, 5 mm thick, 128 × 128 × 22 voxels) for aligning EPI to T1-weighted anatomical images.

fMRI Behavioral Paradigm

Subjects performed an alternating hand-squeezing task to localize the motor cortex. Prompted by a visual cue, they alternated 9-second blocks of rest with 9-second blocks of opening and closing one hand (≈1/sec). One full task cycle was 9 seconds rest, 9 seconds left hand motion, 9 seconds rest, 9 seconds right hand motion. Each fMRI scan lasted 6:24 (384 sec). The first 10 full task cycles (360 sec) were used in our analyses; in some cases only the first two task cycles (72 sec) were used, as indicated in the text.

Data Analysis

All data processing was performed using the fScan analysis program for fMRI (2,24) on a Pentium IV computer running RedHat FC6 Linux. Analysis for each subject involved the following steps (all steps were fully automated except where indicated): 1) Spin-echo EPI images were registered with the whole-brain T1-weighted images and manually affine adjusted by visual inspection to ensure that the central sulcus regions were aligned near the top of the brain. 2) Two subset datasets were extracted from the hand motor fMRI data series, one containing the first 10 complete task cycles (360 sec) and one containing only the first two task cycles (72 sec). 3) Each subset dataset was detrended to remove low-frequency signal drifts and spatially smoothed in-plane. 4) t-value activation maps were generated comparing left–right and right–left hand movement conditions. t-maps were spatially smoothed

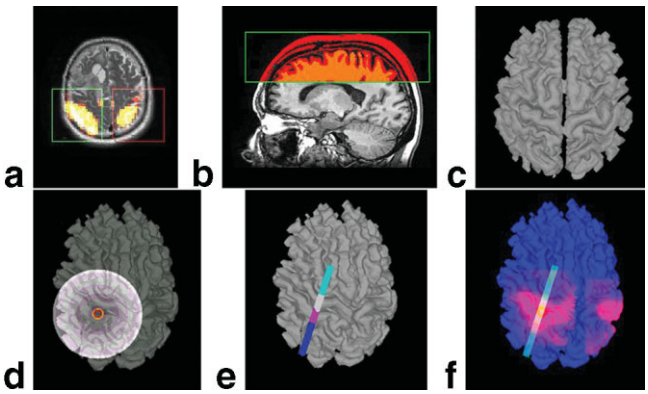

Figure 1. Methods for quantifying the spatial extent of fMRI activation in each subject. **a:** 3D rectangular ROIs were drawn to completely encompass the fMRI activation in each hemisphere. **b:** A 3D rectangular ROI was drawn in T1-weighted images to include the superior portion of the brain, which was then segmented to separate brain from surrounding tissues and find the gray/white matter boundary. **c:** The 3D cortical surface of the brain was reconstructed from the segmented T1-weighted images. **d:** Fifteen concentric 5-mm wide annular regions of interest centered on the peak of fMRI activation (colored circle) were automatically superimposed on the 3D surface rendering of each sensorimotor area. **e:** The central sulcus and pre- and postcentral gyri were manually traced on the surface view of each cortical hemisphere, and then projected onto a rectangular ROI drawn perpendicular to the central sulcus, passing through the activation peak. **f:** t-value and AMPLE maps were projected onto each cortical hemisphere and the spatial distribution of voxels at different activation levels were automatically sampled along the perpendicular rectangular ROI and quantified as a function of anatomical ROI gyrus and distance from the local peak of sensorimotor activation (see Figs. 4, 5).

across adjacent voxels in 3D. 5) Nonoverlapping 3D rectangular regions of interest (ROIs) were manually defined for each motor cortex area; each ROI was drawn to be large enough to extend beyond the hand motor activation region on all sides (Fig. 1A). 6) AMPLE maps were created by converting t-values within each ROI to percentage of the peak t-value for that ROI (AMPLE value = t-value/ROIpeak_t-value $\times$ 100). 7) AMPLE stability plots were generated by counting the number of voxels at or above each relative activation level (10%–90% of peak t-value), as a function of scan time (2). 8) T1-weighted images were segmented semiautomatically to separate brain from surrounding tissue and identify the gray/white matter tissue boundary; segmented images of the top portion of the brain were then converted to a 3D reconstruction of the superior aspect of the cortical surface (Fig. 1B,C). 9) t-value and AMPLE value maps with different activation thresholds were projected onto the superior surface reconstructions and saved as JPEG images. All maps projected onto cortical surfaces included any active voxel within 5 cm of the surface. 10) t-value and AMPLE maps were similarly projected onto cortical surface views approximately tangential to the hand regions of the central sulcus in each hemisphere and saved as both projected statistical maps and JPEG images. 11) 3D surface locations for the peak of sensorimotor activation were calculated from the t-value maps and projected onto the cortical surface reconstructions, along with 15 concentric annular regions of interest spaced 5 mm apart (Fig. 1D). 12) Irregular ROIs were manually drawn on the left and right hemisphere superior surface views by tracing the central, precentral, and postcentral sulci to identify the sensorimotor pre- and postcentral cortical gyri; to generate activation profiles across the sensorimotor gyri a 10 pixel-wide rectangular ROI was added perpendicular to the central sulcus, passing through the activation peak (Fig. 1E). 13) t-value and AMPLE surface-projected map regions corresponding to each surface-defined ROI were extracted automatically, and the spatial distribution of voxels at different activation levels was quantified as a function of anatomical ROI gyrus and distance from the local peak of sensorimotor activation (Fig. 1F).

RESULTS

We analyzed presurgical diagnostic fMRI data for 42 patients (25 male, 17 females) with ages between 13 and 83 (mean 48 $\pm$ 17) years old. These 42 patients were all of the most recent 150 consecutive patients with complete hand motor datasets (T1-weighted, hand fMRI, and coplanar spin-echo EPI), who did not have brain tumor pathology within 5 cm of the hand cortical sensorimotor areas (omega bend of the central sulcus), nor such large tumors that it was difficult to generate satisfactory 3D reconstructions of the superior cortical surface. Of the 42 patients included, 40 had brain tumors and two had vascular malformations.

Comparison of Standard t-Value and AMPLE Relative Activation Maps

Satisfactory fMRI maps were obtained for every subject, showing bilateral activation of the cortical sensorimotor areas along the central sulcus in both hemispheres (Fig. 2A). Standard t-value parametric maps showed large brain regions with highly significant (t-value $\geq$ 6.0, $P <$ 0.0001) task-dependent BOLD activation. At this significance level, thresholded activation maps identified not only the precentral and postcentral gyri, but also large regions of activation in more anterior and posterior gyri as well. Increasing the threshold for t-value maps reduced the apparent size of activation (not shown). For any particular subject and statistical threshold, the apparent spatial extent of activation was also highly variable, depending on how long the fMRI task lasted. Thus, maps generated after 10 task cycles (360 sec) resulted in apparently larger brain areas activated than in maps generated from just two task cycles (72 sec) of the same scan data (Fig. 2B). Activation thresholds could be adjusted to change the apparent size of activation, but there was no statistical threshold that consistently localized activation to the sensorimotor cortex region, either within the two hand regions of single subjects or across subjects (Fig. 2C). Counting the number of voxels at different statistical significance levels as a function of scan duration demonstrated that the apparent spatial extent of activation varied initially and then increased continuously for all subjects (Fig. 2D).

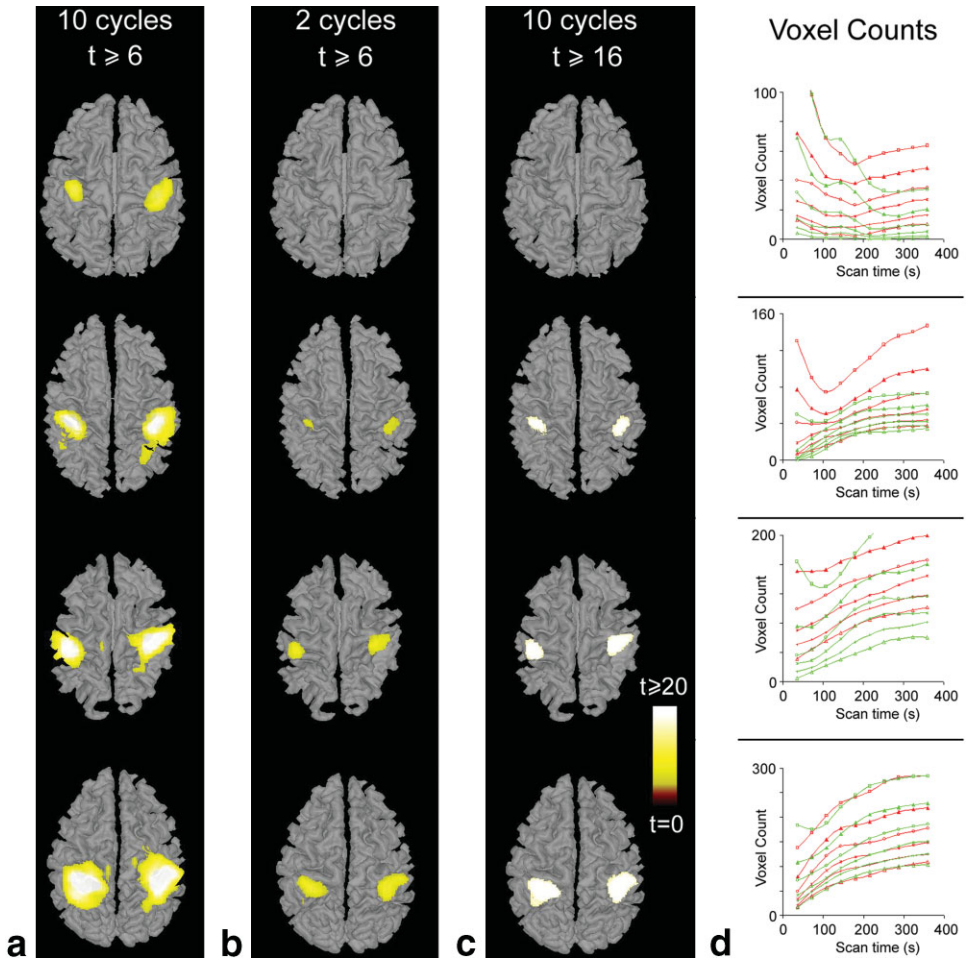

Figure 2. Spatial extent of standard t-value activation maps. t-value activation maps contrasting left hand and right hand BOLD signals were sorted by the mean peak t-value for both hemispheres, and the 1st, 11th, 31st, and 41st subjects' results were arbitrarily selected to demonstrate the full range of fMRI responses. Each row shows surface-rendered activation maps and voxel counts for a single subject. Although the contrast was between hands, both hand activations are shown as positive t-values using the same color scale. **a:** Hand-movement activations for four subjects after 10 task cycles (360 sec) thresholded at t-value ≥ 6.0. **b:** t-value maps generated from the first two task cycles (72 sec) at the same, t ≥ 6.0, threshold. **c:** The 10-cycle data from A with t-value threshold adjusted to t-value ≥ 16.0, which was approximately midway between subjective optimal thresholds for all 42 subjects. At t ≥ 16.0, subjects with the weakest BOLD signal changes had no active voxels, while the strongest had activations that extended beyond the primary sensorimotor cortex. **d:** Plots of voxel counts for each hand ROI (left = red, right = green) are shown as a function of time across 10 task cycles for six different t-value thresholds (square: t ≥ 5, filled triangle: t ≥ 6, circle: t ≥ 7, asterisk: t ≥ 8, plus: t ≥ 9, open triangle: t ≥ 10). Most curves increased continuously over time.

When activation maps were converted to relative-amplitude AMPLE maps (see Materials and Methods) the apparent spatial extent of fMRI activation was more consistent than in the standard t-value maps (Fig. 3). In color-coded AMPLE activation maps, the peak of hand movement activation in each ROI was consistently in or near the central sulcus. Moreover, the top 40% of active voxels was consistently within the precentral or postcentral gyrus. The spatial distribution of relative fMRI activation in AMPLE maps was also independent of how long the scan lasted. Thus, the top 40% of AMPLE maps generated after just two task cycles resulted in active brain areas with similar spatial extents of activation as in maps generated from 10 task cycles of the same scan (Fig. 3B). The effect of adding eight more cycles of scan data was to increase the overall statistical significance of all AMPLE voxels, without changing the spatial distribution of voxels with different relative activation levels. In each case, the top 40% of activation was anatomically localized to the sensorimotor cortex pre- and postcentral gyri. Counting the number of voxels at different relative activation levels as a function of scan duration demonstrated that the apparent spatial extent of activation fluctuated initially but then reached stable plateau levels for all subjects (Fig. 3C).

Consistency of Anatomical Localization of AMPLE Peak Across Subjects

The consistency of anatomical localization to the sensorimotor cortex was confirmed by manually tracing the pre- and postcentral gyri for each subject and ex-

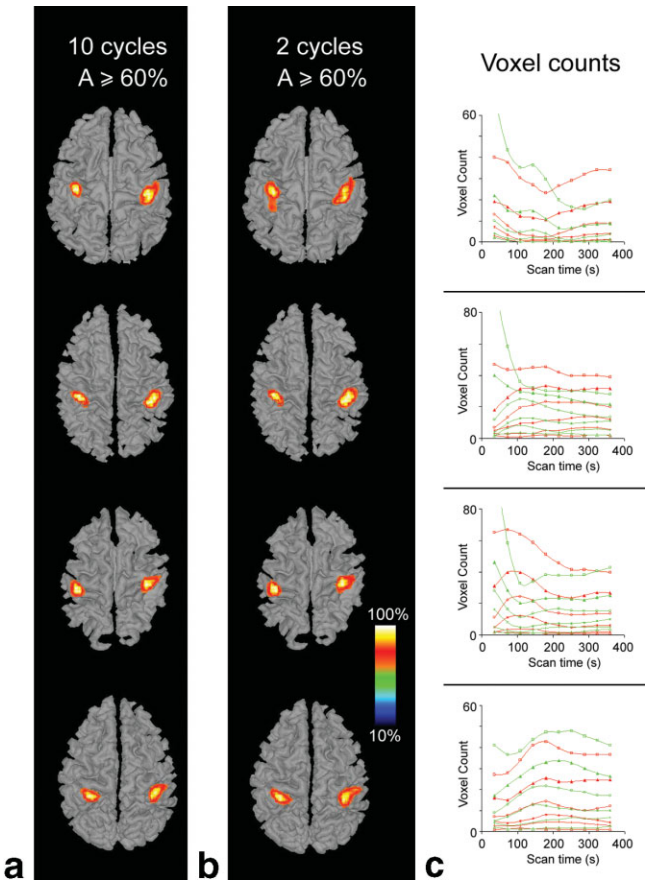

Figure 3. Spatial extent of AMPLE activation maps. Data converted to AMPLE relative activation values are shown for the same four subjects as in Fig. 2. Only voxels with absolute t-values ≥ 2.0 were included in these maps. **a:** The 40% most active voxels in each hand movement ROI after 10 task cycles. **b:** The 40% most active voxels after only the first 2 task cycles. **c:** Plots of voxel counts for each hand ROI (left = red, right = green) are shown as a function of time across 10 task cycles for six different AMPLE relative activation levels (square: A ≥ 40%, filled triangle: A ≥ 50%, circle: A ≥ 60%, asterisk: A ≥ 70%, plus: A ≥ 80%, open triangle: A ≥ 90%). Most curves reached stable levels over time.

tracting spatial profiles oriented perpendicular to the central sulcus, where each profile passed through the peak of activation. Figure 4 shows these activation profiles under different analysis conditions for both hand regions of every patient in the study. To determine the specificity of anatomical localization, the profile through the sensorimotor cortex (precentral plus postcentral gyri) is shown separated from the surrounding regions. In all 42 subjects, the top 40% of AMPLE peaks for both hand regions lay within the primary motor (precentral) and somatosensory (postcentral) gyri. Outside these sensorimotor gyri, only the least active (lower 60%) voxels were seen in AMPLE maps (Fig. 4B). In AMPLE maps made from only the first two cycles (72 sec) of the hand movement task, the top 40% peak regions were also confined to the primary sensorimotor gyri (Fig. 4C). The AMPLE spatial distributions seen after 2 or 10 cycles were very similar for every subject.

In contrast, sampling the same cortical regions in standard t-value maps demonstrated that the spatial profile of statistically significant hand activation often extended well beyond the pre- and postcentral gyri (Fig. 4E). Moreover, the spatial extent of active voxels varied greatly depending on how many task cycles were included (Fig. 4D,F).

Consistency of AMPLE Peak Shape Across Subjects

The spatial distribution of AMPLE activation was quantified by calculating a weighted average of relative activation amplitude as a function of distance from the peak activated voxels (Fig. 5). Similar spatial distribution curves were observed for all 84 cortical ROIs. When only the first two task cycles of fMRI data were considered there was more variability across the 84 hand activations than after 10 task cycles. On average, however, the mean distribution of relative activation amplitude calculated as a function of distance from the peak was quite similar regardless of scan duration. The number of strongly activated voxels (above 50% peak amplitude) fell rapidly as a function of distance within 15 mm of the peak, and the spatial rate of fall was the same for both sampling durations. The number of less activated voxels (below 50% peak amplitude) fell more gradually over greater distances. The spread of these less active voxels was somewhat narrower after 10 task cycles than after two cycles.

Quantifying the spatial distribution of absolute t-values resulted in very different curves after 10 task cycles compared to after two cycles (Fig. 5D) because statistical significance of all active voxels increased with the length of the task. For the two cycle maps, voxels beyond 40 mm had low t-values ($t < 2$) and would normally not be considered statistically "active." For the full 10 cycle maps, however, voxels over 40 mm from the peak of activation still had highly significant ($t \geq 4$) task-dependent BOLD signal changes. Those voxels would normally be considered "active," therefore, despite lying well outside the anatomical region of the sensorimotor cortex.

Combining Statistical Significance and AMPLE-Coding in the Same Map

The AMPLE maps shown in Fig. 3 were color-coded to show relative BOLD activation amplitude, and thresholded to highlight the anatomical localization of the upper portion of the activation peak. This approach demonstrates that such maps result in more consistent spatial patterns of functional activation than do standard t-value maps. However, AMPLE maps presented in that way convey little information about the absolute statistical significance of BOLD activation, nor about relative amplitude differences between different AMPLE peaks. In practice, therefore, AMPLE maps are usually combined with t-value maps for visualization. Figure 6 shows examples of AMPLE maps, in which the t-value map was used to set the display threshold of AMPLE color-coded voxels. In this case, only voxels with t-value at least 6.0 were included in the AMPLE maps. Such maps show the color-coded spatial distribution of activation within each region, as well as how much of each peak passed the specified absolute statistical signifi-

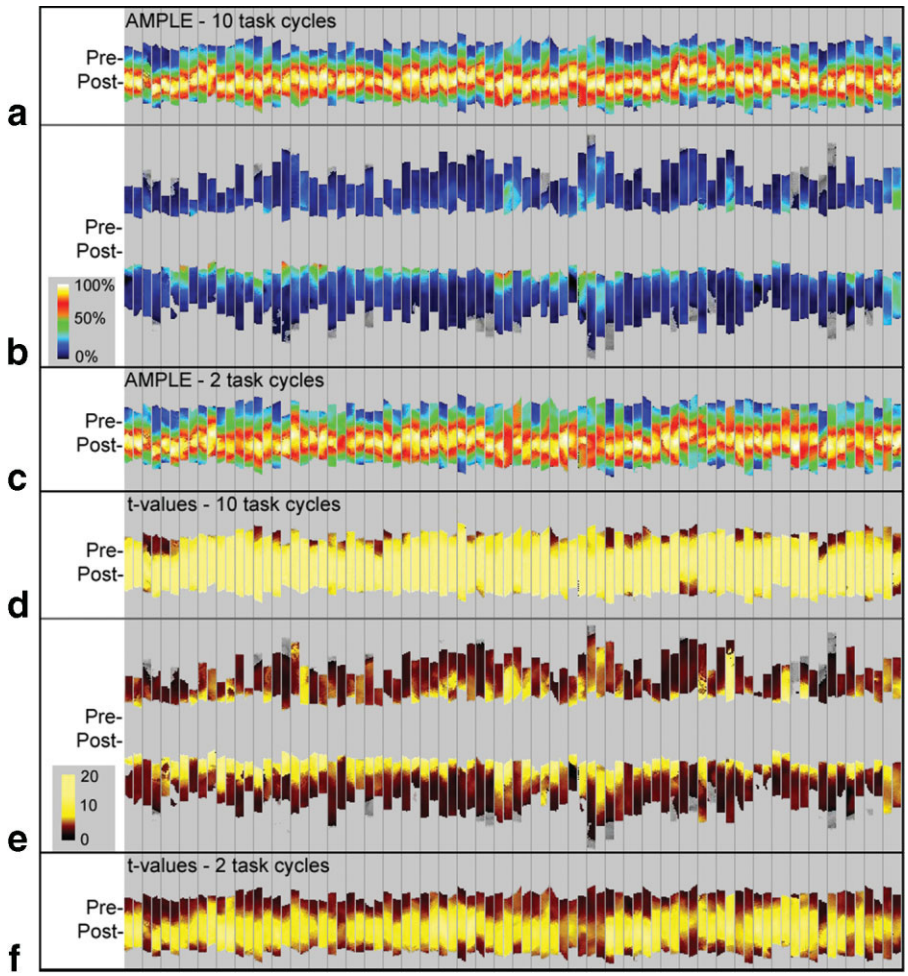

Figure 4. Profiles of hand activation through the sensorimotor cortex. Rectangular regions perpendicular to the central sulcus and passing through the peak of activation were used to extract hand activation profiles from surface-rendered views of AMPLE maps and t-value maps. To assess the anatomical extent of activations, the sensorimotor cortex (precentral and postcentral) was extracted from the surrounding anterior and posterior regions of the sampling rectangle. Both the left and right hemisphere activation ROIs are shown for all 42 subjects in the study (columns show the same ROIs across panels). **a:** Sensorimotor pre- and postcentral gyrus regions of AMPLE maps from the full 10-cycle (360 sec) hand movement task. **b:** The same AMPLE maps as A showing activation levels in the brain regions surrounding the sensorimotor cortex (the sensorimotor region of A would fit in the gap). There is almost no strong activation outside the sensorimotor region. **c:** Sensorimotor regions of AMPLE maps from the first two task cycles (72 sec) only. Activation patterns in A and C were similar despite differences in task duration. **d:** Sensorimotor regions of standard t-value maps from the full 10-cycle task. **e:** Regions of the t-value maps in D surrounding the sensorimotor cortex, showing variable activation outside the central gyri. **f:** Sensorimotor regions of t-value maps from the first two task cycles only. Activation patterns in D and F varied with task duration.

cance criterion. For any single map, changing the t-threshold would change how many voxels were visible, but the relative activation color of voxels included in the map was independent of threshold level. Conversely, changing statistical significance by comparing 2 versus 10 task cycles increased the number of AMPLE voxels above a fixed t-value threshold, but the AMPLE map color of each active voxel again remained relatively constant.

DISCUSSION

The hand area spanning the primary motor and somatosensory cortex is one of the few functional regions of the brain with a well-characterized anatomical location. In the normal brain it lies on either side of the central sulcus, near the omega-shaped bend of the precentral gyrus. In this study we used this known anatomical location of the hand sensorimotor region as a reference against which to assess the accuracy and consistency of fMRI mapping of hand motion.

Our results demonstrate that fMRI mapping using a simple hand movement task results in statistically significant BOLD signal in the hand region of the precentral and postcentral gyri, but also produces statistically significant activation that extends well beyond these gyri. Moreover, the apparent spatial extent of significant activation varies considerably among individuals and is highly dependent on scan duration. In contrast, the spatial distribution of relative voxel activation is quite consistent among different individuals and is essentially independent of scan duration. A previous re-

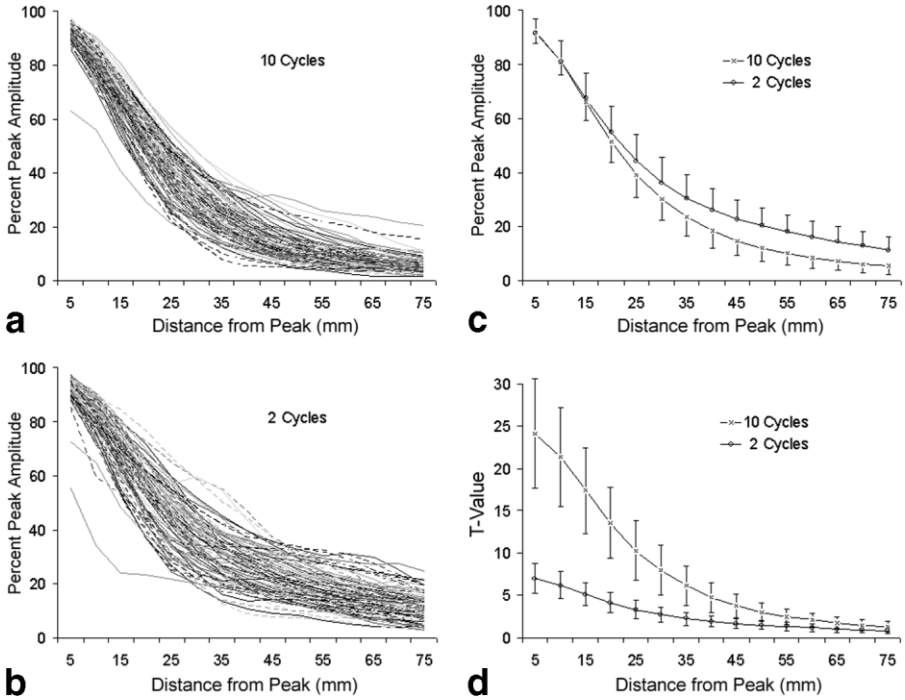

Figure 5. Spatial distribution of AMPLE normalized activation peaks. The sampling rectangle perpendicular to the central sulcus was used to measure the distribution of relative activation amplitude as a function of distance from the most active voxels. **a:** Relative amplitude profiles from the full 10-cycle (360 sec) task for all 84 hand movement ROIs. **b:** Relative amplitude profiles from the first two task cycles only for every ROI. **c:** Mean relative activation amplitude profiles for 10 task cycles (x) and 2 task cycles (o) with SD bars. **d:** Mean absolute t-value amplitude profiles for 10 task cycles (x) and two task cycles (o).

port (2) showed that mapping brain function as a percentage of local activation resulted in consistent relative activation maps when individual subjects performed the same hand movement task under different imaging conditions (spiral or linear EPI) and at different field strengths (1.5 T or 4 T). The current results extend those earlier findings by showing that AMPLE activation maps consistently identify the known anatomical location and spatial extent of the hand cortex across a large subject population. Thus, in every subject tested (84 hand regions), and for two different scan durations (72 and 360 sec) the upper 40% of each AMPLE area consistently fell within the expected anatomical gyri of the hand sensorimotor cortex.

Although normalizing fMRI activation maps to a percentage of the local peak value is not mathematically sophisticated, this simple transformation has important implications. These arise because the important voxels in fMRI are all those with statistical values above the minimum activation threshold. Traditional fMRI maps focus on identifying which voxels are above the minimum threshold and thus define the entire activation relative to the least active voxels, which are highly variable and presumably the least important. By normalizing to the peak, AMPLE maps redefine activation as relative to the most active voxels, which are presumably the most important (25) and which we demonstrate to be highly stable. An advantage of color-coding activation maps relative to the peak is that the color of individual active voxels does not change if the statistical significance of the entire activation increases. Both the current study and previous findings (2) demonstrate that the spatial distribution of relative voxel activations are stable for a particular task, despite large increases in overall BOLD activation levels. Adjusting statistical thresholds changes how much of the active region is visible, but the spatial pattern of the color-coded AMPLE map is unaffected by changing statistical threshold values (see Fig. 6).

An important goal of this study was to empirically determine what fraction of the peak of activation for our clinical motor fMRI task actually coincides with the anatomically relevant sensorimotor cortex, and whether that fraction is consistent among different patients. The results suggest that the 40% most active voxels in each hand area do consistently correspond to the expected sensorimotor hand area along the central sulcus. Active voxels below the top 50% were frequently located outside the pre- and postcentral gyri. Although statistically significant, those less active portions of the fMRI map would be considered negative from a clinical perspective because they are not essential sensorimotor regions. Having a reproducible method that consistently identifies the spatial extent of clinically relevant functional regions is very important when interpreting diagnostic fMRI scans.

Our results confirm previous findings (2) that the spatial distribution of AMPLE activation maps fluctuates initially during a scan but then stabilizes (eg, Fig 3) and remains consistent relatively independent of scan duration. This property therefore provides a simple and powerful quality control metric for objectively assessing the reliability of each fMRI scan. In our diagnostic fMRI scans, for example, we routinely perform real-time image analysis to assess the stability of the activation map while the patient performs the task. Once the pattern stabilizes, as indicated by plateau behavior in the AMPLE voxel count plots, the scan is terminated because our data show that continued scanning will not significantly affect the result. Having this simple stability metric thus provides an immediate assessment of data quality during acquisition, and also provides a tool for evaluating confidence in the reliability of the maps when interpreting activation results. If the pattern was

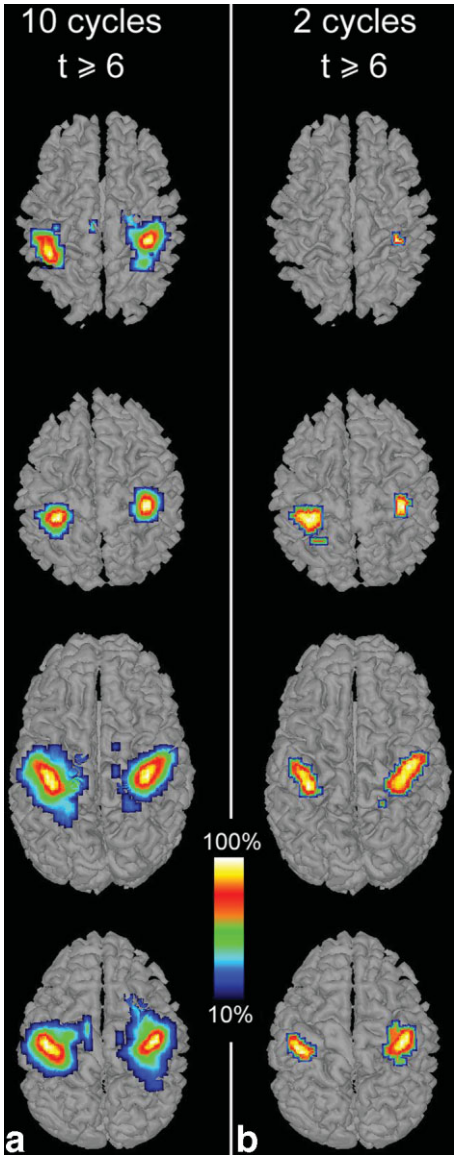

Figure 6. Relative AMPLE maps with absolute t-value thresholds. Four different subjects than those used in Figs. 2 and 3 were selected to cover the full range of BOLD activation amplitudes. Surface-rendered AMPLE activation maps are shown for all voxels with absolute t-values ≥ 6.0. **a:** AMPLE maps for 10 task cycles. **b:** AMPLE maps for the first two task cycles. Using fixed t-value activation thresholds, the AMPLE color coding of each active voxel remained constant, whereas the overall number of active voxels expanded as a function of scan duration.

not stable the results should probably be interpreted with caution.

In conclusion, a hand movement task provides a good test case for analyzing the anatomical specificity and spatial extent of fMRI activation because the task elicits robust BOLD signals and the functional anatomy of the sensorimotor cortex is well understood. Our results empirically demonstrate the reproducibility and anatomical correlates of AMPLE maps for hand motor mapping in the absence of obvious pathology. Additional studies using direct validation with intracranial stimulation mapping will be needed to evaluate the anatomical reliability of this approach in the clinically important context of language mapping and to see how the spatial distribution of active voxels is affected by tissue pathology. However, we have already found that the AMPLE approach provides a useful stability metric for assessing scan quality and highly consistent spatial distribution maps of relative voxel activity. By combining such relative maps with standard activation maps showing the absolute statistical significance of overall activation, the AMPLE approach may help to improve the overall reliability of fMRI brain mapping.

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REFERENCES

1. Huettel SA, Song AW, McCarthy GM. Functional magnetic resonance imaging. Sunderland, MA: Sinauer; 2004:245–250.
2. Voyvodic JT. Activation mapping as percentage of local excitation (AMPLE): fMRI stability within scans, between scans, and across field strengths. Magn Res Imaging 2006;24:1249–1261.
3. Malonek D, Grinvald A. Interactions between electrical activity and cortical microcirculation revealed by imaging spectroscopy: implications for functional brain mapping. Science 1997;272:551–554.
4. Jack CR Jr, Thompson RM, Butts RK, et al. Sensory motor cortex: correlation of presurgical mapping with functional MR imaging and invasive cortical mapping. Radiology 1994;190:85–92.
5. Puce A, Constable RT, Luby ML, et al. Functional magnetic resonance imaging of sensory and motor cortex: comparison with electrophysiological localization. J Neurosurg 1995;83:262–270.
6. Cuenod CA, Bookheimer SY, Hertz-Pannier L, Zeffiro TA, Theodore WH, Le Bihan, D. Functional MRI during word generation, using conventional equipment: a potential tool for language localization in the clinical environment. Neurology 1995;45:1821–1827.
7. Pujol J, Conesa G, Deus J, et al. Presurgical identification of primary sensorimotor cortex by functional magnetic resonance imaging.“ J Neurosurg 1996;84:7–13.
8. Binder JR, Frost JA, Hammeke TA, Cox RW, Rao SM, Prieto T. Human brain language areas identified by functional magnetic resonance imaging. J Neurosci 1997;17:353–362.
9. FitzGerald DB, Cosgrove GR, Ronner S, et al. Location of language in the cortex: a comparison between functional MR imaging and electrocortical stimulation. Am J Neuroradiol 1997;18:1529–1539.
10. Modayur B, Prothero J, Ojemann G, Maravilla K, Brinkley J. Visualization-based mapping of language function in the brain. Neuroimage 1997;6:245–258.
11. Schlosser MJ, McCarthy G, Fulbright RK, Gore JC, Awad IA. Cerebral vascular malformations adjacent to sensorimotor and visual cortex: functional magnetic resonance imaging studies before and after therapeutic intervention. Stroke 1997;28:1130–1137.
12. Rutten GJ, van Rijen PC, van Veelen CW, Ramsey NF. Language area localization with three-dimensional functional magnetic resonance imaging matches intrasulcal electrostimulation in Broca’s area. Ann Neurol 1999;46:405–408.
13. Schlosser MJ, Luby M, Spencer DD, Awad IA, McCarthy G. Comparative localization of auditory comprehension by using functional magnetic resonance imaging and cortical stimulation. J Neurosurg 1999;91:626–635.
14. Beisteiner R, Lanzenberger R, Novak K, et al. Improvement of presurgical patient evaluation by generation of functional magnetic resonance risk maps. Neurosci Lett 2006;290:13–16.
15. Hirsch J, Ruge MI, Kim KH, et al. An integrated functional magnetic resonance imaging procedure for preoperative mapping of cortical areas associated with tactile, motor, language, and visual functions. Neurosurgery 2000;47:711–722.

16. Bartsch AJ, Homola G, Biller A, Solymosi L, Bendszus M. Diagnostic functional MRI: illustrated clinical applications and decision-making. J Magn Res Imaging 2006;23:921–932.
17. Bizzi A, Blasi V, Falini A, et al. Presurgical functional MR imaging of language and motor functions: validation with intraoperative electrocortical mapping. Radiology 2008;248:579–589.
18. McGonigle DJ, Howseman AM, Athwal BS, Friston KJ, Frakowiak RSJ, Holes AP. Variability in fMRI: an examination of intersession differences. Neuroimage 2000;11:708–734.
19. Liu JZ, Zhang L, Brown RW, Yue GH. Reproducibility of fMRI at 1.5T in a strictly controlled motor task. Magn Reson Med 2004;52: 751–760.
20. van Gelderen P, Wu CWH, de Zwart JA, Cohen L, Hallett M, Duyn JH. Resolution and reproducibility of BOLD and perfusion functional MRI at 3.0 Tesla. Magn Reson Med 2005;54:569–576.
21. Vincent DJ, Bloomer CJ, Hinson VK, Bergmann KJ. The range of motor activation in the normal human cortex using bold fMRI. Brain Topogr 2006;18:273–280.
22. Friedman L, Glover G, Krenz D, Magnotta V. Reducing inter-scanner variability of activation in a multicenter fMRI study: role of smoothness equalization. Neuroimage 2006;32:1656–1668.
23. Costafreda SG, Brammer MJ, Vencio RZN, et al. Multisite fMRI reproducibility of a motor task using identical MR systems. J Magn Reson Imaging 2007;26:1122–1126.
24. Voyvodic JT. Real-time fMRI paradigm control, physiology, and behavior combined with near real-time statistical analysis. Neuroimage 1999;10:91–106.
25. Arthurs OJ, Boniface SJ. What aspect of the fMRI BOLD signal best reflects the underlying electrophysiology in human somatosensory cortex? Clin Neurophys 2003;114:1203–1209.