BOLD fMRI – Establishing A More Quantitative Approach for Clinical Application

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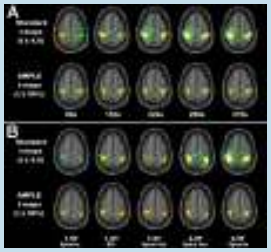
BOLD fMRI as a Quantitative Biomarker

In the clinical context of image-guided neurosurgery, BOLD fMRI is used to map brain regions that are responsive to sensory, motor or language tasks and at risk if in proximity to planned resection sites. In this context, quantitative measures of the spatial location and extent of BOLD foci are of prime interest. To establish a claim that BOLD fMRI provides such quantitative information, we have developed metrics for spatial location, extent and hemispheric lateralization and examined several factors that affect reproducibility or validity of BOLD imaging metrics. Results from 3 QIBA-funded projects are described. These results motivate ongoing efforts to characterize and control sources of variance in the BOLD technique and set the stage for completion of a QIBA profile for BOLD fMRI.

BOLD fMRI is Reproducible

A key issue for the clinical use of BOLD fMRI to guide brain surgery is the consistency of brain maps evoked by sensory, motor or language tasks. Results from two QIBA-funded subprojects indicate that the weighted center of mass of motor-, vision-, and language-related activation foci are reproducible to within 5 mm within the same patient across days. Repeatability is enhanced by use of a local, statistical normalization procedure described by Voyvodic[1,2]. The mean number of voxels in such repeated foci are repeatable to within 30% without normalization and within 20% with normalization, though this can vary with task (eg. language vs vision). A lateralization index comparing the number of voxels in left vs right hemisphere language activations is reproducible to better than 90%.

BOLD Reproducibility with AMPLE Normalization



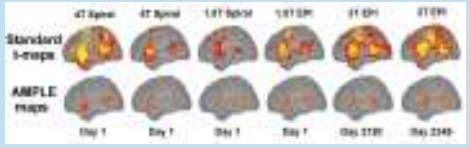
Hand Motor Mapping

A) Comparison of fixed-threshold t-maps versus AMPLE maps as a function of scan duration for a hand motor fMRI scan,

B) Similar hand motor comparison for a single subject scanned 5 times under different acquisition conditions

Sentence Reading Language Mapping

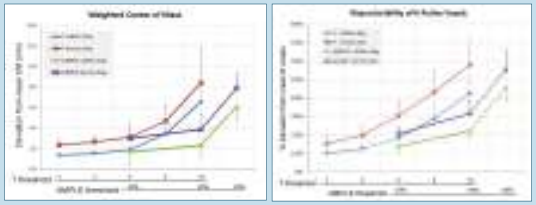
Comparison of fixed-threshold t-maps versus AMPLE maps for a single subject scanned 6 times under different conditions. Frontal and temporoparietal language activations are shown.



Conclusion: AMPLE normalization improves reproducibility.

BOLD Reproducibility Metrics – Vision Mapping

Reproducibility of weighted center-of-mass and # active voxels for visual cortex activation across a range of statistical threshold settings for conventional T-valued data and AMPLE normalized data for both within-day and across-day repeated measurements. At very high statistical thresholds, patterns become sparse and less reproducible.



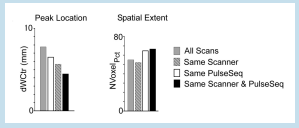
Factors Affecting Reproducibility

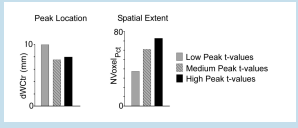
Language mapping reproducibility

fMRI quantitative reproducibility metrics were compared as a function of magnetic field strength, pulse sequence, mean t-value, raw BOLD signal amplitude, head motion, days between scan sessions, sex, and age to see which parameters were correlated with reproducibility. (Data not normalized.)

Reproducibility of Peak Location varied with changes in acquisition method.

Reproducibility of Spatial Extent varied with overall amplitude of BOLD signals.





Graphs show the averaged reproducibility metrics calculated from all test-retest pairing combinations of AMPLE-masked t-maps (ts4 and AMPLE≥60%) for 12 subjects. Peak location **dWCtr** is the average distance (mm) between activation-weighted peak locations. Spatial extent **NVoxel**$_{pct}$ is percent agreement between test-retest pairs. **Left graph** compares metrics as a function of the similarity in scanner and pulse-sequence used in the 2 scans in the pair; "All Scans"=any combination of scanner (1.5T, 3TA, 3TB, or 4T) and pulse sequence (linear EPI or spiral), "Same Scanner"=both scans performed on the same scanner using any pulse sequence, "Same PulseSeq"=scans performed on any scanner but both performed using the same pulse sequence, "Same Scanner and PulseSeq"=both scans performed on the same scanner using the same pulse sequence. **Right graph** compares metrics as a function of overall t-value amplitude of the 2 scans in each test-retest pair; t-value amplitude was calculates as the average of the peak t-value for the 2 scans, averaged in 3 groups: "Low" (peak t-values < 9.0), "Medium" (9.0 < t-value < 14.0), and "High" (t-value > 14.0).

Conclusion: Standardized acquisition is important; overall strength of activation is best predictor of reproducibility.

Data Qualification: NVU

NeuroVascular Uncoupling (NVU) appears as a reduced or absent BOLD fMRI signal despite robust neuronal activation to a stimulus or task. NVU can produce "false negatives" in fMRI brain maps thereby increasing the potential for inadvertent resection of "BOLD-silent" but eloquent cortex and subsequent postoperative neurological deficits. Breath-hold (BH) cardiovascular reactivity mapping is superior to T2* DSC perfusion mapping for detection of NVU potential in brain tumors of various grades.[3]

Here we demonstrate enhancement of ipsilesional motor activation in expected regions of primary motor cortex using a modified version of a calibration algorithm by Thomason et al.[4]

$$t_{calib} = t_{meas}\left(1 - x + x\frac{\overline{S_{BH\_CL}^{average}}}{S_{BH}}\right)$$

$$x = \begin{cases} 1 & \text{if } t_{meas} < t_{thr} \text{ AND } S_{BH} > 0.5 * S_{BHmean\_IL} \\ 0 & \text{elsewhere} \end{cases}$$

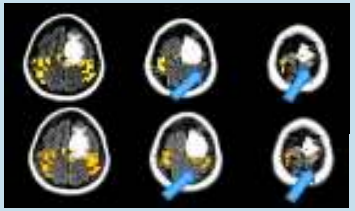
t_{calib}= corrected voxel-level t-value following calibration, t_{meas}=non-calibrated t-value, S_{BH}=BOLD percentage signal change on BH task in ipsilesional (IL), contralesional (CL) ROIs, or in the individual voxel of interest (no subscript)

Calibration Enhanced fMRI

Patient with frontal lobe glioma. Arrows indicate zone of undetectable activation before calibration and newly detectable activation after calibration of fMRI, hand motor activation maps.

Before Calibration

After Calibration



Literature cited
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[2] Voyvodic JT (2012). Reproducibility of single-subject fMRI language mapping with AMPLE normalization, J. Mag. Res. Imaging, 36:569-80.
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[4] Thomason ME, Foland LC, Glover GH (2007). Calibration of BOLD fMRI using breath holding reduces group variance during a cognitive task. *Hum Brain Mapp.* 28(1):59-68.

Various QIBA projects and activities have been funded in whole or in part with Federal funds from the National Institute of Biomedical Imaging and Bioengineering, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN268201000050C.