The Limitations of Functional MR Imaging: A Caveat

The blood oxygen level dependent (BOLD) technique forms the technical basis for most functional magnetic resonance (fMR) imaging. The technique relies on the detection of elevated oxyhemoglobin levels draining an activated region of the brain. This recent development has great potential for further understanding cognitive behavior, monitoring pharmacologic actions, and, in particular, for preoperatively localizing functional foci of the brain. Many groups have used this technique to localize the primary motor, sensory, and visual cortex. More recently, language centers have also been localized by the BOLD technique, fostering hopes that the more invasive aspects of the Wada test may be replaced by fMR imaging in the near future.

Although fMR imaging is somewhat reproducible, which is indeed exciting for neuroscientists and clinicians, several inherent limitations of this technique are well known and bear repeating. The signal is detected in the venules and larger veins overlying the cortical activity, not from the activated neurons themselves. Thus, the ability of the BOLD technique to localize neuronal activity, as currently applied at 1.5 tesla, depends on the anatomic proximity of these vessels to the activated cortex. In addition, subcortical functional pathways are not identified readily with this technique. The infusion of oxygen-rich blood in response to a stimulus is a small effect, in the range of 3% of background, and its detection is only possible with subtraction of activated and resting states as well as statistical analysis of the differences to determine true signal from ''noise.'' Thus, the potential for statistical error and mislabeled activated regions is great. Finally, a ''hemodynamic lag'' of several seconds in the response to neuronal activity after task stimulus seen on BOLD fMR images, combined with the still relatively low temporal resolution of even echo-planar MR imaging, lessens the ability to decode the sequence of neuronal activity after task activation.

In this issue of the *AJNR*, Holodny et al (page 609) add to this list of potential pitfalls and limitations with their observation of decreased activity on fMR images of the sensorimotor cortex adjacent to a brain tumor. In their case of a patient presenting with sensorimotor impairment from a glioblastoma (GBM) involving the sensorimotor cortex, BOLD revealed significantly less on the tumor side compared with the unaffected contralateral hemisphere. The patient had presented with his GBM near the right sensorimotor region 14 months prior to his current admission for weakness and disorientation. He had been treated previously with stereotactic biopsy, fractionated radiotherapy, chemotherapy, and stereotactic radiation therapy. After a short course of steroid treatment, the patient's neurologic symptoms had improved, and fMR imaging was performed prior to reresection of the residual tumor. Edema and mass effect surrounded the tumor. The patient's performance of the motor paradigm showed no differences between the left and right sides. The authors found a significantly reduced volume of motor activation on the side of the tumor at the same correlation coefficients, and no activation of the sensory cortex, compared with the unaffected side. Even though the location of the motor cortex was accurately defined on the side of the lesion, as determined intraoperatively, the reduced activity raises important questions about the limitations of this technique in the setting of mass effect, and, more broadly, challenges the quantitative interpretation of fMR imaging. As the authors state, present technology should not be applied indiscriminately to guide resection, especially for areas directly adjacent to activation sites or within the motor gyrus itself, because this may lead to the resection of a functioning cortex that cannot be revealed by BOLD fMR imaging. They hypothesize that increased mass effect may compress the venous vasculature, ''speeding'' the egress of oxyhemaglobin from the activated region, and that the abnormal vasculature of the gliomas may have lost the capacity to autoregulate, precluding an increase in blood flow in response to a stimulus. Other factors that could conceivably influence the appearance of the BOLD effect on vasculature include the results of radiation therapy, stereotactic radiosurgery, or steroid therapy. These cautionary notes extend to other patient populations with vascular anomalies such as arteriovenous malformation and, indeed, cerebral ischemia. In cases for which hemodynamically based functional imaging methods such as fMR (or indeed positron emission tomography) may be limited, it seems that functional mapping based on electrical activity of neurons detected by electroencephalography or magnetoencephalography might be applied. Although there was ''no detectable [left vs. right] difference'' of motor task function in the patient cited by Holodny et al, if a patient with hemiparesis cannot perform a motor or sensory task, the amplitude of the response could be reduced, and remains a potential source of error. Standardization of calibrated, reproducible stimuli is a necessary step toward addressing this issue.

As fMR imaging moves into the clinical realm, and is used for preoperative mapping, we hope its limitations will be noted and remembered.

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