Functional magnetic resonance imaging: you get what you (barely) see.

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Functional Magnetic Resonance Imaging: You Get What You (Barely) See

The mad rush to Functional Magnetic Resonance Imaging (fMR) for localization of brain functions is a reflection of the power of the technique and the need for a practical, noninvasive method of studying the human brain in action. It is clear that fMR will be an increasingly important investigative technique that will be embraced by a wide variety of both basic and clinical neuroscientists. As with any 'mad' rush, it is important to verify the rationale behind the madness. There is now abundant literature validating fMR, and its predecessor fPET, as legitimate tools for identifying regions of brain activity. Many concerns remain however, about the overall robustness of the technique. Some questions arise from one of the most basic neuroscience controversies. Are all brain functions regionally localized? Certainly many are, but the classical 'regionalist' *versus* 'distributed' arguments about brain functional organization continue, particularly in relation to nonsensorimotor areas of the cerebral cortex. Other questions relate to uncertainties about the physiology of fMR. Cerebral blood flow (CBF)-based functional imaging does not directly image neurophysiological, ie electrical or biochemical, activity. The variety of perhaps region-specific mechanisms linking neural activity to CBF remain unknown; a major limitation to understanding empirical functional imaging results. Yet other questions arise from technical challenges. Is signal/noise adequate and what kind of statistical analysis should be performed on the raw data?

Some of these problems of functional imaging can be emphasized by reversing the usual perspective from a positive to a negative query: "What is the significance of an 'inactive' area?" For instance, assume a complex cognitive task does not elicit an fMR response. Does that mean that the task is handled in a widely distributed fashion and there is little regional localization of the task? Or could it be that the underlying neurophysiology of the task is not tightly coupled to changes in CBF, a more likely possibility when dealing with pathologic states? Or is it simply that technological limitations remain, resulting in inadequate signal/noise? The different explanations carry significantly different implications. Response one implies that the task is not localized in a particular region. Responses two and three imply that the task was localized to a region, but it was missed.

Two articles in this issue relate to this discussion of 'negative' results. In the paper by Hedera et al (see page 853), fMR failed to identify an activated visual cortex in 7 of 13 men presented with the most powerful cortical stimuli known—8 hz photic stimulation. Were the results simply a question of technique and poor signal to noise? Many critics would opt for this response, but the amount of signal detected in the responders is comparable to other reports. We believe it more likely that the problem was not simply technical. In fact, the authors are to be thanked for presenting 'negative' results, which by anecdote occur far more frequently than reported in the literature. The strong correlation of the fMR signal changes and EEG synchronization suggests that the nonactivators, all men, responded to the signal in a neurophysiologically different way. In what different way is unknown. Is it simply a less intense response, or a less coordinated, more widely distributed response? Did these subjects fail to 'see' the flashing lights? We doubt this possibility, though the subjects were not directly questioned on this point. Regardless, these nonresponders should probably be viewed as 'false negative' results. The technique, for unknown reasons, missed neurophysiologically active 'critical' cortices.

In the paper by Lee et al (see page 847), a relatively pure sensory task resulted in a similar cortical activation pattern as a combined sensory/motor task. In both tasks, the activated regions were predominantly in the postcentral gyrus—the primary sensory cortex. Activity of the motor cortex, strongly supported by the moving fingers and presumably in the precentral gyrus, was basically missed. There are many good explanations for why this might have happened. Spatial resolution limitations could fail to resolve the two cortical regions which are very close together on either side of the central sulcus. Blood oxygenation level dependent (BOLD)-dominated draining veins might preferentially pass over the postcentral gyrus. Sensory stimulation may activate the motor cortex as well as the sensory cortex, as has been shown in electrophsiologic studies. Technical limitations could be invoked, but the methods described and the results presented would indicate reasonably state-of-the-art methodology. Regardless of why motor cortex activity was not identified, the implications of the 'negative' results are significant.

The authors make an interesting and practical argument that their findings can be used to advantage in paretic patients since sensory stimulation alone can suffice for localization of sensorimotor cortex. This argument, however, is based on prior knowledge that there is a close approximation of the sensory and motor cortices and assumes that this relationship holds in all subjects, which may not always be true. But what if we didn't already know about the relationship between the motor and sensory cortex? After all, much of current functional imaging is directed toward finding functional localizations that we don't already know. If the experimental goal had been to identify where the motor cortex was located on the basis of finger tapping, the conclusion might have been that the motor cortex is located in the postcen-

tral gyrus—the location of fMR activation. Furthermore, a dangerous negative corollary, based on the assumption that nonactivated regions are not involved with the activation task, might have been reached: precentral gyrus is not activated, ergo it is not the motor cortex, ergo it could be surgically resected without risk of paresis. This is obviously carrying the argument to the absurd and 'no one' would actually do such a thing.

In summary, these two intriguing fMR papers emphasize the problem of negative results and demonstrate the usefulness of reporting them in relation to the robustness of the technique. They also show the need for analyzing functional brain imaging results within the framework of what is already known about the anatomic and physiologic features of the system being studied, and that results that do not fit into a pattern of converging lines of neuroscientific evidence should be interpreted cautiously. A safe position for now might be: "Be skeptical of what you see and make nothing of what you don't see."

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Developing Tumor Management for the Developing Brain

We must never forget, and often we need a reminder, that the developing brain requires a delicate homeostatic balance that can often be upset by human intervention. In the treatment of childhood cancer, often this intervention is a necessary evil to assure some survival from an even greater menace that threatens the life of the child. Any pediatric oncologist knows too well that the search for improved cancer survival in children must be carefully weighed with the potential harmful effect such therapy may have on the developing brain.

In this issue of the *American Journal of Neuroradiology*, Waldrop et al (see page 963) provide further evidence that such therapy may impact areas remote to the primary site of the tumor. The investigators uncovered proton spectroscopic abnormalities in the form of reduced NAA and increased choline ratios in regions remote to the primary site of tumor in a significant number of their subjects. Of concern was the frequent involvement of areas related to neurocognitive development and behavior such as the frontal lobes. While the authors made no attempt to correlate the metabolic effects with developmental outcome, the potential still exists for this information to yield clues about the relationships between certain forms of cancer therapy, patient age when these treatments are administered, and clinically-evident neurocognitive deficits that develop after treatment.

The most exciting message in this paper relates not to the actual findings, but to the changing role of imaging, clinical physicists, and neuroradiologists in cancer management. It is exciting to see how teams of clinical physicists collaborating with neuroradiologists can accomplish the tasks at hand. Such collaborations are as much a part of our future, as are the new tools we hope to use in our trade. In addition, imaging continues to play an increasing role in cancer therapy beyond simply determining the presence or absence of recurrent tumor. In the traditional role, imaging centered on assessment of the shortcomings rather than the excesses of therapy. The effect cancer treatment has on the developing brain is currently seen after long-term follow up when therapy has ceased. Even then, the mechanism of this interaction is not understood. Advanced imaging applications such as spectroscopy, diffusion/perfusion imaging, and functional MRI may change all that. The potential to understand more clearly how therapeutic measures directly effect brain development should be a goal of neuroimaging research in the future.

Neuroradiologists and clinical physicists alike should become as involved in assessing what effects therapy may have on the host brain, as much as it may have on the tumor itself. We must remember that outcome in children with cancer is as much an issue of what is left as what appears to have disappeared.

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The Role of CT Angiography in the Long-Term Management of Cerebrovascular Dissection

There is increasing utilization of CT angiography (CTA) for the diagnosis of cerebrovascular disease, including chronic occlusive disease, aneurysm detection and post-treatment follow-up, and acute stroke by embolic occlusion of an intracranial artery or acute vascular dissection. The excellent and thoughtful paper by Leclerc et al (see page 831) is an important contribution because it addresses the technique of assessing the healing of vascular dissection, the natural history of this healing process, and the implica-