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Commentary

Stimulus-Correlated Signals in Functional MR of the Brain

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Over the last 5 years, functional magnetic resonance (MR) imaging has grown from a highly speculative, specialist activity to a widely acknowledged and well-funded method. In its initial phase of development, it seemed so simple that one was amazed that signals correlated with brain activity had not been observed before. Standard paradigms soon emerged to study basic visual, motor and other functions, in which subjects were repeatedly imaged while being placed alternately in active and control states. Thus, left-hand activity was compared with right-hand activity, full or hemifield flashing lights were compared with darkness, and so on. The resulting series of images were analyzed to extract signal changes that correlated with the task paradigms, and results were presented with statistical measures of the certainty of correlation. That there were correlated signals present is beyond doubt, with paper after paper appearing in reputable journals demonstrating the same basic effect, using a wide variety of different techniques.

All of this work rests on a single fundamental assumption, namely that *a signal is evidence of brain activation if its correlates with the activation protocol used* (see for example Bandettini et al [1]). Initially, this fact seemed so obvious that it was not worth questioning. Surely a signal in the head that correlates with the movement of the big toe must originate from a process in the brain. Unfortunately, this simple clarity has gradually been eroded as various researchers have discovered other mechanisms that can produce the same result.

The first of these related to changes in subject position during activation experiments (2) (D. C. Noll, W. Schneider, J. D. Cohen, "Artifacts in Functional MRI Using Conventional Scanning," presented at the 12th Annual Scientific Meeting of the Society of Magnetic Resonance in Medicine, New York, NY, 1993) (D. L. G. Hill, A. Simmons, C. Studholme, D. J. Hawkes, S. C. R. Williams, "Removal of Stimulus Correlated Motion from Echo Planar fMRI Studies," presented at the Third Annual Meeting of the Society of Magnetic Resonance, Nice, France, 1995). It was found that subjects changed their head position in a way that correlated with the task being performed (2) (Hill et al, "Removal"). For example, subjects moved their heads to follow (or avoid) the light when illumination appeared. They also tended to shift their heads from side to side in concert with finger-tapping exercises. These displacements were tiny, being small fractions of a millimeter in most cases. However, the strong contrast of MR images translated them into signal changes that were then extracted by data processing because they conformed to the basic requirement that they were correlated with the stimulus. In a recent paper, for example, Friston et al (3) suggest "(in extreme situations) over 90% of [functional MR] signal can be attributed to movement."

Other sources of error soon emerged, with Hu and Kim (4) focusing on intraimage movement, Weisskoff et al (R. M. Weisskoff, J. Baker, J. Belliveau, et al, "Power Spectrum Analysis of Functionally-Weighted MR Data: What's in the Noise?" presented at the 12th Annual Meeting of the Society of Magnetic Resonance in Medicine, New York, NY, 1994) detecting effects caused by heart beat and respiration, and Bates et al (5) finding that echo-planar functional MR imaging can be so vulnerable to trace paramagnetics that change in the concentration of molecular oxygen in air is sufficient to disrupt it. Now, in this issue of *AJNR*, Yetkin et al (6) have shown that movement of objects outside the field of view can produce both localized and nonlocalized changes, and that these may correlate with the paradigm under appropriate cir-

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cumstances. Their statements that such changes do not have "the latency that characterizes activation" and are of "greater magnitude" clearly depend on the nature of the motion outside the field of view, so that these differences from the accepted form of brain activation signals are not fundamental. Thus, one is forced yet again to conclude that correlation with the paradigm is not a criterion sufficient to define brain activation.

This growing body of evidence is leading to a reappraisal of functional MR imaging. The question is no longer "What is the best way to optimize the functional MR signal characteristics?" but rather "Is there any genuine signal from brain activation buried within the artifacts?"

The increasing recognition of false-positive signals has stimulated efforts to correct them. Already, postprocessing solutions are being presented in the hope of maintaining business as usual (3). However, as in many other areas of MR imaging, long-lasting and robust solutions require an appropriate combination of scanner hardware, data acquisition techniques, and data processing. So, for example, the classic single-section form of functional MR study is not amenable to correction for motion that moves the brain in the through-section direction. Likewise, multisection data with gaps are unlikely to form the basis of a robust technique, because a change in subject position may cause a particular brain region to appear from or disappear into an unsampled area. In addition, other effects such as extraneous susceptibility-induced changes may modify the image data in a manner that is not amenable to simple correction (D. H. Wu, J. S. Lewis, J. L. Duerk, "Inadequacy of Motion Correction Algorithms in Functional MR: Role of Susceptibility Induced Artifacts," presented at the Third Annual Meeting of the Society of Magnetic Resonance, Nice, France, 1995).

It is to be hoped that papers such as the one by Yetkin et al will stimulate informed debate on this subject and result in a thorough look at all aspects of functional MR imaging, so that secure techniques with clearly defined failure modes eventually emerge.

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