AJNR

Functional Connectivity MR Imaging: Fact or Artifact?

Joseph A. Maldjian

AJNR Am J Neuroradiol 2001, 22 (2) 239-240
http://www.ajnr.org/content/22/2/239

Functional Connectivity MR Imaging: Fact or Artifact?

When the topic of functional MR (fMR) imaging comes up, most of us probably picture a subject performing a task (ie, finger tapping) within a magnet, while rapid imaging is being performed. Typically, the task has a baseline built into it, and some statistical test is performed on the data relative to the known reference input function. For example, a voxel-by-voxel *t* test or cross-correlation might be performed with the time course voxel data as one column and a boxcar representation of the paradigm as the second column. Leaving the wide variety of statistical tests and postprocessing options aside, there are other ways of analyzing fMR imaging data. Methodologies are under active development that make no a priori assumptions of the input paradigm. Some of these methods are principal component analysis, eigenimage analysis (a form of principal component analysis), fuzzy clustering, and more recently, independent component analysis. From the ''conventional'' fMR imaging experiment, which involved a known input paradigm and a standard statistical test, we have methods that require no knowledge of the paradigm in identifying areas of activation. Taking this progression one step further, fMR imaging experiments can even be performed without a task.

In 1995, Biswal et al reported on functional connectivity in the motor cortex of the human brain at rest (1). Essentially, they performed a standard fMR imaging experiment without a task to determine what would occur if the temporal signal from a region in the motor cortex on one side was used as the input function to the correlation analysis. They found that the contralateral motor cortex showed activation using this region of interest from the opposite hemisphere in the resting brain. Using functional connectivity MR (fcMR) imaging, they identified low frequency (< 0.1 Hz) fluctuations in the signal of the resting brain, revealing a high degree of temporal correlation. This is a very robust finding that can be duplicated for many other eloquent areas of the brain, including the visual and auditory cortical regions, as well as the subcortical structures (2, 3). To some extent, it is surprising that these regional low-frequency synchronizations in signal exist between the hemispheres. This may reflect correlated fluctuations in blood oxygenation or blood flow between the hemispheres, mediated by neuronal connections through the corpus callosum and commissural pathways. These synchronous fluctuations may represent changes of local blood flow secondary to fluctuations in firing rates in distributed neural networks.

In this issue of the *AJNR,* Quigley et al (page 294) assess resting state functional connectivity in eloquent cortical regions in response to a variety of cerebral lesions. They examined 12 patients with tumors, cysts, and arteriovenous malformations; one subject had agenesis of the corpus callosum. They also performed task-related blood oxygenation level–dependent fMR imaging in the patients to identify seed voxels for the cross-correlation connectivity analysis. They found close concurrence between the task fMR maps and fcMR maps for the patients with focal lesions. Nonetheless, for the patient with agenesis of the corpus callosum, functional connectivity between the hemispheres could not be demonstrated for motor cortex and frontal lobe language areas. Curiously, the fcMR effect was preserved for the auditory cortex in this patient.

The structural anatomy of the auditory system provides a tempting explanation for these observations. The auditory pathways have numerous interconnections independent of the corpus callosum, with projections from each cochlear nucleus to bilateral superior olivary nuclei and the inferior colliculi. It is important to keep in mind that the underlying brain in a patient with a developmental lesion may not behave in a functionally ''normal'' fashion. Despite this, the observation suggests that integrity of the white matter pathways may be necessary for the fcMR effect, and further supports the notion that functional connectivity requires intact anatomic axonal connections. It has been previously shown that brain tumors can diminish the observed task-related blood oxygenation level–dependent response, despite adequate task performance (4). This may reflect a lack of vasodilatory reserve in these areas. It remains to be determined if the low-frequency fluctuations identified by functional connectivity within these regions are still present. This may represent a method of observing activations in this subset of patients (using the contralateral healthy side) for which conventional fMR imaging fails despite adequate task performance.

Functional connectivity studies are not limited to measuring resting fluctuations. In a recent study performed by Li et al, functional connectivity of the visual and sensorimotor areas was assessed in cocaine abusers as a response to cocaine and saline injection (5). They found marked reductions in functional connectivity in these areas after cocaine injection compared with the baseline condition. This suggests that functional connectivity may also offer a method of assessing drug effects.

Although the first resting functional connectivity maps using fcMR imaging were generated over 5 years ago, the literature in this area has been limited compared to the exponential growth in fMR imaging research in general. Much of the fcMR imaging work has been done by the same group that published the original article. Although patient studies are now emerging, it is somewhat disap-

pointing that the true basis of the fcMR imaging response remains poorly characterized. For example, is this merely an effect of mechanical symmetry between the hemispheres in response to cardiac and CSF pulsations? Can the response be explained by vasomotor oscillations (and therefore be modulated by hypercarbia)? Is this response modulated by levels of consciousness? Are crossing white matter pathways truly necessary and, if so, can a difference be shown before and after callosotomy? These questions can be readily answered using carefully designed studies in animal models.

Despite the limited work thus far, a variety of potentially exciting applications of this method immediately become apparent. For instance, is functional connectivity affected in other disease states (demyelinating conditions, vascular diseases, psychiatric illnesses) and, more importantly, can functional connectivity be used as a method to monitor effectiveness of therapies? Perhaps in the near future, we may see combinations of functional connectivity maps and diffusion tensor fiber tractography for mapping axonal connections between cortical regions. fcMR imaging should not be considered a substitute for task-related fMR imaging. Task-related activation maps can involve widely distributed neural processes, whereas fcMR imaging implies phase-locked fluctuations in blood flow in functionally related areas. Although the clinical applications for fcMR imaging have not yet been developed, it represents a powerful tool in the armamentarium of functional imaging researchers. Nonetheless, before the potential of fcMR imaging can be fully realized, the mechanisms underlying the fcMR imaging response must be thoroughly studied.

JOSEPH A. MALDJIAN, M.D.
Hospital of the University of Pennsylvania
Philadelphia, PA

References

1. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. **Functional connectivity in the motor cortex of resting human brain using echo-planar MRI.** *Magn Reson Med* 1995;;34::537–541
2. Lowe MJ, Mock BJ, Sorenson JA. **Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations.** *Neuroimage* 1998;;7::119–132
3. Kleinschmidt A, Merboldt KD, Hanicke W, Steinmetz H, Frahm J. **Correlational imaging of thalamocortical coupling in the primary visual pathway of the human brain.** *J Cereb Blood Flow Metab* 1994;;14::952–957
4. Holodny AI, Schulder M, Liu WC, Maldjian JA, Kalnin AJ. **Decreased BOLD functional MR activation of the motor and sensory cortices adjacent to a glioblastoma multiforme: implications for image- guided neurosurgery.** *AJNR Am J Neuroradiol* 1999;;20::609–612
5. Li SJ, Biswal B, Li Z, et al.**Cocaine administration decreases functional connectivity in human primary visual and motor cortex as detected by functional MRI.** *Magn Reson Med* 2000; ;43::45–51