

The Brain Stress Test

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Functional MRI (fMRI) has become a widely used tool for investigating the working human brain, and yet it has had surprisingly little direct clinical impact. When fMRI studies have been applied to disease they almost always analyze effects at the group level, rather than the individual level. And yet clearly there is the potential for fMRI to become a tool to evaluate individual brain function—a brain stress test. This talk will consider some of the challenges involved in achieving this goal and some interesting directions to pursue. The concept of a stress test can be quite broad, but here the focus is on a basic question: Can we give a patient a challenge and quantitatively measure a physiological response in their brain that will be useful for gauging how well their brain is working?

The problem with the BOLD signal. Every fMRI experiment measuring blood oxygenation level dependent (BOLD) signal changes is a kind of stress test, in the sense that the goal is to look at how the brain responds to a particular challenge (a chosen stimulus or task, or a change of state due to a drug or other physiological manipulation). However, the goal in these studies is usually not to look at the absolute magnitude of the BOLD change but rather the pattern of activation. This approach could potentially identify individual brain dysfunction (perhaps as a “network” disruption), but the magnitude of the BOLD signal itself cannot be interpreted as a measure of brain function. The problem is that it is an intrinsically complex signal, depending in opposing ways on the changes in blood flow and oxygen metabolism, and also depending on technical aspects of the image acquisition method. For this reason, BOLD-fMRI alone is unlikely to provide a reliable stress test (although it may be useful in evaluating brain tumor function [1]).

Measuring vascular reactivity with ASL. With arterial spin labeling (ASL) methods we can make quantitative measurements of cerebral blood flow (CBF) in absolute physiological units, and this technique is already being applied in a number of studies to measure vascular reactivity. A typical application is to measure the change in CBF in response to inhaled CO₂ [2], and this approach looks promising for evaluating cerebrovascular disease [3].

Future directions. While the applications to vascular disease are clear and useful, they do not fully tap the potential of fMRI to test neural function in some way. The next step is to consider oxygen metabolism (CMRO₂) measurements as a biomarker. In repeated studies we found that the coupling ratio of CBF to CMRO₂ changes was more reproducible than the individual responses themselves [4]. Recently we proposed an approach for improving the sensitivity for measuring CBF fluctuations as well as the CBF/CMRO₂ coupling ratio when the driving stimulus is unknown [5], and this may provide a window for a more complex, interactive stress test.

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