Using a white matter reference to remove the dependency of global signal on experimental conditions in SPECT analyses.

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Proportional scaling models are often used in functional imaging studies to remove confounding of local signals by global effects. It is generally assumed that global effects are uncorrelated with experimental conditions. However, when the global effect is estimated by the global signal, defined as the intracerebral average, incorrect inference may result from the dependency of the global signal on preexisting conditions or experimental manipulations. In this paper, we propose a simple alternative method of estimating the global effect to be used in a proportional scaling model. Specifically, by defining the global signal with reference strictly to a white matter region within the centrum semiovale, the dependency is removed in experiments where white matter is unaffected by the disease effect or experimental treatments. The increase in the ability to detect changes in regional blood flow is demonstrated in a SPECT study of healthy and ill Gulf War veterans in whom it is suspected that brain abnormalities influence the traditional calculation of the global signal. Controlling for the global effect, ill veterans have significantly lower intracerebral averages

than healthy controls (P = 0.0038), evidence that choice of global signal has an impact on inference. Scaling by the modified global signal proposed here results in an increase in sensitivity leading to the identification of several regions in the insula and frontal cortex where ill veterans have significantly lower SPECT emissions. Scaling by the traditional global signal results in the loss of sensitivity to detect these regional differences. Advantages of this alternative method are its computational simplicity and its ability to be easily integrated into existing analysis frameworks such as SPM.
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