Functional MRI: Pitfalls in fMRI Quantification Processing

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Background

The use of MRI for performing non-invasive assessment has grown dramatically over the past two decades. Functional MRI (fMRI) is now a critical tool in basic neuroscience, and is gradually being used in the clinical arena as well. One of the reasons that fMRI has been slow to be utilized clinically, however, is that it is quite prone to confounding artifacts that can be particularly problematic in clinical cases. This means that clinicians need to be conversant with the sorts of artifact that can corrupt fMRI data, with ways in which the risk of these artifacts being present can be reduced, and with some of the correction procedures that can be applied to reduce their effect.

A number of categories of artifact will be presented and discussed. These include:

Signal dropout problems

The majority of fMRI studies use gradient echo protocols to create blood oxygenation level dependent (BOLD) image contrast. BOLD contrast is very sensitive to microscopic field inhomogeneities caused by changes in the balance between oxy- and deoxy-hemoglobin in the voxel, but is also sensitive to more macroscopic magnetic field inhomogeneities caused by poor magnet shim and by inherent magnetic susceptibility differences between air and tissue in the head. These latter effects lead to significant signal reduction and loss in fMRI sensitivity in certain parts of the brain, particularly in frontal and temporal regions. Various simple methods can mitigate these effects, such as selecting a relatively thin slice thickness, orientating the slices away from pure axial, and optimizing the phase encoding direction (Deichmann et al. 2003). With advanced pulse program features it is also possible to perform region-specific shimming (Wilson et al. 2002) and to employ the concept of "z-shimming" (Constable and Spencer, 1999).

Geometric distortion problems

Another consequence of the macroscopic field inhomogeneities, when data are acquired by echo planar imaging (EPI) methods, is that the images become geometrically distorted with respect to conventional imaging sequences. This leads to subtle (or sometimes dramatic) non-linear registration problems between the EPI functional data and standard high resolution images that are acquired for structural identification purposes. In order to avoid such confounds the EPI data must be "unwarped" by some form of non-linear registration procedure. The information required to accomplish this can either be obtained by acquiring a field map at the same slice locations (Jezzard and Balaban, 1995), or by collecting additional EPI information (Robson et al. 1997; Holland et al. 2009).

Head motion artifacts

Head motion is a problem for all fMRI studies, but tends to be a particular problem in clinical fMRI where patients may be in discomfort or may be especially apprehensive. In BOLD fMRI head motion leads to image mis-registration problems between subsequent time points in the fMRI time series, ultimately leading to additional "noise" and reduced fMRI sensitivity. If the head motion is correlated with the stimulus then false activations can result (Hajnal et al. 1994). Certain simple precautions can be taken to minimize the amount of motion made by the subject, such as acclimatizing the patient to the scanner, minimizing the scan time, and gently cushioning the patient with foam pads. Post processing using motion correction algorithms can also improve data quality (Jenkinson et al. 2002; Friston et al. 1996).

Orthogonality of the paradigm design matrix
A simple principle that must always be followed is to ensure that an experimental design that seeks to probe more than one stimulus type has sufficient "orthogonality" between the timing of the tasks that they can be successfully separated in data analysis. If the time course of the signals of interest overlap too much then the analysis software will fail to separate the tasks properly. This issue can arise in a clinical context when the investigator seeks to minimize scan time by simultaneously probing multiple brain areas (e.g. combined visual, motor and language tasks). Careful design of the paradigm will avoid this problem.

Physiological noise contamination
The fMRI signal in BOLD-based imaging sequences is generally on the order of 1-5% and may be even lower. Thus, any noise processes that introduce instabilities into the data will compromise the ability to detect activation patterns. One prominent source of instability, once the system hardware is well optimized, is physiological variability, particularly caused by the effects of respiration and cardiac cycle. Various proposals have been made to monitor physiological noise processes and then correct for them or at least minimize them in post processing. Where the ability to monitor respiratory and cardiac variability exists these types of correction procedure can improve the data quality (Hu et al. 1995; Glover et al. 2000; Birn et al. 2008).

Disrupted baseline physiology
There is much evidence that abnormal resting physiology can affect the interpretation of standard BOLD fMRI data, potentially leading to misinterpretation of activations, for example by causing "false negatives". Altered resting cerebral blood flow (CBF) is known to cause an increased BOLD response (decreased resting CBF) or decreased BOLD response (increased resting CBF), all other parameters being equal (Brown et al. 2003). Likewise, normal ageing alters the BOLD response, presumably due to gradual vessel stiffening with age (D'Esposito et al. 1999). A variety of methods have been proposed to account for these types of confounding effects when comparing subject groups where differences of this sort may otherwise obscure or confound any desired assessment of underlying neuronal activity. Examples include calibration using a brief hypercapnic challenge (Handwerker et al. 2007), and calibration based on resting CBF or resting brain venous oxygenation (Lu et al. 2008), which are correlated with one another. In extreme cases in clinical populations with cerebrovascular disease and associated disruptions to autoregulation, it may even be possible to see negative activations or null activations, simply due to the complex competing effects of cerebral blood flow, cerebral blood volume and cerebral oxygen metabolism in forming the resultant BOLD signal changes. Without additional information on these other parameters (for example through the use of arterial spin labeling CBF-fMRI (Yongbi et al. 2001), or vascular space occupancy CBV-fMRI (Lu et al. 2003)) it may not be possible to properly interpret BOLD fMRI results in these types of patient.

Hardware imperfections
One of the most important prerequisites to obtaining reliable fMRI data is to have a stable MRI scanner that is known to have sufficient system stability to achieve a demanding fMRI protocol. Various system instabilities such as unstable RF coils, gradient heating-induced signal drifts, low signal-to-noise RF coils, and gradient-switching induced "spiking" can all lead to poor resultant fMRI data and an inability to detect reliable activation maps. It is therefore vital to perform regular "pseudo-fMRI" quality assurance procedures to ensure and maintain good performance of the scanner (Weisskoff et al. 1996; Friedman and Glover 2006).

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