Resting state BOLD calibration

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Synopsis:
An increasing number of fMRI studies are looking not only at the activation of certain brain areas, but also at the connections between regions. This measure of “functional connectivity” is inferred from the correlation of signal fluctuations in time. These fluctuations can be the result of tasks or stimuli, but can also be unrelated to the task, occurring either during rest or on top of task activation, particularly at low temporal frequencies (<0.1Hz). The hypothesis is that these signal fluctuations reflect synchronized variations in the neuronal activity of a network of regions. A key difficulty in estimating this functional connectivity is that there are many non-neuronal processes that can also cause the fMRI signal fluctuations of two regions to be correlated, including cardiac pulsation, breathing changes, and subject motion. An accurate mapping of neuronal connections with fMRI therefore requires that these confounds be addressed. In addition, functional connectivity is often measured under quite different experimental conditions, complicating the interpretation of what precisely is giving rise to correlated fluctuations.

Overview:

- Sources of fluctuations in fMRI time series data
  There are many sources of fluctuations in fMRI time series data. These can be either minimized or accentuated by the choice of paradigm, imaging parameters, or post-processing techniques.
  - Thermal noise
  - Scanner instabilities and artifacts
  - Subject motion
  - Cardiac pulsation (inflow effects, tissue motion)
  - Respiration (B0-field changes from chest motion, tissue motion, ΔCO2)
  - Vasomotion
  - Neuronal activity

- “Functional Connectivity” in fMRI (“fcMRI”)
  (Biswal et al., 1995; Lowe et al., 1998)
  - Low temporal frequency (<0.1 Hz)
  - Correlated between functionally related brain regions
  - Fluctuations can occur during rest (i.e. no explicit stimulus or task) or during task
    (Fair et al., 2007; Fox et al., 2007)
  The hypothesis is that these low frequency fMRI signal fluctuations reflect correlated neuronal fluctuations in a network of task-related brain regions

- The “Default Mode Network”
  - A set of brain regions has been shown to consistently deactivate during a wide range of tasks. (Raichle et al., 2001)
  These are hypothesized to reflect brain areas that are more active during rest.
  - Fluctuations in these brain areas are correlated at rest (Greicius et al., 2003)
Methods for computing functional connectivity

- Seed-voxel or Seed-ROI
  Select a seed voxel or region of interest (ROI) from the pre-processed data, and correlate this time series (or the average time series within this region) with the rest of the brain.

- Independent Component Analysis (ICA)
  A data driven approach, such as ICA, has been shown to identify a consistent set of components during resting-state data (Damoiseaux et al., 2006; De Luca et al., 2006). This technique may also be more effective at reducing the impact of respiration-induced signal fluctuations.

- Common pre-processing steps
  - Traditional physiological noise correction (e.g. RETROICOR, IMPACT, …)
    Since cardiac and respiratory fluctuations can be correlated across the brain, these signal changes should be removed, or filtered, prior to functional connectivity analyses (Chuang et al., 2001; Glover et al., 2000; Josephs et al., 1997).
  - Low-pass (<0.1Hz) or Band-pass (0.01 – 0.1 Hz) filtering
    Neuronally-induced spontaneous fluctuations in the fMRI data typically occur at low frequencies (<0.1Hz). (Biswal et al., 1996)

- The Influence of respiration rate and depth changes
  Breath-to-breath changes in the depth or rate of breathing, which occur naturally during rest, can cause changes in the levels arterial CO2, a potent vasodilator. This can result in significant MR signal changes. Fluctuations in breathing during rest typically occur at around 0.03Hz. The signal changes induced by these fluctuations occur throughout gray matter and in larger vessels, and overlap in particular with many regions of the default mode network. (Birn et al., 2006; Wise et al., 2004)

Dealing with respiration-related changes in functional connectivity analysis:
  - Filtering
    Can help, but fully removing respiration-induced changes requires knowing the dynamics of the MR signal induced by respiration changes.
  - Keep respirations constant
    Potentially reduces respiration-related signal changes, but is this a “resting state”? 
  - Global regression
    Potentially reduces respiration-related signal changes, but removing the global signal could remove the signal of interest. In addition, this procedure introduces anti-correlations to the seed region in a seed-ROI based connectivity analysis.
  - Regress out signal from CSF & white matter
    Can help to reduce the influence of some of the non-neuronal fluctuations.

- The Influence of cardiac rate changes
  Changes in the cardiac rate have also been shown to result in fMRI signal changes. These may be mediated both by neuronal and hemodynamic mechanisms. (Shmueli et al., 2007)
Evidence that correlated low-frequency resting-state fluctuations are (at least in part) neuronal

- Direct neuronal measurements
  Correlations between fMRI signal fluctuations and neuronal activity at rest have been observed using more direct measures of neuronal activity acquired at the same time as the fMRI signal. (Laufs et al., 2003; Shmuel et al., 2008)

- Spontaneous fluctuations and behavior
  Recent data suggests that low frequency “spontaneous” fluctuations in the fMRI time series data account for significant trial-to-trial variations in both the fMRI response and behavior (Fox et al., Neuron 2007).

Conclusions:

Functional MRI time series contain many sources of noise. Many of these can be reduced by the choice of imaging parameters, or by post-processing techniques, in order to improve detection of neuronal activation induced signal changes. Studies of functional connectivity, which look at the correlation of fMRI time series between brain regions, are showing promising results for a variety of neuroscience questions and disorders. Since these techniques rely on the correlation of fluctuations between regions, removing correlated non-neuronal fluctuations, such as those induced by the cardiac pulsations and respirations, is critical.
References:


