

**Session:** Functional Connectivity: MRI Measures of Spontaneous Fluctuations in Intrinsic Networks

**Title:** Spontaneous Signal Fluctuations in Intrinsic Networks  
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### Highlights

- Spontaneous hemodynamic fluctuations display spatio-temporal organization.
- Task-free fMRI has become a powerful approach for studying properties of large-scale brain networks and their clinical implications.
- There remain challenges in interpreting results of task-free fMRI studies, as the neural origins of spontaneous hemodynamic signals are not well understood and fMRI data also contain non-neural (noise) fluctuations.

**Target audience:** Faculty and trainees interested in fMRI methodology, specifically resting-state functional connectivity.

**Purpose:** To introduce the study of spontaneous BOLD signal fluctuations and the characteristics thereof, surveying current evidence and theories about their origins and relevance. Material in this lecture will serve as background for the other talks in the session.

**Outcome/Objectives:** To obtain a basic understanding of spontaneous BOLD signal fluctuations and functional connectivity.

### Synopsis

Functional MRI studies have traditionally focused on brain activity evoked by external stimuli or task demands, while disregarding fluctuations that are unrelated to the task or which occur in the absence of stimuli or behavioral output (known as *intrinsic, ongoing, or spontaneous* activity). Yet, spontaneous activity has been shown to account for the majority of the brain's energy consumption, with sensory stimulation eliciting a surprisingly small increase (usually <5%) [1]. Interest in studying spontaneous fluctuations with fMRI was initiated by the landmark publication of Biswal et al., which showed that regions activated in a sensorimotor task exhibited temporally correlated BOLD signal fluctuations in a *resting-state* (task-free) scan [2]. Subsequent studies revealed that spontaneous fluctuations across the brain possess a high degree of spatio-temporal structure and consistency (forming *resting-state networks*) that align well with known functional systems [3].

The practice of mapping correlations in the BOLD signal fluctuations (*functional connectivity*) in resting-state data is now widely used for interrogating the structure of large-scale brain networks and their modulation with disease, development, aging, and cognition [4,5]. However, much remains to be understood about the neural origins and relevance of spontaneous BOLD fluctuations and functional connectivity (see, e.g., [6,7] for reviews). We will discuss characteristics of these fluctuations and their relationship to electrophysiological measures, structural connectivity, task activation, and behavior.

The precise link between spontaneous BOLD signals and neural activity is still under investigation [6]. Some degree of correspondence has been observed with fluctuations in the power of EEG and local field potentials at certain frequency bands [e.g. 8-10]; for example, studies using invasive electrophysiological recordings have shown that power in the gamma band of the local field potential (LFP) correlates with the spontaneous BOLD signal and mirrors patterns of functional connectivity observed with fMRI [9,11,12], though an association with lower frequencies in the electrical signal has been described as well [13,14]. It is also suggested

that the joint behavior of multiple frequency bands provides more information about observed BOLD signal fluctuations than that of any single band [15,16].

Direct anatomical connections are believed to shape, but not fully constrain, the strength and topology of spontaneous BOLD signal correlations. DTI and tract tracing studies report correlations between functional connectivity and structural connectivity [17-19], though regions without direct structural connections can still display high functional connectivity that is presumably mediated by indirect connections. Factors such as synaptic efficiency and myelination also affect the magnitude of BOLD signal correlations [7]. Nonetheless, because of the close correspondence between anatomic connections and BOLD signal correlations, several studies have demonstrated the ability to map fine-scale organization (e.g. of thalamus [20] and insula [21]) from resting-state scans.

The behavioral relevance of spontaneous BOLD fluctuations has been demonstrated through studies showing, for instance, that pre-stimulus levels of intrinsic activity can significantly predict task responses [22]. In addition, changes in behavioral and vigilance state appear to be reflected in the amplitude and correlations of spontaneous BOLD fluctuations [23-25], providing a window into the neural correlates of such changes but suggesting as well that it may be important to account for state-related variability when interpreting resting-state fMRI data.

Inferences made from resting-state fMRI can be severely confounded by the presence of non-neural “noise”, such as due to respiratory/cardiac processes and head motion [26]. Variations in the rate and depth of breathing across the scan, for example, modulate BOLD signal across much of gray matter in a common way, artificially increasing correlations between voxel time series [27]. In the absence of a task, the distinction between signal and noise cannot be informed by *a priori* models of the timecourse of activity, nor can one use event-related averaging to improve the signal-to-noise ratio. Employing noise reduction strategies in resting-state data is, therefore, of critical importance.

## References

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