**Session: Advanced fMRI: Techniques & Applications**
**Title**: Dynamic Functional Connectivity
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**Highlights**
• Metrics of functional connectivity in resting-state fMRI have been observed to change over time (seconds to minutes) and in conjunction with natural variation in physiological, cognitive, and vigilance states.
• The study of dynamic functional connectivity requires careful analysis and modeling, as well as reduction of non-neural influences on the fMRI signal, in order to minimize spurious variability.
• Dynamic features of functional connectivity are emerging as promising biomarkers for clinical and cognitive neuroscience applications.

**Target audience**: Faculty and trainees interested in fMRI methodology, specifically resting-state functional connectivity.
**Outcome/Objectives**: To understand potential sources of variability in fMRI functional connectivity analysis, to recognize the issues that complicate dynamic analyses, and to learn how dynamic features may provide novel information about brain function and clinical abnormalities.

**Synopsis**
Most approaches to analyzing functional connectivity (FC) in resting-state fMRI characterize the interactions between brain regions as constant over time. This practice has yielded tremendous insight into functional organization, revealing the presence of resting-state "networks" that align closely with known anatomic and functional pathways [1-3]. However, FC is also known to vary across states such as sleep [4,5], as a function of caffeine intake [6], and over cognitive activities such as mind-wandering, learning, and focused attention [7,8]. Therefore, in addition to its remarkable consistency, the *variability* of resting-state FC can provide valuable information about state-dependent changes in large-scale network activity.

In recent years, resting-state fMRI studies have also moved toward examining changes in FC that occur over scales of seconds to minutes (reviewed in [9,10]). This perspective, along with novel approaches for "dynamic" analysis of resting-state data, are providing further insight into functional relationships between brain regions and their alteration with disorders such as schizophrenia (e.g. [11,12]). However, the study of dynamic FC is complicated; for instance, spurious variability can easily arise from non-neural fluctuations ("noise") in the fMRI signal [13], and as a consequence of particular analysis strategies (such as pointed out in [14,15]). Proper analysis, validation, and noise-reduction procedures are essential for obtaining an interpretable picture of FC dynamics.

We will first review sources of variability in functional connectivity as determined from experimentally induced contexts. We will then address the topic of spontaneous, time-varying changes in FC, with observations from both empirical and computational modeling work [16,17]. We will discuss studies into the neural basis of such changes [18], and how examining the dynamics of resting-state FC with multimodal imaging and physiological recordings can reveal neural correlates of endogenous shifts in the state of the brain/body [19,20]. We will show examples of recent literature proposing methods for analyzing dynamic FC, and the potential for temporal features of FC to serve as biomarkers for clinical applications. Finally, we will discuss the importance of reducing non-neural sources of variability, and illustrate how appropriate modeling and analysis techniques are critical when drawing inferences about FC dynamics.

### References


[1] Biswal, B., Yetkin, F.Z., Haughton, V.M., Hyde, J.S., 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn. Reson. Imaging 34, 537–541.

[2] Smith, S.M., Fox, P.T., Miller, K.L., Glahn, D.C., Fox, P.M., Mackay, C.E., Filippini, N., Watkins, K.E., Toro, R., Laird, A.R., Beckmann, C.F., 2009. Correspondence of the brain's functional architecture during activation and rest. Proc. Natl. Acad. Sci. U. S. A. 106, 13040–13045.

[3] Buckner, R.L., 2010. Human functional connectivity: new tools, unresolved questions. PNAS 107, 10769-10770.

[4] Horovitz, S.G., Braun, A.R., Carr, W.S., Picchioni, D., Balkin, T.J., Fukunaga, M., Duyn, J.H., 2009. Decoupling of the brain's default mode network during deep sleep. Proc. Natl. Acad. Sci. U. S. A. 106, 11376–11381.

[5] Tagliazucchi E., Laufs H. Decoding wakefulness levels from typical fMRI resting-state data reveals reliable drifts between wakefulness and sleep. Neuron 82 (3), 695-708

[6] Wong CW, Olafsson V, Tal O, Liu TT. The amplitude of the resting-state fMRI global signal is related to EEG vigilance measures, 2013. Neuroimage. 83:983-90.

[7] Bassett, D.S., Wymbs, N.F., Porter, M.A., Mucha, P.J., Carlson, J.M., Grafton, S.T., 2011. Dynamic reconfiguration of human brain networks during learning. Proc. Natl. Acad. Sci. U. S. A. 108, 7641–7646.

[8] Shirer, W.R., Ryali, S., Rykhlevskaia, E., Menon, V., Greicius, M.D., 2012. Decoding subject-driven cognitive states with whole-brain connectivity patterns. Cereb. Cortex 22, 158–165.

[9] R.M. Hutchison et al. Dynamic functional connectivity: Promise, issues, and interpretation. NeuroImage 80 (2013) 360–378

[10] Calhoun, Vince D., Miller, R., Pearlson, G., Adali T., 2014. The Chronnectome: Time-Varying Connectivity Networks as the Next Frontier in fMRI Data Discovery. Neuron, Volume 84 , Issue 2, 262–274.

[11] Allen, E., Damaraju, E., Plis, S.M., Erhardt, E., Eichele, T., Calhoun, V.D., 2013. Tracking whole-brain connectivity dynamics in the resting state. Cereb. Cortex.

[12] Damaraju E., EA Allen, A Belger, JM Ford, S McEwen, DH Mathalon, BA Mueller, GD Pearlson, SG Potkin, A Preda, JA Turner, JG Vaidya, TG van Erp, VD Calhoun. Dynamic functional connectivity analysis reveals transient states of dysconnectivity in schizophrenia. NeuroImage: Clinical (5) 298-308.

[13] Birn, R.M., Diamond, J.B., Smith, M.A., Bandettini, P.A., 2006. Separating respiratory variation-related fluctuations from neuronal-activity-related fluctuations in fMRI. Neuroimage 31, 1536–1548.

[14] Handwerker, D.A., Roopchansingh, V., Gonzalez-Castillo, J., Bandettini, P.A., 2012. Periodic changes in fMRI connectivity. Neuroimage 63, 1712–1719.

[15] Leonardi, N., Van De Ville, D. (2015). On spurious and real fluctuations of dynamic functional connectivity during rest, NeuroImage, 104(1), 430-436,

[16] Honey, C.J., Kötter, R., Breakspear, M., Sporns, O., 2007. Network structure of cerebral cortex shapes functional connectivity on multiple time scales. Proc. Natl. Acad. Sci. U. S. A. 104, 10240–10245.

[17] Deco, G., Corbetta, M., 2011. The dynamical balance of the brain at rest. Neuroscientist 17, 107–123.

[18] Keilholz, S.D. The neural basis of time-varying resting-state functional connectivity. Brain Connect. 2014 Dec;4(10):769-79.

[19] Chang, C., Liu, Z., Chen, M.C., Liu, X., Duyn, J.H., 2013b. EEG correlates of time-varying BOLD functional connectivity. Neuroimage 72, 227–236.

[20] Chang, C., Metzger, C.D., Glover, G.H., Duyn, J.H., Heinze, H.J., Walter, M., 2013a. Association between heart rate variability and fluctuations in resting-state functional connectivity. Neuroimage 68, 93–104.