EDITORIAL

Endogenous Oscillations and Networks in Functional Magnetic Resonance Imaging

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INTRODUCTION

Since functional magnetic resonance imaging (fMRI) first emerged as a new tool for mapping human brain function in the early 1990s, we have seen an extraordinary growth in the number of papers and research groups using this technique. Because of its relatively high resolution, sensitivity, and ease of use, fMRI has largely eclipsed positron emission tomography (PET) as a tool for locating changes in brain hemodynamics associated with performance of an experimentally controlled task. Indeed, the dominant paradigm for fMRI research to date has been strongly informed by conceptual or statistical tools—such as principles of cognitive subtraction for experimental design and linear modeling for data analysis—that had first proven their value in relation to PET and could be rapidly translated to fMRI, as the newer technology became available. The array of available activation strategies for fMRI has continued to grow rapidly, progressing beyond blocked and event-related designs to those that involve more natural behavior in a scanner, and further informed by more precise, temporally registered, and continuous behavioral and physiologic measures.

In the last few years, the field has also witnessed the explosive emergence of interest in what can broadly be described as endogenous aspects of fMRI data. Alongside the prior preoccupation with identifying regions of task-related activation (BOLD amplitude increases driven by an exogenous, experimental task), there is increasing awareness that regional deactivation (BOLD amplitude decreases, often in the same or similar regions regardless of task details) might point to the existence of spatiotemporally coordinated systems of physiological activity, sometimes described as default mode or resting state networks, that are characteristic of the brain's endogenous state [Greicius et al., 2008]. There is also convergent evidence for complex organization of resting state or "no task" fMRI signals following from the seminal observation by Biswal et al. [1995] that BOLD time series measured in the motor cortex at rest are highly correlated with contralateral motor cortex and other spatially distributed components of the motor system. It has subsequently been shown by many groups, using diverse methods of data analysis, that the very low frequency (<0.1 Hz) oscillations captured by echo planar imaging are typically correlated between laterally symmetric and/or functionally related brain regions and that the overall topological organization of these functional connections between regions has the attributes of a complex, small-world network [Achard et al., 2006]. Moreover, investigators have begun to address integrative questions, relating endogenous fMRI dynamics to variability of task-related activation or cognitive performance [Fox et al., 2006], and exploring the potential utility of endogenous fMRI markers for characterizing neurophysiological changes associated with disease or drug treatments.

In general, one could summarize the current position by saying that fMRI was originally assimilated by the field as a faster, safer, easier, and anatomically more precise form

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DOI: 10.1002/hbm.20607
Published online 8 May 2008 in Wiley InterScience (www.interscience.wiley.com).

of PET, but recent work has tended to refocus attention on its capacity—like EEG or MEG—to inform us also about the brain's ability to sustain spatially coherent systems of endogenous oscillations. Another way of framing this distinction, following Raichle and Snyder [2007], is in terms of the long-standing historical tension between reflexive and intrinsic models of brain function: the recent shift of emphasis to consideration of endogenous fMRI properties marks a step away from the field's nearly unanimous prior assumption of reflexive brain models and toward formulation of more intrinsically informed models.

While the field has seen a rapid increase in the number of papers related to endogenous contrast, many open issues remain. These include how to best analyze, and more generally, how to best interpret these data. Lastly, the question of how to best apply these fascinating findings is perhaps the most exciting and wide open. So this is a strategically important issue for the functional MRI community, which raises a host of interesting new questions, and we thought it would be timely to draw together in a special issue of *Human Brain Mapping* a selection of original contributions from some of the leading groups working in this area. The papers represent many aspects of the field, including some contributions primarily using electrophysiological data or computational analysis to inform interpretation of fMRI data, and can be subdivided into two approximately equal sets of papers on *Modeling* and *Applications*.

MODELING

One of the outstanding questions central to any consideration of endogenous fMRI data is: do these very low frequency fluctuations represent neuronal oscillations or systemic (nonneuronal) low frequency cycles that might also be expected to modulate BOLD signals? Birn et al. [2008] explore this issue by focusing on slow variations in depth and rate of respiration and the impact that these factors might have on identification of default-mode or resting state networks using the multivariate method of independent component analysis (ICA). They conclude that respiration-related systems of BOLD oscillation can sometimes mimic default mode components and that independent measures of respiratory activity are an important experimental prerequisite for less ambiguous interpretation of resting state fMRI data. A complementary perspective is presented by Shmuel and Leopold [2008], who combined intracortical neurophysiological recording and fMRI to explore directly the relationships between BOLD oscillations and slow fluctuations in the power of gamma band oscillations and multiunit activity in the monkey visual cortex. Their work provides strong evidence that correlation between BOLD signals recorded from remote sites can indeed be linked to synchronization of slow fluctuations in the underlying neuronal signals.

The general topic of combining fMRI and EEG measurements in the same human subjects, to cross-validate BOLD with more direct measures of intrinsic brain activity, is comprehensively reviewed by Laufs [2008], who finds that the correspondence of resting state EEG and fMRI is extremely complex. An innovative area of methodological convergence between electrophysiological and fMRI measurements of intrinsic brain dynamics is represented by the papers from Linkenkaer-Hansen [2008], Duff et al. [Duff et al., 2008] and Wink et al. [2008], all of which examine the scaling or fractal properties of neurophysiological measurements. Linkenkaer-Hansen et al. analyzed the power law scaling of temporal correlations in MEG data and relate these empirical observations to a model of neuronal avalanches propagating in a network at a critical state. Duff et al. [2008] examine the power spectral density scaling of endogenous fMRI measurements and relate this to cognitive task performance. In addition, power spectral density and connectivity measures were assessed. Performance of a task reduced low frequency power spectral density and functional connectivity between activated areas. Wink et al. used measures of stationary and nonstationary scaling of variance in fMRI (the Hurst exponent and Hölder exponents, respectively) and showed that performance of a cognitive task up to 30 min before resting state data acquisition was associated with significant change in the scaling properties of fMRI dynamics in task-related regions.

Sporns and Honey [2008] offer a distinctive contribution, using a computational model realistically based on the known anatomical connectivity of Macaque cortex, to investigate the effects of simulated local "lesions" on distributed systems of coherent network dynamics. Specifically, they found that lesions in parietal and frontal regions cause the greatest disruption of integrative neocortical function.

APPLICATIONS

In parallel with work toward understanding and optimally characterizing endogenous oscillations are studies directed at determining their utility both in the clinic and in the effort to understand normal brain organization. An important potential application of endogenous fMRI markers will be the characterization of neuropsychiatric disorders. Kiviniemi [2008] provide an overview of the work to date and emergent opportunities in this area. The work by Lowe [2008] combines fMRI with diffusion tensor imaging (DTI) in patients with multiple sclerosis to demonstrate that disease-related variation in functional connectivity between right and left primary cortices was inversely correlated with DTI measures of callosal integrity, providing direct support for the hypothesis that resting state correlations in fMRI are mediated by axonal connectivity between regions and may be diagnostic of anatomical dysconnectivity syndromes. Calhoun et al. [2008] review the literature using ICA to map temporally coherent networks in fMRI (both resting and task-related) and present convincing new data illustrating the robustness of ICA-driven network analysis and its applicability to characterization of abnormal neurocognitive networks in people with schizophrenia. Greicius et al. [2008] report one of the first examples of endogenous fMRI as a marker of psychopharmacological effects in humans. Normal subjects lightly sedated by a GABA agonist drug (midazolam) were found to show persistent but attenuated functional connectivity between components of a default-mode network.

Highlighting the potential also to apply endogenous fMRI in elucidation of normal physiological processes in the human brain, Eckert et al. [2008] measured functional connectivity between visual and auditory cortices in resting and visual task-related fMRI data and were able to demonstrate that anterior and posterior parts of visual cortex had functionally distinct cross-modal relationships with auditory cortex. Gaab et al. [2008] reported suppression in functional connectivity between components of a default mode network in the presence of scanner noise, reminding us of the importance of well-controlled experimental conditions, even in acquisition of so-called "resting state" data, and reiterating the principle that the interplay between environmental conditions and intrinsic brain activity is likely to be fundamental to understanding human brain function. Lastly, Boly et al. [2008] provide convincing evidence that baseline fluctuations may partially explain within-subject variability in perceptual experiments. These baseline fluctuations in visual cortex may reflect moment to moment alterations in attention, thus correlating with perceptual performance.

In short, this special issue includes 14 original articles offering substantively diverse but equally expert perspectives on emerging issues related to the potential of fMRI to inform us about endogenous brain dynamics, (as well as the brain's capacity to respond to exogenous experimental stimulation). We consider this to be one of the critical points of scientific growth in our field at this time and we are grateful to all the authors, editors, and staff at *Human Brain Mapping* who have contributed their time and expertise to this publication. We hope you enjoy it!

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