

Toward discovery science of human brain function

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Although it is being successfully implemented for exploration of the genome, discovery science has eluded the functional neuroimaging community. The core challenge remains the development of common paradigms for interrogating the myriad functional systems in the brain without the constraints of a priori hypotheses. Resting-state functional MRI (R-fMRI) constitutes a candidate approach capable of addressing this challenge. Imaging the brain during rest reveals large-amplitude spontaneous low-frequency (<0.1 Hz) fluctuations in the fMRI signal that are temporally correlated across functionally related areas. Referred to as functional connectivity, these correlations yield detailed maps of complex neural systems, collectively constituting an individual's "functional connectome." Reproducibility across datasets and individuals suggests the functional connectome has a common architecture, yet each individual's functional connectome exhibits unique features, with stable, meaningful interindividual differences in connectivity patterns and strengths. Comprehensive mapping of the functional connectome, and its subsequent exploitation to discern genetic influences and brain-behavior relationships, will require multicenter collaborative datasets. Here we initiate this endeavor by gathering R-fMRI data from 1,414 volunteers collected independently at 35 international centers. We demonstrate a universal architecture of positive and negative functional connections, as well as consistent loci of inter-individual variability. Age and sex emerged as significant determinants. These results demonstrate that independent R-fMRI datasets can be aggregated and shared. High-throughput R-fMRI can provide quantitative phenotypes for molecular genetic studies and biomarkers of developmental and

pathological processes in the brain. To initiate discovery science of brain function, the 1000 Functional Connectomes Project dataset is freely accessible at www.nitrc.org/projects/fcon_1000/.

database | neuroimaging | open access | reproducibility | resting state

Much like the challenge of decoding the human genome, the complexities of mapping human brain function pose a challenge to the functional neuroimaging community. As dem-

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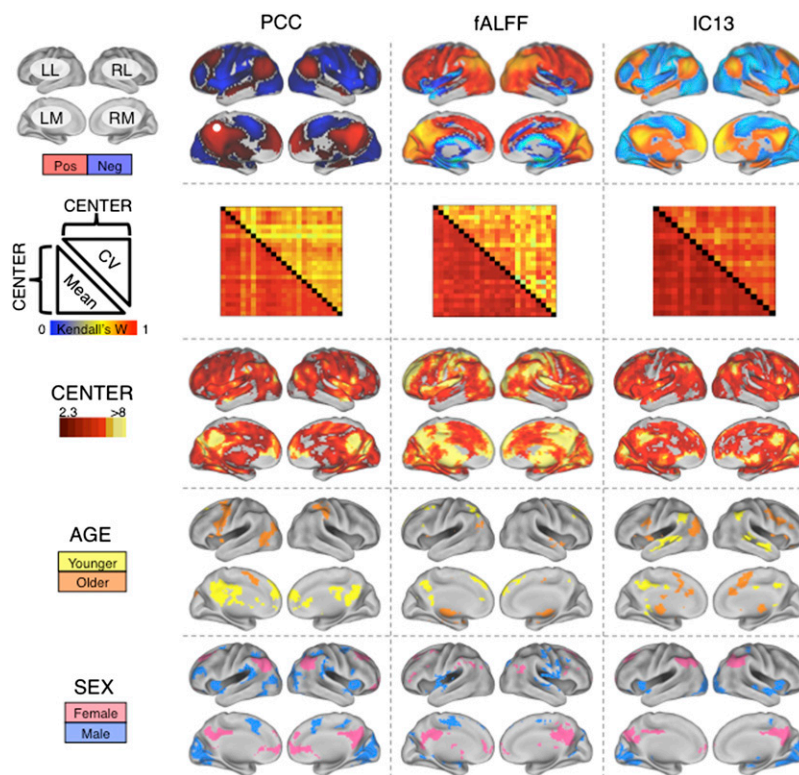
Data deposition: All data used in this work were released on December 11, 2009 via www.nitrc.org/projects/fcon_1000/.

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Buttressed by moderate to high test–retest reliability (8–10) and replicability (11, 12), as well as widespread access, R-fMRI has overcome initial skepticism (13) regarding the validity of examining such an apparently unconstrained state (5, 8, 14). Recent R-fMRI studies have identified putative biomarkers of neuropsychiatric illness (12, 15–18), provided insight into the development of functional networks in the maturing and aging brain (19–22), demonstrated a shared intrinsic functional architecture (23) between

Here we provide an initial demonstration of the feasibility of pooling R-fMRI datasets across centers. Specifically, we (i) establish the presence of a universal functional architecture in the brain, consistently detectable across centers; (ii) investigate the influence of center on R-fMRI measures; (iii) explore the potential impact of demographic variables (e.g., age, sex) on R-fMRI measures; and (iv) demonstrate the use of an intersubject variance-based method for identifying putative boundaries between functional networks.



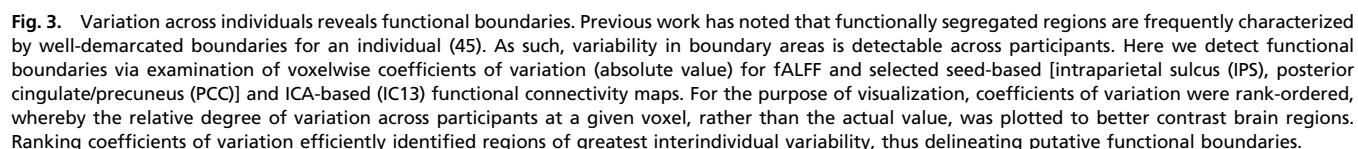
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in structural connectivity. For instance, functional connectivity is modulated by cognitive (47) and emotional state (48), arousal, and sleep (26), whereas structural connectivity is grossly unaffected by such factors. In short, the presence of a demonstrable structural connection does not necessitate that of a functional connection, nor does the demonstration of a functional connection imply the presence of a direct structural connection.

Task-based fMRI and R-fMRI approaches have complementary roles in the study of human brain function. Task-based approaches require sufficient a priori knowledge to articulate specific hypotheses, and they are invaluable in refining such hypotheses. But when the knowledge base is insufficient, task-based approaches may be compared to candidate gene studies, which have had limited success when applied to complex genetic disorders. In contrast, genome-wide association studies are increasingly providing initial findings for complex traits (49) and diseases that are subsequently validated through replication, extension, and deep sequencing (50). Our demonstration that R-fMRI data can be aggregated and pooled, and that variability among individuals can be explained in terms of specific subject variables (e.g., sex, age), suggests that this approach can provide quantitative phenotypes to be integrated into molecular studies.

Our results must be considered in light of several limitations of the present study. First, we used a convenience sample comprising previously collected data from an array of centers, without prior coordination of acquisition parameters or scanning conditions. Although the robustness of our results attests to the consistency of intrinsic brain activity, it still represents a potential underestimate of the true across-center consistency. Our demographic data warrant caution, because centers were heterogeneous with respect to male:female ratio, mean age, and age range. Our findings should motivate more systematic exploration of these variables, because future high-throughput imaging studies will need to take such factors into account.

Despite the promise of R-fMRI, some theoretical and pragmatic issues need to be addressed. Examples include the determination of



the origins and biological significance of spontaneous low-frequency fluctuations of neuronal and hemodynamic activity, the impact of intrinsic activity on evoked responses (and vice versa), and the ideal means of acquiring, processing, and analyzing R-fMRI data. Nevertheless, the potential of discovery science is vast, from the development of objective measures of brain functional integrity to help guide clinical diagnoses and decision-making, to tracking treatment response and assessing the efficacy of treatment interventions. Finally, whereas the present work examines functional connectivity alone, future studies may combine R-fMRI with other modalities (e.g., EEG, magnetoencephalography, diffusion-tensor imaging, volumetrics) and genetics to achieve a more complete understanding of the human brain.

All data and analytic tools used in the present work will be made available at www.nitrc.org/projects/fcon_1000/. We anticipate that the open availability of the 1000 Functional Connectomes dataset will recruit the broad participation and collaboration among the scientific community necessary for successful implementation of discovery-based science of human brain function. In addition, we hope that it will further advance the ethos of data sharing and collaboration initiated by such efforts as fMRIDC (www.fmridc.org), FBIRN (www.birncommunity.org), OASIS (www.oasis-brains.org), BrainScope (www.brainscope.org), and BrainMap (www.brainmap.org).

Methods

Resting-state fMRI scans were aggregated from 35 community-based datasets ($n = 1,414$). The present analysis was restricted to 24 centers ($n = 1,093$; 21 published, 3 unpublished; mean age <60 years; only participants over age 18; one scan per participant; duration: 2.2–20 min; $n = 970$ at 3 T, $n = 123$ at 1.5 T; voxel size, 1.5–5 mm within plane; slice thickness, 3–8 mm). Each contributor's respective ethics committee approved submission of deidentified data. The institutional review boards of NYU Langone Medical Center and New Jersey Medical School approved the receipt and dissemination of the data.

For functional connectivity, we used seed-based correlation analysis, based on six previously identified seed regions (31), and model-free ICA, using temporal

concatenation to generate group-level components and dual regression to generate individual participant maps. For amplitude measures at each voxel, we used the FFT-based ALFF (2, 17, 43) and its normalized variant, fALFF (44).

Standard image preprocessing was performed (i.e., motion correction, spatial filtering with FWHM = 6 mm, 12-dof affine transformation to MNI152 stereotactic space). For seed-based correlation approaches and dual regression following ICA analysis, nuisance signals (e.g., global signal, WM, CSF, motion parameters) were regressed out. Temporal filtering was tailored for each analytic approach (29, 31, 32, 44).

ICA components for dual regression analyses were determined by (i) low-dimensional (20 components) temporal concatenation ICA carried out 25 times (each with 18 participants randomly selected from each of 17 centers with minimum of 165 time points) and (ii) low-dimensional (20 components) meta-ICA, a second concatenation-based ICA using the component sets produced by the 25 runs (see *SI Results* for a description of an alternative method). For each participant, dual regression (32–34) was performed using the 20 components identified by the meta-ICA (Fig. S3), yielding a connectivity map for each component.

Aggregate statistical analyses of center, sex, and age effects were based on a generalized linear model implementation of one-way ANOVA (factor: center; covariates: age and sex). To identify functional boundaries, we calculated voxelwise coefficients of variation across all 1,093 participants, and ranked each voxel based on the absolute value of its coefficient of variation.

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