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Functional independence in resting-state connectivity facilitates higher-order cognition

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ABSTRACT

Growing evidence suggests that intrinsic functional connectivity (i.e. highly structured patterns of communication between brain regions during wakeful rest) may encode cognitive ability. However, the generalizability of these findings is limited by between-study differences in statistical methodology and cognitive domains evaluated. To address this barrier, we evaluated resting-state neural representations of multiple cognitive domains within a relatively large normative adult sample. Forty-four participants (mean(sd) age = 31(10) years; 18 male and 26 female) completed a resting-state functional MRI scan and neuropsychological assessments spanning motor, visuospatial, language, learning, memory, attention, working memory, and executive function performance. Robust linear regression related cognitive performance to resting-state connectivity among 200 *a priori* determined functional regions of interest (ROIs). Only higher-order cognitions (such as learning and executive function) demonstrated significant relationships between brain function and behavior. Additionally, all significant relationships were negative – characterized by moderately positive correlations among low performers and weak to moderately negative correlations among high performers. These findings suggest that functional independence among brain regions at rest facilitates cognitive performance. Our interpretation is consistent with graph theoretic analyses which represent the brain as independent functional nodes that undergo dynamic reorganization with task demand. Future work will build upon these findings by evaluating domain-specific variance in resting-state neural representations of cognitive impairment among patient populations.

1. Introduction

Functional neuroimaging studies of brain organization during wakeful rest have become increasingly popularity over the past decade (Allen et al., 2011; Beckmann, DeLuca, Devlin, & Smith, 2005; Greicius, Krasnow, Reiss, & Menon, 2003; van den Heuvel, Mandl, Kahn, & Hulshoff Pol, 2009; van den Heuvel & Pol, 2010). These *resting-state fMRI* (rs-fMRI) studies seek to model patterns of connectivity between brain regions in the absence of overt task, thus capturing the brain's *intrinsic* functional organization. Brain networks identified at rest have strong correspondence with networks recruited by tasks (Kristo et al., 2014; Smith et al., 2009; Thomason et al., 2011) and exhibit high within-subject replicability (Damoiseaux et al., 2006; Shehzad et al., 2009). rs-fMRI scans are more easily replicated across sites than task-based fMRI scans and do not require effort from the participant, thus avoiding confounds from individual differences in task performance or behavior. These factors have contributed to rs-fMRI's emerging popularity for studying clinical disorders, notably major depressive disorder (Craddock, Holtzheimer, Hu, & Mayberg, 2009; Greicius et al., 2007; Kerestes, Davey, Stephanou, Whittle, & Harrison, 2014; Sheline, Price, Yan, & Mintun, 2010) and schizophrenia (Amad et al., 2013; Arbabshirani, Kiehl, Pearlson, & Calhoun, 2013; Bassett et al., 2008; Bullmore et al., 2010; Cole, Anticevic, Repovs, & Barch, 2011; Lynall et al., 2010).

Among healthy participants, rs-fMRI has been used to predict individual differences in traits including age (Allen et al., 2011; Dosenbach et al., 2010; Fair et al., 2007) and personality (Adelstein et al., 2011; Kunisato et al., 2011). rs-fMRI has also been used to predict individual differences in cognitive ability, including working memory capacity (Alavash, Doebler, Holling, Thiel, & Giessing, 2015; Keller et al., 2015; Magnuson et al., 2015; Reineberg, Andrews-Hanna, Depue, Friedman, & Banich, 2015; Xu et al., 2014), memory (Wang et al., 2010), motor learning (Stillman et al., 2013; Wu, Srinivasan, Kaur, & Cramer, 2014),

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reading comprehension (Koyama et al., 2011), and spatial orientation (Arnold, Protzner, Bray, Levy, & Iaria, 2014). But the methodology varies considerably across these studies, including differences in neuroimaging data acquisition parameters, neuroimaging data preprocessing, statistical approach, participant characteristics, and cognitive modalities evaluated. This variance limits our ability to broadly generalize these findings to the larger population.

To address this limitation, we studied resting-state neural representations of cognition within a single, well-characterized normative sample across multiple cognitive domains. The characterization of a homogenous healthy sample circumvents the methodological variance that is inherent in cross-study comparisons, thus improving the generalizability of our findings. Participants were from the Cognitive Connectome project (Gess, Fausett, Kearney-Ramos, Kilts, & James, 2014; Kearney-Ramos et al., 2014), which pairs clinical neuropsychological assessment with both task- and resting-state fMRI to evaluate the neural encoding of cognition among nine domains: motor, visuospatial, attention, language and cognitive fluency, memory, affective processing, decision making, working memory, and executive function. We hypothesized that performance among these cognitive domains would positively regress to resting-state connectivity of brain regions previously associated with each domain. For example, we hypothesize that working memory performance will predict resting-state connectivity of the left prefrontal cortex, whereas motor performance will predict connectivity of the ipsilateral motor cortex.

2. Materials and methods

2.1. Participants

Seventy-nine participants met inclusionary criteria for the Cognitive Connectome project and were enrolled in the study. Of these, 26 (33%) met exclusion criteria (see below) and were excluded from further participation. Of the remaining 53 participants, 44 (83%) completed clinical neuropsychological assessment and at least one of the two resting-state sessions. Demographic information for the resulting sample is provided in Table 1. All participants were recruited with approval and oversight by the UAMS Institutional Review Board (protocol #130825).

2.2. Procedures

All study procedures were conducted in the Brain Imaging Research Center at the University of Arkansas for Medical Sciences. Study participation was typically conducted in two sessions on separate days. Session 1 included study description, obtaining informed consent to participate, a structured clinical interview (SCID-IV/NP) to assess study exclusionary criteria, behavioral surveys and questionnaires (e.g., State-Trait Anxiety Inventory and Big Five Personality Inventory), and the first of two neuroimaging session (with neuroimaging session order counterbalanced across subjects). Session 2 included neuropsychological assessment and the second neuroimaging session. Exclusionary criteria included current psychopathology, current or past neurologic illness, lifetime history of loss of consciousness exceeding 10 min, or ferromagnetic implants.

Table 1
Demographic information.

n	44 participants
Age	mean(sd) = 31(10) years, range 20–50
Sex	26 female 18 male
Ethnicity*	26 Caucasian 16 African–American 1 Hispanic *1 self-reporting as Cauc and AA
Handedness	38 right 4 left 2 unreported
Education	3 (7%) did not complete high school/GED 3 (7%) completed high school or GED 16 (36%) partial college/currently enrolled 2 (5%) graduated from 2 year college 6 (14%) graduated from 4 year college 9 (20%) enrolled in graduate/professional 5 (11%) had graduate/professional degree

2.2.1. Neuropsychological assessment

Neuropsychological assessment was performed in a private, quiet room by a graduate student (TKR) with training and oversight by a board-certified clinical neuropsychologist (JKF). The following assessments were administered as per standardized instruction: LaFayette Grooved Pegboard test, Halstead-Reitan Finger-Tapping Test, Judgment of Line Orientation Task, Rey-Osterrieth Complex Figure test (Copy condition); Test of Everyday Attention subtests 1–5; Digit Span (WAIS-IV); Spatial Span (WMS-III); Boston Naming Test; D-KEFS Verbal Fluency; Verbal Paired Associates Task (WMS-IV); California Verbal Learning Test; Brief Visuospatial Memory Test-Revised (BVMT-R); D-KEFS Tower Test; D-KEFS Color-Word Test; D-KEFS Trails Test; D-KEFS Proverbs Test; Booklet Category Test, and Wisconsin Card Sorting Task (PAR WCST:CV4). Scoring was conducted per standardized instructions for each test. Although these tests have normative scores by age and education, normative scores do not exist for rs-fMRI data; consequently, all analyses used raw test scores with age and education as covariates.

2.2.2. Image acquisition

Imaging data were acquired using a Philips 3T Achieva X-series MRI scanner (Philips Healthcare, Eindhoven, The Netherlands). Anatomic images were acquired with a MPRAGE sequence (matrix = 256 × 256, 220 sagittal slices of 1 mm thickness, TR/TE/FA = shortest/shortest/8°, final resolution = 1 × 0.94 × 0.94 mm^3 resolution). Functional images for early participants (001–050) were acquired using an 8-channel head coil with an echo planar imaging (EPI) sequence (TR/TE/FA = 2000 ms/30 ms/90°, FOV = 240 × 240 mm, matrix = 80 × 80, 37 oblique slices parallel to orbitofrontal cortex to reduce sinus artifact, interleaved ascending slice acquisition, slice thickness = 4 mm, final resolution 3.0 × 3.0 × 4.0 mm^3). For these subjects, one session's resting-state scan was acquired with 3-mm slice thickness to be consistent with data acquired for other BIRC studies. Functional images for later participants (051+) were acquired using a 32-channel head coil with the following EPI sequence parameters: TR/TE/FA = 2000 ms/30 ms/90°, FOV = 240 × 240 mm, matrix = 80 × 80, 37 oblique slices, ascending sequential slice acquisition, slice thickness = 2.5 mm with 0.5 mm gap, final resolution 3.0 × 3.0 × 3.0 mm^3. Parameters for the 32-channel coil were selected to reduce orbitofrontal signal loss due to sinus artifact. We have previously shown that coil type (8- or 32-channel) did not significantly influence the relationship between brain activity and performance (Gess et al., 2014), so did not model coil type as a covariate in these analyses.

2.2.3. Identifying ROIs

Using previously published methods (Craddock, James, Holtzheimer, Hu, & Mayberg, 2012), we generated a 200 region-of-interest (ROI) atlas via functional parcellation of all fMRI data (task and rest) acquired from the Cognitive Connectome project (James, Hazaroglu, & Bush, 2016). Functional parcellation is an approach for identifying *nodes* or *clusters* of spatially contiguous voxels that represent functionally independent brain regions.