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Underlying sources of cognitive-anatomical variation in multi-modal neuroimaging and cognitive testing

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ABSTRACT

Healthy adults have robust individual differences in neuroanatomy and cognitive ability not captured by demographics or gross morphology (Luders, Narr, Thompson, & Toga, 2009). We used a hierarchical independent component analysis (hICA) to create novel characterizations of individual differences in our participants ($N = 190$). These components fused data across multiple cognitive tests and neuroanatomical variables. The first level contained four independent, underlying sources of phenotypic variance that predominately modeled broad relationships within types of data (e.g., "white matter," or "subcortical gray matter"), but were not reflective of traditional individual difference measures such as sex, age, or intracranial volume. After accounting for the novel individual difference measures, a second level analysis identified two underlying sources of phenotypic variation. One of these made strong, joint contributions to both the anatomical structures associated with the core fronto-parietal "rich club" network (van den Heuvel & Sporns, 2011), and to cognitive factors. These findings suggest that a hierarchical, data-driven approach is able to identify underlying sources of individual difference that contribute to cognitive-anatomical variation in healthy young adults.

Introduction

Every brain is unique. These differences in brain structure and physiology contribute to the stunning diversity of human thought and identity. Magnetic resonance imaging (MRI) scanning and post-processing techniques provide a new window on individual differences, characterizing volume, cortical thickness, and white-matter integrity. Further, these techniques categorize the massively multivariate raw MRI images into a set of robust and meaningful summary variables tied to brain health or function rather than performance on a specific task.

Extensive literature focuses on the complex network of interactions between sex, age, cognitive factors, brain size and shape, gray matter, education, fitness, and a host of other variables (Gray et al., 2003; Rypma and Prabhakaran, 2009; Goh et al., 2011). One way to approach this complex series of interactions is as a source separation problem: the many manifest variables are a phenotype produced by mixing of smaller number of underlying sources of variation. Identifying the underlying sources could help discover and differentiate anatomical brain phenotypes. Building a model of these sources would allow us to better control for individual variation and to identify how brain measures cluster at multiple levels of specificity.

However, finding joint contributions to anatomical and cognitive variables in MRI image sets has been challenging, especially in healthy young adults (Haier et al., 2004; Luders et al., 2009; McDaniel, 2005; Wickett et al., 2000). Such relationships are often limited to broad morphological effects such as a correlation between brain size and fluid intelligence (gf; McDaniel, 2005), or are characterized more in special populations with greater individual brain variation such as in older adults (Goh et al., 2011).

Yet lesion studies robustly link cognitive factors to anatomy (Allen et al., 2006; Barbey et al., 2012; Barbey et al., 2014), as do functional and resting state imaging (Buckner et al., 2008; Von den Heuvel and Sporns, 2011; Wang et al., 2013). Specific anatomical hypotheses

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developed from such data, the parieto-frontal integration theory (PFIT), maps high-level cognitive factors such as fluid intelligence to a network of superior parietal and frontal regions that integrate multiple sources of information in service of a goal (Jung and Haier, 2007). A parallel framework maps these functions to a highly functionally interconnected "rich club" of fronto-parietal regions (Van den Heuvel and Sporns, 2011). Why aren't these sources readily apparent as variation in individual anatomical data?

There are converging reasons that joint sources of cognitive and anatomical variation could be difficult to identify. Anatomical scans lack the robust time-series data of functional scans, and thus cognitive-anatomical relationships require larger sample sizes to assess effects. Additionally, the hypothesized fluid intelligence network is distributed across multiple anatomical regions and tissue types (e.g., gray vs. white matter) best assessed by different imaging methods (e.g., T1 weighted scans v. diffusion tensor imaging). Thus, the common variation associated with these functional networks is likely distributed throughout multiple regions and imaging modalities and might not pass statistical thresholds in any single region, let alone across all regions of the entire network. Finally, there might be different relationships between anatomy and cognitive factors at different levels of analysis: with strong, low-level sources of anatomical variability obscuring more subtle signals tying cognitive functions to anatomical networks.

In the current paper, we employ a hierarchical independent component analysis (hICA) to fuse 124 measures of phenotypic variance across cognitive, neuroanatomical, and demographic values assessed in 190 healthy adults. Similar approaches have been used before to fuse functional data (Groves et al., 2011; Laird et al., 2011; Smith et al., 2009; Sui et al., 2011, 2012). We compare variation across four types of MRI-assessed individual difference measures (cortical and subcortical volumes, cortical thickness, white-matter integrity), and a battery of demographic, fitness, and cognitive measures. This first-level ICA serves to identify sources of phenotypic variation that make joint contributions to multiple cognitive factors and multiple regions and types of brain anatomy. We then regress these first-level components from our data and perform ICA on the residual correlations in our data, to produce second-level components that describe additional sources of cognitive-anatomical variation, but were not well captured in the first-level analysis.

By examining the anatomical maps of these independent sources of variation, and exploring their relationships with specific cognitive factors, we hope to better characterize underlying sources of variation that jointly contribute to anatomical and cognitive variations across multiple levels. As a test-case, we also examine how these high-level factors relate to PFIT "rich club" network hypothesized to be related to general intelligence including higher cognitive functions such as fluid intelligence (Colom et al., 2009; Jung and Haier, 2007).

Methods

Sample

Participants were recruited from East-Central Illinois for the INSIGHT ("An integrative system for enhancing fluid intelligence through human cognitive activity, fitness, brain stimulation, and nutritional intervention") study. All participants received a battery of 12 cognitive tests and a fitness assessment. Half of these individuals received an additional battery of anatomical and functional MRI scans. Excluding individuals with incomplete data, our total sample is 518 individuals (239 females, mean age: 24.3 years) with cognitive and fitness assessments, of whom 190 had complete imaging data (i.e., we excluded any individual missing any of the measures assessed by our analysis). The independent component analyses presented here include only this imaging sub-set of the total sample.

To confirm that this sample was representative of the larger dataset from which the factor scores were computed we performed a one-way ANOVA (imaging group v. full sample) and found no significant between-group differences on age, sex, education or any of the four cognitive factors (d.f. = 2515, all F values between 0 and 2.1, all $p > .12$).

Demographics

The 190 participants consisted of 85 females, and 105 males. The age range in our sample was 18–44 years, with a median of 22 years, and a mean of 24.3 years. The mean educational level of the participants was "some college" (i.e., median score 3, mean score 3.6) as reported on a scale from 1 to 5, where 1 denoted "less than a high school diploma", 2 denoted "high school diploma or equivalent", 3 denoted "some college", 4 denoted "college degree", and 5 denoted "post-graduate education." (See Table 1)

Aerobic fitness assessment

Cardiovascular fitness has previously been shown to have important contributions to neural health and cognitive function (Kramer et al., 2001, 2005). Maximal oxygen consumption (VO_{2max}) was measured using a computerized indirect calorimetry system (ParvoMedics True Max 2400) and a modified Balke protocol (American College of Sports Medicine. ACSM's Guidelines for Exercise Testing and Prescription, 2014) with averages for oxygen uptake (VO_2) and respiratory exchange ratio (RER) assessed every 20 s. Participants ran on a motor-driven treadmill at a constant speed, with 2.0% increases in grade every 2 min until volitional exhaustion. The raw value was adjusted for body size, age, and gender to produce a VO_{2max} percentile score.

Cognitive tests and factor scores

Participants received a battery of 12, standardized cognitive tests designed to estimate underlying latent variables corresponding to cognitive constructs (see Table 2). The four latent variables of interest were fluid intelligence (gf), working memory (wm), executive function (ef), and episodic memory (em).

Procedures for these tests are described in detail in the associated citations. Brief descriptions are as follows: The BOMAT is an untimed, thirty-item matrix-reasoning test. Number series involves generating the next element in a string of numbers related by a common function. In letter sets, participants pick which of five sets of four letters differs from the others. Reading, rotation, and symmetry span are all complex span tasks, involving holding items in working memory while processing intervening distractors. The target items are words, arrows of different lengths and angles, and the locations of elements in a grid. Garavan involves keeping track of multiple internal counts, and measures errors in counts and the cost of switching between them. Keep track involves viewing an array of categories, and then identifying and remembering words belonging to those categories. Stroop involves identifying the color a word is printed in while inhibiting reading of the word. All three episodic memory tasks involve timed study of a list of words, pictures, or paired associates (respectively), and are scored by the number of items a participant can produce immediately after study.

Using a structural equation modeling approach (Kane et al., 2004), across the larger sample of 518 participants, we extracted estimates of the four cognitive construct latent variables (i.e., gf, wm, ef, em).

Table 1
Demographics.

	Imaging sample (N = 190)	Full sample (N = 518)
% Female	45%	50%
Mean age (std)	24.3 (6.6)	24.3 (6.0)
Mean education (std)	3.5 (0.9)	3.5 (0.8)