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General cognitive ability and fluctuating asymmetry of brain surface area

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ABSTRACT

The developmental roots of individual variation in general cognitive ability (GCA) are the subject of intense scientific interest. One unique perspective is offered by developmental instability theory, which suggests that variation in GCA in part reflects the ability to buffer brain development from key environmental and genetic perturbations. Support for this approach comes mainly from assessment of fluctuating asymmetry, or deviations from symmetry of body features that are symmetric at the population level. In this study of healthy young adults (N = 244) we assessed fluctuating asymmetry (FA) of total cortical surface area (CSFA) from 33 regions using automated analysis. Overall CSFA was negatively related to GCA, consistent with meta-analytic results from body FA studies. A correlated vectors analysis indicated that the CSFA-cognition relationship varied systematically with a test's *g* loading. Further, FA of frontoparietal regions was a significant predictor of GCA, but FA non-frontoparietal regions was not, consistent with the Parieto-Frontal Integration Theory (P-FIT) model of intelligence. Frontoparietal FA was less than non-frontoparietal FA, i.e., consistent with the hypothesis that regions linked with GCA are better buffered from perturbation, perhaps a reflection of the importance of GCA for important life outcomes.

Individual variation in general cognitive ability (GCA) matters greatly for many life outcomes, including educational and occupational success as well as vulnerability to a host of neurodevelopmental disorders. Though clearly heritable, specific genetic influences on GCA have proven extremely difficult to identify, most likely a reflection of very small effect sizes from a very large number of genetic features (Davies et al., 2015). Similarly, non-genetic sources of variation are universally acknowledged, but there is great debate about the specific nature of such effects and their developmental windows (Plomin & Deary, 2014). Most common genetic and environmental influences probably have their maximal effect quite early in development (von Ehrenstein, Mikolajczyk, & Zhang, 2009), consistent with the strikingly high correlations between GCA at age 7 and age 81 (Gow et al., 2011). A novel approach to understanding such early influences, attempting to integrate both genetic and environmental perturbations, has emphasized the constructs of "developmental instability" and "canalization" (Yeo, Gangestad, & Thoma, 2007).

The roots of developmental instability (DI) theory lie in Waddington's writings about canalization, the ability of an individual to produce the same phenotype despite variation in its environment or genotype (Waddington, 1957; Waddington, 1942). Natural selection generally favors organisms capable of buffering the impact of "noise" on an organism's observable characteristics—that is, its phenotype. Contemporary biometric perspectives suggest that individual variation in canalization is best understood in the context of genotype-by-environment and/or genotype-by-genotype interactions (McGrath, Hannan, & Gibson, 2011). DI refers to "the inability of a developing organism to buffer its development against random perturbations, due either to frequent, large perturbations (e.g., frequent illness, many deleterious mutations, significant oxidative stress) or to a poor buffering system (e.g., a poorly co-adapted genome)" (p. 380, Van Dongen & Gangestad, 2011). At least two different kinds of factors can impact fidelity in development – the magnitude of the perturbations (including sickness and mutations) and the strength of buffering systems. Substantial research supports the existence of a general, cross-stressor buffering system, supplemented by local, stressor-specific buffering systems (Gangestad, Bennett, & Thornhill, 2001; Gibson, 2009; Van Dongen & Gangestad, 2011). Thus, the nature and extent of developmental imprecision is

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not entirely unique for each type of perturbation confronting the organism. Rather, developmental precision also depends in part on a genetically regulated, cross-trait capacity to deal effectively with misfortune's slings and arrows.

The most commonly used marker of DI across species is fluctuating anatomic asymmetry (FA) (Gangestad & Thornhill, 1999). Fluctuating asymmetry refers to random deviations in the symmetry of bilateral features that are, on average, symmetric at the population level. The underlying logic of using FA as a measure of DI is that the two sides of a bilateral feature represent independent replicates of the same developmental event. Anatomic differences between left and right body sides thus reflect minor developmental "errors" or perturbations affecting one side of the body and not the other. FA decreases between 4 and 15 in healthy children, suggesting an "active developmental process" (Hope, Bates, Dykiert, Der, & Deary, 2013).

Several prior studies have now demonstrated that an aggregate score reflecting greater overall fluctuating asymmetry of body features is associated with lower GCA, but the effect size is small. One meta-analyses revealed an overall correlation of $r = -.16$ (Banks, Batchelor, & McDaniel, 2010). However, the ability of FA measures to tap the underlying construct of DI is limited by the modest relationship between the observed, aggregate FA score and the underlying trait of DI (Gangestad et al., 2001). This indicates that the true relationships between DI and other phenotypes are substantially underestimated by the obtained correlations using FA (Van Dongen & Gangestad, 2011). We have previously reported that the FA-cognition relationship appears stronger for general cognitive ability (GCA or "g") than for specific cognitive abilities (Prokosch, Yeo, & Miller, 2005). Additional studies have recently shown a relationship between FA and choice reaction time, which is highly correlated with GCA, in both children (Hope, Bates, Der, & Deary, 2015) and older adults (Penke et al., 2009). Diverse neurodevelopmental disorders are also characterized by both reduced GCA and greater FA (Yeo & Gangestad, 2015).

Prior studies of the FA-GCA relationship have derived FA measures from various external body features, especially the head and hands (e.g., Bates, 2007; Furlow, Armijo-Prewitt, Gangestad, & Thornhill, 1997; Prokosch et al., 2005). In this report we calculated FA from many cortical brain regions identified through the automated neuroanatomic analysis provided by Freesurfer (Fischl et al., 2004) in a large sample of healthy young adults. Recent studies have demonstrated that the two constituents of cortical volumes, regional surface area and cortical thickness, have different genetic influences (Panizzon et al., 2009) and developmental trajectories (Lyall et al., 2015; Schnack et al., 2015). The greater volume of the human brain as compared to other primates reflects increased surface area far more than increased cortical thickness (Hill et al., 2010). Especially relevant for this study is evidence that surface area is correlated with cognition (Vuoksimaa et al., 2015) and contributes more to anatomic volume asymmetries (Koelkebeck et al., 2014) than does cortical thickness. Additionally, less cortical surface area, rather than reduced thickness, is associated with lower brain volume (Kong et al., 2015) and increased clinical severity in schizophrenia (Xiao et al., 2013). So, rather than basing FA measures on regional cortical volumes or cortical thickness, we focused on surface areas. As is the case for FA of body characteristics, diverse biological processes likely contribute to lateral variation in size. Increases in the number of rounds of neural stem cell division in the primordial ventricular zone may be especially relevant, as these lead to exponential increases in the founder cells giving rise to cortical columns (Rakic, 2009). In contrast, during subsequent development asymmetric division of neural progenitors leads to only linear increases in cell number per column.

Our primary goal in this study was to investigate the relationship between the brain's cortical surface area FA (CSFA) and GCA. We predict that greater overall cortical surface FA is associated with lower ability. A secondary goal was to determine if surface area FA predicts GCA better than it predicts more specific cognitive skills, as we found for measures of body FA (Prokosch et al., 2005). Finally, we predicted that a measure of surface area FA derived from frontoparietal cortex would predict GCA better than FA derived from other cortical regions, consistent with the Parieto-Frontal Integration Theory of intelligence (P-FIT; Jung & Haier, 2007; Vakhtin, Ryman, Flores, & Jung, 2014).

1. Methods

1.1. Participants

Two hundred and fifty-six participants, with no history of neurological or psychological disorder, were recruited for this study. All participants provided written informed consent before the collection of data and subsequent analysis. Twelve individuals (4.7%) were excluded from data analysis due to the low quality of their neuroimaging data (i.e. motion or image artifacts) or missing cognitive testing data, resulting in 242 participants in the final sample (224 right-handers, 12 ambidextrous, 6 left-handed). Participants were young adults (125 males, mean age = 21.84, range: 16–35, SD = 3.55; and 117 females, mean age = 21.72, range: 16–31, SD = 3.47). All participants expressed an interest in or were actively pursuing higher education or work within the science, technology, engineering, and math (STEM) fields, broadly defined using the 2012 revised list of USA degree programs (http://www.ice.gov/sites/default/files/documents/Document/2014/stem-list.pdf). Participants were recruited by postings in various departments and classrooms around the University of New Mexico. This study was conducted according to the principles expressed in the Declaration of Helsinki and was approved by the Institutional Review Board of the University of New Mexico.

1.2. Procedures

1.2.1. Cognitive assessment

Cognitive tasks included the Block Design, Similarities, and Matrix Reasoning subtests from the Wechsler Abbreviated Intelligence Scale II (WASI-II, (Wechsler, 2011)), and the Coding subtest From the Wechsler Adult Intelligence Scale - IV (WAIS IV, Wechsler, 2008). From the Johnson O'Conner Research Foundation (JCOF) battery we administered the Vocabulary and the Paper Folding subtests (Condon & Schroeder, 2003; Haier et al., 2009). Finally, the paper and pencil Mental Rotations Test (MRT) (Peters, Laeng, Latham, Azyyouna, & Richardson, 1995) was given to all participants. Using Principle Component Analysis (PCA) we calculated scores for all participants on the first component, providing an operational definition of GCA.

1.2.2. Neuroimaging

MRI data were acquired on a 3-Tesla Siemens Triotim MRI scanner located at the Mind Research Network in Albuquerque, New Mexico using a 32-channel head coil. The multiecho MPRAGE protocol was followed to obtain the T1 image: [TE 1.64/3.5/5.36/7.22/9.08 ms; TR 2530 ms; voxel size 1x1x1mm; 192 slices; Field of View = 256 mm; acquisition time 6.03].

The MPRAGE T1 image was used for all anatomical analyses. Methods for cortical reconstruction and volumetric segmentation were performed with the FreeSurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/) and are described in detail elsewhere (Fischl et al., 2004). Briefly, this process includes averaging of volumetric T1-weighted images, removal of non-brain tissue, automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures, intensity normalization, tessellation of the gray matter, white matter boundary, automated topology correction, and surface deformation following intensity gradients to optimally place the gray matter/white matter boundary and gray matter/cerebrospinal fluid borders (also known as the pial surface). Surface area and cortical thickness measurements were obtained by reconstructing representations of the gray matter/white matter

boundary and the pial surface. The results of Freesurfer's automatic segmentations were quality controlled and any errors were manually corrected. This Freesurfer parcellation yields thirty-three paired measures of surface area across the two hemispheres based on the Desikan-Killiany atlas.

1.2.3. Fluctuating asymmetry

Because brain regions commonly demonstrate *directional* asymmetry (i.e., one side is larger than the other at the population level), calculation of brain FA differs from that of symmetrical structures of the body. Using the entire sample, we first calculated the mean directional asymmetry, i.e., left minus right surface areas, for each of the 33 paired surface area measurements. To calculate individual FA values for the 33 pairs of measures, this mean directional asymmetry value was subtracted from the observed individual left–right differences. Then, the absolute value of this quantity was calculated, providing a non-directional measure of deviance from the sample-mean directional asymmetry. Next, we divided this quantity by the average of that individual's left and right side surface areas to ensure that each of the 33 FA contributed equally to the aggregate cortical surface CSFA score (as is typical for aggregate measures of FA based on body features). To obtain the overall CSFA score for each participant we simply averaged the 33 individual FA measures. To test hypotheses about the P-FIT model (Jung & Haier, 2007), we calculated frontoparietal FA by averaging individual measures from these nine paired regions: inferior parietal, superior parietal, supramarginal, caudal middle frontal, lateral orbital frontal, rostral middle frontal, frontal pole, medial orbital frontal, and superior frontal. Similarly, non-frontoparietal FA was calculated by averaging the FA values from all other regions. All analyses were conducted with SPSS v. 23.

Table 1
Cortical surface area fluctuating asymmetry (FA) means and standard deviations for the 33 Freesurfer-defined paired cortical regions. Regions are listed in order of mean FA. Correlations of each FA measure with general cognitive ability (GCA) are shown in the last column.

	Mean regional FA	Standard deviation	Correlation with GCA
Fronto-parietal regions			
Frontal pole	.039	.027	−.189**
Caudal middle frontal	.029	.022	−.147*
Fusiform	.017	.015	−.149*
Superior parietal	.017	.014	−.126
Inferior parietal	.019	.015	−.077
Medial orbitofrontal	.028	.018	−.043
Rostral middle frontal	.016	.013	−.010
Superior frontal	.013	.010	−.001
Supramarginal	.025	.018	.019
Lateral orbitofrontal	.015	.011	.057
Non-fronto-parietal regions			
Isthmus cingulate	.029	.021	.168**
Lingual	.018	.016	−.136*
Paracentral	.024	.018	−.092
Rostral anterior cingulate	.039	.033	−.086
Bank superior temporal sulcus	.031	.023	−.079
Postcentral	.017	.017	−.069
Posterior cingulate	.031	.021	−.063
Transverse temporal	.032	.022	−.058
Entorhinal	.046	.035	−.052
Pars triangularis	.033	.026	−.049
Pericalcarine	.018	.017	−.038
Insula	.017	.013	−.032
Parahippocampal	.022	.016	.007
Temporal pole	.031	.024	.008
Caudal anterior cingulate	.051	.036	.012
Cuneus	.020	.016	.022
Pars orbitalis	.028	.023	.034
Pars opercularis	.033	.026	.065
Inferior temporal	.021	.015	.067
Middle temporal	.017	.013	.030
Rostral middle frontal	.016	.013	−.010
Precentral	.016	.011	.014
Superior frontal	.013	.010	−.001
Precuneus	.013	.011	−.009
Superior temporal	.005	.014	−.064

* $p < .05$.
** $p < .01$.

2. Results

2.1. Descriptive statistics

We first computed simple directional asymmetries (left minus right) for each cortical region. To evaluate the extent and significance of directional asymmetries across these measures we conducted one-sample t-tests, comparing each asymmetry value to zero. Of the 33 variables, only six did not show significant directional asymmetries (superior parietal, fusiform, parahippocampal, posterior cingulate, lingual, and precentral gyri), while 25 were significantly asymmetric at $p < .001$. Each of the 33 FA measures was inspected for outliers using the SPSS v. 23 Explore procedure, which defines extreme outliers in a box-and-whisker plot as those more than three box lengths from the upper or lower quartiles. Of the 7986 FA scores (242 participants × 33 variables) 11 outliers (.14%) were detected. These values were replaced by the means for the sample. Table 1 ranks the 33 Freesurfer-defined paired brain regions by their FA value. These FA values were averaged to provide a measure of CSFA. No extreme outliers were found for this variable; see Supplementary Fig. 1 for the frequency distribution.

Mean values (and SDs) of all FA measures were: CSFA mean = .025 (.005), frontoparietal FA = .022 (.006), and non-frontoparietal FA = .025 (.005). Frontoparietal FA and non-frontoparietal FA were correlated $r = .224$ ($p < .001$). No FA variable was correlated with age (all p values > .44) and the sexes did not differ on any measure (all p values > .46).

Table 2 provides descriptive statistics for all cognitive tests. A Principal Components Analysis with direct oblimin rotation yielded three factors and the first PC accounted for 31.55% of total variance.

2.2. Fluctuating asymmetry and GCA

The correlation between CSFA and GCA was significant, $r = -.149$, $p = .02$ ($r = -.150$, $p = .02$, controlling for handedness). To investigate this relationship more fully, we conducted a GLM analysis with CSFA, sex, and the interaction of CSFA with sex, as predictors of GCA. Only the CSFA effect was significant ($F(1, 238) = 7.46$, $p = .007$, partial eta squared = .041). For comparison, the correlation between frontoparietal FA and GCA was $r = -.195$ ($p = .002$; see Fig. 1 for a scatterplot), whereas the correlation of non-frontoparietal FA and GCA was $r = -.088$ ($p = .171$). A follow-up GLM analysis included both frontoparietal FA and non-frontoparietal FA measures, sex, and both

Table 2
Descriptive statistics for cognitive tests.

Test	Source	Mean	SD
Block design (T score)	WASI II	56.29	8.30
Similarities (T score)	WASI II	58.76	9.54
Matrix reasoning (T score)	WASI II	54.04	8.01
Digit symbol (T score)	WAIS IV	54.56	8.72
Vocabulary (std. score)	JOCF	102.82	14.16
Paper folding (std. score)	JOCF	107.49	16.10
Inductive (std. score)	JOCF	92.48	13.40
Foresight (std. score)	JOCF	98.84	11.30
Mental rotations test (raw)	Peters et al., 1995	3.46	2.31

Note: WASI II = Wechsler Abbreviated Scale of Intelligence II, WAIS IV = Wechsler Adult Intelligence Scale IV, JOCF = Johnson O'Conner Foundation Battery.

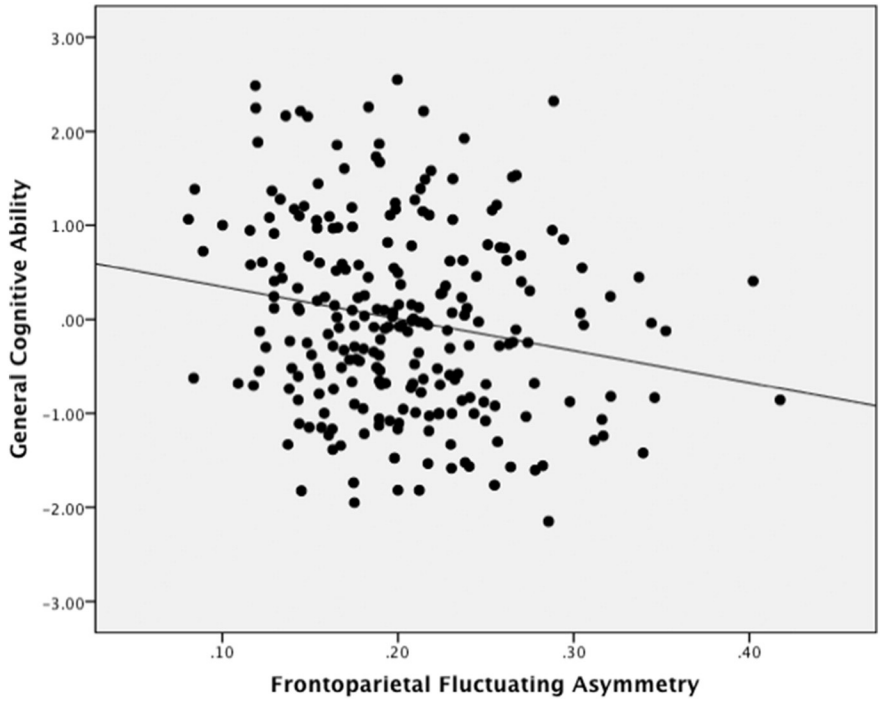

Fig. 1. Scatterplot of the relationship between frontoparietal surface area fluctuating asymmetry and general cognitive ability (GCA) ($r = -.195$, $p = .002$).

sex by FA interactions. Only the effect of frontoparietal FA was significant ($F(1, 235) = 10.06$, $p = .002$, partial eta squared $= .041$). There was a non-significant trend for an interaction between non-frontoparietal FA and sex ($F(1, 235) = 3.23$, $p = .074$).

2.3. Fluctuating asymmetry and g-loadings

To evaluate the hypothesis that the relationship between FA and cognition is proportional to a tests' *g* loading we performed a correlated vectors analysis. Cognitive tests were ranked by their loading on the first principal component as well as by the magnitude of that tests' correlation with CSFA. The correlation between these two rankings was significant with only nine data points ($r = -.71$, $r = .033$), indicating that the greater a tests' g-loading, the more negative the correlation with CSFA. The corresponding rank order correlation for frontoparietal FA was significant ($r = -.67$, $p = .049$), but the non-frontoparietal effect was not ($r = -.43$, ns).

2.4. Regional variation in FA

Given the importance of GCA for life outcomes, one might expect that those brain regions most important for GCA would be better

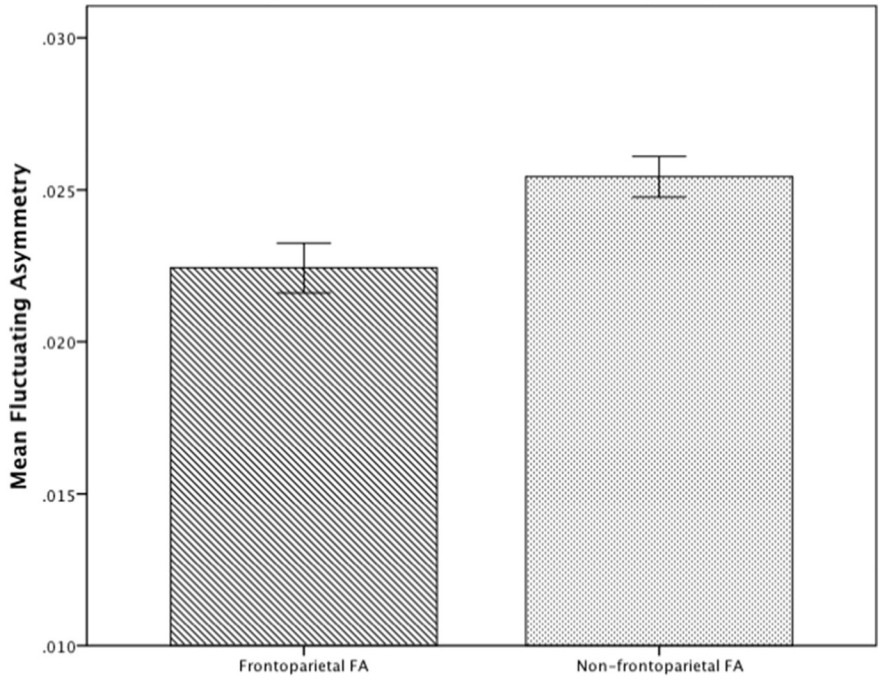

Fig. 2. Comparison of mean frontoparietal vs. non-frontoparietal fluctuating asymmetry measures. Error bars represent SEM.

buffered from perturbation than those unrelated to GCA. Thus, we conducted paired samples t-tests on frontoparietal FA and non-frontoparietal FA. Frontoparietal FA was less than non-frontoparietal FA ($t = -6.44$, $p < .001$). See Fig. 2.

2.5. Fluctuating asymmetry and brain size

To evaluate relationships between CSFA and measures of brain size (total brain volume, cortical volume, frontoparietal cortical volume, cortical surface area, average cortical thickness) we obtained partial correlations controlling for sex. None approached significance (all p values > .32).

3. Discussion

The current results provide additional evidence that individual variation in developmental stability contributes to GCA. To our knowledge, this sample is the largest ever studied for an investigation of FA-cognition relationships, and we relied upon a set of unique anatomic variables to define an aggregate measure of FA – cortical surface area measurements. With these FA variables we were also able to evaluate the importance of developmental instability of frontoparietal vs. non-frontoparietal surface area, and in doing so, provide unique support for the cortical component of the P-FIT model (Jung & Haier, 2007). Note, though, that the P-FIT model also specifies important white matter and subcortical structures not assessed in this study (Basten, Hilger, & Fiebach, 2015). Consistent with the importance of GCA for mating and other life outcomes, the frontoparietal substrates for GCA appear to be better buffered from perturbation than other cortical regions. That is, the regions most important for GCA demonstrate relatively greater canalization, perhaps because of the fitness costs associated with reduced GCA and its many health-related correlates. However, greater buffering (i.e., capacitance) also allows the accumulation of cryptic genetic variance, which can contribute to neurodevelopmental variation under certain circumstances and also limit the capacity to respond to selection (Gibson & Wagner, 2000).

It is important to note that our effect sizes were quite modest, consistent with prior meta-analyses (Banks et al., 2010; Van Dongen & Gangestad, 2011). However, because FA measures imperfectly tap the latent variable of interest (that is, DI), the FA-GCA effect size underestimates the DI-GCA effect size (Gangestad et al., 2001). In studies based on a limited set of body features, Van Dongen and Gangestad (2011) demonstrated that the latent DI effect sizes could be estimated by doubling the obtained FA effect size. However, the psychometric characteristics of our brain-based FA measures may differ from those based on body measures.

The neural mechanisms underlying the GCA-FA relationship are not well understood. However, it now seems clear that the relationship is not mediated by measures of brain size. We found no relationships between any measure of brain size (e.g., surface area, cortical volume) and CSFA. These results are consistent with our prior, much smaller study (Thoma et al., 2005). Future studies may attempt to link CSFA with more proximate mechanisms causally related to individual variation in GCA. In our recent work, for example, we have emphasized the possible importance of global network features such as efficiency, connectivity, and characteristic path length (Yeo et al., 2016), and also neurophysiological responses to novel stimuli (Euler, Weisend, Jung, Thoma, & Yeo, 2015). At a more cognitive level of analysis, these global brain features may confer greater processing speed and complex reaction time, which in turn contributes greatly to GCA (Hope et al., 2015; Penke et al., 2009; Thoma et al., 2006). However, the current results most clearly draw attention to frontal and parietal functioning, consistent with growing evidence from structural and functional neuroimaging (e.g., Basten et al., 2015) for the P-FIT model of intelligence (Jung & Haier, 2007).

The association of GCA with FA, the primary marker of developmental instability, may contribute to the longstanding discussion of the role of intelligence in mate selection. A potential mate with relatively greater GCA might be a mate with better health (e.g., Wraw, Deary, Gale, & Der, 2015), due to greater resilience to environmental and genetic threats to development. This might be one benefit (among many) from mating with an individual high in GCA. We do not know if this possible benefit would be passed on to offspring. However, there is a great deal of evidence demonstrating genetically-mediated correlations of GCA with health (e.g., Luciano et al., 2010) and mortality (Arden et al., 2015). Additionally, the association of lower DI with greater GCA may help account for several important correlates of greater GCA, including a reduced risk of neurodevelopmental disorders (Yeo & Gangestad, 2015), PTSD (Gilbertson et al., 2006) and Alzheimer's Disease (Yeo, Arden, & Jung, 2011), and as well, better buffering from the consequences of traumatic brain injury (Yeo, Gasparovic, Merideth, Ruhl, Doezema and Mayer, 2011), HIV infection (Foley et al., 2012), and hepatitis C infection (Sakamoto et al., 2013). Network analysis based on graph theory also demonstrate that brains of more intelligent individuals are more resistant to insults (Santarnecchi, Rossi, & Rossi, 2015).

An impediment to prior FA research has been the rather laborious and sometimes unreliable methods needed to evaluate very small differences in the physical size of bilateral characters (e.g., ear width). The current, automated methods may be applied to many existing neuroimaging data sets to evaluate CSFA. For example, an etiological role for developmental instability has been suggested for schizophrenia (Yeo, Gangestad, Edgar, & Thoma, 1999) and large imaging data sets with rich genetic data have been established (e.g., Gollub et al., 2013). CSFA may be a relevant endophenotype for schizophrenia, and its genetic underpinnings could be readily evaluated. More generally, the rank order of cortical regions established here identifies which brain regions may be best buffered from perturbation, both genetic and environmental. We hypothesize that diverse perturbations, both genetic and environmental, will have effects on cortical regions in proportion to their observed CSFA.

There are several important limitations to consider in interpreting these results. As compared to the general population, our sample was above average in GCA and characterized by a modest restriction in range. Participants were also specifically interested in STEM fields; we do not know if results generalize to other samples. Also, we did not obtain body FA data, so we cannot directly relate the current results to prior studies. Further, the individual CSFA measurements were made on bilateral structures that are generally not symmetric, in contrast to prior FA studies, requiring a different FA calculation. Nonetheless, the magnitude of the correlations obtained are entirely consistent with the results of meta-analyses based on body FA studies (Banks et al., 2010).

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.intell.2016.03.002.

Competing interests

We have no competing interests.

Author contributions

RAY designed the study, performed analyses, and helped draft the manuscript. SGR, JP, RJT, and REJ helped draft the manuscript, and REJ supervised all data collection.

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