Fronto-Parietal Gray Matter and White Matter Efficiency Differentially Predict Intelligence in Males and Females

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Abstract: While there are minimal sex differences in overall intelligence, males, on average, have larger total brain volume and corresponding regional brain volumes compared to females, measures that are consistently related to intelligence. Limited research has examined which other brain characteristics may differentially contribute to intelligence in females to facilitate equal performance on intelligence measures. Recent reports of sex differences in the neural characteristics of the brain further highlight the need to differentiate how the structural neural characteristics relate to intellectual ability in males and females. The current study utilized a graph network approach in conjunction with structural equation modeling to examine potential sex differences in the relationship between white matter efficiency, fronto-parietal gray matter volume, and general cognitive ability (GCA). Participants were healthy adults ($n = 244$) who completed a battery of cognitive testing and underwent structural neuroimaging. Results indicated that in males, a latent factor of fronto-parietal gray matter was significantly related to GCA when controlling for total gray matter volume. In females, white matter efficiency and total gray matter volume were significantly related to GCA, with no specificity of the fronto-parietal gray matter factor over and above total gray matter volume. This work highlights that different neural characteristics across males and females may contribute to performance on intelligence measures. *Hum Brain Mapp 00:000–000, 2016*.

Key words: intelligence; efficiency; fronto-parietal gray matter; sex differences

INTRODUCTION

Intelligence is the single best predictor of outcomes across a wide range of life domains, including socioeconomic status (e.g., education, occupation, income, incarceration) [Gottfredson, 2002] and health [Deary et al., 2012]. It is well established that measures of intelligence are consistently related to total [McDaniel, 2005; Pietschnig et al., 2015; Ritchie et al., 2015] and regional brain volume within

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the frontal and parietal regions [Basten et al., 2015; Jung and Haier, 2007] as well as efficiency of white matter organization [Li et al., 2009]. It is unclear, however, why minimal sex differences in overall intelligence exist, despite the fact that women have significantly smaller brains on average [Cosgrove et al., 2007; Leonard et al., 2008]. Sex differences in the relationship between intelligence and regional gray matter volume [Gur et al., 1999; Haier et al., 2005], white matter microstructure [Dunst et al., 2014], and neurochemical concentrations [Jung et al., 2005] have been examined independently. However, no single study has examined the relative contributions of white matter efficiency and frontal and parietal gray matter to intelligence in males and females.

Examination of neural differences across sex highlights several structural [Giedd et al., 2012; Luders and Toga, 2010; Ruigrok et al., 2014] and organizational [Ingalhalikar et al., 2014] differences between males and females. Males, on average, have larger total brain volumes (TBV) and corresponding white matter and gray matter volumes [Leonard et al., 2008; Ruigrok et al., 2014] and a larger white matter to gray matter ratio (WM:GM) [Cosgrove et al., 2007]. Additionally, there are differences in the white matter volume and cytological features in males and females quantified by measures of fractional anisotropy (FA), the coherence of white matter diffusion and fiber density [Good et al., 2001; Hsu et al., 2008; Luders and Toga, 2010]. Interestingly, when examining the white matter structural organization through the use of graph theoretical approaches [Bullmore and Sporns, 2009], both males and females exhibit small world properties, indicating a beneficial tradeoff between local and global connectivity [Iturria-Medina et al., 2008], but differ in other organizational properties [Gong et al., 2011]. Females demonstrate greater local and global efficiency [Gong et al., 2009; Yan et al., 2011] as well as between-hemisphere connectivity, whereas males demonstrate greater modularity and within-hemisphere connectivity [Ingalhalikar et al., 2014]. Of note, these quantifications of efficiency correspond solely to white matter organization [Rubinov and Sporns, 2010], not functional efficiency that has been examined extensively within the field of intelligence research [Neubauer and Fink, 2009; Neubauer et al., 2002, 2005]. These sex differences in white matter efficiency suggest that greater global efficiency among females may be a relevant brain characteristic enabling females to perform similarly to males on intelligence tests.

Despite the diverse and consistent sex differences in brain structure [Luders and Toga, 2010; Ruigrok et al., 2014], few neuroimaging studies have examined sex differences in the relationship between brain structure and intelligence taking a multimodal approach. Structural neuroimaging studies examining general intelligence indicate that more intelligent females exhibit stronger brain–behavior relationships with white matter volume [Gur et al., 1999; Haier et al., 2005] and spectroscopic *N*-acetylaspartate in both the gray [Pfleiderer et al., 2004] and white matter [Jung et al., 2005]. More intelligent males, however, exhibit more extensive regional gray matter relationships with intelligence, primarily within frontal and parietal lobes [Haier et al., 2005]. There have been inconsistent results examining sex differences in the relationship between FA and intelligence, with males exhibiting a positive relationship between FA and intelligence within the anterior corpus callosum [Dunst et al., 2014], whereas females exhibited positive relationships between intelligence and FA in the posterior corpus callosum [Tang et al., 2010] and other regions within the frontal and parietal lobes [Schmithorst, 2009]. In sum, there is evidence that intelligent males exhibit brain–behavior relationships predominantly within gray matter and TBV, whereas females, possibly exhibit such relationships with the GM:WM ratio and white matter volume. To date, no study has examined whether white matter organizational characteristics (e.g., efficiency) contribute to equal performance on general intelligence measures among males and females.

To address this question, the current study utilizes structural equation modeling (SEM) in conjunction with a graph theoretical approach. Rather than utilizing voxel-based morphometry, as has been done previously, we constructed a fronto-parietal gray matter factor of the a priori regions implicated in intelligence [Jung and Haier, 2007]. Previous reports have found that there is covariation across gray matter regions with similar behavioral or cognitive function [Alexander-Bloch et al., 2013a,2013b].Limited research has examined whether the fronto-parietal regions implicated in intelligence exhibit such covariance across gray matter regions, and whether this covariance relates to performance on intelligence measures. Thus, we examine the relationships between a fronto-parietal gray matter factor, white matter efficiency, and a factor of general cognitive ability (GCA). Furthermore, we examine whether these relationships differ in males and females, as well as the specificity of these results.

MATERIALS AND METHODS

Participants

Two hundred and fifty-six participants, with no history of neurological or psychological disorders, participated in the study. 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. All participants provided written informed consent before the collection of data and subsequent analysis. Twelve individuals 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 (described below), resulting in 244 human participants in the final sample. All participants had an interest in or were actively pursuing higher education or work within the science, technology, engineering, and

math fields. Participants were recruited by postings in various departments and classrooms around the University of New Mexico.

Cognitive Measures

To assess GCA, subtests of the Wechsler Abbreviated Scale of Intelligence-II (WASI-II) were used. Block Design (BD), Matrix Reasoning (MR), and Similarities (SM) were administered. Additionally, a Vocabulary (VC) test from the Johnson O'Connor Research Foundation was used. The Johnson O'Connor tests have been recently used as measures of individual differences in several neuroimaging studies [Haier et al., 2009; Jung et al., 2014]. VC (reliability = 0.96) measures participants' knowledge of English words by asking participants to choose, from one of four possible choices, which word is closest in meaning to the target word. Lastly, Coding (CD) from the Wechsler Adult Intelligence Scale-IV (WAIS-IV) was also administered as a measure of processing speed.

Image Acquisition

MRI data were acquired on a 3-Tesla Siemens Trio 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 2,530 ms; voxel size 1 × 1 × 1 mm; 192 slices; Field of View = 256 mm; acquisition time 6.03). For the diffusion weighted imaging (DWI) data echo planar imaging was acquired: (TE 110 ms; TR 3,600 ms; voxel size 2.2 × 2.2 × 2.2 mm^3; 66 slices; Field of View = 229 mm; 150 diffusion directions with $b = 1{,}000$–$3{,}000$ s/mm^2, and 6 measurements with $b = 0$, acquisition time 9:36).

Data Processing

Processing of the DWI data was conducted as described elsewhere [de Reus and van den Heuvel, 2014; Ryman et al., 2014; van den Heuvel and Sporns, 2011]. The signal drop-outs caused by large or abrupt motion were identified and removed by a custom in-house program written in IDL (http://www.exelisvis.com). The smaller and gradual motion through the scan and the eddy current induced distortions, were corrected with an affine transform and mutual information cost index. Participants with greater than 10% of the volumes removed were not included because of the possible bias in their calculated diffusion parameters. Seven of the 256 participants were removed by these criteria. The motion sensitivity of each participant was characterized by the mean frame-displacement index calculated from the six $b = 0$ images, which are interleaved through the scan. Individuals with greater than three standard deviations above the mean were removed. Five subjects were removed by this criteria, resulting in a final sample of 244.

Streamline tractography (fiber assignment by continuous tracking) was used to reconstruct white matter pathways [Mori and van Zijl, 2002]. Within each voxel in the brain mask, eight seeds were started, evenly distributed over the volume of the voxel. Streamlines followed the preferred diffusion direction until the fiber track reached a voxel with a FA value <0.1, the fiber trajectory left the brain mask, or until the fiber track made a sharp turn of more than 45°. As larger brain sizes result in a greater number of voxels, and therefore a greater number of seeds, after connectivity matrices were constructed (described below), they are normalized such that the maximum edge weight becomes 1.

The MPRAGE T1 images were used for anatomical references and for the selection of the nodes of the brain network. Freesurfer was used to classify the gray and white matter of the brain as well as automatically segment the subcortical structures and parcellate the reconstructed cortical surface, resulting in 82 distinct cortical and subcortical brain regions (v5.3.0) [Fischl et al., 2004]. These regions were then used to represent the nodes of the individual brain networks. Additionally, TBV and gray matter volumes of the regions within the frontal and parietal regions relevant to our hypotheses were extracted to use in statistical models.

Connectome Reconstruction

Connectome reconstruction included the following steps, described in detail elsewhere [de Reus and van den Heuvel, 2014; Ryman et al., 2014; van den Heuvel et al., 2012]. First, individual brain networks were modeled on the basis of the set of reconstructed fiber tracts combined with the segmented brain regions [Hagmann et al., 2008; van den Heuvel et al., 2010]. For each participant, the brain network was mathematically described as a graph $G = (V,E)$ consisting of the set of 82 brain parcels (nodes, V) and a set of connections describing the number of streamlines between the nodes (edges, E). The number of streamlines between i and j was taken as the connectivity strength between nodes i and j in the network and included in the connectivity matrix. Edges comprising fewer than 10 streamlines were considered potentially spurious and were deleted from the connection matrix [Hagmann et al., 2008]. The connectivity and distance matrices were normalized within each participant by dividing the matrix by the maximum weight of the matrix, resulting in values between 0 and 1.

Graph Metrics

Statistical analyses

All of the models, described below, were fit to the variance-covariance matrix using maximum likelihood

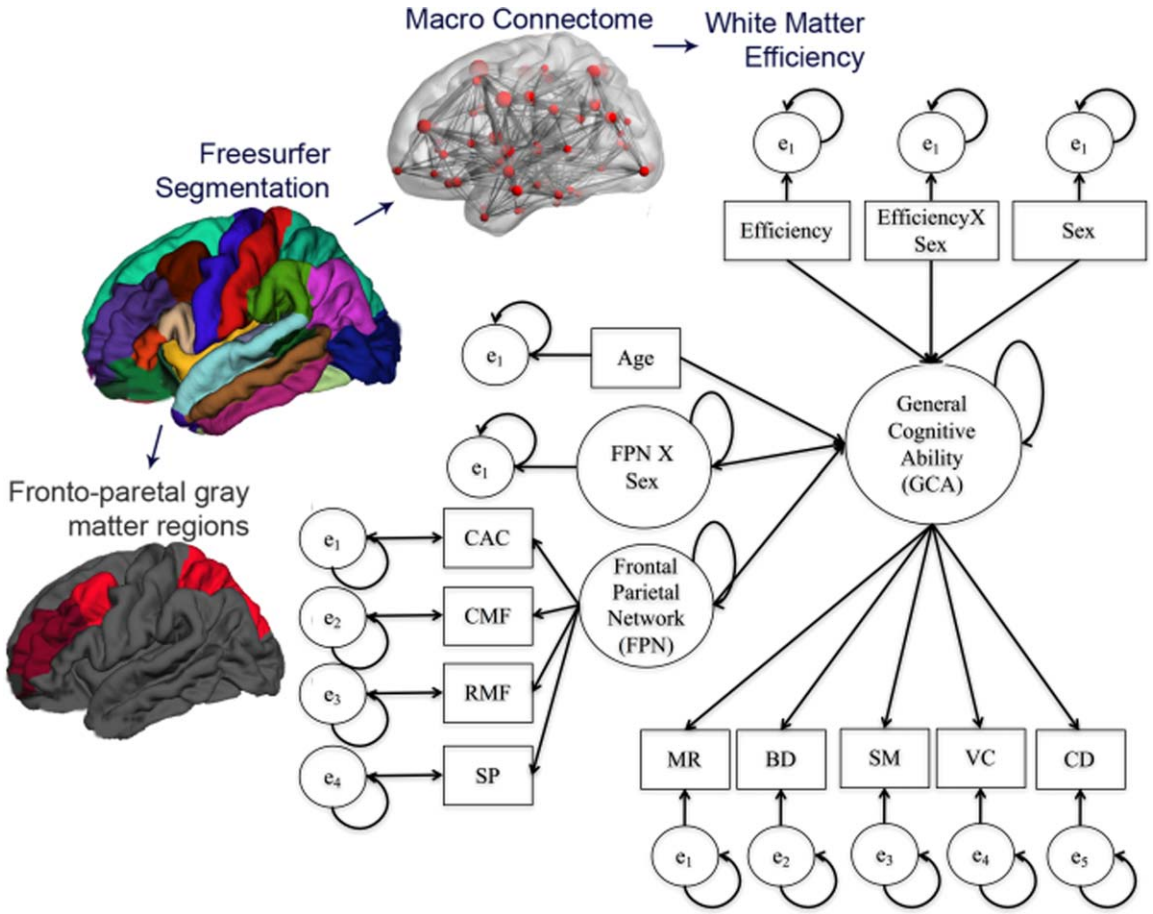

Figure 1.

Variable construction and structural equation model. Fronto-parietal gray matter volume (FPN), white matter efficiency, and their relation to general cognitive ability (GCA). Matrix Reasoning (MR), Block Design (BD), and Similarities (SM) from the Wechsler Abbreviated Scale of Intelligence-II (WASI-II), Coding (CD) from the Wechsler Adult Intelligence Scale-IV (WAIS-IV), and a Vocabulary (VC) test, caudal anterior cingulate volume (CAC), caudal middle frontal (CMF), rostral middle frontal (RMF), and superior parietal (SP). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

(ML) estimation in R version 3.1.2 with the Lavaan package version 0.5–17 [Rosseel, 2012]. Adequate model fit was indicated by a nonstatistically significant χ^2, root mean square error of approximation (RMSEA) ≤ 0.05, and comparative fit index (CFI) ≥ 0.95.

Confirmatory factor analysis of cognitive network and GCA

A confirmatory factor analysis (CFA) was used to examine the factor structures of GCA and fronto-parietal gray matter volume. Scores on the MR, BD, and SM from the WASI-II, Coding from the WASI-IV, and a VC from the Johnson O'Connor Research Foundation's battery of aptitude tests were included as indicators of a single latent factor of GCA. The fronto-parietal gray matter volume factor was constructed by identifying regions within the fronto-parietal regions previously implicated in intelligence. Specifically, we examined caudal anterior cingulate volume (CAC), caudal middle frontal volume (CMF), rostral middle frontal volume (RMF), and superior parietal volume (SP) as indicators of a single latent factor of gray matter volume. To determine the specificity of our results, an additional model including regions of the default mode network (DMN) was examined in the larger SEM. The DMN regions included the rostral anterior cingulate, precuneus, middle temporal gyrus, and superior frontal gyrus.

Measurement invariance

Measurement invariance across sex of the factors GCA and fronto-parietal gray matter volume were examined separately to ensure that there were no significant

TABLE I. Cognitive and brain measures

		Females ($n = 119$)	Males ($n = 125$)	T-value (P value)
	Age	21.71 ± 3.44	21.84 ± 3.55	0.29 (0.77)
Cognitive variables	Block design	55.29 ± 8.11	57.21 ± 8.35	1.82 (0.07)
(t-scores)	Matrix reasoning	53.82 ± 6.85	54.26 ± 8.99	0.42 (0.67)
	Similarities	58.98 ± 9.35	58.47 ± 9.70	0.42 (0.68)
	Coding	55.65 ± 13.27	52.39 ± 7.93	2.32 (0.02)
	Vocabulary	52.22 ± 9.82	51.65 ± 9.10	0.46 (0.64)
Gray matter variables	Total gray matter volume (mL)	632,925.3 ± 47,073.61	695,649.4 ± 49,903.21	10.10 (<0.001)
	Caudal anterior cingulate volume (mL)	2,125.69 ± 362.28	2,314.416 ± 396.98	3.88 (<0.001)
	Caudal middle frontal volume (mL)	6,614.83 ± 1,055.24	7,151.90 ± 1,139.78	3.82 (<0.001)
	Rostral middle frontal volume (mL)	16,184.69 ± 1,768.78	18,062.32 ± 2,024.25	7.72 (<0.001)
	Superior parietal volume (mL)	13,156.4 ± 1,445.05	14,340.41 ± 1,671.79	5.93 (<0.001)
White matter variables	White matter connectivity	357,672.3 ± 52,053.61	402,129 ± 53,226.38	6.59 (<0.001)
	White matter efficiency	0.06 ± 0.01	0.06 ± 0.02	2.33 (0.02)
	White matter volume (mL)	448,187.9 ± 44,057.81	490,106.2 ± 45,844.32	7.29 (<0.001)
Total brain	Total brain volume (mL)	1,128,273 ± 86,406.68	1,235,042 ± 87,756.78	9.57 (<0.001)

differences in the models used across sex. First, CFAs were examined by males and females separately to examine configural invariance. Second, metric invariance was examined by estimating the CFAs for both groups with the loadings constrained to be equal across males and females. Third, scalar invariance was tested by estimating the CFAs for both groups with loadings and intercepts constrained to be equal across males and females. Finally, residual invariance was tested by constraining the loadings, intercepts, and residual variances to be equal across males and females. To examine the subsequent levels of invariance (metric, scalar, and residual), χ^2 difference tests were conducted by comparing the χ^2 of the models constraining the relevant parameters to the χ^2 value of configural invariance model.

Structural equation models

Once the CFA models were identified, we proceeded to fit a SEM relating the GCA latent factor to both the fronto-parietal gray matter volume latent factor and white matter efficiency controlling for age (Fig. 1). To determine if there were sex differences in the relationships between GCA, fronto-parietal gray matter volume, and white matter efficiency, a nested model comparison was conducted. Specifically, the model was run with and without constraining regression coefficients to be equal across sex. A χ^2 difference test was conducted to identify if constraining the regression coefficients resulted in a significant difference in model fit. Additionally, the interaction between sex and each of the predictors, fronto-parietal gray matter volume and white matter efficiency respectively, were examined. Follow up analyses within each sex were conducted when model fit was significantly decreased after constraining regression parameters across sex and when a significant sex interaction was found. To determine if the fronto-parietal gray matter factor accounted for significant independent variance beyond total gray matter volume, an additional model that included total gray matter volume was examined. To determine the specificity of our results we examined if another network implicated in cognitive function was related to GCA, the DMN.

RESULTS

Participants and Cognitive Measures

Participants were young adults ($n = 244$; average age = 21.77 (SD =3.29); 125 males, 119 females). There were no significant differences in cognitive performance, with the exception of processing speed (Table I). Females demonstrated significantly greater processing speed when compared to males, sex differences consistent with previous reports [Camarata and Woodcock, 2006; Halpern, 2013]. Significant differences in regional volumes and white matter measures were found across all measures examined (Table I),

Initial screening of the data indicated no evidence of univariate or multivariate non-normality, multicollinearity, or univariate outliers (measures > 3 standard deviations above the mean). The gray matter volumes were ill scaled. This was due to the segmentation scheme utilized, which included regions of different sizes resulting in variances different in magnitude (range: $SD^2 = 67{,}204.98$–$461{,}431.69$). Transformations were conducted to scale the gray matter volumes. There were two missing data points on a single

TABLE II. Factor loadings for the CFA of GCA

	Total sample		Females		Males	
Measure	Unstandardized loading	Standardized loading	Unstandardized loading	Standardized loading	Unstandardized loading	Standardized loading
Block design	1.00	0.60	1.00	0.77	1.00	0.50
Matrix reasoning	0.94	0.58	0.75	0.68	1.18	0.55
Similarities	1.02	0.53	0.82	0.55	1.09	0.47
Vocabulary	0.84	0.45	0.68	0.43	0.92	0.42
Coding	0.45	0.20	0.41	0.19	0.49	0.26

individual cognitive test (DS coding) due to administration error. ML estimation was used when estimating the following models, thus all available data were included in the analyses and the effective model sample size was 244, despite missing data on two of the cognitive tests. ML estimation is a preferred method for handling missing data, assuming the data are missing at random [Schafer and Graham, 2002].

CFA of GCA

A model of GCA was estimated with the following five indicators: MR, BD, and SM from the WASI-II, Coding from the Wechsler Adult Intelligence Scale-IV (WAIS-IV), and a VC test. Results of the CFA of GCA indicated adequate model fit (χ^2 (5) = 7.45, $P = 0.19$, RMSEA = 0.04 (90% CI [0.00–0.10]), CFI = 0.98), (Table II). Additional analyses within each group indicated that the model provided adequate fit to the data, in females χ^2 (5) = 10.03, $P = 0.08$, RMSEA = 0.09 (90% CI [0.00–0.17]), CFI = 0.94, with the model fitting slightly better in males χ^2 (5) = 4.53, $P = 0.48$, RMSEA < 0.01 (90% CI [0.00–0.12]), CFI = 1.00.

CFA of Fronto-Parietal Gray Matter Volume

The *a priori* fronto-parietal gray matter CFA model consisted of four indicators defined by gray matter in four regions: CAC, CMF, RMF, and SP. Importantly, an average of the regions from each hemisphere were examined as inclusion of both the left and right regions of the brain resulted in issues of collinearity. To ensure results did not differ by each hemisphere, analyses were run within each hemisphere separately. The model fit was similar in models that examined each hemisphere separately to the reported model that examined the average across hemispheres. Scaling of the latent variables was done by using one indicator as a reference for each of the latent factors (unit loading identification). Results indicate that the model provided an adequate fit to the data, $\chi^2(2) = 0.36$, $P = 0.84$, RMSEA < 0.01 (90% CI [0.00–0.07]), CFI = 1.00. The same model was estimated in males and females separately and provided adequate fit to the data [females $\chi^2(2) = 0.26$, $P = 0.88$, RMSEA < 0.01 (90% CI [0.00–0.09]), CFI = 1.00; males $\chi^2(2) = 1.06$, $P = 0.59$, RMSEA < 0.01 (90% CI [0.00–0.15]), CFI = 1.00]. As seen in Table III, factor loadings were all greater than 0.5 for all of the indicators.

Measurement Invariance of GCA

A configural invariance model was specified in which a single factor was estimated simultaneously in each group, providing a χ^2 that was used to test subsequent models against. Similar results were obtained when estimating the models in males and females separately, indicating the general factor structure fits within each sex.

Metric invariance was examined by constraining the factor loadings across groups (males and females) to be equal. The model demonstrated good fit to the data with χ^2 (14) = 15.78, $P = 0.33$, RMSEA = 0.03 (90% CI [0.00–0.09]), CFI = 0.99. A χ^2 difference test indicated no significant differences between the models $\chi^2(4) = 1.20$, $P = 0.88$, providing support for metric invariance. Scalar invariance was examined by constraining the factor loadings and intercepts to be equal across groups. This model demonstrated poor fit with $\chi^2(18) = 26.86$, $P = 0.08$, RMSEA = 0.06 (90% CI [0.00–0.11]), CFI = 0.93. A χ^2

TABLE III. Factor loadings for the CFA of the fronto-parietal gray matter factor

	Total sample		Females		Males	
Measure	Unstandardized loading	Standardized loading	Unstandardized loading	Standardized loading	Unstandardized loading	Standardized loading
Caudal anterior cingulate	1.00	0.58	1.00	0.54	1.00	0.54
Caudal middle frontal	1.44	0.70	1.53	0.70	1.54	0.69
Rostral middle frontal	1.79	0.83	1.71	0.83	1.69	0.76
Superior parietal	1.60	0.74	1.28	0.60	1.79	0.76

TABLE IV. Structural equation models

Model individual predictor	Individual predictor statistics: Standardized Beta	Individual predictor statistics: *P*-value	Model statistics: *P*-value	Model statistics: R^2
Females				
GCA ← Age + Effi + FP			0.194	0.179
Age	0.052	0.605		
Effi	**0.328**	**0.002**		
FP	**0.252**	**0.041**		
GCA ← Age + Effi + FP + TGM			<0.001	0.268
Age	0.048	0.620		
Effi	**0.315**	**0.001**		
FP	−0.157	0.145		
TGM	**0.421**	**<0.001**		
Males				
GCA ← Age + Effi + FP			0.001	0.285
Age	0.074	0.464		
Effi	−0.036	0.721		
FP	**0.527**	**<0.001**		
GCA ← Age + Effi + FP + TGM			<0.001	0.198
Age	0.090	0.429		
Effi	−0.051	0.639		
FP	**0.420**	**0.003**		
TGM	0.141	0.218		

GCA = General Cognitive Ability; Effi = White matter efficiency; FP = Fronto-parietal gray matter factor; TBV = Total Brain Volume; TGM = Total Gray Matter; TWM = Total White Matter. Bold indicates $P < 0.05$

difference test between the metric and scalar models found significant differences between the models $\chi^2(4) = 11.09$, $P = 0.03$. These results indicate that constraining the intercepts across groups resulted in significantly worse model fit. Examination of the intercepts identified in the metric model indicated that the intercepts for Coding differed by the largest magnitude across groups. Lastly, residual invariance was examined by constraining the factor loadings, intercepts, and residual variances to be equal across groups. This model demonstrated poor fit, $\chi^2(23) = 64.35$, $P < 0.001$, RMSEA = 0.12 (90% CI [0.09–0.16]), CFI = 0.66. The χ^2 difference test between the scalar and residual variance models found significant differences between the models $\chi^2(5) = 26.04$, $P < 0.001$, indicating that residual invariance was rejected. Inspection of the residuals indicated that the residuals for BD differed greatly across groups.

Measurement Invariance of Fronto-Parietal Gray Matter Volume

Similar results were obtained when estimating the fronto-parietal gray matter factor model in males and female separately, indicating the general factor structure fits within each sex. A model constraining the factor loadings across groups (males and females) demonstrated good fit to the data with χ^2 $(7) = 4.35$, $P = 0.74$, RMSEA < 0.001 (90% CI [0.00–0.08]), CFI = 1.00. A χ^2 difference test indicated no significant differences between the constrained and unconstrained model $\chi^2(3) = 3.03$, $P = 0.39$, providing support for metric invariance.

A model constraining both the factor loadings and intercepts across groups demonstrated adequate fit with $\chi^2(10) = 11.64$, $P = 0.31$, RMSEA = 0.05 (90% CI [0.00–0.11]), CFI = 0.99. A χ^2 difference test between the metric and this model found no significant differences $\chi^2(3) = 7.29$, $P = 0.06$ between groups, providing support for scalar invariance. Lastly, residual invariance was examined by constraining the factor loadings, intercepts, and residual variances to be equal across groups. This model demonstrated adequate fit, $\chi^2(14) = 15.34$, $P = 0.36$, RMSEA = 0.03 (90% CI [0.00–0.09]), CFI = 0.99. The χ^2 difference test between the scalar and residual variance models found no significant differences between the models $\chi^2(4) = 3.70$, $P = 0.45$, indicating that residual invariance was met.

Structural Equation Model

Figure 1 displays the initial SEM. GCA was regressed on sex, fronto-parietal gray matter volume, white matter efficiency, and the interactions between sex and fronto-parietal gray matter volume and white matter efficiency, respectively, accounting for age. Results indicated a significant interaction between white matter efficiency and sex. Additionally, the models were run using sex as a grouping variable, indicating that there was a significant χ^2 difference between the model across males and females and the

model which included sex as a grouping variable. Based on these results, models were run within each sex separately.

Examination of the model within each sex indicated adequate model fit in males χ^2 (34) = 38.35, $P = 0.05$, RMSEA = 0.05 (90% CI [0.00–0.09]), CFI = 0.95 and in females χ^2 (34) = 41.66, $P = 0.17$, RMSEA = 0.04 (90% CI [0.00–0.08]), CFI = 0.96. Inclusion of age in the model decreased model fit, but did not affect the relationships between variables of interest and GCA. Examination of the regression parameters indicated that there was a significant relationship between fronto-parietal gray matter volume and the GCA factor in males ($\beta = 0.503$, $P < 0.001$; with age included in the model: $\beta = 0.527$, $P < 0.001$) and trend level significance in females ($\beta = 0.239$, $P = 0.052$; with age included in the model: $\beta = 0.252$, $P = 0.041$). However, there was only a significant relationship between the white matter efficiency and the GCA factor in females ($\beta = 0.335$, $P = 0.001$; with age included in the model: $\beta = 0.328$, $P = 0.002$) and not in males ($\beta = -0.030$, $P = 0.759$; with age included in the model: $\beta = -0.036$, $P = 0.721$).

To determine if the fronto-parietal gray matter factor accounted for significant independent variance beyond total gray matter volume, the models were rerun within each sex including the total gray matter volume variable. Results are depicted in Table IV. In males, the relationship between the fronto-parietal gray matter factor and GCA was significant when total gray matter volume was included (FP factor: $\beta = 0.420$, $P = 0.003$), indicating that the FP factor accounted for independent variance beyond total gray matter volume. Total gray matter volume was not a significant predictor of GCA in males ($\beta = 0.141$, $P = 0.218$). The association between white matter efficiency and GCA was not significant after controlling for total gray matter volume ($\beta = -0.051$, $P = 0.639$), consistent with the reports above. Among females, the relationship between the fronto-parietal gray matter factor and GCA was not significant when total gray matter volume was included in the model (FP factor $\beta = -0.157$, $P = 0.145$), indicating that the FP factor did not account for significant variance beyond total gray matter volume. Total gray matter volume, however, was a significant predictor of GCA in females ($\beta = 0.421$, $P < 0.001$). The association between white matter efficiency and GCA was significant after controlling for total gray matter volume (efficiency $\beta = 0.315$, $P = 0.001$).

Lastly, to determine the specificity of our results in males, a factor of other regional brain volumes implicated in cognitive function, the DMN, was constructed and replaced the fronto-parietal gray matter factor. The relationship was also examined in females to determine if the DMN would explain additional variance in the model within females, over and above total gray matter volume, which would indicate a specific DMN contribution to GCA. In males, a model that included the DMN latent factor, white matter efficiency, age, and total gray matter volume indicated that the DMN latent factor ($\beta = 0.251$, $P = 0.448$), white matter efficiency ($\beta = -0.084$, $P = 0.480$), and total gray matter volume ($\beta = 0.243$, $P = 0.394$) were not significant predictors of GCA controlling for age. In females, the same model indicated that the DMN latent factor was not a significant predictor of GCA ($\beta = -0.376$, $P = 0.150$), whereas white matter efficiency ($\beta = 0.258$, $P = 0.002$) and total gray matter ($\beta = 0.566$, $P = 0.016$), were significantly related to GCA, consistent with the results above.

DISCUSSION

The current study aimed to identify the relationships between intelligence, fronto-parietal gray matter volume, and white matter efficiency. Two CFA models were used to derive a GCA factor and a fronto-parietal gray matter factor. The results of the SEM fit across males and females demonstrated a significant sex interaction between white matter efficiency and GCA. Examination of the SEM within each sex indicated that the latent fronto-parietal gray matter factor predicted GCA in males, whereas in females, total gray matter volume predicted GCA, with limited specificity of the fronto-parietal factor. The fronto-parietal gray matter factor accounted for independent variance beyond total gray matter volume in males. The white matter efficiency measure was significantly related to GCA in females, with no significant relationship in males. Taken together, these results demonstrate that regional gray matter volumes within a fronto-parietal network predicted GCA in males. In contrast, efficient white matter organization and total gray matter volume significantly predicted GCA in females.

The results of the measurement invariance testing suggest no differences in the factor structures of both the GCA and fronto-parietal gray matter factor in males and females, as well as any differences in the magnitude of the loadings of each of the indicators on the factor. Thus, the GCA factor we examined is the same across both males and females, exhibiting no differential loading of any single test. For the fronto-parietal factor, this also indicates that the factor is reliant on each of the gray matter regions consistently across males and females.

This is the first study to construct a fronto-parietal gray matter factor and relate this variable to GCA. Results of the SEM highlight that the latent fronto-parietal gray matter factor predicts GCA in males, with greater fronto-parietal gray matter volumes corresponding to greater GCA scores. This is consistent with previous work utilizing different methodological approaches that have found that variation in gray matter in the frontal and parietal regions was related to intelligence [Haier et al., 2009; Jung and Haier, 2007]. As the covariance between cortical regions likely reflects the underlying connectivity between regions [Alexander-Bloch et al., 2013a,b] and males exhibit

greater modularity of structural connectivity [Ingalhalikar et al., 2014], this suggests that males rely on a specialized network of fronto-parietal gray matter regions for GCA, rather than global gray matter, which did not significantly predict GCA. However, in females, the fronto-parietal gray matter factor did not account for independent variance beyond total gray matter volume. Total gray matter volume, however, was significantly related to GCA in females, suggesting that females rely on widespread regions of the cortex for GCA. This would account for previous studies that demonstrate stronger and more extensive regional gray matter relationships within the fronto-parietal regions and intelligence in males [Haier et al., 2005]. Of note, it is important for future studies to determine if there are alternate cortical networks not examined in the current analysis related to GCA in females.

Previous reports relate white matter efficiency to intelligence [Li et al., 2009], however, these studies failed to examine sex differences. The current study highlights that white matter efficiency is a significant predictor of GCA in females, but not males. The quantification of white matter efficiency in the current study was derived from white matter connectivity across widespread cortical and subcortical regions, with greater scores indicating more direct connections between individual regions compared to lower scores [Bullmore and Sporns, 2009]. As the relationship between white matter volume/connectivity and intelligence is stronger for females than males [Gur et al., 1999; Schmithorst, 2009], the results of the current study further suggest that not only are the volume and coherence of white matter important to intelligence in females, but also the efficiency of the organization of the white matter connections. Furthermore, females demonstrated greater local and global efficiency [Gong et al., 2009; Yan et al., 2011], indicating that white matter efficiency may be one factor that facilitates equal intelligence across males and females in spite of different brain volumes.

There are numerous sex differences in the brain's structure that are caused or sustained by a combination of environmental and non-environmental factors [Giedd et al., 2012; Luders and Toga, 2010; Ruigrok et al., 2014]. These differences emerge early in life, with males exhibiting larger TBV, total gray matter volumes, and total white matter volumes compared to females [Giedd et al., 2012]. Over the course of adolescence, volumes of total brain and gray matter volume form inverted U trajectories in which the volumes exhibit significantly greater differences late in adolescence. Females typically demonstrate peak volumes in these volumes earlier than males (1-3 year earlier in females than males), which correspond to the same time frame in which females reach puberty before males. In addition, regional brain volumes that show the largest sexual dimorphisms, most notably the caudate, amygdala, hippocampus, and cerebellum, also demonstrate greater levels of androgen and estrogen receptors [Giedd et al., 2012; Luders and Toga, 2010]. Taken together, these findings highlight the role of hormones as a potential mechanism for divergent brain development in males and females; however, it is critical to also note the impact of environmental factors.

Brain development is a dynamic interplay between genetic (potentially modulating neural development via hormones) and environmental influences, which cannot be reduced to one genetically driven factor responsible for all emerging sex differences (e.g., hormones) [Fine et al., 2013]. It is increasingly appreciated that experience dependent neural plasticity shapes not only behavior but also the underlying neural structures that are involved in that behavior [May, 2011; Zatorre et al., 2012], and the extent of neural plasticity may depend on the steroid-induced alterations in gene expression that can be growth promoting or inhibiting [Luders and Toga, 2010]. As the current study utilized a cohort with a mean age of 21, the individuals are at the latter end of adolescent development and exhibit the largest magnitude of sex dimorphisms in the brain's structure. Of note, it is impossible to determine the extent to which these dimorphisms are due to environmentally or non-environmentally driven factors in the current study. Future studies should aim to investigate the relationship between divergent brain development and intelligence across the lifetime examining the relative contributions of environmental and non-environmental effects.

The current study has several strengths, such as a large sample and high quality neuroimaging data. However, there are certain weaknesses to acknowledge when interpreting our results. While we identified a fronto-parietal gray matter factor, there are numerous regions that could have been included. The goal of this analysis was to determine whether the fronto-parietal gray matter regions factor well, and if they differentially predict GCA over TBV and total gray matter. For this purpose, the fronto-parietal regions were found to factor and predict GCA; however, future work should examine relationships with a broad variety of networks and/or regions throughout the brain to determine whether the fronto-parietal network provides an optimal fit. Such an analysis will require a very large number of subjects, beyond our rather large sample, to account for the large number of comparisons required. The current study also utilized an abbreviated intelligence battery (WASI-II) in conjunction with other intelligence measures (Coding and VC), but did not include a mathematical numerical subtest. Future studies should replicate these results utilizing diverse test batteries to ensure that the results generalize. Finally, the study was carried out in a young, healthy, cohort. Whether our results would generalize to children (e.g., $<$16-year old) or to older subjects (e.g., $>$30) remains to be determined.

Taken together, the results indicate a significant positive relationship between fronto-parietal gray matter region volumes and intelligence across sex in males, but not females. Although gray matter volume did predict intelligence in females, a regionally specific contribution of the

fronto-parietal gray matter volume was not evident. The measure of structural white matter efficiency is significantly positively related to intelligence in females, but not in males. These results suggest that, while intelligence was related primarily to a fronto-parietal gray matter volume in males, efficiency of white matter organization and the total gray matter volume was predictive of intelligence in females.

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