

7-12-2014

Sex differences in the relationship between white matter connectivity and creativity

Sephira Ryman

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SEX DIFFERENCES IN THE RELATIONSHIP BETWEEN WHITE MATTER
CONNECTIVITY AND CREATIVITY

BY
SEPHIRA RYMAN

BACHLORS OF ARTS

THESIS

Submitted in Partial Fulfillment of the
Requirements for the Degree of

Master of Science
Psychology

The University of New Mexico
Albuquerque, New Mexico

May, 2014

ACKNOWLEDGMENTS

I heartily acknowledge Dr. Ron Yeo, my advisor and committee chair, for his continued support and participation in my development as a research scientist. I admire his teaching and mentoring style and am thankful to have benefitted from both.

I also thank my committee members, Dr. Katie Witkiewitz, for her invaluable knowledge of statistics and applications to neuroimaging data, and Dr. Rex Jung, for his ongoing support and assistance in my professional development. Through his faith in my abilities and encouragement, I have gained extensive experience in the analysis of neuroimaging data. Gratitude is extended to the Templeton Foundation for the funding to pursue this research.

To my family and my partner, I thank you for the tolerance and support when I have “lived in the matrix” and for all of the encouragement you have given me along the way.

SEX DIFFERENCES IN THE RELATIONSHIP BETWEEN WHITE MATTER CONNECTIVITY AND CREATIVITY

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ABSTRACT

Creative cognition emerges from a complex network of interacting brain regions. This study investigated the relationship between the structural organization of the human brain and aspects of creative cognition quantified by divergent thinking tasks. Diffusion weighted imaging (DWI) was used to obtain fiber tracts from 83 segmented cortical regions. This information was represented as a network and metrics of connectivity organization, including connectivity strength, clustering and efficiency were computed, and their relationship to personal levels of creativity was examined. Permutation testing identified significant sex differences in the relationship between global connectivity and creativity as measured by divergent thinking tests. Females demonstrated significant inverse relationships between global connectivity and creative cognition; there were no significant relationships observed in males. Node specific analyses found inverse relationships across measures of Connectivity, Efficiency, Clustering and creative cognition in widespread regions in females. Our findings suggest that females involve more regions of the brain in processing to produce novel ideas to solutions, perhaps at the expense of efficiency (greater path lengths). Males, in contrast, exhibited few, relatively weak positive relationships across these measures. Extending recent observations of sex differences in connectome structure, our findings of sexually dimorphic relationships

suggest a unique topological organization of connectivity underlying the generation of novel ideas in males and females.

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Chapter 1 Introduction

Creative cognition is multifaceted, drawing on a wide range of mental faculties that enable individuals to develop novel and useful ideas (Stein, 1953). The process of creativity has been conceptualized as involving two stages: blind variation and selective retention (Campbell, 1960). The two stages utilize different brain regions in functional magnetic resonance imaging (fMRI) studies, suggesting that the blind variation and selective retention might represent distinct cognitive processes (Ellamil et al., 2012). Psychometrically, it is likely to be difficult to disentangle these two processes (Arden et al., 2010); however, divergent thinking has served as the primary measure most analogous to blind variation, as it measures an individual's ability to generate many ideas (Piffer, 2012).

Relative to the wealth of fMRI studies that have investigated divergent thinking, there are relatively few studies that have addressed the variation in underlying gray or white matter morphology and/or anatomical connectivity. Unlike other studies of cognitive abilities, increased creativity has been correlated to both increases *and* decreases in brain connectivity and cerebral volume elucidated through the use of proton magnetic resonance spectroscopic imaging (1H-MRSI), diffusion weighted imaging (DWI), and structural Magnetic Resonance Imaging (sMRI) (Jung et al., 2013). Two DWI investigations have examined the relationship between divergent thinking and Fractional Anisotropy (FA), a measure used to infer information about the underlying integrity of white matter fiber tracts (Johansen-Berg and Behrens, 2009). A whole brain voxel wise analysis found that increased FA near the bilateral prefrontal cortices, the

body of the corpus callosum, the bilateral basal ganglia, the bilateral temporo-parietal junction and right inferior parietal lobule were related to increased creative cognition (Takeuchi et al., 2010). Examining FA values within a skeleton of the major white matter fiber pathways (Smith et al., 2006) Jung et al., (2010a) found lower FA to be related to increased scores on measures of divergent thinking within the left anterior thalamic radiation.

Studies that have examined volume and thickness of gray matter have found both increases and decreases across widespread regions related to higher creative cognition, with increases seen in the mid-brain, striatum, precuneus, dorsolateral prefrontal cortex (Takeuchi et al., 2010), superior parietal lobule (Gansler et al., 2011), posterior cingulate and right angular gyrus (Jung et al., 2010b). Additionally, decreases related to increased creative cognition were found in the lingual, cuneus, angular gyrus, inferior parietal, fusiform gyrus, orbitofrontal cortex (Jung et al., 2010b) and the splenium of the corpus callosum (Gansler et al., 2011). From these studies, it is clear that the manifestation of creativity is associated with both positive and negative relationships between cortical and subcortical regions spanning a widespread network of brain regions (Jung et al., 2013).

From functional connectivity analysis, there is increasing evidence showing correspondence between the regions implicated in creativity and the regions identified as being within the default mode network (DMN) (Jung et al., 2013). The DMN consists of regions where neural activity is greater during the baseline state than during an experimental task (Buckner et al., 2008; Greicius et al., 2003; Raichle et al., 2001; Shulman et al., 1997), and include the medial prefrontal cortex (MPFC), medial temporal lobes (MTLs), and the posterior cingulate cortex (PCC)/retrosplenial cortex (RCS).

Many cognitive functions have been attributed to the DMN, including retrieval and manipulation of past events, both personal and general, in an effort to solve problems and develop future plans (Greicius et al., 2003). Buckner and Carroll (2007) suggest that the DMN is important to remembering the past, envisioning the future and considering the thoughts and perspectives of other people, all processes that could be construed as useful to developing novel ideas within a given context (i.e., creative).

Both the functional and structural studies of divergent thinking highlight the role of widespread variations in brain-behavioral relationships associated with creative cognition, although increasing evidence suggests that the DMN and the ECN are predominant (Jung et al., 2013). The methods used in the vast majority of studies, to date, point to individual regions implicated in creativity; relatively few examine the brain as a network. Instead of investigating the role of specific regions in isolation, fiber tractography can be used to construct and examine all of the connections in the brain, known as a connectome (Bullmore and Sporns, 2009; Craddock et al., 2013). By representing this information as a graph, measures of network organization can be extracted that indicate the extent of segregation and integration of connections (Rubinov and Sporns, 2010). Individual differences in network properties (i.e., higher efficiency) are linked to measures of individual differences including intelligence (Li et al., 2009; van den Heuvel et al., 2009a), and are increasingly used to identify how variations in network metrics relate to cognitive dysfunction (de Haan et al., 2012; Fair et al., 2010).

Several studies have found significant sex differences in the network properties of the brain. Specifically, increased cortical connectivity, local efficiency, global efficiency, hubs with higher betweenness centrality, and small world indices were observed in

females when compared to males (Gong et al., 2009). Moreover, connectivity patterns revealed most supratentorial intrahemispheric connections were stronger in males, whereas interhemispheric connections were stronger in females (Ingalhalikar et al., 2013). These studies examined the sex differences in network connectivity and infer the potential role these differences play in cognitive functioning. To our knowledge, no studies have examined whether the relationship between divergent thinking and structural network connectivity differs between males and females. In light of the recent studies emphasizing sex differences in structural brain organization, this study first investigates whether the relationship between the structural connectome and creativity differ at the level of sex. Second, we investigate whether variations in the network properties of individual regions of the brain are predictive of divergent thinking. Finally, we evaluate whether these regions are primarily within the default mode network and executive control network.

Chapter 2 Methodology

Participants

Participants were young adults (21.53+/-2.93 years; 59 males, 47 females) 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. All subjects provided written informed consent before the collection of data and subsequent analysis. One hundred and nineteen volunteers, with no history of neurological or psychological disorder, participated in the study. Thirteen individuals were excluded in the data analysis due to the low quality of their neuroimaging data (i.e. motion or image artifacts), resulting in 106 human subjects for analysis.

Behavioral Measures

Four divergent thinking tasks were administered: Verbal and Drawing Creativity Tasks, Uses of Objects Test (UOT), described in detail elsewhere (Lezak et al., 2004; Miller and Tal, 2007) and generation of captions to New Yorker Magazine cartoons. Four independent judges (two females, two males) ranked the DT products of each participant using the consensual assessment technique (Amabile, 1982) from which a “composite creativity index” (CCI) was derived. The raters were of the same cohort as the subjects (19–29; college/graduate students). Raters were instructed to rate each subject’s DT product from 1 (lowest creativity) to 5 (highest creativity) according to their own notion of “creativity,” and were instructed to bin rankings to conform to a normal distribution

(e.g., 5% each 1's and 5's, 10% each 2's and 4's, 70% 3's). Rankings for each subject were averaged across the four measures and converted to a standard score to facilitate easy comparisons between FSIQ and the creativity measure, referred to as the Composite Creativity Index (CCI). The raters had excellent inter-rater reliabilities across the four measures of DT (i.e., CCI $\alpha = .81$).

To assess general intelligences, subjects were tested with the Wechsler Adult Inventory Scale (WAIS-III) (Wechsler, 1981). The WAIS battery consists of subtests that measure verbal and non-verbal mental abilities that contribute to general intelligence. The Full Scale Intelligence Quotient (FSIQ) was based on performance on 11 subtests (Comprehension, Picture Arrangement, Object Assembly were not administered).

Imaging Acquisition

Imaging was obtained using a 3 Tesla Siemens Triotim MRI using a 12-channel head coil. The multiecho MPRAGE protocol was followed to obtain the T1 image: [TE 1.64/3.5/5.36/7.22/9.08ms; TR 2530 ms; voxel size 1x1x1mm; 192 slices; Field of View = 256 mm; acquisition time 6.03]. For the diffusion weighted imaging (DWI) data echo planar imaging was acquired: [TE 84 ms; TR 9000ms; voxel size 2x2x2mm³; 72 slices; Field of View = 256mm; 2 set of 30 diffusion directions with $b = 800$ s/mm², and 5 measurements with $b = 0$, acquisition time 5:42].

DWI Preprocessing and deterministic fiber tracking

The two sets of 30 diffusion directions and 5 $b = 0$ were averaged to increase the signal to noise ratio. The remaining processing of the DWI images followed the methods

previously described in detail (van den Heuvel and Sporns, 2011). First, diffusion weighted images were realigned and registered to the first b=0 image, and corrected for eddy-current distortions. Second, a tensor was fitted to the diffusion profile within each voxel using a robust tensor fitting method (Chang et al., 2005). The preferred diffusion direction within each voxel was computed as the principal eigenvector of the eigenvalue decomposition of the fitted tensor. Third, the level of fractional anisotropy (FA) of each voxel was computed based on the eigenvalues. Fourth, the white matter tracts of the brain networks were reconstructed by using the deterministic fiber tracking, based on the FACT (fiber assignment by continuous tracking) algorithm utilizing an FA threshold of 0.2 and an angular threshold of 45 degrees (Mori and van Zijl, 2002).

T1 preprocessing

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 grey and white matter of the brain as well as automatically segment the subcortical structures (i.e. the brain stem, thalamus, pallidum, caudate, putamen, accumbens, hippocampus, and amygdala). Automatic parcellation of the reconstructed cortical surface segmented the images into 68 distinct brain regions (V5; <http://surfer.nmr.mgh.harvard.edu/> Figure 1a)(Fischl et al., 2004). In total, eighty-three brain regions were selected, representing the nodes of the individual brain networks.

FA-weighted reconstruction of individual structural networks.

Individual brain networks were modeled based on segmented brain regions and the collection of reconstructed fiber tracts (Hagmann et al., 2008; van den Heuvel et al., 2010). The network was mathematically described as a graph $G=(V,E)$, with V being the collection of 83 regions and E the set of the reconstructed white matter pathways between these regions. For each subject, the presence of a reconstructed fiber streamline between each pair of brain regions i and j was taken to determine the presence of a connection between region i and j (Figure 1b). To obtain information not only about the presence of a connection, but also about the strength and integrity of the connection, a metric utilizing information about the mean of the FA value was created (w) as the average FA values of all included streamlines. This value was then entered in the FA-weighted connectivity matrices (G) as w_{ij} (Figure 1c).

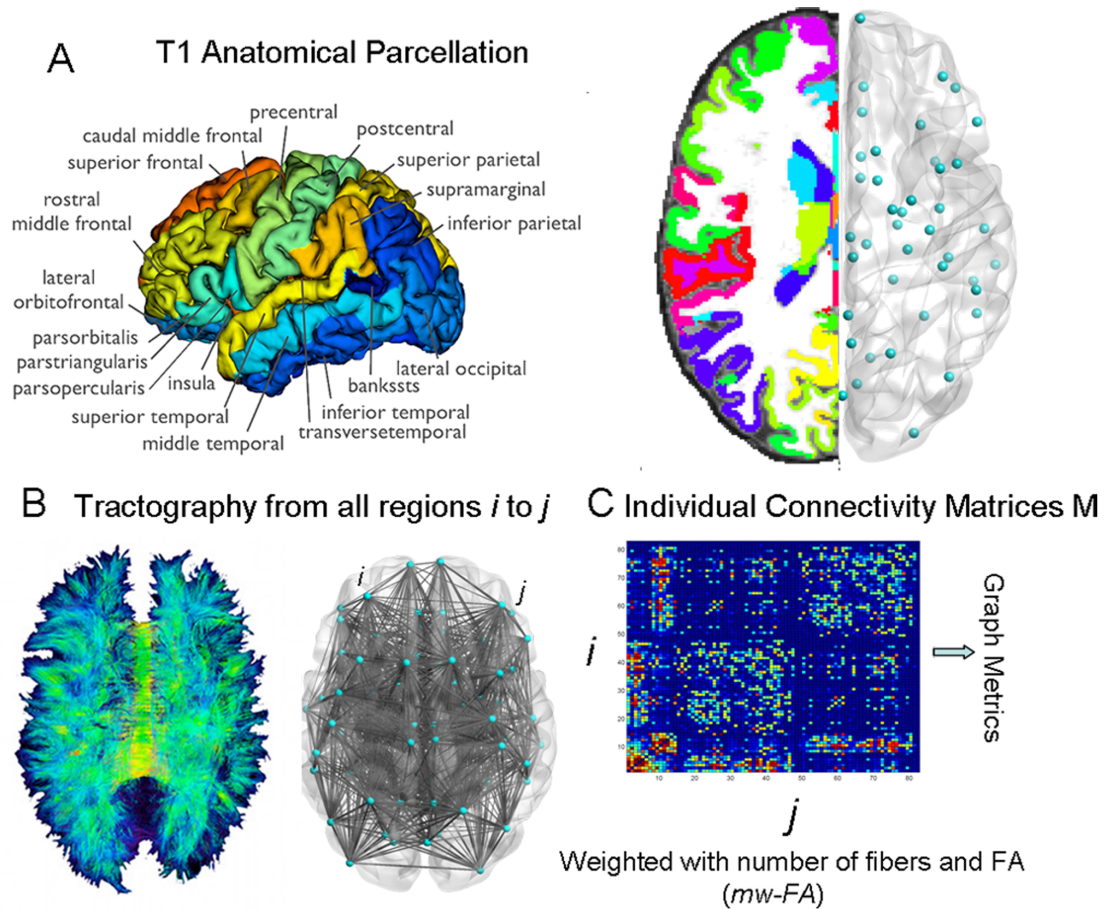


Figure 1. Structural network reconstruction. **A**, First, the T1 images were segmented using freesurfer **B**, the DWI data was processed and all of the possible fibers in the brain were computed using deterministic fiber tracking. The number of streamlines as well as the overall integrity of the connections was calculated for each of the freesurfer regions represented here as nodes. **C**, for each combination of regions i and j nodes of the network, the presence of a connection was determined by those tracts that touched both region i and region j , and the average integrity of each of the tracts (as measured by FA) was entered into the matrix (w_{ij}). From the resulting individual weighted matrices, graph metrics, such as clustering coefficient and efficiency were computed.

Graph metrics.

Graph metrics were computed using the Brain Connectivity Toolbox as described previously (Rubinov and Sporns, 2010). Weighted Connectivity Strength of each node i (S_i) in the network provides information about the total level of the weighted connectivity of a node, formally:

$$S_i^{weighted} = \sum_{j \in N} W_{ij}.$$

The total connection strength of the network was calculated as the sum of S_i in all nodes N .

$$S^{weighted} = \frac{1}{N} \sum_{i \in N} S_i.$$

Weighted Clustering coefficient of the network (C) and of each node (C_i) is used to quantify the extent of segregation in the brain, allowing for specialized processing to occur within densely interconnected groups of brain regions. C_i for each node i corresponds to the number of the connections between all the neighbor nodes of region i , including information on how strong node i and its direct neighbors are clustered, formally:

$$C_i^{weighted} = \frac{\sum_{j,h \in N} (W_{ij} W_{ih} W_{jh})^{\frac{1}{3}}}{k_i (k_i - 1)} \quad \text{With weighted node degree of } i:$$

$$k_i^w = \sum_{j \in N} W_{ij}.$$

Nodes with only one connection were assigned a C_i of 0. The overall clustering-coefficient C characterizes the overall clustering of G and was computed as the average of C_i over all voxels i in G :

$$C^{weighted} = \frac{1}{N} \sum_{i \in N} C_i^{weighted}.$$

Weighted local and global efficiency provide information about the integration of information from distributed brain regions. Paths in a network are sequences of distinct links between nodes that represent route of information flow. In weighted graphs, the distance matrix ($d^{weighted}$) is the inverse of the connection strength, w . Weighted

efficiency (Eff_i) is calculated as the average inverse shortest path length from region i to all other regions j in the network, formally:

$$E_i^{weighted} = \frac{1}{2} \sum_{i \in N} \frac{\sum_{j, h \in N, j \neq i} (w_{ij} \cdot w_{ih} [d_{jh}^{weighted}(N_i)]^{-1})^{1/3}}{k_i (k_i - 1)},$$

with

$$d^{weighted}(i, j) = \sum_{u, v \in g^w} \frac{1}{w_{uv}}.$$

Global efficiency is similarly calculated as the average inverse shortest path length across the whole network, formally:

$$E^{weighted} = \frac{1}{n} \sum_{i \in N} \frac{\sum_{j \in N, j \neq i} (d_{ij}^w)^{-1}}{n - 1}.$$

Statistics

Global Metrics

A General Linear Model (GLM) was fitted to examine the relationship between Efficiency (E), Clustering (C), and Connectivity (S) and the CCI score accounting for age. Analyses were conducted in R Statistics (R version 2.15.13). To determine if sex differences existed in the relationship between the global metrics and CCI, interaction terms were included in the model representing each of the interactions between the global metrics (E, C, and S) and sex. The analysis was conducted twice, first, without inclusion of the FSIQ measure in the model, and second, with the inclusion of FSIQ in the model to determine if the initial relationships differed when accounting for FSIQ. For the analyses of Clustering and Efficiency, the effect of connectivity (S) was also regressed out of the

CCI measure to ensure that any significant relationships found are not driven by the total connectivity, but by the topological organization of connectivity.

As the distribution properties of most graph metrics are poorly characterized, nonparametric statistical tests were also used to examine the differences in the correlations between graph metric and the CCI between males and females (Bullmore and Sporns, 2009; Craddock et al., 2013). First, the observed correlation between global statistics (S , C , and E separately) and CCI was calculated within each sex ($r_{\text{obsFemale}}$, r_{obsMale}). Second, the absolute value of the difference between the correlations was computed. Third, the permutation step consisted of the random reassignment of group (male or female). This was conducted for 10,000 permutations (B). For each B , the absolute values of the differences in correlations between the global statistic and CCI were computed. From this, we obtained a distribution of the differences in correlations. The p-value was calculated as the probability of obtaining differences in correlations that are more extreme than the observed difference in correlations. To remove the effects of age and FSIQ, the analysis was conducted again following the same procedure, however, the correlations between CCI and the graph metric of interest were conducted after the effects of age and FSIQ were regressed out of the CCI measure. For the analyses of Clustering and Efficiency, the effect of connectivity (S) was also regressed out of the CCI measure to ensure that any significant relationships found are not driven by the total connectivity, but by the topological organization of connectivity. All of the analyses were repeated using Fisher's r to z transformation to ensure that the results are consistent across both approaches. If significant differences in correlations were found between the sexes, each global graph metric was then examined within each sex. If no significant

differences in correlations were found, the global graph metric was examined in the whole group. Permutation procedures were followed as above, however, examining only the correlations to determine the probability of obtaining correlations in the permuted data as extreme or more extreme than the observed correlation.

Region Specific Metrics

Permutation testing was conducted to determine which regions exhibited significant sex differences and which regions exhibited significant correlations between graph metrics and creativity in each and sex separately. The same permutation procedure was conducted as with the global metrics, examining the observed absolute value of the difference in correlations between node statistic (S_i , C_i , and E_i) and CCI. For each node i , 10,000 permutations were conducted. To identify which regions within each sex were related to creativity, an additional analysis examined the strength of the correlations in males and females separately. First, the correlation coefficients were calculated within each sex ($r_{\text{obsFemale}}$ r_{obsMale}). Second, the group assignments (male or female) were then randomly reassigned and the correlation between the node statistic and CCI was computed. This was conducted for 10,000 permutations (B), with each permuted correlation coefficient, r_{Female}^* and r_{Male}^* . The p-value was calculated as the probability of obtaining correlations through permutations that are more extreme than the observed correlations. To correct for multiple comparisons, effects were tested to determine if they survived a False Discovery Rate (FDR) threshold of $q = 0.05$ (Benjamini and Hochberg, 1995) across all node specific measures.

Chapter 3 Results

There were no significant differences in age and CCI in males and females (Table 1). Similarly, no significant differences in the global (Table 1) and local graph metrics were observed, corrected for multiple comparisons. There were, however, significant differences in FSIQ, with males scoring (on average) significantly higher than females (Table 1). Correlations between demographic and cognitive variables are shown in Table 2.

TABLE 1. GROUP DIFFERENCES

<i>Cognitive Variables and Graph Metrics</i>	<i>Males, mean ± SD</i>	<i>Females, mean ± SD</i>	p-value
CCI	98.27±8.92	99.76±9.37	0.4137
FSIQ	121.08±14.04	115.25±12.15	0.0265*
Age	21.62±2.80	21.40±3.09	0.6932
Connectivity S ^{weighted}	620.01±65.87	604.04±69.67	0.4633
Clustering C ^{weighted}	0.540±0.01	0.536±0.01	0.1741
Efficiency E ^{weighted}	0.941±0.01	0.943±0.01	0.2374

FSIQ, Full-Scale Intelligence Quotient; CCI, Composite Creativity Index; Connectivity S^{weighted}, Clustering C^{weighted}, Efficiency E^{weighted} *indicates significant at p<0.05.

TABLE 2. GROUP CORRELATIONS

<i>Cognitive Variables</i>		CCI	FSIQ	Age
Males	CCI	1		
	FSIQ	0.42	1	
	Age	-0.01	-0.04	1
Females	CCI	1		
	FSIQ	0.24	1	
	Age	0.22	0.14	1

FSIQ, Full-Scale Intelligence Quotient; CCI, Composite Creativity Index

Global Metrics

GLMs were utilized to determine if the relationship between the global metrics and CCI differed at the level of sex. The results of the analysis of global connectivity

showed a significant interaction between sex and global connectivity (S ; $p = 0.04$), the entire model accounted for 26 percent of the variance ($F(11, 94) = 3.017, p = 0.001$).

These results did not change when accounting for FSIQ.

To further understand the relationship between the global metrics and creativity, the global connectivity was examined *post hoc* in each sex separately. In females, global connectivity ($S, \beta = -0.05, p = 0.012$), controlling for age and FSIQ, predicted CCI ($F(4, 42) = 3.625, p = 0.012$). There were no significant results in males.

The relationship between global connectivity (S) and CCI differed across the sexes ($p < 0.006, p < 0.001$ when accounting for age and FSIQ). There were no significant differences in the correlations with CCI for other global metrics, clustering (C) and efficiency (E). C and E were not significantly related to CCI in either group or the total sample. When the relationship between CCI and S was examined in each sex separately, there was a significant negative correlation between S and CCI when accounting for age and FSIQ ($p = 0.025, r = -0.324$). There was no significant relationship between S and CCI in males. When the effects of FSIQ were not accounted for, results did not significantly differ. Similarly, when S was accounted for in the analyses of C and E , the results did not significantly differ, indicating that the effects were not driven by total connectivity but by the topological organization. In other words, when the connectivity is accounted for, the relationships between creativity and the metrics, C and E , must be driven by the organization of the network that confers clustering and efficiency. All of the results remained significant when the analyses were repeated with Fisher's r to z transformed data.

Region Specific Metrics

Sex Differences

The correlations between connectivity strength (S), Efficiency (E), and Clustering (C) for each region i and creativity significantly differed in males and females in regions primarily within the frontal and parietal lobes, but also within the occipital, temporal, and subcortical regions (Table 2). For each of the regions that demonstrated significant differences in correlations, females demonstrated negative correlations between each graph metric and CCI, while males demonstrated either positive correlations or correlations close to zero (Figure 2). When the effects of FSIQ were not accounted for, results did not significantly differ. Similarly, when S was accounted for in the analyses of C and E, the results did not significantly differ, indicating that the effects were not driven by total connectivity but by the topological organization.

Connectivity S_i

The results of the permutation testing revealed that females exhibited significant negative correlations between Connectivity S_i in regions of the frontal and parietal lobes, as well as a subcortical regions accounting for age and FSIQ. Males exhibited significant positive correlations between Connectivity S_i in accounting for age and FSIQ (Figure 3). Specifically, in females the left banks of the temporal lobe ($p = 0.0012^*$, * indicates region survived critical FDR threshold for multiple comparisons), left caudal anterior cingulate ($p = 0.0218$), right caudal anterior cingulate ($p = 0.0050^*$), right entorhinal ($p = 0.0180$), right fusiform ($p = 0.0043^*$), right inferior parietal ($p = 0.0023^*$), right lateral occipital ($p = 0.0285$), right parahippocampal ($p = 0.0049^*$), right posterior cingulate ($p =$

0.0054), right rostral middle frontal ($p = 0.0482$), right superior frontal ($p = 0.0054$), and right accumbens area ($p = 0.0012^*$) demonstrated significant negative correlations between S_i and CCI, accounting for age and FSIQ. In males, the left middle temporal ($p = 0.018$), right rostral middle frontal ($p = 0.0438$), and right amygdala ($p = 0.0226$) demonstrated significant positive correlations between S_i and CCI, accounting for age and FSIQ.

Efficiency E_i

The results of the permutation testing revealed that females exhibited significant negative correlations between Efficiency E_i in regions of the frontal and parietal lobes, as well as subcortical regions, corrected for age and FSIQ. Males exhibited significant positive correlations between Efficiency E_i , accounting for age and FSIQ (Figure 3). Specifically, in females the left banks of the temporal lobe ($p = 0.0288$), left caudal anterior cingulate ($p = 0.0135$), left medial orbitofrontal ($p = 0.0327$), left rostral anterior cingulate ($p = 0.0187$), left rostral middle frontal ($p = 0.0102$), left temporal pole ($p = 0.027$), right amygdala ($p = 0.0262$), right caudal anterior cingulate ($p = 0.0074$), right entorhinal ($p = 0.0167$), right fusiform ($p = 0.0272$), right inferior parietal ($p = 0.0046$), right inferior temporal ($p = 0.0391$), right isthmus of the cingulate ($p = 0.0298$), right lateral orbitofrontal ($p = 0.0154$), right posterior cingulate ($p = 0.0022$), right superior frontal ($p = 0.0061$), right temporal pole ($p = 0.0018^*$), right caudate ($p = 0.0116$), right amygdala ($p = 0.0262$), and right accumbens area ($p = 0.0004^*$) demonstrated significant inverse correlations between E_i and CCI accounting for age and FSIQ. Whereas males demonstrated significant positive correlations between the left inferior parietal ($p =$

0.0214), left middle temporal ($p = 0.0199$), and right rostral middle frontal ($p = 0.0305$) and CCI accounting for age and FSIQ.

Clustering C_i

The results of the permutation testing revealed that females exhibited significant negative correlations between Clustering C_i in regions of the frontal and parietal lobes, as well as subcortical regions, accounting for age and FSIQ. Males exhibited significant positive correlations between Clustering C_i , accounting for age and FSIQ (Figure 3). Specifically, the left banks of the temporal lobe ($p = 0.0288$), left caudal anterior cingulate ($p = 0.0135$), left medial orbitofrontal ($p = 0.0327$), left rostral anterior cingulate ($p = 0.0187$), left rostral middle frontal ($p = 0.0102$), left temporal pole ($p = 0.0270$), right caudal anterior cingulate ($p = 0.0074$), right entorhinal ($p = 0.0167$), right fusiform ($p = 0.0272$), right inferior parietal ($p = 0.0046$), right inferior temporal ($p = 0.0391$), right isthmus cingulate ($p = 0.0391$), right lateral occipital ($p = 0.0298$), right lateral orbitofrontal ($p = 0.0154$), right posterior cingulate ($p = 0.0022$), right superior frontal ($p = 0.0061$), right temporal pole ($p = 0.0018$), right caudate ($p = 0.0116$), right amygdala ($p = 0.0262$), and right accumbens area ($p = 0.0004^*$).

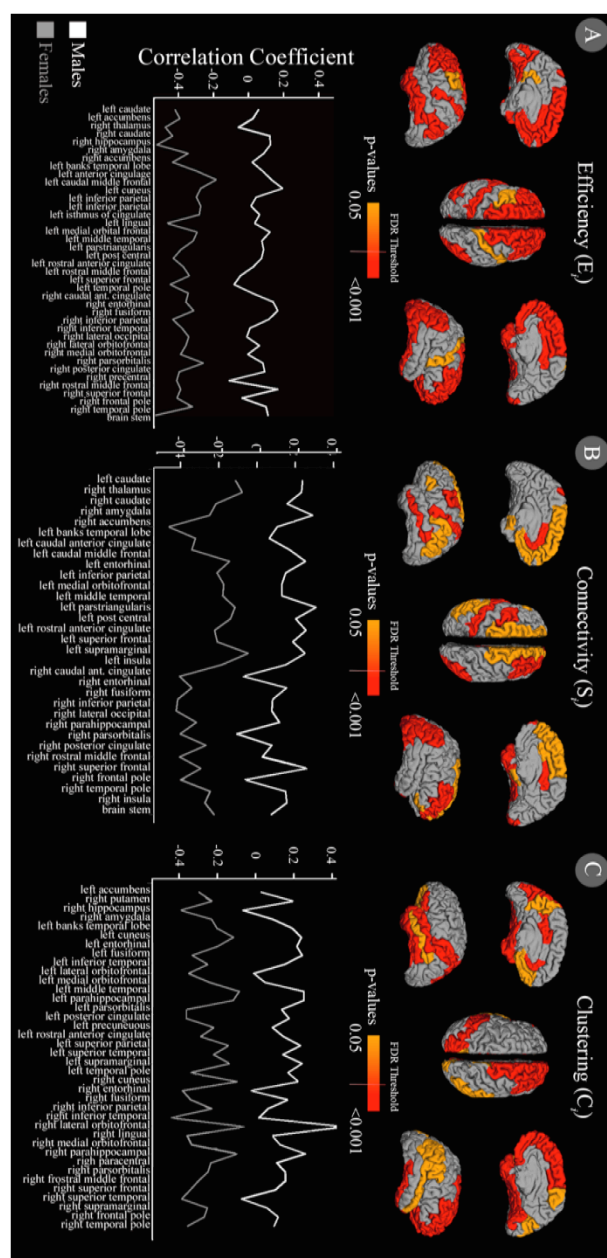


Figure 2. Regions that significantly differ in correlations between graph metrics and creativity in males and females. Upper figures show p-values of significant differences in correlations, color bar indicates magnitude of p-value. Red line indicates critical FDR threshold ($q = 0.05$; see Materials and Methods). Lower figures show correlations between creativity and graph metric for each of the significantly different individual regions with females shown in grey and males shown in white. **A** Efficiency E_i is the average inverse shortest path length from each region to all other regions. **B** Connectivity S_i is the sum of the connections of each region to all other regions. **C** Clustering C_i is the number of connections between all neighbor nodes of the region. As

this is the first study of its kind, results that do not pass FDR threshold are shown to facilitate hypothesis generation in future studies.

TABLE 2: GROUP DIFFERENCES IN CORRELATIONS

<i>Regions that significantly differ in the correlations between graph metric and CC</i>	<i>Connectivity</i>		<i>Efficiency</i>		<i>Clustering</i>	
	$r_{\text{obsFemale}}$ $-r_{\text{obsMale}}$	p-value	$r_{\text{obsFemale}}$ $-r_{\text{obsMale}}$	p-value	$r_{\text{obsFemale}}$ $-r_{\text{obsMale}}$	p-value
Right posteriorcingulate	-0.4329	0.0032*	-0.471	0.0006*		
left caudal middle frontal	-0.397	0.0067*	-0.3728	0.0083*		
left parsorbitalis					-0.4969	0.0004*
left parstriangularis	-0.3408	0.0204	-0.4136	0.0051*		
left superiorparietal					-0.3755	0.0097*
left rostral middle frontal			-0.3961	0.0051*		
left superior frontal	-0.2982	0.0395	-0.3671	0.0102*		
left supramarginal	-0.335	0.0232			-0.3782	0.0072
right parsorbitalis	-0.3446	0.0176	-0.347	0.0188*	-0.4042	0.0041*
right rostralmiddlefrontal	-0.5574	0.0001*	-0.5669	0.0001*	-0.4544	0.001*
right superiorfrontal	-0.3354	0.0224	-0.3765	0.0088*	-0.4441	0.002*
right supramarginal					-0.3117	0.0327
left banks of temporal lobe	-0.3856	0.0074	-0.4382	0.0020*	-0.3938	0.007*
left inferior temporal			-0.3887	0.0067*		

Executive Control Network

TABLE 2: GROUP DIFFERENCES IN CORRELATIONS

<i>Regions that significantly differ in the correlations between graph metric and CC</i>	<i>Connectivity</i>		<i>Efficiency</i>		<i>Clustering</i>	
	$r_{\text{obsFemale}}$ $-r_{\text{obsMale}}$	p-value	$r_{\text{obsFemale}}$ $-r_{\text{obsMale}}$	p-value	$r_{\text{obsFemale}}$ $-r_{\text{obsMale}}$	p-value
left caudal anterior cingulate	-0.5111	0.0002*	-0.4743	0.0011*		
left cuneus			-0.3386	0.0209	-0.3546	0.0150*
l fusiform					-0.5750	0.0001*
l inf parietal	-0.3034	0.0381	-0.4567	0.0009*	-0.4001	0.0053*
l isthmus cing			-0.3009	0.0398		
l entorhinal	-0.3594	0.0145			-0.4135	0.0044*
l posterior cingulate					-0.5360	0.0001*
l precuneus					-0.3038	0.0360
l rostral ant cing	-0.3942	0.0072	-0.5421	0.0001*	-0.4339	0.0029*
r cuneus					-0.3212	0.0300
r caudal ant cing	-0.3308	0.0248	-0.3586	0.0157*		
r entorhinal	-0.4961	0.0005*	-0.5121	0.0003*	-0.3536	0.0139*
r fusiform	-0.4967	0.0004*	-0.4754	0.0008*	-0.5095	0.0005*
r inferior parietal	-0.4993	0.0004*	-0.5534	0.0002*	-0.2928	0.0435
r hippocampal	-0.2964	0.0438			-0.3528	0.0147*

Default Mode Network

	left caudate	-0.3494	0.0169	-0.4627	0.0011*		
Subcortical	left accumbens area			-0.4196	0.0039*	-0.3246	0.0256
	right putamen					-0.4257	0.0031*
	right thalamus proper	-0.3091	0.0347	-0.3102	0.0377		
	right caudate	-0.3722	0.0112	-0.4446	0.0017*		
	right hippocampus			-0.3546	0.0143*	-0.3263	0.0269
	right amygdala	-0.5384	0.0001*	-0.5718	0.0001*	-0.3198	0.0306
	right accumbens area	-0.5686	0.0002*	-0.6496	0.0001*		
	left temporal pole			-0.3910	0.0060*	-0.5105	0.0002
	Right inferior temporal			-0.4088	0.0044*	-0.4598	0.0013*
	Right lingual					-0.4439	0.0016*
Other	left lingual			-0.3779	0.0076*		
	Right superior temporal					-0.3129	0.0329
	Right temporal pole	-0.4283	0.0031*	-0.6476	0.0002*	-0.4516	0.0011*
	left lateral orbitofrontal					-0.3426	0.0173
	left medial orbitofrontal	-0.3097	0.0374	-0.4874	0.0009*	-0.2892	0.0494
	right lateral orbitofrontal			-0.421	0.0028*		
	right medial orbitofrontal			-0.422	0.0026*	-0.4624	0.0009*
	right frontalpole	-0.3941	0.0069*	-0.4443	0.0022*	-0.3861	0.0066*
	Brain Stem	-0.3005	0.041*	-0.3032	0.0388		
	left postcentral	-0.4782	0.0011*	-0.4801	0.0003*		
	right lateral occipital	-0.434	0.0024*	-0.3399	0.0211	-0.5198	0.0002*
	right paracentral			-0.3225	0.0265	-0.3437	0.0182

* indicates region survived critical FDR threshold for multiple comparisons, significance levels here based off of correlation coefficients that were not transformed to z-scores.

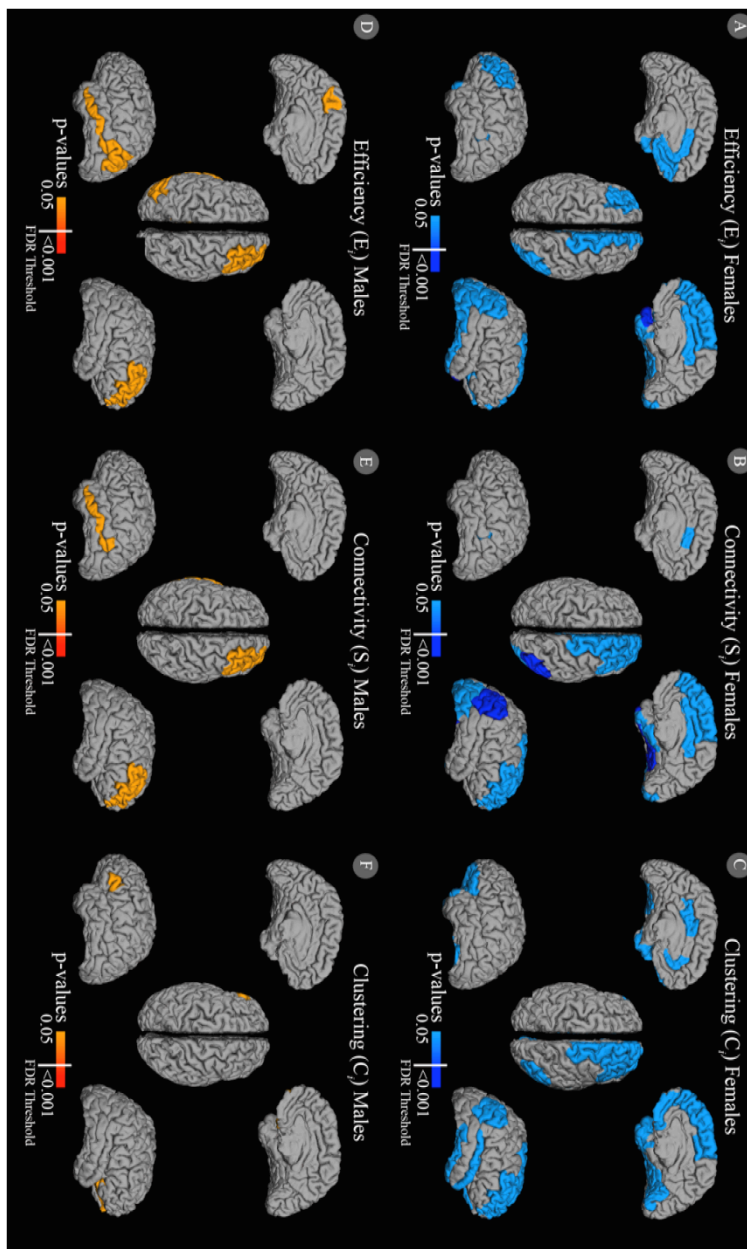


Figure 3. Regions that have significant relationships between graph metric and creativity. Figures show p-values of significant differences in correlations, color bar indicates magnitude of p-value. Upper figures show significant relationships in females where the blue indicates the relationship was inverse, where decreased measure of graph metric was related to increased creativity. Lower figures show significant relationships in males where orange to red indicates the relationship was positive, increased graph metric was related to increased creativity. Line through color bar indicates critical FDR threshold ($q = 0.05$; see Materials and Methods). Results that do not pass FDR threshold are shown to facilitate hypothesis generation in future studies.

Chapter 4 Discussion

This study of large-scale brain connectivity reveals that the relationships between connectivity of the brain and creativity differ in females and males, accounting for age and intelligence. Addressing the cognitive abilities that may relate to previous observations of connectome differences between males and females (Ingallhalikar et al., 2013) our findings show a sexually dimorphic relationship of connectome structure and creativity. Males showed positive, but weak relationships between graph metrics and creativity, while females exhibited an inverse relationship between connectivity of the global structural network and creativity.

Region specific analyses provided further insight into these differences as more creative females demonstrated lower connectivity, efficiency, and clustering in numerous regions across the brain and more creative males exhibited greater connectivity, efficiency, and clustering in few regions. These differing relationships suggest that at the expense of efficiency (greater path lengths), highly creative females are able to develop novel ideas to solutions by involving more regions of the brain in processing. Highly creative males, in contrast, demonstrated more efficiency and clustering of the network, suggesting more direct connections between regions as well as an increase in local processing. The regions implicated include regions of the default mode network (DMN) and the executive control network (ECN), suggesting these networks are critically involved in creativity as measured by divergent thinking. We note that these results are consistent with the emerging data that supports the involvement and interaction of the DMN and the ECN in creative thinking, as reviewed elsewhere (Jung et al., 2013).

Furthermore, we found significant relationships between creativity and regions such as the thalamus, amygdala, caudate, and putamen, regions often neglected in cognitive neuroscience research.

Highly creative females demonstrated inverse relationships across all three measures examined. Global connectivity is the general connectedness of a network, the sum of the weights of all of the connections in the network. For highly creative females, fewer and/or less strong connections were observed, indicated by a lower overall connectivity measure. When the specific nodes of the networks were examined, we observed the same inverse relationships, varying in magnitude across the regions of the brain. This inverse relationship is consistent with previous reports finding lower levels of FA within the left anterior thalamic radiation in creative individuals (Jung et al., 2010a).

Perhaps more informative than general connectivity, however, are the node specific measures of efficiency and clustering, both indirectly related to connectivity strength (van den Heuvel and Sporns, 2011; van den Heuvel et al., 2009b). The brain exhibits a highly efficient small-world functional and structural organization (Achard et al., 2006; Eguiluz et al., 2005; Sporns et al., 2004; Stam and Reijneveld, 2007; van den Heuvel et al., 2008). The small world organization facilitates efficient information transfer via local processing within clusters that work in conjunction with several long-distance connections (Bullmore and Sporns, 2009; Latora and Marchiori, 2001; Watts and Strogatz, 1998). Small worldness is determined through the quantification of minimum path length L , the shortest path needed to move from node i to j in a network, and clustering coefficient C , the extent to which a node's neighbors are connected to each other. A small-world network demonstrates greater clustering and shorter path lengths

than a randomly connected network (Bassett and Bullmore, 2006; Watts and Strogatz, 1998). Interpreting the lower clustering and efficiency within this framework suggests that more creative females have less segregated, modular processing, with longer minimum path lengths between regions. In other words, the networks more closely resemble random networks in terms of the lower clustering observed. Small world networks maximize efficiency with minimum cost (number of paths) (Bassett and Bullmore, 2006). With less clustering, creative females tend to rely on more distributed processing, again suggesting involvement of more widespread regions. In contrast, highly creative males demonstrate more direct paths (connections between nodes have to pass through fewer nodes to reach destination) and greater clustering (more nearby neighbors of a node are connected). This organization is known to facilitate efficient information processing (Bassett and Bullmore, 2006), suggesting that highly creative males rely on a more efficient network.

We found that many of the regions that demonstrated particularly strong relationships between efficiency, clustering and creativity were within the DMN and the ECN; however, the results were by no means limited to these networks. Of note, there is a preponderance of relationships between the regions of the DMN and creativity in females, whereas males seem to demonstrate more relationships within the ECN. Both of these networks are implicated in cognitive abilities required for the development of novel and useful ideas, but they also contribute to a vast array of other cognitive domains (i.e., attention, working memory, visualization, self-reflection), all of which interact with the ability to think divergently. Studies of divergent thinking have examined the extent to which the DMN becomes deactivated in cognitive tasks. Takeuchi et al. (2011) found

that decreased task-induced deactivation (TID) of the precuneus of the DMN during a working memory task correlated to higher measures of divergent thinking. The magnitude of TID of the DMN has been hypothesized to reflect the reallocation of attention from task irrelevant to task relevant cognition (Mckiernan et al., 2003). Highly creative individuals demonstrate increased DMN activation during cognitive tasks (Takeuchi et al., 2012). Furthermore, divergent thinking is positively related to the connectivity between the MPFC and the PCC, suggesting increased fidelity of the DMN in highly creative individuals (Takeuchi et al., 2012). The increased involvement of the DMN in creativity in females found in this study requires additional investigation, but suggests that females possibly rely on self-reflection, retrieval and manipulation of past events, all cognitive abilities linked with DMN function.

Males in contrast, may rely more heavily on the executive control network (ECN), regions of the frontal and parietal lobe that are also implicated in creativity (Ellamil et al., 2012; Liu et al., 2012), primarily the dorsolateral prefrontal cortex (DLPFC), the ventral prefrontal cortex (vPFC), and lateral parietal cortex (Seeley et al., 2007). One study utilized a paradigm in which the individual was asked to first generate ideas in the scanner and separately evaluate and select the best ideas (Ellamil et al., 2012). These authors found that both the ECN and DMN were active during the evaluations of the ideas, whereas the temporal lobe was important to the generation of ideas. Another fMRI study examined neural functioning during freestyle rap improvisation as a means to assess creative generation (Liu et al., 2012). Participants exhibited dissociated activity in the MPFC and DLPFC, with increased activation of the MPFC and decreased activation of the DLPFC during freestyle rap improvisation. One interpretation of this activation

pattern would include the supervisory attention and executive control mechanisms of the DLPFC being down-regulated, allowing for the generation of novel ideas. Future studies should examine directly the interaction between sex and utilization of the DMN and the ECN in creativity tasks.

A more comprehensive understanding of the how these specific cognitive abilities contribute to creative cognition will be necessary to begin to hypothesize how variation in the underlying structure of these networks constrains the manifestation of creative ability. As the functional networks are constrained by the large-scale anatomical network structure (Greicius et al., 2009; Honey et al., 2009; van den Heuvel and Sporns, 2013a, b; van den Heuvel et al., 2009b), the results of this study are expected to be reflected in the functional architectures. However, to our knowledge, there are no studies that have yet examined how creative cognition relates to the functional network architecture using measures of efficiency and clustering.

An important question to address is why females might exhibit strong inverse relationships between network organization and creativity as opposed to males. The studies of sex differences in structural organization highlight the nature of the cognitive strengths of males and females (Gong et al., 2009; Ingalhalikar et al., 2013). Specifically, Gong et al. (2009) discussed female's advantage in aspects of verbal processing as a potential reason for the increased efficiency found within the left hemisphere. Ingalhalikar et al. (2013), in contrast, found that female brains exhibit increased inter hemispheric connectivity, whereas, males had more intra hemispheric connections. These authors suggest that females are better able to integrate information across the hemispheres, whereas males are better able to conduct coordinated action. These studies,

however, do not directly examine how these sex differences in network organization relate to cognitive ability.

Direct work has been done with respect to intelligence. Specifically, anatomical studies find females' global and regional white matter volume is positively correlated with intelligence (Gur et al., 1999; Haier et al., 2005). Males' FA negatively correlates with IQ in the same regions that females have a positive correlation between FA and IQ (Schmithorst, 2009; Schmithorst and Holland, 2007). These results suggest that females display a greater dependence on white matter structure for cognitive function.

Interestingly, while the current utilized different measures of white matter connectivity, the results find that the opposite relationship is true with respect to creativity, while females still depend on white matter structure for creativity, they depend on *less* connectivity, efficiency, and clustering for creativity. These results also suggest that the results of studies that did not examine sex interactions are driven by the relationships between female subjects' FA and creativity.

Lastly, it is possible that the sex differences observed are due to developmental or general differences brain size or the grey to white matter ratio. Our sample, aged 21 +/- ~ 3 years is at the tail end of development whereby age related differences in white matter are observed (De Bellis et al., 2001; Tamnes et al., 2010). Specifically, from age 8 to 30, white matter volume steadily increases, whereas regional FA measures demonstrates regional differences and tend to level off at age 20 (Tamnes et al., 2010). Fronto-temporal connections, specifically, tend to develop more slowly than other regions (Lebel et al., 2008), with males exhibiting faster white matter volume increases than females. Additionally, females demonstrate a greater rate of fiber density increase

with age than boys and an increased organization in the right hemisphere, whereas boys displayed increased organization in the left hemisphere (Schmithorst et al., 2008).

Generally, across all age ranges, males have greater total cerebral volume and total white matter volumes compared to females (Allen et al., 2003; Blatter et al., 1995; Caviness et al., 1996; De Bellis et al., 2001; Filipek et al., 1994; Nopoulos et al., 2000; Reiss et al., 1996). When examining the proportion of white matter to total cerebral volume, men possess greater proportion of white matter compared to women (Allen et al., 2003; Gur et al., 1999), demonstrating regionally specific effects (Luders et al., 2005). With respect to cognitive functioning, studies suggest that women display a greater dependence on white matter volume and men a greater dependence on grey matter volume (Gur et al., 1999). This research suggests two potential lines of inquiry to understand the sex differences in the relationship between creativity and network structure. First, the sex differences may reflect the differential stages of development, with females and males exhibiting different white matter characteristics (i.e. total gray matter/total white matter ratio) at the time of the study. Second, the sex differences are possibly due to the fact that men and women's white matter organization is utilized differently due to the differences in volumes and ratios. Future studies should disentangle these two potential reasons for the sex differences found in the current study.

It is possible that we did not find substantial relationships between network architecture and creativity in males because we did not examine the network measures that are relevant in this group, such as modularity and transitivity as examined by Ingahalikar et al. (2013). Other potential weaknesses of the study include the relatively small sample size (~100), the focus on measures of divergent thinking as a proxy for

creative cognition, and the lack of functional graph measures (e.g., fMRI) by which to compare structural networks.

This study provides initial data relevant to our understanding of sex differences in the relationships between structural networks and creativity. Emerging applications of complex network theory to the analysis of brain connectivity will provide a more sophisticated means of identifying the nature of the differences in network structure underlying individual differences in creative cognition. Moreover, such applications of graph theory should increase substantially our understanding of the interplay between complex cognitive constructs (e.g., creativity) with discrete functional brain networks.

Chapter 5
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