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Research Article

Right but not Left Hemisphere Connectivity Differs between Genders

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Abstract

Background: Gender differences in language abilities have been frequently reported. These differences may be explained in terms of distinct network architecture involving canonical language areas.

Aims: To utilize graph theory measurements to assess language connectivity differences between genders in a sample of normal right handed children.

Method: Resting-state-fMRI data from 40 strong right handed normal boys and girls were analyzed. Functional connectivity between canonical and ancillary language areas and their homotopic contralateral areas was ascertained utilizing several Graph Theory measurements. For all connectivity correlations a P value (t-test) threshold of $p = 0.01$ corrected for multiple comparisons was selected. Graph theory scores were contrasted between gender groups utilizing t-test technique. Significant statistical values for group effects were set at two-tailed t-test, $p < 0.05$. Effect of age, global and verbal IQ were assessed by regression analysis.

Results: No gender effect was found in the left canonical language areas. Three significant gender differences were found. Boys had greater connectivity values for Global Efficiency in right BA37, and for Between Centrality in right BA45. Girls had greater Cluster Centrality in right BA7.

Conclusion: Gender-related differences were not found on the left hemisphere, instead, right hemisphere differences were found, encompassing BA37, BA7 and BA45.

Keywords: *Gender Differences; Language; Brain Connectivity; Graph Theory*

Introduction

A diversity of studies in psychology and neuropsychology has approached the question of gender differences in cognitive abilities [1-11]. Three major gender differences in cognitive abilities have been reported: (1) higher verbal abilities in women, (2) higher spatial abilities in men, and (3) higher arithmetical abilities in men. However, these three differences may be collapsed in only two as differences in calculation abilities may be the result of men's superior spatial abilities [12,13].

Women not only score higher in a variety of verbal tests [11,14-16]. They usually present a faster language development [17-20], and also have a larger vocabulary, more accurate speech production, and greater fluency [15,16,21,22]. Gender differences in language have also been reported during aging. Ardila and Rosselli [23] found that spontaneous language in general decreased with age; however, a significant interaction-effect between age/gender and language was observed. A steady and pronounced spontaneous language decrease across age-groups was observed in males while only mild differences across age-groups were found in females.

Despite the aforementioned reports and numerous publications in the same direction, gender differences in language abilities remain a controversial topic, as there are also judicious studies questioning the presumed higher verbal abilities in women. Hyde and Linn [24], for example, conducted a meta-analysis of 165 language studies involving both children and adults and including a broad range of language tests (vocabulary, analogies, anagrams, reading comprehension, speaking or other verbal communication, essay writing, the Scholastic Aptitude Test –SAT--Verbal, and general verbal ability tests). Results were mixed: forty-four (27%) of the studies reported that females outperformed males, 109 (66%) found no significant gender differences, and 12 (7%) found males outperforming females. The authors concluded that “the magnitude of the sex difference in verbal ability is currently so small that it can effectively be considered to be zero” [24]. Still the main effect size was found for speech production (d = 0.33), giving some advantage to females. Wallentin [25] performed an extensive review of gender differences in language among children, which reached the conclusion that, “A small but consistent female advantage is found in early language development, but this gender difference seems to disappear during childhood. In adults, sex differences in verbal abilities and in language related brain structure are not readily identified. If they exist, they are not easily picked up with the research methods used today” (p. 181). Other studies have found gender differences but in opposite direction. Boys has been found to outperform girls in language skills. For example, Ardila, Rosselli, Matute and Inozemtseva [26] analyzed gender differences in cognitive test performance among a large sample of Latin-American children from continuous age groups (5 to 16 years). Boys outperformed girls in oral language (language expression and language comprehension). However, gender accounted for only a very small percentage of the variance (1% - 3%).

Some authors have emphasized that gender differences may arise from the dispersion in cognitive abilities between men and women rather than just the mean gender differences. For example, based on analyses of mental test scores from different studies, Hedges and Nowell [7] argued that although average sex differences have generally been small and stable over time, the test scores of males have consistently shown greater variance. Moreover, except for tests of reading comprehension, perceptual speed, and associative memory, males typically outnumber females substantially among high-scoring individuals.

The origin of gender differences in cognitive abilities is not clear yet, though it has been assumed that both biological and environmental factors contribute to the variation that has been demonstrated between males and females. Among the biological factors identified, differences in neurological structure and function have been pointed out [27-29]. Some authors have found that hormones are associated with certain aspects of brain differentiation [14,30,31]. The androgens and ovarian hormones (estrogen and progesterone) have traditionally been considered important in terms of sexual differentiation, and the existence of two sensitive periods in which these differences are induced is widely accepted. The first period is recognized as organizational, when significant and permanent structural changes occur in the brain. High or low steroid hormonal levels during prenatal development determine and induce morphological, anatomical and functional differences between the brains of women and men. The second period is characterized by the effect of circulating hormones on behavior, which has been called the activational effect. In this second period, hormones cannot produce permanent changes in the central nervous system, though they can induce the initiation of previously absent sexual or non-sexual behaviors [32]. On the bases of these physiological facts, some gender differences in the brain organization of language, including differences in connectivity, could be hypothesized.

Different techniques directed to analyze brain connectivity have been recently developed to study functional integration of brain. Such analyses utilize measures of synchrony within or among spatial regions of the brain. These regions of interest (ROI) can be defined based on either prior anatomical knowledge, or on resting states or task-based fMRI maps. Yaesoubi, Miller, and Calhoun [33], showed evidence of cross-frequency dependence between functional networks in resting state fMRI, which was associated to the subject gender. Others have found gender differences in BOLD activation using fMRI during the cognitive tasks; for example, perception of emotions [34].

Graph Theory

The advent in the last decade of brain functional connectivity based on the rs-fMRI technique, has been followed by an explosion of different mathematical and statistical approaches to study brain networks. The connectivity of a given functional area (module) with the remaining of brain areas may be ascertained in terms of strength, directionality, asymmetry (with respect its brain counterpart), stability, etc. These measures, however, are zeroed at the module level. A mathematical description of the role of the node within a given network or the quantification of the network architecture, requires of a virtual representation of the network components. Graph theory fills in this necessity. By representing the functional module into a node or vertex and the connections into lines or edges, a graph of the entire network may be obtained. Several measures may then describe the organization of that network. See for example the network represented in figure 1.

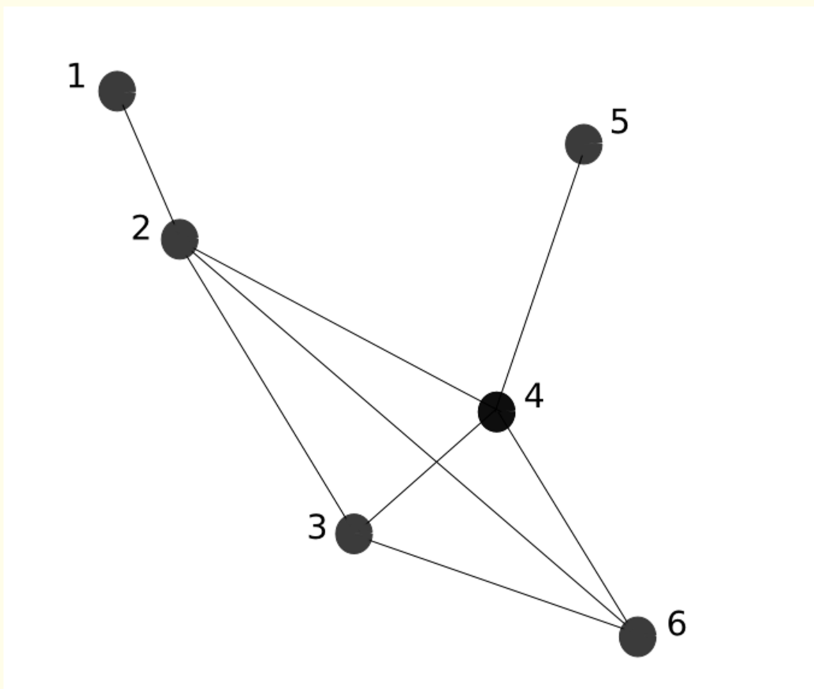

Figure 1: *Basic network example, consisting of 6 nodes (black circles), 8 edges (lines) and 4 triangles. Nodes 1 and 5 have a degree of 1. Nodes 2 and 6 have degree of 3. These same nodes belong as vertices to 3 triangles, each. Average path length for 2 is lower than for node 5 (see text for further explanation).*

Nodes may be described in terms of number of connections. Nodes 1 and 5 have only one connection, nodes 2 and 4 have 4 connections each, while the node 6 has 3 connections. The number of node connections (edges related to a node) is termed Degree. The degree of an entire network could be the average of node degrees on it. Nodes may be described in terms of Clusterization, or roughly, the number of triangles that a vertex belongs to. Node 1 and 5 do not belong to any triangle, and therefore have a clusterization value of zero; nodes 2 and 4 are vertices of 3 triangles each: for node 2, 2-4-6, 2-3-6, and 2-3-4; for node 4: 4-2-6, 4-3-2, and 4-6-3. Similarly to degree, clusterization could be a measure related to a node or to the entire network. Clusterization is a measure of efficiency and resiliency. Indeed, a well interconnected cluster may tolerate a node to fail without impacting critically its output. Another measure important in graph theory is Path length. A quick observation of figure 1 reveals important differences between nodes 2 and 5 in terms of steps to reach the remaining nodes. For node 5 to reach node 1, requires 3 steps in the shortest path; node 2, instead, may reach any of the nodes in the network in less than two steps. Path-length is then another measure of connectivity related to efficiency.

There are several measures to describe the efficiency, resiliency, organization and hierarchy of a network. The following are definitions of the main measurements (we have omitted on purpose the equations describing these measures):

- **Local efficiency**: is the ratio defined by the number of connections between a node with its neighbors divided by the total of possible connections of that node.
- **Global efficiency**: is the average of the node's local efficiency within a network.
- **Degree**: The degree of a vertex is the number of connections or edges it has. The form of the degree distribution provides important information about the structure of the network.
- **Cluster Coefficient**: is the probability that the neighbors of this vertex connect each other. The clustering coefficient of a vertex ranges between 0 and 1.
- **Network Clustering**: is the average of the clustering coefficients of all individual vertices. This measure is associated with robustness of a network, that is its resilience against random network damage.
- **Betweenness Centrality**: The betweenness centrality of a particular vertex is the fraction of shortest paths in the network that pass through this vertex. It is a measure of node relevance withing the network.

In this study, we aim to utilize graph theory measurement to assess language connectivity differences between genders in a sample of normal right handed children. For this purpose, we have extended the criteria of canonical language areas to 16 areas including some relevant ancillary areas. Core Brodmann's area 44 (BA44) and BA45, for Broca's; and BA22 and 21 for Wernicke's, were initially selected. BA6, BA7, BA9, BA19, BA37, BA38, BA39, BA40, BA41, BA42, BA46, and BA47 for a total of 16 areas were also included. These areas have been proved to participate in language activations and networks as shown by several meta-analysis studies recently published by the authors [35-40]. Our general hypothesis was that gender language skills asymmetries referred in the literature and seemingly also found in daily life could be demonstrated by characterizing language networks with graph theory. More specifically we hypothesized that these gender differences are mostly found in nodes related to fluency and executive-related nodes in the left frontal lobe (BA44, BA45, BA46, and BA47).

Methods

Data was selected from a large sample of rs-fMRI publicly released as the "ADHD-200". This dataset is part of the "1000 Functional Connectomes Project" available at http://fcon_1000.projects.nitrc.org/indi/adhd200 [41]. We used the data-series from New York University from which 40 normal children satisfying the following criteria were selected: (1) age older than 7 and below 19 years; we used this age range because at this age range language is sufficiently developed to find potential gender differences; (2) right handedness; (3) minimum verbal IQ 85, (4) minimum full IQ of 80 and (5) absence of neurological conditions, in order to avoid uncontrolled conditions potentially affecting the nervous system development,. The NYU dataset has a large sample of typically developing English-speaker subjects.

Right handedness was evaluated according with the Edinburgh Handedness Inventory [42]. Only subjects with scores higher than 0.30 were included. Verbal and Full IQ were assessed in all subjects utilizing the Wechsler Abbreviated Scale [43]. With these criteria the dataset was confirmed by 19 boys and 21 girls, age 7 - 18 (mean/SD = 11.0/2.64). For detail demographics see table 1.

n = 40 Male = 19	Range	Mean	SD
Age	7 - 18	11.0	2.64
Handedness*	0.31 - 1.0	0.68	0.21
Verbal IQ**	85 - 141	111.3	13.13
Full IQ**	80 - 142	109.3	14.66

Table 1: *General characteristics of the sample.*
**: Edinburgh Handedness Inventory (Oldfield RC, 1971)*
***: Wechsler Abbreviated Scale*

MRI description

MRI data consisted of anatomical volumes and blood oxygen level dependent (BOLD)-sensitive echo-planar images obtained in a 3.0 Tesla Siemens Magneton Allegra Syngo (Erlangen, Germany). Anatomical T1-weighted MRI 3D-volumes were obtained in the sagittal plane with a FOV of 256, 128 slices per slab, slice thickness of 1.33 mm. Acquisition settings: TR: 2530, TE: 3.25, Flip Angle 7 deg, The echo-planar sequence sensitive to BOLD effect was obtained with the following parameters: 180 time-points (scan time 6:00 min), voxel size 3.0 x 3.0 x 4.0. 33 axial interleaved slices with no gap, FOV 240 mm, Slice thickness 4.0 mm, TR: 2000, TE: 15ms, 1 average, Flip angle: 90 deg, standard shim mode.

Pre-processing

For each subject the 180 time-points of the rs-fMRI data were visually inspected in a dynamic presentation by one of the authors (BB). All cases presenting more than 2 mm of translational or rotational head motion or irregular/asymmetric skull shape were discarded and replaced from other subject from the pool. Pre-processing was performed utilizing SMP12 (http://www.fil.ion.ucl.ac.uk/spm/) [44] and Matlab 8.6, R2015b. Data was re-aligned, normalized and spatial smoothed by use of a Gaussian kernel of full width at half maximum of 7 mm. Anatomical volumes were segmented into gray and white matter, and CSF areas and the resulting masks eroded in one voxel dimension to minimize partial volume effects. The temporal time series characterizing the estimated subject motion (3 translations, 3 rotations and 6 parameters representing their first-order temporal derivatives); the BOLD effect of the white matter mask (3 Principal component parameters (PCA)); and the CSF mask (3 PCA parameters) were used as temporal covariates and removed from the BOLD functional data using linear regression methods. The resulting residual BOLD time series were band-pass filtered ($0.008 < f < 0.09$) to obtain the spontaneous oscillations of the neural networks. The rs-fMRI was corregistered to the structural T1 anatomical image and then to Montreal Neurological Institute-152 standard space.

Processing

First Level

Intrahemispheric ROI to ROI connectivity between specific functional areas was assessed. Seeding sources were derived from the atlas of Brodmann areas (BA) provided by SPM12. Based on prior publications on meta-analysis of co-activations of language tasks [35-40], 32 BAs were selected --16 per each hemisphere: BA6, premotor; BA7, dorso-parietal; BA9, pre-frontal; BA19, secondary visual; BA21 and BA22, Wernicke's area; BA37, fusiform gyrus; BA38, temporal pole; BA39, angular gyrus; BA40, supramarginal gyrus; BA41 and BA42, primary auditory area; BA44 and BA45, Broca's area; BA46, prefrontal; and BA47, pars orbitalis of the inferior frontal gyrus (IFG). Graph Theory Functional Connectivity was performed utilizing the Toolbox "Conn15.g" available at http://www.nitrc.org/projects/conn [45]. For each subject a seed-to-intra-hemispheric target-ROI graph theory measures were computed utilizing a weighted general linear model (ROI-to-ROI analyses).

Second Level

For the second level analysis average of graph theory measures were obtained. All subject's ROI-to-ROI connectivity maps were pooled with the following settings: Between subject contrast, 1 (Effect of All subjects, one group); between-conditions contrast, 1 (Effect of Rest); Between-sources contrast, 1 (Effect of [BA] against all brain BA).

Within-subject effects of the between-sources contrasts analyses correspond to multivariate/repeated-measures analyses of the selected effects modeled with a general linear model. The output is a within-subjects linear combination of effects specified by the "between-conditions" and "between-sources" contrasts, applied to the first-level connectivity-measure matrix (the ROI-to-ROI analyses).

We intentionally avoided the intergroup contrast effect [e.g., 1 - 1] at this level, as we were inclined to obtain subject-level measures to be able to regress those values against independent variables scalars considered as confounding interactions.

For both levels, six graph theory measures were found for each of the 32 nodes. These measures are: Degree, Cluster Coefficient, Global Efficiency, Local Efficiency, Betweenness Centrality, and Average Path-length. ROI-to-ROI connectivity was thresholded at $p < 0.01$ (two sided) corrected for multiple comparisons with False Discover Rate (FDR) technique. From the report provided by Conn independent tables of intra-hemispheric graph theory connectivity measures were obtained, selecting as target only the language related BAs referred previously. The following parameters were computed per node and measure: t score, p uncorrected and p corrected (FDR). Only nodes to BA connectivity was accepted with $p < 0.01$ p FDR corrected . This resulted in t minimum value of 2.03.

Tables of subject/BA-node per graph-theory measure were obtained. Graphic schematic representation of the graph per BA/ hemisphere were obtained. ROI-isocenters are presented as spheres and connectivity as lines. Spheres' radio relates to the strength of the graph theory measure value (t value).

Asymmetry measures

Global graph theory connectivity measures were assessed per hemisphere as the sum of all measures connectivity values and per Brodmann area/per side. Left vs right group values were also contrasted.

The interaction gender to graph-theory measures were performed with two-sided t test, utilizing GNU-PSPP 0.7.9, 2012, available at https://www.gnu.org/software/pspp/pspp.html [46]. Null hypotheses were rejected with p values equal or less than 0.05. Interactions between gender group vs age, global IQ and verbal IQ were assessed with two-tailed t test, at $p < 0.05$. Global IQ scores vector was regressed against each graph theory measures to ascertain its effect at subject level, given its interaction at group level (gender).

Results

No interaction between gender group and age (p = 0.52; CI (95%) = -2.1918 <-0.5372 < 1.1174) or between gender and Verbal IQ (p = 0.13; CI (95%) = -14.4435 <-6.43609 < 1.5714) were found. However, significant interaction was found between Global IQ and gender, boys having greater IQ scores than girls (p = 0.029; CI (95%) = -18.7646 <-10.05514 < -1.3456). There was no interaction between age and Global or Verbal IQ (R = -0.0621, -0.0274, respectively).

Global asymmetries: The graph theory measures of all averaged BAs across subjects did not show any significant interaction with gender (t values: minimum 0.236, for Local Efficiency; maximum 0.988 for Global Efficiency) (See Table 2). The graph theory measures of each BA (16 left and 16 right pairs) are shown in table 2.

	Right				T-test	Left				T-test
	Males		Females			Males		Females		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
BA 19										
Global Efficiency	0.355	0.085	0.360	0.130	0.874	0.362	0.090	0.361	0.131	0.976
Local Efficiency	0.649	0.351	0.706	0.283	0.598	0.584	0.349	0.595	0.306	0.923
Betweenness Centrality	0.020	0.023	0.027	0.044	0.527	0.037	0.035	0.043	0.056	0.651
Cost	0.117	0.044	0.116	0.067	0.982	0.113	0.047	0.129	0.069	0.424
Average Path Length	3.382	0.748	2.944	0.880	0.100	3.318	0.700	2.995	0.964	0.236
Clustering Coefficient	0.572	0.326	0.628	0.268	0.586	0.501	0.311	0.499	0.259	0.979
Degree	3.631	1.382	3.619	2.085	0.982	3.526	1.466	4	2.144	0.424

	Right				T-test	Left				T-test
	Males		Females			Males		Females		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
BA 21										
Global Efficiency	0.445	0.119	0.478	0.056	0.259	0.046	0.073	0.495	0.065	0.261
Local Efficiency	0.666	0.180	0.663	0.217	0.963	0.671	0.210	0.684	0.164	0.822
Betweenness Centrality	0.077	0.070	0.066	0.066	0.627	0.075	0.067	0.078	0.061	0.822
Cost	0.190	0.070	0.202	0.063	0.553	0.203	0.075	0.227	0.078	0.337
Average Path Length	2.638	0.625	2.566	0.387	0.660	2.715	0.517	2.503	0.393	0.150
Clustering Coefficient	0.527	0.188	0.491	0.190	0.559	0.516	0.198	0.502	0.178	0.816
Degree	5.894	2.183	6.285	1.953	0.553	6.315	2.334	7.047	2.418	0.337

	Right				T-test	Left				T-test
	Males		Females			Males		Females		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
BA 22										
Global Efficiency	0.492	0.087	0.504	0.099	0.681	0.486	0.088	0.471	0.102	0.630
Local Efficiency	0.654	0.146	0.596	0.181	0.280	0.655	0.207	0.593	0.277	0.379
Betweenness Centrality	0.104	0.061	0.139	0.095	0.173	0.100	0.060	0.106	0.097	0.832
Cost	0.225	0.076	0.239	0.058	0.522	0.229	0.075	0.199	0.071	0.212
Average Path Length	2.635	0.842	2.306	0.456	0.127	2.717	0.870	2.457	0.545	0.258
Clustering Coefficient	0.476	0.172	0.411	0.173	0.527	0.501	0.212	0.444	0.216	0.406
Degree	7	2.380	7.428	1.804	0.522	7.105	2.354	6.190	2.204	0.212

	Right				T-test	Left				T-test
	Males		Females			Males		Females		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
BA 37										
Global Efficiency	0.405	0.096	0.404	0.127	0.983	0.411	0.124	0.420	0.127	0.816
Local Efficiency	0.657	0.184	0.419	0.269	0.005	0.449	0.341	0.612	0.229	0.087
Betweenness Centrality	0.083	0.076	0.058	0.078	0.309	0.086	0.091	0.077	0.094	0.773
Cost	0.129	0.057	0.150	0.078	0.334	0.152	0.083	0.164	0.068	0.632
Average Path Length	2.857	0.720	3.034	0.984	0.529	2.905	0.630	2.895	0.853	0.967
Clustering Coefficient	0.364	0.240	0.496	0.178	0.074	0.374	0.297	0.494	0.185	0.137
Degree	4	1.795	4.666	2.435	0.334	4.736	2.578	5.095	2.119	0.632

	Right				T-test	Left				T-test
	Males		Females			Males		Females		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
BA 38										
Global Efficiency	0.354	0.129	0.373	0.136	0.646	0.386	0.116	0.433	0.073	0.131
Local Efficiency	0.707	0.319	0.782	0.250	0.457	0.729	0.297	0.588	0.314	0.185
Betweenness Centrality	0.011	0.019	0.009	0.015	0.778	0.027	0.042	0.043	0.073	0.430
Cost	0.103	0.057	0.122	0.071	0.353	0.122	0.071	0.150	0.077	0.241
Average Path Length	3.030	0.660	2.974	0.359	0.756	3.076	0.524	2.820	0.417	0.099
Clustering Coefficient	0.644	0.312	0.680	0.251	0.720	0.646	0.304	0.488	0.269	0.112
Degree	3.210	1.781	3.809	2.204	0.353	3.789	2.225	4.666	2.415	0.241

	Right				T-test	Left				T-test
	Males		Females			Males		Females		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
BA 39										
Global Efficiency	0.374	0.114	0.399	0.068	0.374	0.411	0.083	0.422	0.072	0.638
Local Efficiency	0.756	0.245	0.738	0.326	0.856	0.740	0.303	0.776	0.205	0.668
Betweenness Centrality	0.027	0.049	0.028	0.043	0.935	0.045	0.068	0.036	0.049	0.666
Cost	0.112	0.061	0.116	0.059	0.806	0.142	0.076	0.155	0.070	0.592
Average Path Length	3.148	0.745	3.023	0.585	0.562	3.090	0.761	2.924	0.529	0.425
Clustering Coefficient	0.68	0.249	0.663	0.330	0.870	0.648	0.318	0.669	0.237	0.820
Degree	3.473	1.896	3.619	1.829	0.806	4.052	1.747	4.809	2.182	0.236

	Right				T-test	Left				T-test
	Males		Females			Males		Females		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
BA 40										
Global Efficiency	0.436	0.104	0.425	0.086	0.697	0.406	0.106	0.427	0.094	0.520
Local Efficiency	0.450	0.235	0.560	0.317	0.227	0.438	0.307	0.544	0.306	0.315
Betweenness Centrality	0.105	0.118	0.055	0.069	0.108	0.078	0.093	0.065	0.069	0.627
Cost	0.162	0.067	0.149	0.073	0.535	0.123	0.067	0.156	0.079	0.169
Average Path Length	2.549	0.523	2.942	0.705	0.055	2.713	0.484	2.940	0.737	0.261
Clustering Coefficient	0.353	0.160	0.442	0.286	0.244	0.374	0.258	0.420	0.275	0.612
Degree	5.052	2.094	4.619	2.268	0.535	3.842	2.088	4.857	2.455	0.169

	Right				T-test	Left				T-test
	Males		Females			Males		Females		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
BA 41										
Global Efficiency	0.407	0.059	0.369	0.122	0.233	0.410	0.068	0.387	0.082	0.333
Local Efficiency	0.747	0.317	0.723	0.315	0.821	0.797	0.269	0.739	0.213	0.464
Betweenness Centrality	0.016	0.022	0.030	0.043	0.209	0.026	0.045	0.019	0.028	0.567
Cost	0.142	0.048	0.113	0.061	0.109	0.149	0.045	0.124	0.044	0.089
Average Path Length	3.155	0.802	2.979	0.890	0.519	3.173	0.832	2.986	0.771	0.466
Clustering Coefficient	0.672	0.303	0.653	0.305	0.851	0.732	0.271	0.617	0.201	0.148
Degree	4.421	1.502	3.523	1.913	0.109	4.631	1.422	3.857	1.388	0.089

	Right				T-test	Left				T-test
	Males		Females			Males		Females		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
BA 42										
Global Efficiency	0.348	0.139	0.330	0.163	0.714	0.411	0.066	0.388	0.089	0.387
Local Efficiency	0.763	0.304	0.645	0.348	0.342	0.820	0.178	0.691	0.316	0.138
Betweenness Centrality	0.011	0.020	0.052	0.100	0.086	0.024	0.034	0.028	0.041	0.788
Cost	0.112	0.069	0.101	0.072	0.638	0.154	0.063	0.124	0.050	0.102
Average Path Length	3.317	0.780	2.908	0.916	0.160	3.144	0.688	3.005	0.797	0.560
Clustering Coefficient	0.710	0.310	0.564	0.338	0.235	0.727	0.184	0.617	0.320	0.209
Degree	3.473	2.169	3.142	2.242	0.638	4.789	1.960	3.857	1.558	0.102

	Right				T-test	Left				T-test
	Males		Females			Males		Females		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
BA 44										
Global Efficiency	0.389	0.148	0.323	0.169	0.206	0.426	0.093	0.390	0.113	0.284
Local Efficiency	0.566	0.293	0.596	0.364	0.799	0.589	0.319	0.577	0.353	0.916
Betweenness Centrality	0.054	0.135	0.033	0.072	0.379	0.035	0.034	0.028	0.029	0.501
Cost	0.125	0.081	0.093	0.066	0.079	0.140	0.083	0.119	0.077	0.411
Average Path Length	2.811	0.651	2.985	0.772	0.469	2.915	0.493	2.902	0.762	0.955
Clustering Coefficient	0.452	0.252	0.504	0.315	0.618	0.493	0.306	0.494	0.339	0.993
Degree	4.210	2.529	2.904	2.047	0.079	4.368	2.586	3.714	2.390	0.411

	Right				T-test	Left				T-test
	Males		Females			Males		Females		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
BA 45										
Global Efficiency	0.418	0.162	0.388	0.120	0.501	0.433	0.129	0.420	0.063	0.686
Local Efficiency	0.493	0.298	0.611	0.284	0.255	0.641	0.237	0.571	0.302	0.452
Betweenness Centrality	0.092	0.104	0.034	0.040	0.025	0.072	0.075	0.046	0.075	0.279
Cost	0.154	0.083	0.124	0.075	0.236	0.162	0.084	0.133	0.067	0.230
Average Path Length	2.618	0.438	2.977	0.863	0.128	2.716	0.553	2.856	0.556	0.437
Clustering Coefficient	0.381	0.225	0.513	0.256	0.127	0.514	0.222	0.495	0.267	0.818
Degree	4.789	2.572	3.857	2.329	0.236	5.052	2.634	4.142	2.080	0.230

	Right				T-test	Left				T-test
	Males		Females			Males		Females		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
BA 46										
Global Efficiency	0.439	0.068	0.414	0.078	0.286	0.357	0.170	0.388	0.152	0.552
Local Efficiency	0.618	0.274	0.564	0.352	0.604	0.606	0.360	0.586	0.241	0.851
Betweenness Centrality	0.069	0.096	0.048	0.064	0.439	0.0187	0.022	0.037	0.063	0.222
Cost	0.149	0.070	0.125	0.080	0.335	0.106	0.075	0.130	0.078	0.337
Average Path Length	2.765	0.492	2.905	0.599	0.428	2.867	0.461	2.872	0.779	0.984
Clustering Coefficient	0.486	0.236	0.449	0.305	0.684	0.501	0.338	0.467	0.197	0.717
Degree	4.631	2.191	3.904	2.488	0.335	0.717	0.337	4.047	2.418	0.337

	Right				T-test	Left				T-test
	Males		Females			Males		Females		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
BA 47										
Global Efficiency	0.464	0.083	0.465	0.70	0.969	0.494	0.075	0.505	0.063	0.633
Local Efficiency	0.610	0.287	0.703	0.177	0.226	0.526	0.178	0.628	0.188	0.089
Betweenness Centrality	0.062	0.073	0.051	0.051	0.591	0.106	0.090	0.111	0.100	0.875
Cost	0.176	0.084	0.185	0.068	0.703	0.213	0.061	0.222	0.080	0.701
Average Path Length	2.639	0.550	2.633	0.463	0.971	2.552	0.710	2.391	0.336	0.357
Clustering Coefficient	0.475	0.252	0.539	0.181	0.364	0.382	0.133	0.460	0.177	0.129
Degree	5.473	2.63	5.761	2.119	0.703	6.631	1.891	6.904	2.508	0.701

	Right				T-test	Left				T-test
	Males		Females			Males		Females		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
BA 6										
Global Efficiency	0.458	0.059	0.418	0.123	0.205	0.456	0.068	0.474	0.093	0.496
Local Efficiency	0.442	0.351	0.535	0.313	0.391	0.478	0.354	0.479	0.233	0.998
Betweenness Centrality	0.069	0.061	0.080	0.091	0.665	0.090	0.106	0.111	0.095	0.512
Cost	0.159	0.075	0.141	0.085	0.479	0.156	0.069	0.179	0.090	0.364
Average Path Length	2.586	0.432	2.763	0.594	0.297	2.615	0.538	2.573	0.838	0.854
Clustering Coefficient	0.386	0.333	0.455	0.296	0.507	0.404	0.301	0.360	0.173	0.586
Degree	4.947	2.344	4.380	2.635	0.478	4.842	2.141	5.571	2.803	0.364

	Right				T-test	Left				T-test
	Males		Females			Males		Females		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
BA 7										
Global Efficiency	0.321	0.141	0.358	0.126	0.706	0.321	0.141	0.349	0.125	0.514
Local Efficiency	0.549	0.366	0.727	0.260	0.104	0.731	0.313	0.635	0.347	0.433
Betweenness Centrality	0.037	0.045	0.043	0.072	0.741	0.025	0.047	0.026	0.040	0.929
Cost	0.021	0.057	0.121	0.058	0.965	0.112	0.077	0.109	0.607	0.892
Average Path Length	2.959	1.048	3.021	1.039	0.852	3.202	1.127	3.051	0.974	0.650
Clustering Coefficient	0.479	0.332	0.686	0.256	0.043	0.659	0.315	0.546	0.334	0.336
Degree	3.737	1.790	3.761	1.813	0.965	3.473	2.412	3.380	1.883	0.892

	Right				T-test	Left				T-test
	Males		Females			Males		Females		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
BA19										
Global Efficiency	0.463	0.073	0.454	0.132	0.788	0.456	0.073	0.486	0.082	0.235
Local Efficiency	0.460	0.333	0.562	0.200	0.260	0.643	0.226	0.628	0.176	0.815
Betweenness Centrality	0.111	0.103	0.071	0.058	0.138	0.051	0.053	0.095	0.113	0.131
Cost	0.159	0.074	0.182	0.099	0.410	0.169	0.072	0.190	0.077	0.389
Average Path Length	2.559	0.453	2.555	0.546	0.980	2.677	0.501	2.476	0.549	0.235
Clustering Coefficient	0.378	0.284	0.434	0.189	0.476	0.501	0.234	0.461	0.151	0.532
Degree	4.947	2.296	5.666	3.071	0.410	5.263	2.232	5.904	2.406	0.389

Table 2: *Statistical Analysis of the Graph Theory biomarkers by Brodmann's area and their interactions with gender. Significant differences (p values <0.05) are found under T-test column. See body text for details.*

We analyzed the effect of global and verbal IQ on the three right BA-related most-significant graph-theory measures in which boys and girls showed differences. Results showed that neither Global IQ nor Verbal IQ or age interacted significantly with the three graph-theory measures showing gender differences (Table 3).

Interactions					
Variable 1	vs	Variable 2	Test	Stats	Score
Age		Global IQ	Linear Regression	R	-0.062
Age		Verbal IQ	Linear Regression	R	-0.027
Gender		Verbal IQ	T-test	P	0.13
Gender		Global IQ	T-test	P	0.029
Global IQ		Local Efficiency Right BA37	Linear Regression	R	0.32
Global IQ		Betweenness Centrality Right BA45	Linear Regression	R	0.2
Global IQ		Cluster Coefficient Right BA7	Linear Regression	R	0.18
Verbal IQ		Local Efficiency Right BA37	Linear Regression	R	0.29
Verbal IQ		Betweenness Centrality Right BA45	Linear Regression	R	0.23
Verbal IQ		Cluster Coefficient Right BA7	Linear Regression	R	0.12
Age		Local Efficiency Right BA37	Linear Regression	R	-0.217
Age		Betweenness Centrality Right BA45	Linear Regression	R	-0.254
Age		Cluster Coefficient Right BA7	Linear Regression	R	0.009

Table 3: *Neuropsychology and demographic interactions with graph theory significant variables. Note all weak interactions except Global IQ vs. Local Efficiency on the right BA37, where a mild interaction is found.*

Three comparisons showed significant statistical difference between genders:

(1) Boys > girls in right BA37, Local Efficiency: mean/SD: 0.419/0.269, girls; 0.657/0.184, boys; P = 0.0052, CI (95%): 0.082 < 0.23797 < 0.3939; (2) Boys > girls in right BA45, Between-centrality: mean/SD: 0.035/0.041, girls; 0.092/0.104 boys; P = 0.0248, CI (95%) -0.1057 < -0.05751 < -0.0093; and (3) Girls > boys in right BA7, Clustering Coefficient: mean/SD: 0.6865/0.2562, girls; 0.4794/0.3325, boys; P = 0.0428, CI (95%) 0.0143 < 0.2071 < 0.3999.

Figure 2 shows exemplary graph representation of the studied language network.

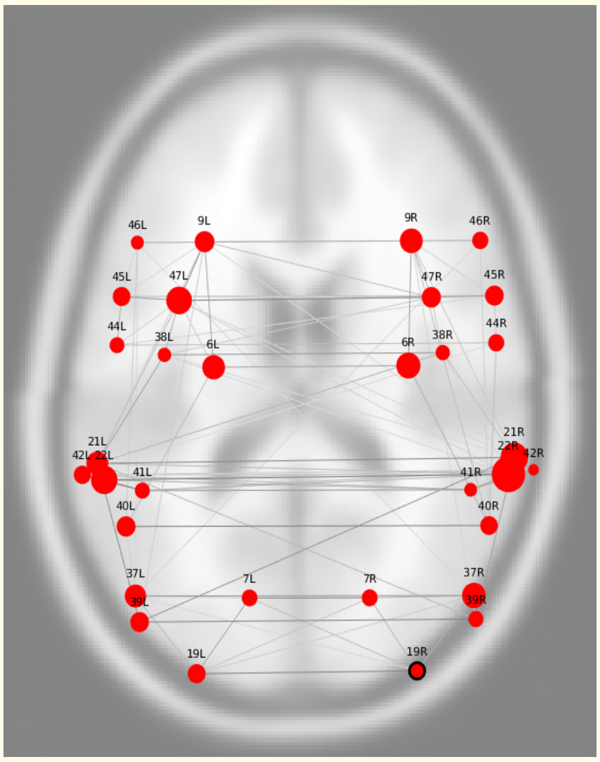

Figure 2: *Graph representation of Between Centrality. Nodes, represented by red circles, correspond to the 32 language-related Brodmann areas; Edges, represented by gray lines correspond to inter-BA connectivity. The circle's radio represent the Between Centrality score. The graph is collapsed on top of a transversal brain cut at the level of the Sylvian plane. Note the higher Between Centrality scores for primary and secondary auditory areas(BA41, BA42 and BA21).*

Discussion

We describe here the findings of contrasting specific graph theory measures of the language network with gender in a population of normal right-handed girls and boys. Significant effect of gender group on three distinct graph theory measures were found. Interestingly, all three biomarker differences were found in the right hemisphere: boys had higher connectivity values than girls for Local Efficiency in BA37 and Between Centrality in BA45; and girls had higher Cluster Coefficient values than boys in BA7. Our hypothesis is rejected as we failed to demonstrate any significant asymmetry related to canonical language areas on the left hemisphere. However, the resulting asymmetries are worthy of further analysis since significant hemisphere-related gender differences in the regional nodal characteristics in various brain regions have been previously reported [47].

Broadly, Local Efficiency and Between Centrality show how relevant or crucial a node is within the network. Local Efficiency is inversely related to the node fraction contribution into the sum of shortest pathways, the more short-paths go through the node the higher the node efficiency is as it may reach other nodes in fewer steps. Similarly, Between Centrality is the fraction of all short-pathways of the network going through a given node. Cluster coefficient is more related to inter-connectivity of the neighbors and transitivity, hence close related to resilience.

The function of the homotopic contralateral canonical language areas is still understudied. Right BA45, as part of the inferior frontal gyrus, has been found involved in motor inhibition tasks and other tasks involving inhibition like skills, for example, processing rules learned by observation (mirror neuron system) [48]. Right BA 37 has been found to activate in tasks involving emotional attention [49]; processing of affective interactions (from a visual task aimed to elucidate differences in mirror neuron system between cooperative vs affective representing actions) [50]; and naming living objects [51], task in which female subjects activate right BA37 more than the left one. Right BA7 (superior parietal cortex) has been reported to activate in a specific manner in visuo-spatial attention tasks [52] although other functions have been also described, e.g.: "in the integration of reach-to-grasp movements of the two arms" [53]. However, to the authors' knowledge there is no publications showing gender asymmetries in the activation of the right BA7 using functional MRI. With respect right BA45, an fMRI study demonstrated different involvement of brain inhibitory networks in stop tasks, which include the right IFG, between males and females [54] but the activation of BA45 was not specifically distinct.

Functional connectivity is in its infancy and still many of the findings yielded by this technique are difficult to interpret, and even harder to correlate with physiological and pathological data. Our results are not the first to prove gender differences utilizing functional connectivity. A recent publication shows nodes differences in a connectivity study contrasting males and females. Although the authors utilized a graph theory approach, their methods are limited to a comparison of vectorized patterns derived from adjacency matrices built from a specific anatomical brain segmentation [55]. Tian., *et al*. [47] utilized resting state fMRI (rs-fMRI) and graph theoretical approaches to investigate the hemisphere- and gender-related differences in the adult brain functional networks. The authors main finding was that males lean towards being more locally efficient in their right hemispheric networks, whereas females tended to be more locally efficient in their left hemispheric networks. To our knowledge no previous studies have used our markers to contrast differences between genders.

Our study may have an important shortcoming. The interaction between gender and global IQ confounds the results. Indeed, the boys group had significant higher global IQ scores than girls. Therefore the gender differences on network architecture as revealed by the graph theory measures may be ascribed not to the language differences but to a global effect of intelligence. We sought to disambiguate these effects regressing the global and verbal IQ scores as the independent variable and the three significant scores as the dependent variables. The highest correlation was found between Global IQ scores and right BA37 Local Efficiency ($R = 0.32$; Std Er = 0.26; Anova $F = 3.88$, $p = 0.06$). The remaining correlations have lower values. Therefore, although a trend may be accepted, in right BA37-Local Efficiency, these findings show no statistical significant effect of Global or Verbal IQ on the connectivity scores.

The fact that verbal IQ did not show groups differences would suggest that indeed the effect is most likely related to visuospatial sub-parts of the global IQ scoring system, for which boys seem to have an advantage. This may explain better score for BA37 in which boys have higher values of local efficiency, but obscures the origin of right BA7 effect that is also related to visuo-spatial skills. The differences in right BA45 points to non-verbal differences between genders. Ad-hoc studies to balance the sample on Global IQ by removing the subjects with the higher scores from the boys group, were attempted and then rejected as the resulting sample became un-balanced in subject number and age, factors that we wanted to keep [56].

Conclusion

We present here the results of a study contrasting functional connectivity of language areas between boys and girls utilizing graph theory biomarkers. Gender-related differences were not found on the left hemisphere; instead, right hemisphere differences were found, encompassing BA37, BA7 and BA45. Boys have higher Local Efficiency and Between Centrality values than girls in BA37 and BA7, respectively, while girls have higher Clustering Coefficient scores on BA7. The results are consistent with prior publications demonstrating higher spatial abilities in males than females. More research is required to elucidate the importance of these asymmetries in language and cognition in general.

Statement

The authors state not to have conflict of interest.

Disclosure

Byron Bernal is President of fMRI Consulting, Inc. USA

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