

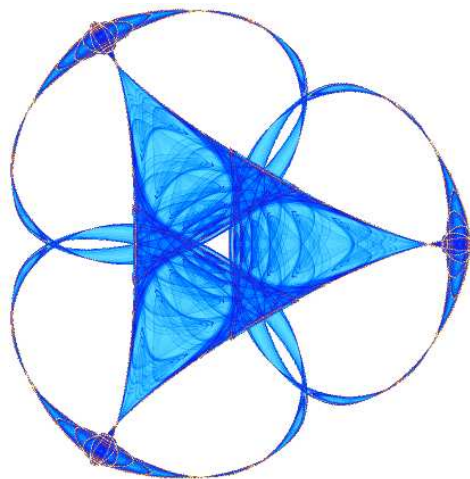
**HIERARCHICAL TOPOLOGICAL NETWORK ANALYSIS OF
ANATOMICAL HUMAN BRAIN CONNECTIVITY AND
DIFFERENCES RELATED TO SEX AND KINSHIP**

By

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14. ABSTRACT Modern non-invasive brain imaging technologies, such as diffusion weighted magnetic resonance imaging (DWI), enable the mapping of neural fiber tracts in the white matter, providing a basis to reconstruct a detailed map of brain structural connectivity networks. Brain connectivity networks differ from random networks in their topology, which can be measured using small worldness, modularity, and high-degree nodes (hubs). Still, little is known about how individual differences in structural brain network properties relate to age, sex, or genetic differences. Recently, some groups have reported brain network biomarkers that enable differentiation among individuals, pairs of individuals and groups of individuals. In addition to studying new topological features, here we provide a unifying general method to investigate topological brain networks and connectivity differences between individuals, pairs of individuals, and groups of individuals at several levels of the data hierarchy while appropriately controlling false discovery rate (FDR) errors. We apply our new method to a large dataset of high quality brain connectivity networks obtained from High Angular Resolution Diffusion Imaging (HARDI) tractography in 303 young adult twins, siblings, and unrelated people. Our proposed approach can accurately classify brain connectivity networks based on sex (93% accuracy) and kinship (88.5 % accuracy). We find statistically significant differences associated with sex and kinship both in the brain connectivity networks and in derived topological metrics, such as the clustering coefficient and the communicability matrix.					
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Hierarchical Topological Network Analysis of Anatomical Human Brain Connectivity and Differences Related to Sex and Kinship

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Abstract

Modern non-invasive brain imaging technologies, such as diffusion weighted magnetic resonance imaging (DWI), enable the mapping of neural fiber tracts in the white matter, providing a basis to reconstruct a detailed map of brain structural connectivity networks. Brain connectivity networks differ from random networks in their topology, which can be measured using small world-

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ness, modularity, and high-degree nodes (hubs). Still, little is known about how individual differences in structural brain network properties relate to age, sex, or genetic differences. Recently, some groups have reported brain network biomarkers that enable differentiation among individuals, pairs of individuals, and groups of individuals. In addition to studying new topological features, here we provide a unifying general method to investigate topological brain networks and connectivity differences between individuals, pairs of individuals, and groups of individuals at several levels of the data hierarchy, while appropriately controlling false discovery rate (FDR) errors. We apply our new method to a large dataset of high quality brain connectivity networks obtained from High Angular Resolution Diffusion Imaging (HARDI) tractography in 303 young adult twins, siblings, and unrelated people. Our proposed approach can accurately classify brain connectivity networks based on sex (93% accuracy) and kinship (88.5 % accuracy). We find statistically significant differences associated with sex and kinship both in the brain connectivity networks and in derived topological metrics, such as the clustering coefficient and the communicability matrix.

Keywords: Anatomical brain connectivity, complex networks, diffusion weighted MRI, topological analysis, hierarchical analysis, false discovery rate, sex and kinship brain network differences.

1. Introduction

Modern non-invasive imaging technologies such as Diffusion Weighted Magnetic Resonance imaging (DWI) make it possible to estimate the local orientation of neural fiber bundles in the white matter, providing reliable anatomical information on brain connectivity and anatomical networks (Iturria-Medina et al., 2007; Hagmann et al., 2008, 2007; Gigandet et al., 2008; Bullmore and Bassett, 2010; Bullmore and Sporns, 2009; Bassett et al., 2011). Topological properties of complex networks, such as those describing brain connectivity, have been analyzed and compared to random networks using traditional (Rubinov and Sporns, 2010; Boccaletti et al., 2006; Sporns and Kotter, 2004; Onnela et al., 2005; Blondel et al., 2008) and new topological metrics (Easley and Kleinberg, 2010; Lohmann et al., 2010; Shepelyansky and Zhirov, 2010; Bullmore and Bassett, 2010; Bassett et al., 2010, 2011; Estrada, 2010; Estrada and Higham, 2010). Still, relatively little is known about how functional and structural brain networks differ between different populations, and how their properties are associated with, for example, age, sex, and genetic factors. Large datasets, as presented here, are vital for making robust statements about network properties and factors that consistently affect them.

Recent work has identified effects of sex, age, heritability, and neurological disorders on some aspects of brain networks derived from structural and functional MRI. Pattern recognition methods, such as feature selection, dimension reduction, and classification, have been used to predict brain maturity (Dosenbach et al., 2010; Thomason et al., 2011) and activity (Richiardi et al., 2010) from functional MRI (fMRI), and also the effects of aging on

26 brain connectivity measured from DWI scans (de Boer et al., 2011). In re-
 27 cent work, we identified significant sex and genetic differences using network
 28 data at the edge (node-to-node connectivity) level, from Diffusion Tensor
 29 Imaging (DTI) (Jahanshad et al., 2010) and High Angular Resolution Dif-
 30 fusion Imaging (HARDI) scans (Jahanshad et al., 2011). In general, these
 31 anatomical studies create a connectivity matrix that describes the proportion
 32 of detected brain fibers that interconnect all pairs of regions, taken from a
 33 set of regions of interest. This results in a matrix of connectivity values, that
 34 can be treated as an $N \times N$ image and analyzed using voxel-based statistical
 35 analysis approaches (Jahanshad et al., 2011). Additional studies have re-
 36 ported age and sex differences in DWI data and in global topological metrics
 37 (Gong et al., 2009); genetic effects (Fornito et al., 2011). Abnormalities
 38 in patients with schizophrenia (Rubinov and Bassett, 2011) have also been
 39 reported in connectivity studies using fMRI.

40 Here we propose a unifying, robust and general method to investigate
 41 brain connectivity differences among individuals, pairs of individuals, and
 42 groups of individuals (classes), at several levels of the network hierarchy:
 43 global, node, and node-to-node or network subgraphs. We use robust pat-
 44 tern recognition techniques to identify brain connectivity/network differences
 45 at the individual level (which also includes pairs of individuals). We also
 46 describe families of hypothesis tests to identify differences at the group or
 47 class level. We apply this method to a large dataset of high quality brain
 48 connectivity networks, obtained from HARDI. This allows us to study orga-
 49 nizational differences between the human brain and random networks, and
 50 brain connectivity differences associated with sex and kinship.

51 Our method has the following unique characteristics:

- 52 • Robust feature selection using Support Vector Machines (SVMs) and
53 n-fold cross-validation.
- 54 • Robust overall classification performance evaluation using n-fold cross-
55 validation and permutation tests.
- 56 • Hierarchical analysis of brain connectivity network differences, simul-
57 taneously studying the networks at multiple structural levels.
- 58 • Robust overall control of the false discovery rate (FDR) error, especially
59 with hierarchies of multiple families of hypothesis tests.
- 60 • Analysis of a large high quality dataset that involves a robust normal-
61 ization step.

62 Using this method, we set out to answer the following questions (research
63 lines):

- 64 1. Can we classify individuals in terms of sex or pairs of individuals in
65 terms of kinship using the HARDI-derived connectivity matrices?
- 66 2. Can we classify individuals in terms of sex or pairs of individuals in
67 terms of kinship using topological measures of the associated network
68 digraphs?
- 69 3. Are there any differences in the connectivity matrices attributable to
70 sex differences or kinship?
- 71 4. Do brain connectivity networks and random networks differ in topol-
72 ogy?

73 5. Is some proportion of the variance in brain network topology attributable
74 to sex or kinship?

75 This study of sex and kinship from connectivity networks illustrates the
76 framework and address key biological questions.

77 The topological metrics considered here can be arranged in a hierarchical
78 tree, from global to node-to-node (Figure 1). Network differences at the
79 individual level (including pairs of individuals) are covered by the proposed
80 research lines 1 and 2. Research lines 3 and 5 refer to class (sex and kinship)
81 properties. We also look for global topological differences between real and
82 random networks, research line 4, as these have been frequently reported
83 in the literature (Iturria-Medina et al., 2007; Gong et al., 2009; Bassett
84 et al., 2010; Fornito et al., 2011; Bassett et al., 2011). Here, we study brain
85 connectivity differences using a wide variety of traditional and recent global,
86 cortical (node), and inter-cortical (node to node) topological metrics not used
87 before on a single large scale study of high quality diffusion MRI data.

88 Our relatively large number of high quality diffusion MRI data allows us
89 to consider more related individuals than have been studied before for ana-
90 lyzing structural connectivity. We consider all possible pair-wise comparisons
91 between the different kinships.

92 The rest of the paper is organized as follows: Section 2 describes the diffu-
93 sion MRI data we analyze. we describe how the data is processed to produce
94 the anatomical brain connectivity information and networks. Section 3 in-
95 troduces the questions we address and our proposed approach using robust
96 pattern recognition methods and multiple hypothesis testing, while control-
97 ling the FDR. Section 4 reports results for sex and kinship classification

based on the brain connectivity matrices and network topology measures. Section 4 also presents results of hypothesis tests on the brain connectivity and brain topological network differences due to sex and kinship, as well as topological differences between human and random brain networks. Section 5 discusses the results, and some caveats and limitations. Section 6 presents the conclusions of this work.

2. Estimation of Brain Structural Connectivity

2.1. Diffusion MRI Data Acquisition and Processing

The raw data set consists of 4 Tesla HARDI and standard T1-weighted structural MRI images, for 303 individuals (193 women and 110 men), between 20 and 30 years old (mean age: 23.5 ± 1.9 SD years). From these subjects, we are able to form different pair-wise kinship relationships between identical twins (50), non-identical multiples (64 non-identical twins and a non-identical triplet, forming 67 pair-wise relationships), and non-twin siblings (35).¹ In addition, there are 35 unrelated individuals, from whom we can obtain $(35 \times 34)/2 = 595$ pairs of unrelated people, but we only choose at random 100 of them, to avoid unbalancing the number of pairs chosen for each class. In summary, we have $50 + 67 + 35 + 100 = 252$ pair-wise relationships for our kinship analysis.

All MR images were collected using a 4 Tesla Bruker Medspec MRI scanner, with a transverse electromagnetic (TEM) head coil, at the Center for

¹The group of non-twin siblings overlaps the group of twins and triplets, since an individual can have 2 or more siblings that are twins (or triplets).

119 Magnetic Resonance, University of Queensland, Australia. T1-weighted im-
 120 ages were acquired with an inversion recovery rapid gradient echo sequence
 121 (TI/TR/TE = 700/1500/3.35 *ms*; flip angle=8°; slice thickness = 0.9 *mm*,
 122 with a 256³ acquisition matrix). Diffusion-weighted images were acquired
 123 using single-shot echo planar imaging with a twice-refocused spin echo se-
 124 quence to reduce eddy-current induced distortions. Imaging parameters were:
 125 TR/TE = 6090/91.7 *ms*, 23 *cm* FOV, with a 128 × 128 acquisition matrix.
 126 Each 3D volume consisted of 55 2-*mm* thick axial slices with no gap, and
 127 a 1.79 × 1.79*mm*² in-plane resolution. We acquired 105 images per subject:
 128 11 with no diffusion sensitization (i.e., b0 images) and 94 diffusion-weighted
 129 (DW) images (b = 1159 *s/mm*²) with gradient directions evenly distributed
 130 on the hemisphere, as is required for unbiased estimation of white matter
 131 fiber orientations. Scan time was 14.2 minutes. Non-brain regions were au-
 132 tomatically removed from each T1-weighted MRI scan, and from a b0 image
 133 obtained from the DWI data set using the BET FSL tool.² A trained neu-
 134 roanatomical expert manually edited the T1-weighted scans to further refine
 135 the brain extraction. All T1-weighted images were linearly aligned using
 136 FSL (with 9 DOF³) to a common space, (Holmes et al., 1998), with 1*mm*
 137 isotropic voxels and a 220 × 220 × 220 voxel matrix.

138 Raw diffusion-weighted images were corrected for eddy current distortions
 139 using the eddy currents distortions correction FSL tool. For each subject,
 140 the 11 non-diffusion-weighted images (with no diffusion sensitization) were

²<http://fsl.fmrib.ox.ac.uk/fsl/>

³The expected deformations are only translation, rotation, and anisotropic scaling; no shearing between T1s of the same subject.

141 averaged and resampled and linearly aligned to a down-sampled version of
142 the same subject, corresponding to a T1-weighted anatomical image ($110 \times$
143 $110 \times 110, 2 \times 2 \times 2mm$). Averaged b0 maps were then elastically registered
144 to the structural scan using an inverse consistent registration algorithm with
145 a mutual information cost function, (Leow et al., 2005), to compensate for
146 high-field echo-planar imaging (EPI) induced susceptibility artifacts. This
147 elastic registration further refines the linear intra-subject registration.

148 Thirty-five cortical labels per hemisphere (Table S1, in the supplementary
149 material) were automatically extracted from all high resolution aligned T1-
150 weighted structural MRI scans using FreeSurfer⁴ (Fischl et al., 2004). The
151 output labels from FreeSurfer (1-35) for each hemisphere were combined into
152 a single image. As a linear registration is performed within the software,
153 the resulting T1-weighted images and cortical models were aligned to the
154 original T1 input image space and down-sampled using nearest neighbor
155 interpolation (to avoid intermixing of labels) to the space of the DWIs. To
156 ensure tracts would intersect labeled cortical boundaries, labels were dilated
157 simultaneously (to prevent overlap) with an isotropic box kernel of 5 voxels.

158 Tractography is performed by randomly choosing seed voxels of the white
159 matter with a prior probability based on the fractional anisotropy (FA) value
160 derived from the diffusion tensor model (Basser and Pierpaoli, 1996). We
161 use a global probabilistic approach inspired by the voting procedure of the
162 popular Hough transform (Gonzales and Woods, 2008; Duda and Hart, 1972).
163 The tractography algorithm tests a large number of candidate 3D curves

⁴<http://surfer.nmr.mgh.harvard.edu/>

164 originating from each seed voxel, assigning a score to each, and returns the
165 curve with the highest score as the estimated pathway. The score of each
166 curve is computed from the agreement between the estimated curve and
167 fiber orientations as derived from the Orientation Distribution Functions
168 (ODFs) (Aganj et al., 2011). At each voxel of the DWI dataset, ODFs are
169 computed using the normalized and dimensionless ODF estimator, derived
170 for HARDI in Aganj et al. 2011, which is mathematically more accurate and
171 also outperforms the original Q-Ball Imaging (QBI) definition (Tuch, 2004),
172 e.g., it improves the resolution of multiple fiber orientations (Aganj et al.,
173 2011).

174 As it is an exhaustive search, this algorithm avoids entrapment in local
175 minima within the discretization resolution of the parameter space. Further-
176 more, the specific definition of the candidate’s tract score attenuates noise
177 by integrating the real-valued local votes derived from the diffusion data.⁵
178 Further details of the method can be found in (Aganj et al., 2011).

179 Elastic deformations obtained from the EPI distortion correction, map-
180 ping the average b0 image to the T1-weighted image, were then applied to
181 the tracts 3D coordinates. To avoid considering small noisy tracts, tracts
182 with fewer than 15 fibers were filtered out.

⁵In the near future, this algorithm will be released through the Neuroimaging Informat-
ics Tools and Resources Clearinghouse (NITRC) online repository, and is available upon
request.

183 2.2. Computing Connectivity Matrices and Brain Networks

184 From the cortical labeling and tractography, symmetric matrices of con-
 185 nectivity (70×70) are built, one per subject. Each entry contains the number
 186 of fibers connecting each pair of cortical regions (Table S1) within and across
 187 each brain hemisphere. Connectivity matrices based on fiber counts should
 188 always be normalized to the $[0, 1]$ range, as the number of fibers detected
 189 varies from individual to individual. In addition, there is a bias in the number
 190 of fibers detected by tractography that start or end in any given cortical re-
 191 gion, due to fiber crossings, fiber tract length, volume of the cortical region,
 192 and proximity to large tracts like the corpus callosum (Jahanshad et al.,
 193 2011; Hagmann et al., 2008, 2007; Bassett et al., 2011). However, there is no
 194 unique way to normalize the fiber tract count (Bassett et al., 2011).

195 We decided not to use the normalizations proposed in (Hagmann et al.,
 196 2008, 2007; Bassett et al., 2011), as they involve geometric measures includ-
 197 ing the volume of the cortical regions and the mean path length of fibers
 198 connecting each two regions. Instead, we considered three purely topologi-
 199 cal normalizations, since, as in (Gong et al., 2009), we want to find pure
 200 topological network differences due to, e.g., sex and kinship:

$$w_{ij} = \frac{a_{ij}}{\sum_{ij} a_{ij}}, \quad (1)$$

$$w_{ij} = \frac{a_{ij}}{\sqrt{\sum_j a_{ij} \sum_i a_{ij}}}, \quad (2)$$

$$w_{ij} = \frac{a_{ij}}{\sum_j a_{ij}}, \quad (3)$$

201 where, a_{ij} represents the entries in the original fiber count matrix, A , and

202 w_{ij} the entries (weights) of the now normalized 70×70 connectivity matrix,
 203 W .

204 Equation (1) (used in our previous work, Jahanshad et al. 2011) nor-
 205 malizes the fiber count for each pair of regions by the total number of fibers
 206 in the entire brain, reducing variability among the connectivity matrices due
 207 to differences in the total number of fibers found. In practice, this normal-
 208 ization can provide biased weights, since it does not take into account that
 209 a higher number of fibers will be found in some regions, e.g., in the vicinity
 210 of the corpus callosum, and also more fibers would be counted in cortical
 211 regions with larger areas (Hagmann et al., 2008; Bassett et al., 2011).

212 Equation (3), first proposed by Behrens et al. 2007 in the context of trac-
 213 tography, can be interpreted as the probability of connecting cortical regions
 214 i and j , given that there are a_{ij} fibers between them and there are $\sum_j a_{ij}$
 215 fibers available on cortical region i . Equation (2), (Crofts and Higham,
 216 2009), divides the number of fibers between any two cortical regions by the
 217 geometric mean of the number of fibers leaving either region. The assump-
 218 tion here is stronger than that of Equation (3), as it assumes the same *total*
 219 number of fibers on each pair of brain regions. This can lead to bias due to
 220 large differences in the total number of fibers on each region (locally), but
 221 it should be correct on average (globally). An equivalent normalization was
 222 used in (Gong et al., 2009), where instead of the geometric mean, they used
 223 an arithmetic mean, averaging w_{ij} and w_{ji} on Equation (3).

224 Equations (1) and (2) lead to undirected connectivity graphs, which are
 225 typical in structural brain connectivity analysis. Equation (3), on the other
 226 hand, leads to directed graphs (digraphs). To see this, note that in general

227 $\sum_i a_{ij} \neq \sum_j a_{ij}$, i.e. the total number of fibers on cortical regions i and j
 228 can be different on either side of the connection, hence, in general, $w_{ij} \neq w_{ji}$
 229 on Equation (3). Normalizations (1)-(3) are further modified as $\frac{w_{ij}}{\max\{w_{ij}\}}$,
 230 where w_{ij} is defined as indicated in equations (1)-(3), in order to reduce the
 231 differences among different connectivity matrices (different subjects), thereby
 232 making $\max\{w_{ij}\} = 1$. Equations (2), (3), modulated by $\max\{w_{ij}\}$, reduce
 233 significantly the mean effect of brain size differences between men and women
 234 (see the regression analysis in the Appendix), which is a known confounding
 235 factor in analyses of sex differences (Leonard et al., 2008).

236 Here, we work with the normalization provided by Equation (3),⁶ because
 237 it reduces the effect of brain size. Connectivity matrices are asymmetric - this
 238 coming from the normalization and not from the tractography results. This is
 239 beneficial as it uses all available entries in the matrix, while traditional sym-
 240 metric matrices, as obtained from the other two normalizations, only use half
 241 of the matrix to store network information. This extra information is not an
 242 artifact of the normalization - it provides more information about differences
 243 between two connected brain regions. Two cortical regions are connected by
 244 the same number of fibers, but the proportion of fibers dedicated to that
 245 particular connection can be very different within each cortical region. For
 246 instance, consider the case where cortical region i connects exclusively to
 247 region j , but region j connects not only to i , but also to many other regions.
 248 In terms of probability of connection, $p_{ij} = 1, p_{ik} = 0, k \neq j$, since i connects

⁶The basic method introduced later for analyzing brain networks, in particular the
 features for undirected networks and the statistical analysis, can still be applied to the
 other possible normalizations as well.

exclusively to j (p_{ij} being the probability of connecting region i with region j). However, $p_{ji} < 1$, and $p_{jk} \neq 0$ for some k regions, satisfying in both cases $\sum_i p_{ij} = \sum_j p_{jk} = 1$ (all the regions must be connected), hence, $p_{ij} \neq p_{ji}$. In the general case, each cortical region connects to a *different* number of other cortical regions, so in general, $p_{ij} \neq p_{ji}$, as on Equation (3). We consider that capturing this asymmetry in the connectivity matrices W is important, and this is validated in the experimental results.

In summary, we derived 303, one per subject, normalized connectivity (network) 70×70 matrices W , by applying probabilistic tractography to HARDI at 4T. These matrices provide our basis for studying anatomical brain connectivity, as described next.

3. Methods

The research lines addressed here (see the Introduction) are independent as they answer different questions and there is no interaction or inference among them. It is important to state the independence of these research lines, as it implies that there is no need for an overall FDR error control, other than the FDR control on each research line (Benjamini and Hochberg, 1995; Yekutieli, 2008). The first two research lines are addressed simultaneously using robust pattern recognition methods that extend well to unobserved data (Section 3.1). The last three research lines are going to be addressed using statistical hypothesis testing (non-parametric bootstrap), where the corresponding null hypotheses are stated as:

1. There are no differences in the connectivity matrix. Given that there are $O(n^2)$ weights on a connectivity matrix of n nodes, there are $O(n^2)$

273 local null hypothesis to be tested, one for each connection, forming a
 274 large family of hypothesis testing. As $n = 70$ in our case, we could
 275 have up to 4900 hypotheses to test for differences in the connectivity
 276 matrices.⁷

277 2. There are no global topological differences between real networks and
 278 random networks. In general, we can have m global topological metrics
 279 (see Figure 1 and Section 3.2 for details), forming a single family of
 280 hypothesis testing.

281 3. There are no topological differences, at any scale, on the directed net-
 282 works due to sex or kinship (Figure 1). Hence, we have m hypotheses
 283 to test at the global level, possibly m families of hypothesis at the node
 284 level (one for each global hypothesis), having each one $O(n)$, $n = 70$,
 285 null hypothesis to test for differences at each node, and several families
 286 of hypotheses at the node-to-node level, where each family corresponds
 287 to a topological metric at the node-to-node level (Figure 1), and each
 288 family consists of $O(n^2)$ hypothesis to test, one for each pair of nodes.

289 The first two null hypotheses require only a single (albeit possibly large)
 290 family of hypothesis tests, while the last one requires several families of hier-
 291 archically related hypothesis tests, where families of hypotheses at the node-
 292 to-node level can consist of $O(n^2)$ local hypotheses (up to 4900 hypotheses
 293 in our case, $n = 70$).

⁷Of course, we only look for statistically significant differences where the number of connections detected is more than zero.

294 At the population level, we consider only average network differences in
 295 the connectivity matrix (research line 3, see Introduction), or in the topo-
 296 logical metrics of the associated graphs (research line 5 in the Introduction),
 297 resulting from sex and kinship, as we know *a priori* that the variability
 298 between the connectivity matrices of individuals can be as large as the vari-
 299 ability between the connectivity matrices within the same group (same sex
 300 or same kinship relationship) – an observation derived both from previous
 301 studies, (Bassett et al., 2011), and from our own dataset.

302 We consider the two classes *women* and *men*, based on sex; and the
 303 four classes *identical twins*, *non-identical multiples*, *non-twin siblings*, and
 304 *unrelated individuals*, based on kinship relationships. These are used for
 305 classification at the individual (including pairs of individuals for kinship)
 306 level and for hypothesis testing at the group level.

307 Our analysis of kinship follows previous genetic studies of brain connectiv-
 308 ity (Jahanshad et al., 2011, 2010; Rubinov and Bassett, 2011; Fornito et al.,
 309 2011; Thompson et al., 2001). One traditional line of analysis in genetic
 310 studies uses a classical twin design to compute intra-pair (or intra-class) cor-
 311 relations between measures of cortical gray matter density (Thompson et al.,
 312 2001), connectivity matrices (Jahanshad et al., 2011, 2010), or wavelets rep-
 313 resenting the connectivity matrices (Fornito et al., 2011), however, these
 314 correlation operations reduce the data to a single matrix of correlations, and
 315 heritability statistics for all pairs of subjects in the same group.

316 For kinship analysis, we work with the *absolute* value of the differences
 317 in the connectivity matrix and with network differences in the topological
 318 metrics considered, between pairs of individuals. These pair-wise differences

319 are differences between pairs of identical twins, differences between pairs
320 of non-identical multiples, differences between siblings who are not twins,
321 and finally differences between pairs of unrelated people. We use *pairwise*
322 *differences* within and across families, as they allow us to detect genetically-
323 mediated effects in pairings with different degrees of known genetic affinity
324 (Thompson et al., 2001).

325 To avoid losing pairs of subjects in the kinship analyses, we did not con-
326 strain the pairwise differences between individuals to be of the same sex,
327 which in our study corresponds approximately to half the non-identical mul-
328 tiples considered. The statistical power of the tests of kinship differences
329 might be reduced by the confounding effects of sex differences, but at the
330 same time, we are also increasing the statistical power of the test (Winer,
331 1971), by considering a larger number of pairwise differences.

332 3.1. Classification

333 Here, we want to classify individual brain connectivity networks in terms
334 of sex (women and men) and pairs of individuals in terms of kinship, using
335 the connectivity matrices or the associated network topology metrics at the
336 node or node-to-node level.

337 In classification, we encounter the multiple comparisons problem (MCP),
338 which arises whenever we test multiple hypotheses simultaneously. If we
339 do not correct for this, then the more hypotheses tested, the higher the
340 probability of obtaining at least one false positive.

341 This can be dealt with in classification via n-fold cross-validation. In
342 fact, cross-validation can be more effective than Bonferroni-type corrections
343 (Jensen and Cohen, 2000), as it does not test on the same data used to derive

the model. Here we use 10-fold cross-validation, a good trade-off between robustness to unobserved data and using as much data as possible to train the classifiers (Refaeilzadeh et al., 2009). In addition to cross-validation, we also use permutation tests (see Appendix for details), to non-parametrically evaluate the null hypothesis that the classifiers might have obtained good classification accuracies just by chance (Ojala and Garriga, 2010). In this work, we use Support Vector Machine (SVM) classifiers, as they extend well to unobserved data, (Vapnik, 1998), and deal with the MCP problem by reducing the number of comparisons to the number of support vectors.

Given the high dimensionality ($\mathbb{R}^{n^2}$, $n = 70$ nodes) of the brain connectivity networks and associated topological metrics consider here (see Section 3.2 for their full description), we use feature selection methods to reduce the effective dimensionality of the data. We call here *feature*, any of the connectivity or topological network differences at the node-to-node and single node levels. Feature selection methods can significantly improve classification accuracy, even for classifiers that exploit the higher discrimination possibilities in high dimensional spaces, such as SVMs (Vapnik, 1998; Guyon and Elisseeff, 2003). In general, there are three methods used for feature selection: filters, wrappers, and embedded methods (Guyon and Elisseeff, 2003). Filter methods employ a ranking criteria such as the Pearson cross-correlation (used for example in Dosenbach et al. 2010), Mutual Information, Fisher criterion, and so on, and a given threshold to filter out low ranked features. Wrappers use the classifier itself to evaluate the importance of each feature and explore the whole feature space using for instance, gradient based methods, genetic algorithms or greedy algorithms. Filter methods are very fast and

369 independent of the selected classifier, however, they can lead to the selec-
 370 tion of redundant features (Guyon and Eliseeff, 2003). They also disregard
 371 features with relatively small individual influence that can potentially have
 372 an influential effect as a group. Wrappers, on the other hand, can avoid
 373 redundant features and identify influential subgroups of features. However,
 374 they are computationally intensive, since the subset feature selection prob-
 375 lem is NP-hard (Amaldi and Kann, 1998), and are strongly dependent on
 376 the classifier used (Guyon and Eliseeff, 2003). Embedded methods also use
 377 a classifier to evaluate the importance of subgroup of features. Hence, they
 378 are wrappers. However, they provide a trade-off between other wrappers and
 379 filter methods, in terms of computational efficiency and reduced number of
 380 features, since they introduce a penalty term that enforces small number of
 381 features (Guyon and Eliseeff, 2003).

382 An alternative to feature selection methods are dimension reduction meth-
 383 ods such as Principal Components Analysis (PCA) and Independent Compo-
 384 nent Analysis (ICA). See Hartmann 2006, for a comparison of both methods
 385 in the context of machine learning. Here, we preferred feature selection meth-
 386 ods, as the features in dimension reduction methods are in general functions
 387 of the original features,⁸ and cannot be associated to a unique “physical”
 388 feature in the original data space. In particular, we use the SVM-based em-
 389 bedded feature selection algorithm proposed by Guyon et al. 2002. When
 390 selecting features with a classifier there is a risk of “double-dipping,” i.e.,
 391 training the feature selection algorithm and testing it with the same data,

⁸PCA for instance is a projection of the original features onto the matrix eigen-space,
 and hence is a linear combination of the original features.

392 which leads to unrealistic high accuracies (over-fitting) that do not extend
 393 well to unseen data (Kriegeskorte et al., 2009; Refaeilzadeh et al., 2009). To
 394 avoid this, the feature selection algorithm uses 10-fold cross-validation,⁹ se-
 395 lecting the features that contributes more to classification, but that are also
 396 more stable across the different cross-validation sets of data (Kriegeskorte
 397 et al., 2009; Refaeilzadeh et al., 2009). In the proposed framework, feature
 398 selection algorithms extract the $m \ll n^2$ most relevant features from the
 399 digraph matrices taken as high-dimensional vectors in $\mathbb{R}^{n^2}$, $n = 70$, then use
 400 the m selected features to classify the reduced features in $\mathbb{R}^m$.

401 We tested classification performance using the following standard mea-
 402 sures:

- 403 • The overall classification accuracy.
- 404 • The sensitivity and specificity.¹⁰
- 405 • The balanced error rate (BER), which corresponds to the average of
 406 the errors on each class.
- 407 • The area under the receiver operating characteristic (ROC) curve, which
 408 measures the probability that the classifier can actually discriminate
 409 the true class from the incorrect one(s).

⁹Training with 90% of the data and testing on the remaining 10%, and repeating the process 10 times with randomly selected training and testing samples.

¹⁰As it is usual in binary classification, we report sensitivity and specificity for women only, given that the sensitivity for men is numerically the same as the specificity for women and the specificity for men is numerically the same as the sensitivity for women.

- 410 • The kappa statistic, which measures the agreement of the classifier with
411 the labels taking into account the probability that the agreement has
412 been obtained by chance. It uses the confusion matrix to make this
413 assessment.
- 414 • Permutation tests p-values, which non-parametrically assess the prob-
415 ability that the classification results were obtained by chance by esti-
416 mating the null hypothesis distribution.

417 For space considerations, the confusion matrices were not included here, and
418 can be found in the supplementary material.

419 3.2. Topological Metrics

420 In addition to studying node-to-node connections, e.g., just the entries
421 of the matrix W as stand-alone features, we would like to consider features
422 that indicate higher levels of interactions between the studied regions.

423 As we do not know *a priori* which topological metrics would provide sta-
424 tistically significant differences between different classes of brain connectivity
425 networks, we have to limit ourselves to a few selected ones, to control the
426 FDR error within each research line. We consider 11 representative topolog-
427 ical metrics at the global, node, and node-to-node level (Figure 1). While
428 some have been studied for brain networks, all these topological features
429 have found relevance in other disciplines, such as social networks (Easley
430 and Kleinberg, 2010), and provide interesting insights into the overall orga-
431 nization of the brain.

432 3.2.1. Node-to-node Level

433 At the node-to-node level we consider the edge betweenness centrality
 434 (*EBC*), a new subgraph based centrality (*SGC*), and the communicability
 435 measures (*COM*) (Estrada and Higham, 2010; Estrada, 2010). The weighted
 436 edge betweenness centrality is defined as (Rubinov and Sporns, 2010),

$$EBC_{ij} = \sum_{hk} \frac{\rho_{hk}^{ij}}{\rho_{hk}}, \quad (4)$$

437 where ρ_{hk}^{ij} is the number of shortest paths between nodes h and k that contain
 438 edge ij and ρ_{hk} is the number of shortest paths between h and k . *EBC*
 439 measures the fraction of all shortest paths in the network that contain edge
 440 ij , and hence, the importance of each edge in the communication among
 441 cortical regions.

442 To understand the subgraph centrality (*SGC*) and communicability (*COM*)
 443 measures (Estrada and Higham, 2010; Estrada, 2010), let us first decompose
 444 the connectivity matrix as $W = \Lambda_W + \widetilde{W}$, where Λ_W is a diagonal matrix,
 445 with non-zero entries corresponding to the diagonal of W , and $\widetilde{W}$ is the re-
 446 sulting matrix of making zero the diagonal of W . Notice that Λ_W contains
 447 the self-connections of each node, while $\widetilde{W}$ the connections between each pair
 448 of nodes. Let us define (Estrada and Higham, 2010; Estrada, 2010),

$$\tilde{P} = \sum_{k=1}^{\infty} \frac{\widetilde{W}^k}{k!} = e^{\widetilde{W}} - I_n, \quad [\widetilde{W}^k]_{ij} = \sum_{i, h_1, \dots, h_{k-1}, j} \tilde{w}_{ih_1} \tilde{w}_{h_1 h_2} \dots \tilde{w}_{h_{k-1} j}, \quad (5)$$

449 where, I_n is the identity matrix of size $n \times n$ and we have used the definition
 450 of the exponential of a matrix. The product $\tilde{w}_{ih_1} \tilde{w}_{h_1 h_2} \dots \tilde{w}_{h_{k-1} j}$ measures the
 451 strength of the walk $(i, h_1, \dots, h_{k-1}, j)$ of length k , between nodes i and j . A

452 walk is a list of connected nodes that can be visited more than once, contrary
 453 to a path, where the nodes are visited at most once. Hence, the elements
 454 of $\widetilde{W}^k$ accounts for the strength of all possible walks of length k between
 455 nodes i and j . Also, the entries of $\widetilde{P}$ correspond to the weighted sum of the
 456 strength of all possible walks of length one and higher, between nodes i and
 457 j , providing thus a measure of how strong the communication is between
 458 them (communicability, Estrada and Higham 2010; Estrada 2010). Given
 459 that the number of walks increases with length, the weight $k!$ is selected to
 460 compensate for this effect, penalizing long walks.

461 Now, we can define (Estrada and Higham, 2010; Estrada, 2010),

$$SGC_i = [\Lambda_{\widetilde{P}}]_{ii}, \quad COM_{ij} = \widetilde{P}_{ij}, i \neq j. \quad (6)$$

462 Hence, the subgraph centrality of a node SGC_i corresponds to the commu-
 463 nicability of a node with itself, while COM_{ij} corresponds to the communica-
 464 bility between two different nodes $i \neq j$.

465 Notice that the diagonal of matrix $\widetilde{P}$ is a weighted sum of all closed walks
 466 (information transfer) of lengths two and higher around each node. The
 467 information provided by the closed walks of length zero in the connectivity
 468 matrix (Λ_W) is lost, however, since it is not used anywhere. To recover it,
 469 we define here $P = \widetilde{P} + \Lambda_W$ as the *generalized communicability matrix*, since
 470 it provides all possible communications among all nodes of length zero and
 471 above, without including self-loops other than the one in the starting node
 472 itself.

473 The communicability matrix has no zero entries, except along the diago-
 474 nal, which implies 4900-70 (4830) hypothesis tests for our data ($n = 70$), one

475 for each non-zero entry. Hence, a spectral analysis of the communicability
 476 matrix can be performed, (Estrada, 2010; Crofts and Higham, 2009), to ob-
 477 tain a family of tests of order $O(n)$, where n are the number of eigenvalues of
 478 the communicability matrix. In particular, the above defined matrix COM
 479 can be decomposed in terms of its eigenvalues and eigenvectors as

$$COM = \sum_{k=1}^n \lambda_k \mathbf{v}_k^T \mathbf{v}_k, \quad (7)$$

480 where λ_k are the eigenvalues of COM , and $\mathbf{v}_k$ its eigenvectors, $k = 1, \dots, n$.

481 3.2.2. Global and Node Levels

482 The undirected network efficiency (E) and clustering coefficient (C), have
 483 been previously reported as indicative of sex and age differences (Gong et al.,
 484 2009). Here, we use the directed weighted versions, defined as (Rubinov and
 485 Sporns, 2010),

$$E = \frac{1}{n} \sum_i E_i, \quad E_i = \frac{\sum_{j \neq i} d_{ij}^{-1}}{n-1}, \quad (8)$$

$$C = \frac{1}{n} \sum_i C_i, \quad C_i = \frac{\frac{1}{2} \sum_{j, h \in N_i} (w_{ih} w_{hj} w_{ji})^{1/3}}{k(k-1) - 2 \sum_j \delta_{ij} \delta_{ji}}, \quad (9)$$

$$\delta_{ij} = \begin{cases} 0 & \text{if } w_{ij} = 0 \\ 1 & \text{if } w_{ij} > 0 \end{cases}, \quad k = \sum_j (\delta_{ij} + \delta_{ji})$$

488 where, n represents the number of nodes, d_{ij} the weighted directed shortest
 489 path length between nodes i and j , and N_i the neighborhood of node i (nodes
 490 connected to node i by a single link). Network efficiency measures how fast
 491 information can be transmitted in the network, globally (E), and locally at
 492 each node (E_i). The clustering coefficient measures how much nodes in a
 493 graph tend to cluster together, globally (C) and locally at the node level

494 (C_i). Basically, the directed weighted clustering coefficient measures the
 495 probability that neighbors of a node are also connected between themselves,
 496 hence, forming clusters around a node.

497 Additional traditional topological metrics at the global and node levels
 498 are the weighted directed betweenness centrality (BC), weighted modularity
 499 (Q), and motifs (Rubinov and Sporns, 2010). The weighted directed node
 500 betweenness centrality is defined as (Rubinov and Sporns, 2010),

$$BC = \frac{1}{(n-1)(n-2)} \sum_i BC_i, \quad BC_i = \sum_{h,j \in N_i; i \neq j \neq h} \frac{\rho_{hj}^i}{\rho_{hj}}, \quad (10)$$

501 where, ρ_{hj}^i represents the number of shortest paths from nodes h and j that
 502 go through i , and ρ_{hj} the total number of shortest paths between h and j .
 503 The directed weighted node betweenness centrality measures how important
 504 each node is in the communication between neighboring nodes.

505 The weighted modularity (Q) is defined as (Rubinov and Sporns, 2010),

$$Q = \frac{1}{l_w} \sum_{ij} \left[w_{ij} - \frac{\sum_i w_{ij} \sum_j w_{ij}}{l_w} \right] \delta_{M_i, M_j}, \quad l_w = \sum_{ij} w_{ij}, \quad (11)$$

506 where the network is assumed to be fully subdivided into non-overlapping
 507 clusters or modules (M), with M_i being the module that contains node i ,
 508 and $\delta_{M_i, M_j} = 1$ if $M_i = M_j$ and zero otherwise. This is a global measure
 509 of the modularity of the network, that is, how tightly nodes are connected
 510 within a module. Identifying modules is of course a first step in analyzing
 511 the structure of the brain at a higher scale. This global topological mea-
 512 sure has a local hierarchical representation, where we can have hierarchies of
 513 modules (clusters). Modules can be found using, for instance, the Louvain

514 hierarchical modularity algorithm (Blondel et al., 2008), a graph partitioning
 515 algorithm that tries to find the partition maximizing Equation (11). Since
 516 graph partitioning is in general an NP-complete problem, the Louvain algo-
 517 rithm computes a local optimum by greedy optimization. Figure S1, in the
 518 supplementary material, is an example of hierarchical module graph parti-
 519 tioning using the full data set.

520 Network motifs, (Rubinov and Sporns, 2010; Onnela et al., 2005), are
 521 also topological metrics that measure the intensity or frequency of certain
 522 subgraph patterns such as directed connections forming a triangle, a square,
 523 etc. The intensity of a weighted motif (F_{motif}) is defined as,

$$F_{motif} = \sum_h F_{motif}^h, \quad F_{motif}^h = \left(\prod_{(i,j) \in L_{motif}^h} w_{ij} \right)^{\frac{1}{|L_{motif}|}}, \quad (12)$$

524 where *motif* indicates a given motif, h a node, L_{motif}^h the set of nodes forming
 525 the motif at node h , and $|L_{motif}|$ the number of directed links in the motif.
 526 Motifs are considered the building blocks of information processing in the
 527 network and can be measured globally (F_{motif}) or locally at the node level
 528 (F_{motif}^h). Figure S2, in the supplementary material, shows the 13 possible
 529 directed motifs of size three.

530 New topological metrics, while popular in studies of other network data,
 531 have not yet been used for anatomical brain networks. We will also consider
 532 the PageRank (PR) (Lohmann et al., 2010; Easley and Kleinberg, 2010;
 533 Shepelyansky and Zhirov, 2010) and the Rentian scale, (Bassett et al., 2010)
 534 here. In essence, the PageRank (critical in Internet network analysis and
 535 search engines performance) is a measure of how important a node is, based
 536 on the importance of its neighbors. Hence, this is a recursive metric that

537 starts with all the nodes having the same measure of importance. More
 538 formally (Brin and Page, 1998),

$$PR(t) = \sum_i PR_i(t)$$

$$PR_i(t+1) = (1 - \alpha) + \alpha \sum_{j \in N_i} \frac{PR_j(t)}{\sum_k w_{jk}}, \quad PR_i(0) = \frac{1}{n}, \quad (13)$$

539 where again n is the number of nodes, N_i the neighborhood of node i , α is
 540 a damping parameter set in the $[0, 1]$ range, and $t = 1, 2, \dots$ the iterations
 541 until convergence, defined as $|PR(t+1) - PR(t)| \leq \epsilon$, for some small number
 542 ϵ . The PageRank tries to identify nodes that are influential in the network,
 543 not only because they have many connections with other nodes, but also
 544 because those neighboring nodes are influential themselves. This may be a
 545 better definition of node importance than traditional hubs, which account
 546 only for the number of connections of a node (node degree).

547 The Rentian scale¹¹ is a measure of the wiring modular complexity of the
 548 network that is self similar (fractal) at different scales. This is a metric of
 549 modularity that differs from the previous one (Q) in that it is hierarchically
 550 represented as modules within modules at different network scales. More
 551 formally (Bassett et al., 2010),

$$EC = kN^r, \quad (14)$$

552 where EC is the number of external connections to a module, k a propor-
 553 tionality constant, N the number of nodes in the module, and r the Rentian

¹¹The Rentian scale does not use actual the weights or the direction information.

554 exponent. Here, we use the physical Rentian scale, which uses the physical
 555 coordinates of the brain cortical regions. In order to avoid introducing the
 556 obvious differences in the brain size due to sex, we use the same physical
 557 coordinates for all brain cortical regions, corresponding to a single brain.

558 The Rentian scale is computed as the mean Rentian exponent on Equation
 559 (14), by partitioning the network into halves, quarters, and so on in physical
 560 space, providing EC and N values at different scales. The constant k and
 561 Rentian scale r are computed by least squares minimization of the linearized
 562 Equation (14), $\log(EC) = \log(k) + r \log(N)$ for all values of EC and N
 563 obtained from such partition (Bassett et al., 2010).

564 Some node-to-node topological metrics can lead to global metrics. For
 565 instance, the trace of $\Lambda_{\tilde{P}}$ is a global measure of node importance called the
 566 *Estrada index*. The *EBC* can also be made global, by averaging it over the
 567 entire network. Nevertheless, this kind of large averaging might destroy local
 568 differences at the edge level and will not be considered here.

569 3.3. FDR Error Control

570 3.3.1. Single Family of Hypothesis Testing

571 To control the FDR for the single families of hypothesis corresponding
 572 to the research lines “are there any global topological differences between
 573 real brain connectivity networks and random networks;” and “are there any
 574 mean differences between connectivity matrices due to sex and kinship?,”
 575 we use here the linear step-up algorithm of Benjamini-Hochberg (Benjamini
 576 and Hochberg, 1995), hereafter BH-FDR. The BH-FDR algorithm has been
 577 applied in many recent multiple hypothesis testing studies, including brain
 578 connectivity analysis (Gong et al., 2009; He et al., 2007; Jahanshad et al.,

579 2010).

580 Other approaches to control the FDR in multiple hypothesis testing that
581 are less conservative than the BH-FDR algorithm have been proposed in the
582 literature (Storey, 2002; Storey et al., 2004; Westfall et al., 1997; Benjamini
583 and Hochberg, 2000; Benjamini and Yekutieli, 2001, 2005), but they require
584 either independence of the hypotheses being tested or a known correlation
585 structure (Reiner-Benaim, 2007). The BH-FDR algorithm is still the most
586 widely used, as it is simple and it controls the FDR for normally distributed
587 tests with any correlation structure (Benjamini et al., 2009; Reiner-Benaim,
588 2007). As we are working with mean differences in a large number of connec-
589 tivity matrices, we can assume that the mean follows a normal distribution,
590 by the central limit theorem (Fisher, 2011). Hence, the simple BH-FDR er-
591 ror control is quite appropriate here. For completeness, we provide here the
592 basic BH-FDR algorithm (Benjamini and Hochberg, 1995; Yekutieli, 2008):

Algorithm 1 BH-FDR

1. Sort in increasing order all the p-values of the null hypothesis: $p_1 \leq p_2 \leq \dots \leq p_L$.
 2. Let $r = \max_i \{p_i \leq q/L\}$, define the threshold $p_{th} = p_r$. If no r could be found, define $p_{th} = q/L$ (pure Bonferroni).
 3. Reject all null hypothesis with $p_i \leq p_{th}$.
-

593 where, L is the number of null hypothesis and q the desired family-wise
594 confidence level.

595 3.3.2. Multiple Families of Hypothesis Testing

596 As explained before, we have a tree of topological metrics at different lev-
597 els of resolution (Figure 1). Hence, we need to test each topological metric
598 at the global, node-to-node, and node levels. Nevertheless, testing the topo-
599 logical metrics at the node-to-node and node level consist of testing families
600 of hypothesis of sizes $O(n)$ and $O(n^2)$, respectively, where n corresponds to
601 the number of nodes in the network. Hence, we have multiple families of
602 hypothesis testing and we need to control the overall FDR on each of the
603 proposed research lines.

604 The FDR error control has been limited so far to a single family of mul-
605 tiple hypothesis testing. The implicit assumption in many large studies has
606 been that there is no need to control the FDR when multiple families of
607 hypotheses are being performed on the same data set, other than the FDR
608 control on each family of hypotheses (Yekutieli, 2008). However, in general,
609 the FDR control separately applied to each family of hypothesis does not
610 imply FDR control for the entire study (Benjamini and Yekutieli, 2005;
611 Yekutieli, 2008). If a separate control of the FDR is performed on each fam-
612 ily of hypotheses, then the overall FDR error corresponds to the sum of FDR
613 errors of each family, which can quickly make the overall p-value of the study
614 too large to be of any use. As we compare different topological metrics at
615 different levels, we have different families of multiple hypothesis tests that
616 require overall control of the FDR for each research line.

617 To control the overall FDR error, we proceed in a hierarchical way, testing
618 from lower to higher resolutions, as suggested by (Yekutieli et al., 2006;
619 Yekutieli, 2008). This strategy makes sense since it avoids testing first at

620 higher resolutions, where the number of hypotheses to be tested on each
621 family could go up to 4900 ($n = 70$). If the fraction of null rejections is small,
622 then the FDR error control becomes as stringent as Bonferroni correction
623 (Yekutieli, 2008), which significantly increases the chance of not rejecting
624 any false null hypotheses (false negatives or Type II error).

625 Figure 1 shows the tree of possible hypotheses while testing the topolog-
626 ical differences due to sex and kinship at three levels: global, node (corti-
627 cal regions), and node-to-node (shortest paths and communicability). The
628 dashed lines on Figure 1 indicate that the higher resolution hypotheses are
629 only tested if the parent null hypothesis was rejected, as indicated by (Yeku-
630 tieli, 2008).

631 An specific example (see Figure 1) is the communicability matrix (COM),
632 which contains $O(n^2)$ non-zero entries, and hence, $O(n^2)$ hypotheses to test.
633 We can test instead its eigenvectors (Equation (7)), which requires only $O(n)$
634 hypothesis tests to determine if COM might be significant.

635 Let $H^0 = \{H_i^0, i = 1, \dots, L_0\}$ be the set of hypothesis to be tested at the
636 lowest resolution level, and $H^k = \{H_{ij}^k, i = 1, \dots, L_k, j \in H^{k-1}\}$ be the set
637 of hypothesis at resolution levels $k = 1, \dots, K$. In our case, $K = 2$, where
638 $K = 0$ corresponds to the topological metrics at the global level, $K = 1$ to the
639 topological metrics at the node level, and $K = 2$ to the topological metrics at
640 the node-to-node level (again, see Figure 1). Hence, we have a hierarchy of
641 hypotheses, where the FDR error is controlled at each level simultaneously on
642 all families of hypotheses, using the BH-FDR algorithm (see Section 3.3.1),
643 imposing as mentioned above the condition that higher resolution hypotheses
644 are tested only if the parent hypothesis has been rejected.

645 If the p-values corresponding to the hypotheses being tested are indepen-
 646 dently distributed, true null hypotheses p-values have uniform distributions,
 647 and for false null hypotheses, the conditional marginal distribution of all the
 648 p-values is uniform, or stochastically smaller than uniform (Yekutieli, 2008).
 649 In such cases, the overall FDR for the whole tree of hypotheses is bounded to
 650 $\text{FDR} \leq 2\delta q$, where q is the family-wise confidence level and $\delta \approx 1.0$ for most
 651 cases, but can be as large as $\delta \approx 1.4$ for thousands of hypothesis with few
 652 discoveries. Hence, controlling the FDR on each level at $q = 0.05$ will bound
 653 the overall FDR at 0.1 in most cases or at 0.14, when thousands of hypothesis
 654 are tested and the number of discoveries is relatively small compared to the
 655 number of hypothesis tested (see Yekutieli 2008).

656 Testing for all the required conditions on the p-values and computing
 657 δ to bound the overall FDR as defined before, is a daunting task that has
 658 been tackled in the past by modeling and multiple simulations with synthetic
 659 data (Yekutieli, 2008; Reiner-Benaim et al., 2007). Instead, we can use the
 660 fact that the bound of the overall FDR is the sum over $k = 0, \dots, K$ of the
 661 bounds for the FDR at each level, $\text{FDR}(k)$ (Yekutieli et al., 2006; Yekutieli,
 662 2008). Hence, the overall tree $\text{FDR} \leq (K + 1)q$, where $K + 1$ is the number
 663 of levels in the tree. Here $K = 2$, hence, $\text{FDR} \leq 3q = 0.15$, for a family-wise
 664 confidence level of 0.05 at each level, which is quite close to the predicted
 665 (most conservative) theoretical overall bound with $\delta = 1.4$.

666 3.3.3. *Screening*

667 Despite the overall control of the FDR described before, for large studies,
 668 it is quite possible that the BH-FDR control would become equivalent to a
 669 simple (too conservative) Bonferroni correction, and no single null hypoth-

670 esis could be rejected (Benjamini and Yekutieli, 2005). Most large studies,
 671 e.g., the expression levels of thousands of genes in microarrays, nowadays
 672 use screening methods to reduce the number of hypotheses tested, improving
 673 the overall statistical power of the FDR control, especially when the fraction
 674 of rejections of the null hypothesis is small (Benjamini and Yekutieli, 2005).
 675 Screening to eliminate some uninteresting hypotheses is valid, so long as the
 676 null hypothesis of the screening method is independent of the null hypothe-
 677 sis being tested (Yekutieli, 2008). Since the null hypothesis in most tests is
 678 that mean differences are zero, a valid screening method is an ANOVA sin-
 679 gle effects F -ratio screening (Reiner-Benaim et al., 2007), in which the null
 680 hypothesis depends on the variance of the data (see details in Appendix).

681 In addition to reducing the number of hypotheses to be tested, it has been
 682 also proposed to use thresholds on the connectivity matrices themselves to
 683 get rid of noisy connections, avoiding thus unnecessary tests on those connec-
 684 tions. To avoid ad-hoc thresholds, we screen the connectivity matrix using
 685 a set of increasing thresholds that produce different connectivity matrices at
 686 different sparsity levels (Rubinov and Sporns, 2010; Bullmore and Bassett,
 687 2010; Achard and Bullmore, 2007; Bassett et al., 2008). This data screening
 688 technique reveals statistical differences at different levels of sparsity that are
 689 not seen with a single ad-hoc threshold (Gong et al., 2009). Optionally, a
 690 single robust threshold can be used on the connectivity matrices themselves,
 691 using the BH-FDR error control (Abramovich and Benjamini, 1996). Here,
 692 we screen the normalized connectivity matrices with thresholds in the $[0, 0.05]$

range,¹² as in (Gong et al., 2009), given that the BH-FDR based threshold is too stringent and may miss important discoveries. Figure S3 illustrates how these thresholds affect the sparsity of the thresholded matrices.

Here, we use then the simple screening method of thresholding the connectivity matrices at different sparsity levels proposed by (Rubinov and Sporns, 2010; Bullmore and Bassett, 2010; Achard and Bullmore, 2007; Bassett et al., 2008), given its simplicity and independence of the hypothesis being tested. Then, we apply an ANOVA single effects F -ratio screening test to eliminate remaining uninteresting hypotheses (see Appendix for details). This kind of selective inference has not yet received proper theoretical or practical consideration in the context of screening uninteresting hypotheses and the less obvious connection between the screening test and the follow-up one (Reiner-Benaim, 2007; Benjamini et al., 2009). Better FDR error control algorithms are needed, especially for cases where the number of null hypotheses is large and the FDR methods reduce to a simple Bonferroni correction.

3.3.4. *Bootstrapping*

We need to describe how are we going to compute the p-values that the BH-FDR error control requires. As we are working with average connectivity and topological network differences between different groups of individuals (including pairs of individuals), then by the central limit theorem, those averages should asymptotically follow a Gaussian distribution (Fisher, 2011). Nevertheless, there could be some small variations from the Gaussian distribution on real finite samples, so we use a non-parametric approach.

¹²Recall that the normalized connectivity matrices are all in the $[0, 1]$ range.

716 Bootstrapping can improve the reliability of inference compared with con-
717 ventional asymptotic tests (Davison and MacKinnon, 1999). We use boot-
718 strapping with replacement to obtain 20,000 samples of the mean for each
719 metric, scale, and class. The p-values (p) required by the BH-FDR error
720 control can be easily computed from the bootstrapped distribution of the
721 mean differences,

$$p = \frac{c}{B} \min \left\{ \sum_{i=1}^B I(s_i) \text{ s.t. } s_i > 0, \sum_{i=1}^B I(s_i) \text{ s.t. } s_i < 0 \right\}, \quad (15)$$

722 where B is the number of bootstrapped samples, $c = 1$ for single-tailed tests,
723 $c = 2$ for double-tailed tests, s_i are the bootstrapped sample differences, and
724 $I(s_i)$ the frequency of those samples. Sample differences are for instance
725 differences in the clustering coefficient at a given brain region (node) i , or
726 differences in the communicability matrix taken as a column vector at the
727 entry i , due to sex. As in (Gong et al., 2009), we consider positive and
728 negative differences in the connectivity matrices and topological metrics of
729 the associated digraphs for both sex and kinship differences, so we will use
730 one-tailed p-values.

731 3.3.5. Z-scores Global Topological Metrics

732 As the global topological metrics of the brain connectivity networks and
733 their corresponding random networks are independent, the Z-score of their
734 differences is

$$Z = \frac{\overline{M} - \overline{M}_R}{\sqrt{\delta_M^2 + \delta_{M_R}^2}}, \quad (16)$$

735 where $\overline{M}$ indicates the mean of metric M and $\overline{M}_R$ the mean metric for the
736 corresponding random network. Here we use a parametric t-test, as there
737 are enough samples of the population to assume Gaussianity, and being con-
738 sistent with previous results comparing real and random networks (Rubinov
739 and Sporns, 2010; Boccaletti et al., 2006).

740 4. Results

741 We show here the results obtained from the 303 HARDI-derived connec-
742 tivity matrices, with a formal statistical analysis of the topological features
743 as described before. For space considerations, the detailed lists of features is
744 presented in the supplement, with corresponding p-values and mean differ-
745 ences.

746 The figures in the next sections showing the features selected by the
747 machine learning methods described in Section 3.1 are color coded according
748 to the score provided by the feature selection algorithm. This score accounts
749 for the effects of each feature on the classification accuracy and its stability
750 across the n-fold cross-validation runs (see more details on the tools employed
751 in the Appendix). We do not indicate here which are the top ranked features,
752 since all the features selected are important for classification purposes, even
753 if they ranked the lowest. For instance, if we only take the 10 top ranked
754 features and use them for classification, the performance would be relatively
755 poor.

756 Figures in the next sections showing the statistically significant features
757 found in hypothesis testing (Section 3.3) are color coded according to their
758 Z-score and the sign of the difference, magenta for positive and cyan for

negative. As the sign of the difference depends on the order of the operands,
we specify in the corresponding text and on each figure what is the meaning
of each color.¹³

4.1. Classification

Tables S2-S4 compare the classification results for the three node-to-node
level metrics considered here, the “raw” connectivity matrices, generalized
communicability matrix (P), and edge betweenness (EBC), using the three
normalizations indicated in Section 2. The performance of sex classifica-
tion for the connectivity matrices, generalized communicability, and edge
betweenness, using Equation (3), are 93%, 92.2%, and 92.5%, respectively.
The corresponding performances for Equation (1) are 88.1%, 88.1%, and
93.7%, respectively, and for Equation (2) are 89.9%, 88.3%, and 80.7%, re-
spectively. The performance of kinship classification for the connectivity ma-
trices, generalized communicability, and edge betweenness, using Equation
(3), are 88.5%, 88.5%, and 87.3%, respectively. The corresponding perfor-
mances for Equation (1) are 89.7%, 85.8%, and 75.2%, respectively, and for
Equation (2) are 87.4%, 83.6%, and 75.5%, respectively.

Notice, that in some cases, Equation (1) produces slightly better classi-
fication results than Equation (3), however, as indicated in the Appendix,
only Equations (2)-(3) reduce significantly the confounding effects of brain

¹³Recall that for the kinship classes, we will be comparing connectivity matrices that represent the absolute connectivity differences within each group, and not the connectivity of each individual or pairs of individuals. Hence, differences between two kinship classes refer here to differences between the two means of the within-group differences.

size. In addition, Equation(3) produces the best overall classification results, considering all the classes and topological metrics.

Classification performance was just slightly better than chance for all topological metrics at the node level (Figure 1), and hence, they were not compared here using Equations (1)-(3). Next sections show in more detail the classification results using Equation (3).

4.1.1. Connectivity Matrices

We start with the classification results when the “raw” connectivity matrices are used, one per individual and one per pairs of individuals. Table 1 and Table S5 (for the confusion matrix, provided in the supplementary material) compare sex classification performance using all features (probabilities of connection between the $n = 70$ cortical regions) of the connectivity matrix against feature selection. Feature selection greatly improves classification performance - the selected features provide more information to distinguish between sexes. Overall, classification accuracy improved from 49.5% using up to 2763 features of the connectivity matrices, to 93% after feature selection that reduced the number of features to 297. According to our permutation tests, the probability of achieving this classification performance by chance is 0.001 or lower. Figure 2a. shows the features that provide the best classification results for sex, in the raw connectivity matrix. Table S7 in the supplement lists the selected features in more detail.

The feature selection algorithm selected 70 inter-hemispheric features as influential for sex classification purposes and about the same number of features on the left (113) and right (114) hemispheres (Figure 2a.).

Table 2 and Table S6 (for the confusion matrix, in the supplementary

material) compare kinship classification performance using all features of the connectivity matrix versus feature selection. Here, the overall classification accuracy improved from 63.5% using up to 2763 features of the connectivity matrix to 88.5% using the 250 features, automatically selected by feature selection. Permutation tests indicate that the probability of arriving to this classification performance by chance is equal or below to 0.001. Figure 2b. shows the features that provide the best classification results for kinship, in the connectivity matrix. Table S8 in the supplementary material list the corresponding selected features in more detail.

The feature selection algorithm selected 59 inter-hemispheric features as influential for kinship classification purposes and about the same number of features selected on the left (97) and right (94) hemispheres (Figure 2b.).

4.1.2. Topological Metrics

The best results at the node level correspond to the clustering coefficient and for sex classification, as indicated in Table 3. Overall classification accuracy improved from 55.4% using the clustering coefficient on all 70 nodes to 62.7% using the 53 (not a significant reduction) nodes selected using automatic feature selection.

On the other hand, good classification results were obtained for sex and kinship using the node-to-node topological metrics: edge betweenness centrality (EBC) and the generalized communicability matrix (P), respectively. The results from the generalized communicability matrix are slightly better than those using EBC for sex, while those from EBC are slightly better for kinship. Hence, we present here the best classification performances.

Tables 4 and Table S9 in the supplement (confusion matrices) show the

sex classification performance using the generalized communicability matrix. For comparison purposes, we also compute the classification performance using FDR (Abramovich and Benjamini, 1996) to select the most statistically significant elements of the generalized communicability matrix at the $q=0.05$ level. Sex classification accuracy improved from 51.8% using all 4900 features of the generalized communicability matrix to 92.2%¹⁴ using the 301 features automatically selected by feature selection. The overall accuracy of sex classification degraded to 46.2% using the 935 features selected by FDR thresholding.

Tables 5 and Table S10 in the supplement show the kinship classification performance using edge betweenness centrality, where as before, we included the classification performance using FDR for feature selection. The overall kinship classification accuracy improved from 57.1% using 2388 features of P to 87.3% using the 251 features selected by feature selection. The overall accuracy of kinship classification degraded to 32.1% using the 1031 features selected by FDR thresholding.

Figure 3.a shows the 301 features (entries) of the generalized communicability matrix that provide the best classification results for sex (listed in more detail on Table S11), while Figure 3.b shows the 251 features (edges) of the EBC metric that provide the best classification results for kinship (listed in more detail on Table S12). The 301 best entries of the communicability matrix for sex classification represent weighted walks of different lengths (or

¹⁴Notice in tables S3-S4 that EBC has a slightly higher classification than communicability, but it has a higher BER error, hence we choose here the generalized communicability matrix.

851 subgraphs, see Section 3.2.1) centered on the connections indicated on Figure
852 3a.

853 The total number of automatically selected entries of the communicability
854 matrix were distributed as 99 centered on inter-hemispheric connections, 116
855 centered on the left hemisphere, and 86 on the right hemisphere. On the other
856 hand, the 251 entries of the *EBC* for zygotity classification represent (see
857 Section 3.2.1) the importance of each connection in the connectivity matrix
858 in terms of shortest paths using such connections. In particular, the selected
859 entries of the *EBC* were distributed as (Figure 3b) 51 inter-hemispheric, 94
860 in the left hemisphere, and 107 in the right hemisphere.

861 Even though classification with cross-validation does not require Bonfer-
862 roni correction, the p-values of the permutation tests do require correction,
863 as each permutation test corresponds to testing the null hypothesis that the
864 reported classification performance was obtained by chance (Ojala and Gar-
865 riga, 2010). In these two lines of research (sex and kinship), we performed
866 permutation tests for the 11 proposed topological metrics (not all shown here)
867 indicated on Figure 1 at the node and node-to-node levels, plus the permuta-
868 tion tests performed to compare equations (1)-(3) and those to compare the
869 generalized communicability matrix with the communicability matrix (also
870 not shown for space reduction). Hence, we did in total 13 permutation tests
871 for sex and 13 for kinship. The BH-FDR correction keeps the overall false
872 discovery rate for the permutation tests to 0.001, since all tests rejected the
873 null hypothesis at this confidence level.

874 4.2. Hypothesis Testing

875 4.2.1. Connectivity Matrices

876 We now present the results of hypothesis testing on differences in the
877 connectivity matrix due to sex and kinship. Prior work on connectivity ma-
878 trices for differentiating sex and kinship classes have focused on just a few
879 connections (10) (Jahanshad et al., 2011). Previous work also did not con-
880 sider all possible pair-wise comparisons between identical twins, non-identical
881 multiples, non-twin siblings, and unrelated subjects.

882 *Sex Differences.* Figure 4 shows the 36 statistically significant sex differences
883 found in the connectivity matrices after BH-FDR error control, requiring a
884 Z-score 1.75 or higher (p-value of 0.0405 or lower, for a single tailed normal
885 distribution). The color map indicates where the probability of connection
886 is higher for women (magenta) than for men (cyan). As seen in this figure,
887 on average, women have higher brain connectivity than men in both hemi-
888 spheres, on the directed connection pairs shown. Figure 4 also shows that
889 women have higher inter-hemispheric connectivity than men, in agreement
890 with (Jahanshad et al., 2011). Nevertheless, men have some higher probab-
891 ities of connection than women, mainly on the right hemisphere (Figure 4).
892 Table S13 in the supplement shows in more detail each pair of connection
893 statistics (36) with their means and p-values. The first five largest rela-
894 tive differences with the lowest p-values were in the following connections:
895 Pars Opercularis - Post Central and Frontal Pole - Caudal Anterior Cingu-
896 late, in the left hemisphere, Inferior Parietal - Corpus Callosum, in the right
897 hemisphere, and the inter-hemispheric connections Cuneus (right) - Lateral
898 Occipital (left) and Inferior Parietal (left) - Corpus Callosum (right).

899 *Kinship Differences.* Figure 5 shows the statistically significant differences
900 between a) identical twins and non-identical multiples, b) identical twins
901 and non-twin siblings, c) identical twins and unrelated pairs of individuals,
902 d) non-identical multiples and non-twin siblings, e) non-identical multiples
903 and unrelated pairs of individuals, and f) non-twin siblings and unrelated
904 pairs of individuals; covering thus all possible pair-wise comparisons between
905 these four groups. The reported differences have a Z-score of 2.67 or higher as
906 required by the FDR error control overall possible pair-wise comparisons. As
907 may be expected for a genetically influenced trait (Thompson et al., 2001),
908 greater differences are found between unrelated pairs of individuals and sib-
909 lings than between non-twin siblings and twins. Also, greater differences
910 are found between siblings and twins than between identical twins and non-
911 identical multiples. The color map indicates where the differences are higher
912 for the first group (magenta) or for the second (cyan).

913 Of special interest are the connections that show the highest Z-score differ-
914 ences between identical twins and non-identical twins (Figure 5): Lateral Or-
915 bitofrontal - Middle Temporal, Rostral middle frontal - Supra-marginal, and
916 Supra-marginal - Rostral middle frontal, in the left hemisphere, and the inter-
917 hemispheric connection Corpus callosum (left) - Medial Orbitofrontal (right).
918 Most of the differentiating connections between identical twins and non-
919 identical twins are either in the left hemisphere or in the inter-hemispheric
920 connections. A similar behavior can be observed on the differences between
921 identical twins and non-twin siblings.

922 4.2.2. Topological Metrics

923 We now concentrate on the topological metrics and study their strength in
924 distinguishing between the different groups and between real brain networks
925 and random ones.

926 *Random Networks.* We first report differences between real brain connectiv-
927 ity networks and random networks, obtained by rewiring, at random, the
928 original brain connectivity networks while preserving the in and out node
929 degrees (recall that following the normalization, the obtained networks are
930 directed). Table 6 shows the mean and standard deviation (within paren-
931 thesis) of the topological metrics tested, and the Z-score for the difference
932 between the real networks and the corresponding random networks for each
933 topological metric.

934 The exponent γ of the scale-free, node degree truncated power law distri-
935 bution, (Bullmore and Bassett, 2010; Boccaletti et al., 2006), is also shown.
936 From the 13 possible directed motifs of size three mentioned before (Fig-
937 ure S2), only motifs 9 and 13 are present in the brain connectivity matrices
938 analyzed here, and therefore only the intensity (Section 3.2.2) of these two
939 motifs are compared in the table.

940 The FDR multiple hypothesis testing error control rejects all null hypoth-
941 esis with a Z-score equal or above 2.12, at a family-wise error control level of
942 0.05. Hence, the global clustering coefficient, modularity, and motifs 9 and
943 13, can be used to differentiate real brain connectivity networks from their
944 corresponding random network.

945 As the nodes' degree in the brain connectivity networks follows a trun-
946 cated power law, we can say that these networks are scale-free.

947 Since the characteristic path of these networks is as efficient as that of the
 948 corresponding random networks, while the clustering coefficient and modu-
 949 larity are higher, we can infer that brain networks satisfy the *small-world*
 950 *property*, i.e., they combine high modularity with a robust number of inter-
 951 modular short paths (Rubinov and Sporns, 2010; Boccaletti et al., 2006).

952 We have then demonstrated small-worldness of anatomical brain connec-
 953 tivity networks using a relatively large number of samples, and found that,
 954 according to other topological metrics, the networks are non-random.

955 *Sex Differences.* Following the hierarchical scheme of Section 3.3.2 (see also
 956 Figure 1), we threshold the connectivity matrices at different screening val-
 957 ues and compute the one-tailed p-values obtained from the bootstrapped
 958 distributions of the mean (Equation (15)), for each one of the 9 topological
 959 metrics considered. Figure S4 details these results in terms of the Z-score for
 960 each topological metric, when the connectivity matrices are thresholded in
 961 the $[0, 0.05]$ range, as well as the BH-FDR threshold. The BH-FDR method
 962 requires a minimum Z-score of 2.5, from which we conclude that only the
 963 clustering coefficient satisfies the FDR error control at the node level. In
 964 addition, the eigenvalues of the communicability matrix may be tested for
 965 statistical significance at this level (Figure 1), to check if the communicability
 966 matrix should be tested at the node-to-node level.

967 Figure 6a shows the Z-score for the differences in the clustering coeffi-
 968 cient, due to sex, on each node; while Figure 6b shows the Z-score for the
 969 eigenvalue differences of the communicability matrix, also due to sex. Higher
 970 clustering coefficients for women are shown in magenta, while higher cluster-
 971 ing coefficients in men are indicated in cyan. Figures 6a and 6b also indicate,

972 in black dashed lines, the minimum Z-score (2.13) required by the BH-FDR
973 error control on both families of tests, at $q=0.05$. Table S14 in the supple-
974 ment details the sex differences in the clustering coefficient. In this figure,
975 most differences are in the left hemisphere, which agrees with previous re-
976 sults indicating women have a higher brain connectivity than men in the left
977 hemisphere (Jahanshad et al., 2011; Gong et al., 2009). Here, we obtained
978 similar results with a relatively larger number of HARDI images and using
979 all the brain regions indicated in Table S1.

980 We found that the following cortical regions in the left hemisphere have
981 a larger clustering coefficient in women than in men: Caudal Anterior Cin-
982 gulate, Pars Orbitalis, Rostral Anterior Cingulate, Rostral Middle Frontal.
983 In the right hemisphere, we found that the Cuneus and Middle Temporal
984 cortical regions have also a larger clustering coefficient in women than in
985 men.

986 Figure 6b indicates that in the spectral decomposition of the communi-
987 cability matrix (Section 3.2.1), one eigenvalue was found to be statistically
988 significant for the differences between women (magenta) and men (cyan), so
989 there are sex differences in the communicability matrix at the node-to-node
990 level.

991 Figures 7a and 7b show the Z-score for the statistically significant sex
992 differences in the edge betweenness centrality (EBC) and the communica-
993 bility matrix, respectively, due to sex. For simplicity, the figures only show
994 the Z-scores for the sex differences exceeding the minimum Z-score (3.29)
995 required by the BH-FDR error control over both families of hypothesis tests
996 at the 0.05 level. In both figures, higher EBC or communicability values

997 for women are indicated in magenta, while higher *EBC* or communicability
998 values for men are indicated in cyan.

999 As seen in Figure 7a, only five entries in the *EBC* matrix are statistically
1000 significant at this confidence level, and are indicated in more detail in Table
1001 S15 (supplementary material). In particular, the *EBC* metric is higher in
1002 women than in men for the following connections in the left hemisphere: Non-
1003 cortical - Lingual and Lingual - Parahippocampal. In the right hemisphere,
1004 we found that the *EBC* metric is higher in women than in men for the
1005 Precuneus - Corpus Callosum connection. Finally, the *EBC* metric on the
1006 inter-hemispheric connection Supra-marginal (left) - Peri-calcarine (right) is
1007 also higher in women than in men. The p-values are around 10^{-4} , indicating
1008 a very high confidence level.

1009 Figure 7b shows that 12 differences in the directed communicability ma-
1010 trix are statistically significant. These differences are explained in more detail
1011 in Table S16 (supplementary material). In general, women have higher di-
1012 rected communicability values, in the inter-hemispheric region, than men.
1013 These communicability values are very small (3×10^{-8} to 7×10^{-4}); this is
1014 because only long walks are present between the indicated nodes, and the
1015 contribution of those walks to the communicability matrix are significantly
1016 reduced by the factorial of the walk length on Equation (15). For subsequent
1017 studies that focus on the communicability matrix, we recommend zooming
1018 in on longer walks, as suggested in (Estrada, 2010).

1019 Most of the statistically significant differences found between women and
1020 men in the communicability matrix are in the inter-hemispheric region and
1021 the p-values of these differences are of the order of 10^{-4} . In particular, the

highest differences found were Middle Temporal (left) - Medial Orbitofrontal (right), Frontal pole (right) - Parahippocampal (left), Superior Temporal (left) - Medial Orbitofrontal (right), Transverse temporal (right) - Parahippocampal (left), and Lingual (right) - Parahippocampal (left).

Finally, the overall FDR for this line of research is $\text{FDR} \leq 3q = 0.15$ (see Section 3.2).

Kinship Differences. As in the previous section, we thresholded the connectivity matrices at different screening values and compute the one-tailed p-values obtained from the bootstrapped distributions of the mean (Equation (15)), for each one of the 9 topological metrics considered and for all pair-wise comparisons of kinship groups. The BH-FDR method requires a minimum Z-score in the 2.8-3.0 range, depending on the threshold used (Figure S5 shows these results in greater detail). None of the global topological metrics was statistically significant, when controlling the false discoveries at the 0.05 or even at the 0.1 level. This is likely because there are $9 \times 6 = 54$ hypothesis tests for all possible pair-wise comparisons of kinship. ANOVA single factor F -ratio reduces this number to 34 on average, but still there are too many comparisons and most global metrics have very low Z-scores (high p-values). One possibility for future analysis would be to consider each case independently, providing different metrics for each pair-wise comparison. However, we decided to follow the hierarchical screening process (see Figure 1), and test only the communicability matrix eigenvalues at the node level.

Figure 8 shows the communicability eigenvalues for all possible pair-wise comparisons. The communicability eigenvalues do not provide differentiation

1047 between identical twins and unrelated pairs of individuals at the minimum
 1048 Z-score (2.12) required by the BH-FDR error control. This indicates that
 1049 the communicability matrix might not be able to distinguish kinship rela-
 1050 tionships at the node-to-node level. The fact that the eigenvalues of the
 1051 communicability matrix could not distinguish all kinship pair-wise compar-
 1052 isons does not necessarily imply that we cannot find differences using the
 1053 communicability matrix. However, as explained in Section 3.3.2, we follow
 1054 a conservative approach, and do not test the communicability matrix at the
 1055 highest resolution. A complementary study focusing just on the communica-
 1056 bility matrix could test it directly to see if it provides statistically significant
 1057 differences in kinship.

1058 Figure 9 shows the statistically significant edge betweenness centrality
 1059 (*EBC*) differences for all pair-wise kinship comparisons. The *EBC* matrix
 1060 does provide significant differences for kinship identification at the required
 1061 BH-FDR error control (Z-score above 2.87). In particular, the connections
 1062 that show the highest Z-score differences between identical twins and non-
 1063 identical twins were (Figure 9): Superior Frontal (right) - Caudal Anterior
 1064 Cingulate (left), Middle temporal (right) - Parahippocampal (right), Pre-
 1065 cuneus (left) - Precuneus (right), Corpus Callosum (right) - Rostral Middle
 1066 Frontal (right), and Parahippocampal (left) - Middle temporal (left).

1067 The overall FDR for this line of research is $\text{FDR} \leq 3q = 0.15$ (see Section
 1068 3.2).

5. Discussion

5.1. Normalization

On section 2.2, we chose a normalization (Equation (3)) that aims to reduce cortical volume differences (caused by brain size differences for instance). It would be very interesting to study how this normalization affects the results if there are global differences in brain size between groups. In a degenerative disease such as Alzheimers disease, for example, there is interest in whether network measures of brain connectivity are altered by the disease. If they are, it is incumbent on those analyzing the data to find out of the network differences are reducible to a simpler effect, such as the absolute or relative size of a cortical region becoming smaller. In Alzheimers disease and mild cognitive impairment, for example, we know there is disproportionate atrophy in the temporal, entorhinal, and cingulate cortices (Thompson et al., 2003; Apostolova and Thompson, 2008), and so any changes in the counts and density of fibers innervating those areas should be tested to see if the changes are due to volume differences in the cortical projection areas. If the proportion of fibers connecting a given cortical region to the other cortical regions remains the same in an atrophic brain relative to a healthy brain, then the network properties of connectivity would not differ after such a normalization. However, if we do normalize the connectivity matrices for the sizes in the cortical regions, it would be possible to infer if the disease affects connectivity above and beyond what would be expected from the size of the cortical regions alone. Alzheimers disease is thought to preferentially impair temporal and limbic connectivity, at least early in the disease, and it is interesting to know if the level of cortical disconnection goes beyond what

would be seen in a normal person with smaller cortical subregions in these areas. Normalization of network measures to cortical ROI size can achieve this. Most neurodegenerative diseases are expected to influence some connections more than others, generating a change in the proportion of fibers dedicated to each connection, when compared to the same cortical region and corresponding connections on a healthy brain. The overall network analysis framework here developed is currently under investigation for such studies, such as neurodegeneration in HIV where basal ganglia, motor and frontal circuits tend to be more greatly impaired than others (Thompson et al., 2005).

5.2. Classification using Machine Learning Methods

Best overall classification performance was obtained using the normalization indicated by Equation (3) (sections 2 and 4.1). With this normalization, we classified brain connectivity networks, according to sex and kinship classes, with high accuracy, based on the raw connectivity matrices and their associated topological metrics, mainly at the node-to-node level. In particular, the edge betweenness and the generalized communicability matrix were powerful for this task. These results should extend well to unobserved data, as evaluated by the formal 10-fold cross-validation and permutation tests. On the other hand, sex and kinship classification results were weak using topological metrics at the node level. This makes sense due to the large variability of the connectivity matrices that live in a very high dimensional space ($\mathbb{R}^{n^2}, n = 70$), requiring a higher number of features at the node-to-node resolution.

We cannot numerically compare our sex and kinship machine learning

1119 based classification results with previous work, since to the best of our knowl-
1120 edge, no previous work has performed such studies, starting from the raw
1121 connectivity matrices or associated topological metrics.¹⁵

1122 A key advantage in achieving the classification results reported here was
1123 provided by the embedded SVM-based automatic feature selection algorithm
1124 (Section 3.1). This feature selection algorithm evaluates subgroups of fea-
1125 tures, eliminating redundancies and identifying features, that when consid-
1126 ered individually might not be very influential, but can be so as a group.
1127 The number of features selected by this feature selection method is close to
1128 (but lower than) the number of samples. This hints that each connectivity
1129 matrix provides distinctive features, unobtainable from the remaining ones.
1130 Therefore, it will be interesting to investigate, as we increase the number of
1131 samples, where the number of features increases to a point where it saturates.

1132 Of interest, also, would be to compare ranking versus wrappers feature
1133 selection methods; in combination with different classifiers such as logistic,
1134 Bayesian, neural networks. A larger study should be conducted to test these
1135 classifiers on different datasets and with different tractography algorithms
1136 (see Section 5.4 for a discussion).

1137 5.3. Hypothesis Testing

1138 5.3.1. Sex Differences

1139 We found significant statistical differences, due to sex, in the mean val-
1140 ues of 36 edges in the connectivity matrices. In line with prior work, we

¹⁵Of course, other studies focusing on sex and inheritance differences have been con-
ducted in the past, as mentioned in the text and cited in the bibliography.

1141 found that there are, on average, structural brain connectivity differences
1142 between women and men. In particular, women have higher probability of
1143 inter-hemispheric connections than men, as well as higher probabilities of
1144 connections on both hemispheres (as defined on Section 2), with some ex-
1145 ceptions of course (Figure 4). This seems to suggest that on average, women
1146 have great structural connectivity supporting inter-hemispheric communica-
1147 tion than men. The higher strength of the connections in both hemispheres
1148 seems to suggest that the communication between the cortical regions as-
1149 sociated with those connections is slightly better supported structurally in
1150 women than in men.

1151 We must point out here however that these differences are on average.
1152 Given the large variability of brain connectivity networks, we can always
1153 find individual men with higher connectivity values than some women, e.g.,
1154 for the features indicated in Figure 4 (and Table S10).

1155 We also found here that the topological metrics mean clustering coeffi-
1156 cient, communicability matrix, and edge betweenness centrality, allow us to
1157 distinguish between men and women. In particular, the mean clustering co-
1158 efficient is higher in women than in men, especially in the left hemisphere
1159 and in the cortical regions indicated in Section 4.2.2. On average, the neigh-
1160 borhood of these cortical regions is more strongly connected for women than
1161 for men. We also find that women have a statistically significant higher edge
1162 betweenness centrality metric in five connections (Section 4.2.2). This means
1163 that these connections are more frequently used on shortest path communi-
1164 cations in women than in men. Finally, we found that women have also
1165 statistically significant higher communicability values centered on the inter-

1166 hemispheric connections indicated in Section 4.2.2. This suggest that the
1167 inter-hemispheric communication is stronger in women than in men, sup-
1168 porting the results from the connectivity matrices, but now at a higher scale
1169 that includes walks of any length.

1170 Previous results on structural differences in the brain connectivity ma-
1171 trix (Jahanshad et al., 2011) and some topological metrics (different from the
1172 ones used here), on the associated graph (Gong et al., 2009), agree with the
1173 results of this work. In particular, these studies indicate that women have
1174 stronger inter-hemispheric connections than men (Jahanshad et al., 2011),
1175 that women show greater overall cortical connectivity, and that the underly-
1176 ing organization of their cortical networks is more efficient, both locally and
1177 globally (Gong et al., 2009), all in agreement with our results. We arrived
1178 here at the same overall conclusions using a larger number of high quality
1179 HARDI images, a larger number of topological metrics, and formal control
1180 of the overall FDR.

1181 5.3.2. *Kinship Differences*

1182 We found significant statistical differences in the mean distribution of
1183 the pair-wise absolute differences in the connectivity matrices and associated
1184 topological metrics, allowing us to distinguish among the kinship classes of
1185 identical twins, non identical twins, non-twin siblings, and unrelated pairs of
1186 individuals. As expected from a genetically influenced trait, these differences
1187 increases as the pair of subjects are less and less related. For instance, the
1188 structural differences between identical twins and non-identical twins are
1189 less than the structural differences between twins and non-twin siblings. We
1190 cannot make the same kind of comparisons we did between females and males,

1191 since the differences reported correspond to differences among classes, where
1192 each class is constituted by within-class pair-wise differences. The differences
1193 reported here were made explicitly for classification purposes, using machine
1194 learning methods and hypothesis testing.

1195 Previous and complementary studies on structural brain connectivity dif-
1196 ferences due to inheritance (Jahanshad et al., 2010; Thompson et al., 2001)
1197 cannot be directly compared with our results, since those studies do not work
1198 directly with the raw connectivity matrices.

1199 Overall the sex and kinship classification performances (with automatic
1200 feature selection) are very good using the communicability and edge be-
1201 tweenness topological metrics, but slightly inferior to using the connectivity
1202 matrices directly. We believe that the reason for this is that topological
1203 metrics are at a higher scale and offer less detail than edges.

1204 *5.4. Dependence on the Tractography Algorithm*

1205 A key issue in the repeatability of the findings of any study on struc-
1206 tural brain differences based on the DWI-derived connectivity matrix, is the
1207 (possible) strong dependence on the tractography algorithm, and the pa-
1208 rameters used for such algorithm. Indeed, this study, as well as previous
1209 studies on structural brain connectivity, assume that the number of path-
1210 ways connecting any pair of cortical regions have been correctly identified by
1211 tractography. Nevertheless, tractography results can vary significantly de-
1212 pending on the algorithm and its parameters, the signal to noise ratio of the
1213 data, and registration (see for instance Hagmann et al. 2006; Shimony et al.
1214 2006). In particular, simple tensor-based tractography algorithms produce
1215 quite different results from ODF-based models (Hagmann et al., 2006), and

1216 even the most sophisticated tractography algorithms can produce different
1217 results when different parameters are employed.

1218 Taking into account this caveat, we used a state-of-the-art probabilistic
1219 HARDI tractography algorithm (Section 2), performing an exhaustive search
1220 of all the possible anatomical connections, avoiding thus local minima, and
1221 hence being robust to the variability with respect to different parameters.
1222 The results presented here, as well as previous similar studies, are subject to
1223 the (unknown) accuracy of the tractography algorithm, and thus statistical
1224 results may vary.

1225 In order to further increase the confidence on our results, in addition
1226 to the ODF-based probabilistic tractography algorithm used here, we tested
1227 a simpler, less robust but very popular tensor-based tractography algorithm
1228 implemented in the Trackvis toolbox.¹⁶ We do not report in detail the results
1229 from this tractography, since in general probabilistic tractography algorithms
1230 are superior (Hagmann et al., 2006), and in particular the one used here
1231 (Aganj et al., 2011). Nevertheless, we now briefly discuss how the results
1232 using this tensor-based tractography model compare with the detailed results
1233 reported in Section 4. Selected snapshots of the results with this tractography
1234 are presented in the supplementary material, figures S6-S8.

1235 Overall, the classification accuracies are similar using both tractography
1236 models. In addition, the overall sex differences are qualitatively the same:
1237 higher inter-hemispheric and overall within hemisphere connections in fe-
1238 males than in males. We also obtained statistically significant features to

¹⁶<http://trackvis.org/>

discriminate all the kinship classes using the same topological metrics indicated before. However, the particular features identified as significant for classification, and using hypothesis testing, are different for both tractography algorithms. This is clearly not a failure of the methodology proposed here, but a limitation of the current state-of-the-art tractography algorithms. Moreover, the lower robustness of the tensor-based tractography algorithms is expected to lead to such difference in selected features, since for example, certain less-complex pathways can be more consistent and less affected by such lower tractography performance. Features selected by ODF-based probabilistic tractography are expected to be more reliable.

While the methodology here proposed is expected to be robust to small variations in the connectivity matrices, it can certainly be affected by artifacts coming from tractography or other sources that could seriously bias the connectivity matrices. The robustness of the proposed method relies in turn on the robustness of the feature selection, classification, performance evaluation, and FDR error control methods, that as shown in the Methods, have strong theoretical and practical foundations.

5.5. *FDR Error Control*

There is a general consensus in the scientific community that the FDR must be controlled when multiple hypotheses are being tested on the same data. There is however no general agreement on *how* to control the FDR when multiple families of hypotheses are tested along the same line of research. As shown in Section 4.2, a strict FDR error control on multiple families of hypotheses can significantly reduce the number of null-hypotheses that are rejected, hence, the making of more discoveries.

1264 This is an issue that has been seriously addressed recently, especially in
 1265 gene expression studies, where multiple families of thousands of hypotheses
 1266 must be tested on each gene (Yekutieli, 2008). We combined the screening
 1267 method proposed by Rubinov and Sporns 2010; Bullmore and Bassett 2010;
 1268 Achard and Bullmore 2007; Bassett et al. 2008, and the ANOVA F-ratio test,
 1269 to reduce the number of uninteresting null-hypotheses, with the novel hier-
 1270 archical approach of Yekutieli 2008; Benjamini and Yekutieli 2005; Yekutieli
 1271 et al. 2006, to control the FDR, increasing thus the statistical power when
 1272 compared to a naive overall FDR error control. In spite of this, we can not
 1273 reject any null-hypothesis on the kinship classes, at the topological global
 1274 level, and only one of the hypotheses tested at this level was significant for
 1275 sex differences. We could have dropped the control of the overall FDR error
 1276 considering that is was too strict, but did not, because that undermines the
 1277 essence of the FDR error control. Indeed, the same reason why we must con-
 1278 trol the false discovery rate on single families of hypotheses testing, subsists
 1279 on multiple families of hypotheses testing (on the same research line): the
 1280 higher the number of hypotheses being tested on the *same* data, the higher
 1281 the probability of rejecting null-hypotheses by chance, especially, when most
 1282 of the null-hypotheses are true or can barely be rejected either individually
 1283 or at the family level.

1284 There is however a need for less conservative FDR error control, especially
 1285 when the expected proportion of true null-hypotheses is high, i.e., we expect
 1286 few true discoveries among many true null-hypotheses. The high number of
 1287 individuals considered here improve the accuracy of the estimated distribu-
 1288 tion of the mean (via bootstrapping). However, the FDR error control is

blind to this, since the number of hypotheses being tested depends only on the number of features at each scale (see Methods), which, in our case, can be $O(n^2)$, n being the number of nodes in the network. The FDR error control penalizes all the same smaller and larger studies. Further studies should be conducted to make the FDR error control less conservative, especially, on larger population studies.

6. Conclusion

In this large scale HARDI study of 303 individuals, we introduced a unifying, robust and general method to investigate brain connectivity differences among individuals (including pairs of individuals) using machine learning and hypothesis testing methods. We also reported differences among groups or classes of individuals using multiple hypotheses tests at several levels of data hierarchy.

We considered both: raw connectivity matrices and derived topological metrics, at multiple levels: global, single node, and node-to-node. Feature selection using a wrapper (or embedded method) was critical to eliminate, for classification purposes, uninformative connections in the connectivity matrix or topological metrics on the associated digraphs.

Future work will focus on metrics at different scales and at the highest resolution scale (as was done with the connectivity matrices). The study will also be extended to larger datasets, permitting other kinds of genetic studies, and to denser connectivity matrices derived from various tractography methods. Of great interest is a formal study of the sensitivity of classification, feature selection, and multiple hypotheses testing to the tractography model.

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1330 **References**

- 1331 Abramovich, F., Benjamini, Y., 1996. Adaptive thresholding of wavelet co-
1332 efficients. *Comput. Stat. Data An.* 22, 351–361.
- 1333 Achard, S., Bullmore, E. T., 2007. Efficiency and cost of economical brain
1334 functional networks. *PLoS Comput. Biol.* 3 (e17).

1335 Aganj, I., Lenglet, C., Jahanshad, N., Yacoub, E., Harel, N., Thompson,
1336 P. M., Sapiro, G., 2011. A hough transform global probabilistic approach
1337 to multiple-subject diffusion mri tractography. *Med. Image Anal.* Epub
1338 ahead of print 2011 Jan 26.

1339 Amaldi, E., Kann, V., 1998. On the approximation of minimizing non zero
1340 variables or unsatisfied relations in linear systems. *Theoretical Computer*
1341 *Science* 209, 237–260.

1342 Apostolova, L., Thompson, P. M., 2008. Mapping progressive brain struc-
1343 tural changes in early alzheimer’s disease and mild cognitive impairmen.
1344 *Neuropsychologia* 46 (6), 1597–1612.

1345 Basser, P. J., Pierpaoli, C., 1996. Microstructural and physiological features
1346 of tissues elucidated by quantitative-diffusion-tensor mri. *J. Magn. Reson.*
1347 111 (3), 209–219.

1348 Bassett, D. S., Brown, J. A., Deshpande, V., Carlson, J. M., Grafton, S.,
1349 2011. Conserved and variable architecture of human white matter connec-
1350 tivity. *Neuroimage* 54 (2), 1262–1279.

1351 Bassett, D. S., Bullmore, E. T., Verchinski, B. A., Mattay, V. S., Weinberger,
1352 D. R., Meyer-Lindenberg, A., 2008. Hierarchical organization of human
1353 cortical networks in health and schizophrenia. *J. Neurosci.* 28 (37), 9239–
1354 9248.

1355 Bassett, D. S., Greenfield, D. L., Meyer-Lindenberg, A., Weinberger, D. R.,
1356 Moore, S. W., Bullmore, E. T., 2010. Efficient physical embedding of topo-

1357 logically complex information processing networks in brains and computer
1358 circuits. PLoS Comput. Biol. 6 (4), e1000748.

1359 Behrens, T. E. J., Berg, H. J., Jbabdi, S., Rushworth, M. F. S., Woolrich,
1360 M. W., 2007. Probabilistic diffusion tractography with multiple fibre ori-
1361 entations: What can we gain? Neuroimage 34 (1), 144–55.

1362 Benjamini, Y., Heller, R., Yekutieli, D., 2009. Selective inference in complex
1363 research. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 367 (1906), 4255–4271.

1364 Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a
1365 practical and powerful approach to multiple testing. J. Roy. Stat. Soc. B.
1366 Met. 57 (1), 289–300.

1367 Benjamini, Y., Hochberg, Y., 2000. On the adaptive control of the false
1368 discovery rate in multiple testing with independent statistics. J. Educ.
1369 Behav. Stat. 25 (1), 60–83.

1370 Benjamini, Y., Yekutieli, D., 2001. The control of the false discovery rate in
1371 multiple testing under dependency. Ann. Statist. 29 (4), 1165–1188.

1372 Benjamini, Y., Yekutieli, D., 2005. False discovery rate-adjusted multiple
1373 confidence intervals for selected parameters. J. Am. Stat. Assoc. 100, 71–
1374 81.

1375 Benjamini, Y., Yekutieli, D., 2005. Quantitative trait loci analysis using the
1376 false discovery rate. Genetics 171 (2), 783–790.

1377 Blondel, V., Guillaume, J., Lambiotte, R., Lefebvre, E., 2008. Fast unfolding
1378 of communities in large networks. J. Stat. Mech., P1008.

1379 Boccaletti, S., Latorab, V., Moreno, Y., Chavez, M., Hwanga, D.-U., 2006.
1380 Complex networks: Structure and dynamics. *Phys. Rep.* 424 (4-5), 175–
1381 308.

1382 Brin, S., Page, L., 1998. The anatomy of a large-scale hypertextual web
1383 search engine. In: Publishers, E. S. (Ed.), *Proc. Intl. Conf. World Wide*
1384 *Web*. Vol. 30. pp. 1–7.

1385 Bullmore, E. T., Bassett, D. S., 2010. Brain graphs: Graphical models of the
1386 human brain connectome. *Annu. Rev. Clin. Psycho.* Epub ahead of print
1387 2010 April 5.

1388 Bullmore, E. T., Sporns, O., 2009. Complex brain networks: graph theo-
1389 retical analysis of structural and functional systems. *Nat. Rev. Neurosci.*
1390 10 (3), 186–198.

1391 Crofts, J. J., Higham, D. J., 2009. A weighted communicability measure
1392 applied to complex brain networks. *J. R. Soc. Interface* 6 (33), 411–414.

1393 Davison, R., MacKinnon, J. G., 1999. The size distortion of bootstrap tests.
1394 Vol. 15 of *Econometric Theory*. Cambridge University Press.

1395 de Boer, R., Schaap, M., van der Lijn, F., Vrooman, H. A., de Groot, M.,
1396 van der Lugt, A., Ikram, M. A., Vernooij, M. W., Breteler, M. M., Niessen,
1397 W. J., 2011. Statistical analysis of minimum cost path based structural
1398 brain connectivity. *Neuroimage* 55 (2), 557–565.

1399 Dosenbach, N. U. F., Nardos, B., Cohen, A. L., Fair, D. A., Power, J. D.,
1400 Church, J. A., Nelson, S. M., Wig, G. S., Vogel, A. C., Lessov-Schlaggar,

1401 C. N., Barnes, K. A., Dubis, J. W., Feczko, E., Coalson, R. S., Pruett,
 1402 J. R., Barch, D. M., Petersen, S. E., Schlaggar, B. L., 2010. Prediction of
 1403 individual brain maturity using fmri. *Science* 329 (5997), 1358–1361.

1404 Duda, R. O., Hart, P. E., 1972. Use of the hough transformation to detect
 1405 lines and curves in pictures. *Commun. ACM* 15 (1).

1406 Easley, D., Kleinberg, J., 2010. *Networks, Crowds, and Markets: Reasoning*
 1407 *about a Highly Connected World*. Cambridge University Press.

1408 Estrada, E., 2010. Generalized walks-based centrality measures for complex
 1409 biological networks. *J. Theor. Biol.* 263 (4), 556–565.

1410 Estrada, E., Higham, D. J., 2010. Network properties revealed through ma-
 1411 trix functions. *SIAM Review* 52 (4), 696–714.

1412 Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Ségonne, F., Salat,
 1413 D. H., Busa, E., Seidman, L. J., Goldstein, J., Kennedy, D., Caviness,
 1414 V., Makris, N., Rosen, B., Anders M. Dale, A. M., 2004. Automatically
 1415 parcellating the human cerebral cortex. *Cereb. Cortex* 14 (1), 11–22.

1416 Fisher, H., 2011. *A History of the Central Limit Theorem. From Classical to*
 1417 *Modern Probability Theory*, 1st Edition. Springer. ISBN 978-0-387-87856-
 1418 0.

1419 Fornito, A., Zalesky, A., Bassett, D. S., Meunier, D., Ellison-Wright, I., Yu,
 1420 M., Wood, S. J., Shaw, K., O'Connor, J., Nertney, D., Mowry, B. J.,
 1421 Pantelis, C., Bullmore, E. T., 2011. Genetic influences on cost-efficient
 1422 organization of human cortical functional networks. *J. Neurosci.* 31 (9),
 1423 3261–3270.

- 1424 Gigandet, X., Hagmann, P., Kurant, M., Cammoun, L., Meuli, R., Thiran,
1425 J.-P., 2008. Estimating the confidence level of white matter connections
1426 obtained with mri tractography. PLoS ONE 3 (12), e4006.
- 1427 Gong, G., Rosa-Neto, P., Carbonell, F., Chen, Z. J., He, Y., Evans, A. C.,
1428 2009. Age- and gender-related differences in the cortical age- and gender-
1429 related differences in the cortical anatomical network. J. Neurosci. 29 (50),
1430 15684–15693.
- 1431 Gonzales, R. C., Woods, R. E., 2008. Digital Image Processing, 3rd Edition.
1432 Prentice Hall.
- 1433 Guyon, I., Eliseeff, A., 2003. An introduction to variable and feature selec-
1434 tion. J. Mach. Learn. Res. 3, 1157–1182.
- 1435 Guyon, I., Weston, J., Barnhill, S., Vapnik, V., 2002. Gene selection for
1436 cancer classification using support vector machines. Mach. Learn. 46 (1-
1437 3), 389–422.
- 1438 Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C. J., Wedeen,
1439 V. J., Sporns, O., 2008. Mapping the structural core of human cerebral
1440 cortex. PLoS Biology 6 (7), e159.
- 1441 Hagmann, P., Jonasson, L., Maeder, P., Thiran, J.-P., Wedeen, V. J., Meuli,
1442 R., Oct. 2006. Understanding diffusion mr imaging techniques: From scalar
1443 diffusion-weighted imaging to diffusion tensor imaging and beyond. Radio-
1444 Graphics 26, S205–S223.
- 1445 Hagmann, P., Kurant, M. and Gigandet, X., Thiran, P., Wedeen, V. J., Meuli,

1446 R., Thiran, J.-T., 2007. Mapping human whole-brain structural networks
1447 with diffusion mri. PLoS ONE 2 (7), e597.

1448 Hartmann, W. M., 2006. Dimension Reduction vs. Variable Selection. Vol.
1449 3732 of Lecture Notes in Computer Science. Springer, pp. 931–938.

1450 He, Y., Chen, Z. J., Evans, A. C., 2007. Small-world anatomical networks
1451 in the human brain revealed by cortical thickness from mri. Cereb. Cortex
1452 17 (10), 2407–2419.

1453 Holmes, C. J., Hoge, R., Collins, L., Woods, R., Toga, A. W., Evans, A. C.,
1454 1998. Enhancement of mr images using registration for signal averaging.
1455 J. Comput. Assist. Tomogr. 22 (2), 324–333.

1456 Iturria-Medina, Y., Canales-Rodríguez, E., Melie-García, L., Valdés-
1457 Hernández, P., Martínez-Montes, E., Alemán-Gómez, Y., Sánchez-Bornot,
1458 J. M., 2007. Characterizing brain anatomical connections using diffusion
1459 weighted mri and graph theory. Neuroimage 36 (3), 645–660.

1460 Jahanshad, N., Aganj, I., Lenglet, C., Joshi, A., Jin, Y., Barysheva, M.,
1461 McMahon, K., de Zubiricaray, G., Martin, N., Wright, M., Toga, A. W.,
1462 Sapiro, G., Thompson, P. M., 2011. Sex differences in the human con-
1463 nectome: 4-tesla high angular resolution diffusion imaging (hardi) trac-
1464 tography in 234 young adult twins. In: Proc. IEEE Int. Symp. Biomed.
1465 Imaging.

1466 Jahanshad, N., Lee, A. D., Barysheva, M., McMahon, K. L., de Zubiricaray,
1467 G. I., Martin, N. G., Wright, M. J., Toga, A. W., Thompson, P. M., 2010.

1468 Genetic influences on brain asymmetry: A dti study of 374 twins and
1469 siblings. *Neuroimage* 52 (2), 455–469.

1470 Jensen, D. D., Cohen, P. R., 2000. Multiple comparisons in induction algo-
1471 rithms. *Mach. Learn.* 38, 309–338.

1472 Kriegeskorte, N., Simmons, W. K., Bellgowan, P. S. F., Baker, C. I., 2009.
1473 Circular analysis in systems neuroscience: the dangers of double dipping.
1474 *Nat. Neurosci.* 12, 535–540.

1475 Leonard, C. M., Towler, S., Welcome, S., Halderman, L. K., Otto, R., Eckert,
1476 M. A., Chiarello, C., 2008. Size matters: Cerebral volume influences sex
1477 differences in neuroanatomy. *Cereb. Cortex* 18 (12), 2920–2931.

1478 Leow, A., Huang, S.-C., Geng, A., Becker, J., Davis, S., Toga, A. W., Thomp-
1479 son, P. M., 2005. Inverse Consistent Mapping in 3D Deformable Image Reg-
1480 istration: Its Construction and Statistical Properties. Vol. 3565 of *Lecture*
1481 *Notes in Computer Science*. Springer-Verlag, pp. 23–57.

1482 Lohmann, G., Margulies, D. S., Horstmann, A., Pleger, B., Lepsien, J., Gold-
1483 hahn, D., Schloegl, H., Stumvoll, M., Villringer, A., Turner, R., 2010.
1484 Eigenvector centrality mapping for analyzing connectivity patterns in fmri
1485 data of the human brain. *PLoS ONE* 5 (4), e10232.

1486 Ojala, M., Garriga, G. C., 2010. Permutation tests for studying classifier
1487 performance. *J. Mach. Learn. Res.* 11, 1833–1863.

1488 Onnela, J. P., Saramäki, J., Kertész, J., Kaski, K., 2005. Intensity and coher-
1489 ence of motifs in weighted complex networks. *Phys. Rev. E* 71 (6), 065103.

1490 Refaeilzadeh, P., Tang, L., Liu, H., 2009. Cross Validation. Encyclopedia of
1491 Database Systems. Springer.

1492 Reiner-Benaim, A., 2007. Fdr control by the bh procedure for two-sided
1493 correlated tests with implications to gene expression data analysis. *Biom.*
1494 *J.* 49 (1), 107–126.

1495 Reiner-Benaim, A., Yekutieli, D., Letwin, N. E., Elmer, G. I., Lee, N. H.,
1496 Kafkafi, N., Benjamini, Y., 2007. Associating quantitative behavioral traits
1497 with gene expression in the brain: searching for diamonds in the hay.
1498 *Bioinformatics* 23 (17), 2239–2246.

1499 Richiardi, J., Eryilmaz, H., Schwartz, S., Vuilleumier, P., Van De Ville, D.,
1500 2010. Decoding brain states from fmri connectivity graphs. *Neuroimage*
1501 Epub ahead of print 2010 June 9.

1502 Rubinov, M., Bassett, D. S., 2011. Emerging evidence of connectomic abnor-
1503 malities in schizophrenia. *Neuroscience* In press.

1504 Rubinov, M., Sporns, O., 2010. Complex network measures of brain connec-
1505 tivity: Uses and interpretations. *Neuroimage* 52 (3), 1059–1069.

1506 Shepelyansky, D. L., Zhirov, O. V., 2010. Towards google matrix of brain.
1507 *Phys. Lett. A* 374, 3206–3209.

1508 Shimony, J., Burton, H., Epstein, A. A., McLaren, D. G., Sun, S. W., Sny-
1509 der, A. Z., November 2006. Diffusion tensor imaging reveals white matter
1510 reorganization in diffusion tensor imaging reveals white matter reorgani-
1511 zation in diffusion tensor imaging reveals white matter reorganization in
1512 early blind humans. *Cereb. Cortex* 16, 1653–1661.

1513 Sporns, O., Kotter, R., 2004. Motifs in brain networks. *PLoS Biol.* 2, e369.

1514 Storey, J. D., 2002. A direct approach to false discovery rates. *J. R. Statist.*
1515 *Soc. B* 64 (3), 479–498.

1516 Storey, J. D., Taylor, J. E., Siegmund, D., 2004. Strong control, conserva-
1517 tive point estimation and simultaneous conservative consistency of false
1518 discovery rates: a unified approach. *J. R. Statist. Soc. B* 66 (1), 187–205.

1519 Thomason, M. E., Dennis, E. L., Joshi, A. A., Joshi, S. H., D., D. I., Chang,
1520 C., Henry, M. L., Johnson, R. F., Thompson, P. M., Toga, A. W., Glover,
1521 G. H., Van Horn, J. D., Gotlib, I. H., 2011. Resting-state fmri can reliably
1522 map neural networks in children. *Neuroimage* 55 (1), 165–75.

1523 Thompson, P. M., Cannon, T. D., Narr, K. L., van Erp, T., Poutanen, V.-P.,
1524 Huttunen, M., Lonnqvist, J., Standertskjold-Nordenstam, C.-G., Kaprio,
1525 J., Khaledy, M., Dail, R., Zoumalan, C. I., Toga, A. W., 2001. Genetic
1526 influences on brain structure. *Nat. Neurosci.* 4 (12), 1253–1258.

1527 Thompson, P. M., Dutton, R. A., Hayashi, K. M., Toga, A. W., Lopez, O. L.,
1528 Aizenstein, H. J., Becker, J. T., 2005. Thinning of the cerebral cortex in
1529 hiv/aids reflects cd4+ t-lymphocyte decline. In: *Proc. Nat. Acad. Sci. Vol.*
1530 *102.* pp. 15647–15652.

1531 Thompson, P. M., Hayashi, K. M., de Zubiricaray, G., Janke, A. L., Rose,
1532 S. E., Semple, J., Herman, D., Hong, M. S., Dittmer, S., Doddrell, D. M.,
1533 Toga, A. W., 2003. Dynamics of gray matter loss in alzheimer’s disease. *J.*
1534 *Neurosci.* 23 (3), 994–1005.

- 1535 Tuch, D. S., Dec. 2004. Q-ball imaging. *Magn. Reson. Med.* 52, 1358–1372.
- 1536 Vapnik, V. N., 1998. *Statistical Learning Theory*. Wiley-Interscience.
- 1537 Westfall, P. H., Johnson, W. O., Utts, J. M., 1997. Bayesian perspective on
1538 the bonferroni adjustment. *Biometrika* 84 (2), 419–427.
- 1539 Winer, B. J., 1971. *Statistical Principles in Experimental Design*, 2nd Edi-
1540 tion. Mc Graw-Hill, Inc.
- 1541 Yekutieli, D., 2008. Hierarchical false discovery rate controlling methodology.
1542 *J. Amer. Statistical Assoc.* 103 (481), 309–316.
- 1543 Yekutieli, D., Reiner-Benaim, A., Benjamini, Y., Elmer, G. I., Kafkafi, N.,
1544 Letwin, N. E., Lee, N. H., 2006. Approaches to multiplicity issues in com-
1545 plex research in microarray analysis. *Stat. Neerl.* 60 (4), 414–437.

1546 **Appendix**

1547 *Additional Implementation Details*

1548 We used the publicly available implementations of topological metrics in
1549 the Brain Connectivity Toolbox (BCT),¹⁷ that works with weighted directed
1550 graphs. Newer metrics such as the PageRank and centrality and communi-
1551 cability measures, based on subgraphs, are not available in the BCT toolbox.
1552 Nevertheless, a free implementation of the PageRank can be found on the

¹⁷<https://sites.google.com/a/brain-connectivity-toolbox.net/bct/Home>

1553 web,¹⁸ and Ernesto’s centrality and communicability measures can be easily
1554 obtained using the new matrix exponential function (expm) in Matlab.¹⁹

1555 In this work, we use the Waikato Environment for Knowledge Analysis
1556 (weka) data mining software,²⁰ which provides feature selection, classifica-
1557 tion, regression and n-fold cross-validation tools.²¹ Permutation tests were
1558 implemented in JAVA using the weka, libsvm,²² and Java Statistical Classes²³
1559 (jsc) libraries. The permutation tests consist on training the classifier with
1560 the selected features and 10-fold cross-validation, over 1,000 random per-
1561 mutations of the data set labels, in order to generate the null-hypothesis
1562 distribution. Since, the computed p-values of the permutation tests strongly
1563 depends on the performance of the classification being tested (Ojala and
1564 Garriga, 2010), we used the average of the classification performance over
1565 1,000 different random splittings of the data set.²⁴ In addition, the clas-
1566 sification performance is not evaluated using a single parameter. We used
1567 here overall classification accuracy, Balanced Error Rate (BER)²⁵ area under
1568 the Receiver Operating Characteristic (ROC), kappa statistic, and confusion
1569 matrices.

¹⁸<http://read.pudn.com/downloads149/sourcecode/math/642925/pagerank.m...htm> or
<http://www.levmuchnik.net/Content/Networks/NetworkPackageReference.html#Algorithms>

¹⁹<http://www.mathworks.com/help/techdoc/ref/expm.html>

²⁰<http://www.cs.waikato.ac.nz/ml/weka/>

²¹Alternatively, the rapidMiner package provides multithreading and more flexibility
than weka, at the expense of a steeper learning curve.

²²<http://www.csie.ntu.edu.tw/~cjlin/libsvm/>

²³<http://www.jsc.nildram.co.uk/>

²⁴This is achieved in weka by changing at random the seed.

²⁵Chosen in the NIPS 2003 feature selection challenge as the main judging criterion.

1570 In general, classifier performance can be biased due to large differences
 1571 in the number of samples for each class. The weka toolbox allows the use
 1572 of a weight to compensate for the differences in the number of samples.
 1573 Nevertheless, this weight did not produce significant classification differences
 1574 as compared to the unweighted samples, as SVMs are less dependent on
 1575 sample size, because they rely on a few support vectors.

1576 *Single Effects F-ratio*

1577 Here, we will refer to populations, factors and treatments as it is usual in
 1578 experimental design. The population here refers to the bootstrapped mean
 1579 differences, due to sex for instance. Factors refer here to sex differences
 1580 measured by each one of the topological metrics considered (Section 3.2,
 1581 Figure 1), while treatments refer to the differences on each node or node to
 1582 node that produce differences in the mean value of the topological metric at
 1583 those scales. For instance, a factor is the clustering difference (measured by
 1584 the clustering coefficient) due to sex, while the treatments correspond to the
 1585 clustering differences on each node that lead to differences in the clustering
 1586 coefficient on each node. Here, we use single factor ANOVA F -ratios to
 1587 screen out treatments that are not statistically significant.

1588 The single effects F -ratio is computed as the ratio of the mean square
 1589 treatment (main) effect and the mean square (variance within) treatment
 1590 error (Winer, 1971),

$$F_i = \frac{\text{Mean Square}_{\text{treatment } i}}{\text{Mean Square}_{\text{error } i}} = \frac{(\bar{d}_{i.} - \bar{d}_{..})^2}{\frac{\sum_j (d_{ij} - \bar{d}_{i.})^2}{B-1}},$$

1591 where d_{ij} are the observed differences at the i^{th} node or node to node $i =$

1592 $1, \dots, n$ and j^{th} bootstrapped sample $j = 1, \dots, B$, $\bar{d}_i$ the mean value of
1593 the bootstrapped samples at i , and $\bar{d}_.$, the overall population mean. Now,
1594 F -ratios where $F_i \geq F_{(q,1,B-1)}$, being F the F -distribution, are considered
1595 statistically significant at the error control level q .

1596 The usual ANOVA F -ratios divide main effects by the pooled experimen-
1597 tal error, assuming that error variances (within treatment variability) are all
1598 equal, which is a strong assumption not usually met in practice. The F -ratio
1599 used here allows differences in the experimental error on each treatment.
1600 This implies that this F -ratio does not follow exactly an F -distribution,
1601 however, the sampling distribution of these F -ratios can be approximated
1602 by the F -distribution (Winer, 1971). In addition, ANOVA F -ratios also
1603 assume independence (no interaction) on each treatment. In general, this
1604 independence is not met in our case, since nodes are neighbors of other
1605 nodes. For instance the neighbors of a node with a high clustering coefficient
1606 might also have high clustering coefficient, since the neighbors are also in
1607 the same cluster. However, we are working here with differences and dif-
1608 ferences reduce or eliminate these positive interaction effects. Hence, in our
1609 case dependence among treatments should be weak. Nevertheless, if there is
1610 dependence among treatments, the results of the F -ratio test are optimistic
1611 (Winer, 1971), meaning that more treatments are accepted as influential. In
1612 our case, it means that the test never rejects a true influential effect, while
1613 non-influential treatments will be rejected by the subsequent FDR tests. The
1614 only purpose of this screening test is to reduce the number of non-interesting
1615 hypotheses to test using FDR error control, and as we have seen here, this
1616 test does just that despite its simplicity and assumptions.

1617 The single effects F -ratio screening is performed here controlling the error
 1618 rate at $q=0.15$ at the global and node level in order to avoid overly reducing
 1619 the number of hypotheses to be tested, and a 0.05 level of significance at the
 1620 node-to-node level, when thousands of hypotheses are present.

1621 *Regression Analysis*

1622 We tested the statistical significance of different linear regression models
 1623 including the variables sex (coded as -1 men, +1 women), brain volumes,²⁶
 1624 age, and different degrees of interactions, in modeling the probability of con-
 1625 nection on the whole data set. We found that the following model has sta-
 1626 tistical significance modeling the connectivity matrices, on average,

$$y = \beta_0 + \beta_1 S + \beta_2 B + \beta_3 A + \beta_4 SB, \quad (17)$$

1627 where predictors S, B, A represents sex, brain volume, and age respectively,
 1628 while SB represents the interaction between sex and brain volume. Given
 1629 the strong correlation between sex and brain size, we employed ridge regres-
 1630 sion that provides regularization when there is strong collinearity between
 1631 predictors. The used Matlab implementation of ridge regression also centers
 1632 and standardize the predictors internally, which improves stability and allow
 1633 for proper comparison of the regression coefficients.

1634 Using the normalization provided by Equation (3), the regression coeffi-
 1635 cients were $\beta_1 = 6.15 \times 10^{-3}$, $\beta_2 = -1.87 \times 10^{-5}$, $\beta_3 = -2.12 \times 10^{-4}$, $\beta_4 =$
 1636 -6.23×10^{-3} . Where we can see that the effect of sex is about 328 times

²⁶The brain volume was calculated from the manually skull-stripped images in mm^3 and then converted to liters.

1637 larger than that of brain size and about 30 times larger than that of age.
1638 However, there is still strong negative interaction due to brain size.

1639 We perform an F-test of significance of the regression model using the
1640 un-centered and un-standardized predictors. We found that we can reject
1641 the null hypothesis that all regression coefficients in the model are zero, with
1642 a level of significance of 0.002. Now, testing the significance of each fac-
1643 tor (using standard t-test), we found that the sex and age coefficients are
1644 statistically significant with a level of significance of 2.8×10^{-4} and 0.048,
1645 respectively, but the brain volume coefficient and interaction term are not sta-
1646 tistically significant. Given that the effect of age and interaction with brain
1647 volume are both negative and much lower than the effect of sex, we disregard
1648 those effects in the analysis. The effect of age and brain size (through inter-
1649 action) causes a reduction in the statistical power of the analysis performed
1650 (since their effect is negative), which means that some brain connectivity dif-
1651 ferences due to sex that might have been influential could not been detected.
1652 This is a small price to pay in exchange for simplicity in the analysis and
1653 proves the importance of the normalization chosen.

1654 The regression coefficients for the centered and standardized predictors
1655 using the normalization provided by Equation (1) were $\beta_1 = 1.52 \times 10^{-3}$, $\beta_2 =$
1656 7.93×10^{-4} , $\beta_3 = 2.07 \times 10^{-4}$, $\beta_4 = -8.9 \times 10^{-3}$, which means that the sex
1657 effect is about 2 times larger than that of brain size, 7 times larger than
1658 that of age, and about 2 times the interaction with brain size. Formally,
1659 the model is statistically significant, with a significance level of 7.5×10^{-4} ,
1660 and the t-test on each factor reveals that the coefficients of brain size and
1661 age are statistically significant with a significance level of 1.5×10^{-7} and

1662 0.035, respectively, while the sex coefficient is only statistically significant at
1663 a significance level of 0.18. This means that the brain volume and age are
1664 more significant than sex differences and hence any differences found using
1665 this normalization alone (without further processing) could be false.

1666 The regression coefficients for the centered and standardized predictors
1667 using the normalization provided by Equation (2) were $\beta_1 = 7.58 \times 10^{-3}$, $\beta_2 =$
1668 4.49×10^{-5} , $\beta_3 = 3.7 \times 10^{-4}$, $\beta_4 = -7.6 \times 10^{-3}$, which means that the sex effect
1669 is about 170 times larger than that of brain size, 20 times larger than that of
1670 age, and there is strong interaction with brain size. Formally, the model is
1671 statistically significant, with a significance level of 0.05, and the t-test on each
1672 factor reveals that the regression coefficients of sex and age are statistically
1673 significant with a significance level of 0.007 and 0.046, respectively, while
1674 brain size and its interaction with sex are not statistically significant. As can
1675 be seen this normalization is almost as good as Equation (3), but we preferred
1676 Equation (3), since it is also superior in terms of classification performance
1677 (see Section 3.1) and holds the interpretation described above.

Table 1: Sex classification performance (see Section 3.1) obtained from the connectivity matrix (node-to-node level). We observe significantly improved results when feature selection is incorporated.

Test	All features (2763)	Feature selection (297)
Classification accuracy (%)	49.5	93.0
Sensitivity (%)	56.5	95.5
Specificity (%)	37.3	88.5
Balanced error rate (BER)	0.5313	0.0797
Area under the ROC curve	0.473	0.9203
Kappa statistic	-0.067	0.8470
p-value	-	0.001

Table 2: Kinship classification performance (see Section 3.1) obtained from the connectivity matrix (node-to-node level).

Test	All features (2763)	Feature selection (250)
Accuracy (%)	63.49	88.5 (0.010)
Sensitivity Identical Twins (%)	28.0	80.4
Specificity Identical Twins (%)	88.2	94.5
Sensitivity non-Identical Twins (%)	46.8	86.2
Specificity non-Identical Twins (%)	77.8	96.0
Sensitivity Siblings (%)	28.6	72.2
Specificity Siblings (%)	92.5	97.4
Sensitivity Unrelated People (%)	100.0	99.9
Specificity Unrelated People (%)	88.3	96.9
BER	0.3671	0.1535 (0.016)
ROC area	0.759	0.904 (0.01)
Kappa	0.4796	0.838 (0.017)
p-value	-	0.001(0)

Table 3: Sex classification performance (see Section 3.1) using the clustering coefficient (node level).

Test	All features (70)	Feature selection (53)
Classification accuracy (%)	55.4	62.7
Sensitivity (%)	64.8	89.6
Specificity (%)	37.0	25.2
Balanced error rate (BER)	0.4983	0.4261
Area under the ROC curve	0.502	0.7309
Kappa statistic	0.0035	0.5214
p-value	-	0.001

Table 4: Sex classification performance (see Section 3.1) using the generalized communicability matrix (node-to-node level).

Test	All features (4900)	FDR thresholding (935)	Feature selection (298)
Accuracy (%)	51.8	46.2	92.2
Sensitivity (%)	58.0	45.1	93.7
Specificity (%)	26.4	30.9	89.6
BER	0.5268	0.5780	0.0835
ROC area	0.473	0.429	0.917
Kappa	-0.054	-0.139	0.832
p-val	-	-	0.001

Table 5: Kinship classification performance (see Section 3.1) using edge betweenness centrality (node-to-node level).

Test	All features (2388)	FDR thresholding (1031)	Feature selection (251)
Accuracy (%)	57.1	32.14	87.3
Sensitivity Identical Twins (%)	22.0	16.0	76.4
Specificity Identical Twins (%)	84.7	85.6	97.0
Sensitivity non-Identical Twins (%)	40.3	31.3	86.7
Specificity non-Identical Twins (%)	82.2	71.9	92.0
Sensitivity Siblings (%)	25.7	11.4	70.9
Specificity Siblings (%)	91.2	90.8	97.5
Sensitivity Unrelated People (%)	97.0	48.0	98.8
Specificity Unrelated People (%)	83.6	53.9	96.1
BER	0.5636	0.8870	0.1677
ROC area	0.708	0.511	0.8945
Kappa	0.3843	0.0234	0.820
p-val	-	-	0.001

Table 6: Global topological metrics comparing brain connectivity with random networks.

Metric	Human Brain	Random	Z-score
γ	2.84 (1.44)	-	-
Clustering Coefficient	0.0766 (0.0130)	0.0148 (0.0019)	13.6
Characteristic Path	77.50 (18.9)	77.5 (18.9)	0
Node Betweenness	155.17 (12)	147.64 (8.72)	0.51
Modularity	0.7029 (0.0195)	0.3380 (0.0187)	13.51
Rentian Scale	0.6958 (0.0394)	0.7957 (0.031)	2.0
PageRank	0.0143 (0.0096)	0.0143 (0.084)	0
Estrada Index	73.1 (0.87)	71.78 (0.55)	1.28
Triangular motif 9	3.8680 (0.7077)	0.589 (0.173)	4.50
Triangular motif 13	1.8591 (0.4685)	0.042 (0.0253)	3.87

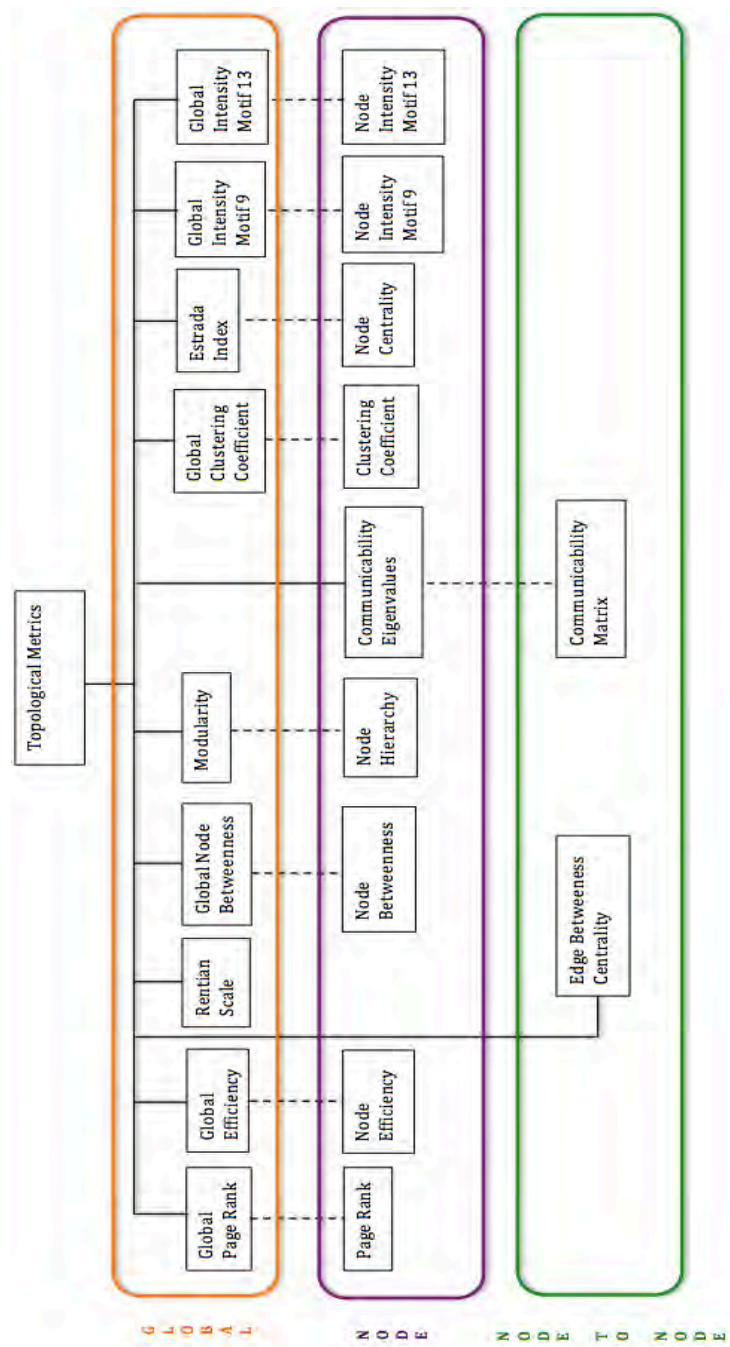


Figure 1: Hierarchy of multiple families of hypothesis testing

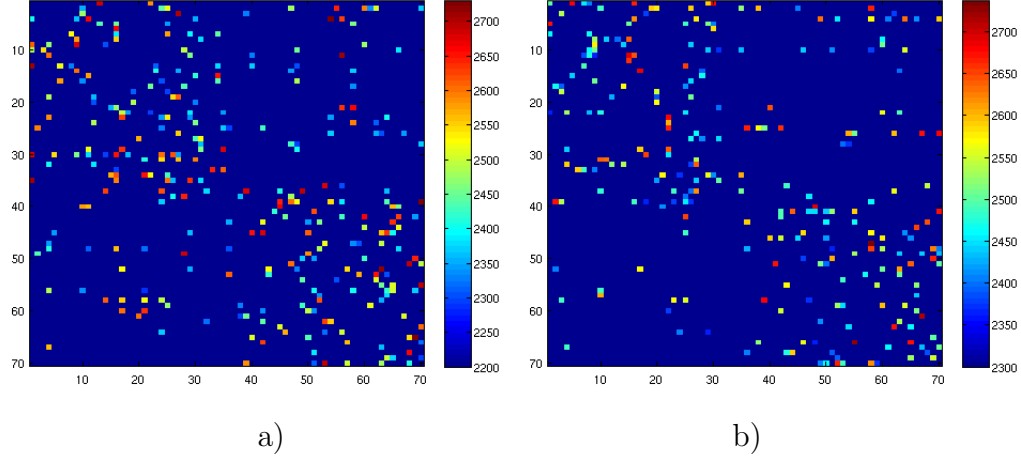


Figure 2: Selected features on the connectivity matrix for a) Sex and b) Kinship classification.

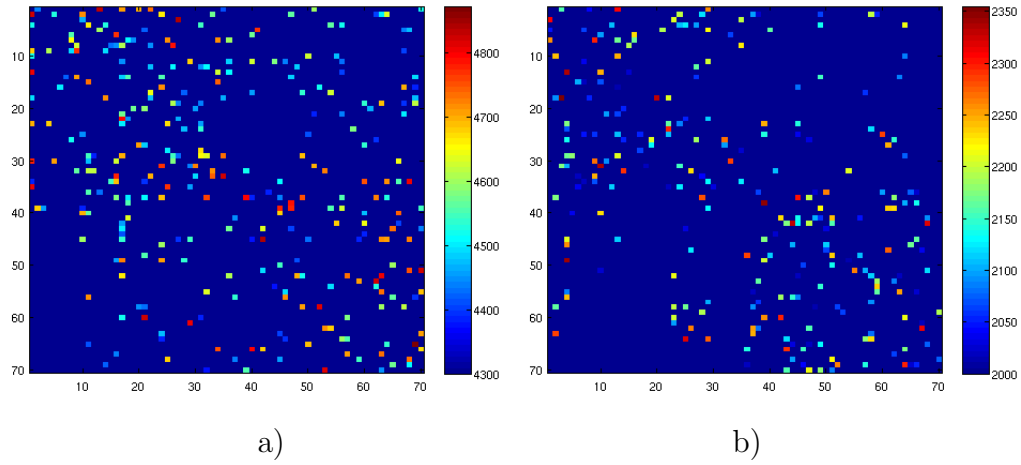


Figure 3: a) Selected features on the communicability matrix for sex classification, b) Selected features on the edge betweenness centrality matrix for kinship classification. Color code corresponds to the score given by the feature selection algorithm.

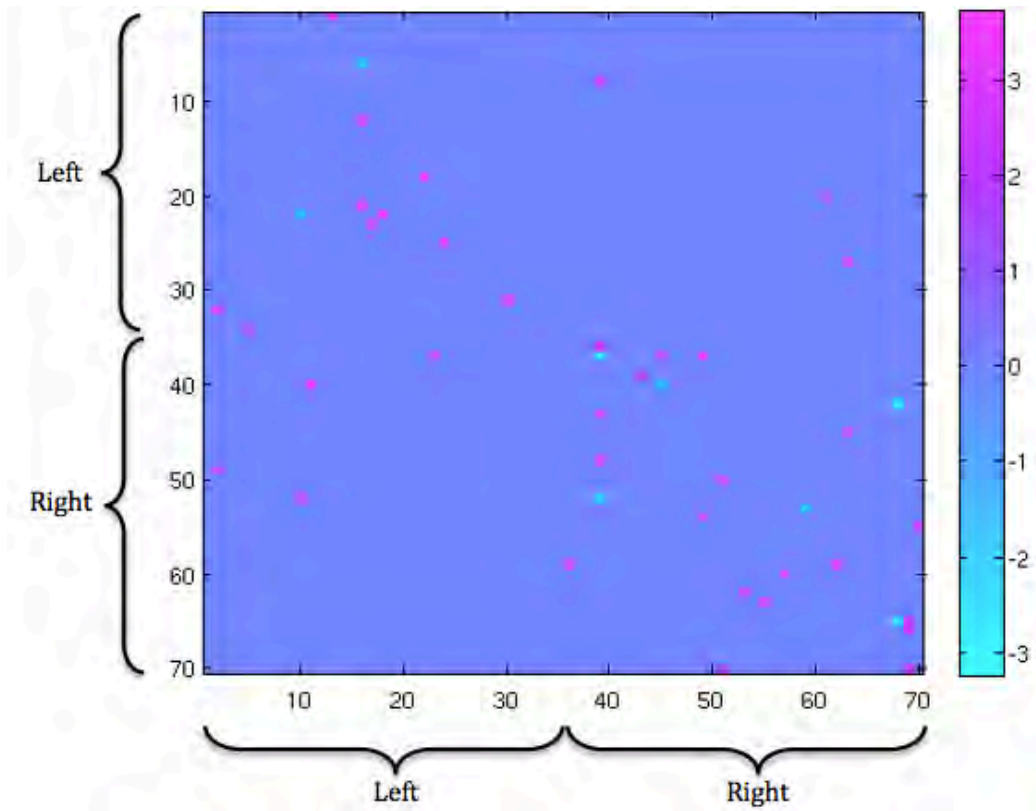


Figure 4: Z-score sex differences from the connectivity matrix. The color map indicates where the probability of connection is higher for women (magenta) or for men (cyan). Color code corresponds to the score given by the feature selection algorithm.

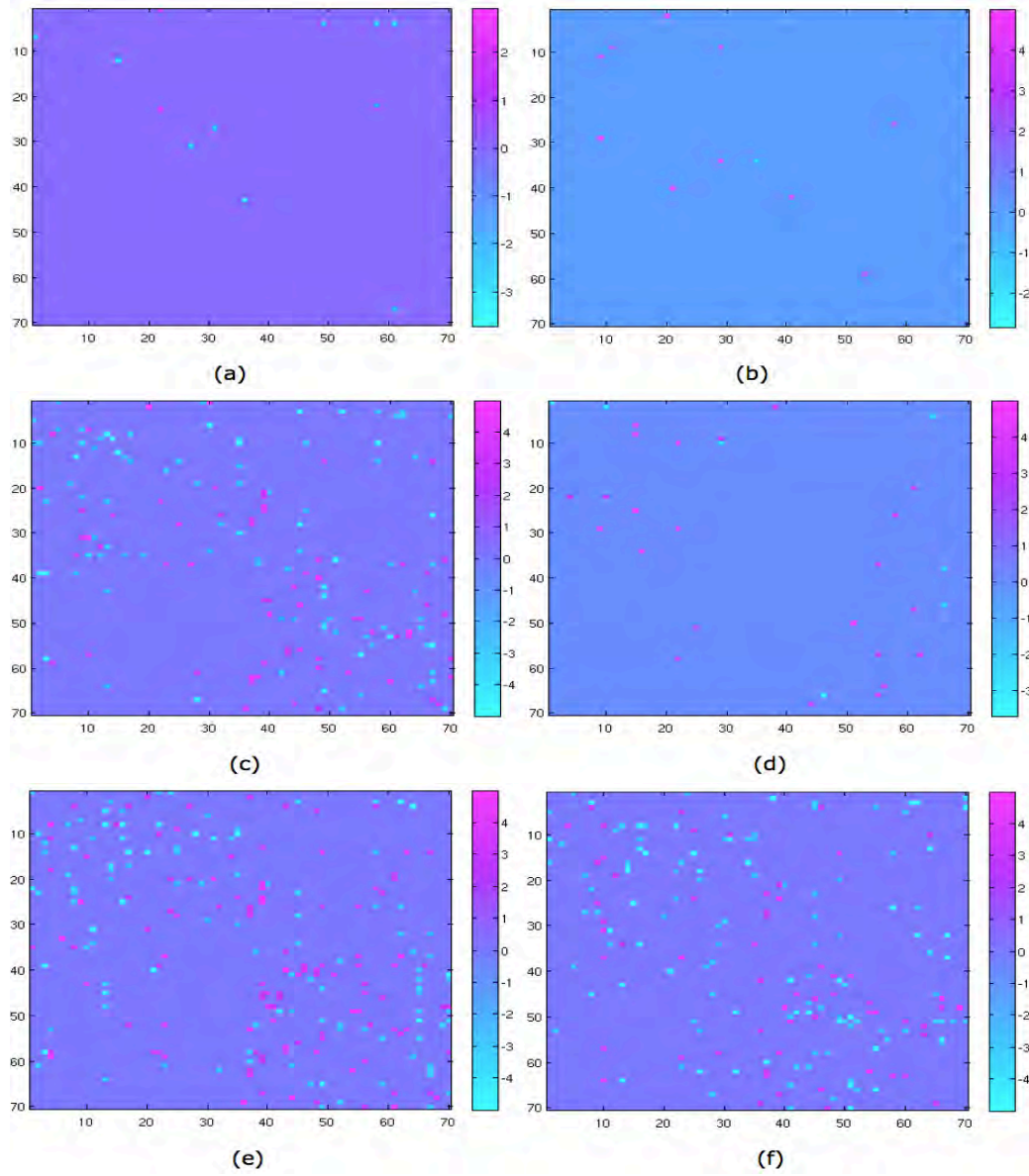


Figure 5: Z-score Kinship differences using the connectivity matrix. a) Identical twins vs non-identical multiples, b) identical twins vs siblings, c) identical twins vs unrelated, d) non-identical multiples vs siblings, e) non-identical multiples vs unrelated, and f) siblings vs unrelated. The color map indicates where the differences are higher for the first group (magenta) or for the second (cyan).

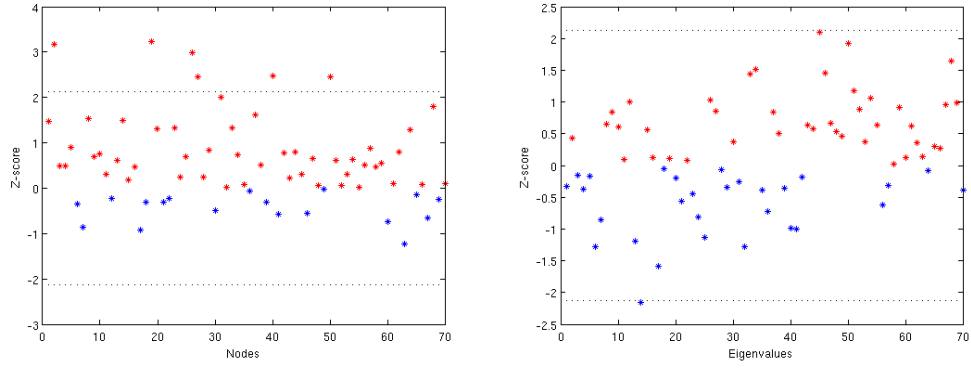


Figure 6: Sex differences considering a) the clustering coefficient, b) the communicability eigenvalues.

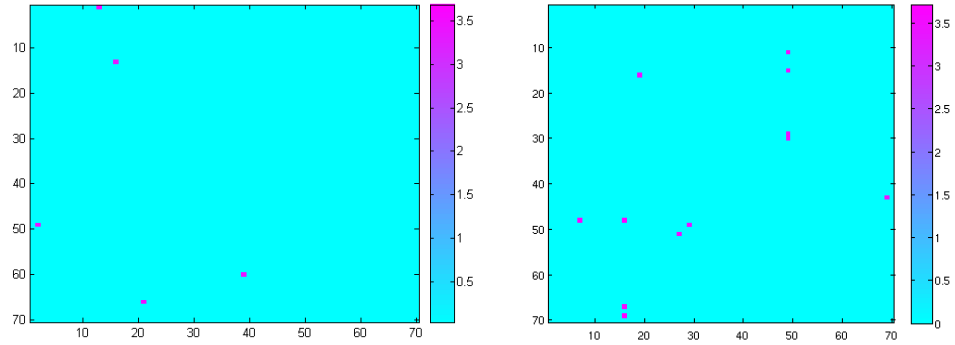


Figure 7: Sex differences considering a) the edge betweenness centrality, b) the communicability matrix.

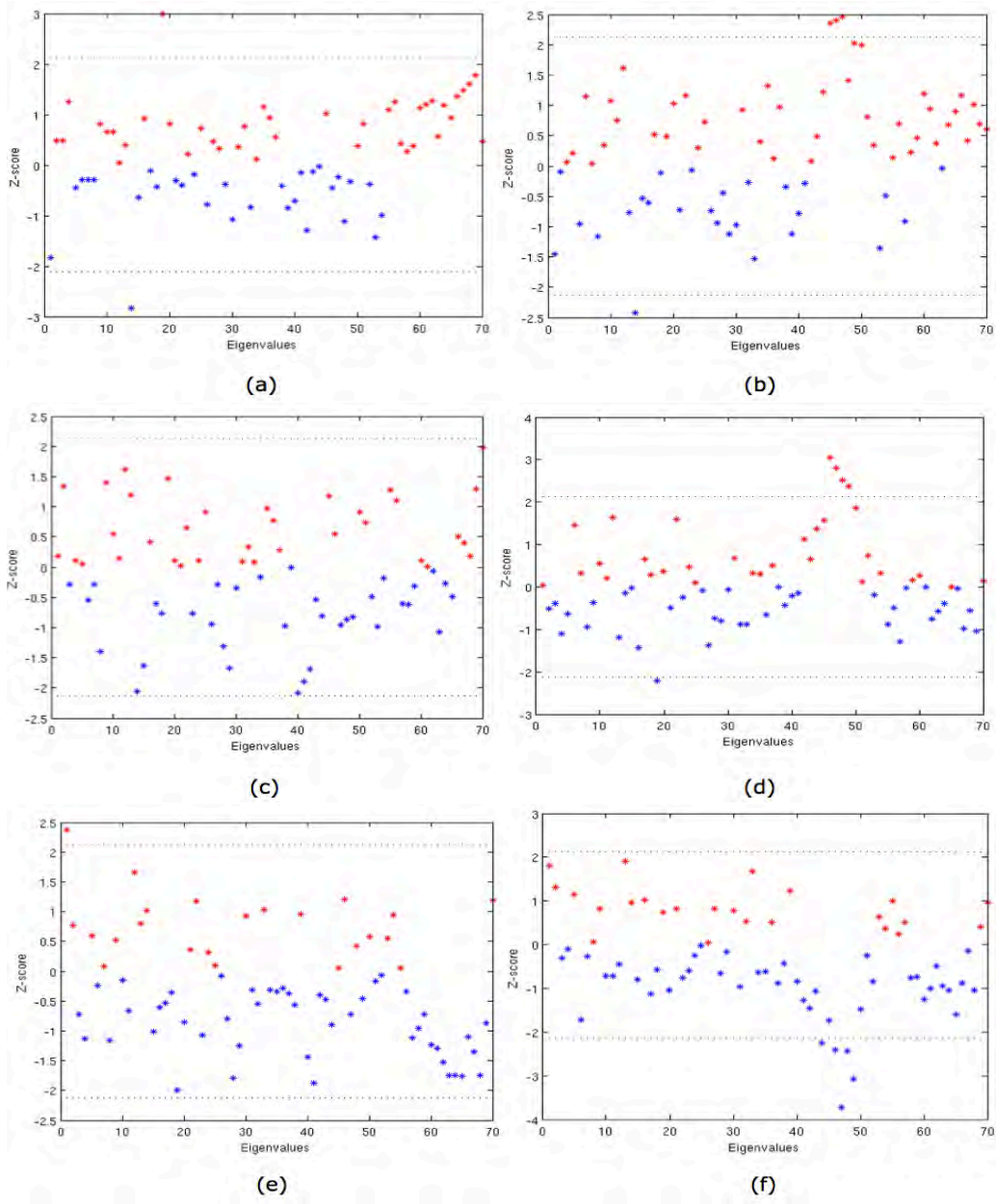


Figure 8: Z-score kinship differences considering the communicability eigenvalues: a) Identical twins vs non-identical multiples, b) identical twins vs siblings, c) identical twins vs unrelated, d) non-identical multiples vs siblings, e) non-identical multiples vs unrelated, and f) siblings vs unrelated.

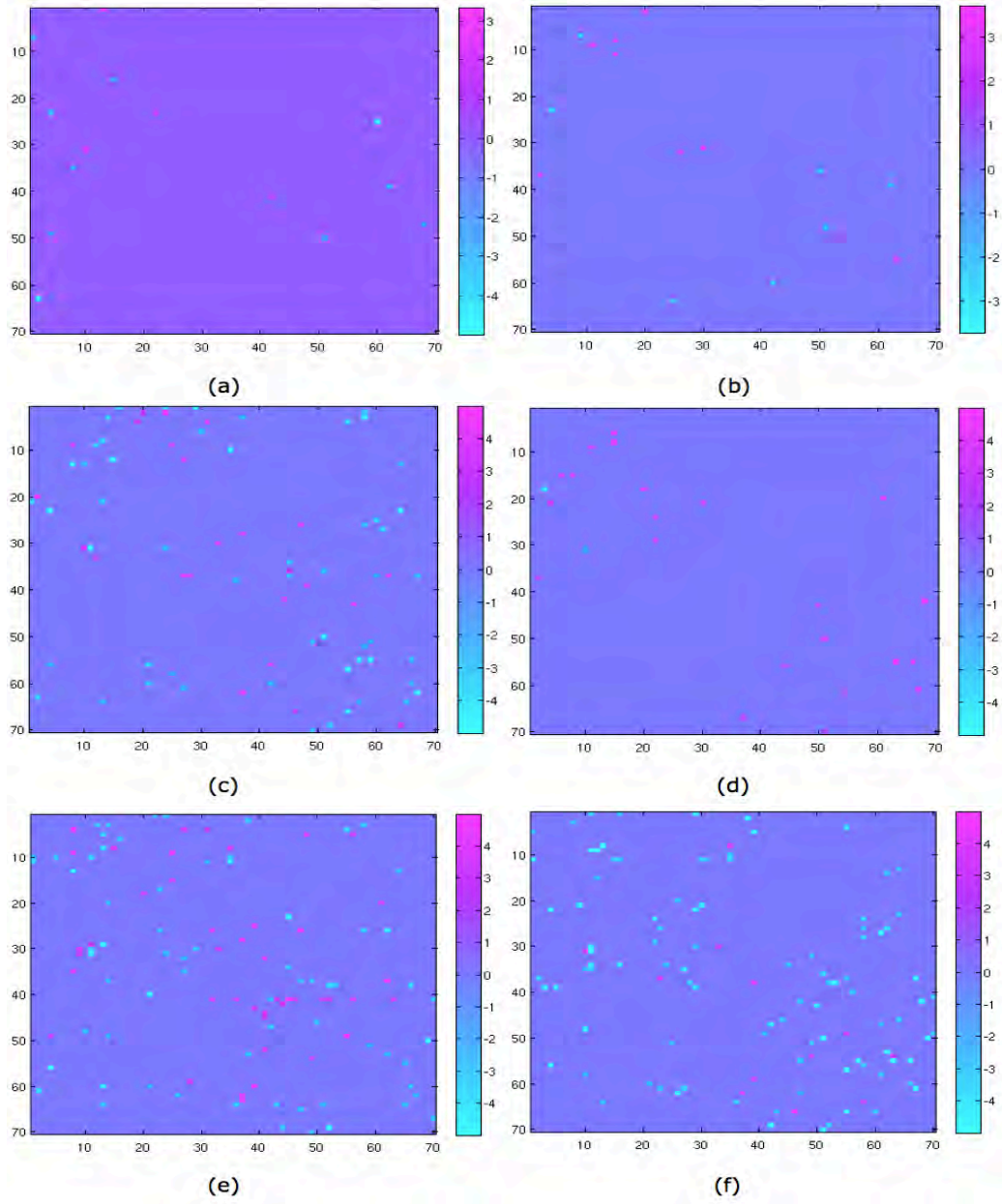


Figure 9: Z-score kinship differences considering edge betweenness centrality: a) Identical twins vs non-identical multiples, b) identical twins vs siblings, c) identical twins vs unrelated, d) non-identical multiples vs siblings, e) non-identical multiples vs unrelated, and f) siblings vs unrelated.

Supplementary Material

Hierarchical Topological Network Analysis of Anatomical Human Brain Connectivity and Differences Related to Sex and Kinship

Julio M. Duarte-Carvajalino et al.

Table 1: Cortical labels. Labels 1 (left) and 36 (right) were reserved for non-cortical surfaces.

Left hemisphere	Right hemisphere	Region
2	37	Caudal anterior cingulate
3	38	Caudal middle frontal
4	39	Corpus callosum
5	40	Cuneus
6	41	Entorhinal
7	42	Fusiform
8	43	Inferior parietal
9	44	Inferior temporal
10	45	Isthmus of the cingulate
11	46	Lateral occipital
12	47	Lateral orbitofrontal
13	48	Lingual
14	49	Medial orbitofrontal
15	50	Middle temporal
16	51	Parahippocampal
17	52	Paracentral
18	53	Pars opercularis
19	54	Pars orbitalis
20	55	Pars triangularis
21	56	Peri-calcarine
22	57	Postcentral
23	58	Posterior cingulate
24	59	Pre-central
25	60	Precuneus
26	61	Rostral anterior cingulate
27	62	Rostral middle frontal
28	63	Superior frontal
29	64	Superior parietal
30	65	Superior temporal
31	66	Supra-marginal
32	67	Frontal pole
33	68	Temporal pole
34	69	Transverse temporal
35	70	Insula

Table 2: Classification performance (see Section 4.1) using the “raw” connectivity matrices and different normalizations.

Test	Equation (1)	Equation (2)	Equation (3)
SEX			
Accuracy (%)	88.1	89.9	93.0
Sensitivity (%)	92.3	93.8	95.5
Specificity (%)	80.8	83.1	88.5
BER	0.1345	0.1156	0.0797
ROC area	0.8655	0.8844	0.9203
Kappa	0.7397	0.7788	0.8470
p-val	0.001	0.001	0.001
KINSHIP			
Accuracy (%)	89.7	87.4	88.5
Sensitivity Identical Twins (%)	87.6	72.0	80.4
Specificity Identical Twins (%)	95.4	94.1	94.5
Sensitivity non-Identical Twins (%)	83.9	82.2	86.1
Specificity non-Identical Twins (%)	95.9	93.4	96.1
Sensitivity Siblings (%)	74.7	83.1	72.3
Specificity Siblings (%)	96.9	97.7	97.3
Sensitivity Unrelated People (%)	99.9	100.0	99.9
Specificity Unrelated People (%)	98.5	98.2	96.92
BER	0.1346	0.1568	0.1535
ROC area	0.9161	0.9009	0.9040
Kappa	0.8556	0.8222	0.8380
p-val	0.001	0.001	0.001

Table 3: Classification performance (see Section 4.1) using the generalized communicability matrix and different normalizations.

Test	Equation (1)	Equation (2)	Equation (3)
SEX			
Accuracy (%)	88.1	88.3	92.2
Sensitivity (%)	91.4	90.3	93.7
Specificity (%)	82.4	84.7	89.6
BER	0.1311	0.1247	0.0835
ROC area	0.8689	0.8753	0.9165
Kappa	0.7417	0.7475	0.8320
p-val	0.001	0.001	0.001
KINSHIP			
Accuracy (%)	85.8	83.6	86.7
Sensitivity Identical Twins (%)	74.8	67.8	71.7
Specificity Identical Twins (%)	94.3	93.6	94.7
Sensitivity non-Identical Twins (%)	83.1	72.6	85.2
Specificity non-Identical Twins (%)	92.3	90.3	94.4
Sensitivity Siblings (%)	66.6	82.5	74.0
Specificity Siblings (%)	96.7	97.4	97.4
Sensitivity Unrelated People (%)	99.9	99.2	99.7
Specificity Unrelated People (%)	98.0	96.8	95.5
BER	0.1891	0.1950	0.1735
ROC area	0.8821	0.8750	0.8908
Kappa	0.8000	0.7684	0.8121
p-val	0.001	0.001	0.001

Table 4: Classification performance (see Section 4.1) using Edge Betweenness Centrality and different normalizations.

Test	Equation (1)	Equation (2)	Equation (3)
SEX			
Accuracy (%)	93.7	80.7	92.5
Sensitivity (%)	96.4	87.2	97.1
Specificity (%)	89.1	69.2	84.5
BER	0.0727	0.2178	0.0923
ROC area	0.927	0.7822	0.9077
Kappa	0.8631	0.5748	0.8341
p-val	0.001	0.001	0.001
KINSHIP			
Accuracy (%)	75.2	75.5	87.3
Sensitivity Identical Twins (%)	53.0	56.4	76.4
Specificity Identical Twins (%)	91.8	91.4	97.0
Sensitivity non-Identical Twins (%)	74.0	72.9	86.7
Specificity non-Identical Twins (%)	89.6	90.5	92.0
Sensitivity Siblings (%)	54.0	45.9	70.9
Specificity Siblings (%)	95.9	94.8	97.5
Sensitivity Unrelated People (%)	94.4	97.3	98.8
Specificity Unrelated People (%)	88.3	89.8	96.1
BER	0.3113	0.3190	0.1677
ROC area	0.8013	0.7987	0.8945
Kappa	0.6460	0.6512	0.8201
p-val	0.001	0.001	0.001

Table 5: Sex confusion matrices when classifying directly from the connectivity matrix.

All features	Women	Men
Women	109	84
Men	69	41
Feature selection	Women	Men
Women	184.4	8.6
Men	12.6	97.4

Table 6: Kinship confusion matrices when classifying directly from the connectivity matrix.

All features	Identical Twins	Non-identical Multiples	Siblings	Unrelated
Identical Twins	14	26	5	5
Non-identical Multiples	16	36	12	13
Siblings	9	15	10	1
Unrelated	0	0	0	100
Feature selection	Identical Twins	Non-identical Multiples	Siblings	Unrelated
Identical Twins	40.2	4.1	3.7	2.0
Non-identical Multiples	4.8	57.7	2.1	2.4
Siblings	6.3	3.1	25.3	0.3
Unrelated	0.0	0.1	0.0	99.9

Table 7: Connectivity best features for Sex classification.

Region 1	Region 2	Region 1	Region 2
Corpus callosum (L)	Noncortical (L)	Lingual (R)	Noncortical (R)
Inferior temporal (L)	Noncortical (L)	Pars opercularis (R)	Noncortical (R)
Isthmus of the cingulate (L)	Noncortical (L)	Caudal middle frontal (R)	Caudal middle frontal (R)
Lingual (L)	Noncortical (L)	Pre-central (R)	Caudal middle frontal (R)
Superior temporal (L)	Noncortical (L)	Rostral anterior cingulate (R)	Caudal middle frontal (R)
Insula (L)	Noncortical (L)	Caudal middle frontal (L)	Corpus callosum (R)
Precuneus (L)	Caudal anterior cingulate (L)	Caudal anterior cingulate (R)	Corpus callosum (R)
Medial orbitofrontal (R)	Caudal anterior cingulate (L)	Rostral anterior cingulate (R)	Corpus callosum (R)
Isthmus of the cingulate (L)	Caudal middle frontal (L)	Insula (R)	Corpus callosum (R)
Inferior temporal (L)	Corpus callosum (L)	Lateral occipital (L)	Cuneus (R)
Lateral occipital (L)	Corpus callosum (L)	Lingual (L)	Cuneus (R)
Pars orbitalis (L)	Corpus callosum (L)	Isthmus of the cingulate (R)	Cuneus (R)
Posterior cingulate (L)	Corpus callosum (L)	Superior temporal (R)	Cuneus (R)
Frontal pole (L)	Corpus callosum (L)	Precuneus (L)	Fusiform (R)
Lateral orbitofrontal (R)	Corpus callosum (L)	Inferior parietal (R)	Fusiform (R)
Lingual (R)	Corpus callosum (L)	Isthmus of the cingulate (R)	Fusiform (R)
Peri-calcarine (R)	Corpus callosum (L)	Precuneus (R)	Fusiform (R)
Frontal pole (R)	Corpus callosum (L)	Rostral middle frontal (R)	Fusiform (R)
Superior temporal (L)	Cuneus (L)	Supra-marginal (R)	Fusiform (R)
Isthmus of the cingulate (R)	Cuneus (L)	Paracentral (R)	Inferior parietal (R)
Lingual (L)	Entorhinal (L)	Pars opercularis (R)	Inferior parietal (R)
Parahippocampal (L)	Entorhinal (L)	Entorhinal (R)	Inferior temporal (R)
Fusiform (L)	Inferior parietal (L)	Caudal anterior cingulate (R)	Isthmus of the cingulate (R)
Lingual (L)	Inferior parietal (L)	Corpus callosum (R)	Isthmus of the cingulate (R)
Corpus callosum (L)	Inferior temporal (L)	Cuneus (R)	Isthmus of the cingulate (R)
Inferior parietal (L)	Inferior temporal (L)	Superior frontal (R)	Isthmus of the cingulate (R)
Inferior temporal (L)	Inferior temporal (L)	Fusiform (R)	Lateral occipital (R)
Medial orbitofrontal (L)	Inferior temporal (L)	Superior parietal (R)	Lateral occipital (R)
Superior temporal (L)	Inferior temporal (L)	Caudal anterior cingulate (L)	Lateral orbitofrontal (R)
Caudal anterior cingulate (L)	Isthmus of the cingulate (L)	Medial orbitofrontal (L)	Lateral orbitofrontal (R)
Caudal middle frontal (L)	Isthmus of the cingulate (L)	Superior frontal (L)	Lateral orbitofrontal (R)
Parahippocampal (L)	Isthmus of the cingulate (L)	Caudal middle frontal (R)	Lateral orbitofrontal (R)
Cuneus (R)	Isthmus of the cingulate (L)	Corpus callosum (R)	Lateral orbitofrontal (R)
Peri-calcarine (R)	Isthmus of the cingulate (L)	Parahippocampal (R)	Lateral orbitofrontal (R)
Corpus callosum (L)	Lateral occipital (L)	Isthmus of the cingulate (L)	Lingual (R)
Middle temporal (L)	Lateral occipital (L)	Lingual (L)	Lingual (R)
Superior parietal (L)	Lateral occipital (L)	Parahippocampal (L)	Lingual (R)
Superior temporal (L)	Lateral occipital (L)	Superior frontal (L)	Lingual (R)
Cuneus (R)	Lateral occipital (L)	Superior parietal (L)	Lingual (R)
Lingual (R)	Lateral occipital (L)	Corpus callosum (R)	Lingual (R)
Pars orbitalis (L)	Lateral orbitofrontal (L)	Paracentral (R)	Lingual (R)
Pars triangularis (L)	Lateral orbitofrontal (L)	Caudal anterior cingulate (R)	Medial orbitofrontal (R)
Pre-central (L)	Lateral orbitofrontal (L)	Middle temporal (R)	Medial orbitofrontal (R)
Frontal pole (L)	Lateral orbitofrontal (L)	Pars orbitalis (R)	Medial orbitofrontal (R)
Noncortical (L)	Lingual (L)	Pre-central (R)	Medial orbitofrontal (R)
Cuneus (L)	Lingual (L)	Inferior parietal (R)	Middle temporal (R)
Inferior temporal (L)	Medial orbitofrontal (L)	Isthmus of the cingulate (R)	Middle temporal (R)
Superior temporal (L)	Medial orbitofrontal (L)	Medial orbitofrontal (R)	Middle temporal (R)
Caudal anterior cingulate (R)	Medial orbitofrontal (L)	Precuneus (R)	Middle temporal (R)

Table 7 – continued from previous page

Region 1	Region 2	Region 1	Region 2
Posterior cingulate (R)	Medial orbitofrontal (L)	Superior temporal (R)	Middle temporal (R)
Peri-calcarine (L)	Middle temporal (L)	Entorhinal (R)	Parahippocampal (R)
Transverse temporal (L)	Middle temporal (L)	Middle temporal (R)	Parahippocampal (R)
Cuneus (L)	Parahippocampal (L)	Peri-calcarine (R)	Parahippocampal (R)
Entorhinal (L)	Parahippocampal (L)	Precuneus (R)	Parahippocampal (R)
Fusiform (L)	Parahippocampal (L)	Temporal pole (R)	Parahippocampal (R)
Inferior parietal (L)	Parahippocampal (L)	Insula (R)	Parahippocampal (R)
Peri-calcarine (L)	Parahippocampal (L)	Inferior parietal (R)	Paracentral (R)
Superior temporal (L)	Parahippocampal (L)	Lingual (R)	Paracentral (R)
Temporal pole (L)	Parahippocampal (L)	Postcentral (R)	Paracentral (R)
Transverse temporal (L)	Parahippocampal (L)	Posterior cingulate (R)	Paracentral (R)
Insula (L)	Parahippocampal (L)	Noncortical (R)	Pars opercularis (R)
Lingual (R)	Parahippocampal (L)	Lateral orbitofrontal (R)	Pars opercularis (R)
Postcentral (L)	Paracentral (L)	Rostral middle frontal (R)	Pars opercularis (R)
Posterior cingulate (L)	Paracentral (L)	Superior parietal (R)	Pars opercularis (R)
Superior parietal (L)	Paracentral (L)	Insula (R)	Pars opercularis (R)
Paracentral (R)	Paracentral (L)	Corpus callosum (L)	Pars orbitalis (R)
Posterior cingulate (R)	Paracentral (L)	Posterior cingulate (L)	Pars orbitalis (R)
Precuneus (R)	Paracentral (L)	Rostral anterior cingulate (L)	Pars orbitalis (R)
Postcentral (L)	Pars opercularis (L)	Corpus callosum (R)	Pars orbitalis (R)
Superior temporal (L)	Pars opercularis (L)	Rostral middle frontal (R)	Pars orbitalis (R)
Pars opercularis (L)	Pars orbitalis (L)	Caudal anterior cingulate (L)	Pars triangularis (R)
Pars triangularis (L)	Pars orbitalis (L)	Pars orbitalis (R)	Pars triangularis (R)
Rostral middle frontal (L)	Pars triangularis (L)	Corpus callosum (L)	Peri-calcarine (R)
Rostral anterior cingulate (R)	Pars triangularis (L)	Lateral occipital (L)	Peri-calcarine (R)
Supra-marginal (L)	Peri-calcarine (L)	Peri-calcarine (L)	Peri-calcarine (R)
Transverse temporal (L)	Peri-calcarine (L)	Noncortical (R)	Peri-calcarine (R)
Lingual (R)	Peri-calcarine (L)	Corpus callosum (R)	Peri-calcarine (R)
Peri-calcarine (R)	Peri-calcarine (L)	Fusiform (R)	Peri-calcarine (R)
Posterior cingulate (R)	Peri-calcarine (L)	Superior parietal (R)	Peri-calcarine (R)
Precuneus (R)	Peri-calcarine (L)	Paracentral (R)	Postcentral (R)
Noncortical (L)	Postcentral (L)	Supra-marginal (R)	Postcentral (R)
Paracentral (L)	Postcentral (L)	Insula (R)	Postcentral (R)
Postcentral (L)	Postcentral (L)	Cuneus (L)	Posterior cingulate (R)
Transverse temporal (L)	Postcentral (L)	Medial orbitofrontal (L)	Posterior cingulate (R)
Lingual (L)	Posterior cingulate (L)	Paracentral (L)	Posterior cingulate (R)
Medial orbitofrontal (L)	Posterior cingulate (L)	Peri-calcarine (L)	Posterior cingulate (R)
Caudal anterior cingulate (L)	Pre-central (L)	Pre-central (L)	Posterior cingulate (R)
Parahippocampal (L)	Pre-central (L)	Lateral orbitofrontal (R)	Posterior cingulate (R)
Posterior cingulate (L)	Pre-central (L)	Peri-calcarine (R)	Posterior cingulate (R)
Precuneus (L)	Pre-central (L)	Lateral orbitofrontal (R)	Pre-central (R)
Superior temporal (L)	Pre-central (L)	Pars opercularis (R)	Pre-central (R)
Supra-marginal (L)	Pre-central (L)	Caudal anterior cingulate (L)	Precuneus (R)
Caudal anterior cingulate (R)	Pre-central (L)	Inferior temporal (L)	Precuneus (R)
Corpus callosum (R)	Pre-central (L)	Fusiform (R)	Precuneus (R)
Posterior cingulate (R)	Pre-central (L)	Inferior temporal (R)	Precuneus (R)
Superior parietal (R)	Pre-central (L)	Middle temporal (R)	Precuneus (R)
Caudal anterior cingulate (L)	Precuneus (L)	Caudal anterior cingulate (L)	Rostral anterior cingulate (R)
Cuneus (L)	Precuneus (L)	Pre-central (R)	Rostral anterior cingulate (R)
Fusiform (L)	Precuneus (L)	Caudal anterior cingulate (L)	Rostral middle frontal (R)

Table 7 – continued from previous page

Region 1	Region 2	Region 1	Region 2
Pars opercularis (L)	Precuneus (L)	Pre-central (L)	Rostral middle frontal (R)
Posterior cingulate (L)	Precuneus (L)	Rostral anterior cingulate (L)	Rostral middle frontal (R)
Transverse temporal (L)	Precuneus (L)	Pars opercularis (R)	Rostral middle frontal (R)
Insula (L)	Precuneus (L)	Pars orbitalis (R)	Rostral middle frontal (R)
Pre-central (R)	Precuneus (L)	Rostral anterior cingulate (L)	Superior frontal (R)
Pars orbitalis (L)	Rostral anterior cingulate (L)	Isthmus of the cingulate (R)	Superior frontal (R)
Superior temporal (L)	Rostral anterior cingulate (L)	Lateral orbitofrontal (R)	Superior frontal (R)
Insula (L)	Rostral anterior cingulate (L)	Paracentral (R)	Superior frontal (R)
Caudal middle frontal (R)	Rostral anterior cingulate (L)	Pars triangularis (R)	Superior frontal (R)
Caudal middle frontal (L)	Rostral middle frontal (L)	Posterior cingulate (R)	Superior frontal (R)
Medial orbitofrontal (L)	Rostral middle frontal (L)	Frontal pole (R)	Superior frontal (R)
Pars orbitalis (L)	Rostral middle frontal (L)	Insula (R)	Superior frontal (R)
Rostral anterior cingulate (L)	Rostral middle frontal (L)	Posterior cingulate (L)	Superior parietal (R)
Superior temporal (L)	Rostral middle frontal (L)	Caudal anterior cingulate (R)	Superior parietal (R)
Supra-marginal (L)	Rostral middle frontal (L)	Corpus callosum (R)	Superior parietal (R)
Isthmus of the cingulate (L)	Superior frontal (L)	Isthmus of the cingulate (R)	Superior parietal (R)
Paracentral (L)	Superior frontal (L)	Pars opercularis (R)	Superior parietal (R)
Caudal middle frontal (R)	Superior frontal (L)	Peri-calcarine (R)	Superior parietal (R)
Medial orbitofrontal (R)	Superior frontal (L)	Postcentral (R)	Superior parietal (R)
Fusiform (L)	Superior parietal (L)	Transverse temporal (R)	Superior parietal (R)
Lateral occipital (L)	Superior parietal (L)	Cuneus (R)	Superior temporal (R)
Postcentral (L)	Superior parietal (L)	Inferior parietal (R)	Superior temporal (R)
Posterior cingulate (L)	Superior parietal (L)	Isthmus of the cingulate (R)	Superior temporal (R)
Insula (L)	Superior parietal (L)	Pars triangularis (R)	Superior temporal (R)
Isthmus of the cingulate (R)	Superior parietal (L)	Peri-calcarine (R)	Superior temporal (R)
Paracentral (R)	Superior parietal (L)	Transverse temporal (R)	Superior temporal (R)
Corpus callosum (L)	Superior temporal (L)	Isthmus of the cingulate (L)	Supra-marginal (R)
Middle temporal (L)	Superior temporal (L)	Cuneus (R)	Supra-marginal (R)
Pars triangularis (L)	Superior temporal (L)	Fusiform (R)	Supra-marginal (R)
Pre-central (L)	Superior temporal (L)	Inferior temporal (R)	Supra-marginal (R)
Rostral middle frontal (L)	Superior temporal (L)	Lingual (R)	Supra-marginal (R)
Supra-marginal (L)	Superior temporal (L)	Rostral anterior cingulate (L)	Frontal pole (R)
Inferior parietal (L)	Supra-marginal (L)	Rostral anterior cingulate (R)	Frontal pole (R)
Rostral middle frontal (L)	Supra-marginal (L)	Parahippocampal (R)	Temporal pole (R)
Superior frontal (L)	Supra-marginal (L)	Superior temporal (R)	Temporal pole (R)
Superior parietal (L)	Supra-marginal (L)	Temporal pole (R)	Temporal pole (R)
Insula (L)	Supra-marginal (L)	Insula (R)	Temporal pole (R)
Caudal anterior cingulate (R)	Frontal pole (L)	Fusiform (R)	Transverse temporal (R)
Rostral middle frontal (R)	Frontal pole (L)	Middle temporal (R)	Transverse temporal (R)
Temporal pole (L)	Temporal pole (L)	Peri-calcarine (R)	Transverse temporal (R)
Fusiform (L)	Transverse temporal (L)	Superior temporal (R)	Transverse temporal (R)
Lingual (L)	Transverse temporal (L)	Caudal anterior cingulate (L)	Insula (R)
Middle temporal (L)	Transverse temporal (L)	Superior frontal (L)	Insula (R)
Parahippocampal (L)	Transverse temporal (L)	Corpus callosum (R)	Insula (R)
Postcentral (L)	Insula (L)	Parahippocampal (R)	Insula (R)
Precuneus (L)	Insula (L)	Pars triangularis (R)	Insula (R)
Superior parietal (L)	Insula (L)	Superior frontal (R)	Insula (R)
Temporal pole (L)	Insula (L)	Supra-marginal (R)	Insula (R)
Precuneus (L)	Noncortical (R)	Transverse temporal (R)	Insula (R)
Inferior parietal (R)	Noncortical (R)		

Table 8: Connectivity best features for kinship classification.

Region 1	Region 2	Region 1	Region 2
Noncortical (L)	Noncortical (L)	Precuneus (L)	Noncortical (R)
Cuneus (L)	Noncortical (L)	Inferior parietal (R)	Noncortical (R)
Fusiform (L)	Noncortical (L)	Lingual (R)	Noncortical (R)
Postcentral (L)	Noncortical (L)	Temporal pole (R)	Noncortical (R)
Paracentral (L)	Caudal anterior cingulate (L)	Caudal anterior cingulate (L)	Caudal middle frontal (R)
Corpus callosum (R)	Caudal anterior cingulate (L)	Precuneus (L)	Caudal middle frontal (R)
Paracentral (R)	Caudal anterior cingulate (L)	Supra-marginal (R)	Caudal middle frontal (R)
Caudal middle frontal (L)	Caudal middle frontal (L)	Precuneus (L)	Corpus callosum (R)
Paracentral (L)	Caudal middle frontal (L)	Posterior cingulate (R)	Corpus callosum (R)
Pars opercularis (L)	Caudal middle frontal (L)	Peri-calcarine (L)	Cuneus (R)
Corpus callosum (R)	Caudal middle frontal (L)	Lateral occipital (R)	Cuneus (R)
Posterior cingulate (R)	Caudal middle frontal (L)	Parahippocampal (R)	Entorhinal (R)
Postcentral (L)	Corpus callosum (L)	Precuneus (L)	Fusiform (R)
Superior parietal (L)	Corpus callosum (L)	Entorhinal (R)	Fusiform (R)
Frontal pole (L)	Corpus callosum (L)	Fusiform (R)	Fusiform (R)
Frontal pole (R)	Corpus callosum (L)	Lateral occipital (R)	Fusiform (R)
Noncortical (L)	Cuneus (L)	Precuneus (R)	Fusiform (R)
Middle temporal (L)	Cuneus (L)	Noncortical (R)	Inferior parietal (R)
Temporal pole (L)	Entorhinal (L)	Pars triangularis (R)	Inferior parietal (R)
Noncortical (L)	Fusiform (L)	Temporal pole (R)	Inferior parietal (R)
Lateral occipital (L)	Fusiform (L)	Entorhinal (R)	Inferior temporal (R)
Lingual (L)	Fusiform (L)	Temporal pole (R)	Inferior temporal (R)
Temporal pole (L)	Fusiform (L)	Caudal anterior cingulate (L)	Isthmus of the cingulate (R)
Noncortical (L)	Inferior parietal (L)	Lateral occipital (R)	Isthmus of the cingulate (R)
Fusiform (L)	Inferior parietal (L)	Isthmus of the cingulate (L)	Lateral occipital (R)
Isthmus of the cingulate (L)	Inferior parietal (L)	Isthmus of the cingulate (R)	Lateral occipital (R)
Lateral occipital (L)	Inferior parietal (L)	Middle temporal (R)	Lateral occipital (R)
Lingual (L)	Inferior parietal (L)	Supra-marginal (R)	Lateral occipital (R)
Postcentral (L)	Inferior parietal (L)	Caudal middle frontal (R)	Lateral orbitofrontal (R)
Inferior parietal (L)	Inferior temporal (L)	Entorhinal (R)	Lateral orbitofrontal (R)
Inferior temporal (L)	Inferior temporal (L)	Posterior cingulate (R)	Lateral orbitofrontal (R)
Isthmus of the cingulate (L)	Inferior temporal (L)	Cuneus (R)	Lingual (R)
Lateral occipital (L)	Inferior temporal (L)	Entorhinal (R)	Lingual (R)
Parahippocampal (L)	Inferior temporal (L)	Supra-marginal (R)	Lingual (R)
Temporal pole (L)	Inferior temporal (L)	Corpus callosum (L)	Medial orbitofrontal (R)
Caudal anterior cingulate (L)	Isthmus of the cingulate (L)	Parahippocampal (R)	Medial orbitofrontal (R)
Postcentral (L)	Isthmus of the cingulate (L)	Rostral middle frontal (R)	Medial orbitofrontal (R)
Supra-marginal (L)	Isthmus of the cingulate (L)	Insula (R)	Medial orbitofrontal (R)
Caudal anterior cingulate (R)	Isthmus of the cingulate (L)	Entorhinal (R)	Middle temporal (R)
Peri-calcarine (R)	Isthmus of the cingulate (L)	Inferior parietal (R)	Middle temporal (R)
Postcentral (R)	Isthmus of the cingulate (L)	Lateral occipital (R)	Middle temporal (R)
Inferior parietal (L)	Lateral occipital (L)	Parahippocampal (R)	Middle temporal (R)
Supra-marginal (L)	Lateral occipital (L)	Insula (R)	Middle temporal (R)
Pars orbitalis (L)	Lateral orbitofrontal (L)	Isthmus of the cingulate (L)	Parahippocampal (R)
Frontal pole (L)	Lateral orbitofrontal (L)	Entorhinal (R)	Parahippocampal (R)
Inferior parietal (L)	Lingual (L)	Lingual (R)	Parahippocampal (R)

Table 8 – continued from previous page

Region 1	Region 2	Region 1	Region 2
Inferior temporal (L)	Medial orbitofrontal (L)	Middle temporal (R)	Parahippocampal (R)
Paracentral (L)	Medial orbitofrontal (L)	Temporal pole (R)	Parahippocampal (R)
Frontal pole (L)	Medial orbitofrontal (L)	Corpus callosum (L)	Paracentral (R)
Cuneus (L)	Middle temporal (L)	Pre-central (R)	Paracentral (R)
Inferior parietal (L)	Middle temporal (L)	Transverse temporal (R)	Paracentral (R)
Lateral occipital (L)	Middle temporal (L)	Insula (R)	Paracentral (R)
Lateral orbitofrontal (L)	Middle temporal (L)	Superior frontal (L)	Pars opercularis (R)
Noncortical (L)	Parahippocampal (L)	Pars orbitalis (R)	Pars opercularis (R)
Corpus callosum (L)	Parahippocampal (L)	Pre-central (R)	Pars opercularis (R)
Lateral occipital (L)	Parahippocampal (L)	Insula (R)	Pars opercularis (R)
Corpus callosum (R)	Parahippocampal (L)	Rostral anterior cingulate (L)	Pars orbitalis (R)
Medial orbitofrontal (L)	Paracentral (L)	Superior frontal (L)	Pars orbitalis (R)
Superior parietal (L)	Paracentral (L)	Superior frontal (R)	Pars orbitalis (R)
Paracentral (R)	Paracentral (L)	Rostral anterior cingulate (L)	Pars triangularis (R)
Caudal middle frontal (L)	Pars opercularis (L)	Entorhinal (R)	Pars triangularis (R)
Superior temporal (L)	Pars opercularis (L)	Inferior parietal (R)	Pars triangularis (R)
Corpus callosum (R)	Pars opercularis (L)	Medial orbitofrontal (R)	Pars triangularis (R)
Caudal anterior cingulate (L)	Pars orbitalis (L)	Supra-marginal (R)	Pars triangularis (R)
Caudal anterior cingulate (L)	Pars triangularis (L)	Pars opercularis (R)	Postcentral (R)
Pars opercularis (L)	Pars triangularis (L)	Caudal anterior cingulate (L)	Posterior cingulate (R)
Pars orbitalis (L)	Pars triangularis (L)	Corpus callosum (L)	Posterior cingulate (R)
Pars triangularis (L)	Pars triangularis (L)	Isthmus of the cingulate (L)	Posterior cingulate (R)
Insula (L)	Pars triangularis (L)	Corpus callosum (R)	Posterior cingulate (R)
Transverse temporal (L)	Peri-calcarine (L)	Isthmus of the cingulate (R)	Posterior cingulate (R)
Cuneus (R)	Peri-calcarine (L)	Lateral orbitofrontal (R)	Posterior cingulate (R)
Posterior cingulate (L)	Postcentral (L)	Lingual (R)	Posterior cingulate (R)
Pre-central (L)	Postcentral (L)	Insula (R)	Posterior cingulate (R)
Precuneus (L)	Postcentral (L)	Pars triangularis (R)	Pre-central (R)
Superior parietal (L)	Postcentral (L)	Insula (R)	Pre-central (R)
Superior temporal (L)	Postcentral (L)	Inferior parietal (L)	Precuneus (R)
Precuneus (R)	Postcentral (L)	Inferior temporal (L)	Precuneus (R)
Caudal anterior cingulate (R)	Posterior cingulate (L)	Postcentral (L)	Precuneus (R)
Corpus callosum (R)	Posterior cingulate (L)	Lateral occipital (R)	Precuneus (R)
Posterior cingulate (R)	Posterior cingulate (L)	Lingual (R)	Precuneus (R)
Transverse temporal (L)	Pre-central (L)	Paracentral (R)	Precuneus (R)
Superior parietal (R)	Pre-central (L)	Pre-central (R)	Precuneus (R)
Cuneus (L)	Precuneus (L)	Corpus callosum (L)	Rostral anterior cingulate (R)
Lingual (L)	Precuneus (L)	Frontal pole (R)	Rostral anterior cingulate (R)
Paracentral (L)	Precuneus (L)	Caudal middle frontal (L)	Rostral middle frontal (R)
Postcentral (L)	Precuneus (L)	Rostral anterior cingulate (L)	Rostral middle frontal (R)
Caudal middle frontal (R)	Precuneus (L)	Caudal anterior cingulate (R)	Rostral middle frontal (R)
Corpus callosum (R)	Precuneus (L)	Superior frontal (R)	Rostral middle frontal (R)
Fusiform (R)	Precuneus (L)	Medial orbitofrontal (L)	Superior frontal (R)
Isthmus of the cingulate (R)	Precuneus (L)	Postcentral (L)	Superior frontal (R)
Posterior cingulate (R)	Precuneus (L)	Medial orbitofrontal (R)	Superior frontal (R)
Caudal anterior cingulate (L)	Rostral anterior cingulate (L)	Paracentral (R)	Superior frontal (R)
Inferior temporal (L)	Rostral anterior cingulate (L)	Pars opercularis (R)	Superior frontal (R)
Parahippocampal (L)	Rostral anterior cingulate (L)	Rostral middle frontal (R)	Superior frontal (R)
Pars orbitalis (L)	Rostral anterior cingulate (L)	Corpus callosum (L)	Superior parietal (R)
Rostral middle frontal (L)	Rostral anterior cingulate (L)	Isthmus of the cingulate (L)	Superior parietal (R)

Table 8 – continued from previous page

Region 1	Region 2	Region 1	Region 2
Frontal pole (L)	Rostral anterior cingulate (L)	Isthmus of the cingulate (R)	Superior parietal (R)
Caudal anterior cingulate (R)	Rostral anterior cingulate (L)	Pre-central (R)	Superior parietal (R)
Corpus callosum (R)	Rostral anterior cingulate (L)	Lateral occipital (R)	Superior temporal (R)
Corpus callosum (L)	Rostral middle frontal (L)	Parahippocampal (R)	Superior temporal (R)
Rostral anterior cingulate (L)	Rostral middle frontal (L)	Superior frontal (R)	Superior temporal (R)
Supra-marginal (L)	Rostral middle frontal (L)	Supra-marginal (R)	Superior temporal (R)
Frontal pole (L)	Rostral middle frontal (L)	Transverse temporal (R)	Superior temporal (R)
Insula (L)	Rostral middle frontal (L)	Corpus callosum (L)	Supra-marginal (R)
Caudal anterior cingulate (R)	Rostral middle frontal (L)	Inferior temporal (R)	Supra-marginal (R)
Medial orbitofrontal (L)	Superior frontal (L)	Pars triangularis (R)	Supra-marginal (R)
Middle temporal (L)	Superior frontal (L)	Postcentral (R)	Supra-marginal (R)
Rostral middle frontal (L)	Superior frontal (L)	Precuneus (R)	Supra-marginal (R)
Noncortical (L)	Superior parietal (L)	Rostral anterior cingulate (L)	Frontal pole (R)
Cuneus (L)	Superior parietal (L)	Medial orbitofrontal (R)	Frontal pole (R)
Isthmus of the cingulate (L)	Superior parietal (L)	Rostral anterior cingulate (R)	Frontal pole (R)
Transverse temporal (L)	Superior parietal (L)	Frontal pole (R)	Frontal pole (R)
Superior parietal (R)	Superior parietal (L)	Noncortical (R)	Temporal pole (R)
Noncortical (L)	Superior temporal (L)	Inferior parietal (R)	Temporal pole (R)
Cuneus (L)	Superior temporal (L)	Temporal pole (R)	Temporal pole (R)
Entorhinal (L)	Superior temporal (L)	Lingual (R)	Transverse temporal (R)
Inferior parietal (L)	Superior temporal (L)	Middle temporal (R)	Transverse temporal (R)
Transverse temporal (L)	Superior temporal (L)	Superior temporal (R)	Transverse temporal (R)
Isthmus of the cingulate (L)	Supra-marginal (L)	Transverse temporal (R)	Transverse temporal (R)
Peri-calcarine (L)	Supra-marginal (L)	Corpus callosum (L)	Insula (R)
Rostral middle frontal (L)	Supra-marginal (L)	Rostral anterior cingulate (L)	Insula (R)
Insula (L)	Supra-marginal (L)	Entorhinal (R)	Insula (R)
Caudal anterior cingulate (L)	Insula (L)	Lingual (R)	Insula (R)
Isthmus of the cingulate (L)	Insula (L)	Medial orbitofrontal (R)	Insula (R)
Transverse temporal (L)	Insula (L)	Parahippocampal (R)	Insula (R)
Caudal anterior cingulate (R)	Insula (L)	Frontal pole (R)	Insula (R)

Table 9: Sex confusion matrices obtained with the generalized communicability topological metric.

All features	Women	Men
Women	112	81
Men	81	29
FDR selected features	Women	Men
Women	106	87
Men	34	76
Feature selection	Women	Men
Women	180.9	12.1
Men	11.5	98.5

Table 10: Kinship confusion matrices with the edge betweenness centrality topological metric.

All features	Identical Twins	Non-identical Multiples	Siblings	Unrelated
Identical Twins	11	21	9	9
Non-identical Multiples	18	27	10	12
Siblings	11	11	9	4
Unrelated	2	1	0	97
FDR selected features	Identical Twins	Non-identical Multiples	Siblings	Unrelated
Identical Twins	8	12	7	23
Non-identical Multiples	8	21	5	33
Siblings	3	14	4	14
Unrelated	18	26	8	48
Feature selection	Identical Twins	Non-identical Multiples	Siblings	Unrelated
Identical Twins	38.2	8.1	2.4	1.3
Non-identical Multiples	3.7	58.1	2.9	2.3
Siblings	2.2	5.7	24.8	2.3
Unrelated	0.2	1	0	98.2

Table 11: Communicability best features for sex classification.

Region 1	Region 2	Region 1	Region 2
Caudal anterior cingulate (L)	Noncortical (L)	Temporal pole (L)	Temporal pole (L)
Corpus callosum (L)	Noncortical (L)	Fusiform (L)	Transverse temporal (L)
Inferior temporal (L)	Noncortical (L)	Lingual (L)	Transverse temporal (L)
Isthmus of the cingulate (L)	Noncortical (L)	Middle temporal (L)	Transverse temporal (L)
Lingual (L)	Noncortical (L)	Supra-marginal (R)	Transverse temporal (L)
Pars opercularis (L)	Noncortical (L)	Noncortical (L)	Insula (L)
Posterior cingulate (L)	Noncortical (L)	Pars opercularis (L)	Insula (L)
Superior temporal (L)	Noncortical (L)	Superior parietal (L)	Insula (L)
Transverse temporal (L)	Noncortical (L)	Temporal pole (L)	Insula (L)
Insula (L)	Noncortical (L)	Fusiform (L)	Noncortical (R)
Noncortical (L)	Caudal anterior cingulate (L)	Lateral occipital (L)	Noncortical (R)
Corpus callosum (R)	Caudal anterior cingulate (L)	Lingual (L)	Noncortical (R)
Corpus callosum (R)	Caudal middle frontal (L)	Inferior parietal (R)	Noncortical (R)
Inferior temporal (L)	Corpus callosum (L)	Paracentral (R)	Noncortical (R)
Posterior cingulate (L)	Corpus callosum (L)	Entorhinal (R)	Caudal anterior cingulate (R)
Caudal anterior cingulate (L)	Cuneus (L)	Peri-calcarine (R)	Caudal anterior cingulate (R)
Superior temporal (L)	Cuneus (L)	Temporal pole (R)	Caudal anterior cingulate (R)
Parahippocampal (L)	Entorhinal (L)	Frontal pole (L)	Corpus callosum (R)
Medial orbitofrontal (L)	Fusiform (L)	Caudal anterior cingulate (R)	Corpus callosum (R)
Entorhinal (L)	Inferior parietal (L)	Insula (R)	Corpus callosum (R)
Fusiform (L)	Inferior parietal (L)	Entorhinal (L)	Cuneus (R)
Inferior temporal (L)	Inferior parietal (L)	Lateral occipital (L)	Cuneus (R)
Rostral anterior cingulate (L)	Inferior parietal (L)	Paracentral (L)	Cuneus (R)
Inferior parietal (L)	Inferior temporal (L)	Caudal anterior cingulate (R)	Cuneus (R)
Inferior temporal (L)	Inferior temporal (L)	Isthmus of the cingulate (R)	Cuneus (R)
Medial orbitofrontal (L)	Inferior temporal (L)	Supra-marginal (R)	Cuneus (R)
Frontal pole (L)	Inferior temporal (L)	Cuneus (L)	Entorhinal (R)
Caudal anterior cingulate (L)	Isthmus of the cingulate (L)	Inferior parietal (R)	Fusiform (R)
Caudal middle frontal (L)	Isthmus of the cingulate (L)	Isthmus of the cingulate (R)	Fusiform (R)
Precuneus (L)	Isthmus of the cingulate (L)	Parahippocampal (R)	Fusiform (R)
Corpus callosum (R)	Isthmus of the cingulate (L)	Supra-marginal (R)	Fusiform (R)
Cuneus (R)	Isthmus of the cingulate (L)	Noncortical (R)	Inferior parietal (R)
Isthmus of the cingulate (R)	Isthmus of the cingulate (L)	Lateral occipital (L)	Inferior temporal (R)
Corpus callosum (L)	Lateral occipital (L)	Pars orbitalis (R)	Inferior temporal (R)
Middle temporal (L)	Lateral occipital (L)	Transverse temporal (L)	Isthmus of the cingulate (R)
Superior parietal (L)	Lateral occipital (L)	Caudal anterior cingulate (R)	Isthmus of the cingulate (R)
Superior temporal (L)	Lateral occipital (L)	Corpus callosum (R)	Isthmus of the cingulate (R)
Frontal pole (L)	Lateral occipital (L)	Cuneus (R)	Isthmus of the cingulate (R)
Noncortical (R)	Lateral occipital (L)	Middle temporal (R)	Isthmus of the cingulate (R)
Cuneus (R)	Lateral occipital (L)	Superior frontal (R)	Isthmus of the cingulate (R)
Peri-calcarine (R)	Lateral occipital (L)	Temporal pole (R)	Isthmus of the cingulate (R)
Superior temporal (R)	Lateral occipital (L)	Lateral occipital (L)	Lateral occipital (R)
Superior parietal (L)	Lateral orbitofrontal (L)	Pars triangularis (R)	Lateral occipital (R)
Frontal pole (L)	Lateral orbitofrontal (L)	Peri-calcarine (R)	Lateral occipital (R)
Noncortical (L)	Lingual (L)	Superior parietal (R)	Lateral occipital (R)
Cuneus (L)	Lingual (L)	Caudal anterior cingulate (L)	Lateral orbitofrontal (R)
Noncortical (R)	Lingual (L)	Medial orbitofrontal (L)	Lateral orbitofrontal (R)
Corpus callosum (L)	Medial orbitofrontal (L)	Caudal middle frontal (R)	Lateral orbitofrontal (R)
Inferior temporal (L)	Medial orbitofrontal (L)	Corpus callosum (R)	Lateral orbitofrontal (R)

Table 11 – continued from previous page

Region 1	Region 2	Region 1	Region 2
Pars opercularis (L)	Medial orbitofrontal (L)	Inferior parietal (R)	Lateral orbitofrontal (R)
Transverse temporal (R)	Medial orbitofrontal (L)	Lateral orbitofrontal (L)	Lingual (R)
Inferior parietal (L)	Middle temporal (L)	Medial orbitofrontal (R)	Lingual (R)
Transverse temporal (L)	Middle temporal (L)	Paracentral (R)	Lingual (R)
Entorhinal (L)	Parahippocampal (L)	Paracentral (L)	Medial orbitofrontal (R)
Inferior parietal (L)	Parahippocampal (L)	Superior parietal (L)	Medial orbitofrontal (R)
Superior temporal (L)	Parahippocampal (L)	Caudal anterior cingulate (R)	Medial orbitofrontal (R)
Temporal pole (L)	Parahippocampal (L)	Paracentral (R)	Medial orbitofrontal (R)
Transverse temporal (L)	Parahippocampal (L)	Posterior cingulate (R)	Medial orbitofrontal (R)
Caudal anterior cingulate (R)	Parahippocampal (L)	Isthmus of the cingulate (L)	Middle temporal (R)
Medial orbitofrontal (R)	Parahippocampal (L)	Precuneus (L)	Middle temporal (R)
Frontal pole (R)	Parahippocampal (L)	Isthmus of the cingulate (R)	Middle temporal (R)
Noncortical (L)	Paracentral (L)	Superior temporal (R)	Middle temporal (R)
Inferior parietal (L)	Paracentral (L)	Noncortical (L)	Parahippocampal (R)
Lateral occipital (L)	Paracentral (L)	Peri-calcarine (L)	Parahippocampal (R)
Medial orbitofrontal (L)	Paracentral (L)	Supra-marginal (L)	Parahippocampal (R)
Peri-calcarine (L)	Paracentral (L)	Parahippocampal (L)	Paracentral (R)
Postcentral (L)	Paracentral (L)	Posterior cingulate (R)	Paracentral (R)
Posterior cingulate (L)	Paracentral (L)	Frontal pole (L)	Pars opercularis (R)
Superior parietal (L)	Paracentral (L)	Rostral middle frontal (R)	Pars opercularis (R)
Fusiform (R)	Paracentral (L)	Insula (R)	Pars opercularis (R)
Inferior parietal (R)	Paracentral (L)	Corpus callosum (L)	Pars orbitalis (R)
Inferior temporal (R)	Paracentral (L)	Paracentral (L)	Pars orbitalis (R)
Isthmus of the cingulate (R)	Paracentral (L)	Corpus callosum (R)	Pars orbitalis (R)
Medial orbitofrontal (R)	Paracentral (L)	Pars orbitalis (R)	Pars orbitalis (R)
Paracentral (R)	Paracentral (L)	Rostral middle frontal (R)	Pars orbitalis (R)
Precuneus (R)	Paracentral (L)	Isthmus of the cingulate (L)	Pars triangularis (R)
Fusiform (L)	Pars opercularis (L)	Fusiform (R)	Pars triangularis (R)
Medial orbitofrontal (L)	Pars opercularis (L)	Corpus callosum (L)	Peri-calcarine (R)
Postcentral (L)	Pars opercularis (L)	Lateral occipital (L)	Peri-calcarine (R)
Caudal anterior cingulate (R)	Pars opercularis (L)	Lingual (L)	Peri-calcarine (R)
Caudal middle frontal (R)	Pars opercularis (L)	Peri-calcarine (L)	Peri-calcarine (R)
Entorhinal (R)	Pars opercularis (L)	Caudal anterior cingulate (R)	Peri-calcarine (R)
Fusiform (L)	Pars orbitalis (L)	Corpus callosum (R)	Peri-calcarine (R)
Pars triangularis (L)	Pars orbitalis (L)	Superior parietal (R)	Peri-calcarine (R)
Noncortical (L)	Pars triangularis (L)	Paracentral (R)	Postcentral (R)
Rostral middle frontal (L)	Pars triangularis (L)	Precuneus (R)	Postcentral (R)
Posterior cingulate (R)	Pars triangularis (L)	Superior parietal (R)	Postcentral (R)
Rostral anterior cingulate (R)	Pars triangularis (L)	Frontal pole (R)	Postcentral (R)
Cuneus (L)	Peri-calcarine (L)	Pre-central (L)	Posterior cingulate (R)
Pars triangularis (L)	Peri-calcarine (L)	Isthmus of the cingulate (R)	Pre-central (R)
Rostral middle frontal (L)	Peri-calcarine (L)	Pars opercularis (R)	Pre-central (R)
Transverse temporal (L)	Peri-calcarine (L)	Temporal pole (R)	Pre-central (R)
Caudal anterior cingulate (R)	Peri-calcarine (L)	Pars orbitalis (L)	Precuneus (R)
Lingual (R)	Peri-calcarine (L)	Rostral middle frontal (L)	Precuneus (R)
Posterior cingulate (R)	Peri-calcarine (L)	Transverse temporal (L)	Precuneus (R)
Precuneus (R)	Peri-calcarine (L)	Cuneus (R)	Precuneus (R)
Noncortical (L)	Postcentral (L)	Fusiform (R)	Precuneus (R)
Inferior parietal (L)	Postcentral (L)	Inferior temporal (R)	Precuneus (R)
Lateral orbitofrontal (L)	Postcentral (L)	Pars triangularis (L)	Rostral anterior cingulate (R)

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Region 1	Region 2	Region 1	Region 2
Paracentral (L)	Postcentral (L)	Caudal anterior cingulate (L)	Rostral middle frontal (R)
Pars opercularis (L)	Postcentral (L)	Rostral anterior cingulate (L)	Rostral middle frontal (R)
Temporal pole (L)	Postcentral (L)	Caudal anterior cingulate (R)	Rostral middle frontal (R)
Caudal anterior cingulate (L)	Pre-central (L)	Pars opercularis (R)	Rostral middle frontal (R)
Medial orbitofrontal (L)	Pre-central (L)	Pars orbitalis (R)	Rostral middle frontal (R)
Parahippocampal (L)	Pre-central (L)	Caudal anterior cingulate (L)	Superior frontal (R)
Supra-marginal (L)	Pre-central (L)	Pars orbitalis (L)	Superior frontal (R)
Caudal anterior cingulate (R)	Pre-central (L)	Isthmus of the cingulate (R)	Superior frontal (R)
Lateral occipital (R)	Pre-central (L)	Paracentral (R)	Superior frontal (R)
Medial orbitofrontal (R)	Pre-central (L)	Pars triangularis (R)	Superior frontal (R)
Superior frontal (R)	Pre-central (L)	Posterior cingulate (R)	Superior frontal (R)
Superior parietal (R)	Pre-central (L)	Frontal pole (R)	Superior frontal (R)
Fusiform (L)	Precuneus (L)	Insula (R)	Superior frontal (R)
Posterior cingulate (L)	Precuneus (L)	Caudal anterior cingulate (L)	Superior parietal (R)
Superior frontal (L)	Precuneus (L)	Transverse temporal (L)	Superior parietal (R)
Insula (L)	Precuneus (L)	Caudal anterior cingulate (R)	Superior parietal (R)
Temporal pole (R)	Precuneus (L)	Isthmus of the cingulate (R)	Superior parietal (R)
Inferior parietal (L)	Rostral anterior cingulate (L)	Superior temporal (R)	Superior parietal (R)
Lateral orbitofrontal (L)	Rostral anterior cingulate (L)	Inferior parietal (R)	Superior temporal (R)
Pars orbitalis (L)	Rostral anterior cingulate (L)	Middle temporal (R)	Superior temporal (R)
Superior parietal (L)	Rostral anterior cingulate (L)	Pars triangularis (R)	Superior temporal (R)
Superior temporal (L)	Rostral anterior cingulate (L)	Peri-calcarine (R)	Superior temporal (R)
Caudal middle frontal (L)	Rostral middle frontal (L)	Transverse temporal (R)	Superior temporal (R)
Pars orbitalis (L)	Rostral middle frontal (L)	Superior temporal (L)	Supra-marginal (R)
Postcentral (L)	Rostral middle frontal (L)	Transverse temporal (L)	Supra-marginal (R)
Superior parietal (L)	Rostral middle frontal (L)	Cuneus (R)	Supra-marginal (R)
Isthmus of the cingulate (R)	Rostral middle frontal (L)	Fusiform (R)	Supra-marginal (R)
Paracentral (L)	Superior frontal (L)	Cuneus (L)	Frontal pole (R)
Pre-central (L)	Superior frontal (L)	Inferior temporal (L)	Frontal pole (R)
Medial orbitofrontal (R)	Superior frontal (L)	Parahippocampal (L)	Frontal pole (R)
Lateral occipital (L)	Superior parietal (L)	Pars orbitalis (L)	Frontal pole (R)
Supra-marginal (L)	Superior parietal (L)	Peri-calcarine (L)	Frontal pole (R)
Insula (L)	Superior parietal (L)	Posterior cingulate (R)	Frontal pole (R)
Isthmus of the cingulate (R)	Superior parietal (L)	Cuneus (L)	Temporal pole (R)
Rostral anterior cingulate (R)	Superior parietal (L)	Transverse temporal (L)	Temporal pole (R)
Pars triangularis (L)	Superior temporal (L)	Isthmus of the cingulate (R)	Temporal pole (R)
Supra-marginal (L)	Superior temporal (L)	Parahippocampal (R)	Temporal pole (R)
Temporal pole (L)	Superior temporal (L)	Temporal pole (R)	Temporal pole (R)
Corpus callosum (L)	Supra-marginal (L)	Transverse temporal (R)	Temporal pole (R)
Lateral orbitofrontal (L)	Supra-marginal (L)	Medial orbitofrontal (L)	Transverse temporal (R)
Pars orbitalis (L)	Supra-marginal (L)	Parahippocampal (L)	Transverse temporal (R)
Posterior cingulate (L)	Supra-marginal (L)	Pars opercularis (L)	Transverse temporal (R)
Pre-central (L)	Supra-marginal (L)	Pars orbitalis (L)	Transverse temporal (R)
Superior frontal (L)	Supra-marginal (L)	Peri-calcarine (R)	Transverse temporal (R)
Superior parietal (L)	Supra-marginal (L)	Superior temporal (R)	Transverse temporal (R)
Precuneus (R)	Supra-marginal (L)	Noncortical (L)	Insula (R)
Lateral orbitofrontal (L)	Frontal pole (L)	Corpus callosum (R)	Insula (R)
Superior parietal (L)	Frontal pole (L)	Inferior parietal (R)	Insula (R)
Caudal anterior cingulate (R)	Frontal pole (L)	Parahippocampal (R)	Insula (R)
Pars triangularis (R)	Frontal pole (L)	Pars triangularis (R)	Insula (R)

Table 11 – continued from previous page

Region 1	Region 2	Region 1	Region 2
Insula (R)	Frontal pole (L)	Superior frontal (R)	Insula (R)
Caudal anterior cingulate (L)	Temporal pole (L)	Supra-marginal (R)	Insula (R)
Frontal pole (L)	Temporal pole (L)		

Table 12: Edge betweenness centrality best features for kinship classification.

Region 1	Region 2	Region 1	Region 2
Caudal middle frontal (L)	Noncortical (L)	Rostral middle frontal (R)	Caudal anterior cingulate (R)
Cuneus (L)	Noncortical (L)	Superior frontal (R)	Caudal anterior cingulate (R)
Fusiform (L)	Noncortical (L)	Caudal anterior cingulate (L)	Caudal middle frontal (R)
Isthmus of the cingulate (L)	Caudal anterior cingulate (L)	Noncortical (R)	Caudal middle frontal (R)
Pars opercularis (L)	Caudal anterior cingulate (L)	Pars opercularis (R)	Caudal middle frontal (R)
Caudal anterior cingulate (R)	Caudal anterior cingulate (L)	Postcentral (R)	Caudal middle frontal (R)
Posterior cingulate (R)	Caudal anterior cingulate (L)	Rostral middle frontal (R)	Caudal middle frontal (R)
Superior frontal (R)	Caudal anterior cingulate (L)	Posterior cingulate (L)	Corpus callosum (R)
Noncortical (L)	Caudal middle frontal (L)	Precuneus (L)	Corpus callosum (R)
Pars opercularis (L)	Caudal middle frontal (L)	Caudal middle frontal (R)	Corpus callosum (R)
Supra-marginal (L)	Caudal middle frontal (L)	Isthmus of the cingulate (R)	Corpus callosum (R)
Lingual (L)	Corpus callosum (L)	Medial orbitofrontal (R)	Corpus callosum (R)
Posterior cingulate (L)	Corpus callosum (L)	Precuneus (R)	Corpus callosum (R)
Pre-central (L)	Corpus callosum (L)	Cuneus (L)	Cuneus (R)
Rostral anterior cingulate (L)	Corpus callosum (L)	Lingual (R)	Cuneus (R)
Superior parietal (L)	Corpus callosum (L)	Frontal pole (L)	Entorhinal (R)
Supra-marginal (L)	Corpus callosum (L)	Inferior temporal (R)	Entorhinal (R)
Isthmus of the cingulate (R)	Corpus callosum (L)	Entorhinal (R)	Fusiform (R)
Lateral occipital (R)	Corpus callosum (L)	Peri-calcarine (R)	Fusiform (R)
Medial orbitofrontal (R)	Corpus callosum (L)	Precuneus (R)	Fusiform (R)
Pars triangularis (R)	Corpus callosum (L)	Fusiform (R)	Inferior parietal (R)
Peri-calcarine (R)	Corpus callosum (L)	Superior parietal (R)	Inferior parietal (R)
Superior parietal (L)	Cuneus (L)	Supra-marginal (R)	Inferior parietal (R)
Cuneus (R)	Cuneus (L)	Insula (R)	Inferior parietal (R)
Middle temporal (L)	Entorhinal (L)	Fusiform (R)	Inferior temporal (R)
Temporal pole (L)	Entorhinal (L)	Lateral occipital (R)	Inferior temporal (R)
Insula (L)	Entorhinal (L)	Peri-calcarine (R)	Inferior temporal (R)
Cuneus (L)	Fusiform (L)	Superior temporal (R)	Inferior temporal (R)
Lateral occipital (L)	Fusiform (L)	Temporal pole (R)	Inferior temporal (R)
Middle temporal (L)	Fusiform (L)	Parahippocampal (L)	Isthmus of the cingulate (R)
Precuneus (L)	Fusiform (L)	Posterior cingulate (L)	Isthmus of the cingulate (R)
Transverse temporal (L)	Fusiform (L)	Precuneus (L)	Isthmus of the cingulate (R)
Noncortical (L)	Inferior parietal (L)	Caudal anterior cingulate (R)	Isthmus of the cingulate (R)
Pars opercularis (L)	Inferior parietal (L)	Entorhinal (R)	Isthmus of the cingulate (R)
Fusiform (L)	Inferior temporal (L)	Fusiform (R)	Isthmus of the cingulate (R)
Precuneus (L)	Inferior temporal (L)	Paracentral (R)	Isthmus of the cingulate (R)
Superior temporal (L)	Inferior temporal (L)	Peri-calcarine (R)	Isthmus of the cingulate (R)
Temporal pole (L)	Inferior temporal (L)	Middle temporal (R)	Lateral occipital (R)
Transverse temporal (L)	Inferior temporal (L)	Supra-marginal (R)	Lateral occipital (R)
Entorhinal (L)	Isthmus of the cingulate (L)	Transverse temporal (R)	Lateral occipital (R)
Lingual (L)	Isthmus of the cingulate (L)	Rostral anterior cingulate (L)	Lateral orbitofrontal (R)
Middle temporal (L)	Isthmus of the cingulate (L)	Caudal anterior cingulate (R)	Lateral orbitofrontal (R)
Supra-marginal (L)	Isthmus of the cingulate (L)	Fusiform (R)	Lateral orbitofrontal (R)
Cuneus (R)	Isthmus of the cingulate (L)	Rostral middle frontal (R)	Lateral orbitofrontal (R)
Parahippocampal (R)	Isthmus of the cingulate (L)	Superior temporal (R)	Lateral orbitofrontal (R)
Peri-calcarine (L)	Lateral occipital (L)	Insula (R)	Lateral orbitofrontal (R)
Superior temporal (L)	Lateral occipital (L)	Noncortical (R)	Lingual (R)
Corpus callosum (L)	Lateral orbitofrontal (L)	Entorhinal (R)	Lingual (R)
Insula (L)	Lateral orbitofrontal (L)	Posterior cingulate (R)	Lingual (R)

Table 12 – continued from previous page

Region 1	Region 2	Region 1	Region 2
Noncortical (L)	Lingual (L)	Caudal anterior cingulate (L)	Medial orbitofrontal (R)
Cuneus (L)	Lingual (L)	Corpus callosum (L)	Medial orbitofrontal (R)
Fusiform (L)	Lingual (L)	Medial orbitofrontal (L)	Medial orbitofrontal (R)
Isthmus of the cingulate (L)	Lingual (L)	Corpus callosum (R)	Medial orbitofrontal (R)
Parahippocampal (L)	Lingual (L)	Entorhinal (R)	Medial orbitofrontal (R)
Peri-calcarine (L)	Lingual (L)	Pars orbitalis (R)	Medial orbitofrontal (R)
Precuneus (L)	Lingual (L)	Superior temporal (R)	Medial orbitofrontal (R)
Superior parietal (L)	Lingual (L)	Insula (R)	Medial orbitofrontal (R)
Isthmus of the cingulate (R)	Lingual (L)	Noncortical (R)	Middle temporal (R)
Pars triangularis (L)	Medial orbitofrontal (L)	Inferior parietal (R)	Middle temporal (R)
Rostral anterior cingulate (L)	Medial orbitofrontal (L)	Lateral occipital (R)	Middle temporal (R)
Frontal pole (L)	Medial orbitofrontal (L)	Lateral orbitofrontal (R)	Middle temporal (R)
Inferior parietal (L)	Middle temporal (L)	Entorhinal (R)	Parahippocampal (R)
Lingual (L)	Middle temporal (L)	Fusiform (R)	Parahippocampal (R)
Entorhinal (L)	Parahippocampal (L)	Lingual (R)	Parahippocampal (R)
Fusiform (L)	Parahippocampal (L)	Middle temporal (R)	Parahippocampal (R)
Precuneus (L)	Paracentral (L)	Temporal pole (R)	Parahippocampal (R)
Superior frontal (L)	Paracentral (L)	Insula (R)	Parahippocampal (R)
Supra-marginal (L)	Pars opercularis (L)	Posterior cingulate (R)	Paracentral (R)
Rostral anterior cingulate (L)	Pars orbitalis (L)	Transverse temporal (R)	Paracentral (R)
Rostral middle frontal (L)	Pars orbitalis (L)	Pre-central (R)	Pars opercularis (R)
Pars opercularis (L)	Pars triangularis (L)	Frontal pole (L)	Pars orbitalis (R)
Cuneus (L)	Peri-calcarine (L)	Medial orbitofrontal (R)	Pars orbitalis (R)
Pars opercularis (L)	Postcentral (L)	Parahippocampal (R)	Pars triangularis (R)
Posterior cingulate (L)	Postcentral (L)	Entorhinal (R)	Peri-calcarine (R)
Pre-central (L)	Postcentral (L)	Lingual (R)	Peri-calcarine (R)
Precuneus (L)	Postcentral (L)	Paracentral (L)	Postcentral (R)
Insula (L)	Postcentral (L)	Parahippocampal (R)	Postcentral (R)
Caudal middle frontal (L)	Posterior cingulate (L)	Superior parietal (R)	Postcentral (R)
Paracentral (R)	Posterior cingulate (L)	Transverse temporal (R)	Postcentral (R)
Posterior cingulate (R)	Posterior cingulate (L)	Caudal anterior cingulate (L)	Posterior cingulate (R)
Precuneus (R)	Posterior cingulate (L)	Pre-central (L)	Posterior cingulate (R)
Rostral anterior cingulate (R)	Posterior cingulate (L)	Paracentral (R)	Posterior cingulate (R)
Caudal anterior cingulate (L)	Pre-central (L)	Postcentral (R)	Posterior cingulate (R)
Corpus callosum (L)	Pre-central (L)	Superior frontal (R)	Posterior cingulate (R)
Posterior cingulate (L)	Pre-central (L)	Superior parietal (R)	Posterior cingulate (R)
Supra-marginal (L)	Pre-central (L)	Caudal anterior cingulate (L)	Pre-central (R)
Insula (L)	Pre-central (L)	Pars opercularis (R)	Pre-central (R)
Corpus callosum (L)	Precuneus (L)	Pars orbitalis (R)	Pre-central (R)
Postcentral (L)	Precuneus (L)	Pars triangularis (R)	Pre-central (R)
Inferior parietal (R)	Precuneus (L)	Precuneus (L)	Precuneus (R)
Posterior cingulate (R)	Precuneus (L)	Noncortical (R)	Precuneus (R)
Superior parietal (R)	Precuneus (L)	Rostral middle frontal (L)	Rostral anterior cingulate (R)
Frontal pole (L)	Rostral anterior cingulate (L)	Corpus callosum (R)	Rostral anterior cingulate (R)
Lateral orbitofrontal (R)	Rostral anterior cingulate (L)	Lateral orbitofrontal (R)	Rostral anterior cingulate (R)
Rostral middle frontal (R)	Rostral anterior cingulate (L)	Rostral anterior cingulate (L)	Rostral middle frontal (R)
Corpus callosum (L)	Rostral middle frontal (L)	Caudal anterior cingulate (R)	Rostral middle frontal (R)
Lateral orbitofrontal (L)	Rostral middle frontal (L)	Corpus callosum (R)	Rostral middle frontal (R)
Medial orbitofrontal (L)	Rostral middle frontal (L)	Pars opercularis (R)	Rostral middle frontal (R)
Rostral anterior cingulate (L)	Rostral middle frontal (L)	Frontal pole (R)	Rostral middle frontal (R)

Table 12 – continued from previous page

Region 1	Region 2	Region 1	Region 2
Caudal anterior cingulate (L)	Superior frontal (L)	Medial orbitofrontal (L)	Superior frontal (R)
Temporal pole (L)	Superior frontal (L)	Paracentral (R)	Superior frontal (R)
Caudal anterior cingulate (R)	Superior frontal (L)	Pars triangularis (R)	Superior frontal (R)
Pre-central (R)	Superior frontal (L)	Corpus callosum (L)	Superior parietal (R)
Noncortical (L)	Superior parietal (L)	Isthmus of the cingulate (L)	Superior parietal (R)
Cuneus (L)	Superior parietal (L)	Superior parietal (L)	Superior parietal (R)
Lateral occipital (L)	Superior parietal (L)	Caudal middle frontal (R)	Superior parietal (R)
Postcentral (L)	Superior parietal (L)	Precuneus (R)	Superior parietal (R)
Transverse temporal (L)	Superior parietal (L)	Supra-marginal (R)	Superior parietal (R)
Corpus callosum (R)	Superior parietal (L)	Transverse temporal (R)	Superior parietal (R)
Postcentral (R)	Superior parietal (L)	Noncortical (R)	Superior temporal (R)
Superior parietal (R)	Superior parietal (L)	Lateral occipital (R)	Superior temporal (R)
Insula (L)	Superior temporal (L)	Transverse temporal (R)	Superior temporal (R)
Rostral anterior cingulate (L)	Frontal pole (L)	Noncortical (R)	Supra-marginal (R)
Rostral middle frontal (L)	Frontal pole (L)	Caudal middle frontal (R)	Supra-marginal (R)
Entorhinal (L)	Temporal pole (L)	Isthmus of the cingulate (R)	Supra-marginal (R)
Superior temporal (L)	Temporal pole (L)	Pars triangularis (R)	Supra-marginal (R)
Caudal middle frontal (L)	Insula (L)	Transverse temporal (R)	Supra-marginal (R)
Inferior parietal (L)	Insula (L)	Lateral orbitofrontal (R)	Frontal pole (R)
Superior frontal (L)	Insula (L)	Rostral anterior cingulate (R)	Frontal pole (R)
Transverse temporal (L)	Insula (L)	Rostral middle frontal (R)	Frontal pole (R)
Lingual (R)	Noncortical (R)	Entorhinal (R)	Temporal pole (R)
Supra-marginal (R)	Noncortical (R)	Fusiform (R)	Temporal pole (R)
Transverse temporal (R)	Noncortical (R)	Parahippocampal (R)	Temporal pole (R)
Caudal anterior cingulate (L)	Caudal anterior cingulate (R)	Superior temporal (R)	Temporal pole (R)
Pars triangularis (R)	Caudal anterior cingulate (R)	Pre-central (R)	Insula (R)
Posterior cingulate (R)	Caudal anterior cingulate (R)	Temporal pole (R)	Insula (R)

Table 13: Differences in the probability of connection (connectivity matrix) due to sex.

Region 1	Region 2	Women	Men	p-value
Frontal pole (L)	Caudal anterior cingulate (L)	0.0032	0	2.10E-03
Medial orbitofrontal (R)	Caudal anterior cingulate (L)	0.0115	0.0094	2.66E-02
Transverse temporal (L)	Cuneus (L)	0.0011	0	1.94E-02
Paracentral (R)	Isthmus of the cingulate (L)	0.0073	0.0053	7.70E-03
Cuneus (R)	Lateral occipital (L)	0.0029	0	5.00E-04
Noncortical (L)	Lingual (L)	0.0925	0.0631	1.20E-03
Lateral orbitofrontal (L)	Parahippocampal (L)	0.0031	0.002	1.93E-02
Peri-calcarine (L)	Parahippocampal (L)	0.0055	0.0037	5.00E-03
Posterior cingulate (L)	Paracentral (L)	0.1544	0.1383	1.66E-02
Postcentral (L)	Pars opercularis (L)	0.0042	0.0017	4.00E-04
Pars opercularis (L)	Postcentral (L)	0.0044	0.0022	1.00E-04
Caudal anterior cingulate (R)	Posterior cingulate (L)	0.0321	0.0232	1.07E-02
Precuneus (L)	Pre-central (L)	0.0087	0.008	1.82E-02
Supra-marginal (L)	Superior temporal (L)	0.0321	0.0244	2.80E-03
Pre-central (R)	Noncortical (R)	0.003	0.0017	1.81E-02
Inferior parietal (L)	Corpus callosum (R)	0.0022	0.0009	1.78E-02
Noncortical (R)	Corpus callosum (R)	0.0012	0.0007	1.61E-02
Inferior parietal (R)	Corpus callosum (R)	0.0054	0.0015	5.90E-03
Lingual (R)	Corpus callosum (R)	0.0028	0.0014	1.70E-02
Corpus callosum (R)	Inferior parietal (R)	0.0037	0.0019	3.30E-02
Caudal anterior cingulate (R)	Isthmus of the cingulate (R)	0.0209	0.0154	2.79E-02
Caudal anterior cingulate (R)	Medial orbitofrontal (R)	0.0164	0.0097	2.40E-03
Pars orbitalis (R)	Medial orbitofrontal (R)	0.0378	0.0238	1.78E-02
Middle temporal (R)	Parahippocampal (R)	0.0043	0.0027	1.82E-02
Insula (R)	Parahippocampal (R)	0.0046	0.0031	1.79E-02
Rostral middle frontal (R)	Pars opercularis (R)	0.0269	0.0226	1.04E-02
Superior frontal (R)	Pars triangularis (R)	0.0054	0.0037	7.70E-03
Precuneus (R)	Postcentral (R)	0.0079	0.0056	5.80E-03
Pars triangularis (L)	Rostral anterior cingulate (R)	0.0107	0.0059	2.75E-02
Pre-central (R)	Rostral middle frontal (R)	0.0037	0.0029	6.10E-03
Rostral middle frontal (L)	Superior frontal (R)	0.0044	0.0023	2.90E-03
Isthmus of the cingulate (R)	Superior frontal (R)	0.0077	0.0056	1.50E-02
Superior temporal (R)	Transverse temporal (R)	0.0382	0.0306	2.21E-02
Supra-marginal (R)	Transverse temporal (R)	0.0171	0.013	9.50E-03
Insula (R)	Transverse temporal (R)	0.0118	0.0112	1.24E-02
Pars triangularis (R)	Insula (R)	0.1671	0.1428	5.80E-03

Table 14: Sex differences via the topological clustering coefficient.

Region	Women	Men	p-value
Caudal anterior cingulate (L)	0.0449	0.0385	6.0e-4
Pars orbitalis (L)	0.2715	0.2143	1.8e-3
Rostral anterior cingulate (L)	0.0501	0.0451	1.7e-3
Rostral middle frontal (L)	0.0628	0.0572	6.2e-3
Cuneus (R)	0.1417	0.1224	5.0e-3
Middle temporal (R)	0.0783	0.0729	7.3e-3

Table 15: Sex differences via the topological edge betweenness centrality from region 1 to region 2.

Region 1	Region 2	Women	Men	p-value
Medial orbitofrontal (R)	Caudal anterior cingulate (R)	3.6796	0.1343	3.0e-4
Non-cortical (L)	Lingual (L)	10.0475	3.8471	3.0e-4
Lingual (L)	Parahippocampal (L)	9.5410	2.9989	4.0e-4
Supra-marginal (R)	Peri-calcarine (L)	0.0470	0.0003	2e-4
Precuneus (R)	Corpus callosum (R)	2.6160	0.4481	3e-4

Table 16: Sex differences via the topological communicability matrix from region 1 to region 2.

Region 1	Region 2	Women	Men	p-value
Lingual (R)	Fusiform (L)	0.000193818	6.6184E-05	0.00E+00
Lingual (R)	Parahippocampal (L)	1.44873E-05	1.18653E-06	0.00E+00
Frontal pole (R)	Parahippocampal (L)	2.02031E-06	3.4342E-08	2.00E-04
Transverse temporal (R)	Parahippocampal (L)	3.76227E-07	3.06979E-08	1.00E-04
Parahippocampal (L)	Pars orbitalis (L)	6.93337E-06	9.09265E-07	2.00E-04
Parahippocampal (R)	Rostral middle frontal (L)	6.00877E-06	7.85872E-07	2.00E-04
Medial orbitofrontal (R)	Superior parietal (L)	6.58429E-05	2.26133E-05	3.00E-04
Lateral occipital (L)	Medial orbitofrontal (R)	1.74974E-06	3.49259E-07	2.00E-04
Middle temporal (L)	Medial orbitofrontal (R)	4.61992E-05	7.96382E-08	2.00E-04
Superior parietal (L)	Medial orbitofrontal (R)	1.16508E-05	3.44506E-06	2.00E-04
Superior temporal (L)	Medial orbitofrontal (R)	7.71885E-06	3.86133E-07	3.00E-04
Inferior parietal (R)	Transverse temporal (R)	0.000685963	0.000223199	3.00E-04

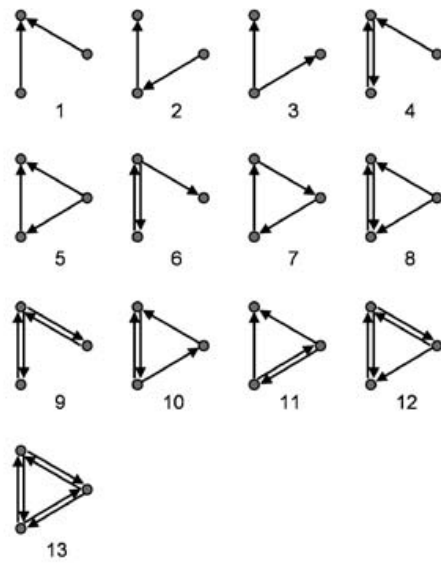


Figure 2: Motifs of size three (taken from Sporns, O., Kotter, R., 2004. Motifs in brain networks. PLoS Biol. 2, e369.

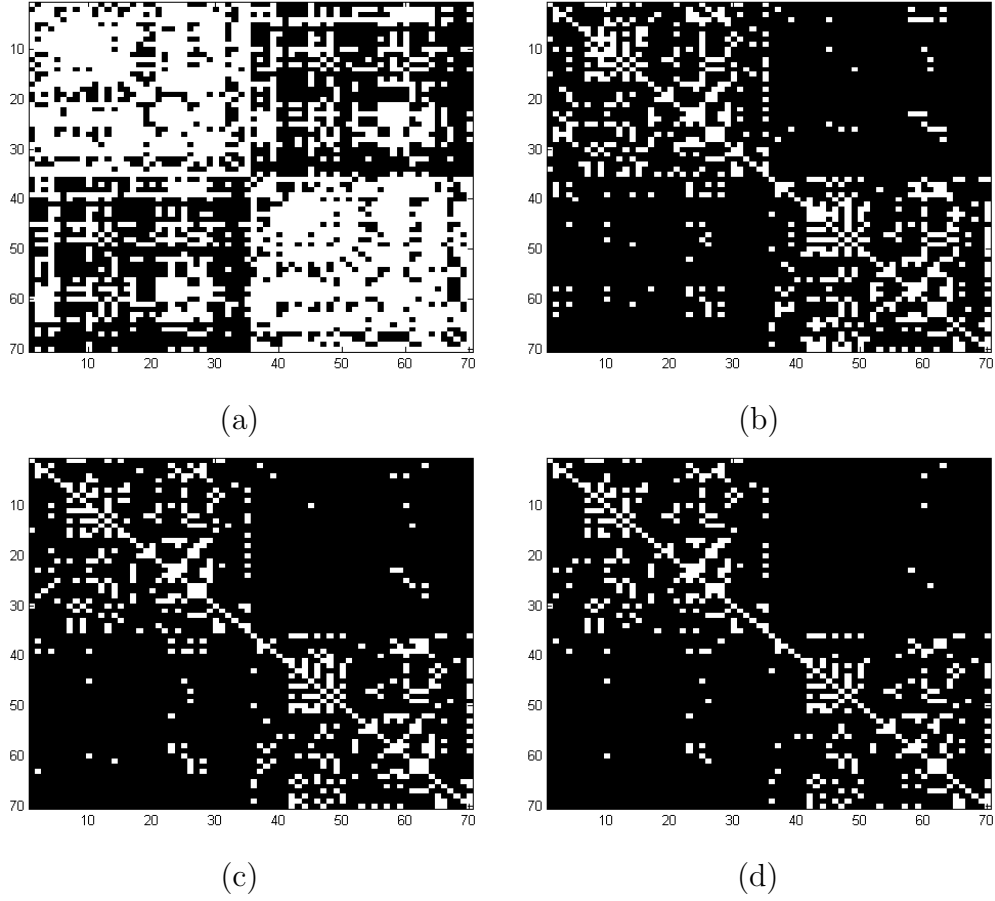


Figure 3: Levels of sparsity (proportion of non-zeros) of the mean connectivity matrix thresholded at different values. a) No thresholded, level of sparsity 0.564, b) thresholded at 0.0125, level of sparsity 0.151, c) thresholded at 0.025, level of sparsity 0.116, and d) thresholded at 0.0375, level of sparsity 0.095.

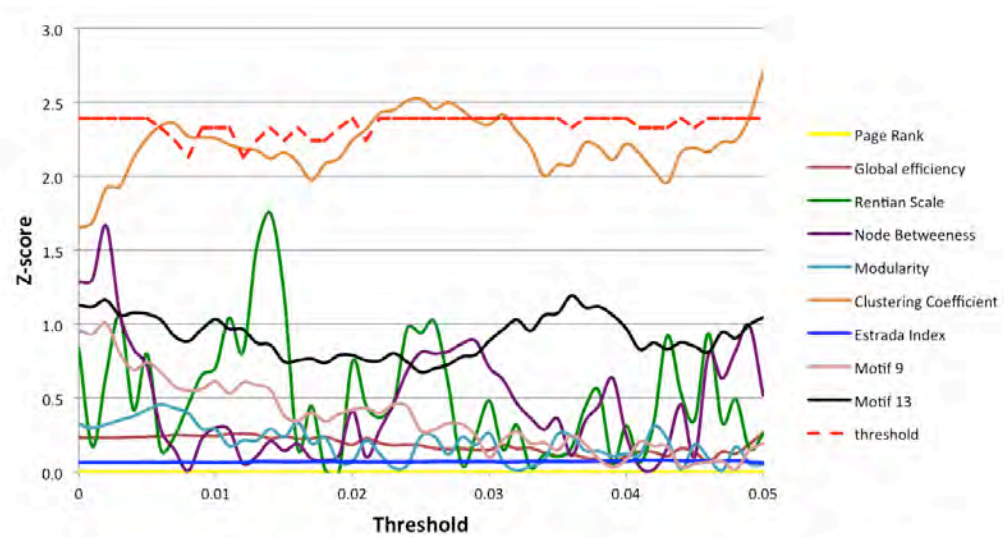


Figure 4: Sex differences considering global topological metrics.

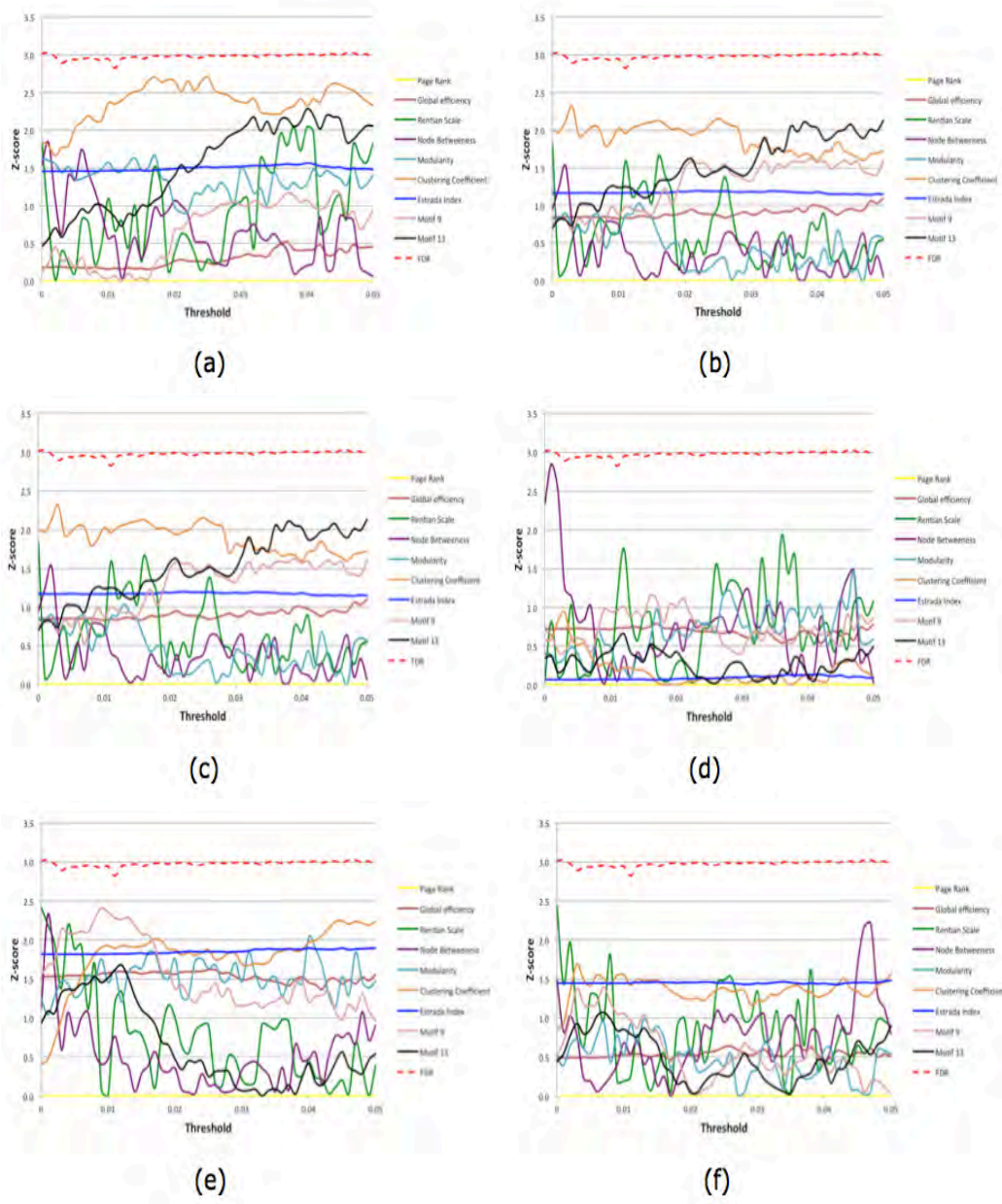


Figure 5: Z-score kinship differences considering global topological metrics: a) Identical twins vs non-identical multiples, b) identical twins vs siblings, c) identical twins vs unrelated, d) non-identical multiples vs siblings, e) non-identical multiples vs unrelated, and f) siblings vs unrelated.

Selected Results Using Diffusion Tensor-Tractography

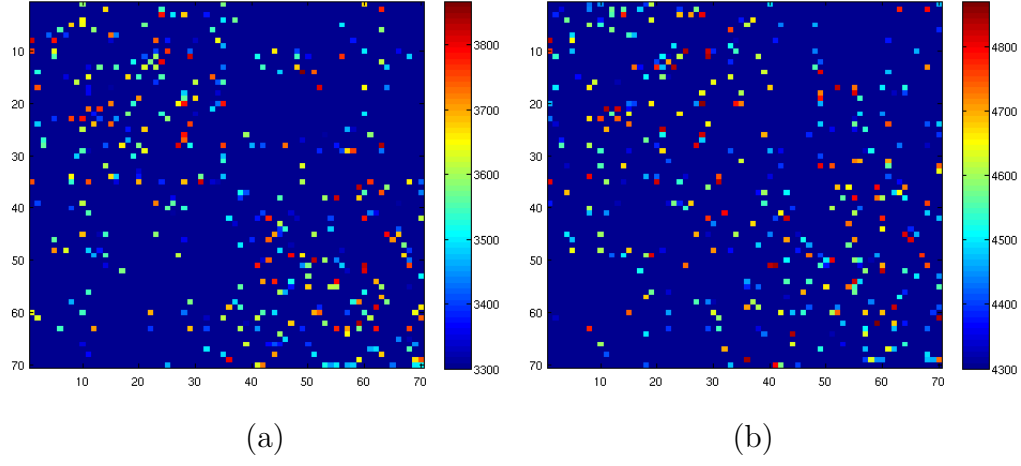


Figure 6: Selected features on the connectivity matrix for a) sex and b) kinship classification. Color code corresponds to the score given by the feature selection algorithm.

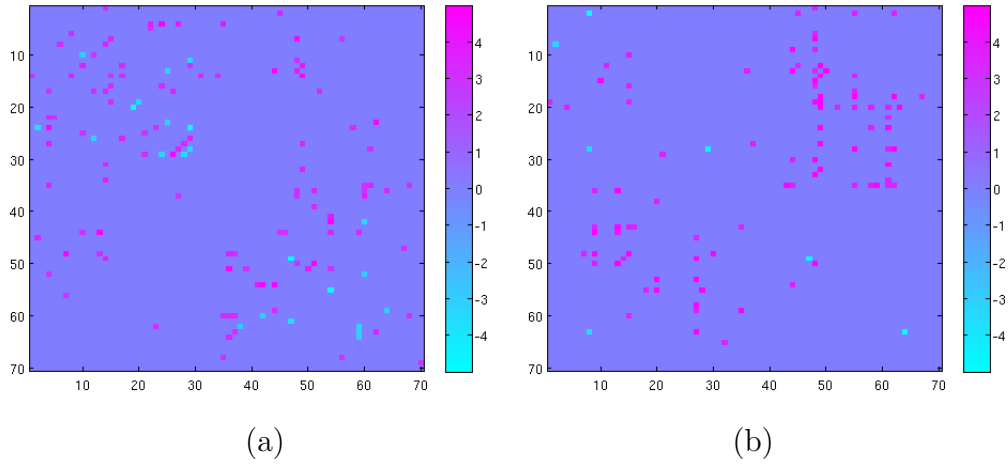


Figure 7: Z-score sex differences from a) the connectivity matrix, b) the communicability matrix. The color map indicates where the probability of connection is higher for women (magenta) or for men (cyan).

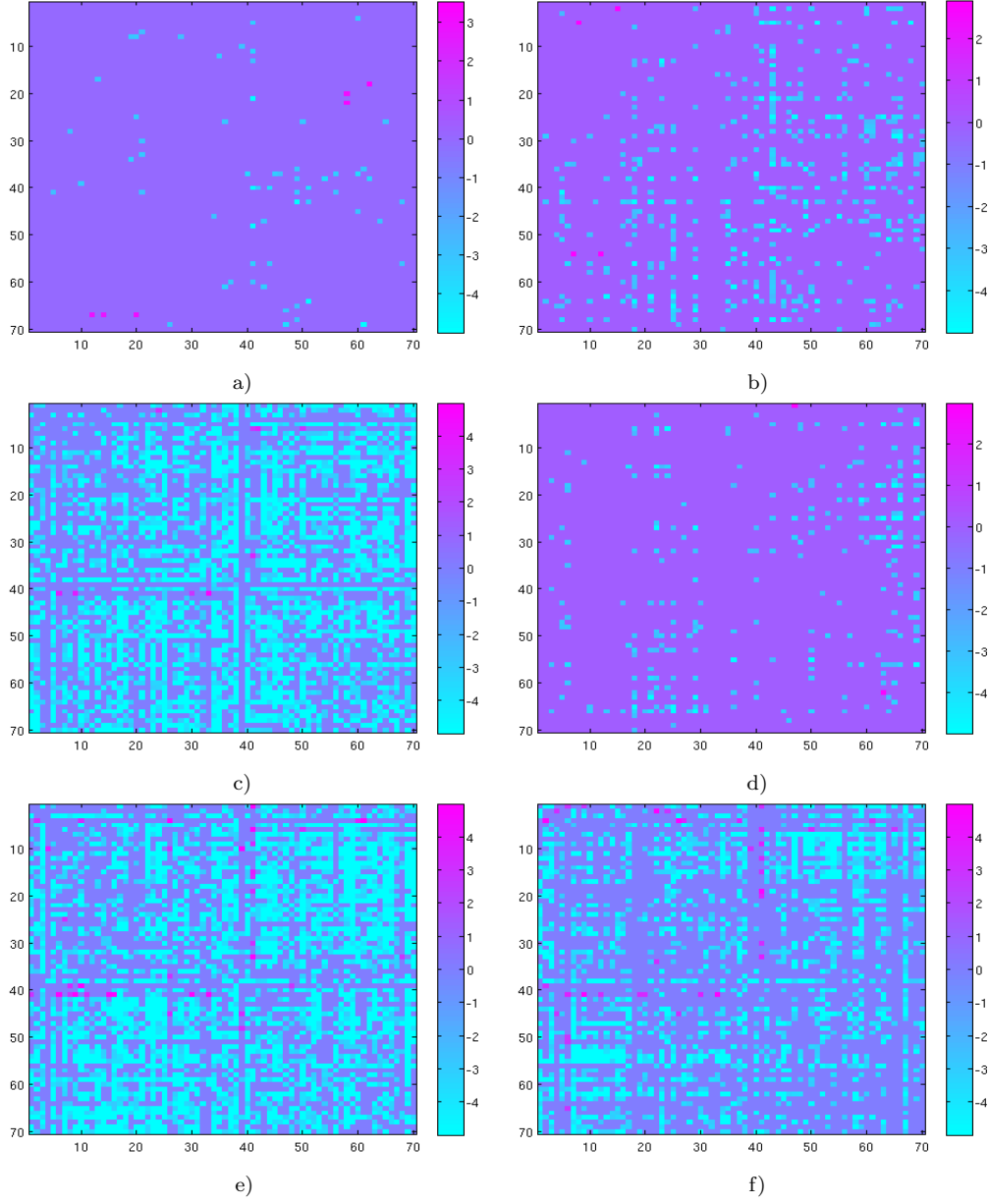


Figure 8: Z-score kinship differences considering the communicability eigenvalues: a) Identical twins vs non-identical multiples, b) identical twins vs siblings, c) identical twins vs unrelated, d) non-identical multiples vs siblings, e) non-identical multiples vs unrelated, and f) siblings vs unrelated.