Published in final edited form as:

Brain Connect. 2015 April ; 5(3): 156–165. doi:10.1089/brain.2014.0306.

Individual diversity of functional brain network economy

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Abstract

On average, brain network economy represents a trade-off between communication efficiency, robustness and connection cost, though, an analogous understanding on an individual level is largely missing. Evaluating resting-state networks of 42 healthy participants with 7 Tesla functional MRI and graph theory revealed that not even half of all possible connections were common across subjects. The strongest similarities among individuals were observed for interhemispheric and/or short-range connections, which may relate to the essential feature of the human brain to develop specialized systems within each hemisphere. Despite this marked variability in individual network architecture, all subjects exhibited equal small-world properties. Furthermore, interdependency between four major network economy metrics was observed across healthy individuals. The characteristic path length was associated with the clustering coefficient (peak correlation $r=0.93$), the response to network attacks ($r=-0.97$) and the physical connection cost in 3D space ($r=-0.62$). On the other hand, clustering was negatively related to attack response ($r=-0.75$) and connection cost ($r=-0.59$). Finally, increased connection cost was associated with better response to attacks ($r=0.65$). This indicates that functional brain networks with high global information transfer also exhibit strong network resilience. However, it seems that these advantages come at the cost of decreased local communication efficiency and increased physical connection cost. Except for wiring length, the results were replicated on a subsample at 3 Tesla ($n=20$). These findings highlight the finely tuned interrelationships between different parameters of brain network economy. Moreover, the understanding of the individual diversity of functional brain network economy may provide further insights in the vulnerability to mental and neurological disorders.

Keywords

brain network; resting-state fMRI; functional connectivity; graph theory; diversity; optimization

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CONFLICT of INTEREST

The authors declare no conflict of interest in the context of this study.

INTRODUCTION

Comprising more than 10^{10} neurons and 10^{14} synapses the human brain represents one of the most complex organs. To cope with the dynamics of an ever-changing environment, the brain's architecture is subject to a continuous process of optimization and adaptation (Wu et al., 2013), while maintaining well-balanced economical trade-offs (Bullmore and Sporns, 2012). This is reflected by the best compromise between efficient information processing, performance of specialized functions, robustness against error and physical wiring cost (Achard and Bullmore, 2007; Bullmore and Sporns, 2009; Guye et al., 2008). One of the best studied trade-offs is the existence of long-distance connections within the brain (Markov et al., 2013). Although they entail a high physical wiring cost, direct connections between remote areas represent important communication short cuts, which are in turn essential for an efficient global information transfer (Achard and Bullmore, 2007; Bullmore and Sporns, 2009). This presence of few, but properly placed long-distance connections enables the brain to exhibit small-world properties (Bullmore and Sporns, 2009). Furthermore, a set of costly links has been demonstrated to provide important connections between hub regions forming a high capacity center of global information processing (van den Heuvel et al., 2012).

Graph theoretical methods have been successfully applied to describe the performance and economy of functional and structural networks (Sporns et al., 2004). The brain can be modeled as a connectivity matrix (graph) by a set of brain regions (nodes) and their connections (edges) (Craddock et al., 2013). This approach enables a description of the brain on a systems level by deriving global and local neurobiological meaningful metrics (Rubinov and Sporns, 2010). So far the majority of research emphasized on the investigation of brain networks averaged across subjects. There is however a marked variability in connectivity strength in structural as well as functional networks even among healthy humans (Hermundstad et al., 2013). Various studies report that inter-individual variation in network metrics was related to cognitive parameters such as intelligence (Li et al., 2009; van den Heuvel et al., 2009) as well as performance during working memory (Hampson et al., 2006) and attention tasks (Giessing et al., 2013). Furthermore, averaging across subjects may actually change network properties in terms of modular organization, clustering and efficiency (Moussa et al., 2012). Taken together, important economical trade-offs have been revealed for average brain network architecture, though, it is not clear to which extent such generalizations apply to a single person. Conversely, insights into the individual organization of the brain may improve our understanding of differences in performance as well as vulnerability to mental disorders.

To address this issue, the individual resting-state networks of 42 healthy subjects were investigated with functional magnetic resonance imaging (fMRI) at 7 Tesla. Following an assessment of individual differences in network architecture, economical parameters were compared across subjects, including the global communication efficiency, local information transfer, resilience to attacks and physical connection cost. To rule out potential drawbacks regarding signal drop-out and artifacts at ultra-high field strengths, the analyses were replicated in a subsample at 3 Tesla.

MATERIALS and METHODS

Participants

Forty-two healthy subjects were included in this study (mean age $\pm$ sd = 25.5 $\pm$ 3.5 years, 20 male), all of them being naïve to MRI scanning. At the screening visit all participants were examined by an experienced psychiatrist regarding their physical, psychiatric and neurological health. This comprised standard medical assessment with routine laboratory blood tests and hormone levels and the Structural Clinical Interview (SCID) for Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) axis I and axis II disorders. Further exclusion criteria included pregnancy, past or current substance abuse (assessed by urine tests), intake of psychotropic or hormonal medication as well as metal implants or grafts. Furthermore, the structural MRIs were without any clinically relevant pathological findings. All subjects provided written informed consent after detailed explanation of the study protocol and they received reimbursement for participation. This project was approved by the Ethics Committee of the Medical University of Vienna and all procedures were conducted in accordance with the Declaration of Helsinki.

Magnetic resonance imaging (MRI)

Functional MRI was carried out between noon and 5pm on a 7T scanner (Siemens Magnetom, Erlangen, Germany) using a 32-channel head coil. Acquisition parameters for functional MRI (fMRI) measurements were set as described previously (Hahn et al., 2013). An echo-planar imaging sequence was employed with TE/TR = 23/1400ms obtaining 32 axial slices with a voxel-size of 1.5 $\times$ 1.5 $\times$ 2mm plus 1mm slice gap (matrix = 128 $\times$ 128). All subjects completed a 6min resting-state fMRI scan while fixating at a white crosshair on dark background. Subjects were instructed to relax in the scanner, stay awake and not to focus on anything in particular (“allow thoughts to come and go freely”).

For spatial normalization, subjects underwent an additional structural MRI measurement on a 3T scanner (Siemens Trio, Erlangen, Germany) on the same day except for 2 participants (9d and 25d between sessions). Here, a T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence was used with TE/TR = 4.2/2300ms obtaining 160 sagittal slices with a voxel-size of 1.1 $\times$ 1 $\times$ 1mm (matrix = 240 $\times$ 256). For replication of the connectivity results, a subsample (n=20, 8 male) also completed a 6min resting-state fMRI scan at 3 Tesla in the same scanning session (TE/TR = 38/1800ms, 23 axial slices, voxel-size = 1.48 $\times$ 1.48 $\times$ 3mm plus 1.8mm slice gap, matrix = 128 $\times$ 128).

Data preprocessing

Preprocessing was carried out in the same manner for 7T and 3T fMRI data in SPM8 (Wellcome Trust Centre for Neuroimaging, <http://www.fil.ion.ucl.ac.uk/spm/>) with default parameters unless specified otherwise. This included slice timing correction (reference = middle slice) (Sladky et al., 2011), motion correction (reference = mean image), spatial normalization to stereotactic space as defined by the Montreal Neurological Institute (MNI) and spatial smoothing (8 $\times$ 8 $\times$ 8mm Gaussian kernel). For optimal spatial normalization (Klein et al., 2009), T1-weighted MRI scans were first segmented into gray matter volume and normalized with the DARTEL algorithm (Diffeomorphic Anatomical Registration using

Exponentiated Lie algebra) (Ashburner, 2007) as implemented in the VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm/>). The obtained deformation fields were then applied to the coregistered functional MRI scans. To investigate the influence of individual vs. group-based brain parcellation, T1-weighted images were also segmented with Free Surfer (<https://surfer.nmr.mgh.harvard.edu/>), enabling an analysis specifically tailored to the individual gyral pattern. Data quality and all preprocessing steps were inspected visually where no major artifacts or failures were observed. In addition, individual head motion was assessed from the realignment parameters with the adapted version of framewise displacement, i.e., without calculating the difference between time frames (Hahn et al., 2013). For comparison, we also report displacement values from the original publication (Power et al., 2012) and the percentage of frames exceeding the threshold of 0.5mm.

Resting-state functional MRI (rsfMRI) analysis

rsfMRI data were analyzed in MatlabR2011a as described previously (Hahn et al., 2012). In short, potentially confounding signals were removed by linear regression against motion parameters, white matter, ventricular and global signal as well as subsequent band-pass filtering (12-term finite impulse response filter, $0.007 < f < 0.08\text{Hz}$). To compute resting-state functional connectivity matrices, the cross-correlation coefficient was calculated between BOLD signal time courses for each region of interest (ROI) pair.

Region of interest definition

Individual connectivity matrices were constructed for three different standard brain parcellations to avoid bias related to spatial resolution (Fornito et al., 2010). This included a symmetrical version of the automated anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) with 89 ROIs (Savli et al., 2012) as well as publicly available 200 and 1000 ROI sets (version: two-level clustering with time series similarity) (Craddock et al., 2012). ROI atlases were masked with the averaged gray matter volume across all subjects (threshold = 0.1) to remove spurious signals, resulting in 198 and 808 ROIs for the latter two parcellations. These two ROI sets, however, are not symmetrical and labeled arbitrary. Hence, for the assessment of common connections across subjects (see descriptive statistics) these ROIs were re-labeled in order that left-hemisphere regions comprise consecutive numbers, followed by right hemisphere areas. The corresponding contralateral region was defined as the one exhibiting the biggest spatial overlap with the left-hemisphere region. In other words, the subsequently computed connectivity matrices first comprised left-hemisphere ROIs only, which were followed by the corresponding right-hemisphere ROIs. For the individual parcellation carried out with Free Surfer, the Desikan-Killiany atlas with 78 ROIs was used.

Graph theoretical analysis

Graph theory metrics were computed with the Brain Connectivity Toolbox (Rubinov and Sporns, 2010) and networks were visualized with the BrainNet Viewer (<http://www.nitrc.org/projects/bnv/>) (Xia et al., 2013). Individual connectivity matrices were binarized at sparsities between 10% and 50% in 5%-steps, i.e., at network densities comprising the strongest 10% to 50% of connections (=edges). This represents a widely accepted range, which maintains highly interconnected graphs (=networks, Fig. 2) while

they still separate from random topology, respectively (Achard et al., 2006; Bassett et al., 2008) (Suppl. Fig. S3).

To evaluate the association between different optimization parameters of human brain networks, we computed several global metrics for the binary connectivity matrices of each subject. First, the characteristic path length was calculated. This parameter describes the average number of (geodesic) connections which must be traversed to connect two regions (=nodes) and gives an indication of global information processing efficiency. Second, the clustering coefficient was computed as the number of connections between neighboring nodes divided by all possible connections. Complex networks such as the brain comprise high clustering which indicates efficient local information transfer. Third, small-worldness was calculated as the ratio between clustering coefficient and characteristic path length after normalizing with 100 Erdős-Renyi random graphs of equal network density and number of nodes. More detailed descriptions and corresponding equations have been described elsewhere (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010).

Next, we aimed to assess the physical connection cost of functional brain networks. Here, the Euclidian distance was computed in 3-dimensional space between ROI centroids. The individual connection cost was then calculated as the average of all suprathreshold connections for each level of sparsity. Although this approach has been widely used as an estimate for the physical wiring cost of a network (Alexander-Bloch et al., 2013; Bassett et al., 2008; Bullmore and Sporns, 2012; Giessing et al., 2013; Kaiser, 2011), the Euclidian distance comprises a major disadvantage: the connections are oversimplified and underestimated as white matter tracts hardly follow straight lines within the brain. Therefore and as an alternative to the Euclidian distance, we computed the distance along known white matter connections using the skeletonized fractional anisotropy (FA) template as provided in FSL (<http://fsl.fmrib.ox.ac.uk/>). For each voxel in the FA skeleton all adjacent connections were identified and the shortest path between any two ROIs was computed along the tracts using Dijkstra's path search algorithm as implemented in Matlab (tract-based distance). We did not correct for distance penalization as proposed earlier (Lord et al., 2012) as this would actually cancel out the possibility to assess the relationships with physical wiring cost.

To investigate the robustness of brain networks against errors, individual connectivity matrices were lesioned in three ways (Achard et al., 2006; Kaiser et al., 2007). This included the random deletion of connections (edge=0), random elimination of nodes as well as targeted removal of hub nodes (all edges=0 for a particular node). Attacks were carried out by damaging 10% to 90% of edges/nodes in 10%-steps, respectively. For targeted attacks, hub regions were sorted according to their node degree (the number of connections) and elimination started with the strongest hubs. Each of these attacks was computed at 100 random selections of edges or nodes, respectively. For each elimination the characteristic path length and the size of the largest connected cluster were again calculated for each level of sparsity. Integrating the response profile of the largest connected cluster across all attacks gives a single value per subject and sparsity, which was used as a metric of network resilience. This is reasonable as the largest connected cluster is a monotonically decreasing function (in contrast to the response pattern of the characteristic path length) (Achard et al., 2006).

Voxel-wise resting-state analysis

In addition to graph theory metrics, exploratory voxel-wise functional connectivity analysis was carried out to evaluate resting-state networks averaged across subjects as well as their individual variation (Suppl. Fig. S1). Following linear regression analysis and band-pass filtering (see rsfMRI analysis) the cross-correlation coefficient was computed voxel-wise. The posterior cingulate cortex was taken as seed region with a cubical volume of $3 \times 3 \times 3$ voxels centered at $x/y/z = 0/-52/30$ mm MNI-space (Hahn et al., 2012). Correlation coefficients were converted to z-scores using Fisher's r-to-z transformation for group statistics.

Statistical procedures

To compare the similarity of individual brain networks across subjects we calculated the Conformity coefficient (Chang et al., 2009) between connectivity matrices for each sparsity level. The overlap metric of the Conformity coefficient is defined as

$$1 - \text{all errors} / \text{true positives}$$

In this case, all errors refer to the sum of non-overlapping connections. This means that the Conformity coefficient equals 0 if two graphs comprise the same number of overlapping and non-overlapping connections. For comparison, this situation corresponds to a Jaccard coefficient of 0.5 and a Dice coefficient of 0.67 (Chang et al., 2009). To further investigate the similarity of individual brain networks, we simply counted the number of subjects which exhibit the same connections at the lowest sparsity of 10%. Statistical inference was drawn by correlation analysis. This included associations between graph metrics of the characteristic path length and clustering coefficient as well as the physical connection cost and network resilience using Matlab. Correction for multiple comparisons was carried out with Bonferroni-correction at $p_{\text{corrected}} < 0.0083$ ($(4 \text{ variables}^2 - 4)/2 = 6$ comparisons). To rule out that the observed results were inherent to any graph independent of neuronal representation, correlations were also computed between network metrics of $n=42$ Erdős-Renyi random networks comprising 89 ROIs. The creation of random networks was repeated 100 times for each level of sparsity and average correlations are presented.

RESULTS

Average displacement estimates from SPM8's realignment were 0.46 ± 0.31 mm and 0.52 ± 0.32 mm for the 7T and 3T, respectively. None of the graph theory parameters were correlated with individual head motion, independent of network density, number of ROIs or distance computation (all $p > 0.05$). For comparison, displacement according to the original publication (Power et al., 2012) was 0.10 ± 0.03 mm and 0.10 ± 0.05 mm. Here, the percentage of frames exceeding the threshold of 0.5mm was $0.38 \pm 0.99\%$ and $1.22 \pm 2.76\%$.

Individual diversity of functional networks

The average Conformity coefficient was surprisingly low indicating that less than half of the connections were common across subjects at 10% sparsity (-2.62 ± 0.74 , -3.86 ± 0.76 and -4.76 ± 0.80 for 89, 198 and 808 ROIs, respectively). Even for an increased network density

of 50% this metric never reached positive values (-0.39 ± 0.09 , -0.48 ± 0.08 , -0.59 ± 0.07). Computing the Conformity coefficient separately across men ($10/50\% = -2.86/-0.38$, $-4.01/-0.49$, $-4.86/-0.59$) or women ($-2.34/-0.38$, $-3.65/-0.47$, $-4.53/-0.58$) did not change this finding (i.e., all values were below 0, independent of the number of ROIs or network density). The Conformity metric was similarly low when using the individual parcellation as ROI definition (-2.83 ± 0.64 and -0.42 ± 0.09 for 10% and 50% sparsity, respectively). We further aimed to investigate how such diversity relates to previously reported consistent functional connectivity (Damoiseaux et al., 2006) and graph theory metrics (Moussa et al., 2012) among subjects. Voxel-wise connectivity analysis demonstrated robust extraction of resting-state networks (Suppl. Fig. S1a). However, the computation of average networks was rather insensitive to the high individual variability in connectivity strength across brain areas (Suppl. Fig. S1b). More precisely, even in the same subject and the same network high functional connectivity between any two regions did not imply equally high connectivity with another region. To further investigate the similarity of individual networks, the fraction of subjects exhibiting a particular connection was calculated. Interestingly, those edges which were similar for the majority of subjects, were almost exclusively represented by interhemispheric and/or short-range connections independent of the parcellation scheme (Fig. 1). In line with previous reports, these data highlight the marked inter-individual differences in sparse functional connectivity networks (Hahn et al., 2012; Hermundstad et al., 2013) with the most robust connections comprising interhemispheric and short-range ones (Hermundstad et al., 2013).

Economy metrics of functional networks

Such a high between-subject variation brings up the question of individual network optimization. All subjects exhibited a markedly uniform pattern of small-worldness, especially for higher number of ROIs (Suppl. Fig S2). This indicates that individual networks were equally well separated from a random graph, again despite the high diversity among subjects.

Investigating the associations of these parameters we observed a strong correlation between the characteristic path length and clustering coefficient across subjects (summarized in figure 2 and table 1). Increasing the sparsity also increased this association reaching its peak around 25-30% network density. For 89 regions the association was slightly non-linear, but this turned linear for higher number of ROIs. Hence, it appears that higher global communication efficiency comes at the cost of lower local information transfer.

Furthermore, the characteristic path length and the clustering coefficient were both negatively correlated with network resilience. In other words, an increased robustness to attacks was associated with higher global but lower local information transfer. These relationships were similar for the three attack modes and reached peak values at a sparsity of 20-25%. However, significant correlations were found only at lowest network densities for 198 ROIs and not present for 808 ROIs. This emerged from the observation that for a high number of ROIs and connections (i.e., sparsity) the response pattern became almost indistinguishable between individual subjects.

Regarding physical connection cost, negative correlations were observed for the tract-based distance with the characteristic path length and the clustering coefficient. On the other hand, positive correlations were found between connection distance and network resilience. These associations were observed for all three parcellation schemes but were shifted toward lower network densities for higher number of ROIs. Furthermore, all correlations with physical connection cost were stronger for tract-based than Euclidian distance.

These associations were also observed when using the individual parcellation. The characteristic path length was positively correlated with the clustering coefficient (peak $r=0.95$). The network resilience to random attacks was negatively related to the characteristic path length ($r=-0.89$) and the clustering coefficient ($r=-0.77$). Correlations with the tract-based distance were lower when using individual parcellations for the network resilience ($r=0.45$) and the characteristic path length ($r=-0.32$) and not evident for the clustering coefficient ($r=-0.18$). In contrast, these associations were not observed between network metrics of random graphs independent of the network density (all $r<0.38$, none withstanding correction for multiple comparisons).

Replication at 3 Tesla

To exclude influence by potential drawbacks of increased field strength, the reported results were replicated on a subsample which underwent rsfMRI also on a 3T scanner. More precisely, the average Conformity coefficient across subjects again did not reach positive values for 10% sparsity (-1.17 ± 0.24 , -2.20 ± 0.38 and -2.98 ± 0.46 for 89, 198 and 808 ROIs, respectively) nor for an increased network density of 50% (-0.16 ± 0.07 , -0.28 ± 0.08 , -0.41 ± 0.07). In line with the results obtained at 7T, similar links for subjects at 3T were mostly represented by interhemispheric or short-range connections (Suppl. Fig S3).

Also, associations between different graph metrics were mostly replicated at 3T (Suppl. Fig S4). There was a strong positive correlation between the characteristic path length and clustering coefficient. Again, these two parameters were negatively associated with network resilience independent of the attack mode and shifted to lower network densities for increasing number of ROIs. Notably, no significant correlations were observed between the above parameters and the physical connection cost (tract-based or Euclidian distance).

DISCUSSION

In this study we demonstrate a marked variety of sparse functional brain networks among healthy subjects as measured by resting-state functional MRI. Except equal small-world properties, this resulted in interdependency between four major economical network metrics across individuals, namely global and local information transfer as well as connection cost and resilience to attacks.

Surprisingly, the overlap between individual networks was less than half of the connections, independent of the network density and parcellation scheme. However, the high diversity of entire networks observed here would not have been expected from further reports of consistent functional connectivity across subjects and sessions (Damoiseaux et al., 2006) as well as robust graph theory metrics across study sites (Moussa et al., 2012). Our finding is

however still compatible with these previous results as voxel-wise functional connectivity analysis showed robust extraction of networks such as the default mode. Though, average resting-state networks are insensitive to individual variations in connectivity. Detailed evaluation revealed that high connectivity between any two regions did not imply an equally high connectivity between another two regions even within a given network of a single subject. Hence, resting-state networks indeed show a robust average pattern, however, there is a marked variation in individual connectivity strengths for any given pair of brain regions.

Interestingly, those connections which were still present in all of the subjects exclusively comprised interhemispheric and/or short-range ones. This matches with a recent report that interhemispheric links regardless of length but not long intrahemispheric connections exhibit strong functional connectivity (Hermundstad et al., 2013). The linkage between the two hemispheres by the corpus callosum represents a key for cognitive processing (Hinkley et al., 2012) and functional specialization of the human brain (Gazzaniga, 2000). By enabling communication across the two hemispheres it allows for the emergence of lateralized systems such as attention-perception (e.g., visuo-spatial and facial) processing within the right hemisphere but language and speech on the left side. This evolutionary aspect of human brain optimization decreased redundancy of hemispheric systems without implying deficits in either one, given that the communication link between these systems is intact (Gazzaniga, 2000). It is possible that the required interhemispheric communication is reflected by the resting functional connectivity, which was maintained across healthy subjects despite the high diversity of individual brains. This is supported by studies of split-brain patients showing that higher-order brain functions as well as interhemispheric functional connectivity require the structural link of the corpus callosum (Gazzaniga, 2000; Johnston et al., 2008).

The specialization of human brain function has been successfully modeled by small-world brain architecture (Bullmore and Sporns, 2009). In line with the lateralization of functional systems, segregated processes such as visual perception benefit from clustered connections, whereas integrated processes like executive functions are related to global network efficiency. Accordingly, all subjects exhibited pronounced small-world properties with high clustering and low characteristic path length (inverse of global information transfer). Interestingly, relating these two parameters showed a strong positive association. This indicates a trade-off between local vs. global information transfer which might reflect an optimization for either specialized or integrative processing among healthy subjects (Bullmore and Sporns, 2012).

This compromise between global and local communication is further reflected in the associations with the individual network's robustness to attacks. More precisely, strong resilience was related to high global information transfer but came at the cost of decreased local specialization. Although unexpected, the latter may emerge from the fact that highly clustered networks require more connections between different modules, whereas these highly connected hubs make networks more vulnerable to attacks (Albert et al., 2000; He et al., 2009b). The shift of these associations towards lower levels of sparsity for increasing number of ROIs seems reasonable as more redundant pathways can be constructed for larger networks, which in turn decreases the chance that the network collapses into unconnected

clusters. Proceeding from a previous speculation that small-world networks may offer developmental fitness (Achard et al., 2006), our findings embed this property in a specific relationship with global and local information processing. Moreover, robustness was additionally associated with physical connection cost, indicating that increased wiring expenses are beneficial in terms of network resilience. On the other hand, an increased connection cost was associated with a higher global but again lower local communication transfer. Such a trade-off between wiring cost and global efficiency has been thoroughly described in a previous review (Bullmore and Sporns, 2012). That is, few long-range connections indeed strongly reduce the characteristic path length with a minimal premium in wiring cost. In other words, the gain in communication efficiency outweighs its physical cost while keeping the network “near-minimally” wired (Bullmore and Sporns, 2012). Still, observing this association across healthy individuals indicates that “near-minimal wiring” substantially differs among subjects. Considering that the correlations with physical wiring length were less pronounced than across the other network parameters, it seems that optimization is far more emphasized at communication transfer and robustness than wiring cost. In line with our observations it has been noted that (independent of the species) the complexity of brain networks does not allow the optimization to be solely based on physical connection cost (Bassett et al., 2010; Bullmore and Sporns, 2012; Kaiser and Hilgetag, 2006). This might explain that correlations with wiring length were lower as compared to other network metrics and were not fully replicated when using individual parcellations. Associations with the wiring length were also not replicated at 3 Tesla, which may be related to the decreased statistical power given the lower sample size. Indeed, a power calculation using G*Power (<http://www.gpower.hhu.de/>) showed that $n=26$ subject would be required for statistically significant effects of $r=0.6$ ($\alpha=0.5$, $\text{power}=0.95$). On the other hand, it is possible that scans at higher field strength are more sensitive (Hahn et al., 2013). The remaining relationships were however robustly reproduced also for lower field strength and for individual parcellations. Although potential effects of increased distortion at 7T were not directly evaluated, the former result indicates that this was a negligible issue.

To summarize, healthy individuals with high global information transfer also showed high network resilience, which however was also more costly in terms of wiring length. On the other hand, networks with strong local specialization were physically less expensive but also more vulnerable to attacks. We further speculate that such an individual diversity in brain optimization parameters might give interesting insights not only in healthy brain function but also important indications to stress and vulnerability to psychiatric disorders. For instance, alterations in cost-efficiency trade-offs have been reported in schizophrenia (Alexander-Bloch et al., 2013; Bassett et al., 2009) as well as Alzheimer’s disease (Lo et al., 2010; Stam et al., 2007) and multiple sclerosis (He et al., 2009a) with specific loss of hub nodes and long-range connections, respectively.

It is important to note, that our findings are based on functional connectivity obtained by resting-state fMRI, which might differ from structural connections. More precisely, two brain regions can be functionally connected (i.e., exhibit high correlations of their signal time courses) even without a direct structural link (Honey et al., 2009). In this context it needs to be kept in mind that graph metrics such as the path length between regions represent geodesic steps, which in turn can be seen as the number of processing steps

(Kaiser and Hilgetag, 2006). Furthermore, functional networks are non-stationary and can change even within seconds (Hutchison et al., 2013), whereas changes in structural connectivity may take place on a longer time scale (Bullmore and Sporns, 2009). Accordingly, a recent investigation of resting-state networks at subsecond resolution showed that functional connections can rapidly change between high and low efficiency states (Zalesky et al., 2014). These dynamics were predominant for intermodular and long-range connections, which in turn are more energy demanding than short-range links (Liang et al., 2013).

Another limitation is that graph theoretical networks only represent a model and we cannot exclude that some of the observed associations may emerge independent of a neuronal context. However, biologically relevant associations of graph metrics have been repeatedly demonstrated for various cognitive aspects (Giessing et al., 2013; Hampson et al., 2006; Li et al., 2009; Ryman et al., 2014; van den Heuvel et al., 2009). This further includes similarities on a neuronal level (Bullmore and Sporns, 2012). For instance, neuronal connections as well as resting-state connectivity decay with physical distance. Moreover, the strength of synchronized oscillations is enhanced by long-distance axonal projections. These long-distance short-cuts represent an essential feature of small-world networks, which in turn have generated realistic simulations of cortical architecture. Accordingly, the associations observed in the current study were not simply attributable to random network topology. Finally, usage of a white matter skeleton to calculate the physical connection cost may not represent a perfect estimate for all of the available functional connections since the latter ones may even emerge without a direct anatomical link as a result of polysynaptic detours. However, as anatomical structures constitute the basis for brain function and connectivity, we argue that a tract-based distance calculation is still more accurate than the Euclidian distance metric (i.e., a straight line in 3D space, neglecting any anatomical constraints). This is supported by the observation that all associations were stronger for tract-based than Euclidian distance calculations.

In conclusion, we observed a marked variation across individual wiring architectures of sparse functional brain networks in healthy humans. Despite this diversity the fundamental characteristic of interhemispheric connections was preserved in all subjects, which may reflect lateralized specialization of functions such as language and attention-perception processing. Though, economical network parameters were highly interdependent. Optimization for segregated systems was less costly in terms of wiring length, but implied a trade-off for lower global communication transfer across subjects and decreased robustness to attacks, and vice versa. These findings provide further insight into the diversity and common characteristics of individual human network organization, which may in turn offer novel strategies for the assessment of mental disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

This research was supported by a grant of the Austrian Science Fund (FWF P23021) to R. Lanzenberger. The authors would like to thank Pia Baldinger, Anna Höflich, Dietmar Winkler, Marie Spies and Martin Küblböck for medical and/or technical support.

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Figure 1.

Similar brain connections across healthy subjects at a network density of 10%. For each connection, the fraction of subjects exhibiting that particular link was calculated for the three parcellation sets with 89, 198 and 808 regions of interest (blue dots). For 75%-100% of the subjects common functional connections were almost exclusively represented by interhemispheric and/or short-range connections. Only when reducing the level of similarity to 50% of the subjects, several intrahemispheric long-range connections could be observed.

Figure 2.

Associations across subjects between graph metrics of brain network economy for 89 regions of interest (ROIs) at a sparsity of 20%. Correlations show interdependency of four major network parameters, namely the characteristic path length, clustering coefficient, physical wiring length (tract-based distance) and robustness to attacks (random deletion of edges). r represents Pearson's correlation coefficients. $^{***}p < 0.001$.

Table 1

Associations between graph metrics for 89 regions of interest and all computed network densities (sparsities).

Pearson's correlation coefficient between graph metrics for 89 regions of interest									
Network density	10%	15%	20%	25%	30%	35%	40%	45%	50%
CPL vs									
Clustering	0.31 *	0.7 ***#	0.76 ***#	0.89 ***#	0.93 ***#	0.93 ***#	0.90 ***#	0.83 ***#	0.64 ***#
Resilience Random	0.22	-0.47 ***#	-0.97 ***#	-0.93 ***#	-0.80 ***#	-0.59 ***#	-0.41 ***#	-0.25	0.15
Resilience Nodes	0.24	-0.43 ***#	-0.96 ***#	-0.91 ***#	-0.72 ***#	-0.52 ***#	-0.40 **	-0.25	0.16
Resilience Target	0.31 *	-0.37 *	-0.86 ***#	-0.55 ***#	-0.21	-0.22	-0.21	-0.11	0.26
Cost tract-based	0.17	-0.38 *	-0.62 ***#	-0.61 ***#	-0.51 ***#	-0.43 ***#	-0.35 *	-0.25	-0.10
Cost Euclidian	0.14	-0.34 *	-0.49 ***#	-0.53 ***#	-0.45 ***#	-0.36 *	-0.32 *	-0.23	-0.05
Clustering vs									
Resilience Random	-0.11	-0.46 ***#	-0.66 ***#	-0.75 ***#	-0.65 ***#	-0.50 ***#	-0.38 *	-0.32 *	-0.30
Resilience Nodes	-0.13	-0.47 ***#	-0.64 ***#	-0.73 ***#	-0.62 ***#	-0.48 ***#	-0.4 **	-0.36 *	-0.32 *
Resilience Target	-0.12	-0.48 ***#	-0.68 ***#	-0.46 ***#	-0.15	-0.21	-0.23	-0.22	-0.25
Cost tract-based	-0.08	-0.48 ***#	-0.50 ***#	-0.59 ***#	-0.51 ***#	-0.46 ***#	-0.42 ***#	-0.40 **	-0.41 ***#
Cost Euclidian	-0.13	-0.43 ***#	-0.43 ***#	-0.51 ***#	-0.44 ***#	-0.38 *	-0.36 *	-0.35 *	-0.39 *
Cost tract-based vs									
Resilience Random	0.47 ***#	0.58 ***#	0.65 ***#	0.64 ***#	0.54 ***#	0.42 ***#	0.29	0.27	0.20
Resilience Nodes	0.47 ***#	0.58 ***#	0.64 ***#	0.62 ***#	0.53 ***#	0.41 ***#	0.32 *	0.27	0.21
Resilience Target	0.48 ***#	0.56 ***#	0.57 ***#	0.42 ***#	0.09	0.23	0.25	0.22	0.17

CPL: characteristic path length, Clustering: clustering coefficient, Resilience random: random deletion of edges, Resilience nodes: random deletion of entire nodes, Resilience target: targeted deletion of hub nodes, Cost tract-based/Euclidian: physical wiring length computed along known white matter tracts or with the Euclidian distance in 3D-space.

* p<0.05,

** p<0.01,

*** p<0.001,

withstanding Bonferroni-correction for multiple comparisons at $p_{corrected} < 0.0083$.