Efficient hubs in the intelligent brain: Nodal efficiency of hub regions in the salience network is associated with general intelligence

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Abstract
Intelligence-related differences in the intrinsic functional organization of the brain were studied with a graph-theoretical approach, comparing effects on nodal measures of brain network efficiency (concerning specific nodes of the network) and global measures (concerning the overall brain network). Functional imaging data acquired for 54 healthy adult participants during wakeful rest were modeled as graphs representing individual functional brain networks. Nodal and global measures of efficient network organization (i.e., nodal efficiency and global efficiency) were correlated with intelligence scores (IQ from the Wechsler Abbreviate Scale of Intelligence, WASI). While global efficiency showed no significant association with intelligence, the nodal efficiency was significantly associated with intelligence in three brain regions. Participants with higher IQ scores showed higher nodal efficiency in right anterior insula (AI) and dorsal anterior cingulate cortex (dACC), two hub regions of a functional brain network previously described as salience network. Furthermore, higher IQ was associated with lower nodal efficiency in the left temporoparietal junction area (TPJ). Distinct connectivity profiles were observed for brain regions showing a positive versus negative correlation between IQ and nodal efficiency. Our analyses suggest that intrinsic (i.e., task-independent) connectivity profiles of brain regions that have previously been associated with salience processing (AI and dACC) and the filtering of irrelevant information from higher-level processing (TPJ), play a role in explaining individual differences in intelligence. Based on these intelligence-related effects in resting-state fMRI data, we discuss the potential relevance of processing salient information for the explanation of differences in cognitive performance and intelligence.

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1. Introduction
Biological correlates of intelligence differences have been identified in structural and functional properties of the brain (Basten, Hilger, & Fiebach, 2015; Jung & Haier, 2007). Specifically, individual differences in intelligence have been linked to differences in the local amount of gray matter (e.g., Haier, Jung, Yeo, Head, & Alkire, 2004), the integrity of white matter (e.g., Penke et al., 2012), and the strength of brain activation during cognitive demands in circumscribed regions of the brain (Basten, Stelzel, & Fiebach, 2013; Gray, Chabris, & Braver, 2003). Recent investigations turned the focus from studying segregated correlates of intelligence in distinct regions of the brain, to the study of intelligence-related differences in functional interactions between brain regions (Song et al., 2009; Van den Heuvel, Stam, Kahn, & Hulshoff Pol, 2009). The latter approach accounts for the fact that the human brain is a complex network – characterized by interactions between functionally segregated regions – that continually integrates and processes information across various temporal and spatial scales (Achard, Salvador, Whitcher, Suckling, & Bullmore, 2006; Hagmann et al., 2008; Sporns, 2011). Fundamental properties of the intrinsic organization of functional brain networks can be observed even in the absence of cognitive demands, i.e., based on so-called resting state fMRI scans in which participants are awake but without a specific task (see, for example, van den Heuvel & Hulshoff Pol, 2010; Rosazza & Minati, 2011). The brain’s intrinsic functional organization during this resting state is suggested to influence the ability to form flexible and appropriate behavioral responses to cognitive demands (Sala-Llonch et al., 2012). Recent research has begun to investigate whether patterns of intrinsic functional connectivity in the brain are also related to intelligence. Functional connectivity between brain regions during resting state can be inferred from temporal correlations between changes in functional magnetic resonance imaging (fMRI) blood-oxygen-level dependent (BOLD) signals in different regions of the brain (Friston, Frith, Liddle, & Frackowiak, 1993). Such resting state connectivity has been shown...
to be relatively stable over time (Shehzad et al., 2009; Zuo et al., 2010), to relate closely to underlying anatomical connections (Greicius, Supekar, Menon, & Dougherty, 2009; Hagmann et al., 2008; Honey, Kötter, Breakspear, & Sporns, 2007; for review, see Honey, Thivierge, & Sporns, 2010), and to represent fundamental topological principles of the functional networks in the brain (Biswal, Yetkin, Haughton, & Hyde, 1995; van den Heuvel & Hulshoff Pol, 2010). Furthermore, it has been reported that individual differences in the connectivity patterns of resting state data are associated with stable individual differences in personality traits (e.g., Adelstein et al., 2011; Beaty et al., 2015; Kim, Gee, Loucks, Davis, & Whalen, 2011) as well as cognitive functions (e.g., Song et al., 2008, 2009; van den Heuvel et al., 2009; Cole, Yarkoni, Repovs, Anticevic, & Braver, 2012; Langer et al., 2012; Xu et al., 2013; Markett et al., 2014; Santaronecci, Rossi, & Rossi, 2015). Many functional connectivity studies of the human brain have used seed-based correlation analyses or independent component analyses. Whereas seed-based approaches estimate the strength of associations between a circumscribed region of interest and all other voxels in the brain, independent component analyses enable the identification of distinct networks comprising brain regions that can be separated on the basis of statistical patterns in their time series dynamics (Beckmann, Deluca, Devlin, & Smith, 2005; Damoiseaux et al., 2006). More recently, neuroimaging investigations have begun to apply graph theory to the analysis of large-scale functional dynamics in the brain. This method can take into account the entire pattern of correlations across the whole brain in an unbiased way (as opposed to seed-based analyses) and provides the opportunity to calculate metrics that characterize the interaction between brain regions and the information transfer in the brain. Graph theory is a computational approach for the detailed modeling and characterization of large-scale networks (for overview, see Park & Friston, 2013; Rubinov & Sporns, 2010; Sporns, 2011; Wang, Zuo, & He, 2010). In contrast to seed-based approaches or independent component analyses, graph theory provides a set of measures that can be used to characterize the brain network as a whole (global level) as well as to characterize specific nodes or regions within the network (nodal level). To model the brain’s neural network as a graph, the brain is spatially parcellated into a set of homogeneous regions (i.e., voxels or anatomical regions of interest) that serve as network nodes. Functional connections between these nodes, called edges, are then defined by the correlations between the nodes’ BOLD activation time series, as measured with fMRI. The nodes and edges define a graph with a specific topology that reflects functional properties of the brain network. Different indices can be calculated for a graph that describe aspects of this topology, and thereby provide information about the brain’s functional organization (Rubinov & Sporns, 2010; Sporns, 2011). As a typical finding, for example, graph models of human brain networks show small-world organization, i.e., relatively high local clustering along with low average path lengths (Achard et al., 2006; Wang et al., 2009; for review, see Bassett & Bullmore, 2006). This small-world organization enables highly efficient information processing by ensuring high connectedness within as well as integration of information across different processing sites. Recently, graph theoretical methods have also been applied to study intelligence-related differences in brain network organization. These studies differ in the types of connectivity that were studied (i.e., functional versus structural connectivity) and the neuroimaging techniques used to acquire the data for the network modeling. Intelligence-related differences in the efficiency of functional networks were studied with functional magnetic resonance imaging (fMRI; e.g., van den Heuvel et al., 2009; Song et al., 2009; Santaronecci, Galli, Polizzotto, Rossi, & Rossi, 2014; Santaronecci et al., 2015; Pamplona, Santos Neto, Rosset, Rogers, & Salmon, 2015); electroencephalography (EEG; e.g., Langer et al., 2012; Smit, Stam, Posthuma, Boomsma, & De Geus, 2008), and magnetoencephalography (MEG; e.g., Duan et al., 2014). The efficiency of structural connectivity was investigated with diffusion tensor imaging (DTI; e.g., Li et al., 2009; Fischer, Wolf, Scheurich, & Fellgiebel, 2014; Pineda-Pardo, Martínez, Román, & Colom, 2016; Ryman et al., 2016). In the following, we focus on research that used fMRI to study efficiency of functional networks. One of the pioneer studies of the association between intelligence and brain network topology suggested that higher IQ was associated with a brain network organization that renders information processing within the brain globally more efficient (van den Heuvel et al., 2009). In that study, higher global efficiency of brain networks in participants with higher IQ was inferred from a more pronounced small-world organization due to on average shorter path lengths in their functional brain networks. While some later studies also report significant associations between intelligence and global measures of efficient network organization (i.e., global efficiency, characteristic path length), these studies focused on different aspects of connectivity as they were based either on specific sub networks (DMN: Song et al., 2009), weak connections (Santaronecci et al., 2014), on groups of patients with altered network topology (Xu et al., 2013), used fundamentally different data (EEG: Langer et al., 2012), or relied on the investigation of structural connections (Li et al., 2009) – and thus did not provide a strict replication of the findings reported by van den Heuvel et al. (2009). In contrast, other studies did not observe a significant association between psychometric intelligence and global efficiency in functional networks (fMRI: Pamplona et al., 2015; MEG: Duan et al., 2014; EEG: Smit et al., 2008), structural networks (Fischer et al., 2014; Pineda-Pardo et al., 2016), or in specific populations (children: Wu et al., 2013; elderly: Fischer et al., 2014). While not concerning intelligence in a strict sense, global network efficiency has also been associated with intelligence-related factors, such as processing speed, visuospatial ability, and executive functioning (Wen et al., 2011). Taken together, empirical results concerning the relationship between intelligence and global network efficiency are heterogeneous, necessitating further research into the topological network properties underlying intelligence. On the other hand, intelligence has also been associated with differences in local – i.e., node-specific – topological properties of brain networks. Rather than characterizing properties such as network efficiency for the entire brain, local (or nodal) graph theoretical measures describe the connectivity patterns of individual nodes (or regions) within the rest of the brain. While some researchers focused their analyses on the lateral prefrontal cortex (PFC) and reported that it was more closely connected to the rest of the brain in more intelligent individuals (Song et al., 2008; Cole et al., 2012, 2015), the above-mentioned study by van den Heuvel et al. (2009) suggests intelligence-related differences also in the functional connectivity of brain regions outside the lateral PFC. Specifically, in addition to their results for global efficiency, van den Heuvel et al. (2009) also tested for nodal topological differences in the entire brain and reported that the above-mentioned intelligence-related differences in global network efficiency came along with differences in the node-specific measure or efficiency (normalized path length) in medial PFC, posterior cingulate cortex (PCC), inferior parietal cortex (IPC), left superior temporal gyrus (STG), and left inferior frontal gyrus (IFG). Van den Heuvel et al. (2009) suggest that these regions are embedded within the network more efficiently, i.e., are characterized by shorter functional paths to other parts of the brain network in subjects with higher IQ scores. However, these findings were reported for a declaredly exploratory statistical threshold. With the current investigation, we extend the study of node-specific differences in the topological organization of brain networks, further investigating the idea that the connection efficiency of specific regions within the brain’s functional network varies with intelligence. At the nodal level, we specifically expect an association between intelligence and nodal efficiency in so-called hub regions of the brain network, i.e., in regions that take a position of high centrality in the network. Centrality as a graph theoretical concept characterizes the importance of a node in relation to all other nodes of the network (van den Heuvel & Sporns, 2013) and is usually quantified as degree centrality by the number of direct edges connecting a given node to other nodes in
the network. Hub regions with high degree centrality are crucial for the global communication flow within the network. They show high inter-connectedness to each other and are implicated in influential long-distance connections between distinct brain modules (Zamora-López, Zhou, & Kurths, 2010), thereby (i) forming a core component of the brain network in which information can be integrated especially quickly (referred to as a connectivity backbone or rich club; van den Heuvel & Sporns, 2011) and (ii) encoding them important for the integrative processing of information (Crossley et al., 2013; Ekman, Derrfuss, Tittgemeyer, & Fiebach, 2012; Van den Heuvel, Kahn, Goñi, & Sporns, 2012). Consistent across studies, hub character has been ascribed to a set of cortical brain regions located along the midline of the brain (medial frontal cortex, dACC and PCC, and precuneus) as well as in lateral cortical regions (dorsal prefrontal, posterior parietal, temporal, visual, and insular cortices; Grayson et al., 2014; Zuo et al., 2012; for review, see van den Heuvel & Sporns, 2013). Hub regions, as focal points of neural communication, may also function as “neural bottlenecks” for information flow in the brain, possibly defining capacity limits in cognitive processing by setting upper bounds for neural integration and controlling the chaining or serializing of mental operations (van den Heuvel & Sporns, 2013). This makes individual differences in the connectivity of hub regions an interesting candidate for explaining individual differences in general cognitive ability, i.e., intelligence.

Overall, the aim of the current study was to compare nodal and global graph theoretical measures of network efficiency in their relation to individual differences in intelligence. To summarize the specific goals of the present study, (i) we expect intelligence to be associated with a nodal measure of network efficiency, i.e., nodal efficiency; (ii) we test for an association between intelligence and a global measure of network efficiency, i.e., global efficiency, to determine whether intelligence is related to network efficiency averaged across the entire network; (iii) we expect intelligence-related differences in nodal efficiency for hub regions of the functional network, i.e., for brain regions with high degree centrality; and (iv) for all brain regions showing a significant association between intelligence and nodal efficiency, we will illustrate the regions’ embeddedness within functional networks by plotting the anatomical localizations of all nodes directly connected to these regions in the functional graph.

To address these questions, we conducted whole brain analyses of fMRI resting state functional connections using a graph theoretical approach of network characterization. We modeled individual brain networks as unweighted, thresholded graphs. For every individual graph, we calculated the graph metrics of global efficiency to test for an association between intelligence and connectivity across the whole brain network and, for each network node, nodal efficiency to test for nodal differences in the association between intelligence and network efficiency. Nodal efficiency is defined as inverse of the average length of the shortest paths between a given node and every other node in the brain network (Latora & Marchiori, 2003, 2001). Regions with high nodal efficiency are embedded within the overall network in a more efficient manner, i.e., they have closer functional connections to the rest of the network (Achard & Bullmore, 2007). Global efficiency is the global counterpart of nodal efficiency (Latora & Marchiori, 2003, 2001). It is calculated as the average of the nodal efficiency values of all nodes in the network. Hub regions were identified by degree centrality, which is the most local and directly quantifiable measure of local network centrality. Degree centrality represents the number of direct links to the node’s functional “first neighbors” (Rubinov & Sporns, 2010; Zuo et al., 2012). The connectivity pattern of the intelligence-related brain regions was illustrated by plotting the anatomical locations of these first neighbors in the network.

2. Material and methods

2.1. Participants

The data used for the present study was acquired by the Nathan S. Kline Institute for Psychiatric Research (NKI), founded and operated by the New York State office of mental health. The NKI takes part in the 1000 functional connectomes project, which is an international neuroimaging data-sharing initiative (INDL, www.fcon_1000.projects.nitrc.org/indi/pro/nki.html). For 207 healthy subjects aged between four and 85 years, the NKI dataset contains neuroimaging measures (anatomical scan, functional resting state scan, diffusion tensor imaging (DTI) data) as well as a broad range of phenotypic variables, such as personality and intelligence (for a detailed description see Noonier et al., 2012). For the current study, we selected a subsample of 54 participants in the age range of 18 to 30 years (M = 23.37, SD = 3.35; gender: 23 female, 31 male; handedness: 46 right, 5 left, 3 ambidextrous). We restricted the age range of our sample to minimize the influences of developmental changes in network topology that have been reported to occur during childhood and later adult age (Betzel et al., 2014; Fair et al., 2009; for review, see Menon, 2013) and to allow for comparability with previous research on the relation between graph theoretical network characteristics and intelligence that also focused on samples of healthy young adults (e.g., Cole et al., 2012, 2015; Song et al., 2009, 2008; van den Heuvel et al., 2009).

2.2. Assessment of intelligence

Intelligence was assessed with the WASI (Wechsler, 1999). The WASI is a short version of the Wechsler Adult Intelligence Scale (WAIS-III, Wechsler, 1997) and allows the computation of a Verbal Intelligence Quotient (VIQ) measuring crystallized abilities, a Performance Intelligence Quotient (PIQ) measuring fluid aspects of intelligence, and a Full Scale Intelligence Quotient (FSIQ). The WASI’s test manual reports high concurrent validity (r = 0.92) for the correlation of FSIQ scores from the WASI and the WAIS-III as well as good discriminant, factorial and construct validities. For the 54 subjects included in our sample, the WASI FSIQ ranged from 85 to 138 (M = 113.17; SD = 11.78).

2.3. fMRI data acquisition

fMRI data were acquired on a 3 Tesla whole body magnetic resonance imaging scanner (MAGNETOM Trio Tim, Siemens Medical Solutions, Erlangen, Germany). Functional resting state data were obtained using a T2*-weighted BOLD-sensitive gradient-echo EPI sequence with 38 transversal axial slices of 3 mm thickness (260 volumes; field of view (FOV) 216 × 216 mm; repetition time (TR) 2500 ms; echo time (TE) 30 ms; flip angle 80°; voxel size 3.0 × 3.0 × 3.0 mm; acquisition time 10.55 min.). For coregistration, three-dimensional high-resolution anatomical scans were obtained via a sagittal T1-weighted, Magnetization Prepared-Rapid Gradient Echo (MP-RAGE) sequence scan (192 sagittal slices; FOV 256 × 256 mm; TR 2500 ms; TE 3.5 ms; flip angle 8°; voxel size 1.0 × 1.0 × 1.0 mm; acquisition time 10.42 min with a shorter sequence, in 5 of 54 cases due to technical problems).

2.4. Preprocessing

Data was preprocessed using the software FSL (FSL Version 5.0; FMRIB Software Library, http://www.fmrib.ox.ac.uk/fsl/; Smith et al., 2004) and AFNI (http://afni.nimh.nih.gov/afni) with the preprocessing scripts that have been released as part of the 1000 Functional Connectomes Project (http://www.nitrc.org/projects/fcon_1000; Biswal et al., 2010). Preprocessing comprised the following steps: 1. The first four EPI volumes from each resting-state scan were discarded to allow for equilibration of the signal, 2. Slice time correction, 3. Three-dimensional motion correction, 4. Time series despling, 5. Spatial smoothing by using a 6 mm full-width half-maximum (FWHM) Gaussian kernel, 6. Four-dimensional mean-based intensity normalization, 7. Bandpass temporal filtering (0.005–0.1 Hz), 8. Removing of linear and quadratic trends, 9. Estimation of a nonlinear transformation from each individual space to MNI152 space (3.0 × 3.0 × 3.0 mm...
resolution) via each subject’s high-resolution anatomical scan, 10. Elimination of nine nuisance signals by regression (signals of white matter and cerebrospinal fluid, global mean, and six motion parameters). Regression of the global mean was applied to eliminate non-neural noise in the data and to enhance the specificity of our analyses (Fox, Zhang, Snyder, & Raichle, 2009; Weissenbacher et al., 2009). The application of global signal regression in preprocessing has been criticized for introducing spurious anti-correlations into resting state data (Murphy, Birn, Handwerker, Jones, & Bandettini, 2009). However, as we exclusively focus our analyses on positive correlations, potentially arising spurious negative correlations will not affect the interpretation of our results.

2.5. Graph analyses

2.5.1. Node definition

All analyses were restricted to gray matter regions of the brain by applying a gray matter mask on the data. For node definition the functional data was down-sampled to 6.0 x 6.0 x 6.0 mm resolution, which resulted in 5411 voxels that cover the entire gray matter of each individual and that served as nodes for the graph analyses.

2.5.2. Graph construction

For network construction, the time series of each node was correlated with the time series of each other node across 260 time points using Pearson’s product moment correlation. The correlation matrix $A$ with the dimension $5411 \times 5411$ was calculated for each subject separately and edges were assumed to be present between nodes showing high positive correlations. In a first step, we excluded all edges of physically short distance (i.e., all ties terminating within 20 mm of a source node; see Power et al., 2011). Following previously published suggestions for the comparison of graph structures between persons in the study of individual differences (e.g., van den Heuvel et al., 2009), we modeled the brain’s functional network by constructing thresholded binary graphs. As most graph metrics are strongly influenced by (a) the number of nodes and (b) the density of the graph (Van Wijk, Stam, & Daffertshofer, 2010), it has been suggested that these parameters should be held constant for the comparison of graphs, when the primary interest lies in comparing measures of network structure between persons (Bollbás and Thomason, 1985; Bullmore & Bassett, 2011; van Wijk et al., 2010). In our analyses, the number of nodes is fixed as all individual networks were based on the same parcellation scheme (i.e., 5411 voxel nodes).

Also following suggestions for individual differences analyses, we realized a fixed density of the graphs by applying proportional thresholds and binarizing the graphs. In a binary graph, a fixed density is guaranteed by an identical number of edges for all individuals. In contrast, weighted graphs will usually vary in density (mean weight of edges), even if the number of edges is held constant across individuals. In the context of individual differences studies, the presence of individual differences in the mean weight of edges has been criticized for biasing the comparison of topological properties (Van Wijk, 2010; Ginestet et al., 2011, 2014). Specifically, the use of weighted graphs has been criticized as inappropriate for the calculation of graph metrics based on the identification of shortest paths, as the weighted versions of these measures are strongly influenced by (and sometimes even equivalent to) the mean of all weights in the graphs (Ginestet et al., 2014). This directly concerns the measures used in our study, i.e., nodal efficiency and global efficiency, which is why we decided to base the calculation of all graph metrics on proportionally thresholded binary graphs. Nevertheless for the purpose of comparison, we also calculated as supplemental analyses the graph metrics of interest on the basis of weighted graphs. However, it is important to keep in mind that differences in results between binary and weighted graphs are to be expected as nodal efficiency reflects different local network properties for binary as opposed to weighted graphs. In both cases, nodal efficiency describes the inverse of the average length of shortest paths that connect the given node to all other nodes in the network. However, shortest paths are defined differently in binary and weighted graphs. While in binary graphs, the shortest path is the one with the smallest number of edges, in weighted graphs, it is the one with the highest average edge weights in relation to the number of involved edges (Ginestet et al., 2011; example: Imagine 2 alternative paths connecting two nodes. Path 1 consists of fewer edges [e.g., 3] with lower weights [e.g., 0.9, 0.4, 0.1]. Path 2 consists of more edges [e.g., 6] with higher weights [e.g., 0.9, 0.8, 0.9, 0.9, 0.8, 0.7]. In a binary graph, path 1 will be identified as shortest path. In a weighted graph, in contrast, path 2 will be identified as shortest path). Thus, in binary graphs, shortest paths are identified based on connectivity structure, while in weighted graphs, shortest paths are defined by connectivity strength in relation to structure. Consequently, nodal efficiency values from binary and weighted graphs are not directly comparable.

Proportional thresholds for graph construction were defined by selecting a specific percentage of edges with highest correlations as the basis for binary adjacency matrices. This thresholding procedure also excluded all negative edges from the analysis (for discussion, see Fox et al., 2009; Weissenbacher et al., 2009; Murphy et al., 2009). Across individuals, the number of excluded negative edges varied between 6,694,077 and 7,786,425 ($M = 7,265,955$; $SD = 233,317$; total number of edges = 14,636,755) and was not related to intelligence ($r = 0.00$, $p = 0.98$; Bayes Factor representing evidence for the null hypothesis: $BF_{01} = 5.89$; see below Section 2.5.4 for more details). We used five different thresholds of 10, 15, 20, 25, and 30% edge density. This resulted in five different binary adjacency matrices per person, representing the strongest 10, 15, 20, 25, and 30% of functional connections between nodes, respectively. These adjacency matrices define the graphs that model the brain’s functional network. Graph theoretical metrics describing topological characteristics of the graphs were calculated separately for the five graphs and then averaged for each participant, providing an integrated measure of graph characterizing properties. We decided to model the individual brain networks over this range of thresholds to enhance the reliability of our findings, as graph theoretical measures have been shown to be sensitive to different connectivity thresholds (Power et al., 2011; Power, Fair, Schlaggar, & Petersen, 2010, for discussion see van Wijk et al., 2010), and our aim was to detect effects that are robust across a wider range of thresholds.

2.5.3. Graph theoretical metrics

To study efficiency-related topological characteristics of the functional brain network graphs and to investigate how these properties relate to individual differences in intelligence, we computed the graph metrics of nodal efficiency and global efficiency. To identify hub regions in the functional network, we determined each node’s degree centrality as a measure of its relative importance for network communication.

2.5.3.1. Nodal efficiency. Nodal efficiency is defined as inversely proportional to the average shortest distance between node $i$ and all other nodes $j$ of the graph:

$$E_i = \frac{1}{N-1} \sum_{j \neq i} \frac{1}{d_{ij}}$$

where $N$ is the number of nodes and $d_{ij}$ is the shortest path length between node $i$ and node $j$ in graph $A$ (Latora & Marchiori, 2003, 2001). Thus, for every node in the network, the algorithm identifies the length of the shortest paths between a given node $i$ and all other nodes $j$ in the network. Then it calculates the average of the lengths of all shortest paths identified for node $i$.

2.5.3.2. Global efficiency. Global efficiency was computed as the mean of all nodes’ nodal efficiency values. This is defined as inversely
network graphs. For the illustration of has been developed for the analysis of structural and functional brain measures of centrality, for the network (Rubinov & Sporns, 2010). While there exist multiple other nodes and are consequently topologically central and important perspective, nodes with a high degree are directly interacting with many aspects of information transfer (Achard & Bullmore, 2007).

2.5.3.3. Degree centrality. The degree of each node in the network was computed as the number of edges connected to this node:

$$k_i = \sum_{j \in N} a_{ij}$$

where \( N \) is the set of all nodes in the network and \( a_{ij} \) is the connection status (i.e., 1 for connected vs. 0 for disconnected) between node \( i \) and node \( j \) (Rubinov & Sporns, 2010). A node’s degree centrality therefore specifies the number of its direct neighbors. From a neurobiological perspective, nodes with a high degree are directly interacting with many other nodes and are consequently topologically central and important for the network (Rubinov & Sporns, 2010). While there exist multiple measures of centrality, degree centrality represents the most local and directly quantifiable metric for graph analyses (Zuo et al., 2012).

All graphs were modeled and metrics calculated using the open source python package network-tools (Ekman & Linssen, 2015), which has been developed for the analysis of structural and functional brain network graphs. For the illustration of nodal efficiency and degree centrality in Figs. 1 and 3, the brain maps of these metrics were smoothed with a 3 mm FWHM Gaussian kernel.

2.5.4. Intelligence-related differences in network efficiency

To investigate the relationship between intelligence and nodal efficiency, we set up a regression model with SPM8 (Statistic Parametric Mapping, Welcome Department of Imaging Neuroscience, London, UK) predicting the individual maps of nodal efficiency (upsampled to \( 3.0 \times 3.0 \times 3.0 \) mm) by WASI FSIQ. To statistically control for effects of age, sex, and handedness, these variables were included as covariates of no interest. The resultant \( p \)-values of the test statistic were corrected for multiple comparisons using a cluster-level thresholding procedure (Forman et al., 1995). An overall threshold of \( p < 0.05 \) (FWE-corrected) was achieved by combining a voxel-level threshold of \( p < 0.005 \) with a cluster-level threshold of \( k > 26 \) voxels (calculated with AlphaSim; 10,000 permutations; voxel size: \( 3.0 \times 3.0 \times 3.0 \) mm; Ward, 2000). To test for an association between intelligence and global network efficiency, WASI FSIQ scores and individual values of global efficiency were correlated using SPSS 22 (IBM Corp., Armonk, NY) and a critical alpha level of \( p < 0.05 \). A partial correlation was calculated to control for the effects of age, sex, and handedness.

Furthermore, we used Bayesian statistics to quantify the evidence for the null hypothesis (i.e., absence of an association between intelligence and global efficiency). A Bayes Factor (BF\(_{01}\); Jeffreys, 1961; Wetzels & Wagenmakers, 2012; for discussion see Wagenmakers, 2007) was calculated for the correlation between intelligence and global efficiency using the Bayesian test for correlated pairs (Jeffreys, 1961) with a Jeffery prior (stretched beta distribution of width 1) as implemented in the software “JASP” (Love et al., 2015). Concerning the partial correlation between intelligence and global efficiency, controlling for age, sex, and handedness, we used Bayesian linear regression for an approximation of the BF\(_{01}\) as the software does not provide a specific procedure for partial correlations. For the regression model, we used the default prior as implemented in JASP and described in detail in Rouder and Morey (2012).

Fig. 1. Nodal efficiency values averaged across all participants. High efficiency values are shown in warm colors (red), low efficiency values are shown in cool colors (blue). For the anterior, posterior, and lateral view, efficiency values were projected to the surface of the brain. The sagittal slice displays efficiency values in the \( x \)-plane. L, left; R, right.
To investigate whether the regions in which we observed a significant association between intelligence and nodal efficiency potentially function as hubs (van den Heuvel & Sporns, 2013) in the overall brain network, we quantified their hubness by calculating their rank position with respect to all network nodes’ degree centrality values (Cole, Ito, & Braver, 2015). To illustrate the embeddedness of the identified intelligence-related regions within the overall brain functional network, we further determined the anatomical locations of these regions’ first neighbors in the network. For this purpose, we used the individual network graphs that had been averaged across five different thresholds (i.e., 10, 15, 20, 25, and 30%; see above) and extracted all nodes that demonstrated first neighborhood with the intelligence-related regions. This was done for each intelligence-related cluster and each subject separately. Technically, first neighbors were identified by an edge in the binary adjacency matrix connecting this node to the respective intelligence-related region. Individual maps of first neighbors were averaged across subjects. We illustrate the nodes that were identified as first neighbors in at least 90% of all participants.

3. Results

3.1. Intelligence and nodal efficiency

Nodal efficiency was significantly associated with intelligence in three regions of the brain (Fig. 2, Table 1). In right AI and dACC, we observed a positive association between intelligence and nodal efficiency (AI: \( t_{\text{max}} = 3.38 \); dACC: \( t_{\text{max}} = 3.89 \)). This means that in subjects scoring higher on the WASI FSIQ, these regions were connected with the rest of the network via shortest paths of lower topological distance. Such shorter paths are generally interpreted as reflecting facilitated information transfer between the respective regions and the rest of the brain network. In contrast, a significant negative association was observed in the left TPJ (\( t_{\text{max}} = -2.68 \)), reflecting that the average length of shortest paths that connect the TPJ to the rest of the brain network was higher in subjects who scored higher on the WASI. As a control analysis, we additionally controlled for the number of negative connections that were excluded from the modeling of the individual graphs.

Fig. 2. Clusters of nodes showing significant associations between intelligence and nodal efficiency (see also Table 1). Positive associations are shown in red, negative associations in blue. Statistic parametric maps are shown at a voxel-level threshold of \( p < 0.005 \), uncorrected, and a cluster-level threshold of \( k > 26 \) voxels, corresponding to an overall threshold of \( p < 0.05 \), corrected for multiple comparisons (see Methods section: Intelligence-related differences in network efficiency). The scatterplots illustrate the associations between intelligence (i.e., WASI Full Scale Intelligence Quotient; FSIQ) and nodal efficiency for (A) the dorsal anterior cingulate cortex (dACC), (B) the anterior insula (AI), and (C) the left temporo-parietal junction (TPJ). The \( x \), \( y \), and \( z \) coordinates represent coordinates of the Montreal Neurological Institute template brain (MNI) and refer to the points of origin at which the slices were partially cut out. L, left; R, right.
This changed the results only marginally (AI: $t_{\text{max}} = 3.15$; dACC: $t_{\text{max}} = 3.59$; TPJ: $t_{\text{max}} = -2.70$), suggesting that results were not influenced by individual differences in the number of excluded negative network edges. Finally, when repeating the analyses with weighted instead of binary graphs (applying the same thresholding procedure), right AI and left TPJ also showed an association with FSIQ when lowering the statistical threshold to $p < 0.005$ (voxel-level, without correction for multiple comparisons, AI: $t_{\text{max}} = 2.98$; TPJ: $t_{\text{max}} = -2.69$). For nodal efficiency of dACC, we did not observe a significant association with intelligence in the weighted graphs.

3.2. Intelligence and global efficiency

Global efficiency, which is mathematically equivalent to the average of all nodal efficiency values across the modeled network, was not significantly related to intelligence in the present sample. Neither the simple correlation between FSIQ and global efficiency ($r = -0.01$; $p = 0.95$) nor the partial correlation controlling for effects of age, sex, and handedness ($r = 0.01$; $p = 0.97$) were statistically significant. The Bayesian test for correlations resulted in a Bayes Factor of $\text{BF}_{01} = 5.88$, indicating that the null hypothesis (i.e., absence of correlation) is 6 times more likely than the alternative hypothesis (i.e., presence of correlation). A $\text{BF}_{01} > 3$ is considered as substantial evidence for the null hypothesis (Jeffreys, 1961). For our study, this suggests that there was no relation between intelligence and global efficiency. Controlling for effects of age, sex, and handedness in a Bayesian linear regression model predicting intelligence from global efficiency, resulted in $t_{\text{BF}} = 3.64$, also suggesting that there was no association of intelligence and global efficiency in our sample.

To allow for direct comparability with the findings of van den Heuvel et al. (2009), we additionally calculated the metric of normalized characteristic path length that these authors used to study the global efficiency of the brain network. In our sample, the correlation between intelligence and normalized characteristic path length, averaged across graph thresholds 10–30% (see Material and methods), was $r = 0.005$ ($p = 0.97$; $\text{BF}_{01} = 5.89$) and $r = -0.024$ ($p = 0.87$; $\text{BF}_{01} = 3.65$) when controlling for age, sex, and handedness.

3.3. Hub character of intelligence-related regions

To investigate whether the brain regions in which we observed an association between intelligence and nodal efficiency function as hubs in the brain network, we computed the degree centrality of every node in our network. Brain regions with high degree centrality are considered network hubs (van den Heuvel & Sporns, 2013). Averaged across all participants (i.e., not taking into account individual differences in intelligence), hub regions were located along the midline of the brain in cingulate cortex, supplementary motor area (SMA), and precuneus, as well as in bilateral insular cortices, STG, IFC, middle frontal gyrus (MFG), and parts of the TPJ (Fig. 3) – a distribution of central network regions that is well in line with previous reports (e.g., Buckner et al., 2009; Grayson et al., 2014; Zuo et al., 2012; for review, see van den Heuvel & Sporns, 2013).

Fig. 3 relates the spatial localizations of the three regions in which we observed a significant association between intelligence and nodal efficiency to the spatial distribution of degree centrality as a measure of each node’s hub character across the brain. The two regions in which we observed a significant positive association between intelligence and nodal efficiency belonged to the top 4% (dACC) and top 10% (AI) of nodes in terms of degree centrality, respectively. These high ranks with respect to degree centrality suggest hub function of dACC and AI. In the region for which we observed a negative association between intelligence and nodal efficiency (TPJ), degree centrality was only higher in 44% of all other nodes in the network.

3.4. Embeddedness of intelligence-related hubs within the brain network

As described above, individual differences in intelligence are significantly linked to the average length of shortest paths (i.e., nodal efficiency) connecting three regions (i.e., right AI, dACC, and left TPJ) to the rest of the brain network. To illustrate to which other nodes of the brain network these three intelligence-related regions are connected most closely, we illustrated the anatomical locations of their direct topological neighbors in the graph, i.e., the location of nodes that are connected to the three regions via paths of length 1.

Fig. 4 shows the brain regions that were direct functional neighbors of the intelligence-related regions in >90% of all subjects. This illustration revealed two distinct connectivity patterns (for details see Table 2). For the two regions where intelligence was positively correlated with nodal efficiency (i.e., AI and dACC), the first neighbors were located in a set of brain regions that is known as the task-positive network (TPN; cf. Fox et al., 2005) comprising lateral prefrontal cortex, parietal, insular, and thalamic regions. In contrast, TPJ, for which intelligence was negatively correlated with nodal efficiency, had direct neighbors in the middle temporal gyrus (MTG), precuneus, and TPJ. Parts of these brain regions have been assigned to the so-called task-negative or default mode network (TNN; Fox et al., 2005). However, with no neighbors in ventromedial prefrontal and the neighbors in PPC appearing slightly displaced in comparison to available descriptions of the TNN (e.g., Basten et al., 2013; Buckner, Andrews-Hanna, & Schacter, 2008; Fox et al., 2005; Raichle et al., 2001; Shulman et al., 1997), the TPJ seems less clearly connected to a specific functional network of the brain than AI and dACC.

4. Discussion

In the current study, we investigated the relationship between graph theoretical measures of brain network efficiency and individual differences in intelligence on the basis of fMRI resting state data. We differentiated between a nodal graph metric that characterizes differences in the efficiency with which each individual node is connected to the rest of the network (nodal efficiency) and a global graph metric that describes the overall efficiency of the entire functional brain network (global efficiency). We found that intelligence was significantly positively related to nodal efficiency in the right anterior insula (AI) and the dorsal anterior cingulate cortex (dACC), while we observed a negative correlation in the left temporo-parietal junction (TPJ). On the other hand, intelligence was not associated with higher global efficiency of the brain network in our sample. The brain regions showing a positive correlation between intelligence and nodal efficiency were identified as functional hub regions. Finally, an illustration of the most closely connected network nodes (first neighbors in the graph) revealed different connectivity profiles for the regions showing a positive versus a negative correlation between intelligence and nodal efficiency. While AI and dACC showed close connections to the so-called task-positive network, left TPJ was mainly connected to contralateral TPJ.

Table 1

<table>
<thead>
<tr>
<th>Brain region</th>
<th>BA</th>
<th>Hem</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>$t_{\text{max}}$</th>
<th>k</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive association</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior insula</td>
<td>13</td>
<td>47</td>
<td>R</td>
<td>51</td>
<td>18</td>
<td>-6</td>
<td>3.38</td>
</tr>
<tr>
<td>Dorsal anterior</td>
<td>32</td>
<td>24</td>
<td>R/L</td>
<td>6</td>
<td>15</td>
<td>39</td>
<td>3.89</td>
</tr>
<tr>
<td>cingulate cortex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Negative association

| Temporo-parietal junction | 39, 22 | L    | -45  | -57  | 9    | -2.68           | 42                |

BA, approximate Brodmann’s area; Hem, hemisphere; L, left; R, right; coordinates referring to the Montreal Neurological Institute template brain (MNI); $t_{\text{max}}$, maximum t statistic in the cluster; k, cluster size in voxels of size $3 \times 3\times 3$ mm.
4.1. Intelligence-related differences in nodal efficiency

The graph theoretical measure of nodal efficiency describes how closely a given node is connected to the rest of the network. Higher nodal efficiency reflects that a given node is connected to all other nodes of the network via on average shorter paths, which is generally interpreted as allowing for faster signal transmission associated with lower energetic costs (Bullmore & Sporns, 2012). The observed intelligence-related differences in nodal efficiency thus imply that in persons with higher IQ, the right AI and the dACC are well positioned to quickly and easily receive input from and/or to exert influence over many other brain regions. Our findings furthermore suggest that the left TPJ, in contrast, is topologically less tightly embedded into the functional brain network for people with higher IQ. This may reflect a weaker or more flexible coupling of this region with the rest of the network, possibly associated with a special disposition for context-dependent changes in connectivity structure (see below and Anticevic, Repovs, Shulman, & Barch, 2010).

Two of the three brain regions showing an association between intelligence and nodal efficiency, i.e., AI and dACC, were identified as hub regions showing high degree centrality, i.e., a high number of direct links to other nodes in the network (Rubinov & Sporns, 2010; Zuo et al., 2012). Across subjects and independent of individual differences in intelligence, the spatial distribution of network hubs resembled the findings of previous studies, corroborating a highly central role of regions along the midline of the brain as well as of lateral frontal and temporo-parietal regions (e.g., Buckner et al., 2009; Grayson et al., 2014; Zuo et al., 2012; for review, see van den Heuvel & Sporns, 2013). Hubs are focal points of communication in the brain network that have crucial influence on the integration of information within the network via long-distance connections (van den Heuvel et al., 2012; Zamora-López et al., 2010). Simulated lesions to hub regions entail changes to the overall network architecture and efficiency of information transfer that are much stronger than those of random lesions to other sites of the network (Alstott, Breakspear, Hagmann, Cammoun, & Sporns, 2009; Honey & Sporns, 2008), suggesting an essential role of hub regions in ensuring the functional integrity of the brain network (van den Heuvel & Sporns, 2013). Based on the observation that hub regions are involved in a high number of communication paths (de Reus & van den Heuvel, 2013; Sporns, 2011), it has been suggested that hub regions may act as bottlenecks in the neural processing of information by setting upper bounds for neural integration (van den Heuvel & Sporns, 2013) – potentially explaining well-known bottlenecks in cognitive information processing (Marois & Ivanoff, 2005) and individual differences in general cognitive ability.

Furthermore, the illustration of anatomical locations for the first neighbors, i.e., for nodes that were directly connected to the three intelligence-related regions in the functional graph (path length = 1), revealed two different connectivity profiles. The two regions positively associated with intelligence (i.e., AI and dACC) demonstrated very similar patterns, with direct functional connections to neighbors in a set of brain regions that is known as the task-positive network (TPN; cf. Fox et al., 2005). In contrast, for the region where intelligence was negatively associated with nodal efficiency (TPJ), direct neighbors were located in brain regions that could not clearly be assigned to a previously described functional network of the brain. We observed some overlap with structures that have been assigned to the task-negative network (TNN; cf. Fox et al., 2005), e.g., PCC. However, with no neighbors in ventromedial PFC and the neighbors in PCC appearing slightly displaced in comparison to available descriptions of the TNN (e.g., Basten et al., 2013; Buckner et al., 2008; Fox et al., 2005; Raichle et al., 2001; Shulman et al., 1997), the TPJ seems less clearly connected to a specific functional network of the brain than AI and dACC. The differential patterns of network connectivity suggest that AI and dACC on the one hand and TPJ on the other hand are involved in distinct neural circuits. Based on our findings linking individual differences in the nodal efficiency of AI, dACC, and TPJ to intelligence, it may be speculated that individual differences in the function of these distinct neural circuits contribute to differences in human intelligence. The specific effects of individual differences in the connectivity profiles of the three brain regions on
measures of cognitive ability, however, will depend on the functional roles they take during cognitive demand, which we discuss in the next section.

4.2. The functional role of intelligence-related brain regions in cognition

Knowledge about the functional roles of the three regions, in which we observed intelligence-related differences in nodal efficiency, comes from functional imaging studies conducted in task contexts. All three regions (AI, dACC, and TPJ) have been associated with the detection of salient, behaviorally relevant stimuli and attentional reorienting towards these stimuli (Dosenbach et al., 2006; Downar, Crawley, Mikulis, & Davis, 2002; Gruber, Diekhof, Kirchenbauer, & Goschke, 2010). AI and dACC constitute the core components of the so-called salience network (Menon & Uddin, 2010; Seeley et al., 2007). The TPJ represents a key structure of the ventral attention network (Corbetta, Patel, & Shulman, 2008; Corbetta & Shulman, 2002).

AI and dACC are the two core cortical components of a functional brain network described as the salience network, along with subcortical structures including the amygdala, substantia nigra/ventral tegmental area, and the thalamus (Menon & Uddin, 2010). These structures are constituents of the TPN, consistently co-activated during cognitive tasks (Dosenbach et al., 2006), and show high intrinsic functional connectivity during resting state (Dosenbach et al., 2007; Power et al., 2011; Seeley et al., 2007; van den Heuvel & Hulshoff Pol, 2010). The salience network is assumed to be responsible for the detection of salient information (Downar et al., 2002), for evaluating the behavioral relevance of that information and setting markers for further processing (Goulden et al., 2014; Sridharan, Levitin, & Menon, 2008; Uddin, 2015). While the network

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**Fig. 4.** Functional first neighbors of intelligence-related regions. Intelligence-related regions (cf. Fig. 2) are depicted in black and were projected to the surface of the brain in B and D. Percentage of participants: The color overlays illustrate the percentage of participants (>90% overlap) for which the specific node is a first neighbor of the respective intelligence-related region. (A) Schematic illustration of edges between an intelligence-related reference node and its first neighbors, defined by time series correlated at varying strengths. (B–D) nodes identified as first neighbors of (B) the right AI, (C) the dACC, and (D) the left TPJ in >90% of the participants. For the anterior, posterior, and lateral view, values were projected to the surface of the brain. The sagittal slices display values in the x-plane. The x-coordinates refer to the left-right axis of the Montreal Neurological Institute template brain (MNI). AI, anterior insula; dACC, dorsal anterior cingulate cortex; TPJ, temporo-parietal junction; L, left; R, right.
literature describes the salience network as functionally rather homogeneous (Menon & Uddin, 2010; Uddin, 2015), other imaging studies have tried to differentiate the specific functions of AI and dACC in cognitive processing. Frequent coactivation makes it difficult to disentangle the specific contributions of AI and ACC to cognitive control and there is generally no clear consensus on distinct roles of AI and ACC in cognitive processing (for a discussion, see, for instance, Medford & Critchley, 2010; Shenlav, Botvinick, & Cohen, 2013). However, the AI seems to play a particularly important role in the detection of salient information and its evaluation with respect to goal-relevance (Corbetta et al., 2008; Downar et al., 2002) as well as in the initiation of signals for further cognitive processing and the coordination of activity in other functional networks (Sridharan et al., 2008). The dACC, on the other hand, has been associated with performance monitoring and control signal specification (Botvinick, Cohen, & Carter, 2004; Shenlav et al., 2013), and with the initiation of adaptive behavioral responses by providing a close link to the brain’s motor system (Downar et al., 2002; Rushworth, 2008; Shackman et al., 2011). 

The TPJ, in turn, has been linked to the reorientation of attention to environmental stimuli based on their behavioral relevance – as opposed to mere salience (Corbetta et al., 2008). It was shown that TPJ activation increases for goal-relevant information (e.g., Shulman et al., 2003). The TPJ, as part of the ventral attention network, is assumed to act as a ‘circuit breaker’ for the goal-driven dorsal attention network, interrupting ongoing processing and initiating the reorientation of attention towards goal-relevant information (Corbetta & Shulman, 2002). In contrast, decreases in activation of the TPJ were observed for the presentation of behaviorally irrelevant information (Shulman, Astafiev, McAvoy, D’Avossa, & Corbetta, 2007; Shulman et al., 2003; Todd, Fougnie, & Marois, 2005). The suppression of TPJ activity during the presentation of irrelevant information has been interpreted as reflecting the filtering of goal-irrelevant inputs from the TPJ to prevent the reorienting of attention to goal-irrelevant events that could interfere with the maintenance and processing of currently goal-relevant content (Todd et al., 2005; see filter hypothesis of TPJ function, Shulman et al., 2007, 2003). Corbetta et al. (2008) assume that the filtering of input from TPJ depends on top-down signals carrying information about stimulus relevance, and discuss AI and dACC as well as lateral prefrontal cortex (dorsal attention network) as possible sources of such a top-down signal. Interestingly, it could also be shown that the TPJ dynamically couples with different functional networks of the brain depending on the current context. During the reorientation of attention, the TPJ is activated along with other regions of the task positive or cognitive control network. In contrast, when the reorientation of attention must be prevented to shield ongoing cognitive processes against salient new information that may act as distractor, TPJ activation is suppressed and the region couples with the task negative or default mode network (Anticevic et al., 2010).

### 4.3. Explaining differences in intelligence with differences in salience processing

Based on functional imaging studies linking AI, dACC, and TPJ to salience processing, the following paragraph outlines the proposal of a model for the potential functional relevance of differences in network integration of these regions for cognitive performance and intelligence.

<table>
<thead>
<tr>
<th>Brain region</th>
<th>BA</th>
<th>Hem</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>t&lt;sub&gt;max&lt;/sub&gt;</th>
<th>k</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) First neighbors of right anterior insula</td>
<td>13, 47, 22, 40</td>
<td>R</td>
<td>30</td>
<td>6</td>
<td>6</td>
<td>100</td>
<td>2539</td>
</tr>
<tr>
<td>Anterior insula, inferior frontal gyrus, superior temporal gyrus</td>
<td>13, 22, 40, 47</td>
<td>L</td>
<td>−60</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>1450</td>
</tr>
<tr>
<td>Dorsal anterior cingulate cortex, supplementary motor area</td>
<td>24, 6, 32, 8</td>
<td>R/L</td>
<td>−6</td>
<td>6</td>
<td>42</td>
<td>100</td>
<td>722</td>
</tr>
<tr>
<td>Dorsolateral prefrontal cortex</td>
<td>10</td>
<td>L</td>
<td>−36</td>
<td>24</td>
<td>24</td>
<td>97</td>
<td>42</td>
</tr>
<tr>
<td>Mid-cingulate gyrus</td>
<td>31, 24</td>
<td>R</td>
<td>12</td>
<td>−18</td>
<td>36</td>
<td>93</td>
<td>9</td>
</tr>
<tr>
<td>Thalamus</td>
<td>R</td>
<td>12</td>
<td>−18</td>
<td>0</td>
<td>52</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>(B) First neighbors of anterior cingulate cortex</td>
<td>24, 32, 13, 6</td>
<td>R/L</td>
<td>−12</td>
<td>0</td>
<td>42</td>
<td>100</td>
<td>3447</td>
</tr>
<tr>
<td>Anterior cingulate cortex, supplementary motor area, insula, inferior frontal gyrus, middle frontal gyrus</td>
<td>24, 32, 13, 6</td>
<td>R/L</td>
<td>−12</td>
<td>0</td>
<td>42</td>
<td>100</td>
<td>3447</td>
</tr>
<tr>
<td>Supramarginal gyrus, inferior parietal lobule</td>
<td>40</td>
<td>R</td>
<td>54</td>
<td>−30</td>
<td>24</td>
<td>99</td>
<td>311</td>
</tr>
<tr>
<td>Dorsolateral prefrontal cortex</td>
<td>10, 9</td>
<td>L</td>
<td>−60</td>
<td>24</td>
<td>12</td>
<td>97</td>
<td>190</td>
</tr>
<tr>
<td>Anterior cingulate cortex, supplementary motor area, insula, inferior frontal gyrus, middle frontal gyrus</td>
<td>10, 9, 46</td>
<td>L</td>
<td>−36</td>
<td>48</td>
<td>24</td>
<td>99</td>
<td>128</td>
</tr>
<tr>
<td>Inferior parietal lobule, supramarginal gyrus</td>
<td>40</td>
<td>R</td>
<td>54</td>
<td>−30</td>
<td>24</td>
<td>99</td>
<td>311</td>
</tr>
<tr>
<td>Dorsolateral prefrontal cortex</td>
<td>10, 9</td>
<td>R</td>
<td>30</td>
<td>42</td>
<td>24</td>
<td>100</td>
<td>167</td>
</tr>
<tr>
<td>(C) First neighbors of temporo-parietal junction</td>
<td>39, 21, 22, 19</td>
<td>L</td>
<td>−66</td>
<td>−48</td>
<td>0</td>
<td>100</td>
<td>1271</td>
</tr>
<tr>
<td>Temporo-parietal junction, middle temporal gyrus</td>
<td>39, 22, 40, 21</td>
<td>R</td>
<td>48</td>
<td>−48</td>
<td>12</td>
<td>100</td>
<td>578</td>
</tr>
<tr>
<td>Precuneus, posterior cingulate gyrus</td>
<td>31, 7</td>
<td>R/L</td>
<td>−6</td>
<td>−54</td>
<td>36</td>
<td>96</td>
<td>195</td>
</tr>
<tr>
<td>Inferior frontal gyrus</td>
<td>45, 47, 44</td>
<td>L</td>
<td>−54</td>
<td>18</td>
<td>12</td>
<td>94</td>
<td>22</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>6</td>
<td>L</td>
<td>−42</td>
<td>0</td>
<td>54</td>
<td>91</td>
<td>7</td>
</tr>
</tbody>
</table>

Brain regions identified as first neighbors of the indicated intelligence-related clusters in ≥90% of subjects. BA, approximate Brodmann’s area; Hem, hemisphere; L, left; R, right; %max, maximum value of percentage of participants for which this regions was a first neighbor of the indicated intelligence-related cluster; k, cluster size in voxels of size 3.0 × 3.0 × 3.0 mm; coordinates refer to the Montreal Neurological Institute template brain (MNI).
It is important to keep in mind that in our current study, we observed intelligence-related differences in the connectivity profiles of the three brain regions during a so-called resting state, i.e., when participants did not face a specific cognitive challenge. Consequently, the following ideas should be understood as a theoretical proposal of how intelligence-related differences in the functional connectivity of the identified brain regions could potentially be related to individual differences in cognitive performance. For these theoretical considerations, we draw on insights from task activation studies, with all uncertainty that is associated with such reverse inferences (Poldrack, 2006), and combine these with speculations about potential consequences of a differential network integration of the associated brain regions.

For successful cognitive performance it is essential to quickly detect potentially relevant stimuli, discriminate between goal-relevant and irrelevant input, and to flexibly adjust cognitive processing and behavior in response to relevant information. This assumed role for the processing of salience and the discrimination between relevant and irrelevant information in intelligence is supported by behavioral studies. For example, from a study on individual variability of performance in a simple visual discrimination task that reflects both processing speed and perceptual suppression, Melnick, Harrison, Park, Bennett, and Tadin (2013) conclude that intelligence is fundamentally constrained not only by the ability to rapidly process relevant information, but also by the ability to suppress irrelevant information. Essentially, the processes of detecting salient information and selecting information for further processing are functions of controlled attention (Johnston & Dark, 1986), which in turn have been linked to intelligence (Ren, Altmeier, Reiss, & Schweizer, 2013; Schweizer, 2010; Schweizer, Moosbrugger, & Goldhammer, 2005). Note, however, that there is some debate on the exact relationship between intelligence and controlled attention. Whereas some studies propose a close relationship between both constructs and furthermore suggest that controlled attention is the key factor in mediating the well-established link between intelligence and working memory (Engle, Tuholski, Laughlin, & Conway, 1999; Kane, Hambrick, & Conway, 2005; Burgess, Gray, Conway, & Braver, 2011; for a review see Conway, Kane, & Engle, 2003), other investigations observed no such association (Colom, Rebollo, Abad, & Shih, 2006; Martinez et al., 2011; Chuderski, Taraday, Necka, & Smoleń, 2012) and suggest that simple short term storage capacity is the crucial factor underlying both working memory and intelligence (Colom, Abad, Quiroga, Shih, & Flores-Mendoza, 2008). A third line of recent empirical evidence suggests that attentional control does indeed play an important role for intelligence and working memory, next to other cognitive processes, such as secondary memory (Shipstead, Lindsey, Marshall, & Engle, 2014; Unsworth, Fukuda, Awh, & Vogel, 2014; Unsworth & Spillers, 2010; Unsworth, Spillers, Kane, Engle, & Schmiedek, 2009). In sum, while the exact nature of an association between attentional processes and intelligence is a matter of continued debate, behavioral research has specifically suggested a link between intelligence and the discriminative processing of relevant versus irrelevant information (Melnick et al., 2013).

Further support for a link between psychometric intelligence and the brain’s salience network can be derived from brain imaging studies that employed different methods than used in the current study. Yuan et al. (2012) reported a positive association between intelligence and morphological characteristics of regions in the salience network, i.e., higher IQ was associated with higher gray matter volume of right AI and ACC. Ebisch et al. (2012) reported neural correlates of intelligence in regions of the salience network based on task-induced activation, where higher IQ was associated with stronger activation of AI across different cognitive tasks, as well as task-based functional connectivity (Ebisch et al., 2013), where higher performance in an induction task was associated with stronger-increases in task-related functional connectivity in right AI and right dACC.

Combining these lines of evidence with the above-outlined assumptions about the functional roles of AI, dACC, and TPJ in cognition, we here suggest that the shorter topological distances between the two regions of the salience network (AI and dACC) and the rest of the brain network in persons with higher IQ, may entail an advantage in orienting attention towards salient, goal-relevant information. Furthermore, we speculate that a generally higher variability in the connectivity of the TPJ (which we assume to underline the overall weaker coupling of the TPJ to the rest of the network, based on the previously reported observation of context-dependent dynamical changes in the coupling of the TPJ with different functional networks; Anticevic et al., 2010), could potentially support the filtering of goal-irrelevant information from further processing by facilitating switches between TPJ-coupling with the TPN (when attention is reoriented to behaviorally relevant information) and coupling with the TNN (when ongoing cognitive processing has to be shielded against potentially distracting irrelevant information; Anticevic et al., 2010; Todd et al., 2005). This would support the preferential investment of attentional resources in stimuli with high likelihood of being goal-relevant, which could in turn contribute to high cognitive performance and intelligence, respectively. Note that this argumentation does not only apply to the processing of dynamic sensory input, but can also be transferred to stimulus material used in intelligence tests. For instance, paper-pencil matrix tests require a differentiation between relevant and irrelevant information in stimulus encoding and the manipulation of internal representations. We know that there are strong top-down influences on the salience of information enabling the “goal-driven” or “endogeneous” selection of information (Corbetta et al., 2008). A more efficient organization of the salience network could enable more intelligent individuals to make more effective use of such top-down guided salience signals for the goal-driven selection of relevant information – also with respect to internal representations of task information. Note again that in the present study intelligence-related differences in the connectivity profiles of three brain regions were observed only during resting state. To empirically establish the link between intelligence and the neural processing of salient information as outlined here, future research will have to study task-evoked dynamic changes in the connectivity of these regions during the processing of goal-relevant versus irrelevant salient information.

4.4. Intelligence and intrinsic connectivity of the brain

While earlier studies on neural correlates of intelligence often focused on differences in task-induced activation or morphological characteristics that were localized to circumscribed brain regions (for review, see Basten et al., 2015), the last years have shown a growing interest in the study of intelligence-related differences in functional network properties (e.g., Langer et al., 2012; Pineda-Pardo et al., 2016; Smith et al., 2015; Vakhtin, Ryman, Flores, & Jung, 2014; van den Heuvel et al., 2009). With these research endeavors, the field is moving from a segregated to a more integrated view of the neural bases underlying intelligence – methodologically implementing ideas that theoretical models had long acknowledged – for example by stressing the integration between frontal and parietal brain regions (parieto-frontal integration theory, P-FIT; Jung & Haier, 2007).

In line with previous studies on intelligence and the intrinsic connectivity of the brain, our results support the notion that intelligence is associated with individual differences in fundamental organizational principles of functional brain networks as identified in task-free resting states. Specifically, our observation of intelligence-related differences in the resting-state connectivity of AI, dACC, and TPJ is consistent with the results of other neuroimaging studies of intelligence using different methods, e.g., task-induced activation (e.g., Anticevic et al., 2010; Ebisch et al., 2012; Graham et al., 2010; Gray et al., 2003) as well as task-related functional connectivity (e.g., Ebisch et al., 2013; Haier, White, & Alkire, 2003). Moreover, the link between intelligence and AI, dACC, and TPJ is supported by a recently published large-scale study by Smith et al. (2015), in which these same brain regions most strongly contributed to the brain connections that were associated.
with a factor of co-variation in a large set of cognitive, behavioral, and demographic variables, which these authors interpret as reflecting general intelligence.

On the other hand, our findings do not lend support to other previous studies that reported intelligence-related nodal differences in intrinsic brain connectivity, for lateral PFC (Song et al., 2008; Cole et al., 2012, 2015) and a set of brain regions predominantly falling within the default mode network (van den Heuvel et al., 2009). Differences in findings in comparison to Song et al. (2008) and Cole et al. (2012) can potentially be explained by methodological differences between studies. Song et al. (2008) used a seed-based approach, studying connectivity only for lateral PFC and inspecting the strength of direct connections between DLPC and other brain regions. This study, accordingly, cannot capture more complex aspects of topological network organization like, e.g., the graph-theoretical approach of the present study does. Cole et al. (2012), on the other hand, used a different approach to construct the graph that models the functional brain network as well as a different graph metric to describe the connectivity of nodes in the network. While we modeled the brain as an unweighted thresholded graph, which is best suited to study differences in the structure of neural networks, Cole et al. (2012) used weighted unthresholded graphs, which emphasizes differences in the strength of connections. Furthermore, using nodal efficiency, we look at a nodal measure for network-wide connectivity, while Cole et al. (2012) used degree, a nodal measure of local connectivity. Intelligence may well depend differently on distinct patterns of local vs. network-wide connectivity, which is an important topic for future research. Differences in findings compared to van den Heuvel et al. (2009), on the other hand, can hardly be explained by differences in the investigated graph measures. A potential explanation for the discrepant findings could be that van den Heuvel et al. (2009) reported their findings for nodal connectivity at a declaredly exploratory statistical threshold. Ultimately, these are two studies suggesting different localizations for intelligence-related differences in nodal measures of brain network efficiency. Future research has to show how the discrepancy in findings can be reconciled.

The three brain regions we identified as related to intelligence on the basis of their connectivity profiles – AI, dACC, and TPJ – show substantial overlap with, but also some divergence from existing theoretical models of the neural bases of human intelligence. AI and dACC are core components of the so-called multiple demand (MD) system, an extended network of brain regions commonly activated during cognitive demand that has been suggested as underlying intelligent performance (Duncan et al., 2010). Furthermore, there is substantial overlap with the parieto-frontal integration theory (P-FIT; Jung & Haier, 2007) at the level of the resolution at which P-FIT was defined, i.e., in terms of cytoarchitectonic areas of Brodmann (BA; cf. Jung & Haier, 2007; p. 150, Fig. 5 with threshold of 25% convergence across studies). The anterior cingulate cortex (BA 32) is explicitly mentioned in verbal as well as in visual summaries of the P-FIT. While the P-FIT does not explicitly list the anterior portion of the insula, the effect we observed in AI extends into fronto-opercular cortex and inferior frontal gyrus (BA 47) and thus overlaps with ventral prefrontal regions considered in P-FIT.

Our TPJ cluster is located in BAs 21 and 39, which nominally also establishes an overlap with the P-FIT. However, the location at the junction of temporal and parietal cortex seems to go beyond the regions considered in P-FIT – which focuses on sensory and association areas in temporal and parietal cortex proper. A similar picture emerges when we compare our current findings with the result of our own meta-analysis of neuroimaging studies on intelligence (Basten et al., 2015): Again, overlap in ACC is obvious. However, AI and TPJ were not identified as showing meta-analytic correlates of intelligence based on either studies of task-activation or gray matter correlates of intelligence. We thus conclude that our connectivity analysis (and some others; see discussion above) suggests correlates of intelligence in the connectivity pattern of functional brain networks that can be tracked down to brain regions not yet included in existing models of the brain bases of intelligence. This mainly concerns the junction of temporal and parietal cortex, and partly also the anterior portion of the insular cortex (cf. MD system versus P-FIT and the meta-analysis of Basten et al., 2015).

Beyond the node-specific differences in network topology, there was no association between intelligence and global brain network efficiency in our study. Thus, even though applying a very similar methodical approach to the same type of data (i.e., resting-state fMRI data), we could not replicate the previous finding that brain networks of more intelligent subjects were globally more efficient (van den Heuvel et al., 2009). This result applies to our analyses using the graph metric of global efficiency as well as to an alternative analysis in which we employed the conceptually similar metric of normalized characteristic path length (which was used by van den Heuvel et al., 2009). Importantly, our study is the first to quantify the empirical evidence for the lack of an association between intelligence and global efficiency using Bayesian statistics. As p-values tend to overestimate the evidence against the null hypothesis and crucially depend on sample size (Rouder & Morey, 2012), Bayesian statistics can provide valuable additional information on the presence or absence of an association between two variables. All Bayesian factors we calculated for an association between intelligence test scores and global measures of brain network organization efficiency in our sample yielded substantial evidence for the null hypothesis (Jeffreys, 1961). This suggests that there was no association between intelligence and global network efficiency in our sample.

Even though global network efficiency seems intuitively appealing as a plausible neural correlate of intelligence, results have so far been heterogeneous. Other studies investigating the association of psychometric intelligence and the global efficiency (or average path length) for fMRI resting state brain networks in healthy adults (i) confirmed the finding only for weak connections (Santareccchi et al., 2014), (ii) reported an association only for a specific sub-network of the brain (i.e., the default mode network; Song et al., 2009), or (iii) failed to replicate the association (Pamplona et al., 2015). This state of findings is similar to other fields of research applying graph theory to the study of individual differences in intrinsic network connectivity, such as aging, where it was also observed that nodal differences in network organization are not necessarily accompanied by global differences (Cao et al., 2014; Dennis et al., 2013; Wu et al., 2012). Here, we do not relate our findings to studies investigating intelligence-related differences in global efficiency for network analyses based on other measurement modalities such as EEG (e.g., Langer et al., 2012), MEG (e.g., Duan et al., 2014), or structural connectivity (e.g., Li et al., 2009; Pineda-Pardo et al., 2016), as it is not yet clear how graph characteristics relate across methods.

A straightforward account for the difference between findings for nodal and global measures of network efficiency (or any other graph measure) is that nodal differences may level out when integrated to a global measure by simple averaging. Generally, the theoretical justification of global graph metrics that result from averaging over all nodes of the network may be questionable when at the nodal level differences exist only in circumscribed sets of nodes and/or differ in the direction of their association with the individual differences variable. It seems more appropriate to restrict analyses to nodal metrics for all cases in which heterogeneity in nodal findings (e.g., positive versus negative associations with an individual differences variable) would not adequately be represented by a single integrated global measure. Moreover, we cannot ultimately rule out that our and other studies were underpowered to detect existing effects at the global level. Our sample size of \( N = 54 \), however, allowed us to detect effects of medium size, i.e., \( r = 0.35 \), at a level of \( p < 0.05 \) with a power of 80% (R package pwr, Champely et al., 2013), and other studies in the field worked with similar or smaller samples sizes (e.g., Song et al., 2009: \( N = 59 \); van den Heuvel et al., 2009: \( N = 19 \); Pamplona et al., 2015: \( N = 29 \); Santareccchi et al., 2014: \( N = 98 \)).

Finally, it is a highly interesting, yet currently unsolved question how individual differences in the efficiency of network organization as inferred from the study of intrinsic connectivity during rest relate to
differences in neural efficiency as inferred from task-related increases in brain activation during cognitive demand (e.g., Basten et al., 2013; Gray et al., 2003; see also Neubauer & Fink, 2009, for review). To our knowledge, there exists no study to date that would provide an empirical answer to this question. It can be speculated that brain regions with high nodal efficiency, characterized by relatively short paths to the rest of the network, will get by with less neural effort in terms of activation, as information transfer via shorter paths is assumed to consume less energy and time (Bullmore & Sporns, 2012). In our own study of intelligence-related differences in the activation of task positive (TPN) vs. task negative (TNN) functional brain networks in a different sample (Basten et al., 2013), we observed a positive association between intelligence and task-related BOLD signals in the TPN. Importantly, the TPN includes the regions of the salience network, in addition to the so-called central executive network (Seeley et al., 2007) – yet in a previously unpublished analysis considering the salience sub-network (Al and dACC) separately, the association between intelligence and task-related changes in brain activation was not significant (p = 0.11). We thus conclude that it remains an open question if and how (intelligence-related) individual differences in the organization of intrinsic, i.e., task-independent, functional brain networks are reflected in differences in task-induced brain activation. We consider this question as highly relevant for the integration of results from different research strands that could substantially enhance our understanding of the neural basis of human intelligence. Future studies should, accordingly, specifically aim at relating intelligence-related differences in intrinsic connectivity and task-related activation in data collected for the same samples.

4.5. Conclusion

The current study contributes to the investigation of the neural basis of intelligence from a connectionist perspective and reveals intelligence-related differences in specific topological characteristics of functional brain networks. Our findings stress the importance of individual differences in intrinsic (i.e., task-independent) connectivity between three brain regions (i.e., Al, dACC, and TPJ) and the rest of the brain network, and suggest that the ease with which these brain regions can exchange information with other brain regions is important for intelligence. Previous models of the neural basis of intelligence (Basten et al., 2015; Duncan, 2010; Jung & Haier, 2007) highlighted the importance of lateral frontal, medial frontal, and parietal brain regions for intelligence, on the basis of studies investigating brain activity during cognitive demands (e.g., Basten et al., 2013; Gray et al., 2003) and structural characteristics of gray and white matter (e.g., Haier et al., 2004; Penke et al., 2012). Our findings together with other studies on intelligence and intrinsic brain connectivity (e.g., Cole et al., 2012, 2014; Smith et al., 2015; van den Heuvel et al., 2009) extend these conclusions by demonstrating that intrinsic functional connectivity properties of the brain’s network organization may play a key role in understanding the neural underpinnings of intelligence. Specifically, our analyses imply that with respect to network topology, brain regions that were previously related to salience processing (Al and dACC) and the filtering of irrelevant information from further processing (TPJ), play a crucial role in explaining individual differences in intelligence. We speculate that the observed differences in network integration of these three regions may enable intelligent people to more quickly detect, evaluate, and mark salient new stimuli for further processing and to protect ongoing cognitive processing from interference of irrelevant information, ultimately contributing to higher cognitive performance and high intelligence.

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References
