Supplemental Material of

Efficiency of functional brain networks and intellectual performance

Authors

M.P. van den Heuvel [1], C.J. Stam [2], R.S. Kahn [1], H.E. Hulshoff Pol [1]

Affiliations

1. Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Department of psychiatry, Utrecht, The Netherlands

2. VU University Medical Center, Department of Clinical Neurophysiology, Amsterdam, The Netherlands

Supplemental Materials and Methods

Data acquisition

Resting state fMRI. Our brain is a complex dynamic system in which information is continuously processed and transferred between brain regions with highly correlated functional dynamics (Sporns et al., 2000; Sporns et al., 2004). These coherent dynamics are believed to reflect the existence of functional connections between these regions. Functional connectivity is defined as the temporal coherency between neuronal brain signals of anatomically separated brain regions (Aertsen et al., 1989; Friston et al., 1993) and is widely investigated by measuring the correlation between resting-state Blood Oxygen Level Dependent functional Magnetic Resonance Imaging time-series (Biswal et al., 1995; Cordes et al., 2000; Lowe et al., 2000; Beckmann et al., 2005; Achard et al., 2006; Damoiseaux et al., 2006; Van den Heuvel et al., 2008a).

During rest, brain regions produce a vast amount of spontaneous neuronal activity (Raichle et al., 2001; Raichle and Snyder, 2007) which can be measured with these resting-state BOLD fMRI recordings (Biswal et al., 1995; Salvador et al., 2005b; Damoiseaux et al., 2006). Of special interest

are the low frequency oscillations (~0.01 - 0.1Hz) of the fMRI time-series measured during rest. These slow moving temporal patterns show a high level of correlation between multiple anatomically separated brain regions (Biswal et al., 1995; Cordes et al., 2000; Lowe et al., 2000), especially between brain regions that are involved in the same function, for example primary motor, visual and auditory regions. The exact neurophysiological basis of these low frequency correlations is not yet fully understood. There is an ongoing debate about whether resting-state BOLD correlations predominantly originate from respiratory and cardiac oscillations (Wise et al., 2004; Shmueli et al., 2007) or whether these correlating time-series are related to true synchronization of the neuronal activation patterns of brain regions, observed through a hemodynamic response function (Gusnard et al., 2001; Greicius et al., 2003; Buckner and Vincent, 2007). This latter view is supported by recent observations that report that resting state BOLD time-series show a high correlation with concurrent fluctuations in neuronal spiking, suggesting a direct link between resting-state time-lag BOLD signals and intrinsic neuronal activity (Nir et al., 2008; Shmuel and Leopold, 2008). Furthermore, as mentioned, most of these coherent BOLD patterns have been found between regions of known functional networks, for example the motor and visual network and known high order cognitive networks (Biswal et al., 1995; Biswal et al., 1997; Cordes et al., 2001; Beckmann et al., 2005; Salvador et al., 2005a ; Damoiseaux et al., 2006; Van den Heuvel et al., 2008a). In addition, resting state BOLD time-series of cortical regions have been reported to be mainly dominated by lower frequencies (<0.1 Hz), with only a minimal contribution of higher cardiac and respiratory oscillations (Cordes et al., 2000; Cordes et al., 2001). In this context, it is believed that the observed coherence between resting-state BOLD fluctuations of anatomically separate regions do, at least in part, originate from synchronized intrinsic neuronal activity of these regions and reflect a high level of functional connectivity between these brain areas (Biswal et al., 1995; Gusnard et al., 2001; Fox and Raichle, 2007; Greicius et al., 2008).

Subjects. 19 healthy subjects without a psychiatric history (age mean/std : 29/7.8 ; gender: 14 male, 5 female) participated in this study after providing written informed consent as approved by the medial ethics committee for research in humans (METC) of the University Medical Center Utrecht, The Netherlands.

Intelligence scores. The Intelligence Quotient (IQ) of the participants was measured with the Dutch version of the Wechsler Adult Intelligence Scale III (WAIS-III) test. The WAIS test gives a standardized full scale IQ score based on a number of subtests that assess the level of verbal and non-verbal knowledge and reasoning of the participants. Each sub-test of the WAIS provided a raw score and from these raw-scores the Verbal Comprehension Index (VCI), Working Memory Index (WMI), Perceptual Organization Index (POI) and Processing Speed Index (PSI) index scores, Verbal IQ (VIQ), Performance IQ (PIQ) and Full-Scale IQ (FIQ) were derived. Table 1 and 2 of the main text describe the index-scores, VIQ, PIQ and FIQ scores (Table 1) together with the correlations between the index-scores and IQ-scores (Table 2).

Resting state paradigm. During the resting-state fMRI scans, the scanner room was darkened. Subjects were instructed to relax with their eyes closed and to think of nothing in particular without falling asleep, which was verified directly after the 8 minute scanning session. None of the 19 included subjects reported to have fallen asleep or to be close to falling asleep.

MR acquisition. Resting-state functional Magnetic Resonance Imaging time-series were acquired on a 3 Tesla Phillips Achieva Medical scanner (Philips Medical Systems, Best, The Netherlands) at the University Medical Center Utrecht, The Netherlands. Resting-state Blood Oxygenation Level Dependent (BOLD) signals were recorded during a period of 8 minutes using a fast fMRI sequence (3D PRESTO (Golay et al., 2000; Van den Heuvel et al., 2008a), acquisition parameters: TR/TE 22ms/32ms using shifted echo, flipangle of 9 degrees; SENSE p/s reduction 2/2; a dynamic

scantime of 0.5 sec, 1000 timeframes, total duration 8 minutes; FOV 256x256 mm, voxelsize 4x4x4mm, 32 slices covering whole brain). A high temporal acquisition of 2 Hz was used to minimize aliasing effects of high frequent respiratory and cardiac oscillations (respectively ~0.3 Hz and ~0.9-1.0 Hz) into the low resting-state frequencies of interest (0.01 - 0.1 Hz). PRESTO fMRI scans have a low anatomical contrast in comparison with a T1 image. Therefore, directly after the functional resting-state time-series an additional PRESTO scan with similar scanning parameters, but with a higher anatomical contrast was acquired by increasing the flipangle to 25 degrees. This additional high contrast PRESTO scan was made to improve the co-registration of the functional time-series with the T1 image. Directly after the resting-state time-series, a T1 weighted image was acquired for anatomical reference (3D FFE, acquisition parameters: TR/TE 10ms/4.6ms, SENSE p/s reduction 1.7/1.4; FOV 256x256 mm, voxelsize 0.75x0.75x0.8mm, 200 slices).

Preprocessing. All fMRI preprocessing steps were done with the SPM2 software package (http://www.fil.ion.ucl.ac.uk). First, small head motion effects during the resting experiment were corrected by realigning the fMRI time-series to the last functional scan. Registration to the last functional scan was used to maximize the spatial overlap of the fMRI time-series with the high anatomical contrast functional scan. Second, both the functional time-series and anatomical T1 scan were coregistered to the high contrast functional scan, to provide spatial alignment between the resting-state time-series and the anatomical image. Third, an automatic cortical segmentation procedure was performed on the T1 image to select all cortical and sub-cortical gray matter voxels of the brain. Cortical segmentation was performed with the freely available Freesurfer software package (http://surfer.nmr.mgh.harvard.edu/). Cortical segmentation maps were resliced to a 4x4x4mm resolution to overlap with the resting-state time-series. Fourth, the individual functional time-series and matching cortical segmentation map were normalized to standard MNI 305 space, using the parameters of the normalization of the T1 image to the MNI 305 T1 brain (Collins et al., 1994). Fifth, the low resting-state frequencies of interest were selected by filtering the resting-state

time-series with a finite impulse response (FIR) filter with a bandwidth of 0.01 - 0.1 Hz. The

relatively high sampling-rate of the used resting-state fMRI protocol (i.e. 2 Hz) enabled the proper

sampling of cardiac and respiratory signals. As a result, band-pass filtering minimized the influence

of low frequency MR scanner noise (e.g. slow scanner drifts, typical < 0.01 Hz) and high frequent

cardiac or respiratory oscillations up to 1 Hz (> 0.1 - 1 Hz) (Cordes et al., 2001).

Graph analysis

The organization of the functional connections of the brain network was examined using a graph

theoretical approach, as validated earlier (Van den Heuvel et al., 2008b). All steps of the graph

analysis are illustrated in **Supplemental Figure 1** and described in detail below. In summary, the

graph analysis involved the construction of a functional connected brain network *G* for each

individual dataset, consisting of all gray matter sub-cortical and cortical voxels and connections

between all functionally linked voxels. From these functional networks, key graph characteristics

were computed that describe the architecture of the network, including the *clustering-coefficient C*,

providing information about the level of *local* connectedness of the network and characteristic *path

length L,* which provides information about the level of *global* communication efficiency of a

network (Watts and Strogatz, 1998; Latora and Marchiori, 2001). *C* and *L* are typically compared to

the clustering-coefficient C^{random} and characteristic path length L^{random} of comparable random

organized networks, with the same number of connections and the same distribution of connections

as *G.* For each *G,* up to 20 comparable random networks were formed and the overall C^{random} and

L^{random} were defined as the average *clustering-coefficient* and characteristic *path length* of these

random organized networks. The ratios *gamma*, defined as *C* / C^{random} and *lambda*, defined as *L* /

L^{random} were computed and averaged over the group of subjects to verify a small-world

organization of functional brain networks (Watts and Strogatz, 1998). Next, to examine the

association between the organization of the brain network and inter-subject differences in

intelligence the *gamma* and *lambda* scores of the individual brain networks were correlated with the

individual IQ scores of the participants. Finally, to point out which nodes in the brain network showed the strongest relationship between network organization and intelligence, voxel-wise IQ correlation maps were computed, pointing out those nodes (i.e. voxels) of the functional brain network that showed the strongest correlation with IQ scores over the group of subjects. A detailed step-by-step description of the graph analysis is given below and is illustrated in **Supplemental Figure 1**.

Graph construction. For each individual functional dataset, a connectivity graph $G = (V,E)$ was formed, with V the collection of N grey matter voxels and E the collection of edges (also called connections) between the voxels. The number of points N of the constructed functional brain graph varied around 9500 across the groups of subjects. The zero-lag temporal correlations between all possible voxel-pairs (i.e. ~9500x9500) was computed, reflecting the level of inter-voxel functional connectivity (**Supplemental Figure 1a**). Voxel-wise correlations were stored as a correlation matrix M with cell $M(i,j)$ holding the zero-lag temporal correlation between the fMRI time-series of voxel i and voxel j (**Supplemental Figure 1b**). A binary valued matrix B was formed by thresholding M by a threshold T, putting all cells of M to 1 that exceeded the threshold and all cells to 0 that did not exceed this threshold (**Supplemental Figure 1c**). Thresholding M directly resulted in the formation of an unweighted unidirectional graph G, with V reflecting all sub-cortical and cortical points (i.e. voxels) and E the functional connections between the voxels. In this study, T was varied for multiple settings between 0.05 and 0.5, with steps of 0.05. Increasing T too much would eventually lead to disconnecting a number of voxels from G and this could have an effect on the computed graph characteristics (i.e. clustering-coefficient C and characteristic path length L). Therefore, the maximum T was set to 0.5, to minimize the number of disconnecting nodes in G and to ensure that the largest interconnected cluster included more than 95% of the number of nodes in G over the group of subjects (Van den Heuvel et al., 2008b).

Network characteristics. Next, the clustering-coefficient *C* and characteristic path length *L* of *G*
were computed (**Supplemental Figure 1g**) to examine the overall connectivity architecture of the
functional brain network.

The clustering-coefficient C_i of node *i* expresses the level of connectedness of the direct
neighbors of node *i*. C_i gives information on how strong node *i* and its direct neighbors form a
clustered sub-network within the total network. C_i of voxel *i* was defined as (Watts and Strogatz,
1998; Sporns et al., 2004):

$$C_i = \frac{\#\, edges\ in G_i}{\frac{1}{2}k_i(k_i-1)}$$

$$(1)$$

with G_i the sub-graph of neighbors of voxel *i* and k_i the number of edges of voxel *i*.

In words, C_i is defined as the ratio of the number of edges between its neighbors of voxel *i* and the
total number of possible edges between the neighbors. In turn, the overall clustering-coefficient *C*
of *G* is defined as the average of C_i over all voxels *i* in *G* (Watts and Strogatz, 1998; Sporns et al.,
2004) :

$$C = \frac{1}{N}\sum_{i \in G} C_i$$

$$(2)$$

The definition of C_i (formula 1) is undefined when the number of neighbors of node *i* is zero or
one, which happens when node *i* is disconnected from the graph or when node *i* is a so-called *leaf*
node (i.e. when node *i* has only one connection). In that case C_i was defined as 0. However, as
mentioned by Kaiser the contributing effect of disconnected nodes and leaf nodes on *C* is likely to
increase when the to be examined network becomes more and more sparse, biasing *C* to a mixture
of neighbourhood clustering and edge density (Kaiser, 2008). In our study, the effect of the
disconnected nodes and leaf nodes on *C* was believed to be minimal as the number of disconnected

nodes was kept to a absolute minimum by using low cut-off thresholds T. To verify this minimal effect, an alternative definition of C was used in which all nodes with less than two connections (i.e. disconnected nodes and leaf nodes) were removed, before computing C (Kaiser, 2008). As expected due to the low number of disconnected nodes and leaf nodes in G (due to the relative low T), this did not change our findings. This overlaps with our previous findings on the influence of disconnected nodes in functional brain networks with high T (Van den Heuvel et al., 2008b).

Furthermore, the characteristic path length L of a graph is defined as the averaged minimal distance (in number of edges) between each possible node pair in the graph. The average characteristic path length L expresses how well the graph is connected globally. Formally, L is given by:

$$L = \frac{1}{N(N-1)} \sum_{i \neq j, i, j \in G} d(i,j)$$

(3)

with distance $d(i,j)$ the minimal number of edges that have to be crossed to travel from node i to node j, for i and j in G and N the number of nodes in G. Before computing L, possible disconnected nodes were removed from G. Due to the low number of disconnected nodes in G this was believed to have only a very minimal effect on the computation of L (Van den Heuvel et al., 2008b).

Taken together, the clustering-coefficient C and characteristic path length L of a graph express key characteristics of the examined network. C and L indicate whether a network is connected in a *regular*, *small-world* or *random* fashion (Watts and Strogatz, 1998) (**Supplemental Figure 2**). *Regular* networks show a high level of clustering C and a high characteristic path length L (**Supplemental Figure 2a**). This in contrast to *random* networks, which typically show a low level of clustering and a short average characteristic path length, reflected by low C and low L (**Supplemental Figure 2c**). The high C of a regular network indicates that functional neighbors within the network are high connected, but the high L indicates that it takes a high number of steps to travel to more distant nodes in the network. In contrast, random networks have a more global character, indicated by the low path length L and the low C. The low C indicates a limited

formation of neighborhood connectedness and the low L indicates that on average the number of edges that have to be crossed to another point in the graph is relatively low. Regular and random networks are each the end points of a network spectrum. Defining a probability p that a connection from a fully regular network is randomly rewired will shift a network from a regular organization to a more random organization with increasing p (Watts and Strogatz, 1998). Increasing the rewiring probability p a network becomes more and more randomly organized (**Supplemental Figure 2**). So-called *small-world networks* have an intermediate organization, showing a high level formation of sub-graphs in the network, but still with an average short characteristic path length of around the same length as the characteristic path length of random organized networks, ensuring an optimal level of global connectivity (Watts and Strogatz, 1998; Latora and Marchiori, 2001). As such, *small-world* networks typically show a clustering-coefficient that is much higher than that of a random network, but still with a characteristic path length that is around the same order of that of a random network. More formally, a network has a small-world organization when $C \gg C^{random}$ and $L \sim L^{random}$ (Watts and Strogatz, 1998), with C^{random} and L^{random} defined as the clustering-coefficient and characteristic path length of a comparable random network G^{random} of similar size (Sporns et al., 2004; Sporns, 2006) and connectivity distribution (Sporns and Zwi, 2004; Stam and Reijneveld, 2007).

The local and global connectivity properties of a network are typically expressed by the ratio *gamma* γ between C and C^{random} and *lambda* λ between L and L^{random} (**Supplemental Figure 1h**). Small-world networks have a *gamma* of >1 and *lambda* of ~1 (Sporns and Zwi, 2004; Stam and Reijneveld, 2007). γ and λ are formally given by:

$$\gamma = \frac{C}{C^{random}}$$

(4)

$$\lambda = \frac{L}{L^{random}}$$

(5)

Besides the graph characteristics *C*, *L, gamma* and *lambda* also the average number of connections *k* of each *G* was examined as an indication of the overall level of connectivity of the individual functional brain network (Van den Heuvel et al., 2008b).

Formation of comparable random networks. For normalization of *C* and *L*, for each thresholded *G* a number of *h* comparable random graphs G_h^{random} were formed, by randomizing the binary connectivity matrix *B* (**Supplemental Figure 1e**). It has been stated that for a correct statistical comparison of two networks the connectivity distribution of the two networks have to be similar (Sporns and Zwi, 2004). However, theoretical random networks have a Poisson shaped degree distribution and this is likely not to be the case for high spatial voxel-based functional brain networks as these networks have been suggested to have a scale-free organization, characterized by degree distribution that follows a power-law function (Eguiluz et al., 2005; Van den Heuvel et al., 2008b). Therefore, the formation of each random graph G_h^{random} was based on the original binary connectivity matrix *B*, using the individual connectivity matrix as a starting point for the randomization process. For each node *i* in the graph all connections of node *i* were randomly reconnected to random nodes in the network and made bidirectional, keeping the total number of connections of node *i* similar to the number of connections in the binary functional connectivity matrix *B* (Van den Heuvel et al., 2008b). This resulted in a random graph G_h^{random} with a total degree and degree distribution comparable to that of the individual functional connectivity graph for each of the to be examined *B* (**Supplemental Figure 1f**).

For each of the resulting G_h^{random} the clustering-coefficient C_h^{random} and characteristic path length L_h^{random} were computed (**Supplemental Figure 1g**). Next, C^{random} and L^{random} were computed as the average of the computed graph characteristics of the h random graphs:

$$C^{random} = \frac{1}{h}\sum C_h^{random}$$

(6)

$$L^{random} = \frac{1}{h}\sum L_h^{random}$$

(7)

The number of random networks h was set to 20 for $0.40 \leqq T \leqq 0.50$. For computational reasons, h was set to 10 for $0.20 \leqq T < 0.40$ and to 5 for $T < 0.20$, as for lower T the connectivity matrices and random matrices become less sparse and therefore the computational time increases to compute the graph characteristics. Across all T this procedure resulted in the evaluation of 110 comparable random graphs per individual connectivity dataset. In total, across all 19 subjects and across all settings of T this resulted in the evaluation of 2280 networks (= 19 x (10 connectivity graphs + 110 random graphs)) of size NxN, with N all the number of all sub-cortical and cortical voxels of ~9500.

Group averaged graph characteristics. For each setting of T *(ranging from 0.05 to 0.5, steps of 0.05)*, the performed graph analysis **(Supplemental Figure 1a-h)** resulted in clustering-coefficient *C,* characteristic path length *L,* comparable C^{random}, L^{random} and *gamma* and *lambda* values for each of the individual functional connectivity brain networks *G.* To examine an overall possible small-world organization of the functional brain, the graph characteristics were averaged over the group of 19 subjects.

Association between graph characteristics and IQ. To examine a possible association between the overall architecture of the functional brain network and intelligence, individual *gamma* and *lambda* values were correlated with individual IQ scores (**Supplemental Figure 1i**). *Gamma* and *lambda* are directly related to the level of *global* and *local* communication efficiency of a network (Latora and Marchiori, 2001). A high *gamma* reflects a high level of *local* connectedness in the network, ensuring a high level of local communication efficiency. In addition, a low *lambda* reflects an average short characteristic path length between any two nodes in the network, expressing a high level of global communication efficiency within the network.

For the small-world organized networks *G* of $0.40 \leqq T \leqq 0.50$, the association between the individual IQ scores and the computed graph characteristics *gamma* and *lambda* was computed. Correlations between gamma/lambda values and IQ scores were corrected for possible age effects by regressing out age out of the *gamma* and *lambda* scores.

Correlation coefficient maps. To point out which regions in the functional brain network showed the strongest association between *path length* and IQ, an exploratory post-hoc analysis was performed, in which voxel-wise correlation-coefficient maps for the nodes in *G* of $T = 0.45$ were computed (**Supplemental Figure 1k**). This was done in a 3-step procedure. *Step 1.* For each individual dataset, for each node *i* in the individual functional brain network *G*, voxel *i* (i.e node i) was flagged with its *normalized path length* . This resulted in an individual spatial *normalized path length* map. Voxel-wise path length values were expressed as individual *normalized path length* values, to correct for mean effects on the individual path length scores. The *normalized path length* of node *i* in the network was computed as:

$$normalized\_path\_length_i = \frac{L_i}{L^{random}}$$

(8)

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In this way, the *normalized path length* of node *i* was computed in a similar manner as the computation of overall *lambda*. *Step 2.* To increase cross-subject overlap between the individual cortical segmentation maps, individual *Lmaps* were dilated, by flagging voxel *j* with the mean *normalized path length* of voxels directly touching voxel *j*. *Step 3.* For all voxels that overlapped the group of subjects, the *normalized path length* of each node *i* in the functional brain network was correlated with individual IQ scores. An exploratory threshold of $p < 0.05$ [uncorrected for multiple comparisons] was used to examine which regions in the brain showed a significant correlation between normalized path length and IQ. To minimize the number of false positives, only clusters that consisted of 8 or more spatially adjacent voxels of $p < 0.05$ were considered as significant. To examine the effect size of the regions in the brain network that showed the strongest relationship between normalized path length and IQ, a correlation coefficient *rmap* was formed by flagging all significant nodes with their matching correlation coefficient *r*-values. Figure 3 of the main text shows the group correlation-coefficient *rmap* of $T = 0.45$.

Supplemental results

Characteristic path length and clustering-coefficient. The group averaged L, L^{random}, C, C^{random}, *lambda* and *gamma* are shown in Figure 1 of the main text and clearly indicate a small-world organization of functional brain networks for $T \geq 0.3$. The characteristic path length L was found not to be different from L^{random} (panel a) and for $T \geq 0.3$ the clustering-coefficient C turned out to be $>> C^{random}$ and for $T \leq 0.5$ (panel b) [two-sample t-test, df $= 36$, all $p < \alpha$ of 0.01, Bonferroni corrected for multiple comparisons of T]. This was reflected by *lambda* ~ 1 $T \leq 0.5$ (panel c) and by *gamma* > 1 for $T \geq 0.3$ [one-sample t-test, df $=18$, $p < 0.01$, Bonferroni corrected] (panel d). These results clearly suggest a small-world organization of the functional human brain, supporting the findings of recent studies showing a small-world organization of the brain network on both a regional (Sporns and Zwi, 2004; Stam, 2004; Achard et al., 2006; Achard and Bullmore, 2007; Sporns et al., 2007) and a voxel scale (Eguiluz et al., 2005; Van den Heuvel et al., 2008b).

Association of graph characteristics and IQ. To examine the relationship between the connectivity architecture of the brain network and inter-subject variation in intelligence, the individual graph characteristic *lambda* and *gamma* scores were correlated with the individual IQ scores for *G* within the small-world range of $0.3 \leqq T \leqq 0.5$. Interestingly, a negative association was found between *lambda* and IQ, suggesting a positive relationship between the global level of connectivity in the brain network and intelligence [linear regression, df=18; $T = 0.45$, r = -0.54, p = 0.010 (Figure 2a); $T = 0.5$, r = -0.57, p = 0.017 (Figure 2b), which is significant considering a α of 0.01 after Bonferroni correction for multiple comparisons of *T*; regressions corrected for age]. No association was found between the level of local clustering and intelligence, as reflected by the lack of association between *gamma* and IQ scores. The associations between overall *lambda* and *gamma* and IQ are shown in Figure 2 of the main text and in **Supplemental Figure 3a-f**. Furthermore, to examine whether the individual overall number of connections *k* of the brain network were related to intelligence, *k* was correlated with the IQ scores in a similar manner as the *lambda* and *gamma* scores. No association was found between *k* and IQ scores (corrected for age, **Supplemental Figure 3h-j**). Considering the clear association between IQ and *lambda*, this suggests that intelligence is not related to the absolute number of connections of our brain network or how these connections are organized at the local level, but more related to how efficient the global connections of our brain are organized.

Correlation coefficient *rmaps* of normalized path length with *IQ*. For the small-world brain network *G* of $T = 0.45$ the individual computed *normalized path length* values of each node *i* (i.e. voxel *i*) of the network were correlated with the individual IQ scores seperately. The resulting correlation coefficient *rmap* is shown in Figure 3 of the main text. The strongest associations between IQ and normalized path length were found in medial frontal (BA 9/10, r = -0.75, p < 0.001 age corrected, yellow box), precuneus/posterior anterior cingulate cortex (BA 7, r = -0.55, p < 0.02

age corrected, orange box), and inferior parietal cortex (BA 39/40, r = -0.72, p < 0.001 age corrected, red box). These findings suggest that increased intelligence may be related to increased efficiency of frontal and parietal regions to access information of other sub-networks in the functional brain network. This suggest that inter-subject differences in intelligence may be related to how efficient high order frontal and parietal regions can integrate information of the other functional sub-networks within the brain network. Also regions overlapping left *superior temporal* [BA 22/40, r= -0.69, p = 0.014, df = 18] and left inferior frontal [BA 44/45, r = -0.68, p = 0.012, df = 18] showed a significant negative correlation between normalized path length and full scale IQ.

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Supplemental Figure Legends

Supplemental Figure 1. Graph analysis procedure. Figure illustrates the individual steps of the performed graph analysis. For each individual resting-state fMRI dataset a graph $G = (V,E)$ was formed with V the collection of sub-cortical and cortical voxels and E the collection of connections

between all voxels. First, the level of functional connectivity between voxel i and j was computed by correlating the resting-state BOLD time-series of voxel i and j (panel a) and placed in a connectivity matrix M (panel b). Next, M was threshold by threshold T, setting all connections to 1 that did reach T and all connections to 0 that did not reach T, transforming M into a binary valued connectivity matrix B (panel c). B directly reflected an unidirectional unweighted graph G, representing the functionally connected brain network (panel d). B was randomized resulting in B_h^{random} (panel e), which represented a randomized graph G_h^{random} (panel f). In total, h random graphs were formed, with h set to 20 for $0.40 \leqq T \leqq 0.5$, to 10 for $0.2 \leqq T < 0.40$ and to 5 for $T < 0.2$. Of all formed graphs G and G_h^{random}, the clustering coefficient and characteristic path length were computed (panel g). C^{random} and L^{random} were computed by averaging the clustering coefficients and path lengths of the h random graphs (panel g). Next, *gamma* (i.e. C/C^{random}) and *lambda* (i.e L/L^{random}) were computed (panel h) and associated with IQ (panel i) to examine the association between intelligence and the connectivity architecture of the functional brain network. Finally, to point out which brain regions showed the strongest association between normalized path length and IQ, the *normalized path length* of each node i of G was correlated with IQ over the group of subjects (panel j and k).

Supplemental Figure 2. Regular, small-world and random networks. Figure illustrates the relationships between *regular*, *small-world* and *random* networks (Watts and Strogatz, 1998). On the left side a regular network is shown, with vertices (blue/red points) and the connections (black lines) between the vertices. Regular networks have a high level of local clustering (i.e. high C) but an average long travel distance between all the nodes (i.e. a high characteristic path length L). The high C and high L indicate that a regular network has a high level of local organization. Let p be a probability that the connection between point i and point j is randomly rewired. When $p = 1$, all connections in the network are randomly rewired, resulting in a fully *random* network (network

shown at the right side). In contrast to regular networks, random networks have a more global

character, indicated by a low level of clustering (i.e. low C) and a low average travel distance (i.e.

low L). Interestingly, Watts and Strogatz (Watts and Strogatz, 1998) showed that for a low rewiring

probability *p,* a so-called *small-world* network is formed. Small-world networks have an

intermediate character, showing a high level of clustering (i.e. high *C*), but still with a short

characteristic path length (i.e. low *L*) similar to that of a random network (network shown in the

middle).

Supplemental Figure 3. Associations between characteristic path length *lambda*, clustering-coefficient *gamma* and number of connections *k* with IQ. For networks within the clear small-world range a significant correlation was found between the overall normalized **characteristic** path

length *lambda* and IQ [linear regression, df=18; $T = 0.45$, r = -0.54, p = 0.010 (panel b); $T = 0.5$, r = -0.57, p = 0.017 (panel c), corrected for age], suggesting a positive association between the level of

global communication efficiency within the functional brain network and intelligence. No

significant association was found between the level of local clustering *gamma* and IQ (panel d,e, f)

nor the number of connections *k* and IQ (Supplemental Figure 3 g,h,i). Taken the results of *lambda*,

gamma and *k* together, our findings suggest that intelligence is not directly related to the overall

number of connections of the brain network, or how these connections are organized at the local

level within the many functional sub-networks of our brain, but rather to how efficient information

is integrated globally between different regions of the brain. These results indicate that smarter

brains have a more direct and therefore more efficient access to information across the global brain

network.

Supplemental Figure 4. Association between characteristic path length lambda and IQ sub-scales. Upper panel shows for the cut-off threshold $T = 0.45$, the significant association between

full scale IQ and normalized characteristic path length *lambda* of the functional brain network

[linear regression, p = 0.010, df=18, corrected for age]. Middle panels show the association between Verbal IQ (VIQ) and Performance IQ (PIQ) and characteristic path length. PIQ was found to be significantly correlated with *lambda* [linear regression, p = 0.004, df=18, corrected for age]. Lower panels show the association between *lambda* and VCI, WMI, POI and PSI index scores. Lambda was found to be significantly negatively associated with POI [linear regression, p = 0.004, df = 18, corrected for age].

Supplemental Figure 5. Regional specific patterns between normalized path length of each node and IQ subscales. Figure shows the regional specific patterns between the path length of each node and the full scale IQ, Verbal IQ (VIQ), Performance IQ (PIQ), Verbal Comprehension Index (VCI), Working Memory Index (WMI), Perceptual Organization Index (POI) and Processing Speed Index (PSI), plotted on a 3D rendering of the average T1 image over the group of subjects. As expected from the association between IQ sub-scores and the overall characteristic path length *lambda* (Supplemental Figure 4) the strongest effects were found on PIQ and POI. Shown are correlation coefficient values of those voxels that had a significant negative association between IQ sub-scores and L [$T = 0.45$, p < 0.05 uncorrected for multiple comparisons, df=18, corrected for age].