Predicting human resting-state functional connectivity from structural connectivity

C. J. Honey, O. Sporns, L. Cammoun, X. Gigandet, J. P. Thiran, R. Meuli, and P. Hagmann

*Department of Psychological and Brain Sciences, Indiana University, Bloomington, IN 47405; \( ^{2} \)Signal Processing Laboratory 5, Ecole Polytechnique Fédérale de Lausanne, CH-1011 Lausanne, Switzerland; and *Department of Radiology, University Hospital Center and University of Lausanne, CH-1011 Lausanne, Switzerland

Edited by Marcus E. Raichle, Washington University, St. Louis, MO, and approved December 9, 2008 (received for review November 4, 2008)

In the cerebral cortex, the activity levels of neuronal populations are continuously fluctuating. When neuronal activity, as measured using functional MRI (fMRI), is temporally coherent across 2 populations, those populations are said to be functionally connected. Functional connectivity has previously been shown to correlate with structural (anatomical) connectivity patterns at an aggregate level. In the present study we investigate, with the aid of computational modeling, whether systems-level properties of functional networks—including their spatial statistics and their persistence across time—can be accounted for by properties of the underlying anatomical network. We measured resting state functional connectivity (using fMRI) and structural connectivity (using diffusion spectrum imaging tractography) in the same individuals at high resolution. Structural connectivity then provided the couplings for a model of macroscopic cortical dynamics. In both model and data, we observed (i) that strong functional connections commonly exist between regions without direct structural connection, rendering the inference of structural connectivity from functional connectivity impractical; (ii) that indirect connections and interregional distance accounted for some of the variance in functional connectivity that was unexplained by direct structural connectivity; and (iii) that resting-state functional connectivity exhibits variability within and across both scanning sessions and model runs. These empirical and modeling results demonstrate that although resting state functional connectivity is variable and is frequently present between regions without direct structural linkage, its strength, persistence, and spatial statistics are nevertheless constrained by the large-scale anatomical structure of the human cerebral cortex.

Computational model | diffusion MRI | neuroanatomy | cerebral cortex | brain networks

Populations of neurons in the mammalian cerebral cortex are continuously active during purposeful behavior, as well as during resting and sleep (1). Activity levels are modulated across time by the internal dynamics of each neuronal population and by signals received from cortical, subcortical, and peripheral elements of the nervous system. In the past decade, there has been intense interest in the patterns of correlated activity (“functional connectivity” (2)) in the human brain, because these patterns are believed to reflect the patterns of interaction between neuronal populations. A set of functionally connected regions is referred to as a “functional network.” Some functional networks are most commonly detected when participants are not performing any demanding task (in the resting state); others are observed in the context of task-focused behavior; and some networks persist across both behavioral states (3–6). A set of regions including posterior medial, anterior medial, and lateral parietal cortices comprise the default mode network (DMN) (7, 8), a functional network that is particularly robust across participants and cognitive states. It has been suggested that the more persistent functional networks may be involved with ongoing organizational processes in the brain (9, 10), and that disruptions in reliably present correlations are indicative, and potentially diagnostic, of neuropathology (11, 12).

Because the propensity for 2 areas to interact should vary in proportion to the density and efficacy of the projections connecting them, it is widely assumed that the repertoire of functional configurations assumed by the cerebral cortex is reflective of underlying anatomical linkage (13–18). However, the nature of this structure–function relationship is only beginning to be revealed. A general correspondence between functional connectivity (measured using functional MRI) and structural connectivity (measured using diffusion tractography) has previously been demonstrated in adjacent gyri in a single axial slice (19) and across the cortex in a 66-region parcellation (20). However, several questions remain. First, given that structural and functional connectivity are correlated, is it possible to infer structural connectivity from functional connectivity? Second, how does the structure–function relationship vary as we increase the distance between neuronal populations, and what are the contributions of indirect structural connections to functional connectivity? Third, to what extent does functional connectivity vary across time, and how can anatomical features distinguish persistent functional networks from those that are more transient? To address these questions, we compared structural and functional connectivity maps to one another. We then used the structural connectivity maps as couplings in a computational model of the large-scale dynamics of the cerebral cortex (21, 22), and from these dynamics we extracted simulated blood-oxygenation level dependent (BOLD) signals and functional connectivity, which could be quantitatively compared against empirical observations.

Structural connectivity was measured noninvasively in 5 individuals using diffusion spectrum imaging (DSI). Resting neural activity was then recorded in the same participants on two separate occasions using functional MRI (fMRI). Structural connectivity (SC) maps were constructed using streamline tractography and resting state functional connectivity (rsFC) maps were based on the Pearson correlations between the BOLD time series in all possible pairs of 998 cortical regions.

We hypothesized that, in both empirical and simulated data, more strongly connected region-pairs would exhibit stronger signal correlations, but that underlying SC would not be necessary for the observation of strong rsFC (19). We expected, further, that the SC-rsFC relationship would be mediated by distance and by indirect anatomical connections, although only partially, and that this effect would also be observed in our model. Finally we expected that rsFC would be most reliable where SC is strongest.

**Results**

We report results using 2 cortical parcellations, called the “low resolution” and the “high resolution.” In the low-resolution par-
cellation [supporting information (SI) Fig. S1A], 66 cortical regions (33 per hemisphere) of varying size are identified and matched across participants using an automated landmark-based algorithm (23). The high-resolution parcellation (Fig. S1B) is a refinement of the low-resolution surface partition, and is composed of 998 regions of interest (ROIs) of approximately equal area (~1.5 cm²) (L.C., X.G, J.P.T, K. Q Do, P. Maeder, R.M., P.H., unpublished data).

SC between two ROIs was derived from the number of fibers found by the tractography algorithm that link those ROIs. rsFC was calculated using pairwise Pearson’s correlation coefficients of BOLD time series obtained for each ROI by averaging across voxels within an ROI. Both SC and rsFC were calculated at the high resolution (998 ROIs) and then down-sampled by averaging across ROIs within each of the 66 predefined anatomical regions. For comparison with experimental data, we simulated a nonlinear neural mass model (21, 22) composed of 998 nodes, whose time evolution is governed by a set of differential equations. The strength of connections between nodes was determined by the empirical high-resolution SC, and simulated functional connectivity was then calculated from the simulated BOLD time series. See Methods for further details for each of these steps. All correlations we report are \( P \ll 1 \times 10^{-3} \).

**Overall Structure-Function Relationship**

**Low Resolution (66 Regions).** As described previously (20), after averaging low-resolution data across participants, the SC and rsFC strengths across all region-pairs were found to be highly significantly correlated \( (r = 0.66) \). When excluding ROI-pairs with absent or inconsistent structural connections (see Methods), this correlation strengthens to \( r = 0.82 \).

**High Resolution (998 ROIs).** Because of interparticipant variability in cortical morphology, averaging data at the high resolution did not produce as much of a de-noising effect as at the low resolution. For data averaged across participants (Fig. S2), the SC-rsFC correlation was \( r = 0.36 \) and increased to \( r = 0.53 \) when excluding absent or inconsistent structural connections. For individual participants, the SC-rsFC correlations ranged from \( r = 0.39 \) to 0.48 (Fig. L4).

**Computational Model (998 Nodes).** A comparison of empirical SC (from participant B) and simulated rsFC derived from a single run of the computational model is shown in Fig. 1B. For individual participants, the SC-rsFC correlations (single simulation) ranged from \( r = 0.32 \) to 0.44 when excluding absent connections. For data averaged across participants, the overall correlation between SC and simulated rsFC was \( r = 0.46 \) and increased to \( r = 0.52 \) when excluding absent or inconsistent structural connections. For high- and low-resolution correlations in individual participants and in the model, see Table S1.

**Inference of Structure from Function.** When structural connections are present, the relationship between the strength of SC and rsFC is robust in both the empirical data and computational model. When direct structural connectivity is absent, however, the rsFC values will still vary over a wide range (Fig. 1C and D), a finding consistent with ref. 19. Thus, although the presence of strong SC at an edge is predictive of strong rsFC, the reverse inference is less reliable. When inferring SC by thresholding rsFC, one obtains, for each given threshold value, some number of false-positives and some number of true-positives. The receiver-operating characteristic (ROC) curves in Fig. 1E show how the false-positive and true-positive rates vary as this threshold is adjusted. The area under the ROC curve is greater for the modeled data than the empirical data (0.95 versus 0.79). However, in both cases, thresholding of rsFC yields highly inaccurate prediction of SC. For example, in the empirical data, the threshold at which 80% of structural connections are correctly detected is one at which more than 40% of the unconnected region pairs are incorrectly detected (see Fig. 1E). Because structurally unconnected pairs are about 30 times as numerous as connected pairs within our high-resolution data, only \( \approx 6\% \) of inferred structural connections would be genuine at this threshold. This percentage is improved in the computational model, but still too low for practical inference. For the threshold at which 80% of structural connections are correctly detected, only \( \approx 28\% \) of the inferred SC would correspond to the true structural couplings that underlie the model dynamics.

**The Role of Distance.** On average, both structural connectivity (24, 25) and functional connectivity (26) between cortical regions decrease with the distance between those regions. This effect could result from a combination of factors, including (i) spatial autocorrelation of cortico-cortical connectivity, (ii) spatial autocorrelation of subcortico-cortical projections, (iii) activation spread along the surface of the cortex via local circuitry (27, 28), (iv) spatial blurring of the BOLD signal because of vascular drainage, and (v) MRI acquisition or data preprocessing artifacts (29).

Because most of the structural connectivity we observe is short-range (20), the structure-function relationship we report here could result artifactualy if both SC and rsFC are spatially autocorrelated, but for entirely unrelated reasons. To rule out this possibility we first
we consider only region pairs linked by a shortest path of 2 edges, of SC and inverse fiber distance at high resolution. The model, 29% of the variance in rsFC is explained by the combination structural connectivity is robustly related to the residuals of that relationship is weaker when we control for distance, it remains less subject to sampling variability in finite samples), or whether it stronger because it is more persistent (that is, because the underlying interaction is more stable). In either case, the effect is mediated by the strength of the anatomical connections between pairs.

**Reliability of rsFC.** As rsFC was acquired from each participant on two separate occasions (20- and 15-min scans), we were able to examine the reliability of rsFC. Reliability was operationalized as the correlation between 2 sets of rsFC values. For individual participants at the high resolution, reliability across scans ranged from \( r = 0.38 \) to \( r = 0.69 \), and reliability across two 10-min windows within the first scan ranged from \( r = 0.39 \) to \( r = 0.61 \). Unexpectedly low reliability is also observed in our computational model: across two consecutive 8-min windows within a single run, the simulated rsFC reliability ranged from \( r = 0.69 \) to \( r = 0.80 \) for individual maps at the high resolution.

In models and in data the observed reliability is lower than would be expected based on the sample size (at least 200 time points per window) and distributions of rsFC. Some of the empirical variability is likely because of acquisition and registration artifacts. However, we note that both empirical (30) and simulated rsFC time series exhibit very long-range temporal autocorrelations (or, equivalently, substantial power in very low frequencies), which effectively reduce the number of independent measurements captured within a time window. The values of rsFC measured in this study, as well as more generally in the field, may therefore not reflect a static underlying entity.

We also note that ROI pairs with SC exhibit significantly less variability in empirical rsFC (both across and within sessions) than do ROI pairs without SC (see SI Appendix, Fig. S4). In the present data we cannot distinguish whether rsFC between these ROIs is more persistent because it is stronger (and therefore, statistically, less subject to sampling variability in finite samples), or whether it is stronger because it is more persistent (that is, because the underlying interaction is more stable). In either case, the effect is mediated by the strength of the anatomical connections between pairs.

**SC and rsFC in the DMN.** On an area-by-area basis (Fig. 3B and Fig. S5), correlations between simulated and empirical rsFC were highest for many regions located in the posterior medial cortex, including the precuneus and posterior cingulate cortex, and the medial orbitofrontal cortex. Using previously published focal coordinates of the DMN (31) within the precuneus/posterior cingulate, the medial prefrontal cortex, and the lateral parietal cortex as seed points, we extracted a subset of ROIs most strongly correlated with rsFC values from \( i \) to \( j \) (i.e., \( \text{Indirect } SC_{ij} = \Sigma w_{ai}w_{bj} \) where \( w_{ai} \) is the direct SC between regions \( a \) and \( b \)). When we consider only region pairs linked by a shortest path of 2 edges, the Pearson correlation between the indirect-SC values and rsFC values was found to \( r = 0.29 \) for the average data at the high resolution (Fig. S3). This effect could not be accounted for by the Euclidean distance between region pairs, and was significant in each individual. These data suggest that indirect cortico–cortical linkage does induce some of the rsFC seen between regions lacking direct linkage.

Within the computational model, indirect connections were also observed to induce functional connectivity. When considering participant-averaged functional matrices, the correlation between simulated rsFC and empirical rsFC at direct links in the high-resolution network was at \( r = 0.46 \), and for indirectly connected nodes was at \( r = 0.37 \), indicating that the model was capturing network-level influences of SC on rsFC. In the low-resolution networks, the correlation between simulated and empirical rsFC increased to \( r = 0.70 \) for directly linked pairs (Fig. 3A), but dropped to \( r = 0.23 \) between indirectly linked edges.

**Indirect Connections and Network Effects.** We next sought to examine the potential role of multisynaptic anatomical structures in explaining the presence of rsFC between ROIs without direct SC. We assigned indirect connections to region-pairs that were not directly connected, but for which there existed at least one 2-edge path connecting them. For each such region pair \( ij \), the indirect structural connection had strength equal to the sum of all of the multiplicatively weighted SC paths from \( i \) to \( j \) (i.e., \( \text{Indirect } SC_{ij} = \Sigma w_{ai}w_{bj} \) where \( w_{ai} \) is the direct SC between regions \( a \) and \( b \)). When we consider only region pairs linked by a shortest path of 2 edges, confirmed that average rsFC is linearly related to the inverse of the fiber distance between regions \( r = 0.67 \) (Fig. 2A, low resolution). Then, after regressing rsFC on fiber distance, we checked that structural connectivity is robustly related to the residuals of that rsFC-fiber distance relationship \( r = 0.47 \) (Fig. 2B). This is equivalent to calculating a partial correlation between SC and rsFC, controlling for interregional fiber distance. Although the SC-rsFC relationship is weaker when we control for distance, it remains highly significant in all participants in both high- and low-resolution analyses. A bivariate linear regression using SC and (inverse) fiber distance to predict rsFC can explain 69% of the variance in participant-averaged rsFC at the low resolution, and 50% at the high resolution (see Table S1 and Fig. 2C). In the computational model, 29% of the variance in rsFC is explained by the combination of SC and inverse fiber distance at high resolution.

![Fig. 2. Role of distance. (A) Scatter plot of interregional rsFC against the inverse of the inter-regional fiber distance. (B) Scatter plot of residuals from (A) plotted against SC, at the low resolution. (C) Three-dimensional scatter plot, showing the relationship between SC, rsFC, and inverse fiber distance. The superimposed plane shows the fit of the bivariate linear model. Points above the plane of best-fit are light blue, points below are dark blue.](image)

**Confirmation of model.** In the potential role of multisynaptic anatomical structures in explaining the presence of rsFC between ROIs without direct SC, we assigned indirect connections to region-pairs that were not directly connected, but for which there existed at least one 2-edge path connecting them. For each such region pair \( ij \), the indirect structural connection had strength equal to the sum of all of the multiplicatively weighed SC paths from \( i \) to \( j \) (i.e., \( \text{Indirect } SC_{ij} = \Sigma w_{ai}w_{bj} \) where \( w_{ai} \) is the direct SC between regions \( a \) and \( b \)). When we consider only region pairs linked by a shortest path of 2 edges, the Pearson correlation between the indirect-SC values and rsFC values was found to \( r = 0.29 \) for the average data at the high resolution (Fig. S3). This effect could not be accounted for by the Euclidean distance between region pairs, and was significant in each individual. These data suggest that indirect cortico–cortical linkage does induce some of the rsFC seen between regions lacking direct linkage.

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longitudinal fasciculus. Consistent with the structural DSI data supplied to the model, the simulated rsFC seeded in the DMN reproduces empirical rsFC patterns along the medial axis, but largely fails to include lateral parietal cortex.

Discussion
Computational work has suggested that the underlying anatomical architecture of the cerebral cortex, including its cluster structure, shapes resting-state functional connectivity on multiple time scales (22, 33). Advances in diffusion imaging (34–36) now enable us to empirically examine this structure-function relationship in individual humans at high spatial resolution across the cerebral cortex, and to compare a variety of systems-level features of resting-state functional connectivity against the predictions of computational models informed by the underlying anatomical network.

Earlier work had shown that interhemispheric rsFC is diminished in cases of callosal agenesis (37), is related to callosal integrity in healthy individuals (38), and is almost entirely abolished acutely after callosotomy (39, 40). Structural and functional connectivity were also shown to be correlated in adjacent cortical regions in a single axial slice (19) and across 66 regions of the cerebral cortex (20). The robust SC-rsFC relationship we now report at high spatial resolution provides further evidence that functional connectivity is reflective, at least in part, of interactions between distant neuronal populations. However, because anatomically unconnected edges exhibit a wide range of rsFC values, one cannot simply infer SC by thresholding maps of rsFC. The difficulty of inferring SC from rsFC arises because (i) rsFC can result from mechanisms other than direct SC, and (ii) the base rate of direct SC between 2 randomly selected ROIs at the high resolution is very low. This difficulty is not simply a reflection of the practical limitations of fMRI, because inference was nearly as difficult within our computational model—in which SC provided the exact coupling matrix—as in empirical data.

Our second finding is that both SC and rsFC tend to decrease with interregional distance [consistent with previous studies of SC (24, 25) and rsFC (26)] and that a significant portion of the rsFC variance unexplained by SC alone is explained when distance information is combined with SC information in a bivariate model. Because interregional distance can be expected to influence sources...
of rsFC that are neuronal [e.g., the strength of SC, and activation spread across the cortical surface (27)] as well as nonneuronal [e.g., cardiac, vascular, acquisition and preprocessing artifacts (29)], we cannot definitively determine the origin of this distance-related residual variability in rsFC. We note, however, that although our computational model incorporates only topological (and not explicitly spatial) coupling, it exhibits a distance-associated decrease in rsFC that resembles the empirically observed fall-off. It is therefore not necessary to invoke mechanisms beyond the topology of cortico-cortical projections in explaining the distance effects.

None of the results we report in this study can be fully accounted for by interregional distance, but many are mediated by it, and the prevalence of nearest-neighbor (i.e., lattice-like) anatomical connectivity of the cerebral cortex is fundamental to its small-world (20, 36, 41–43) and hierarchical (44, 45) properties. Another factor contributing to the local clustering in rsFC networks is that indirect SC induces rsFC between region pairs that lack direct anatomical linkage. The relationship between indirect SC and rsFC is weaker than that between direct SC and rsFC, but is highly significant. Previous work (15) suggested that interhemispheric rsFC between the visual cortices most likely requires polysynaptic connectivity, and we note here that indirect cortico-cortical SC is an especially strong predictor of rsFC between the visual cortices of each hemisphere (see Fig. S3).

Our third finding is that rsFC exhibits unexpectedly low reliability within and across scanning sessions. This phenomenon is observed in each participant, as well as in our model, which is not susceptible to physiological or acquisition artifacts. In empirical data, we also observe that ROI pairs linked by SC exhibit more reliable rsFC, so that highly interconnected systems such as the DMN are nevertheless quite persistent. Within our data we cannot determine whether the shifts in rsFC reflect reconfiguration of neuronal interactions, are the result of low-frequency signal components of unknown origin, or result from a combination of the two (see SI Appendix). It is clear, however, that the proportion of the variance in rsFC that is explained by SC must be understood in light of the fact that fMRI rsFC is not static on the timescales used in this and other resting-state IMRI experiments. Studies, which compare IMRI FC against SC in modalities with higher sampling rates (16, 46, 47) remain crucial in determining the potential cognitive and behavioral significance of slow correlated fluctuations in the BOLD signal.

The rsFC of some highly connected regions was matched with high fidelity (see Fig. 3B), and this was found in particular within the posterior medial components of the default mode network (see Fig. 3 C and D). This is likely a consequence of the fact that there is a dense anatomical subnetwork linking DMN member regions (see SI Appendix) (48, 49). In future modeling work it may be fruitful to investigate how dynamical properties of individual nodes vary as a function of the node’s network embedding. Large-scale cortical models will also be improved when we have access to interregional physiological efficiencies, rather than fiber strengths, which only approximate the effective couplings between neuronal populations. It is also important that future models include the thalamus (50, 51) as well as the basal ganglia, which likely mediate diverse cortico-cortical interactions. By limiting ourselves in the present model to aggregate neural dynamics at each node, and by only including cortico-cortical couplings, we have been able to identify systems-level features of empirical rsFC that can be explained without recourse to subcortical input or specialized local circuitry.

The robust correspondence between SC and rsFC measured in independent imaging modalities provides a degree of mutual methodological validation for our SC and rsFC acquisition methods. Nevertheless, the potential for interregional variability in the reliability of these methods limits our ability to examine interregional differences in the strength of the structure-function relationship. While DSI tractography is often successful in resolving crossing fibers, the detection of relatively small fiber bundles running perpendicular to major fasciculi, as well as the reliable detection of very long fiber bundles, remains a technical challenge. Functional MRI is subject to susceptibility artifacts, especially in baso-temporal regions and near the frontal pole, and BOLD correlations can be contaminated by vascular, respiratory, and preprocessing artifacts (30). Preliminary computational analyses in the strength of the SC-rsFC relationship are presented in the SI Appendix, along with considerations of rsFC anti-correlations (see SI Appendix and Fig. S3B) and interparticipant differences (see SI Appendix and Table S2).

Structural connectivity of the adult mammalian brain is essentially constant from day to day, but functional connectivity can substantially reconfigure (41) within a few hundred milliseconds. In this study we confirm (19, 20, 22) at high resolution that the organizations of SC and of rsFC are strongly interrelated: structurally connected cortical regions exhibit stronger and more consistent rsFC than structurally unconnected regions. However, we also demonstrate, and capture in quantitative models, the fact that robust functional connectivity can be found between regions not linked by cortico-cortical projections, that spatial auto-correlation in functional connectivity likely results from underlying anatomy, and that functional networks continually reconfigure around the underlying anatomical skeleton. The timescales on which rsFC changes, and the relation of these changes to cognition, are important questions for future inquiry.

**Methods**

**Extraction and Topology of Structural Networks. DSI Acquisition.** The study protocol was reviewed and approved by the Institutional Review Board at the University of Lausanne. After obtaining written informed consent in accordance with institutional guidelines, 5 healthy right-handed male participants (age 29.4 ± 3.4 years) were scanned on an Achieva 3T Philips scanner. A high-resolution T1-weighted gradient echo sequence was acquired in a matrix of 512 × 512 × 264 voxels of isotropic 1-mm resolution.

Diffusion spectrum was performed using a diffusion-weighted single-shot echo planar imaging sequence (TR = 4,200 ms; TE = 89 ms) encoding 129 diffusion directions over a hemisphere. The maximum diffusion gradient intensity was 80 mT/m, the gradient duration δ was 32.5 ms, and the diffusion time Δ was 43.5 ms, yielding a maximal b-value of 9,000 s/mm². The acquisition matrix was 112 × 112, with an in-plane resolution of 2 × 2 mm. Thirty-six contiguous slices of 3-mm thickness were acquired in 2 blocks, resulting in an acquisition time of 18 min. The reconstruction of the data followed ref. 52. Following diffusion spectrum and T1-weighted MRI acquisitions, the segmented gray matter was partitioned into 66 anatomical regions according to anatomical landmarks using Freesurfer (surfer.nmr.mgh.harvard.edu) and 998 ROIs (see Fig. S1) as described in ref. 20. White matter tractography was performed with a custom streamline algorithm and finally, fiber connectivity was aggregated across all voxels within each of the predefined ROIs. Further details are available in refs. 20 and 34.

**Resampling.** The fiber strengths produced by the streamline tractography algorithm were exponentially distributed and spanned several orders of magnitude. Reasoning that interregional physiological efficacies would not span such a large range, we resampled the fiber strengths into a Gaussian distribution as follows: given N raw data values x₁, x₂, ..., xₙ, we generated N random samples r₁, r₂, ..., rₙ from a unit Gaussian distribution. We then replaced the smallest raw data value with the smallest randomly sampled value, the second-smallest raw data value with the second-smallest randomly sampled value, and so on until all raw data values were replaced. This produced a set of N resampled data values distributed according to a standard Gaussian, which we then rescaled to a mean of 0.5 and a standard deviation of 0.1 dimensionless units. The empirical results we report in this article remain strongly significant when SC is not resampled (Table S3).

**Fiber Distance and Euclidean Distance.** The fiber distance between two ROIs is calculated as the average length of all of the connecting fibers found using streamline tractography. The Euclidean distance between two ROIs is calculated using the mean Talairach coordinates of voxels comprising an ROI. We used the fiber distance where possible, as it more closely reflects the distance along the cortical surface. However, fiber distance is only known where SC is present, and so for analyses in which we compare the effects of SC absence and presence while controlling for distance (see SI Appendix) we used Euclidean distance. The results in Fig. 2 remain robust and significant when Euclidean distance is used.

**Extraction and Topology of Functional Networks. BOLD Acquisition.** The same 5 participants were scanned in eyes-closed resting state using a Siemens Trio 3T
ROI

ROIs were chosen to provide a roughly uniform tiling of the cerebral cortex (each according to an automated landmark-based registration algorithm (23). The 998 resampled onto the b0 image of the diffusion scan using rigid-body registration.

Signal Preprocessing and Correlations. Raw BOLD signals were registered and resampled onto the b0 image of the diffusion scan using rigid-body registration (SPM5, www.fil.ion.ucl.ac.uk/spm). Following slice-time correction BOLD time series were then piecewise-linearly detrended (SPM5, www.fil.ion.ucl.ac.uk/spm). Following slice-time correction BOLD time series were then piecewise-linearly detrended (every 50 s) and mean cortical, ventricular, and white matter signals were regressed from each time series. The results report are essentially unchanged if we regress out only the white matter and ventricular signals, and not the global mean. Finally, Pearson correlations were calculated between all ROI-pairs. Although the data and figures shown in this article are based on the raw correlation maps, the results are essentially unchanged when the 998-ROI correlation maps are Fisher z-transformed and normalized to zero-mean and unit variance within each participant (Table S4).

High- and Low-Resolution Matrices. The 66 anatomical regions were defined according to an automated landmark-based registration algorithm (23). The 998 ROIs were chosen to provide a roughly uniform tiling of the cerebral cortex (each ROI = 1.5 cm²) so that their borders aligned with those of the 66 anatomical regions. BOLD and DSI-fiber counts were captured at voxel resolution and then voxel-averaged to provide ROI-average values. BOLD correlations were calculated using the ROI time series and then down-sampled to the 66-region map by averaging across all ROIs with a region.

When averaging SC structural connections were deemed absent overall if they were absent in more than 3 participants (high resolution) or more than 1 participant (low resolution). The SC map for Participant A was an average of 2 separate DSI scans (20).

Computational Model. Neuronal population dynamics were simulated at 0.2 ms resolution for 16 min using a system of 988 neural masses with coupling strengths linearly proportional to the resampled fiber strengths at each edge. Each neural mass represents a population of densely interconnected excitatory and inhibitory neurons, in which the effects of both ligand- and voltage-gated membrane channels are accounted for. This model has previously been described in detail (21) and used in an anatomically informed model of large-scale functional connectivity in the macaque monkey (22). Further modeling details are provided in the SI Appendix.

Note Added in Proof. Another article has reported correlated rsFC and SC across the whole brain (53).

ACKNOWLEDGMENTS. We thank Van Wedeen for helpful comments. C.J.H. and O.S. were supported by the J. McDonnell Foundation. P.H., L.C., X.G., J.-P.T., and R.M. were supported by a grant for interdisciplinary biomedical research of the University of Lausanne, the Department of Radiology at University Hospital Geneva-Lausanne, the Centre Hospitalier Universitaire, and Ecole Polytechnique Federale de Lausanne, as well as grants from the foundations Leenaards and Louis-Jeantet and the Swiss National Science Foundation.
SI Appendix

Pre-Processing of BOLD Signal and the Origin of Anticorrelations

Pre-processing of BOLD data consists of three steps: first, averaging of BOLD signal across voxels within each of the 998 ROIs; second, linear detrending of the signal in consecutive 50-second time-windows for each ROI in turn; third, linear regression of mean global BOLD signal, mean ventricular BOLD signal and mean white matter BOLD signals from each ROI in turn. The residuals obtained from the linear regression are then entered into Pearson correlations for the calculation of rsFC.

We found that the piecewise linear detrending step and nuisance regression step strengthened the SC-rsFC relationships that we report here, and this suggests that they successfully removed noise in BOLD signal due to hemodynamic, cardiac and vascular effects. However, it is known [1] that the regression step can potentially induce artefacts in the rsFC maps.

Suppose we have two normally distributed random variables, A and B, which are statistically independent, and of which we have taken N samples. If we regress our samples An and Bn on some third data series Cn, then the residuals of this regression (Resid-A_n and Resid-B_n) will sometimes exhibit a statistical dependence. In particular, if C_n is the mean of A_n and B_n, then Resid-A_n and Resid-B_n will be tend to be anti-correlated. Intuitively, this is because whenever A_n is larger than B_n, then A_n will be larger than C_n (i.e. the mean), whereas B_n will be less than C_n. Thus, Resid-A_n will be positive when Resid-B_n is negative (and vice versa).

This simple example illustrates a phenomenon that can also occur in far more complicated systems such as the cerebral cortex. Some of the anti-correlations observed in fMRI rsFC maps are therefore likely to be artefactual, and are not representative of genuine anticorrelation in underlying neuronal activity. An additional complication is the fact that the strength of induced correlations and anti-correlations will vary depending on how strongly correlated each ROI is with the various regressors (mean global, ventricular and white-matter BOLD signals), and that this in turn will depend on whether that ROI is a member of a cluster of ROI whose BOLD signals vary coherently. There is evidence [2] that some regions – including those within the DMN – are more correlated with the global mean signal than others, and if this substantially affects the manner in which time series from these regions respond to data pre-processing, then pre-processing could produce a range of confounding influences in subsequent data analysis.

The effects we report in this paper cannot be explained as a result of global mean regression, however. We note that the structure-function relationship depicted in Figure 1A is only slightly weakened when we exclude from the calculation all edges with FC < 0 (Fig S3B). We recalculated rsFC without performing global mean regression step, instead regressing out only the mean signals from the white matter and the ventricles, which are
spatially distinct from the ROIs in the gray matter. Using this alternate pre-processing step, we continued to observe anticorrelations in the data and as well as a robust SC-rsFC relationship.

The general pattern of our results (e.g. Fig. 1B) is that stronger SC produces stronger rsFC, and the simplest interpretation of the data is that long-range interactions tend to facilitate correlation rather than anti-correlation. Furthermore, because most anti-correlations are observed between region pairs for which SC is absent (Fig. 1D), we expect that most anti-correlations in rsFC do not reflect inhibition mediated by direct cortico-cortical projections. However, when we examine region pairs that exhibit strong anti-correlation but which do have SC, we observe that one member of the region pair is usually located within the Default Mode Network (DMN). One interpretation of this finding is that the Default Mode Network does engage in long range inhibitory interactions. Another interpretation is that regions in the Default Mode Network are particularly susceptible to the artefacts induced by the regression of global BOLD signal. Further work is necessary to settle this important issue.

**Inter-Participant Differences in SC and rsFC**

In order to test whether individual differences in SC are associated with individual differences in rsFC, we computed all pairwise correlations between the SC and rsFC maps of the 5 participants. Table S2 shows the result of the correlations calculated over all region pairs as well as the results over SC-present region pairs.

Across all ROI pairs, the rsFC of 5 out of 5 participants was most highly correlated with their own SC. The mean SC-rsFC correlation within participants was greater than the mean SC-rsFC correlation across participants, but this difference did not reach significance within our sample of five participants (0.223 versus 0.207, p = 0.12, two-sample t-test). When including only SC-present edges, 3 of 5 participant best matched their rsFC with their own SC, and the mean correlation was again slightly greater within participants than across participants (0.425 versus 0.397, p = 0.06, two-sample t-test). In low resolution matrices, we did not observe a substantial effect of individual differences.

Because the differences in correlation are relatively small, because of the potential influence of differences in ROI registration, and because of our limited sample size, these results are far from definitive, but they provide some support for the claim that individual differences in SC and in rsFC are indeed related to one another, as predicted in [7].

**Regional Differences in the SC-rsFC Relationship**

We expect that some regions of the brain are more strongly driven by endogenous dynamics, while others are more strongly influenced by the activity of their neighbors.
Those that are more strongly coupled to their neighbors should show a stronger SC-rsFC relationship. In order to investigate regional differences in the strength of the SC-rsFC relationship we calculated SC-rsFC correlations separately for each region at the low resolution. Correlations were computed between single columns of the low resolution SC and rsFC matrices, which correspond to the SC and rsFC of a single anatomical region with all other regions (regardless of whether structural connections are present or not). Correlations as well as SC and rsFC patterns for regions rPC and IPCUN are shown in Figure 3B. All regional correlations were rank-ordered and are shown in Figure S5A. Regions located along in the posterior medial cortex (e.g the cuneus, precuneus and pericalcarine cortex in both hemispheres) are among those with the strongest SC-rsFC relationship at low resolution. We asked if the strength of the SC-rsFC relationship was related to network parameters. We detected weak but significant positive correlations between the number and strength of a region’s anatomical connections, and the strength of the SC-rsFC correlation for that region.

These results remain preliminary because of two potential confounds. The first potential confound is the location of ROIs within the cerebral cortex. Because the cortical location of an ROI determines its distance to other regions of the brain, and inter-regional distance is known to effect SC and rsFC, as well as the accuracy of tractography algorithms, regional location can affect the SC-rsFC relationship. Secondly, the reliability of the automatic landmark-based registration algorithm differs across the brain. ROIs that can be more consistently localized across scans will tend to exhibit more reliable SC-rsFC relationships.

**Reliability of rsFC Measurement**

Because of the numerous potential sources – some physiological and some non-physiological – of variability in BOLD signal, it is difficult to be definitive regarding the origin of any observed rsFC measurement variability. Below we present some observations regarding this complex issue.

When we separately examined the reliability of rsFC for structurally connected versus unconnected edges, we found that structurally connected edges had more reliable rsFC, both in average data (r=0.90 versus r=0.75) and in each individual (Fig. S4). These effects could not be accounted for by the increased average proximity of structurally connected edges (surrogate data analysis not shown).

The increased reliability of rsFC among SC-present edges was also observed when comparing rsFC from the first 10 minutes against rsFC from the second 10 minutes within a single scanning session. The empirical rsFC reliability across 10 minute windows for SC-present edges is r=0.66 ± 0.08, and for edges without SC the reliability is r=0.47±0.08. (These reliability values represent the mean and standard deviation across 5 participants.)
When comparing across consecutive 8-minute windows of simulated BOLD from our computational model, we found that for ROI pairs linked by SC, the mean inter-window correlations in rsFC was $r=0.75\pm0.04$, and for ROI pairs without SC it was $r=0.69\pm0.05$. (These reliability values represent the mean and standard deviation across 5 simulation runs, with each simulation employing the SC map of an individual participant.)

For all calculations of rsFC between two ROIs, at least 200 data points are employed. Based on numerical tests in which we (a) generated correlated time series, (b) measured the correlation between them, and then (c) re-sampled and re-measured the correlations while keeping the underlying interaction strengths constant, we conclude that both the model and the empirical data exhibit more variability in rsFC than can be attributed simply to sample size effects. Both the model and data exhibit unexpectedly low reliability, but the reliability is still lower in empirical data than in the model, most likely due to MRI acquisition and registration influences.

One of the characteristics shared in the model and the data is the presence of long-range temporal autocorrelation (which is sometimes called “long memory”, and is also related to the presence of substantial power below 0.01 Hz in BOLD signal). In practice it can be impossible to distinguish long memory effects from intermittent changes in the underlying generating mechanisms of a time series [3], and long memory can also arise from the aggregation of numerous simple dynamical processes [4]. Alternatively, power in low frequencies may also arise from physiological sources [2]. We are not in a position to distinguish which combination of these effects we may be observing within our empirical measurements of BOLD signal, but in the model we can rule out physiological and MRI acquisition effects.

The difference in rsFC reliability between those ROI pairs with SC and those without SC may reflect the fact that SC facilitates a more persistent interaction between those ROIs. Alternatively, it may reflect the fact that SC-linked ROIs, for some other reason, have a stronger overall interaction which is then necessarily less variable under repeated finite-sample measurements. In either case, however, researchers can expect to observe more reliable rsFC measurements between ROI pairs that are anatomically linked.

Another consequence of this observation of diminished reliability is that, in quantifying the relationship between empirical SC and rsFC, we must keep in mind that SC can only predict rsFC to the extent that rsFC is constant. In participant B, for example, we observe that 27% of variance in rsFC within the first scan is explained in a bivariate regression using SC and fiber distance. To put this number in context, we observe that only 47% of the variance in rsFC in the second 10-minute window within that same scan is predicted by the rsFC observed in the first 10-minute window. So, SC and fiber distance together may have even more of a role in shaping rsFC than is suggested by the proportion of rsFC variance that they explain.
Computational Models

In the main text we report results using a nonlinear model that produces simulated BOLD time series, but for comparison we also implemented a linear model for which the correlation structure in spontaneous dynamics can be calculated analytically [7]. More information concerning both the linear and nonlinear models are provided below, along with a brief comparison of the prediction performance of the linear and nonlinear models.

Model Performance Comparison. The correlation between simulated rsFC and empirical rsFC at direct links in the high resolution network was slightly higher in the linear than the nonlinear model (r=0.55 and r=0.46 respectively), while the nonlinear model yielded a better prediction of the rsFC between indirectly connected nodes (r=0.37 for the nonlinear versus r=0.26 for the linear model). In the low resolution networks, the correlation for both linear and nonlinear models between simulated and empirical rsFC increased to r=0.70 for directly linked pairs. Indirectly linked pairs were again better captured in the nonlinear model (r=0.23, versus r=−0.03 for the linear model).

Linear Model. The linear model we employed – a small variation on the model of Galán [5] -- is derived from the linearization around a fixed point of a general coupled neural system driven by spatially and temporally independent Gaussian noise sources. Within this framework, the correlation structure of the dynamics can be computed analytically given only the coupling matrix and a single parameter governing the rate of activation leakage from each node.

The model of Galán was derived by linearizing and discretizing the dynamics of a general Wilson-Cowan system. The discretized dynamics are governed by

\[ u(t + \Delta t) = Au(t) + \xi(t) \]

where \( u \) is a vector of regional states, \( \xi \) is a temporally white Gaussian noise term and \( \Delta t \) is a time step. The generalized coupling matrix \( A \) is defined as

\[ A = (I - \alpha \Delta t)I + C \Delta t \]

where \( \alpha \) is a leak variable from the activity within each node, \( I \) is the identity matrix and \( C \) is a matrix describing inter-nodal interaction efficacies. In place of \( C \), we employed the resampled fiber strengths obtained from diffusion spectrum imaging tractography. Because this matrix contains only positive terms, the leak term \( \alpha \) is chosen to be relatively large (\( \alpha = 2 \)), in order to retain a balance of driving and damping in the model.

Within this model, the covariance and correlation matrices of the nodal dynamics can be calculated analytically as a function of the eigenvalues of the matrix \( A \), and of the covariance of noise terms input to each node. See reference [5] for further details.
Nonlinear model. The nonlinear model, as developed in [6] and extended to large-scale network settings in [7], is a neural mass model based on [8]. Each neural mass represents a local ensemble of neurons. The dynamical variables incorporated are the mean membrane potential of pyramidal cells, $V$, and inhibitory interneurons, $Z$, and the average number of ‘open’ potassium ion channels, $W$. The mean cell membrane potential of the pyramidal cells is governed by the conductance of sodium, potassium and calcium ion through voltage- and ligand-gated membrane channels,

$$
\frac{dV}{dt} = -\left(g_\text{Ca} + r_{\text{NMDA}}a_{\text{exc}}Q_V\right)m_\text{Ca}(V-V_\text{Ca}) - (g_{na}m_{na} + a_{\text{exc}}Q_V)(V-V_{na}) - g_K W(V-V_K)
- g_L(V-V_L) + a_{\text{in}} Z Q_Z + a_{\text{exc}} I_\delta,
$$

(1)

$$
\frac{dZ}{dt} = b(a_{\text{in}} I_\delta + a_{\text{exc}} V Q_V),
$$

where $g_{\text{ion}}$ is the maximum conductance of each population of ion species if all channels are open, $m_{\text{ion}}$ is the fraction of channels open, $V_{\text{ion}}$ is the Nernst potential for that ion species and $Q_{V(Z)}$ is the firing rate of the excitatory (inhibitory) neurons. The fraction of open ion channels is determined by the sigmoid-shaped ‘neural activation function’,

$$
m_{\text{ion}} = 0.5\left(1 + \tanh\left(\frac{V-V_\tau}{\delta_{\text{ion}}}\right)\right),
$$

where $\delta_{\text{ion}}$ incorporates the variance of this distribution. The fraction of open potassium channels is governed by $W$, with

$$
\frac{dW}{dt} = \phi(m_k - W),
$$

where $\phi$ is a temperature scaling factor and $\tau$ is a ‘relaxation’ time constant. Cell firing rate is also determined by sigmoid activation functions,

$$
Q_V = 0.5xQ_{V\text{max}}\left(1 + \tanh\left(\frac{V-V_\tau}{\delta_V}\right)\right),
$$

where the $Q_{\text{max}}$ are the maximum firing rate. An analogous term is also introduced for the inhibitory cells.

The firing of excitatory and inhibitory cell populations feeds back onto the ensemble through synaptic coupling to open ligand-gated channels and raises or lowers the mean membrane potential accordingly. In the case of excitatory-to-inhibitory and inhibitory-to-excitative connections, this is modeled as additional input to the flow of ions across the membrane channel, weighted by functional synaptic factors, $a_{\text{ei}}$ and $a_{\text{ie}}$. In the case of excitatory to excitatory connections, the rate of firing $Q_v$ is assumed to lead to a proportional release of glutamate neurotransmitter across the synapse, onto two classes of
ligand-gated ion channels: (1) AMPA channels, which open an additional population of sodium channels, and (2) NMDA receptors, which open an additional population of \textit{voltage-gated} sodium and calcium channels. $r_{NMDA}$ incorporates the ratio of NMDA to AMPA receptors.

The equations above govern the dynamics within each local cell assembly. Coupling between $N$ nodes is introduced as competitive agonist excitatory action at the same populations of NMDA and AMPA receptors. Locating the $i$-th node at position $x_i$ this is incorporated by modifying equation (1) to

$$
\frac{dV(x_i)}{dt} = -(g_{Ca} + (1-c)r_{NMDA}a_{ee}Q_v(x_i) + cr_{NMDA}a_{ee} < Q_v(x) > m_{Ca}(V(x_i) - V_{Ca}) - g_KW(V(x_i) - V_K)
$$
$$
- g_L(V(x_i) - V_L) - \left(g_{na}m_{na} + (1-c)a_{ee}Q_v(x_i) + ca_{ee} < Q_v(x) > \right)(V(x_i) - V_{na})
$$
$$
+ a_{ne}ZQ_x(x_i) + a_{ne}I_\delta,
$$

for $i,j=1,\ldots,N$.

The parameter $c$ controls the strength of excitatory coupling between cortical regions. If $c=0$ the neural masses evolve independently. The setting $c>0$ introduces interdependences between linked regions, and $c=1$ corresponds to maximum coupling, with excitatory input from outside each region surpassing excitatory input from within each region. For the present paper, we chose a value for the excitatory coupling between regions of $c=0.15$, as this seemed to induce a reasonable balance of transient synchronization and desynchronization between regions. This value for the coupling parameter was set slightly higher than in ref [7] to adjust for the larger size and greater number of connections per node in the present model (runs with $c=0.10$ produced similar results but with overall lower cross-correlations). No attempt was made to model realistic conduction delays. All physiologically measurable parameters (conductances, threshold potentials and Nernst potentials) are set to values taken from [8]. The nonlinear model is simulated in Matlab R2007a (Mathworks, Natick, MA) at a time resolution of 0.2 msec. Before data analysis, resulting data sets are downsampled to a time resolution of 1 time step = 1 millisecond. After an initial transient of 2 minutes which was discarded, runs proceeded for a total of 16 minutes (960,000 msecs, $4.8 \times 10^6$ iterations). We ran four simulations with random initial conditions for each of the six structural connectivity matrices derived by DSI (two repeat scans for participant A, one scan for participants B-E).

To estimate BOLD signals for each neural mass, we followed [9] in employing a Balloon–Windkessel hemodynamic model [10,11]. Equations and parameters relating neuronal activity and vasodilatory signal with blood inflow, volume, and deoxyhaemoglobin content are taken directly from [8]. As in [7], the main input to the Balloon-Windkessel model, “neuronal activity,” is taken to be the absolute value of the
time derivative of the mean excitatory membrane potential within each brain region (i.e. a proxy for glutamate turnover). As in the empirical data, we detrended the data and regressed a global mean signal from each node’s time series before calculating simulated rsFC maps. Unlike the empirical BOLD signals, there was not a very strong influence of a coherent global signal observed within the simulated BOLD before pre-processing.

The model performance results reported in Figure 1 and in Table S1 are for individual runs. Unless otherwise stated, the remainder of the model results is based on rsFC maps that are an average of four separate model runs.

Examination of fast voltage-time traces revealed complex synchronization dynamics as previously described in ref [7]. While in the current study we did not attempt to compute information flow patterns at high temporal resolution, the model does in principle allow for an investigation of synchrony and coherence at fast time scales.

**Structural and Functional Connectivity within the Default Mode Network**

The default mode network is reliably and robustly detected in resting state fMRI. We asked if the prominence of the Default Mode Network (DMN) in resting state activity can be accounted for by its structural connectivity. After extracting the 200 most strongly coupled ROIs comprising the DMN (see Fig. S5D) we determined the structural connection density within this network as well as the density of connections between the DMN and the 200 most anti-correlated ROIs. Within-DMN connection density was found to exceed the connection density between DMN and anti-correlated ROIs by more than 8-fold (0.074 versus 0.009, respectively). We then asked how the intra-DMN connection density compared relative to other networks that are extracted from 6 nonoverlapping clusters of seed ROIs symmetrically distributed across the two cerebral hemispheres. We formed a distribution of connection densities by randomly sampling 20,000 such networks. The DMN network is found to be in the top 1% of this distribution which has a mean of 0.050 and a standard deviation of 0.009. This indicates that the DMN represents a very highly and densely connected subnetwork within cortex.

The relationship between SC and rsFC was stronger within the DMN than across the entire cerebral cortex. For the 200 ROIs comprising the DMN, the presence of a structural connection predicted rsFC with $r = 0.64$, while the overall correlation between SC and rsFC was found to be $r = 0.55$. Both values greatly exceed those reported here for the entire cortex (see Table S1, 998 ROI data).

While both of our computational models accurately captured functional connectivity within the DMN along the medial wall of the cerebral cortex (Fig. 3C), they failed to account for the functional linkage of the lateral parietal cortex. An examination of the structural connection within the DMN (Fig. 3D) reveals that very few structural connections were detected between the precuneus/posterior cingulate cortex and the
lateral parietal cortex. The discrepancy between structural and functional connectivity in this portion of the DMN may be due to i) a failure of DSI to detect actually present structural connections, especially when tracking small fibers perpendicular to major fasciculi as in this case; ii) disproportionate physiological strengths within the DMN that compensate for the lack of strong structural coupling; iii) a significant role of other brain regions, not captured in the structural scans (e.g. the thalamus), in functionally linking lateral parietal cortex with the DMN.

These results were obtained using seed clusters for the default mode network derived from data reported in [12]. Similar result were found for slightly different sets of peak foci reported in [13,14].

Supporting References


Fig. S1. (A) Low-resolution (66-region) and (B) high-resolution parcellations (998-ROI) of the cerebral cortex. In the article, the 66 cortical regions are labeled as follows: each label consists of two parts, a prefix for the cortical hemisphere (r, right hemisphere; l, left hemisphere) and 1 of 33 designators. BSTS, bank of the superior temporal sulcus; CAC, caudal anterior cingulate cortex; CMF, caudal middle frontal cortex; CUN, cuneus; ENT, entorhinal cortex; FP, frontal pole; FUS, fusiform gyrus; IP, inferior parietal cortex; IT, inferior temporal cortex; ISTC, isthmus of the cingulate cortex; LOCC, lateral occipital cortex; LOF, lateral orbitofrontal cortex; LING, lingual gyrus; MOF, medial orbitofrontal cortex; MT, middle temporal cortex; PARC, paracentral lobule; PARH, parahippocampal cortex; POPE, pars opercularis; PORB, pars orbitalis; PTRI, pars triangularis; PCAL, pericalcarine cortex; PSTS, postcentral gyrus; PC, posterior cingulate cortex; PREC, precuneus; PCUN, precuneus; RAC, rostral anterior cingulate cortex; RMF, rostral middle frontal cortex; SF, superior frontal cortex; SP, superior parietal cortex; ST, superior temporal cortex; SMAR, supramarginal gyrus; TP, temporal pole; TT, transverse temporal cortex.
Fig. S2. Matrices of SC and empirical rsFC at the high resolution. Both plots represent averages across all 5 participants, including 2 structural scans for participant A, and 2 repeat functional scans for all 5 participants. The structural connection matrix is averaged after connection strengths were resampled to a Gaussian distribution with a mean of 0.5 and a standard deviation of 0.1. Connections that were present in only 1 out of 5 participants were set to zero strength. The functional connection matrix was computed from BOLD time series obtained for each ROI (see Methods). Each correlation value represents an average over 5 participants and 2 repeat scans per participant. The color bars at the left and bottom of the matrices indicate brain regions shown in a corresponding color map in Fig. S1.
Fig. S3.  (A) Indirect SC weakly predicts rsFC. The figure shows rsFC plotted against indirect SC (see Results) in the average high-resolution data. Plotted are those region pairs linked by at least one of the shortest paths of exactly 2 edges. Highlighted in red are the data points showing indirect SC and rsFC between the visual cortices in left and right hemispheres. Visual cortex ROIs within each hemisphere are those located in pericalcarine cortex, lateral occipital cortex, lingual gyrus, and the cuneus. (B) The SC-rsFC relationship for a single session from Participant A, at high resolution (998 ROIs), excluding all ROI pairs that exhibit anticorrelation. The SC-rsFC relationship does not depend on the presence of anticorrelations, nor on regression of a global mean BOLD signal.
Fig. S4. Increased reliability of rsFC mediated by SC. The scatter plot shows rsFC from Scan 1 against rsFC from Scan 2, using high-resolution data for each of the 5 participants, as well as for participant-averaged SC and rsFC maps. Region-pairs with present SC in black, region-pairs without SC in blue.
Fig. S5. Rank-ordered distribution of the strength of the relationships between structural connectivity, empirical functional connectivity, and simulated functional connectivity for single brain areas. Data were obtained at the low resolution from SC and rsFC matrices averaged over all 5 participants. (A) Pearson correlations for SC versus empirical FC. (B) Pearson correlations for empirical FC versus modeled FC (nonlinear model). (C) Pearson correlations for empirical FC versus modeled FC (linear model). All correlations except those marked with an asterisk are $P < 0.01$. (D) Seed ROIs used for extraction of the DMN shown in Fig. 3. These ROIs were determined as follows. We used published Talairach coordinates for 3 peak foci of task-negative network published by Fox et al. (12). These coordinates were (–2, –36, 37) in the posterior cingulate/precuneus, (–3, 39, –2) in the medial prefrontal cortex, and (–47, –67, 36) and (53, –67, 36) in the lateral parietal cortex. We identified clusters of 5 ROIs that were closest to each of these 6 target coordinates, resulting in a set of 30 ROIs. These 30 ROIs were used to compute the SC and rsFC maps shown in Fig. 3C. Given the empirical rsFC map, we then thresholded this map to obtain a set of 200 ROIs that were most strongly correlated (shown here in dark brown). This set of 200 ROIs covered most of the default-mode network and was used to display the structural connectivity linking these 200 ROIs in Fig. 3D.
Table S1. Individual participant SC-rsFC and rsFC-distance correlations and corresponding values from individual runs of the computational model

<table>
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<th>Participant</th>
<th>SC (All)</th>
<th>SC (Present)</th>
<th>Inverse fiber distance</th>
<th>Distance residuals</th>
<th>Model R² SC and fiber bivariate</th>
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</tbody>
</table>

Individual participant SC-rsFC and rsFC-distance correlations (Top 2 sections), and corresponding values from individual runs of the computational model (Bottom section). Empirical rsFC is from the first fMRI scan; simulated rsFC is from a single 16 min simulation. The first 2 columns show the SC-rsFC correlations for “all region pairs” and “region pairs with SC,” respectively. The third column shows the correlation between rsFC and the inverse of fiber distance, and the fourth column shows the correlation between SC and the residuals of the distance-regression. The fifth column provides the full model R² of a bivariate linear regression of rsFC on SC and inverse fiber distance. The bottom row shows the results of each calculation performed using data averaged across participants (it is not the average of the rows above). All correlations are P < 1e-3.
Table S2. Interparticipant SC-rsFC correlations

<table>
<thead>
<tr>
<th>Participant SC</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 0.237</td>
<td>0.211</td>
<td>0.164</td>
<td>0.205</td>
<td>0.197</td>
<td></td>
</tr>
<tr>
<td>B 0.236</td>
<td>0.240</td>
<td>0.173</td>
<td>0.214</td>
<td>0.218</td>
<td></td>
</tr>
<tr>
<td>C 0.232</td>
<td>0.224</td>
<td>0.180</td>
<td>0.215</td>
<td>0.204</td>
<td></td>
</tr>
<tr>
<td>D 0.234</td>
<td>0.220</td>
<td>0.171</td>
<td>0.231</td>
<td>0.206</td>
<td></td>
</tr>
<tr>
<td>E 0.222</td>
<td>0.212</td>
<td>0.165</td>
<td>0.210</td>
<td>0.225</td>
<td></td>
</tr>
</tbody>
</table>

SC Present edges

<table>
<thead>
<tr>
<th>Participant SC</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 0.415</td>
<td>0.407</td>
<td>0.329</td>
<td>0.379</td>
<td>0.383</td>
<td></td>
</tr>
<tr>
<td>B 0.426</td>
<td>0.476</td>
<td>0.353</td>
<td>0.413</td>
<td>0.414</td>
<td></td>
</tr>
<tr>
<td>C 0.450</td>
<td>0.461</td>
<td>0.392</td>
<td>0.422</td>
<td>0.424</td>
<td></td>
</tr>
<tr>
<td>D 0.410</td>
<td>0.429</td>
<td>0.342</td>
<td>0.416</td>
<td>0.380</td>
<td></td>
</tr>
<tr>
<td>E 0.379</td>
<td>0.409</td>
<td>0.345</td>
<td>0.385</td>
<td>0.424</td>
<td></td>
</tr>
</tbody>
</table>

The rsFC map is from the first fMRI scan.
Table S3. Individual participant SC-rsFC and rsFC-distance correlations calculated without resampling of SC values

<table>
<thead>
<tr>
<th>Participant</th>
<th>SC (All)</th>
<th>SC (Present)</th>
<th>Inverse fiber distance</th>
<th>Distance residuals</th>
<th>Model R² SC and fiber bivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>66 Regions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>0.52</td>
<td>0.66</td>
<td>0.55</td>
<td>0.52</td>
<td>0.49</td>
</tr>
<tr>
<td>B</td>
<td>0.46</td>
<td>0.57</td>
<td>0.51</td>
<td>0.44</td>
<td>0.41</td>
</tr>
<tr>
<td>C</td>
<td>0.38</td>
<td>0.53</td>
<td>0.49</td>
<td>0.38</td>
<td>0.35</td>
</tr>
<tr>
<td>D</td>
<td>0.50</td>
<td>0.60</td>
<td>0.45</td>
<td>0.48</td>
<td>0.39</td>
</tr>
<tr>
<td>E</td>
<td>0.44</td>
<td>0.57</td>
<td>0.44</td>
<td>0.48</td>
<td>0.38</td>
</tr>
<tr>
<td>Avg Participant</td>
<td>0.58</td>
<td>0.71</td>
<td>0.66</td>
<td>0.50</td>
<td>0.57</td>
</tr>
<tr>
<td>998 ROIs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>0.18</td>
<td>0.34</td>
<td>0.39</td>
<td>0.21</td>
<td>0.19</td>
</tr>
<tr>
<td>B</td>
<td>0.15</td>
<td>0.30</td>
<td>0.46</td>
<td>0.13</td>
<td>0.24</td>
</tr>
<tr>
<td>C</td>
<td>0.13</td>
<td>0.28</td>
<td>0.40</td>
<td>0.14</td>
<td>0.18</td>
</tr>
<tr>
<td>D</td>
<td>0.16</td>
<td>0.30</td>
<td>0.39</td>
<td>0.17</td>
<td>0.18</td>
</tr>
<tr>
<td>E</td>
<td>0.16</td>
<td>0.31</td>
<td>0.39</td>
<td>0.19</td>
<td>0.19</td>
</tr>
<tr>
<td>Avg Participant</td>
<td>0.30</td>
<td>0.46</td>
<td>0.47</td>
<td>0.27</td>
<td>0.28</td>
</tr>
</tbody>
</table>

rsFC is from the first fMRI scanning session. The SC strength is equal to the number of tractographic streamlines linking two ROIs, divided by the total area of the two ROIs. The first 2 columns show the SC-rsFC correlations for “all region pairs” and for “region pairs with SC,” respectively. The third column shows the correlation between rsFC and the inverse of fiber distance, and the fourth column shows the correlation between SC and the residuals of the distance-regression. The fifth column provides the full model R² of a bivariate linear regression of rsFC on SC and inverse fiber distance. The bottom row shows the results of each calculation performed using data averaged across participants (it is not the average of the rows above).
Table S4. Individual participant SC-rsFC and rsFC-distance correlations, after rsFC maps are Fisher-z transformed and then normalized to zero mean and unit variance across the 998 ROIs of each participant.

<table>
<thead>
<tr>
<th>Participant</th>
<th>SC (All)</th>
<th>SC (Present)</th>
<th>Inverse fiber distance</th>
<th>Distance residuals</th>
<th>Model R² SC and fiber bivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>66 Regions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>0.60</td>
<td>0.75</td>
<td>0.55</td>
<td>0.64</td>
<td>0.58</td>
</tr>
<tr>
<td>B</td>
<td>0.58</td>
<td>0.71</td>
<td>0.52</td>
<td>0.61</td>
<td>0.54</td>
</tr>
<tr>
<td>C</td>
<td>0.45</td>
<td>0.64</td>
<td>0.49</td>
<td>0.52</td>
<td>0.44</td>
</tr>
<tr>
<td>D</td>
<td>0.61</td>
<td>0.71</td>
<td>0.45</td>
<td>0.62</td>
<td>0.51</td>
</tr>
<tr>
<td>E</td>
<td>0.62</td>
<td>0.77</td>
<td>0.44</td>
<td>0.72</td>
<td>0.61</td>
</tr>
<tr>
<td>Avg Participant</td>
<td>0.68</td>
<td>0.82</td>
<td>0.66</td>
<td>0.68</td>
<td>0.69</td>
</tr>
<tr>
<td>998 ROIs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>0.25</td>
<td>0.41</td>
<td>0.38</td>
<td>0.24</td>
<td>0.20</td>
</tr>
<tr>
<td>B</td>
<td>0.25</td>
<td>0.47</td>
<td>0.46</td>
<td>0.24</td>
<td>0.25</td>
</tr>
<tr>
<td>C</td>
<td>0.19</td>
<td>0.39</td>
<td>0.39</td>
<td>0.19</td>
<td>0.18</td>
</tr>
<tr>
<td>D</td>
<td>0.24</td>
<td>0.41</td>
<td>0.38</td>
<td>0.24</td>
<td>0.20</td>
</tr>
<tr>
<td>E</td>
<td>0.24</td>
<td>0.42</td>
<td>0.38</td>
<td>0.26</td>
<td>0.21</td>
</tr>
<tr>
<td>Avg Participant</td>
<td>0.38</td>
<td>0.53</td>
<td>0.46</td>
<td>0.32</td>
<td>0.30</td>
</tr>
</tbody>
</table>

The first 2 columns show the SC-rsFC correlations for “all region pairs” and for “region pairs with SC,” respectively. The third column shows the correlation between rsFC and the inverse of fiber distance, and the fourth column shows the correlation between SC and the residuals of the distance-regression. The fifth column provides the full model R² of a bivariate linear regression of rsFC on SC and inverse fiber distance. The bottom row shows the results of each calculation performed using data averaged across participants (it is not the average of the rows above).

Other Supporting Information Files

SI Appendix