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ORIGINAL ARTICLE

The strength of weak connections in the macaque cortico-cortical network

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Abstract Examination of the cortico-cortical network of mammals has unraveled key topological features and their role in the function of the healthy and diseased brain. Recent findings from social and biological networks pinpoint the significant role of weak connections in network coherence and mediation of information from segregated parts of the network. In the current study, inspired by such findings and proposed architectures pertaining to social networks, we examine the structure of weak connections in the macaque cortico-cortical network by employing a tract-tracing dataset. We demonstrate that the cortico-cortical connections as a whole, as well as connections between segregated communities of brain areas, comply with the architecture suggested by the so-called strength-of-weak-ties hypothesis. However, we find that the wiring of these connections is not optimal with respect to the aforementioned architecture. This configuration is not attributable to a trade-off with factors known to constrain brain wiring, i.e., wiring cost and efficiency. Lastly, weak connections, but not strong ones, appear important for network cohesion. Our findings relate a topological property to the strength of cortico-cortical connections, highlight the prominent role of weak connections in the cortico-cortical structural network and pinpoint their potential functional significance. These findings suggest that certain neuroimaging studies, despite methodological challenges, should explicitly take them into account and not treat them as negligible.

Introduction

Uncovering principles pertaining to the connectional organization of the brain is crucial for understanding its function and elucidating connectional alterations in neuropathologies (e.g., van den Heuvel and Sporns 2013a; Hilgetag and Barbas 2006). By treating the cortico-cortical connections as a network and employing appropriate analytic tools, key principles can be described (e.g., Harriger et al. 2012; Ercsey-Ravasz et al. 2013; Kaiser and Hilgetag 2006). Several approaches for uncovering such principles are inspired by findings in technological and social networks. For instance, a "bow-tie" representation, characterizing the structure of the world wide web (Broder et al. 2000), can also describe the wiring of the macaque brain (Markov et al. 2013a). An additional example is the rich club structure, which describes the interconnected nature of highly connected hub nodes in a graph and facilitates integration across multiple networks (van den Heuvel and Sporns 2013b). It has been described in air transportation and scientific collaboration networks (Colizza et al. 2006), as well as in the human, macaque, and cat brain (van den Heuvel and Sporns 2013a; Goulas et al. 2014).

Recent findings suggest a prominent role of weak connections in biological, ecological, and social networks

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(Csermely 2006). A principle highlighting such unique role of weak connections is the strength of weak ties. This principle, originally proposed for social networks, suggests a relation between connection strength and network topology. Specifically, the weaker the connection between two individuals, the less common friends they will share, i.e., the smaller neighborhood overlap they exhibit. Hence, weak ties can mediate information between diverse social groups. This principle was originally introduced by Granovetter (1973) and recently formally demonstrated through analysis of networks of mobile phone contacts (Onnela et al. 2007). In addition, weak ties seem to play a distinct role in information cascades in communication networks by effectively trapping information within communities (Onnela et al. 2007) and mediating the spread of epidemics (Shu et al. 2012; Cui et al. 2012).

In the context of brain organization, studies have revealed the presence of links between tightly interconnected group of areas, i.e., modules, offering the anatomical substrate for the integration of information across specialized groups of brain areas (e.g., de Reus and van den Heuvel 2013; Hagmann et al. 2008). However, the majority of studies thus far have not explicitly addressed if such connections simply link areas from different modules or if certain principles govern their wiring. Recent histological analysis offering detailed quantitative information on the strength of cortico-cortical connections demonstrates that weak connections in the macaque brain are important for the integration of information from the whole brain to a very small subset of areas (Markov et al. 2014). Moreover, analysis of the aforementioned dataset reveals a decay of connectivity strength and connectivity similarity with spatial distance (Markov et al. 2013b). Such findings are compatible but do not necessitate a connectional architecture complying with the strength-of-weak-ties hypothesis and call for further elaboration. Despite that the predictions of the strength-of-weak-ties hypothesis were confirmed for the structural and functional connectivity of the human brain using non-invasive MRI techniques (Pajevic and Plenz 2012), predictions for different connection classes (e.g., intermodular, intramodular) remain unexamined. Moreover, how "optimal" is such brain wiring and how does this architecture relate to other constraining factors, i.e., wiring cost and efficiency (Kaiser and Hilgetag 2006), is unclear. From a methodological point of view, examination of the relation of connectivity strength and topology, as the strength-of-weak-ties hypothesis dictates, might be hampered by the lack of a reliable method for inferring connection density/strength and directionality of structural connections in the human brain (Jones et al. 2013).

In light of the above findings, we aimed at explicitly examining if direct consequences of the strength-of-weak-ties hypothesis pertain to the totality of cortico-cortical, intra- and intermodular connections and how such a connectional architecture relates to constraints imposed by wiring cost and efficiency. An architecture complying with the predictions of this hypothesis would have functional implications and shed light on previous findings related to information flow and segregation/integration in the mammalian brain (Kaiser et al. 2007; de Reus and van den Heuvel 2013). We also investigated a potential prominent role of weak connections in the cohesion of the brain network, i.e., if their removal leads to the fast fragmentation of the network.

Materials and methods

The dataset used is derived from http://www.core-nets.org which is a database compiled from results obtained from tract-tracing studies in the macaque brain (Markov et al. 2013b). Quantitative information on cortico-cortical connectivity, i.e., strength and physical length, for a set of 29 areas spanning the frontal, parietal, temporal, and occipital cortex, was represented as a 29×29 weighted and directed network. The injections involved the retrograde tracers fast blue and diamidino yellow. Dense sampling of sections allowed stable cell counts across the whole brain and a reliable estimate of the connectivity profile of an area from single injections. The connectivity strength between areas A and B after an injection in area A was expressed as the fraction of labeled neurons involving area B, i.e., the number of neurons located in area B, divided by the total number of neurons observed across the whole brain after injecting area A (excluding "intrinsic" neurons, i.e., neurons located in area A). Physical distance of areas was estimated using a 3D representation of the macaque cortex and the 3D coordinates of the cortical areas thus approximating the trajectory of axons linking two areas (see Markov et al. 2011, 2013b, 2014 for details).

For assessing the strength-of-weak-ties hypothesis, the neighborhood overlap (NEO) for each edge/connection was computed (Kaiser and Hilgetag 2004; Pajevic and Plenz 2012). The relation between strength and NEO of each connection was assessed by computing the Pearson's correlation coefficient between the variables (Pajevic and Plenz 2012). We used the natural logarithm for transforming the connectivity strengths prior to the correlation with the NEO values. Non-parametric correlation measures, i.e., Spearman's rank correlation, were also used for capturing the relation between NEO and strength. The NEO can be calculated by taking into account incoming, outgoing, or all connections for defining neighbors (Fig. 1). Formally, the NEO for a connection from area i to j is defined as:

$$NEO_{A\to B} = NEO_{B\to A} = \frac{3}{5} = 0.6 \qquad NEO_{A\to B} = NEO_{B\to A} = \frac{1}{3} = 0.3 \qquad NEO_{A\to B} = NEO_{B\to A} = \frac{2}{2} = 1$$
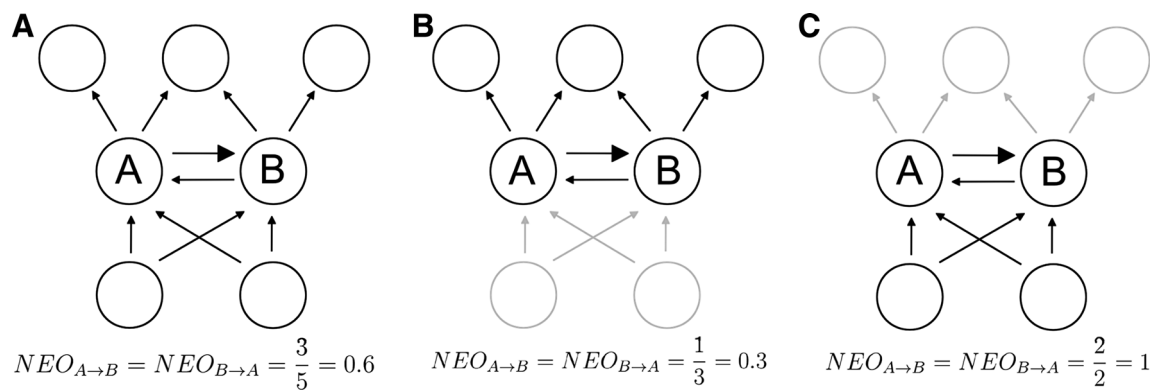
Fig. 1 Example of the NEO calculation for a set of connections in a toy network. Calculation of NEO by taking into account **a** all, **b** outgoing, and **c** incoming connections for defining the neighborhood of a node. Note that the NEO metric is symmetric, i.e., $NEO_{A\to B} = NEO_{B\to A}$ and that the strength of connections does not play a role for defining the neighborhood of a node and the NEO values. Moreover, reciprocal connections do not have the same weight/strength. For instance, the connection from A to B is stronger (indicated with a *big arrowhead*) than the connection of from B to A (indicated with *small arrowhead*). For this reason, the NEO/strength correlation was computed by taking all (main analysis), "incoming", or "outgoing" (upper and lower parts of the connectivity matrix) connections and the distinct NEO definitions (see Table 1)

$$NEO_{i\to j} = \frac{|\Gamma_i \cap \Gamma_j|}{|\Gamma_i \cup \Gamma_j|} \qquad (1)$$

with Γ denoting the neighbors (defined based on all, incoming or outgoing connections) of an area (i or j), $|\Gamma_i \cap \Gamma_j|$ denoting the intersection of the neighbors of areas i and j, $|\Gamma_i \cup \Gamma_j|$ denoting the union, and |.| denoting the size of the intersection/union. Note that NEO is a symmetric measure, i.e., $NEO_{i\to j} = NEO_{j\to i}$. The macaque network contains many reciprocal connections that do not have the exact same strength (Fig. 1). The NEO/strength relation can be estimated by taking into account all connections or only the "incoming" and "outgoing" connections (lower and upper part of the connectivity matrix). The main analysis took into account all connections for defining the NEO values and assessing the NEO/strength relation. We also used all combinations of incoming and outgoing connections for defining the NEO and took into account connections in the upper and lower parts of the connectivity matrix for assessing the NEO/strength correlation, as control analysis.

Since the strength of a connection is related to its physical length, and increasingly distant areas tend to have increasingly diverge patterns of connections (Kaiser et al. 2009; Markov et al. 2013b), physical length was used as covariate for computing the partial correlation between NEO and strength of connections.

The network was partitioned in modules with Newman's spectral decomposition algorithm generalized for directed and weighted networks (Leicht and Newman 2008). This algorithm tries to partition the network in modules in such a way that the modularity value Q is maximized, i.e., find the optimal number of modules that have higher than chance intermodular connectivity (see Leicht and Newman 2008 for details). Therefore, the algorithm does not require a priori number of modules defined by the used. Instead it finds the optimal number of modules that are supported by the data. We ran the algorithm on the weighted graph since connection strengths span several orders of magnitude, from a dozen to thousands of neurons (Markov et al. 2014). This renders information on the strength of connections essential for uncovering the pertinent topological feature of interest. The algorithm was applied 1,000 times to examine possible degeneracy of the solutions of the module decomposition algorithm (Good et al. 2010). The result of this partitioning was used to classify connections as inter- and intramodular. The strength-of-weak-ties hypothesis was also tested for these classes separately. It should be noted that a modular network does not necessarily comply with the strength-of-weak-ties hypothesis. That is, the presence of a significant modular structure does not necessitate a relation between NEO and strength of connections.

For assessing the statistical significance of the results, 1,000 null models were constructed with an edge swapping degree distribution preserving algorithm (Maslov and Sneppen 2002). For examination of intermodular connections the allowed edge swaps were constrained so that only intermodular edge swaps were allowed. In such a highly dense network as the current one employed, and given how module optimization works, intramodular connectivity is expected to be very dense. Consequently, we used the weight reshuffle null model (Opsahl et al. 2008) to assess the significance of the NEO/strength relation for intramodular connections. This null model shuffles the weights of connections while leaving their position in the network intact.

To assess if the macaque cortico-cortical network is wired in a way to optimally comply with the principles of the strength-of-weak-ties hypothesis, an evolutionary algorithm was applied (e.g., Sporns et al. 2000). At first, the original network was used as a seed and bred one generation of networks by swapping ("mutating") two connections. For each of these networks, the correlation between NEO and strength of each connection was computed and used as the "optimality" of these networks, i.e., Optimality = r (NEO, Strength). After each generation, which was defined from a set of 30 networks, the network with the best optimality, here the highest correlation between NEO and strength, was chosen as the seed for the next generation. This procedure leads to an iterative refinement of the population toward the chosen criterion of optimality. The procedure was stopped after 1,000 generations. The number of generations was set empirically since a saturation around a plateau of optimality values was observed after $\sim$800 generations. With the aforementioned procedure, networks that maximally correspond to the strength-of-weak-ties hypothesis were constructed. The same procedure was used for creating networks that minimally correspond to the strength-of-weak-ties hypothesis but now selecting networks with the lowest correlation between NEO and strength. The aforementioned procedure provides the empirical extremes of networks that maximally and minimally comply with the strength-of-weak-ties hypothesis. Similar approaches are used for addressing optimality of neuronal systems with respect to wiring cost (e.g., Kaiser and Hilgetag 2006). It should be noted that optimization procedures as the algorithm currently adopted are not guaranteed to find the global optimum. However, our goal was not to find the global optimum as such, but rather construct networks that exhibit a maximized/minimized property when compared to the original network and address if such network configurations can be obtained. Moreover, the parameters of the algorithm (e.g., the size of each generation) impact on the computational time and the exact outcome but do not hamper our interpretations and conclusions. The evolutionary algorithm was applied separately to the distinct classes of connections (inter- and intramodular) only if the particular class exhibited a significant correlation of NEO and strength. We adopted this class-specific approach since the macaque cortico-cortical network as a whole might have a different degree of correspondence to the hypothesis at hand when compared to some of its subnetworks. In other words, certain classes of connections might optimally correspond to the pertinent hypothesis whereas others do not, as is the case for *Caenorhabditis elegans* and wiring cost (Pérez-Escudero and De Polavieja 2007).

The generated maximally and minimally optimal networks were interrogated for properties demonstrated to

constrain the wiring of the brain, i.e., wiring cost and efficiency (Kaiser and Hilgetag 2006; Chen et al. 2013). The global efficiency, henceforth referred to simply as efficiency, was calculated by transforming the weights by $-\log(w_{ij})$, resulting in a range of values [0.27, 12.84], and applying the following formula:

$$E = \frac{1}{N(N-1)} \sum \frac{1}{r_{ij}} \qquad (2)$$

with r_{ij} denoting the minimum sum of connection weights along all paths running from node i to j (weighted shortest path length) and N the number of nodes in the network. Thus, efficiency, treated as a global network property, took into account the whole network connections, irrespective of specific class of connections that the optimization procedure focused on. As a proxy for wiring cost, the mean of the physical lengths of the connections was used. The wiring cost was computed by taking into account the specific connection class at hand. This analysis aimed at examining if the maximal or minimal optimization of the networks according to the strength-of-weak-ties hypothesis leads to substantial alterations of the aforementioned properties constraining brain wiring, thus highlighting a potentially antagonistic relation.

For addressing how important or negligible the changes in wiring cost and efficiency were in the optimized networks, these values were compared with the ones estimated empirically, i.e., applying the evolutionary algorithm as before but now by trying to minimize or maximize the efficiency or wiring cost of the network. All values (correlation between NEO and strength, wiring cost and efficiency) in the optimized networks were expressed as percent change by taking into account the values characterizing the original network: [(Value_optimized/Value_original) $\times$ 100] $-$ 100.

We also explicitly addressed if "minimal" and "maximal" networks, with respect to the strength-of-weak-ties hypothesis, come at the expense of factors shaping brain wiring (wiring cost and efficiency). We incorporated two extra constrains in the evolutionary algorithm to maximize/minimize the NEO/strength correlation and also push the network configuration toward the less costly, by minimizing wiring cost, and the more efficient, by maximizing efficiency. Hence, in this analysis optimality is defined as: Optimality = r (NEO, Strength) + Efficiency$_{norm}$ + (1 − WiringCost$_{norm}$) when maximizing the NEO/Strength correlation and Optimality = r (NEO, Strength) + (1 − Efficiency$_{norm}$) + WiringCost$_{norm}$ when minimizing the NEO/Strength correlation. Note that Efficiency$_{norm}$ and WiringCost$_{norm}$ correspond to the efficiency and wiring cost of the network divided with the efficiency and wiring cost of the network obtained from an explicit and separate maximization of efficiency and wiring cost, i.e.,

Optimality = Efficiency and Optimality = WiringCost, respectively. Hence, Efficiency$_{norm}$ and WiringCost$_{norm}$ have theoretical values ranging in the interval [0, 1]. We additionally applied the following linear transformation to the r values: $r = (r/2) + 0.5$. Hence, all three factors of the aforementioned optimization procedure range in the [0, 1] interval and have the same impact in the optimality score. The optimization procedure as described above was applied ten times and the values reported below correspond to the mean values obtained.

Weak ties are highlighted for their importance in network cohesion as demonstrated in analysis of mobile calls (Onnela et al. 2007). Such feature was also observed, albeit with differences in degree of the effect, in technological and biological networks including the human brain (Pajevic and Plenz 2012). We explicitly assessed a distinctive role of weak connections in cohesion of the macaque network. We calculated the relative size of the giant strongly connected component, i.e., number of nodes of the giant strongly connected component divided by the total number of nodes in the network, while iteratively removing connections. The giant strongly connected component is the strongly connected component of the graph with the larger number of nodes. For simplicity, we will refer to the giant strongly connected component simply as giant component. The iterative removal of connections was done in the following ways: "bottom-up" (proceeding from weakest to strongest connection removal), "top–down" (proceeding from strongest to weakest connection removal), and random (random removal of connections with no ordering according to strength). A faster decay of the relative giant component after the targeted removal of the weakest or strongest connections, when compared to the decay caused by random removal, indicates a prominent role of a specific connection weight class in network cohesion. Hence, comparing the fractionation of the network for the "bottom-up", "top-down", and random analysis will indicate any significant prominent role of weak connections in network cohesion (Pajevic and Plenz 2012). We conducted 1,000 random pruning analyses.

To address if any potential prominent role of weak connections in network cohesion is due to their non-random placement in the macaque brain network, the decline of the relative giant component during the bottom-up pruning in the original network was compared with a bottom-up pruning in 1,000 null networks matched in number of connections, node, and degree distribution.

To assess the significance of the results, we computed p values and z-scores from the empirical null networks generated as described above.

As a control analysis, we tested the strength-of-weak-ties hypothesis with the aid of a different dataset from the CoCoMac database (http://cocomac.g-node.org/). The data were mapped to the Von Bonin and Bailey (1947) parcellation resulting in a 25×25 weighted and directed graph. Distances between the 25 areas were approximated with the Euclidean distance between their center of mass (see Bezgin et al. 2012; Goulas et al. 2014 for details). The major difference of this control dataset with the one used in our main analysis is that the former is the result of a meta-analytic and literature based data compilation with subjective ordinal scales for connection density, i.e., "weak", "moderate", "strong" (e.g., Bezgin et al. 2012). Despite that such features might render such a dataset inadequate for the pertinent questions, we used it as control analysis to assess the generalizability of our strength-of-weak-ties analysis and link our results with the widely used CoCoMac database. The exact same procedure for addressing the NEO/strength relation, module decomposition, and classification of connections as inter- or intramodular was followed for this control dataset as described for the main analysis.

All the analysis was performed with custom software written in Matlab (Mathworks) and Matlab functions from the Brain Connectivity Toolbox (https://sites.google.com/site/bctnet/) and MatlabBGL (https://github.com/dgleich/matlab-bgl).

Results

The strength of the cortico-cortical connections as a whole correlated positively with their NEO, in line with the prediction of the strength-of-weak-ties hypothesis ($r = 0.28$, $p < 0.001$, z-score = 8.55) (Fig. 2a). The module detection algorithm decomposed the network in five modules, roughly mapping to distinct anatomical divisions: occipito-temporal (V1,V2, V4, DP, MT, TEO, TEpd), parieto-motor (7A, 5, 7B, F1, F2, 7m), temporal (STP, STPi, STPc, PBr), frontal (9/46d, 8m, 24c, F7, 8l, 9/46v, 46d, 8B, 10) and somato-motor (F5, 2, ProM) (Fig. 3). The module detection gave rise to a significant modularity Q value (0.63, $p < 0.001$, z-score = 9.98). No degeneracy was observed across solutions since all partitions were identical across 1,000 runs, i.e., all pairwise partition comparisons led to zero variation of information. The module decomposition resulted in the partition of connections in inter- (378 connections 71 %) and intramodular (158 connections 29 %). Intermodular connections exhibited a significant correlation of strength and NEO ($r = 0.33$, $p < 0.001$, z-score = 5.93) but intramodular failed to exhibit such a relation ($r = 0.10$ $p > 0.1$) (Fig. 2c, e). The within module density was near 1, i.e., all connections that could be present within a module were present. Hence, the rewiring algorithm cannot be applied to construct null network configurations.
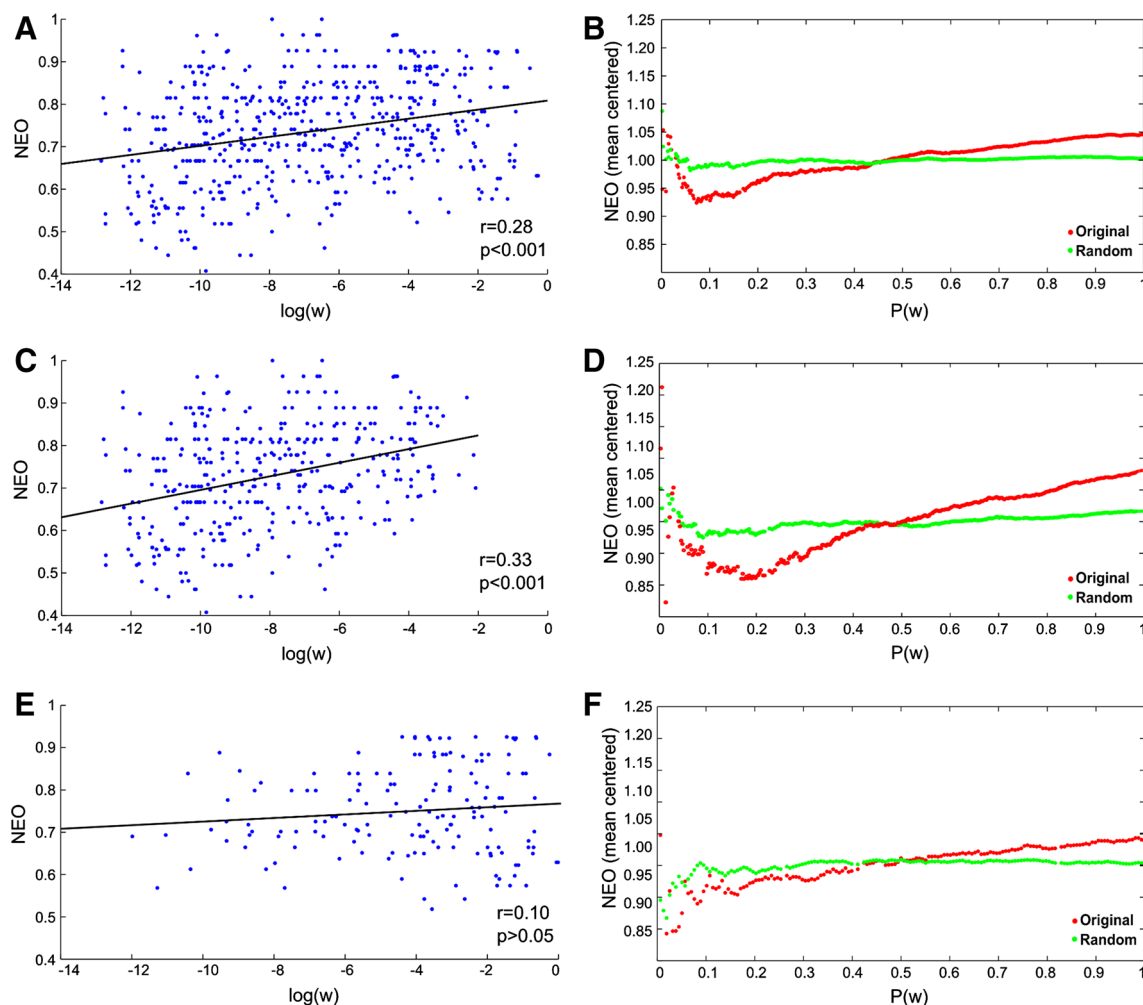
Fig. 2 The relation of NEO and strength confirms the predictions of the strength-of-weak-ties hypothesis for all and intermodular connections. Scatterplots of strength (log transformed, x axis) and NEO values (y axis) for **a** all, **c** intermodular, and **e** intramodular connections. The *lines* correspond to a least-square fit to the data. A positive significant (Pearson's) correlation for all and intermodular was observed (See also Table 1 for Spearman's rank correlation values). NEO values in relation to the cumulative connection strength for the original and random networks are depicted for **b** all, **d** intermodular, and **f** intramodular connections. Note that the NEO values in panels **b**, **d**, and **f** are scaled to the mean of the NEO values for the original and random networks. Note that for the original networks the NEO values increase as a function of the cumulative connection strength more steeply compared to random networks

Consequently, we used the weight reshuffle null model (Opsahl et al. 2008) to assess the significance of the intramodular NEO/strength relation. An interesting pattern was observed in the plot of the cumulative distribution of NEO and connection strength (Fig. 2b, d). While there is an increase in NEO values with increased connection strength, this relation starts to be prominent for connection strengths higher than a small percentage of very weak connections ($\sim$10 % for all and $\sim$20 % for intermodular connections). Hence, while the strength-of-weak-ties hypothesis holds for all and intermodular connections, a very small percentage of the weakest connections of the aforementioned connection classes do not comply with such a principle.

Importantly, all the above significant results were also significant if physical length of the connections was taken into account when computing partial correlations between NEO and strength. Hence, the observed relation between NEO and strength is not attributable to physical distance. Moreover, the aforementioned results did not change if Spearman's correlation was used instead of Pearson's or if only incoming and outgoing connections were used to define the NEO values and compute the NEO/strength correlation (Table 1).

Notably, the strength-of-weak-ties hypothesis was also confirmed with the CoCoMac dataset since a positive NEO/strength Spearman's rank correlation was obtained for all ($\rho = 0.46$, z-score = 7.23), intermodular ($\rho = 0.49$, z-score = 1.79), and intramodular ($\rho = 0.39$, z-score = 4.01)
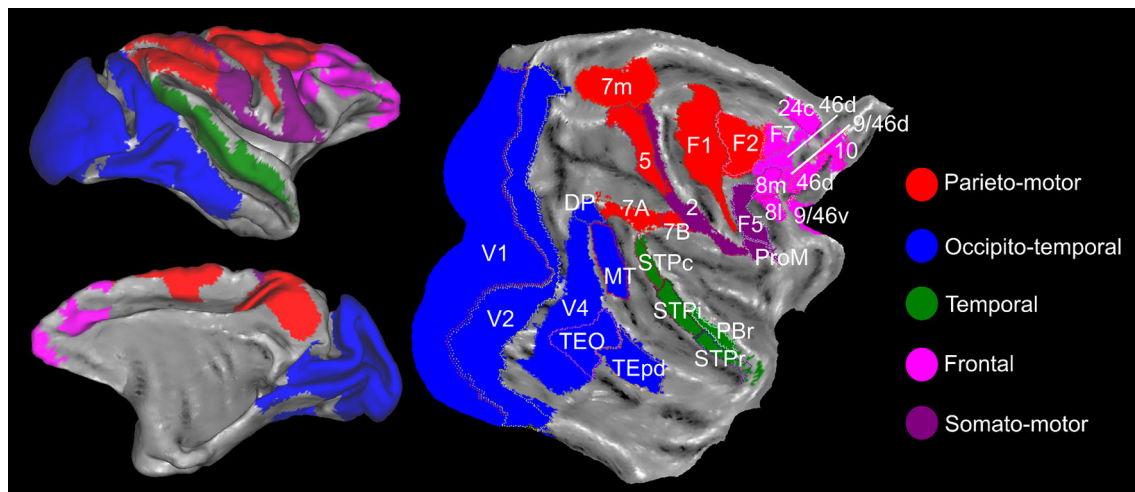
Fig. 3 Decomposition of the cortico-cortical network in five modules. The modules tightly relate to distinct anatomical divisions and labeled accordingly. Boundaries of the distinct areas constituting each module are depicted with *dashed lines* (see Markov et al. 2014 for acronyms of areas)

Table 1 Spearman's rank correlation coefficients for the distinct NEO definitions (all, incoming, outgoing) and distinct classes of connections (all, "incoming"/lower diagonal, "outgoing"/upper diagonal of the connectivity matrix) for computing the NEO/strength correlation

NEO_{type}/ connections	Connection class		
	All	Intermodular	Intramodular
NEO_{All}/all	0.26 (0.21)	0.32 (0.31)	0.06 NS (−0.03 NS)
NEO_{All}/in	0.22 (0.15)	0.24 (0.22)	0.11 NS (0.06 NS)
NEO_{All}/out	0.30 (0.25)	0.40 (0.38)	0.01 NS (−0.07 NS)
NEO_{in}/all	0.32 (0.26)	0.32 (0.33)	0.03 NS (−0.07 NS)
NEO_{in}/in	0.29 (0.23)	0.24 (0.22)	0.10 (0.01 NS)
NEO_{In}/out	0.36 (0.29)	0.40 (0.40)	0.04 NS (−0.16 NS)
NEO_{Out}/all	0.37 (0.28)	0.36 (0.34)	0.16 (0.06 NS)
NEO_{Out}/in	0.32 (0.22)	0.30 (0.29)	0.10 (0.01 NS)
NEO_{Out}/out	0.41 (0.34)	0.41 (0.39)	0.21 (0.12 NS)

Coefficients in parenthesis correspond to values obtained after partialling out physical distance. Note that all coefficients for the distinct NEO definitions and connection types are significant for all and intermodular connections but not for intramodular ones (denoted with NS)

connections (all coefficients $p < 0.05$) (see also Fig. S1). The discrepancy with respect to the intramodular connections does not hamper our main conclusions (see "Discussion"). Significant results were also obtained if physical distance was partialed out.

The evolutionary algorithm revealed network configurations that could substantially increase (expressed as % change below) the correlation between NEO and strength for all the distinct classes of connections previously shown to exhibit a significant NEO/strength relation. Changes for maximizing the NEO/strength correlation: all connections

$r = 0.70$ (154 %), intermodular $r = 0.69$ (107 %). Dramatic changes were achieved when minimizing the correlation between NEO/strength: all connections $r = -0.52$ (−290 %) and intermodular $r = -0.42$ (−226 %). Similar increases (and decreases) were observed in the optimized networks when taking into account physical distance as covariate. We should note that highly modular topologies were obtained (optimization on the intermodular connections) alongside with a negative NEO/strength correlation. This demonstrates empirically that the architecture dictated by the strength-of-weak-ties hypothesis is not necessarily present in networks exhibiting a modular structure.

The aforementioned changes induced by the optimization procedure involved a relatively small percentage of connections. For maximizing the correlation between strength and NEO and taking into account all connections, a total of 22 % of connections differed, and thus "mutated", between the original and the optimized networks. When such an optimization involved only the intermodular connections, the "mutations" involved 30 % of the intermodular connections. For minimizing the correlation between strength and NEO, the percentages were 28 % (all connections) and 32 % (intermodular connections). The aforementioned results demonstrate that despite the positive and significant relation of strength and NEO of the connections, this wiring configuration does not optimally comply with the predictions of the strength-of-weak-ties hypothesis. However, the percentages of decrease of this relation were much higher that the percentages of increase, indicating that the wiring of the original network lies closer to an "optimal" configuration.

Importantly, all optimized configurations exhibited negligible changes in wiring cost and efficiency. These

changes were much smaller when compared to the ones obtained from an explicit maximization/minimization of the efficiency and wiring cost of the network as a whole and for the distinct classes separately (Table 2). Thus, optimizing the wiring of distinct classes of cortico-cortical connections to maximize/minimize the correlation between NEO and strength, does not substantially sacrifice efficiency and wiring cost.

Incorporating explicitly in the evolutionary algorithm constraints on the wiring cost and efficiency of the network revealed that pronounced changes with respect to maximizing/minimizing the NEO/strength relation can be accompanied by efficiency and wiring cost values very close to the original ones or "ameliorating" them, i.e., maintaining a comparable wiring cost and a comparable or higher efficiency as in the original network (Fig. 4; Table 2). Such changes were closer to the original values of the network, compared to the optimization that only took into account the NEO/strength correlation (compare corresponding values of Tables 2, 3). Again the aforementioned changes in the optimized networks involved a relatively low percentage of "mutated" connections. For maximizing the NEO/strength and taking into account all connections, a total of 15 % connections differed between the original and the optimized network. When such an optimization involved only the intermodular connections the "mutations" involved 18 % of the intermodular connections. For minimizing the NEO/strength correlation the percentages were 20 % (all connections) and 21 % (intermodular connections).

The steepest decrease of the relative size of the giant component was observed for the "bottom-up" pruning (Fig. 5a). The corresponding area under curve (AUC) was significantly smaller than the one observed for the random pruning (AUC_{weak} 0.85 vs AUC_{random} mean 0.88 std 0.01 $p < 0.001$, z-score $= -2.73$). The "top-down" pruning led to a non-significant AUC value when compared to random pruning (AUC_{strong} 0.87 $p > 0.1$) (Fig. 5b). Hence, a targeted attack on the weaker connections affects in a prominent way the cohesion of the network. Additionally, the AUC of the "bottom-up" pruning was significantly smaller

from the "bottom-up" pruning applied to null networks (AUC_{weak} 0.85 vs $AUC_{weak\ random\ network}$ mean 0.89 std 0.01 $p < 0.001$, z-score $= -4.36$) (Fig. 5c). This suggests that the non-random placement of the weak connections in the original network gives rise to the rapid fractionation of the network.

Discussion

The main findings of the study are as follows: (1) The architecture proposed by the strength-of-weak-ties hypothesis pertains to the macroscale connectional architecture brain as a whole and to intermodular connections, thus relating a topological factor to the strength of connections. (2) The wiring of all and intermodular connections does not optimally comply with the aforementioned architecture. This configuration is not attributable to a trade-off with wiring cost and efficiency and might have functional benefits over an optimal one. (3) Weak connections, but not strong ones, are important for network cohesion due to their non-random placement in the network.

### The strength-of-weak-ties and functional implications

The macaque cortico-cortical network is characterized by a decay of connection strength with increasing physical distance (Kaiser et al. 2009; Markov et al. 2013b). Moreover, the similarity of connections of two areas is inversely related to their physical distance (Markov et al. 2013b). Our results extend such findings and demonstrate that these two properties exist hand in hand: the smaller the strength of a connection, the less its NEO is. This held true for all but the intramodular connections which constitute the minority of connections (29 %). In addition, a small subset of the weakest connections (~ 10 % for all and ~ 20 % for intermodular connections) seems to escape this relation (Fig. 2). Thus, the principle proposed by the strength-of-weak-ties hypothesis pertains to the majority of cortico-cortical connections.

Table 2 Percentage of changes in NEO/strength correlation, efficiency, and wiring cost when optimizing for NEO/strength correlation only

Type of connection	% Change in NEO/strength maximization/ minimization	% Change for NEO/ strength maximization		% Change for NEO/ strength minimization		% Change in explicit maximization/ minimization	
		Wiring cost	Efficiency	Wiring cost	Efficiency	Wiring cost	Efficiency
All	154/−290	5.3	3.9	9.1	6.2	24.1/−3.6	30.7/−9.4
Intermodular	107/−226	1.9	−0.2	1.8	0.7	10.1/−3.9	7.4/−4.9

Values correspond to the mean values from 10 runs of the evolutionary algorithm

Fig. 4 Changes in network metrics observed in the optimization procedure with optimality defined by taking into account NEO/strength correlation, efficiency, and wiring cost for **a** all and **b** intermodular connections. Substantial changes were observed for the NEO/strength correlation while efficiency and wiring cost were very close to the original values. Efficiency and wiring cost changes were negligible when compared to empirical maximum and minimum values (see also Table 3). Transparency of symbols is used due to the overlap of % values in certain cases
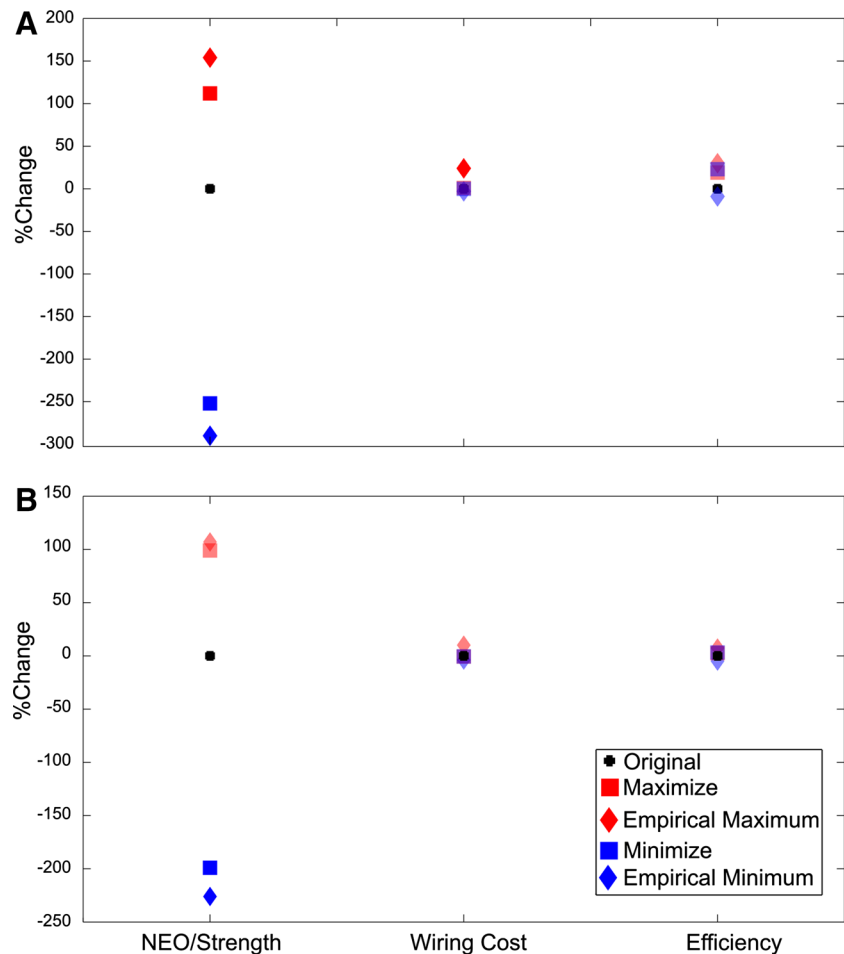
Previous work has demonstrated the important role of intermodular "bottleneck" connections for suppressing information flow without the need of active inhibition (Kaiser et al. 2007). Moreover, a relatively high percentage of connections in the cat cortex links different modules, an anatomical feature indicative of the rather integrative nature of the cat cortico-cortical network (de Reus and van den Heuvel 2013). This observation is at odds with the high number of intermodular connections (71 %) in the macaque dataset employed in the current study. Hence, the macaque cortico-cortical network is also characterized by an overabundance of intermodular connections. The current results refine the picture of intermodular connections by demonstrating that intermodular connections do not simply link areas of different modules. Instead their wiring exhibits an orderly pattern related to network topology: their strength is positively related with the segregation of the interconnected areas, i.e., the number of common areas with which they are in turn connected (Fig. 2b; Table 1).

The aforementioned architecture has functional implications. Higher efficiency of communication between cortical areas positively relates to the strength of their connectivity as shown in computational studies (ter Wel and Tiesinga 2012). This assumption underlies how weights are treated when computing properties of structural networks, such as efficiency (e.g., Ercsey-Ravasz et al. 2013). Hence, increasingly weaker connections between increasingly segregated areas offer an effective mechanism for preventing "activity leakage" between areas belonging to anatomically segregated circuits and avoids uncontrolled spreading across the whole network (Kaiser et al. 2007; Onnela et al. 2007). Thus, this structural configuration can constitute a connectional feature responsible for a baseline segregation of areas. Apart from connection density, coherence between neuronal populations in distinct areas appears important for efficient communication (e.g., Fries 2005). Hence, a baseline state of segregation imposed by the anatomical network can be modulated based on moment-to-moment task demands and cognitive contexts. Such dynamic reconfigurations offer a flexible mechanism for modulating the efficiency of relatively stable, at least at the level of milliseconds, anatomical pathways (Womelsdorf et al.

Table 3 Percentage of changes in NEO/strength correlation, efficiency, and wiring cost when optimizing for NEO/strength correlation, efficiency, and wiring cost simultaneously

Type of connection	% Change in NEO/strength maximization/ minimization	% Change for NEO/ strength maximization		% Change for NEO/ strength minimization		% Change in explicit maximization/ minimization	
		Wiring cost	Efficiency	Wiring cost	Efficiency	Wiring cost	Efficiency
All	113/−253	0.1	0.5	0.4	1.7	24.1/−3.6	30.7/−9.4
Intermodular	96/−201	0.5	0.4	1.0	2.6	10.1/−3.9	7.4/−4.9

Values correspond to the mean values from 10 runs of the evolutionary algorithm
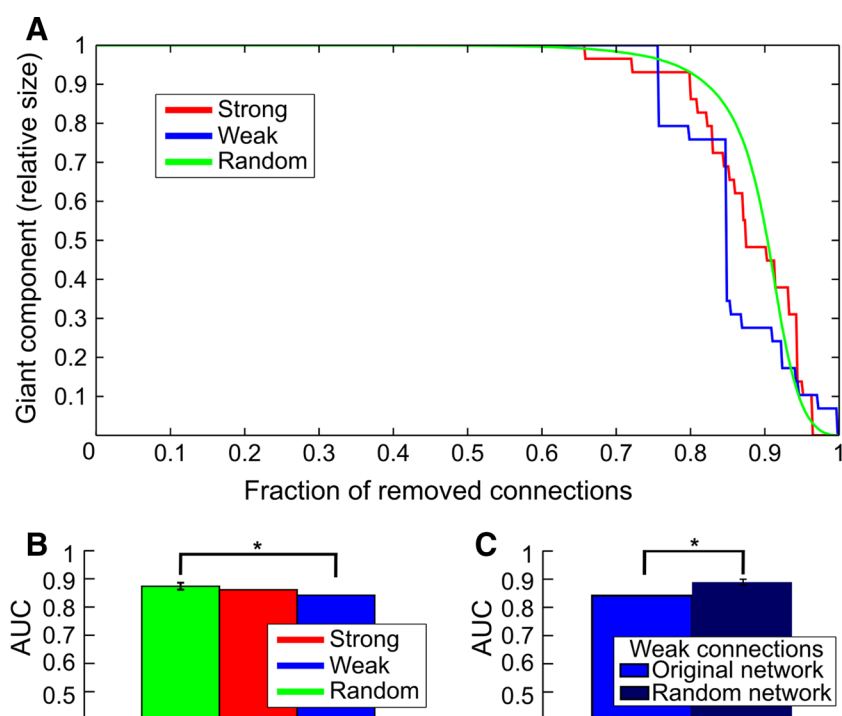

Fig. 5 Role of weak connections in network cohesion. **a** Fractionation of the network, as measured by the relative size of the giant component, i.e., nodes of the giant component divided by the number of nodes of the network, as a function of removal of connections. A targeted removal starting from weaker connections ("bottom-up") leads to a more pronounced fractionation when compared to a targeted removal of strong ("top-down") connections and random removal. Note that the curve for the random removal was computed as the mean over 1,000 random removal steps and thus appears smoother. **b** AUCs resulting from targeted weak, strong, and random removal demonstrate a statistically significant smaller AUC for the weak connection removal when compared to random removal ($p < 0.001$). AUC differences between strong and random removal were not significant. Hence, weak connections appear prominent in network cohesion. **c** The AUC resulting from a targeted weak connection removal is smaller when compared with a targeted weak connection removal in 1,000 random networks ($p < 0.001$). Hence, the prominent role of weak connections is due to their non-random placement in the original network

2007). These mechanisms can render weak connections between segregated regions effective, thus altering the segregation imposed by the anatomical skeleton. This would facilitate the exchange of novel/diverse information, in the sense that weak connections bridge areas with diverse set of neighbors and hence with direct access to information from distinct areas.

Non-optimality, wiring cost, and efficiency

The networks optimized for maximization/minimization of the NEO/strength correlation exhibited very small changes in wiring cost and efficiency, indicating that such configurations can coexist with efficiency and wiring cost values very close to the ones of the original network (Fig. 4;

Tables 2, 3). Consequently, the fact that the original network appears to suboptimally correspond to a configuration as predicted by the strength-of-weak-ties hypothesis is not due to a competitive relation of this wiring principle with efficiency maximization and wiring cost minimization. The observed suboptimality might be explained by the functional properties arising from such a structural configuration. The underlying topology of the anatomical network and features such as the amount and topology of intermodular connections substantially influence the balance between global synchronization (integration) and local within-community synchronization (segregation) (e.g., Zhao et al. 2011; Gómez-Gardeñes et al. 2010). For instance, in synthetic graphs wiring intermodular connections in a random fashion enhances global synchronization but hampers functional segregation, while a preferential intermodular wiring taking into account the degree of the interconnected areas leads to a good balance between segregation and integration. Interestingly, the cat anatomical network seems to correspond to the latter wiring pattern (Zhao et al. 2011). In light of the above, a non-optimal wiring as predicted by the strength-of-weak-ties hypothesis, without substantially hampering wiring cost and efficiency, might constitute a more adequate architecture for balancing global and local synchronization when compared to optimal strength-of-the-weak-ties architectures. Testing the aforementioned functional properties of the distinct structural configurations currently investigated is an important future direction.

Weak ties are crucial for network cohesion

Weak ties are proposed to exhibit a prominent universal role in networks, including importance in cohesion (Csermely 2006). Analysis in communication networks confirms this prominent role of weak ties (Onnela et al. 2007). Indirect assessment of the strength of cortico-cortical connectivity highlights that weak ties are important for network cohesion when it comes to the human brain (Pajevic and Plenz 2012). Our study further corroborates the prominent role of weak connections in network cohesion in a dataset that allows a reliable estimate of connection strength. We have demonstrated that not only the targeted removal of weak connections leads to a faster fractionation of the network when compared to random removal and a targeted removal of strong connections, but that this decay is faster when compared to the targeted removal of weak connections in random networks (Fig. 5). Hence, from the viewpoint of prominence in network cohesion, weak connections appear more important due to their non-random placement, complementing claims that aspects of the strength-of-weak-ties are attributable to their randomness (Pajevic and Plenz 2012).

Factors shaping topology and strength of connections

What could be the factors giving rise to the relation between strength of connections and network topology currently demonstrated in the macaque brain? A simple axonal growth model seems to account for basic properties of cortico-cortical connections such as decay of strength with increased distance (Kaiser et al. 2009). This model explains the relation between the strength of a connection and the levels of segregation of the areas that it links in a basic way, i.e., weak (strong) ones tend to link less (more) segregated areas. This might constitute a basic blueprint to be further refined and give rise to the systematic relation between the NEO and strength of connections. Such refinement might rely on Hebbian-like mechanisms, i.e., two connected areas with shared neighbors might fire more synchronously due to, for example, incoming connections from common neighboring areas or consolidating/preserving the established connections in between them (Vértes et al. 2012). Interestingly, a relation between NEO and synaptic strength seems to exist at the microscopic level, i.e., pyramidal cell connectivity in the rat somatosensory cortex (Perin et al. 2011). Such relations are suggested to be genetically coded since the aforementioned findings concern very early postnatal rats. The above and our own findings conjointly suggest a tight relation between the topology and strength of connections at the macro- and microlevel, with potentially both genetic and Hebian-like mechanisms shaping this relation.

Implications for the organization of the human brain

How can this connectional architecture observed in the macaque brain relate to the architecture of the human brain? Increased brain size seems accompanied by decreases in overall cortico-cortical connectivity (Herculano-Houzel et al. 2010). This would entail that the high proportion (71 %) of intermodular connections currently observed in the macaque brain will be highly reduced in the human brain, a hypothesis that cannot presently be addressed since a good estimate of the number of intermodular connections is not possible owing to limitations of current in vivo imaging techniques. A decreased intermodular connectivity offers the proper anatomical skeleton for increased isolation of the distinct modules. This feature combined with the presence of an organization complying with the strength-of-weak-ties hypothesis can lead to increased segregation of areas in the human brain, leading to a finite area-to-area accessibility in the underlying network which is reminiscent of a "large-world" architecture (Moretti and Muñoz 2013). The later topological architecture seems crucial for extended criticality (Griffith phases) important for selective response to a large

spectrum of stimuli/states (Moretti and Muñoz 2013). It is intriguing to speculate that the aforementioned topological properties might offer an ideal anatomical skeleton for finite network accessibility, leading to dynamic properties that, despite being reported for simple neuronal systems such as the *C. elegans* (Moretti and Muñoz 2013), might be crucial and play a unique role in human adaptive and versatile cognition.

Interestingly, a recent study assessing connectivity in the human brain with functional MRI demonstrates a prominent role of weak connections in explaining variance in intelligence measures, at least within the resolution limits offered by the aforementioned modality (Santarnecchi et al. 2014). Such results, alongside the prominent role of weak connections illustrated in our study, pinpoints the importance of focusing on weak connections and not demoting their role in connectivity studies, e.g., by thresholding and maintaining only a small percentage of the strongest connections. Unfortunately, unraveling in vivo and in detail the totality of such weak connections with the current imaging methods remains challenging (for instance separating very weak but "true" connections from spurious/noisy ones). The inability to uncover weak connections and their elimination after the application of a threshold has different degrees of impact determined by the pertinent aims of each study. Therefore, our findings suggest that a thorough elaboration on the potential impacts of such an omission and relevant control analysis where possible should take place in studies of the human connectome.

Limitations and future perspectives

One potential limitation of our study is that the data currently used involve a subset of cortical areas and do not offer full brain coverage. It could be argued that additional injections throughout all brain areas might unveil an organization that goes against the strength-of-the-weak-ties hypothesis. However, we believe that this is unlikely for the following reasons: Firstly, the current 29 areas are representative since they span the frontal, parietal, temporal, and occipital lobes. Secondly, the strength-of-the-weak-ties hypothesis was confirmed with an independent dataset derived from the CoCoMac database.

One point that warrants attention is that despite the significant correlation between NEO and strength of connections, the explained variance is rather low. What other factors could relate to the strength of cortico-cortical connections? Physical distance and cytoarchitectonic differences of the interconnected areas are related to connection strength in the cat and macaque cortex (e.g., Hilgetag and Grant 2010; Ercsey-Ravasz et al. 2013). Thus, future approaches could combine the aforementioned factors with the topological factor, i.e., NEO, that we currently

demonstrated to be related to strength of connections, to address the total amount of variance explained and the relative importance of each factor when they are examined conjointly.

A question arises as to what extent the connectional features currently investigated pertain to the mammalian brain or are specific characteristics of the primate brain. Collaborative efforts for collation of tract-tracing results in rats (http://brancusi.usc.edu/) (Bota and Swanson 2010), mice (http://www.mouseconnectome.org/) (Zingg et al. 2014) and cats (Scannell et al. 1995) allow for the exploration of the connectome of these species. Hence, future studies should address if the findings currently reported pertain to the brains of other species, potentially constituting a blueprint of the connectional architecture of the mammalian brain. A potential limitation is the lack of quantitative objective information regarding the strength of the connections in the aforementioned databases. Recent efforts circumvent this limitation by offering whole-brain connectomes, including objective quantitative information on connection strengths in animal models such as the mouse (Oh et al. 2014) (http://connectivity.brain-map.org/).

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