Cerebral Cortex doi:10.1093/cercor/bhs399

Mapping the Hierarchical Layout of the Structural Network of the Macaque Prefrontal Cortex

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A consensus on the prefrontal cortex (PFC) holds that it is pivotal for flexible behavior and the integration of the cognitive, affective, and motivational domains. Certain models have been put forth and a dominant model postulates a hierarchical anterior-posterior gradient. The structural connectivity principles of this model dictate that increasingly anterior PFC regions exhibit more efferent connections toward posterior ones than vice versa. Such hierarchical asymmetry principles are thought to pertain to the macague PFC. Additionally, the laminar patterns of the connectivity of PFC regions can be used for defining hierarchies. In the current study, we formally tested the asymmetry-based hierarchical principles of the anterior-posterior model by employing an exhaustive dataset on macaque PFC connectivity and tools from network science. On the one hand, the asymmetry-based principles and predictions of the hierarchical anterior-posterior model were not confirmed. The wiring of the macaque PFC does not fully correspond to the principles of the model, and its asymmetry-based hierarchical layout does not follow a strict anterior-posterior gradient. On the other hand, our results suggest that the laminar-based hierarchy seems a more tenable working hypothesis for models advocating an anterior-posterior gradient. Our results can inform models of the human PFC.

Keywords: connectivity, hierarchy, macaque, network analysis, prefrontal cortex

Introduction

The prefrontal cortex (PFC) is associated with flexible and goaldirected behavior, integrating information from various modalities and bridging the cognitive, affective, and motivational domains (Barbas 2000; Groenewegen and Uylings 2000; Miller and Cohen 2001; Kouneiher et al. 2009). The PFC, as the rest of the brain, can be conceived as a complex system with its distinct subregions interacting through their structural connections. Such a conceptualization, along with the employment of network analysis, has been previously used to elucidate organization principles of the PFC (Kötter et al. 2001), the visual system (Hilgetag et al. 2000), and the large scale brain network of the macaque (Modha and Singh 2010). To understand the organization of a complex system, the concept of hierarchy is often employed. In general terms, "hierarchy" describes the relation among a set of elements indicating which element lies "below" or "above" another (Bond 2004). The concept of hierarchy and appropriate analytic tools have been used, for instance, in systems biology to elucidate regulatory pathways in protein interaction networks (Ispolatov and Maslov 2008).

In neuroscience, the concept of hierarchy has been employed in order to examine the structural architecture of the visual system of the macaque (Felleman and Van Essen 1991). The principles of this hierarchical layout are based on the laminar patterns of connections between the regions constituting the visual system. The laminar origin and termination of a connection are used in order to classify a connection as "feedforward" (FF), "feedback" (FB), and "lateral." FF connections are efferents from regions lower in the hierarchy, for example, V1, toward regions higher in the hierarchy, for example, V4. FB connections follow the reverse order and lateral connections link regions at approximately the same level within the visual processing architecture. Several computational tools have been fruitfully adopted in order to find the hierarchical arrangement of the regions of the visual system (Hilgetag et al. 1996). Similar hierarchical principles seem to also hold for the somatosensory and motor cortices (Felleman and Van Essen 1991).

The definition of hierarchy based on laminar patterns of connections is a popular concept mainly applied to the visual system. Other definitions of hierarchy have been employed in order to formulate principles and models of the PFC. One such model postulates a hierarchical anterior-posterior gradient (Badre and D'Esposito 2009). This model is the culmination of theories and evidence on the hierarchical nature of the PFC built primarily on task-based studies (Koechlin et al. 2003; Koechlin and Summerfield 2007). Task-based functional magnetic resonance imaging (fMRI) paradigms involving humans revealed that increasingly abstract rules engage more anterior regions (Koechlin et al. 2003; Badre and D'Esposito 2007). With such function-related findings as a starting point, additional PFC features such as the structural connections of the PFC of the macaque have been suggested to support a hierarchical anterior-posterior gradient (Badre and D'Esposito 2009). According to the hierarchical anterior-posterior model, the structural connectivity of the PFC adheres to the principles of contiguity and asymmetry. We shall refer to this type of hierarchy as asymmetry-based hierarchy (ABH). The asymmetry principle suggests that regions higher in the hierarchy exhibit a "surplus" of efferents, that is, more connections, to regions lower in the hierarchy. The contiguity principle dictates that spatially adjacent regions can exhibit bidirectional connections. The principle of contiguity is likely adopted in order to accommodate the fact that excessive reciprocal connections exist between adjacent, that is, spatially contiguous, PFC regions (Koechlin and Summerfield 2007; Badre and D'Esposito 2009). Such reciprocity and decrease of connectivity between PFC regions with increased spatial distance, that is, contiguous or separated by other regions, is demonstrated in computational analysis of the connectivity of

the macaque PFC (Kötter and Stephan 2003; Averbeck and Seo 2008).

The hierarchical anterior-posterior model postulates that region 10, that is, the most anterior region, lies at the top of the hierarchy, whereas posterior regions, like region 8, lie at the bottom of the hierarchy. This is inferred from the observation that there are more efferent connections from anterior to posterior regions than vice versa. In other words, according to the model, the dominant direction of the PFC network obeys an anterior-posterior gradient. Consequently, anterior regions are favored to have a "regulatory" role by broadcasting signals to more posterior regions and thus lie higher in the hierarchy. In terms of control theory, regions high in such a hierarchy function as broadcasters, that is, they are ideally positioned to primarily influence other regions rather than being influenced by other regions. Regions low in the hierarchy function as receivers and exhibit the reverse properties (Kötter et al. 2001; Hilgetag et al. 2002).

The hierarchical anterior-posterior model is characterized by some limitations/open issues: Only data from a couple of tracing studies were used (data limitation). Moreover, a descriptive approach was adopted and no formal analyses were employed (quantification limitation). Furthermore, there is no clear consensus about which exact regions should be selected for a subsequent examination of their structural connectivity. The various hierarchical models, employing task-based fMRI paradigms, involve a partially overlapping but not identical set of regions engaged by experimental manipulations (Koechlin et al. 2003; Badre and D'Esposito 2007), and due to excessive intersubject variability (Uylings et al. 2005), no clear unique anatomical substrate can be attributed to them. Additionally, the aforementioned experimental manipulations involved human subjects. Hence, an extrapolation from the human to the macaque PFC can introduce further inaccuracies (localization limitation).

In the current study, we will test the principles and predictions of the hierarchical anterior-posterior model concerning the structural connectivity of the macaque PFC, in a formal way and by employing an exhaustive dataset. We should stress that we chose to base our analysis on the principles of the hierarchical anterior-posterior model, that is, asymmetry and contiguity, and not on other hierarchical principles for the very reason that such principles were put forth in (Badre and D'Esposito 2009). Hence, the core analyses employed in our study are tailored for the evaluation of the hierarchical anterior-posterior model and aim at mapping the ABH layout of the PFC. To unravel the ABH layout of the macaque PFC, we employ an algorithm previously used in systems biology (Ispolatov and Maslov 2008). Moreover, the data currently used represent a manifold of tracing studies collated in the CoCoMac neuroinformatics database (Kötter 2004) and constitute our current best knowledge on macaque connectivity. The localization limitation in conjunction with studies pinpointing a holistic approach for the understanding of the PFC (Barbas 1995, 2000; Kouneiher et al. 2009; Taren et al. 2011) led us to investigate the PFC as a whole. This approach also makes plausible the investigation of a possible anterior-posterior hierarchical gradient in the medial and orbital parts of the PFC (O'Reilly 2010).

As a complementary analysis, we aimed to investigate how the aforementioned ABH layout corresponds to a hierarchical layout of the PFC based on a different concept and principles, that is, the laminar patterns of connections of the PFC regions (Barbas and Rempel-Clower 1997). Within this schema, PFC connections can be termed as FB and FF in analogy with the patterns observed in the visual system. Hence, the laminar patterns of the connections can be used for defining the hierarchical arrangement of the PFC regions. This analysis, which we shall refer to as laminar-based hierarchy (LBH), will elucidate if and how the 2 different hierarchical concepts and principles are related and examine whether the anterior-posterior hierarchical gradient is tenable by either definitions of hierarchy.

Materials and Methods

Datasets

The connectivity of the macaque PFC is represented as an $N \times N$ directed graph G (N, E), where N represents the number of PFC regions and E the edges (or arcs) in between them. Hence, a directed connection from region i to j is represented with an entry G(i,j). The connectivity matrix used in the current study is a binary version of the connectivity matrix used in Kötter et al. (2001). Therefore, entries G(i,j) can be 1, if a connection exists, or 0, if a connection is absent. These connectivity data were collated from 148 tracing studies available in the CoCoMac database (Kötter 2004) and mapped to Walker's parcellation scheme (Walker 1940) with objective relational transformation. This technique permits assembling data from different cortical parcellations in one "reference" parcellation scheme. Such transformations are based on spatial relations between regions from different parcellations schemes, for example, region A from parcellation X is identical to region B from parcellation Y, and dedicated algorithms and algebra that have been developed for this purpose (Stephan et al. 2000, 2001). We shall refer to the first dataset as "Walker 1" (Table 1 and Fig. 1A). Walker's parcellation scheme is coarse, but it allows the gathering of a vast number of data, it is largely compatible with other parcellation schemes and still widely used (Kötter et al. 2001, 2007). Moreover, the adoption of the aforementioned dataset allows results derived from the current study to be combined with insights from previous studies (Kötter et al. 2001; Kötter and Stephan 2003). The connectivity matrix in Kötter et al. (2001) contains entries/connections of unknown status, which were treated as absent. Since the assumption that connections of unknown status are absent ones can bias the results (Kötter and Stephan 2003), we will also use an updated connectivity dataset based on Walker's parcellation scheme (Kötter et al. 2007) that we will refer to as "Walker 2" (Table 1 and Fig. 1B). In the later dataset, only one connection is of unknown status and was treated as absent. Additionally, in order to examine the influence that the adoption of a particular parcellation scheme might have, we will use data on PFC connectivity as presented in a recent network analysis of the data collated in the CoCoMac database involving more than 400 tracing studies (Modha and Singh 2010). We shall refer to this connectivity dataset as "Modha and Singh PFC." We should note that we treated this dataset "as is", that is, as presented by the authors of

Summary of basic features of the datasets used

	Number of nodes	Number of connections	Edge density	Number of connections of unknown status (treated as absent)
Walker 1	12	97	0.73	8
Walker 2	12	101	0.76	1

Note: Basic network features for the main datasets used. While the number of nodes is the same for both datasets, the number of connections is different. This stems from the fact that Walker 2 is an updated connectivity matrix where information about the connections with a previous unknown status has been incorporated. Note that while Walker 1 has 8 connections with unknown status, Walker 2 has only 1. In both cases, such connections were treated as absent. Edge density is the number of existing connections divided by the number of all possible connections in each dataset.

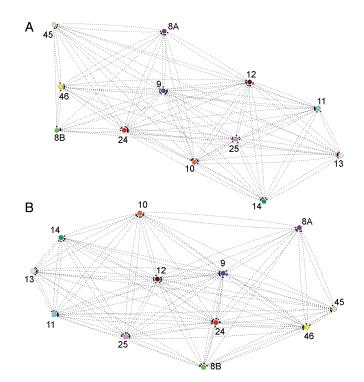


Figure 1. Graph representation of the PFC connectivity datasets. The PFC connectivity based on Walker's parcellation scheme is represented as a directed graph. Dataset (A) Walker 1 and (B) Walker 2. The directed graphs are arranged with the Kamada–Kawai spring embedding algorithm.

the later study: No further regions, for example, cingulate region 24 (Uylings and Van Eden 1990), were added as part of the PFC. The usage of different datasets and/or parcellation schemes allows us to assess their impact on the results and conclusions of the analyses.

Problem Formulation

An ABH organization is characterized by the principles of asymmetry and contiguity dictating that bidirectional connections are allowed between contiguous regions, while for noncontiguous ones an asymmetry should hold. In other words, asymmetry dictates that more efferent connections exist from regions higher in the hierarchy toward regions lower in the hierarchy than vice versa (Fig. 2). Hence, the dominant direction within the structural network obeys the anterior-posterior gradient. To formulate the problem at hand in a rigorous way, we represent the connectivity of the PFC as a directed graph G(N, E), as previously described. Hence, the problem of ABH arrangement of the PFC regions can be formulated as converting the graph to an acyclic one, that is, with no paths that start and end at the same node, in such a way that there is a minimum deletion of "antihierarchical" arcs/connections that form loops/cycles (Ispolatov and Maslov 2008).

This problem is known in graph theory as the minimum feedback arc set problem (e.g. Eades et al. 1993). Such approaches have been employed for the analysis of complex networks in systems biology in order to produce a hierarchical layout and trace nodes functioning as regulators and targets (Ispolatov and Maslov 2008). Other recent applications include the analysis of large-scale biological systems, that is, gene regulatory networks (Soranzo et al. 2012). Similar concepts and the appropriate network metrics have been employed for unraveling PFC regions that are anatomically embedded in such way to predominantly influence rather than get influenced by other regions (Kötter et al. 2001). While the primate cortex is clearly not "naturally" acyclic, for example, it possesses a high clustering coefficient (CC) (e. g. Sporns et al. 2007) and, consequently, the existence of antihierarchical arcs/connections is certain, its conversion to an acyclic graph with the minimal possible arc deletion will allow us to reveal an hierarchical arrangement of the PFC regions (see below). We should note

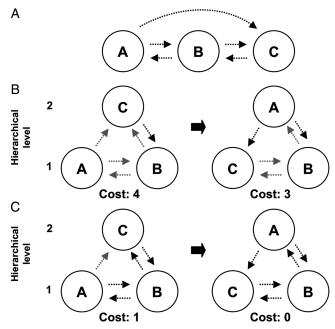


Figure 2. Example of the ABH optimization in a toy network. Given a directed network depicted in A, the nodes are randomly assigned to M levels. Here, for the sake of simplicity M=2. (B) Cost function 1 is used to compute the cost, that is, the number of antihierarchical arcs (colored in light gray), at state 1 (left) leading to $\cos t = 4$. After shuffling the nodes randomly (state 2 on the right), the cost is recomputed, that is, $\cos t = 3$. Hence, this state is favored since it possesses a lower cost and corresponds to a "more hierarchical" arrangement of the nodes. (C) The same example as in B, but cost function 2 is employed, that is, only antihierarchical arcs between noncontiguous regions are taken into account. This toy network is based on the illustration of the principles of the anterior—posterior hierarchical model (Fig. 4 in Badre and D'Esposito 2009). For the sake of simplicity, only 2 hierarchical levels are used.

that such connections should not be considered as "redundant" since their absence would not correspond to a neuroanatomically realistic network. Instead they should be conceived as connections opposing the dominant direction within the macaque PFC network.

To hierarchically arrange the PFC regions, we adopt a probabilistic approach based on simulated annealing that has shown good performance in synthetic and natural graphs (Ispolatov and Maslov 2008). We shall refer to this procedure as ABH optimization. Below we give a brief description of the various steps of the algorithm (for details see Ispolatov and Maslov 2008).

Optimization Procedure

Simulated annealing is a stochastic procedure for the approximation of global optima (Metropolis et al. 1953; Kirkpatrick et al. 1983). In our case, the global optimum is an arrangement of the PFC connectivity, represented as a graph G(N, E), in such a way that an acyclic graph is produced with the fewest possible removals of antihierarchical arcs/connections. To this end, the N nodes of the graph assembled from CoCoMac data are assigned to M levels randomly, where M=2, 3, ... N. Higher numbers indicate levels higher in the hierarchy. The sum of the connections from nodes placed at low hierarchical levels to nodes in higher or equal levels are declared antihierarchical arcs/connections, and constitute the cost, or energy (En), of the system. Thus, the goal is to arrange the nodes in a way that would result in the minimization of En (eqs 1 and 2).

During the optimization procedure, 2 different cost functions, which quantify the energy of the system, are minimized: 1) Sum of antihierarchical connections (Fig. 2*B*; eq. 1):

$$\operatorname{En} = \sum_{i \to j} [H(m_j - m_i)], \tag{1}$$

where $i \rightarrow j$ denotes a structural directed connection (or arc/edge) from node (region) i to node j, m_i and m_j are the hierarchical levels of node i and j, and H is the discrete Heaviside step function. 2) Sum of antihierarchical connections that involve noncontiguous regions (Fig. 2C; eq. 2):

$$En = \sum_{i \to j} [H(m_j - m_i) \cdot \delta_{i,j}], \qquad (2)$$

where,

$$\delta_{i,j} = \begin{cases} 1, C(i,j) = 0 \\ 0, C(i,j) = 1 \end{cases}$$

with C denoting the contiguity matrix. The first cost function represents the asymmetry principle and the second cost function also incorporates the contiguity principle and allows connections to originate from low and terminate to high hierarchical levels, provided that they involve contiguous regions. Thus, in order to code if 2 regions are contiguous or not, a contiguity matrix C was compiled with 0 and 1 as entries, where entry C(i,j)=1 denotes that regions i and j are contiguous. To this end, Walker's map was consulted and entries formulated accordingly.

The minimization of En is achieved by the simulated annealing procedure. The initial value for T was set to the average degree of the network, that is, E/N, as suggested in Ispolatov and Maslov (2008). 1) After the initial random assignment of the nodes to M hierarchy levels, En is computed. 2) A new assignment takes place and is accepted with a probability of min $(1, \exp^{-\Delta E n/T})$, where $\Delta E n$ is the difference in the energy and T the temperature. 3) After several reassignments at each temperature level T, here set to 1000, T is decreased to *T* based on $T = c \times T$, where *c* is the cooling factor (here set to 0.9). 4) The procedure ends when $T < 10^{-3}$, and thus the system has "cooled down." The resulting assignment offers an arrangement of the nodes over the M hierarchy levels. Hence, the dominant direction of the network originates from nodes placed in high hierarchical levels toward nodes placed in low hierarchical levels. Due to the stochastic nature of the approach, the procedure is repeated many times (here 1000), and the resulting arrangements/solutions can be used for the estimation of the frequency of assignment of each node to a particular hierarchical level.

The temperature *T* is set high enough in order to allow the exploration of all the states of the system and to avoid getting stuck in local minima. The gradual cooling leads to less probable acceptance of configurations that do not minimize En and forces the system to move toward a global optimum. Moreover, the number of hierarchical levels M has to be defined empirically if no a priori information exists. This entails the application of the algorithm several times by varying the number of hierarchical levels. Subsequently, the optimal number of levels is selected as the one that from which any further increase in the number of levels does not lead to a decrease in the cost/energy (Ispolatov and Maslov 2008).

The ABH optimization arranges the nodes in levels, but no direct information is provided for the hierarchical and antihierarchical connections of the network. To uncover such connections, the following procedure was followed. For each of the 1000 solutions, the hierarchical, from high to low levels, and antihierarchical, from low to high or same levels, connections were uncovered. Hence, the procedure produces a connectivity diagram quantifying the frequency that each connection is hierarchical or antihierarchical. In this way, we can assess the frequency with which each connection constitutes the dominant direction in the anatomical network (hierarchical connectivity diagram) and the frequency with which it goes against this dominant direction (antihierarchical connectivity diagram).

Network Metrics

Finally, network metrics (Kötter and Stephan 2003; Rubinov and Sporns 2010) will be employed in order to examine how each region is embedded within the PFC network. This will allow us to examine

how and if network properties are related to the hierarchical position of each region. Two basic network properties will be examined, that is, centrality and segregation. The centrality of each region will be assessed with the betweenness centrality (BC). Higher BC values for a node indicate that the node participates in a large fraction of shortest paths between the nodes of the network. Hence, such nodes can be viewed as an "intermediate" station of network traffic. The segregation of the regions will be quantified with the CC. The CC of a node quantifies the probability of the existence of direct connections between its neighboring, that is, directly connected, nodes. Hence, higher values indicate "cooperative" relations between the neighbors of a node and are thought to reflect higher levels of segregation (Rubinov and Sporns 2010). Moreover, we will use the transmission index that captures the efferents to afferents relation (Kötter and Stephan 2003). The higher values indicate that a region exhibits more efferent than afferent connections. We use the transmission index since it is closely linked to the current concept of ABH. Regions with higher transmission index values are more suited for higher levels within the hierarchy. All the above measures were computed by using the formulas for directed networks described in Kötter and Stephan (2003) and Rubinov and Sporns (2010).

The significance of the CC and the BC will be assessed by comparisons with the values obtained from 1000 random networks matched in the number of connections, nodes, and degree distribution, that is, number of connections of each node (e.g. Honey et al. 2007) resulting in a *z*-score and *P*-value for the CC and the BC for each region.

The network metrics of each region will be correlated with their ABH level in order to assess potential relations. For instance, regions higher in the hierarchy, and thus functioning as regulators, might possess lower CC and thus appear less segregated, influencing a diffuse set of regions, while regions successively lower in the hierarchy might exhibit an increased level of segregation. We expect that the transmission index will exhibit high correlation with the hierarchy level since higher values dictate a surplus of efferents, and such regions should end up in high hierarchical levels during the ABH optimization procedure.

Reference "Maximally" and "Minimally" ABH Networks

The previous analysis aims at answering the following questions: How are the PFC regions distributed in the hierarchical levels produced by the ABH optimization procedure? How do these results relate to the predictions of the hierarchical anterior–posterior model (Badre and D'Esposito 2009)?

We next sought to answer a different question: Does the PFC structural network possess a "natural" topology that corresponds to the hierarchy principles of the hierarchical anterior–posterior model? Hence, we examined whether the PFC structural network corresponds to a topology with the minimal possible amount of antihierarchical connections, and in that sense, whether it differs from a maximally ABH network. Moreover, we also examined whether the macaque PFC topology differs from the other "extreme," that is, a minimally ABH network exhibiting a maximal amount of antihierarchical connections. To this end, we constructed ad hoc reference maximally and minimally ABH networks by rewiring the connections of the original network.

The maximally and minimally ABH networks were constructed by an annealing procedure. Initially, a "seed" network was generated by rewiring the edges of the original network and by preserving the node degree. Subsequently, the number of antihierarchical connections was calculated as the cost of the seed network. By using this seed network, a simulated annealing process was used, but, in this case, the energy to be minimized is defined as:

$$En = (Cost_{desired} - Cost_{actual})^{2}.$$
 (3)

Hence, for the generation of the maximally (minimally) ABH networks, we set as the desired cost in equation (3) a number much lower (higher) than the cost obtained in the hierarchy optimization of the original network. At each step of the annealing procedure, a new rewired network is generated, with a rewiring probability of $\min{(1, \exp^{-\Delta En/T})}$

and accepted with probability of $\min(1, \exp^{-\Delta E n/T})$. We should note that the annealing procedure previously described, that is, the ABH optimization that minimizes eqs 1 and 2 is "embedded" within the annealing procedure minimizing equation 3, in order to calculate the cost associated with each step. In this way, we search for networks not only with the exact same number of nodes, edges, and node degree as the original one, but also with a maximum or minimum number of antihier-archical connections. The whole procedure was repeated 100 times and, thus, 100 maximally and minimally ABH reference networks were generated. Similar approaches have been used in order to construct networks that optimize certain features such as transitivity (Maslov et al. 2007). Moreover, the underlying rationale of this approach resembles strategies used to assess the underlying wiring principles of the macaque cortex, that is, if it is wired in such a way to minimize wiring length (Kaiser and Hilgetag 2006).

By comparing the amount of antihierarchical connections of the original network with the ones of the maximally and minimally ABH reference networks, we are able to examine how the original network is related to these 2 extremes, that is, if it exhibits a significantly different amount of antihierarchical connections.

Laminar-Based Hierarchy Optimization

As a final analysis step, we performed a LBH optimization based on a different concept of hierarchy based on laminar patterns of connections (Barbas and Rempel-Clower 1997).

It has been shown that the PFC regions can be differentiated with respect to their degree of eulamination (Barbas and Rempel-Clower 1997; Dombrowski et al. 2001). The PFC regions can be ranked in 5 levels of structural type with 1 denoting the less eulaminated ones, for example, region 13, and 5 denoting the more eulaminated, for example, region 45. With this classification, a connection from region i to j can be associated with an Delta index defined as: Delta = structural type_{origin} - structural type_{destination}. Hence, negative (positive) Delta values denote connections from less (more) eulaminated to more (less) eulaminated regions. This structural model is an excellent predictor of the laminar patterns of connections between the PFC regions (Barbas and Rempel-Clower 1997). More specifically, an almost perfect positive correlation was observed between the Delta index associated with a connection from region i to j and the percentage of anterograde labeling in layers IV-VI (% AL IV-VI). Consequently, the structural type of 2 connected regions is an excellent predictor of the observed % AL IV-VI with a higher (lower) % AL IV-VI, denoting an increasingly FF (FB) connection. Hence, connections originating from less (more) eulaminated regions and targeting more (less) eulaminated ones are comparable with FB (FF) connections. Thus, this information can be used for a LBH arrangement of the PFC regions. We should note that the FF and FB connections among PFC regions bear a resemblance with FF and FB connections in the sensory cortices. However, while FF connections terminate in layer IV in sensory cortices, the PFC FF connections appear more diffuse by terminating in layers IV-VI (Barbas and Rempel-Clower 1997).

For the LBH, the following procedure was adopted. We based our analysis on the findings reported in Barbas and Rempel-Clower (1997). First, since no direct information for the % AL IV-VI of each PFC connection was available, we relied on a summary based on the corresponding Delta index of the PFC connections (Barbas and Rempel-Clower 1997). We assigned the various regions of Walker's parcellation schemes to a structural type level. As an intermediate step, an approximate correspondance was established between Walker's parcellation scheme and the PFC parcellation scheme used in Barbas and Rempel-Clower (1997) by using the mapping relations from the CoCoMac database. Secondly, we used the classification scheme of 5 levels of structural type to assign a level to each region of Walker's parcellation (Supplementary Table 4). Thirdly, for each connection between the PFC regions, a Delta index was computed as described above and assigned to the connection. The Delta index was used to assign a % AL IV-VI value to each connection by using the values reported in Barbas and Rempel-Clower (1997). For Delta values that were not available in the aforementioned study, the % AL IV-VI values were "quasi-interpolated." For instance, for the Delta

values of 2.5, we assigned a % AL IV–VI value below the one corresponding to Delta ranges of 3 and above the ones corresponding to 2. Finally, in order to use the % AL IV–VI values to denote FF and FB connections, a "laminar bias" (LB) index was calculated as LB = 50 – % AL IV–VI (Supplementary Fig. 1). Hence, with the current definitions, the LB index ranges from –50 to +50, with values toward –50 denoting increasingly FF connections and values toward +50 increasingly FB connections. The goal of a LBH arrangement is to produce a layout of the PFC regions with as many as possible FF connections pointing upwards and FB connections pointing downwards. In more formal terms, we seek to minimize the cost/energy defined as:

$$En = \sum_{i \to j} [g((m_i - m_j) \cdot LB_{i \to j}) \cdot abs(LB_{i \to j})]. \tag{4}$$

where,

$$g(x) = \begin{cases} 0, & x > 0 \\ 1, & x \le 0 \end{cases}$$

where $i \rightarrow j$ denotes a structural connection from region i to j, $LB_{i \rightarrow j}$ the LB associated with this connection, and m_i and m_j is the hierarchical level of node i and j. The minimization of the energy and the optimal choice of levels were performed as described in the ABH optimization. A schematic depiction of the approach is illustrated in Figure 3. Similar approaches have been adopted for the laminar-based hierarchical arrangement of the cat visual cortex (Hilgetag and Grant 2010). We should note that we based the above procedure on the connectivity of PFC regions as indicated by the dataset Walker 1.

In order to relate the results from the ABH and LBH optimization, the correlation between the hierarchical levels for the 2 optimization procedures will be assessed. Moreover, for each efferent termed as hierarchical or antihierarchical during the ABH optimization, a corresponding LB index will be calculated as the mean of the values of the positive and negative LB values for each efferent. In this way, information on the laminar patterns of hierarchical or antihierarchical PFC connections according to the ABH, and thus how they correspond to the FF and FB classifications scheme, is readily available and offers a richer picture of the PFC connectivity.

All analyses were performed with functions from the Brain Connectivity Toolbox (Rubinov and Sporns 2010), custom software written in Matlab and modified freely available Matlab functions (http://www.cmth.bnl.gov/~maslov/programs.htm). All datasets and scripts used are available upon request.

Results

ABH Optimization of the PFC Regions

The ABH optimization with Walker 1 and cost function 1 resulted in solutions with 8 hierarchical levels and equal cost (Table 2, Figs 4A and 5A). Regions 25 and 45, medial and lateral, respectively, were assigned at the top of the hierarchy with a very stable assignment across the estimated solutions, that is, in all solutions these regions were placed at the top level (Fig. 5A). These were followed by lateral region 46 and orbital regions 13 and 12 with a peak of the frequency of assignment at level 7. All the other regions had unique peaks and narrow distributions over the solutions, with the exception of region 14 (Fig. 5A). Interestingly, region 10 was placed at lower levels with a peak at level 4, much lower than the more posterior regions 46 and 45. Moreover, lateral region 8A was placed toward the bottom of the hierarchy with a peak at level 2. Hence, the hierarchical arrangement does not follow an anterior-posterior gradient with anterior regions placed higher in the hierarchy than posterior ones. A rather similar

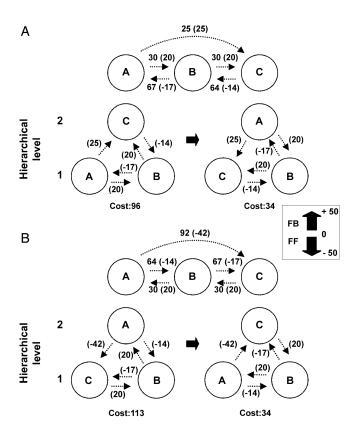


Figure 3. Example of the LBH optimization in a toy network. The toy network involves the same set of regions (A-C) and connections as in Figure 2. Since the LBH relies on the laminar patterns of connections, a % AL IV-VI value must be assigned to the connections. We used the structural model as described in Barbas and Rempel-Clower (1997) to assign such a value based on the level of differentiation of each region. The numbers above each connection represent % AL IV-VI values and numbers in parenthesis the corresponding LB indexes. (A) In this scenario, regions A, B, and C belong to the structural types 2, 3, and 5, respectively. Hence, A is the least and C the most differentiated region. (B) In this scenario, regions A, B, and C belong to the structural types 5, 3, and 2, respectively. In both scenarios, the LBH optimization seeks to arrange the regions in levels in such a way that connections with negative LB index (FF) pointing upwards and connections with positive LB index (FB) pointing downwards. Hence, the "optimal" arrangement corresponds to the ones depicted on the right side of each panel since they exhibit a lower cost that the ones depicted on the left side of each panel. Note that this toy network is the same as in Figure 2 involving the exact same set of regions and connections, but according to the structural type of each region, illustrated in the above scenarios, the LBH might coincide (panel A scenario 1) or differ (panel B scenario 2) with the ABH layout.

Table 2 Solutions obtained for the ABH optimization									
	Number of unique solutions	Similarity of unique solutions (Hamming distance)		Cost (% of edges deleted)					
		Mean	Std						
Walker 1 Walker 1 cost 2 Walker 2	251 19 474	0.594 0.426 0.598	0.164 0.194 0.153	0.422 0.383 0.442					

Note: Characteristics of the 1000 solutions obtained from the hierarchy optimization. Note that all solutions correspond to the exact same cost. Of the 1000 solutions, there were unique solutions exhibiting a high degree of dissimilarity, as indicated by the Hamming distance, and equal cost. The cost is expressed as the number of antihierarchical connections/edges over all the existing PFC connections/edges

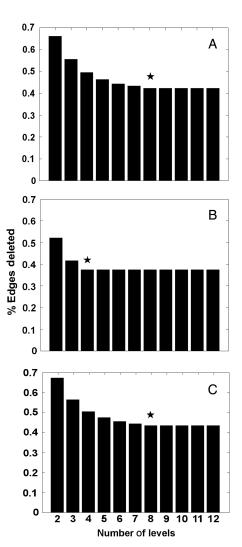


Figure 4. Empirical establishment of the optimal number of levels for the ABH optimization. Walker 1 and (A). Cost function 1 (B). Cost function 2 (C). Walker 2 and cost function 1. The stars point to the levels from which any further increase of the number of levels does not result in a reduction of the cost. These levels were used for the ABH optimization. The cost is expressed as a percentage of the edges deleted over the total number of edges contained in the graph.

picture, with the exception that region 8A was assigned to higher levels, emerged when Walker 1 and cost function 2 were used for the ABH optimization. This combination led to solutions with equal cost and 4 hierarchical levels (Table 2, Figs 4B and 5B). Very similar results were obtained when the hierarchy optimization with cost function 1 was applied to the Walker 2 dataset resulting in 8 hierarchical levels (Table 2, Figs 4C and 5C). Despite certain variations in the resulting hierarchical lay out, lateral regions 45 and 46 dominated again the hierarchy and were placed with high consistency at the higher level, while the more anterior region 10 was placed at lower levels (Fig. 5C). Even when using a different connectivity matrix, that is, Modha and Singh PFC (Supplementary Table 1), for the ABH optimization, lateral region 45 was consistently placed at the higher levels of the hierarchy and never placed below the more anterior region 10. The Modha and Singh PFC dataset is more fine grained since it contains multiple subdivisions of the gross Walker parcellation scheme. Hence, we can gain insights about lateral,

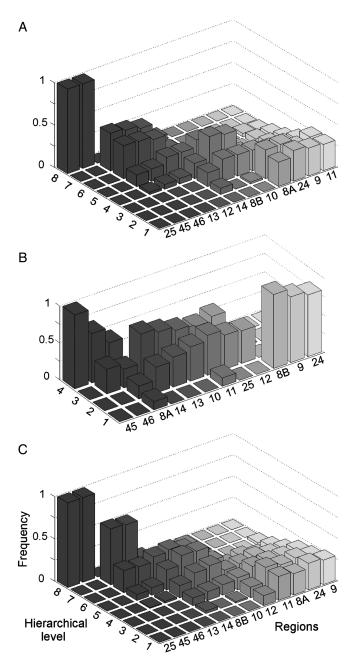


Figure 5. Distribution of solutions of the ABH optimization. Dataset Walker 1 and (A). Cost function 1 (B). Cost function 2 (C). Dataset Walker 2 and cost function 1. This figure depicts the frequency of assignment of the PFC regions at each hierarchical level over the 1000 solutions. The regions are sorted according to the level where they exhibited the highest frequency peak. Regions with the frequency peak involving the same level are further sorted according to their frequency. Darker (lighter) shades of gray denote regions that occupy high (low) levels of the hierarchy. Note that the distribution of the solutions appears segregated with district picks. Such distribution differs from the "flat" distribution of solutions that would be obtained from networks lacking a prominent dominant direction, for example, networks with symmetrical topology (all connections are bidirectional).

medial, and orbital parts of, for example, region 10 and their position in the ABH arrangement. The only subdivision of region 10 that was placed high in the hierarchy was subdivision 10m (Carmichael and Price 1994). Even in that case it was placed consistently lower than subdivisions of more posterior region 45, with the rest of its subdivisions placed lower

 Table 3

 Similarity of ABH scores across datasets and cost functions

	Walker 1	Walker 1 cost 2	Walker 2	
Walker 1	NA	0.66	0.95	
Walker 1 cost 2	P < 0.05	NA	0.60	
Walker 2	<i>P</i> < 0.001	P < 0.05	NA	

Note: Quantification of the similarity of the results of the hierarchy optimization with different datasets and cost functions. The hierarchy score from each combination was calculated as the mean hierarchical levels attributed to a region across the 1000 solutions. Subsequently, all pairwise correlations between the hierarchical scores were computed, and the significance of the observed correlation was assessed with randomization statistics.

than the (sub)divisions of the more posterior region 46 (Supplementary Table 1). Taken together, the above suggest that a strict anterior–posterior gradient does not hold. Regions 45 and 46 were consistently placed at the top levels of the hierarchy, surpassing the most anterior region 10. Only regions 46 and 8A seem to have a hierarchical relation in line with the predictions of the hierarchical anterior–posterior model (Badre and D'Esposito 2009). The above held true irrespective of cost function, connectivity dataset, and parcellation scheme

By taking into account, the PFC as a whole we could assess the hierarchical role of orbital and medial regions. Orbital region 13 was consistently assigned to high levels in the hierarchy, dominating most of the other orbital regions. This was observed when using dataset Walker 1 and cost function 1 (Fig. 5A), cost function 2 (Fig. 5B), dataset Walker 2 (Fig 5C), and the Modha and Singh PFC dataset (Supplementary Table 1). In the later analyses, region 13 was only surpassed by the orbital regions 12, orbital periallocortex (Morecraft et al. 1992), and gustatory cortex (Suzuki and Amaral 1994), which are located at approximately the same or lower level along the anterior-posterior axis. With respect to the medial part of the PFC, region 25 was always placed in higher levels than the more posterior region 24 (Fig. 5). When using the Modha and Singh PFC dataset, region 32, corresponding to region 25 in Walker map (Kötter et al. 2001), was also consistently placed at high levels of the hierarchy (Supplementary Table 1). Hence, with respect to the orbital PFC, the more posterior regions occupy high levels of the hierarchy. Regions in the medial wall follow another pattern, that is, region 25 is placed in higher levels than the more posterior region 24.

To investigate whether the choice of a particular set of regions changes the results, we selected only the lateral PFC regions, the "cognitive" part of the PFC emphasized in Badre and D'Esposito (2009) and performed the ABH optimization. No anterior–posterior gradient was observed, and region 10 was not assigned to the higher levels (Supplementary Tables 2 and 3). Hence, the choice of only the lateral PFC regions does not alter the results and conclusions.

In sum, the ABH optimization does not confirm the anterior–posterior hierarchical gradient with region 10 on top of the hierarchy. The choice of connectivity dataset and cost functions does not significantly alter the results (Table 3). Moreover, out of the 1000 solutions, there were unique solutions with a high degree of dissimilarity and the exact same cost (Table 2). In other words, no unique arrangement best describes the ABH ordering of the PFC, a phenomenon analogous to the indeterminacy of the visual system (Hilgetag et al. 1996).

Hierarchical and Antihierarchical Diagrams for ABH Optimization

The hierarchical diagram demonstrates that the regions at the top of the hierarchy, that is, 25, 45, 46, 13, and 12, exhibit diffuse and extensive projections with all the PFC groups as specified in Kötter et al. (2007), that is, orbitomedial, lateral, and intermediate (Fig. 6). We will use this PFC grouping nomenclature throughout the text. The only exception is region 13 that does not send efferents to the lateral group. The efferents of these regions were termed as hierarchical with very high frequency over the 1000 solutions. Hence, they constitute the dominant direction toward regions at lower hierarchical levels. Regions 9, 24, and 11 lay at the lower parts of the hierarchy and constitute the "end points" of the dominant direction in the PFC anatomical network (Fig. 6). The latter regions also exhibit massive antihierarchical efferents that influence the regions of all the PFC groups, that is, orbitomedial, lateral, and intermediate (Fig. 7). The only exception is the less diffuse pattern of efferents of region 11 that does not exhibit antihierarchical efferents with the lateral group.

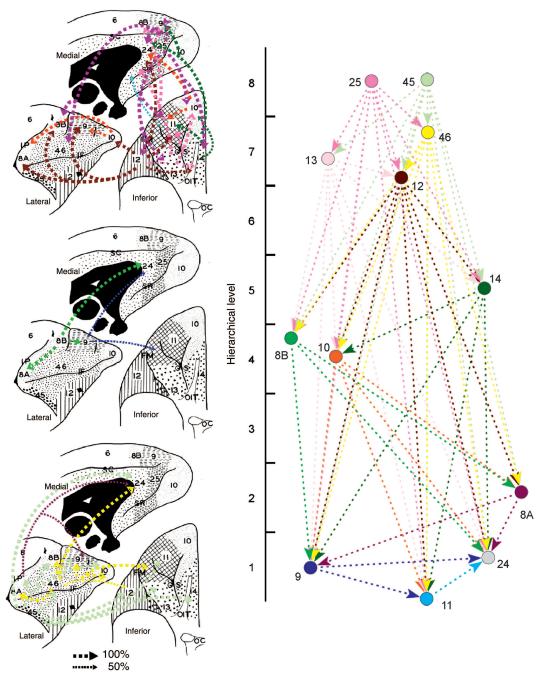


Figure 6. Hierarchical diagram based on 1000 solutions obtained from the ABH optimization for dataset Walker 1 and cost function 1. Each edge represents the frequency that an efferent was termed hierarchical with thicker lines representing the most frequent ones. Only efferents with a frequency higher that 50% were included. The representation overlaid on Walker's parcellation scheme offers an anatomical view of the regions involved in the more frequent hierarchical efferents and offers an overview of the ABH layout. The graph representation offers an overview of the distribution of regions over the ABH levels.

The efferents of the regions low at the hierarchy were termed as antihierarchical with a high frequency over the 1000 solutions and thus constitute the main anatomical routes through which information can be sent back to regions that dominate the hierarchy. Both the hierarchical and antihierarchical efferents traverse several levels and can thus directly link regions at the opposite sides of the hierarchy, that is, high with low regions and vice versa, without the necessity of intermediate regions. Thus, the structural architecture does not imply a cascade-like way of information flow (see also Discussion).

Network Metrics and Hierarchy

The network metrics revealed that the only regions with significant BC (z-score > 2, P<0.001), and consequently highly central in the PFC network, belong to the intermediate PFC group, that is, regions 9 and 24 (Fig. 8A). This finding is in line with analysis of the PFC using Shapley ratings, which revealed regions 9 and 24 as among the ones with the higher contribution to global PFC connectivity (Kötter et al. 2007). The CC involved only regions of the orbitomedial group, that is, 11 and 14 (CC z-score > 2, P<0.001; Fig. 8B). Thus, these regions appear to be more segregated/

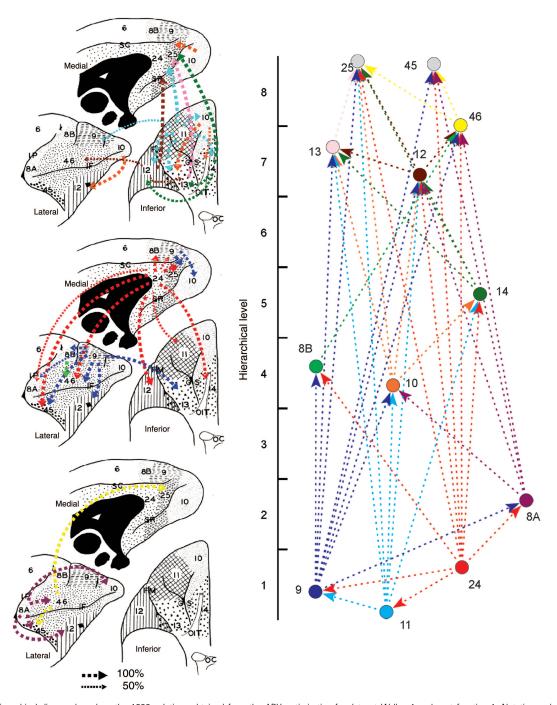


Figure 7. Antihierarchical diagram based on the 1000 solutions obtained from the ABH optimization for dataset Walker 1 and cost function 1. Notation and arrangement of regions as described in Figure 6.

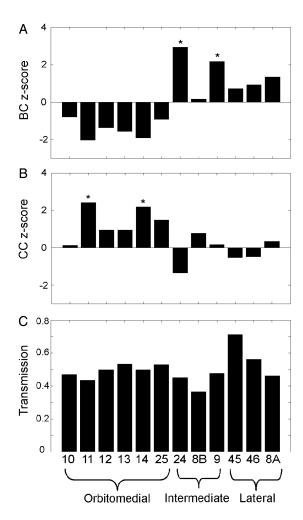


Figure 8. Summary of the network metrics for each separate PFC regions and PFC group: Orbitomedial, intermediate, and lateral. (A) z-scores of the BC, (B) clustering coefficient, and (C) transmission index of the regions constituting each PFC group. Stars indicate significance (z-score > 2, P < 0.001) in relation to values obtained from 1000 matched random networks. Note that these metrics were based on dataset Walker 1, with highly similar results obtained for dataset Walker 2.

specialized. The transmission index has been computed before for all the regions for the current dataset (Kötter and Stephan 2003), and hence, the current results are identical: The lateral group exhibits the highest transmission values >0.5 (regions 45 and 46), exhibiting a "surplus of efferents," while the intermediate group exhibited values <0.5, indicating a predominance of afferents. The orbitomedial group exhibited transmission values around 0.5 (Fig. 8C). In order to directly examine the relation of the networks metrics and the ABH level of the region, the hierarchy score, that is, the mean hierarchical level across 1000 solutions that a region was assigned to, of each region was correlated with each network metric. The only metric that exhibited a significant correlation was the transmission index (r=0.72; P<0.05). This is expected since the transmission index quantifies the efferents to afferents relation, with values >0.5 denoting a surplus of efferents. Hence, it is logical that the regions with the high (or low) transmission index end up in high (or low) hierarchical levels during the ABH optimization.

We should also note that no significant correlation was observed for the LBH and any of the network metrics.

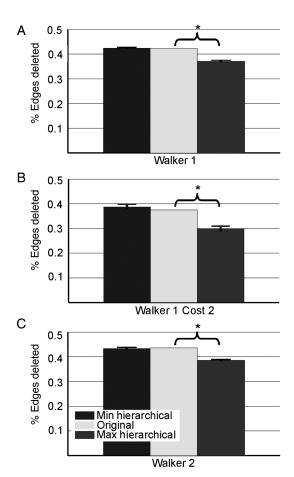


Figure 9. The PFC network exhibits overabundance of antihierarchical connections as defined by the ABH analysis. Comparison of the total number of edges (expressed as a percentage over the total number of edges in the network) that must be deleted in order to convert the directed graph to an acyclic one, for the original and the "maximally" and "minimally" hierarchical networks. The original network has significantly more antihierarchical connections than the maximally hierarchical networks, but does not exhibit significant difference with the minimally hierarchical ones. Thus, the PFC topology could be considered as minimally hierarchical. Asterisks indicate significance (z-score > 2, P < 0.01). Note that the results hold for both datasets based on Walker's parcellation and cost functions. See sections Materials and Methods and Results for details.

Relation to Maximally and Minimally ABH Networks

The costs obtained from the maximally ABH networks resulted in a modest but significant reduction in the cost when compared with the original networks (Fig. 9). These results indicate that the original network topology has an "overabundance" of antihierarchical connections since the reference maximally ABH networks exhibited significantly less antihierarchical connections. The costs obtained from the minimally ABH networks were on average slightly higher than the cost of the original network and did not reach significance (Fig. 9). The above results held true for all datasets, that is, Walker, Walker 2 as well as for both cost functions (Fig. 9). Taken together, the above results dictate that the PFC is wired in a way that does not resemble to an "optimal" maximally ABH topology. Instead, it resembles to networks exhibiting an overabundance of antihierarchical connections and, thus, the PFC wiring could be considered as minimally hierarchical. Importantly, the ABH arrangement of the regions of the maximally and minimally ABH networks was highly similar as the one of the original network. Hence, no hierarchical anteriorposterior gradient, with region 10 on top, was observed for these networks either.

Laminar-Based Hierarchy

The LBH optimization resulted in a layout with 6 levels with, as expected given the way the LB index was estimated, the more (less) differentiated regions occupying low (high) levels of the hierarchy (Supplementary Table 5).

To assess how the ABH and LBH optimization results relate, we computed the correlation between the mean hierarchical level for each region over the 1000 solutions for both the ABH and the LBH. The results from the 2 hierarchy optimization procedures exhibited a near 0 correlation that was not significant (P>0.1).

For a visual depiction of the results and in order to gain more information from the results of the 2 hierarchy optimizations, we plotted the ABH against the LBH mean level for every PFC region. Moreover, a plane was drawn at the mean of the ABH and LBH mean levels dividing the scatterplot in 4 parts (Fig. 10). This dissection can be used as a "classification scheme" for the PFC regions. For instance, regions like 25 and 45 are located at high ABH levels and thus function as broadcasters. The LBH optimization further differentiates these broadcasting structures: While region 25 is also located at high levels according to the LBH, region 45 is located at very low ones (Fig 10). Thus, the hierarchical efferents, according to the ABH, that region 25 exhibits constitute FB connections, whereas the hierarchical efferents of region 45 constitute FF connections (Fig. 11A). FB and FF connections target different laminae and thus influence a different microenvironment containing distinct types of neurons (Dombrowski et al. 2001; Barbas and Hilgetag 2002), resulting in a complex dialog between the PFC regions. The ABH in conjunction with the LBH can summarize and pinpoint aspects of this complex dialog (see Discussion).

Discussion

In the current study, we took a formal stance and used a wealth of data on the anatomical connections of the macaque

PFC in order to quantify the principles and predictions of the hierarchical anterior–posterior model (Badre and D'Esposito 2009). We discuss below the main findings of our analyses.

Relation to the Hierarchical Anterior-Posterior Model and Contribution to PFC Function

The ABH results suggest that the dominant direction in the PFC stems primarily from regions 45, 25, 46, and 13 since they were consistently placed at the higher hierarchical levels. Region 45 has been identified as a broadcasting structure influencing the entire PFC (Kötter et al. 2001). Our analysis illustrates that regions lying on high hierarchical levels, that is, regions 46, 25, and 13, also function as "outflow hubs" or broadcasting structures (Kötter and Stephan 2003; Fig. 6). Contrary to the hierarchical anterior-posterior model, region 10 did not lie on top of the hierarchy. This region was always surpassed by more posterior lateral PFC regions 45 and 46 (Fig. 5). Thus, the most anterior region 10 and its lateral subdivisions (Supplementary Table 1) do not belong to the top of the hierarchy and more posterior lateral regions, that is, regions 45 and 46 (and subdivisions of the later, i.e. 46v) appear more hierarchical (Fig. 5 and Supplementary Table 1). Hence, the hierarchy optimization revealed a set of highly influential regions that are dispersed in the lateral, medial, and orbital surfaces of the PFC. These broadcasting regions can have an analogous role as regulatory nodes in metabolic networks (Ispolatov and Maslov 2008). Hence, with the asymmetry-based concept of hierarchy and by taking into account the structural connectivity of the macaque PFC, the hierarchical arrangement of the PFC regions do not support an anterior-posterior hierarchical gradient with more anterior regions higher in the hierarchy.

The broadcasting structures are dispersed throughout the PFC surfaces, which have been differentially implicated in the cognitive, motivational, and affective domain (Groenewegen and Uylings 2000). Hence, the influence exerted by each of these structures can have a different contribution to PFC function.

Regions in the posterior part of the orbital PFC, for example, region 13, are multimodal and receive information from gustatory, visual, auditory, somatosensory, and olfactory

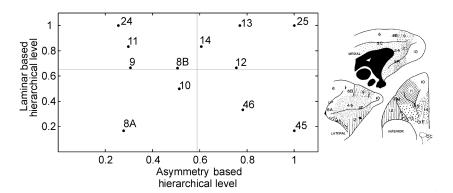
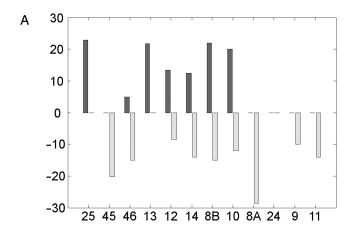


Figure 10. A scatter plot of the ABH and LBH results. The scatter plot depicts the PFC regions according to their mean ABH and LBH level. The ABH and LBH levels are scaled by dividing by the maximum value obtained during each hierarchy optimization. The planes dividing the scatterplot in 4 quartiles are centered at the mean values of the mean ABH and LBH levels. The scatterplot offers a visual inspection of the position that each PFC region occupies in both the ABH and LBH layouts and also functions as a "classification scheme." For instance, regions located in the upper right quartile occupy high levels of both ABH and LBH layouts, while regions located in the lower right quartile occupy high levels of the ABH layout, but low ones of the LBH layout.



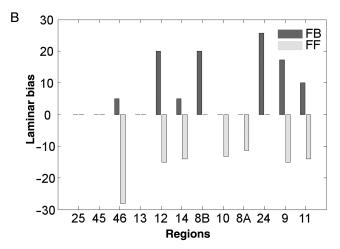


Figure 11. Summary of the LB index of the efferents that were more frequently hierarchical or antihierarchical during the ABH optimization. Mean LB index for (A) the most frequent hierarchical efferents (Fig. 6) and (B) the most frequent antihierarchical efferents (Fig. 7) of each PFC region. The PFC regions are arranged from left to right with a decreasing order of hierarchy based on the ABH results with dataset Walker 1 cost function 1 (Fig. 5A). The mean LB index was calculated separately for positive (FB) and negative values (FF). These values indicate the prelevance of FF or FB type of connections, or an intermediate profile, for the most frequent hierarchical and antihierarchical connections, and thus highlight their potential diverge role in PFC communication (see Discussion for details).

areas (Barbas 2007). Thus, the dominant direction within the PFC that stems from posterior orbital PFC regions, placed high in the hierarchy, can propagate information from diverse modalities. Moreover, regions at the posterior orbital PFC are characterized by dense projections from the amygdala and might be responsible for the attribution of emotional valence to stimuli (Barbas 2007; Ghashghaei et al. 2007; Murray 2007). Consequently, the influence that region 13 exerts as a broadcasting structure might also subserve the propagation of motivational/reward signals through the rest of the PFC. Additionally, the hierarchical efferents, as revealed by the ABH, have a positive LB index and thus constitute FB connections (Fig 11A). The topology of Walker's region 45 and the so called Broca regions in the human brain (Petrides and Pandya 1994) might suggest possible homologies. Consequently, its connectivity might constitute a neural circuitry that functions as a predecessor of language-related circuitry in the human PFC (Kötter and Stephan 2003). However, it should be noted that Walker's parcellation scheme was not performed in a comparative manner, and thus Walker's region

45 might not coincide with what is demarcated as region 45 in Petrides and Pandya (1994). With respect to the medial PFC, region 25 was consistently placed at high hierarchical levels (Fig. 5). Region 25 in Walker's parcellation scheme is equivalent with Broadman's region 32 and region 32 in the Barbas and Pandya (1989) parcellation scheme (Barbas and Pandya 1989; Kötter et al. 2001). Efferents of region 32 that target regions 46 and 10 are thought to have inhibitory and excitatory roles, respectively (Medalla and Barbas 2010). Thus, hierarchical efferents, as revealed by the ABH optimization, of region 32 can send regulatory signals to regions 46 and 10. It is noteworthy that in our analysis region 25 is placed high in both the ABH and LBH optimization (Fig. 10) and, thus, its ABH efferents are FB connections (Fig. 11A). Such features are in line with suggestions that this medial region exerts a tonic influence to lateral PFC regions. Such lateral-medial interplay might be important for multitasking and noise suppression in lateral PFC regions during task execution (Medalla and Barbas 2010).

Hierarchy and Network Metrics

The network metrics in combination with the ABH optimization offer additional insights about the role of each region. No significant correlations were observed between the ABH level of the PFC regions and their CC and BC. This means that regions placed at higher (lower) parts of the hierarchy are not less (more) segregated/specialized, hence regions high in the hierarchy do not influence loosely connected/mutually disinterested regions (Kötter and Stephan 2003). Additionally, the absence of correlation with the BC indicates that regions closer to the top of the hierarchy, that is, close at the "root" of the dominant direction within the network, do not appear to be central. This argues against a "strictly centralized" PFC topology where regions that are ideally embedded to exert a directed influence, that is, placed at the top of the hierarchy, are also topologically central, that is, exhibit high BC.

Network metrics can differentiate the regions that are placed at the same or similar ABH level. Regions 24, 9, and 11 are placed at the bottom of the hierarchy (Fig. 5), but they exhibit different CC and BC values (Fig. 8A,B). Regions 24 and 9 are the only ones with significant BC and, hence, they serve as "intermediate stations" that lie in a large fraction of the shortest paths that connect the PFC regions. This feature along with the fact that they lay at the lowest level of the hierarchy means that they integrate information through hierarchical efferents since they are the end point of the dominant directed influence and, hence, can resemble to "receivers" (Kötter and Stephan 2003), and distribute information through their extensive antihierarchical efferents (Fig. 7). Hence, they constitute an important set of regions that facilitate the traffic of information among the PFC regions. Different techniques than the ones used here, that is, Shapley ratings and multidimensional scaling, highlight regions 9 and 24 as important for the global PFC connectedness and the facilitation of communication of the orbitomedial and lateral PFC groups (Kötter et al. 2001, 2007). On the contrary, region 11, which is also placed at the lowest level of the hierarchy, does not exhibit a significant BC (Figs 5 and 8). Instead, it exhibits a significant CC (Fig. 8). Hence, region 11 appears to be part of a segregated/specialized neural circuitry, and the information that it receives as the end point of the dominant

directed influence seems to directly influence a more segregated set of regions. The antihierarchical diagram of regions 9, 24, and 11 also reflects some of the above differences (Fig. 7). Regions 24 and 9 exhibit diffuse antihierarchical efferents influencing all PFC groups, while antihierarchical efferents of region 11 are restricted to the more segregated orbitomedial group.

"Overrepresentation" of Antihierarchical Connections

Our analysis indicates that the PFC is wired in such a way that there is an overrepresentation of antihierarchical connections (Fig. 9). The hierarchical and antihierarchical diagrams resulting from the ABH (Figs. 6 and 7) indicate direct communication between the levels. The overrepresentation of antihierarchical connections might add to the multiplicity of pathways available for the transmission of information from lower to higher regions. Such architecture permits communication between the hierarchical levels, not through the presence of only a few dedicated antihierarchical connections, but in a rather direct, decentralized and distributed way. Moreover, such features indicate that the PFC exhibits overrepresentation of antihierarchical connections that form loops/ cycles. What can be the role subserved by such a feature? Features as such seem to be essential for the robustness of a network (Kwon and Cho 2007). Moreover, loops with excitatory and inhibitory components are important for sustained oscillations and signal amplification (Kim et al. 2008). We speculate that such features might also give rise to analogous properties when it comes to PFC function. The detailed analysis of such issues can constitute the topics of future research.

In sum, the results of the quantification of the principles of the hierarchical anterior–posterior model dictate that, regardless of adopting or not the contiguity principle, the PFC is not wired in a way to "optimally" comply with the asymmetry principle dictated by the ABH. In other words, the PFC is wired in a nonoptimal way, from the view point of the asymmetry principle since it exhibits an overabundance of antihierarchical connections when compared with maximally ABH networks. Consequently, the hierarchical layout obtained from the ABH optimization (Fig. 6) should be conceived as the layout depicting the dominant direction within the PFC network, which in turn appears to be wired in a way comparable with minimally hierarchical and different from maximally hierarchical networks.

Relation Between Asymmetry-Based Hierarchy and Laminar-Based Hierarchy

The ABH and LBH optimization procedures resulted in uncorrelated hierarchical layouts (Fig. 10). Instead of focusing on the "best" or more "realistic" definition of hierarchy, something that could be dictated by the pertinent questions at hand, our analyses demonstrate that the 2 definitions of hierarchy can be combined and offer a richer picture of the PFC connectivity.

More specifically, while our ABH analysis reveals broadcasting structures within the PFC, along the lines of findings from previous analysis (Kötter et al. 2001), the LBH results reveal additional information about the regions that function as broadcasters and receivers. The ABH designates regions 25, 45, 46, and 13 as broadcasters and thus are more influencing rather than getting influenced by other PFC regions. The dominant exerted influence of regions 25 and 13, through their hierarchical connections revealed by the ABH optimization, involves FB connections, while that of region 45 involves FF connections. Region 46 exhibits both FF and FB connections with a prevalence of FF ones (Fig. 11A). The differentiation of these regions is also reflected in the fact that they are located in different quartiles of the ABH and LBH plot (Fig. 10). Hence, while all regions are broadcasters, their efferents target preferentially different laminae and might have different impact on the dynamics of the PFC microcircuit. The exerted influence from regions 25 and 46 targets predominantly supragranular layers where calbindin-positive neurons are primarily located and target distant dendrites of pyramidal neurons (Barbas and Hilgetag 2002). On the contrary, the exerted influence from region 45 is characterized by FF connections and thus might mostly interact with another class of neurons, that is, presumed inhibitory parvalbuminpositive interneurons, primarily located in middle layers, targeting proximal pyramidal neurons (Barbas and Hilgetag 2002). These connections appear to have different functional roles and might be important for the co-ordination of the intrinsic and associational neural circuitry involving PFC regions (Pucak et al. 1996; Barbas and Zikopoulos 2007). Such interpretations are rendered possible by combining the results from the ABH and LBH. Assigning LB values to efferents that were deemed hierarchical (Fig. 11A) or antihierarchical (Fig. 11B) by the ABH optimization offers hints for the role of the efferents that constitute the dominant direction, or go against it, within the PFC. We should note that, despite that the laminar termination of a connection is informative about its role, additional analysis is needed in order to decipher the exact synaptic targets of a FF or FB connection. For instance, connections from region 32 to regions 10 and 46 terminate predominantly to layers I-III and thus constitute FB connections, but there is a higher number of synapses with presumed inhibitory neurons associated with the connections from region 32 to 46 when compared with the ones from region 32 to 10 (Medalla and Barbas 2010). Hence, quantitative histological data are needed for uncovering the exact synaptic targets of a connection and for inferring a more precise functional role of FB (or FF) PFC connections.

Moreover, the results from the ABH and LBH can be used for developing complementary hypothesis and predictions related to functional studies, for example, electrophysiology in multiple macaque PFC regions. More specifically, the ABH that quantifies the dominant direction within the structural PFC network can be used for assessing which regions are anatomically favored to exhibit directed influence during a task, that is, effective connectivity. Regions in high ABH levels seem more suitable candidates to function as the regions around which more "outflow" effective connectivity configurations can be articulated. Hence, ABH might be informative about the directionality of the flow of information. LBH can be informative about the way that the dialog between the PFC regions takes place. Laminar-based recordings from the macaque V1 reveal a preference of gamma activity in upper layers (Maier et al. 2010). Additionally, effective connectivity from V1 to V4 is primarily observed in the gamma band, whereas effective connectivity from V4 to V1 does not show such a gamma preference (Bosman et al. 2012). V1 is located lower than V4 in the LBH of the visual system and thus V1 to V4 connections can be considered as FF and connections from V4 to V1 as FB

(Hilgetag et al. 2000). FF connections predominantly originate from upper layers, whereas FB connections originate from lower layers (Felleman and Van Essen 1991). Hence, it is hypothesized that the functional dialog between regions of the visual system is shaped from the laminar patterns of their connections, determining the frequency bandwidth that the 2 regions "use" for exerting influence to each other (Bosman et al. 2012). In other words, the preference of gamma band for upper layers in conjunction with the laminar origin of FF and FB connections is reflected in the functional dialog between V1 and V4. These structure-function relations might also hold for the PFC. Our LBH results can be used for generating hypothesis for the functional dialog among the PFC regions, for example, the frequency bandwidth preferences of interregional influences. Such investigation is important since the demonstration of a comparable structure-function correspondance for the PFC, as the aforementioned preliminary evidence suggest for the visual system, would suggest a general structure-function relation pertaining to the macaque cerebral cortex as a whole. In sum, the ABH and LBH offer distinct layouts of the anatomical skeleton of the macaque PFC, which are useful for generating predictions and hypothesis of distinct functional aspects of the PFC.

With respect to the hierarchical anterior-posterior model, while the ABH results do not seem to support its principles and predictions, the LBH results reveal that region 10 is located in higher levels than more posterior regions, that is, 46, 45, and 8A, as expected from the differences of their structural types. This suggests that a LBH is a more plausible working hypothesis for PFC models advocating an anterior-posterior hierarchical gradient that is based on the anatomy of the PFC.

Finally, we should note that the classification of connections as FF and FB constitutes a broad distinction and can mask out further fine-grained differentiations and modes of communication (Rockland 2004). Such differences can include subdifferentiations of FB connections based on the caliber size of the axons and the size of the buttons, features that can give rise to different degrees of conduction velocity and efficiency (Rockland 2004; Medalla and Barbas 2010).

Does a Structural Hierarchical Architecture Imply a Functional Hierarchical Architecture?

Despite that evidence from empirical and modeling studies suggest that the way a region is embedded within a structural network constrains its function (Kötter and Sommer 2000; Passingham et al. 2002; Smith et al. 2006), this relation is far from a simple 1:1 mapping. For instance, while the anatomical architecture of the visual system is hierarchical (Hilgetag et al. 2000), computational modeling demonstrates that functional properties, that is, neural response latencies to visual stimulation, are not sequential and, thus, an anatomical hierarchy does not necessarily entail a functional hierarchy (Petroni et al. 2001). Moreover, structure-function deviations are evident in the discrepancy between the structural hierarchy and the signal timing of the regions of the visual system (Schmolesky et al. 1998; Capalbo et al. 2008).

An analogous picture can also hold for the PFC, and hierarchical diagrams obtained from structural connectivity might not coincide with the flow of information during the execution of a task (Hegdé and Felleman 2007). Such structure-function mismatches seem reasonable when considering findings illustrating the dynamic nature of interactions of brain regions modulated by context and task (Rowe et al. 2005). Additionally, various "functional motifs" can be embedded within a "structural skeleton" of a brain structure, and each functional motif can arise at a particular context or phase of a task (Sporns and Kötter 2004). Hence, a structural hierarchical architecture does not necessarily entail a functional hierarchical architecture, nor does the existence of a particular orientation along an axis, for example, anteriorposterior, of a structural hierarchy, or a nonoptimal hierarchy, entails the same orientation for a possible functional hierarchy. Ultimately, structural connectivity estimates should be combined with functional measurements (see, e.g. Vanduffel et al. 1997; Smith et al. 2006) from the same brain in order to examine the PFC architecture at multiple levels and be able to unravel the rules determining structure-function correspondences and deviations.

Limitations and Perspectives

While we currently examined the PFC as a whole, future analyses can focus on a specific surface. To this end, more fine-grained parcellation schemes can be adopted, instead of the rather coarse Walker scheme (e.g. Petrides and Pandya 1994; Carmichael and Price 1996). Such fine-grained parcellations might be more suitable for the examination of the PFC organization not only along the anterior-posterior, but also the medial-lateral or dorsal-medial axis (O'Reilly 2010).

In the current study, we only considered PFC regions and premotor and motor regions (e.g. BA 6 and 4) were not included in the analysis. This exclusion allowed us to focus on the PFC and exploit the rich published datasets for this brain structure of the macaque. Future analysis can investigate the PFC within a broader context by including fronto-parietal, fronto-temporal, and fronto-thalamic connections.

An intriguing future question is if and how the ABH PFC hierarchical layout is related to architectonic/developmental features of the PFC regions. For instance, the ABH level of a region could be related to its ontogeny. Early development in ontogeny of the ACC favors the diffuse and extensive establishment of its connections (Zikopoulos and Barbas 2010). Hence, such regions could be favored to evolve into a broadcasting structure, that is, a highly influential region with extensive connections. Future studies could, for example, correlate the ABH level of each PFC region with the corresponding onset in ontogeny in order to unveil a potential link. Moreover, an interesting future direction would be to relate the hierarchy results and phylogenetic characteristics of the PFC regions. The gradations from the 2 primordial moieties, that is, archicortex and paleocortex, forming the basoventral and dorsomedial trends (Pandya and Yeterian 1990) have also been interpreted within an evolutionary context (Sanides 1964; but see Preuss and Goldman-Rakic 1991). Hence, the dominant direction within the PFC, as revealed by the ABH, could be related with the direction of the aforementioned gradations, and consequently, the progression from older to newer phylogenetic regions. Since the LBH optimization is highly dependent on the direction of gradations of the basoventral and dorsomedial trends, that is, the progressive eulamination of PFC regions (Barbas and Rempel-Clower 1997), the resulting hierarchical levels are closely linked to such direction. This, in turn, in conjunction with the fact that the ABH and LBH

results do not coincide would mean that the ABH arrangements of the PFC regions do not relate to the direction of the gradations. The explicit quantification of the relation of the ABH and LBH results with ontogeny and phylogeny features constitutes a potential future research topic.

While many meaningful cost functions can be used during the optimization procedure (Hilgetag et al. 2000; Krumnack et al. 2010), we currently used these particular cost functions for the ABH optimization since they correspond to the principles of the hierarchical anterior-posterior model. Despite that the results were not identical, the main conclusions of the study are supported by the results of both cost functions and different datasets (Table 3). In the future, other cost functions that, for example, penalize connections that cross many hierarchical levels can be adopted. Since the strength of the connections between the PFC regions is graded, cost functions that employ weighted information can also be adopted. We employed a cost function that takes into account the weight of the antihierarchical connections and obtained highly similar results with the other cost functions (data not shown). Hence, decisions on graded versus binary connectivity do not influence the current ABH results.

The LBH optimization was based on estimated values of % AL IV-VI by using the Delta index as predictor. Since the values of % AL IV-VI and the Delta index are characterized by an almost perfect correlation, in principle, the hierarchical arrangement could also be based on the Delta index. In the current study, we used the values of % AL IV-VI for the hierarchical optimization in order to directly link the approach with laminar-based hierarchical arrangements previously applied to other parts of the cortex, for example, visual cortex (Hilgetag and Grant 2010) and illustrate how a laminar-based hierarchical arrangement of the PFC regions can be performed in the future by using directly the region to region % AL IV-VI values that might slightly deviate from the ones estimated from the Delta index. Since the Delta index is the best predictor of laminar patterns of connections (Hilgetag and Grant 2010), we predict that such an arrangement will be highly similar with the one obtained in our study.

Despite similarities between the PFC of human and nonhuman primates (Ongür and Price 2000; Petrides et al. 2012), differences also exist. Interestingly, pronounced differences are reported for region 10, which became enlarged and more specialized in humans (Semendeferi et al. 2001). Such potential changes might have an impact on the wiring of this region and affect its hierarchical role within the human PFC.

Lastly, the analytic tools employed can be used for uncovering similarities in the topologies of the structural networks of, for example, the PFC of rodents and higher primates in order to assess preservation of the roles of putative homologous regions (see, e.g. Uylings and Van Eden 1990).

Conclusions

In sum, we have examined the structural connectivity of the macaque PFC by using tools from network science and an exhaustive dataset. On the one hand, the principles and predictions of the ABH do not support the connectivity principles of the hierarchical anterior–posterior model. On the other hand, the LBH seem to be a more tenable hypothesis for models incorporating evidence on the connectivity of the

macaque PFC and advocating the hierarchical anterior-posterior gradient.

Approaches as the current one can inform models of the human PFC and highlight the power of formal analysis for the investigation of PFC organization. Such approaches can be helpful for understanding how integrated behavior is accomplished and what structural alterations might underlie mental diseases.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxford-journals.org/

Notes

We thank Matteo Bastiani, Michael Capalbo, and Claus C. Hilgetag for feedback on previous drafts of the manuscript. We also thank the reviewers for their constructive comments. *Conflict of Interest*: None declared.

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