Statistical Analysis of Parieto-Frontal Cognitive-Motor Networks

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1Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, University College London, London, United Kingdom; 2Department of Physiology and Pharmacology, Sapienza University of Rome, Rome, Italy; and 3Department of Neurophysiology, Sapienza University of Rome, Rome, Italy

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Averbeck BB, Battaglia-Mayer A, Guglielmo C, Caminiti R. Statistical analysis of parieto-frontal cognitive-motor networks. J Neurophysiol 102: 1911–1920, 2009. First published July 22, 2009; doi:10.1152/jn.00519.2009. Considerable information has been gathered on the anatomical connectivity within the parieto-frontal network of the primate brain. To examine the statistical regularities in this connectivity, we carried out hierarchical cluster analysis and found statistically significant clusters of areas: four in the parietal and six in the frontal lobe. Clusters were based on patterns of inputs from all cortical areas. Both parietal and frontal clusters were composed of sets of spatially contiguous architectonic areas. The four parietal clusters were composed of sets of anterior (somatosensory), dorsal, inferior, and medio-lateral parietal cortical areas. The six frontal clusters were composed of sets of dorsal premotor, ventral premotor, primary motor, cingulate motor, and dorsal and ventral prefrontal cortical areas. Furthermore, connectivity between frontal and parietal clusters was topographic and reciprocal. Thus we found substantial statistical structure and organization in the parieto-frontal network that gives a simplified but accurate description of this system.

INTRODUCTION

The anatomical connectivity of the primate cortex has been defined to a large extent, providing a wealth of data on information flow through the macaque brain (Felleman and Van Essen 1991). This rich source of data is highly complex, because there are many architectonically defined areas each projecting to different areas (Brodmann 1909). Thus although a large amount of information is available, assimilating this information into a coherent picture can be difficult (Felleman and Van Essen 1991). We, as well as others before us (Averbeck and Seo 2008; Beckmann et al. 2009; Bullmore and Sporns 2009; Hilgetag et al. 2000; Köttet et al. 2001; Passingham et al. 2002; Stephan et al. 2000; Vezoli et al. 2004; Young 1993), have taken a computational approach to this problem. Our work differs from much of this previous work in several ways. First, the previous work has focused on network topology through the application of graph theoretic tools, whereas our work (as well as Beckmann et al. 2009; Passingham et al. 2002) focuses on understanding the neurophysiological response properties of areas based on their anatomical inputs and the dominant routes of information flow through the cortex. We address this question by applying parametric hierarchical clustering algorithms to the data, where the clustering is defined by the complete set (internal and external to the network) of inputs to each area, as opposed to only other areas within the same network (Hilgetag et al. 2000). Examining inputs only from areas within the same network addresses questions related to the graph theoretic organization of the network, which are not the same as the questions we address here. Furthermore, our approach shows that standard clustering methods that have been used previously (Kötter et al. 2001) do not find optimal trees and as such there are other tree structures and sets of clusters that better fit the data. In addition, our approach indicates how well the trees that were found fit the data. Thus we focus on a question different from that examined in previous studies and we apply newly developed statistical tools that give a more accurate answer to our question.

Our analyses show that there are statistical regularities in the anatomy that allow us to simplify the connectivity of the cortex while still retaining most of the information. We have chosen to use hierarchical cluster analysis, because this allows us to see the data either in its original detail, at the level of the leaves of the tree, or at various levels of simplification as one ascends the hierarchy (Averbeck and Seo 2008). We imported techniques that have been developed in the field of phylogenetics that allow us to carry out statistical tests on our trees to insure that we are extracting valid structure from the data (Edwards and Cavalli-Sforza 1964; Felsenstein 1973, 1981; Margush and McMorris 1981; Thompson 1975). In conjunction with this, we developed a method to search through a large set of trees to find the one that best describes the data, in a statistical sense, and we find that this approach results in trees that better fit the data than standard techniques.

In a previous study, we focused on prefrontal cortex (Averbeck and Seo 2008). In this study, we focus on the parieto-frontal network. In the last 20 yr, a large set of data has been gathered on the organization of the parieto-frontal system, mainly because of the extensive characterization of connections linking reciprocally frontal and parietal cortex (Battaglia-Mayer et al. 2003, 2006; Caminiti et al. 1996; Matelli and Luppino 2001; Rizzolatti and Matelli 2003; Wise et al. 1997). The results of these studies indicate that precise routes connecting a specific parietal to a specific frontal area are uncommon. In most instances, any given parietal area is linked to a constellation of frontal areas, and vice versa, with differing strength. This pattern of connectivity identifies in the brain different cortico-cortical systems with varying degrees of parallelism (Battaglia-Mayer et al. 2003, 2006; Caminiti et al. 1996; Johnson et al. 1993, 1996; Marconi et al. 2001; Matelli and Luppino 2001; Matelli et al. 1998; Rizzolatti and Matelli 2003; Rozzi et al. 2006; Tanné-Gariety et al. 2002; Wise et al. 1997). This study is an attempt to put into a statistically validated, coherent framework the large body of anatomical knowledge now available on the parieto-frontal networks and to relate it with known physiological observations.
Methods

The methods are similar to those used in our previous study (Averbeck and Seo 2008). The database of connectivity was compiled into a table by exhaustively examining the primary literature on the parietal and frontal cortex (for the list of papers and the resulting table see the supplementary material). Most inputs were based on injections of retrograde tracers; however, in a few cases, anterograde transport was also considered. In each case, we examined inputs to each area and classified them as nonexistent (0), weak (33), medium (67), or strong (100), where classifications were based on reported connection strengths where possible. Our categories are based on the categories presented in the original manuscripts, which are often 0/1/+/-/+,... etc, or a direct mapping of cell counts into these categories. Reported connections whose strength could not in any way be identified were given a value of 50, although we only did this for 3 of 724 connections taken into account in our study. All areas were further given a strong (100) self-connection, because strong local connectivity is always seen within the cortex (Huntley and Jones 1991; Kritzer and Goldman-Rakic 1995; Lund et al. 1993). Furthermore, the clustering analysis assumed that areas are similar to themselves, and this is implemented by giving a strong self-connection.

Because of the important role the medial intraparietal area (MIP) plays in visuo-motor integration for reaching (Caminiti et al. 1996), we wanted to include it in our analysis. However, there have been no direct injections of retrograde tracers into area MIP. Nevertheless, there are a few studies that have used anterograde tracers in parietal cortex to examine the inputs to this area (Leichnetz 2001; Pandya and Seltzer 1982; Seltzer and Pandya 1984), and its outputs have been well documented. Therefore we filled in the frontal inputs to area MIP by assuming reciprocal connectivity. Thus the frontal inputs to area MIP were assumed to be the same as the efferents from MIP to frontal cortex. This is the only area for which this was done.

We fit hierarchical trees to the data in the table. This analysis proceeded in multiple steps. First, we generated 10,000 bootstrap datasets by sampling with replacement from the rows of the table, where the rows are the inputs to the areas. This created datasets with random combinations of the inputs to each of the areas, where an entire row was always kept from the table when it was sampled. We used the agglomerative tree fitting algorithm from Matlab to generate a tree structure for each bootstrap dataset as well as the original dataset. This algorithm defined the branch points of the tree, but not the lengths of each branch or how well the tree fit the data. This gave us a set of 10,001 candidate trees to search to find trees that fit the data well; 10,000 trees from the bootstrapped tables and 1 tree from the original table. In this way we could see whether or not the tree fit to the original data was in fact the best-fitting tree when fit back to the original data. In pilot studies, we found that sets of \( l \leq 1,000 \) trees were always unique when generated with this method. Comparison was too computationally demanding, however, to verify that all 10,000 trees were unique.

Subsequent to this, we used a maximum likelihood tree fitting algorithm to optimize the fit of each tree to the original dataset (Averbeck and Seo 2008; Felsenstein 1973) and generate a fit of each tree, based on the log-likelihood of the data, given the tree. The algorithm models the distances between nodes as a branching Gaussian diffusion process. The strength of this algorithm is that it gives us an objective estimate of how well the tree fits the data, and it allows us to do hypothesis testing to confirm that we are describing significant structure in the data. We sorted through the 10,001 trees and found the 100 trees that fit the original data best, in terms of the likelihood. It is important to point out that trees that were found by the agglomerative algorithm on bootstrapped tables were tested against the original table. The bootstrap procedure was only used to identify candidate trees, because it is known that tree-fitting algorithms do not necessarily identify optimal trees.

The fit of the trees was assessed as the log-likelihood. The likelihood function for this model is given by

\[
L(d \mid T, l) = 2\pi^{-1/2}(l_1 + l_2)^{-1} \exp \left( -\frac{d_{12}^2}{2(l_1 + l_2)} \right)
\]

where the measured differences between nodes are given by the summed differences in connections, defined as

\[
d_{ij}^2 = \sum_{k=1}^{N} (C(k, i) - C(k, j))^2
\]

The values \( C(i, j) \) are directly from the table (see supplementary material). The variable \( T \) is the tree structure provided by the agglomerative algorithm in Matlab for each of the 10,001 trees. The distances estimated in the tree are given by the lengths \( l \), which are adjusted by the maximum likelihood algorithm to best approximate the measured distances between areas.

Subsequent to this, we used an algorithm developed for fitting phylogenetic trees (Margush and McMorris 1981) to fit a consensus tree to the 100 best trees (Averbeck and Seo 2008; Romanski et al. 2005). The consensus tree contained the clusters that occurred most often in the 100 best (i.e., highest likelihood) trees. The algorithm also returned the number of times that each cluster was found across the 100 trees, which provided an estimate of how robust each cluster was. In effect, we were trying to characterize the distribution around the maximum likelihood point, to see how reliable the trees were.

Results

We compiled a matrix of the inputs to 15 parietal and 20 frontal areas from published anatomy studies (see supplementary material). The frontal architectonic subdivisions were based on the work of Petrides and Pandya (2002) and Matelli et al. (1991), whereas the parietal subdivisions were based on the work of Pandya and Seltzer (1982) and Borra et al. (2008). Our primary goal was to examine the parietal-frontal network. However, we included several prefrontal areas, which were studied in detail in a previous study (Averbeck and Seo 2008), because they have important interconnections with parts of the parietal-frontal system. On average, each parietal area had 19.7 inputs and each frontal area had 17.3 inputs with a total of 76 different architectonic areas providing a nonzero input to the set of regions considered in this study. The difference in number of inputs to individual architectonic areas between parietal and frontal cortex was not significant \( (P > 0.05; \text{unequal variance } t\text{-test, } df = 32) \). Overall, individual areas received inputs from about one quarter of the total areas we considered (parietal: 19.7/76 = 0.26; frontal: 17.3/76 = 0.23).

Tree fitting

We next carried out parametric hierarchical cluster analysis on the parietal and frontal areas using the database of connectivity. We fit 10,000 trees to bootstrap sampled datasets and 1 tree to the original dataset, resulting in a candidate set of 10,001 trees. We optimized each of these trees to the original data and estimated the fit of each tree (the log likelihood) using the maximum likelihood algorithm. After this, we identified the 100 trees that had the highest likelihood for both the parietal and frontal cortex. As we found previously (Averbeck and Seo 2008), all 100 of these trees fit the original data better than

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1 The online version of this article contains supplemental data.
random trees generated by scrambling the leaves of the best ML tree (\(P < 0.001\)), and as such, we were describing a statistically significant structure in the data. Furthermore, the single tree that was found using standard tree fitting tools on the original dataset was not the tree that fit the data best for either the parietal or frontal cortex. In all cases, many of the trees identified on the bootstrapped data fit the original data better than the single tree fit to the original data. Specifically, the single tree fit to the average data was 3,287/10,001 in the parietal cortex and 252/10,001 in the prefrontal cortex. Thus our bootstrap approach finds many trees that fit the data better than standard clustering tools. This is perhaps not surprising because these algorithms are not guaranteed to find optimal trees. It is perhaps more surprising that the standard trees were quite far from the optimal trees, especially in parietal cortex.

We estimated the likelihood (i.e., fit of each tree to the original data) of individual trees by assuming that our data followed a branching Gaussian diffusion process. This means that we were assuming that distances between areas could be modeled by the variance of a Gaussian distribution. To examine this assumption, we used a bootstrap approach to generate a distribution of distances for our data and checked that this distribution was approximately \(\chi^2\), which is the distribution of variances for a Gaussian. We found that, although individual connections were approximately exponentially distributed, the distances that were summed across many inputs (see METHODS) were well approximated by a \(\chi^2\) distribution (Fig. 1), and thus the Gaussian distribution assumptions of our parametric clustering algorithm were well met, because the variance of a Gaussian follows a \(\chi^2\) distribution. In fact, given the amount of data we were assimilating, the \(\chi^2\) essentially converged to a Gaussian (Fig. 1). Thus we found significant cluster structure in both the parietal and frontal cortex, and this significance was based on distribution assumptions that were well met by the data.

After the fitting of individual trees, we estimated a consensus tree from the 100 best trees in both cases (Fig. 2). This defined the clusters that were most common and indicates how often those clusters were present in the 100 most-likely trees. For descriptive purposes, we describe clusters at a particular level of the hierarchy. However, we are not suggesting that these clusters are privileged with respect to the rest of the clusters in the tree. They do, however, represent statistically legitimate levels of organization in the data. Additional detail could be considered at lower levels of the hierarchy. (For comparison, equivalent tree fitting analyses were carried out on binary connectivity data, where only presence or absence of connections was considered and not their strength; see supplementary material for the trees which were found on this data).

**Parietal and frontal clusters**

In the parietal cortex, we describe a set of four well-defined clusters that all lie below a bifurcation in the tree and thus represent a complete cluster (Fig. 2, right). The first cluster (dorsal parietal: \(\text{PARd; red—clusters will be italicized, individual architectonic areas in nonitalic}\)) was composed of areas lying in the dorsal bank of the intraparietal sulcus and the adjacent caudal part of the superior parietal lobule (PEa, MIP, PEc). A second cluster (SS; blue) was composed of the first somatosensory cortex (SI) and the higher-order somatosensory areas SII and PE. The third group (ventral parietal: \(\text{PARv; orange}\)) was composed of areas located in the exposed part of the inferior parietal lobule (IPL; areas PF, PFG, PG), as well as by area AIP within the adjacent ventral-anterior part of the intraparietal sulcus. The fourth group (medio-lateral parietal: \(\text{PARml; yellow}\)) was composed of areas belonging to the medial part of the superior parietal lobule (SPL; areas V6A and PGM),
postero-lateral IPL (Opt), and ventral intra-parietal sulcus (IPS; areas LIP and VIP). The clusters were generally robust, occurring in the 100 best ML trees 95, 98, 71, and 50 times, respectively. The PARml cluster was the least robust of the parietal clusters. Additionally, higher-order clusters were composed of the SS/ParD clusters, which were formed by the ParV clusters, followed by the PARml cluster. These higher-order clusters were also robust in the data (Fig. 2). Finer-grained clusters also tended to contain spatially adjacent areas, for example, PF and AIP, followed by PFG and then by PG. Thus as one ascends the hierarchy, one tends to accumulate spatial neighbors first, followed by neighbors of neighbors.

A similar analysis of frontal areas showed six clusters (Fig. 2, left). A first group of areas (PMd; red) corresponded to the dorsal premotor cortex, including F2 vr, F2 precd, F3-supplementary motor area (SMA), F6-preSMA, and F7 excluding the part of it known as supplementary eye fields (F7-SEF). A second cluster (PMv; orange) was formed by the ventral premotor areas (F4 and F5), and these areas were joined by the primary motor cortex (MI; blue). We consider MI separately from PMv because it has strong reciprocal connectivity with the parietal cluster SS, as shown in Fig. 3. An additional cluster (CING; green) was formed by the cingulate areas (23a, b, c and 24a, b, c). Finally, we had two PFC clusters (PFCv; light-yellow and PFCd; dark-yellow). The ventral cluster was formed by prefrontal areas (46v, 45a, 45b, and F7-SEF), and the dorsal cluster was composed of 46d, 8B and 8A—often referred to as 8d. We included 46v with 45a, 45b, and F7-SEF, even though it did not lie explicitly below a bifurcation, because it is closer in the tree to these other areas than it is to the PFCd areas, and in our previous study, we found that 46v clustered with 45 (Averbeck and Seo 2008).

Frontal clusters, like parietal, were robust. The PMd cluster occurred 52 times, the MI/PMv cluster occurred 78 times, the CING cluster occurred 46 times, the PFCd cluster occurred 58 times, and PFCv (i.e., the set of just 46v, 45a, 45b, and F7-SEF) occurred 12 times (not shown on Fig. 2 because only counts at bifurcations are shown). Thus the PFCv cluster was the least robust, but it was reasonably well supported by the data. The cluster formed by areas 45a/45b/F7-SEF was highly robust, occurring in the data 90 times, and thus it was the inclusion of area 46v that makes this cluster less common. It is also worth pointing out that areas F3/F6 (SMA/preSMA) were included with the rest of the PMd cluster only 52 times, whereas the rest of this cluster occurred together 93 times (Fig. 2). Thus the supplementary motor areas did not cluster as tightly with the rest of the dorsal premotor areas. Additionally, F3/F6 clustered together 44 times, which is the second lowest of the frontal clusters (the PFC areas clustered together 49 times, not including area 46v). In summary, the SMA/preSMA cluster was robust in the data, but less robust than many of the other frontal clusters.

Additionally, higher level clusters were composed of the PFC/CING clusters, and the PMv/MI/PMd motor clusters and, as with the parietal clusters, as one ascends the hierarchy, one tends to agglomerate neighbors first, followed by neighbors of neighbors, etc. Overall, all of the frontal and parietal clusters corresponded to spatially contiguous areas, similar to what was found for prefrontal areas (Averbeck and Seo 2008). Thus there is an orderly, hierarchical structure to the anatomically defined frontal and parietal areas.

Connectivity within and between parietal and frontal clusters

We next examined the connectivity of each cluster based on inputs coming from within and outside the parieto-frontal network (Figs. 3 and 4). This allowed us to determine the dominant pathways relaying information to and among clusters as well as exactly how dominant they were. Each parietal and frontal cluster was characterized on the basis of the dominant inputs from other parietal and frontal clusters, as well as from areas that were not leaves of the trees we fit to the data. More specifically, connections were based on retrograde tracers in-
jected into the relevant cortical area. Therefore external connections were defined as labeled cells found in any architectonic areas that were not members of the set of parietal-frontal areas that were leaves in the cluster analysis. It can be seen that, in most instances, the main input to each cluster from the same lobe came from inside the cluster, because of intrinsic connectivity within areas and strong local connections, similar to what we had previously seen in prefrontal cortex (Averbeck and Seo 2008). This was not the case for PMv, but it had only two areas.

The parietal inputs to frontal areas followed a topographic pattern (Fig. 3). Specifically, if considering just the parietal inputs, the dominant input to M1 came from the somatosensory cluster (SS: 34% of total), the strongest inputs to the ventral premotor cluster (PMv) came from the ventral parietal regions (PARv: 14% of total), the strongest inputs to the dorsal premotor cortex (PMd) came from the dorsal parietal areas (PARd: 10% of total), and the strongest input to the CING cluster came equally from PARml (2%) and SS (2%), although clearly both of these inputs were small. Finally, the strongest parietal input to both PFCv and PFCd came from PARml (5 and 9% of total, respectively).

We also found that connections between frontal and parietal clusters were largely reciprocal (Fig. 4), such that, considering just the frontal inputs to parietal clusters, the strongest input to SS came from M1 (15% of total), the strongest input to PARd came from PMd (19% of total), and the main frontal inputs to PARv originated in PMv (9% of total). Summed together, the dorsal and ventral prefrontal clusters PFCd and PFCv provided the largest input to PARml (13% of total). Perfect reciprocation would be highly unlikely if connections were random ($P < 0.01$, binomial probability, random = 0.25).

We also examined the fraction of inputs to each cluster that came from outside the parieto-frontal network (Figs. 3 and 4, right column, Ext). Specifically, what fraction of the total input to each cluster originated from areas that were not leaves in either the parietal or frontal tree? We found that the PARml, SS, PARd, and PARv clusters received 31, 10, 7, and 23% of their inputs from outside the network, respectively. For the frontal clusters, M1, PMv, PMd, PFCv, PFCd, and CING received 0, 3, 12, 44, 21, and 54% of their inputs from outside the parieto-frontal network. Thus PFCv, CING, and PARml clusters received a large fraction of their inputs from outside the parieto-frontal network. Thus PFCv, CING, and PARml clusters received a large fraction of their inputs from outside the parieto-frontal network. Thus PFCv, CING, and PARml clusters received a large fraction of their inputs from outside the parieto-frontal network. Thus PFCv, CING, and PARml clusters received a large fraction of their inputs from outside the parieto-frontal network. Thus PFCv, CING, and PARml clusters received a large fraction of their inputs from outside the parieto-frontal network.

Finally, as an estimate of whether clusters received an equal number of inputs from all other clusters or tended to receive almost all inputs from a few clusters, we calculated the entropy of the input distributions (Figs. 3 and 4), where the entropy is given by $H = -\sum_{i=1}^{N} p(i)\ln p(i)$, where $p(i)$ is the probability of connection $I$ (the y-axis as shown in Figs. 3 and 4) and

![Fig. 3. Inputs to frontal clusters. Distribution of inputs to frontal clusters from frontal (light gray), parietal (medium gray), and areas external (Ext, dark gray) to the parieto-frontal system.](http://jn.physiology.org/doi/abs/10.1152/jn.00969.2008)
\[ \frac{\ln(1/11)}{11} = 2.39 \]

We found that clusters were composed of contiguous architectonic areas and that parietal and frontal clusters had topographic, reciprocal connections. Although this has been seen at the level of individual areas, we found that it also scaled to clusters of areas.

Because the cluster analysis defines groups of architectonic areas based on their anatomical inputs, areas belonging to a given cluster should share similar physiological properties, underlying similar behaviors. This has been studied quantitatively using a functional MRI (fMRI) diffusion tensor imaging (DTI) approach (Beckmann et al. 2009). Many of the areas we considered have been studied physiologically and in general areas within clusters do share response properties. In particular, the medio-lateral parietal cluster (\( PAR_{ml} \)) is at the core of the visuomotor transformation underlying eye and to some extent hand movements to salient visual targets, as well as belonging to the early stages of eye–hand coordination underlying reaching movements (Battaglia-Mayer et al. 2000, 2001, 2003, 2005; Colby and Goldberg 1999; Ferraina et al. 1997a,b; Mascaro et al. 2003). As further evidence of the visual nature of this cluster, 31% of the inputs come from outside the parieto-frontal network, originating primarily from extrastriate visual areas. Additionally, this cluster was the least robust of the parietal clusters, occurring in 50% of the best 100 trees. As such, it is the least robustly defined and therefore likely the most heterogeneous, although there is substantial statistical evidence for the grouping.
The dorsal parietal cluster (PARd) is crucial for the integration of visual and somatic information, which occurs at the single cell level, for reaching movements (Colby and Duhamel 1991; Georgopoulos et al. 1984; Hamel-Paquet et al. 2006; Johnson et al. 1996; Kalaska et al. 1990; Lacquaniti et al. 1995). In humans, lesions of the SPL result in optic ataxia, an impaired visual control of hand movements, which has been interpreted as a parieto-frontal disconnection syndrome (Battaglia-Mayer and Caminiti 2002; Battaglia-Mayer et al. 2003, 2006; Caminiti et al. 2005).

The ventral parietal cluster (PARv) is composed of areas involved in the visual control of hand-object interaction, such as grasping (Rizzolatti and Matelli 2003; Taira et al. 1990), and to a certain extent reaching. Furthermore, areas PFG and PG have been proposed as a parietal node in the mirror system that underlies action and intention recognition (Fogassi et al. 2005). Finally, it has been proposed that the functional properties of neurons in area 7a (PG, Opt) provide a “positive image” of the motor disorders of neglect patients suffering from directional hypokinesia after IPL lesions (Battaglia-Mayer et al. 2005), and extensive correlates of object and viewer based neglect have been found in PG neurons (Chafee et al. 2005, 2007; Crowe et al. 2005, 2008). This cluster is also involved in both the processing of visual stimuli and in the preparation of movements in the context of more complex visuo-motor tasks, such as interception of moving targets (Merchant et al. 2004). Finally, the somatosensory cluster (SS) represents somatosensory information such as limb position and velocity (Archambault et al. 2009; Averbeck et al. 2005; Georgopoulos and Massey 1985; Prud’homme and Kalaska 1994) and conveys this information to frontal cortex via its direct access to M1.

The frontal tree was composed of six clusters. The dorsal premotor cluster (PMd) receives inputs from the dorsal parietal cluster (PARd) and represents the frontal node of the network underlying visually guided reaching (Johnson et al. 1996; Kalaska and Crammond 1995), mental rehearsal (Cisek and Kalaska 1995), and aspects of decision making in the reach system (Cisek and Kalaska 2005; Pesaran et al. 2008). Areas F6 and F3, often referred to as pre-SMA/SMA were clustered with areas F7 and F2. The latter is traditionally referred to as a premotor area for its direct projection to the primary motor cortex (Muakkassa and Strick 1979), whereas the first, because of its preferential connection with prefrontal cortex, could be an important node of the distributed system responsible for cognitive decisions about behavioral strategies that give rise to action. This supplementary motor complex (Nachev et al. 2008), however, forms a separate subcluster within the PMd cluster, and the SMA/pre-SMA were less strongly clustered with these other areas (52 times) and with each other (44 times) than many of the frontal areas. The ventral premotor cluster (PMv), on the other hand, receives inputs from the ventral parietal cluster (PARv) and is involved in action recognition, as the premotor component of the mirror system (di Pellegrino et al. 1992; Rizzolatti and Craighero 2004). The ventral premotor cluster is, however, likely involved both in reaching (F4) and grasping (F5), with area F5 involved in nonstandard visuospatial processing for goal-oriented behavior (Borra et al. 2008; Rozzi et al. 2006).

The prefrontal clusters (PFCv and PFCd) subend diverse functions. The dorsal cluster that contains the frontal eye fields and dorsal area 46 (approximately area 8a, but also perhaps part of area 45) clearly has a role in motor (Bruce and Goldberg
1985) and cognitive (Averbeck et al. 2006; Kim and Shadlen 1999; Pasupathy and Miller 2005) aspects of oculomotor processes including working memory (Chafee and Goldman-Rakic 2000; Funahashi et al. 1989; Fuster and Alexander 1973) and flexible, rule contingent behavior (Bunge et al. 2003; Collins et al. 1998; Miller 2000; Wallis et al. 2001). Many of these functions are studied across 46v and 46d. Some studies have identified differences between areas 46v and 46d (Hoshi et al. 1998), whereas others have emphasized the similarities (Rao et al. 1997). Recent studies on area 46d (Genovesio et al. 2005) have also shown neural responses related to strategies used in reversal learning paradigms.

A large number of studies have also been carried out on the oculomotor function of the SEF, part of the PFCv cluster. Responses in this area have been seen to sequential motor control as well as (in some studies) error and conflict monitoring (Histed and Miller 2006; Nakamura et al. 1998, 2005; Schall et al. 2002; Tanji 2001). Also, within the PFCv cluster, area 45b is associated closely with the SEF, suggesting its involvement in oculomotor functions (Bruce et al. 1985), perhaps as a ventral extension of the FEF. The PFCv cluster receives 44% of its inputs from outside the parieto-frontal network. Many of these inputs come from visual and auditory areas in the temporal lobe (Romanski et al. 1999; Webster et al. 1994). As such, sensory signals from parietal and temporal cortical areas converge on this cluster where they are integrated. For example, responses to complex auditory and visual stimuli have been seen in area 45a/46v (Averbeck and Romanski 2006; Romanski et al. 2005; Scaliaidhe et al. 1999; Sugihara et al. 2006), suggesting a role in communicative behavior in monkeys.

The cingulate cluster receives >50% of its input from outside the parieto-frontal network. Much of this input comes from limbic areas, including the hippocampus, amygdala, ventral-medial prefrontal regions including areas 25 and 32, and orbital frontal cortex (Carmichael and Price 1995). On the output side, several of the cingulate areas project directly to the spinal cord, as well as projecting back to the motor areas in lateral frontal cortex (Strick et al. 1998). As such, this cluster of areas has often been considered an interface between the limbic and motor systems (Devinsky et al. 1995). Studies have shown that cingulate neurons are important for reward-guided action selection (Shima and Tanji 1998) as well as switching between memory-guided and anti-saccade tasks (Johnston et al. 2007). Lesion studies have also suggested a specific role of the cingulate areas in processing social stimuli (Rudebeck et al. 2006), which would accord with the limbic aspects of cingulate function.

We also examined the connectivity between clusters, because previous studies have shown that neurons across areas that are part of cortico-cortically connected clusters display similar functional properties (Chafee and Goldman-Rakic 2000; Johnson et al. 1996). In this analysis, we found that inputs from parietal cortex into frontal cortex were highly topographic and defined by four streams of information flow (Petrides and Pandya 1984). We found a ventral stream from PARv to PMv, a dorsal stream from PARd to PMd, a somatomotor stream from S3 to M1, and a dorsal/medial stream from PARmL to PFC. Furthermore, these parietal-frontal connections were largely reciprocal, with parietal areas receiving inputs from the frontal areas to which they sent projections. Thus similar to the anatomical organization at the level of single architectonic areas, connectivity tended to be relatively reciprocal between clusters of areas. We also found, however, that these parietal-frontal connections always made up less than one third of the total inputs to a given area, so although these connections are obviously important, areas also integrate information from other sources.

We also characterized the entropy of the inputs to parietal and frontal clusters. In the parietal cortex, the lowest entropy cluster, SS, is a primary sensory area, whereas the higher entropy areas are association areas and thus the entropy reflects, to a certain extent, simple versus diverse inputs from the frontal-parietal network. This relationship does not hold in frontal cortex, mostly because of the fact that external inputs play a large role in these clusters, and we have not split external inputs into various groups. However, the entropy should be interpreted with respect to the frontal-parietal network. As such, the low entropy frontal clusters, including M1, PFCv, and CING, do not get inputs from across the various frontal and parietal clusters.

Conclusions
The cluster analyses in this and our previous study (Averbeck and Seo 2008) showed that clusters were composed of spatially contiguous architectonic areas. This suggests an additional regularity in the anatomical organization of the cortex above that defined by columns (~100 μm) and architectonic areas (approximately a few centimeters). Here we showed that the next level of organization can be based on clusters of areas that receive similar anatomical input and therefore likely process similar information. Furthermore, identified clusters in parietal and frontal cortex were reciprocally interconnected. The cortico-cortically connected clusters we identified across different lobes form a distributed cortical system (Mountcastle 1978) underlying the corresponding function.

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