Statistical analysis of parieto-frontal cognitive-motor networks

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Abstract

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, as there are many architectonically defined areas each projecting to different areas (Brodmann 1909). Thus, while 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; Kötter 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, as well as 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 which 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 than that examined in previous studies and we apply newly developed statistical tools which 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, as 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 have 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 1981, 1973; Margush and McMorris 1981; Thompson 1975). In conjunction with this we have developed a method to search through a large set of trees to find the one which best describes the data, in a statistical sense, and we find that this approach results in trees which better fit the data than standard techniques.

In a previous study we focused on prefrontal cortex (Averbeck and Seo 2008). In the current study we focus on the parieto-frontal network. In the last 20 years, a large set of data has been gathered on the organization of the parieto-frontal system, mainly due to the extensive characterization of connections linking reciprocally frontal and parietal cortex (Battaglia-Mayer et al. 2006; Battaglia-Mayer et al. 2003; 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. 2006; Battaglia-Mayer et al. 2003; Caminiti
1998; Matelli and Luppino 2001; Rizzolatti and Matelli 2003; Rozzi et al. 2006; Tanné-
Gariepy 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 non-
existent (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/+/++, ... 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 connections out of 724 taken into account in our study. All areas were
further given a strong (100) self-connection, as strong local connectivity is always seen
within the cortex (Huntley and Jones 1991; Kritzer and Goldman-Rakic 1995; Lund et al.
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 which 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 then fit hierarchical trees to the data in the table. This analysis proceeded in multiple steps. First, we generated 10000 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 then 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 10001 candidate trees to search to find trees which fit the data well; 10000 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 up to 1000 trees were always unique, when generated with this method.
Comparison was too computationally demanding, however, to verify that all 10000 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 then sorted through the 10001 trees and found the 100 trees which fit the original data best, in terms of the likelihood. It is important to point out that trees which 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, as 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

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

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

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

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 10001 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 which 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 info). The frontal architectonic
subdivisions were based on the work of Petrides and Pandy (Petrides and Pandya 2002)
and Matelli et al. (Matelli et al. 1991), whereas the parietal subdivisions were based on
the work of Seltzer and Pandya (Pandya and Seltzer 1982) and Luppino and colleagues
(Borra et al. 2008). Our primary goal was to examine the parietal-frontal network.
However, we included several prefrontal areas, which were investigated in detail in a
previous study (Averbeck and Seo 2008), as 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 non-zero 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 ($p > 0.05$; unequal variance t-test, $df = 32$). Overall, individual
areas received inputs from about $\frac{1}{4}$ of the total areas we considered (parietal: $19.7/76$
$= 0.26$ and 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 10000 trees to bootstrap
sampled datasets and 1 tree to the original dataset, resulting in a candidate set of
10001 trees. We then optimized each of these trees to the original data and estimated
the fit of each tree (the log likelihood) using the maximum likelihood algorithm.
Following this we identified the 100 trees which had the highest likelihood for both
parietal and frontal cortex. As we found previously (Averbeck and Seo 2008), all 100 of
these trees fit the original data better than random trees generated by scrambling the
leaves of the best ML tree ($p<0.001$), and as such we were describing 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 which fit the data best
for either parietal or frontal cortex. In all cases many of the trees identified on the
bootsrapped 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 $3287/10001$ in parietal cortex and
$252/10001$ in prefrontal cortex. Thus, our bootstrap approach finds many trees which fit
the data better than standard clustering tools. This is perhaps not surprising as 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-square, which is the distribution of variances for a
Gaussian. We found that, although individual connections were approximately
exponentially distributed, the distances which were summed across many inputs (see
methods) were well approximated by a chi-square distribution (Fig. 1), and thus the
Gaussian distribution assumptions of our parametric clustering algorithm were well met,
as the variance of a Gaussian follows a chi-square distribution. In fact, given the
amount of data we were assimilating, the chi-square essentially converged to a Gaussian
(Fig. 1). Thus, we found significant cluster structure in both parietal and frontal cortex
and this significance was based on distribution assumptions which were well met by the
data.

Following the fitting of individual trees, we estimated a consensus tree from the
100 best trees in both cases (Fig. 2). This defined the clusters which 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 parietal cortex we describe a set of 4 well defined clusters which all lie below a bifurcation in the tree and thus represent a complete cluster (Fig. 2, right). The first cluster (dorsal parietal: \textit{PARd}; red – clusters will be italicized, individual architectonic areas in non-italic) 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 (\textit{SS}; blue) was composed of the first somatosensory cortex (SI) and the higher-order somatosensory areas SII and PE. The third group (ventral parietal: \textit{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: \textit{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 intraparietal 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 \textit{PARml} cluster was the least robust of the parietal clusters. Additionally, higher order clusters were composed of the \textit{SS/PARd} clusters, which were then joined by the \textit{PARv} cluster, followed by the \textit{PARml} cluster. These higher-order clusters were also robust in the data.
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, etc.

A similar analysis of frontal areas revealed 6 clusters (Fig. 2, left). A first group of areas (PMd; red) corresponded to the dorsal premotor cortex, including F2 vr, F2 pre-cd, F3 - supplementary motor area or SMA, F6 -pre-SMA 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 as it has strong reciprocal connectivity with the parietal cluster SS, as illustrated in Fig. 3. An additional cluster (CING; green) was formed by the cingulate areas (23a, b, c and 24a, b, c).

Finally we had 2 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, as 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 as 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/pre-SMA) 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/pre-SMA 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/M1/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. 3-4). 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 which were not leaves of the trees we fit to the data. More specifically,
connections were based upon retrograde tracers injected 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, due to 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 2 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 (right column labeled $\text{Ext}$ in Figs. 3-4). 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 $\text{PARml}$, $\text{SS}$, $\text{PARd}$, and $\text{PARv}$ clusters received 31%, 10%, 7% and 23% of their inputs from outside the network, respectively. For the frontal clusters, $\text{MI}$, $\text{PMv}$, $\text{PMd}$, $\text{PFCv}$, $\text{PFCd}$ and $\text{CING}$ received 0%, 3%, 12%, 44%, 21% and 54% of their inputs from outside the parieto-frontal network. Thus, $\text{PFCv}$, $\text{CING}$ and $\text{PARml}$ clusters received a large fraction of their inputs from outside the parieto-frontal network, and interestingly, these clusters also shared strong interconnections. The motor and somatosensory areas, on the other hand were very heavily embedded receiving 85% or more of their inputs from within the parieto-frontal network. It is also interesting that $\text{PFCd}$ receives a large fraction of inputs from within the parietal-frontal network (79%).

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. 3-4) and $N = 11$ is the number of input clusters we considered (i.e. the x-axis in Figs 3-4). A uniform distribution would have maximum entropy ($\ln(1/11) = 2.39$) and a distribution where all of the inputs came from one other cluster would have minimum entropy ($\ln(1) = 0$). We found that, $\text{PARml}$, $\text{SS}$, $\text{PARd}$, and $\text{PARv}$ clusters had entropies of 1.99, 1.20, 2.03 and 2.06 nats, respectively. Thus, $\text{SS}$ had lower entropy and the other clusters had similar entropy. For frontal clusters, we found that $\text{MI}$, $\text{PMv}$, $\text{PMd}$, $\text{PFCv}$, $\text{PFCd}$ and $\text{CING}$ had entropies of 1.62, 2.23, 1.91, 1.49, 1.72 and 1.34 nats,
respectively. Thus, MI, PFCv and CING had low entropies, with the low entropy in PFCv and CING driven largely by a high proportion of external inputs, and the low entropy in MI driven by a dominant input from SS. On average, frontal areas had entropy of 1.72 nats and parietal areas had similar entropy of 1.82 nats.

An overall picture of the reciprocal parieto-frontal connectivity as it emerged from the hierarchical cluster analysis is shown in Figure 5, where the results are referred to the physical location of the different brain areas we have studied.

Discussion

We examined the statistical structure of the parieto-frontal network in the macaque, based on the anatomical inputs of its architectonically defined areas. In our analysis, areas which were clustered together were those which received similar inputs. 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.

As 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 an fMRI/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 (PARml) 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. 2003; Battaglia-Mayer et al. 2001; Battaglia-Mayer et al. 2000; Battaglia-Mayer et al. 2005; Colby and Goldberg 1999; Ferraina et al. 1997a; Ferraina et al. 1997b; 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 et al. 2006; Battaglia-Mayer and Caminiti 2002; Battaglia-Mayer et al. 2003; 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 which 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. 2007; Chafee et al. 2005; Crowe et al. 2008; Crowe et al. 2005). This cluster is also involved in both the processing of visual stimuli as well as in the preparation of movements in the context of more complex visuo-motor tasks, such as interception of moving targets (Merchant, Battaglia-Mayer, et al., 2004). Finally, the somatosensory cluster (SS) represents somatosensory information such as limb position and velocity (Archambault et al. In Press, 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 6 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 2004) 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), while 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 sub-cluster within the PMd cluster, and the SMA/pre-SMA were less strongly clustered with these other areas (52 times), and indeed 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 non standard visuospatial processing for goal-oriented behavior (Borra et al. 2008; Rozzi et al. 2006).

The prefrontal clusters (PFCv and PFCd) subextend diverse functions. The dorsal cluster which 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 employed 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. 2005; Nakamura et al. 1998; 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; Scalaidhe et
al. 1999; Sugihara et al. 2006), suggesting a role in communicative behavior in monkeys.

The cingulate cluster receives over 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, since 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 4 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 somato-motor stream from SS to M1 and a dorsal/medial stream from PARml to
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 1/3 of the total inputs to a given area, so while 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 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 vs. diverse inputs from the frontal-parietal network. This relationship does not hold in frontal cortex, mostly due to 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 (~ a few cm). Here we show that the next level of organization can be based upon 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 have identified across different lobes form a distributed cortical system (Mountcastle 1978) underlying the corresponding function.
**Figures**

**Fig. 1.** Distribution of connections and distances. A. Frontal distribution of connection strengths in our dataset. B. Frontal distribution of distances. We have plotted the corresponding chi-square (black solid line) and Gaussian (grey solid line) distribution as well as our empirically estimated bootstrap distribution (black points) of distances. Values of distances were z-transformed before pooling into the distribution. C and D. Parietal connections and distribution of distances.

**Fig. 2.** Clusters of architectonically defined areas based upon their inputs. The identified clusters were represented in different colors on the basis of the dominant connections (arrows) that each cluster of the parietal (frontal) lobe has with groups of frontal (parietal) areas. Left. Clusters of frontal areas. (PMd: red, MI: blue, PMv: orange, CING: green, PFCv: light-yellow, PFCd: dark-yellow). Right. Clusters of parietal areas. (PARd: red, SS: blue, PARv: orange, PARml: yellow). Arrows indicate connectivity, and percentages indicate the fraction of the total input to each area that corresponds to each input.

**Fig. 3.** Inputs to frontal clusters. Distribution of inputs to frontal clusters from frontal (light grey), parietal (medium grey), and areas external (Ext, dark grey) to the parieto-frontal system.

**Fig. 4.** Inputs to parietal clusters. Distribution of inputs to parietal clusters from frontal (light grey), parietal (medium grey), and areas external (Ext, dark grey) to the parieto-frontal system.

**Fig. 5.** Gross anatomy of parietal and frontal clusters. Within the frontal and parietal lobes, the color code (same as in Fig.2) indicates areas belonging to the same cluster and similar colors in the frontal and parietal cortex are associated to clusters related on the basis of their dominant connections (arrows).


Fig. 1
Fig. 3
Fig. 4

PARml

SS

PARv

PARd

Fig. 4