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Principles of inter-areal connections of the macaque cortex

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ABSTRACT

The operation of real world networks is largely determined by their weighted and spatial characteristics. Surprisingly little is known about these features in cortex. We generated in macaque, a consistent database of inter-areal connections comprising projection densities (link weights) and physical lengths. Contrary to previous assumptions, the cortical connection matrix is dense (66%) and therefore, not a small-world graph. Link weights are both highly specific and heterogeneous and we show that it is these properties that characterize the network. The embedding of this weighted network is governed by a distance rule that predicts both its binary features as well as the global and local communication efficiencies. Analysis of the efficiency of this weighted network suggests that small changes in global communication efficiency are offset by large changes in local efficiency. These findings indicate a weight-based hierarchical layering in cortical architecture and processing.

KEY WORDS

Inter-areal, connectivity, network modelling, cortex

1. Introduction

There is a long history of attempts at understanding how information flow through the cortex is shaped by the organizational principles of cortical connectivity. The work of Hubel and Wiesel was greatly inspired by the structure/function relations in the visual system and their formulation of the functional architecture of the visual cortex is a monument in favor of this approach to understanding mechanisms underlying perception and development [1]. Using both single unit recording and transynaptic labeling of thalamic terminals in area V1 they were able to describe the ocular dominance and orientation columns. They extended this approach to tackle the issue of interareal connectivity from a functional perspective. Their

insight into the anatomy of the cortex coupled with single-unit recording suggested that simple, complex and hypercomplex receptive fields reflected stages of information processing in successive and distinct levels of the system.

With the discovery of increasing numbers of connections, the more interesting approaches to the issue of cortical connectivity have looked at general principles rather than the detailed connectivity of a single area. Probably one of the most influential publications in this direction is that of the investigation of the hierarchy of the cortex, conducted by Felleman and Van Essen [2]. Their study employed concepts of cortical organization developed earlier by Pandya and Rockland [3]. In their pioneering work, Rockland and Pandya had noted that the laminar organization of interareal connections shows strong regularities. Projections from the primary sensory areas to subsequent levels of cortical processing (associated to the increase of both size and complexity of the receptive field) predominantly stem from supragranular layers, whereas projections from higher to lower areas originate mostly from infragranular layers. This and the analogy with cortical projections to subcortical structures led to the suggestion that these two sets of projections constitute bottom-up (feed-forward) and top-down (feed-back) pathways of a sequential processing of information.

In their meta-analysis of the connections linking cortical areas, obtained from numerous tract-tracing experiments in different laboratories, Felleman and Van Essen presented a model in which their 32 cortical areas are distributed over 10 hierarchical levels (Fig 1). In this layout, virtually all known feedforward projections link a source area to a target higher up in the hierarchy, and these feedforward projections are reciprocated by feedback ones. They had been able to find a hierarchical ordering of the cortical areas with almost no exceptions to these simple topological rules, which were subsequently shown to be a consistent feature of sensory cortex [2, 4]. In many ways the famous Felleman and Van Essen model of the cortical hierarchy

is the best map we have of the cortex. It captures many features of the cortex, it reveals a clearly hierarchical structure with numerous parallel pathways including the main trunks of the ventral and dorsal streams, it shows that feedforward information can only go from lower to higher levels, whereas feedback information travels in the opposite direction. In their study Young and colleagues showed that non-metric multidimensional scaling of an adjacency matrix (a matrix containing the binary connection information within a set of areas) obtained from the database compiled by Felleman and Van Essen confirmed a hierarchical organization of the major cortical pathways as well as their levels of convergence [5]. However, because of the numerous parallel pathways and given the arbitrary number and positions of levels used in the Felleman and Van Essen model, the analysis of Young's group showed that there were 150,000 equally plausible solutions to the model [6]. One way to resolve this ambiguity is to use a hierarchical distance measure that holds the promise of allowing a definitive solution to the hierarchy [7].

While the Felleman and Van Essen map reveals important unifying features of the cortex, it remains conceptually frustrating. Its construction depends entirely on the notion that there are feedforward, ascending pathways versus feedback or descending pathways. The common assumption is that feedforward pathways contribute to determining the receptive field features in their target areas while feedback projections have a modulatory role. At the systems level there are few experimental verifications of these notions [8, 9], and none at the cellular level. This is in large part due to the fact that interareal cortico-cortical projection cells are hard to identify, for they are only a minute fraction of cortical cells, and we still do not dispose of molecular marker for this cellular type.

Recently an alternative approach to understanding cortical pathways appeals to graph theoretic analysis of cortical networks. Since the early 1990s there has been an increasing focus on network representations of complex systems with the goal of gaining an insight into the functional processes supported by these networks [10, 11]. Among the major discoveries coming out of this approach was the recognition that many real-world networks, on the binary connectivity level, share small-world [12] and scale-free properties [10]. The description of the small-world and scale-free phenomena seemed to be particularly relevant to understanding the brain [13]. In particular, small-world networks are characterized by short path lengths between nodes, coupled with high levels of clustering and ensure maximum integration with minimum wire length. Translated in to anatomical terms, nodes are areas and a small world network would imply that the average number of areas (hops or steps) crossed in the path between any two areas would be small even though areas are mostly linked to a few other areas forming a densely clustered neighborhood. Minimum wire would mean that there would be multiple interconnections within a set of areas but only some of these areas will have extensive connections that form long-distance pathways, to other tightly grouped

areas. These would effectively provide the shortcuts necessary to keep average path lengths optimally short, while avoiding the expense of direct pathways between numbers of areas. Small world networks were initially used for describing social networks where it has been claimed that no two individuals on the planet are more than 6 handshakes from each other. Truly a small world, made possible, because although most of your friends know each other (clustering), some of them plug into other social groups (and provide the shortcuts across the graph). These features provide the integrative function typical of modern society, and it is easy to imagine that they are important in cortical function [14]. Inspired from these early studies on small worlds, and using the compilation of Felleman and Van Essen [2], several studies have confirmed the clustering of functionally related areas and found evidence of short average path lengths suggestive of small-world architecture [15, 16].

Previous graph theory studies of the cortex have largely described cortical topology obtained from binary data (i.e. describing areas as being connected or not connected) [15, 16]. Modeling studies of the cortex have used published databases compiled from numerous studies, many using antiquated techniques, variable definitions of a cortical area, and restricting their investigations to limited regions of the cortex, so that the present day cortical graph is predicted to be incomplete. Further, it is increasingly recognized that new and fundamental insight into the functional organization of real-world systems requires the use of *weighted* networks (i.e. the strength of connections), possibly incorporating spatial distance [17]. In cortex however, the study of spatial, weighted networks is hindered by the absence of reliable published data concerning the distance and numbers of neurons involved in the links between cortical areas [18]. We have therefore undertaken a detailed anatomical investigation of the macaque cortex using stereotyped protocols. This has amounted to a huge work effort (on the order of 70 man-years). It has enabled us to compile a consistent and extensive database of the weight and distance of interareal connections, which we have analyzed using graph theoretic procedures. To achieve this goal we used retrograde fluorescent tracers, which as we have previously demonstrated have maximum sensitivity. These tracers are picked up by axon terminals at the injection site, and retrogradely transported back to the cell body of the neuron projecting to the injected area. Previously, we have also shown that folding of the cortex makes it necessary to have high frequency sampling of the projection zone in each area [19]. Many previous studies have suffered from the "looking under the street lamp" bias, restricting their observations to those areas which are known to project to the injected area. Here we show that the optimization of tracer sensitivity coupled with brain-wide examination reveals many (in the region of 30%) pathways that have not been previously reported. We have made retrograde tracer injections in 26 target areas distributed across occipital, temporal, parietal, frontal and prefrontal lobes. The number of labeled neurons in a given source structure (cortical area or sub-

cortical nuclei) over the total number of labeled neurons in the brain defines the fraction of labeled neurons (FLN) of that structure.

Cortical Connectivity Profiles.

If connectivity weight does play a role in shaping the network properties of the cortex, then we predict that cortical areas would exhibit weight-specific connectivity profiles. That is to say, we would predict that if area X, Y, and Z have respectively strong, medium or weak projections to area W, that this will be consistent across animals. There have been very few studies that have attempted to test this possibility. The few quantitative studies that have been reported claim that there is a 100-fold, inter-individuals variation in the density of connections of a given cortical pathway [18, 20-23]. We have therefore examined this issue in visual areas V1, V2 and V4. Here the advantage is that the areal limits of these large areas are well established as are the retinotopic maps, making it possible to make large, stereotypic injections of retrograde tracers in similar retinotopic positions across animals. By employing standardized methods to define areal boundaries, within the whole cortical sheet, we obtained a range of variations for FLN values with median and means less than a factor of two. Thus, while the observed values are over-dispersed with respect to a Poisson distribution, importantly they are systematically less than that predicted by a geometric distribution. The negative binomial distribution has proven valuable in the analysis of over-dispersed count data [24-26] and provides a reasonable prediction of the relationship between the mean and the standard deviation of FLN values. For repeated injections in the same site (V1, V2 or V4), the model that best predicts without over-parametrization, includes no main effect of the factor “injection CASE” and therefore each area exhibits a connectivity profile (Fig 2). These results show that there is a connectivity profile despite large inter-case variation and the observed consistency is possible because the connection weights span nearly 7 orders of magnitude. The FLN distribution is heavy-tailed and resembles a lognormal distribution (Figure 1). Globally the connectivity profile is expressed as follows. The mean intrinsic connectivity FLN % was nearly 80% (68-89%) of the total connectivity, and is highly local occurring within 1.2-1.9mm from the injection site. The next largest contribution is from the neighboring cortical areas (14%). The remaining connectivity is shared between 3.3% long-range cortico-cortical connections and 1.3% subcortical connections. This pattern of high local connectivity coupled with very small sub-cortical input and weak long distance connectivity is consistent across the

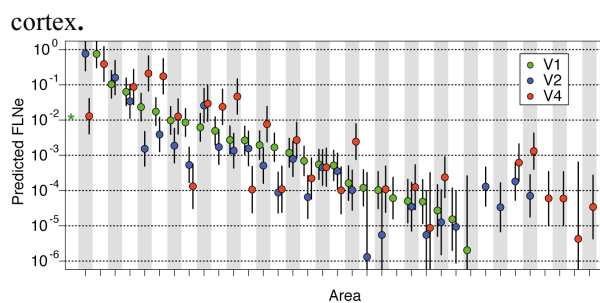


Figure 1 Connectivity profiles of areas V1, V2, V4.

Effects of distance on connectivity weight

The lognormal distribution of the FLN is the expression of a distance rule, which has a profound effect on the organization of the cortex. The pathways linking cortical areas were measured through the white matter and their distribution estimated, by determining the fraction of labeled neurons extending to a given distance. This showed that in all injections there is an exponential decay in the density of connections with distance. This distance information enabled us to show that the strength of interconnections follows an exponential distance rule (EDR) (i.e. strength of connections decays exponentially with increasing projection distance). We examined how distance and strength of connections shapes cortical connectivity by building random models of connectivity based on the same number of pathways and areas as in the experimental data and complying to the EDR, and compared this to the properties of networks generated by using a constant distance rule (CDR).

We then examined the capacity of the two models (EDR and the CDR) to capture the measured features of the data. The rationale being that if the EDR is an important principle governing cortical connectivity then it will show an enhanced capacity compared to the CDR to capture the characteristic features.

The average number of uni-directional and bi-directional (reciprocated) connections (as area pairs) measured on 1000 random graphs based on the EDR gives an almost perfect match to the experimental data, while that for CDR differs considerably. One characteristic binary feature of a network is the relative frequency distribution of directed triads (Figure 2). Any three areas are taken and the connections examined giving a total of 16 possible motifs.



Figure 2 The 16 possible triadic motifs.

Studies looking at motifs distribution frequencies have reported that specific types of network (signal transduction, gene transcription, social etc) have characteristic motif distributions, which are thought to constrain the function of the network [27]. We were able to show that random models of cortical connectivity constructed with CDR failed to capture the motifs and bi-directionality of the data. This contrasted with the EDR model that leads to excellent estimations of these binary features.

Graph density and efficiency

Global Efficiency reflects the average bandwidth for information flow through the weighted graph [28]. Regardless of the pattern of terminal arbors a projection build from numerous neurons is able to convey higher dimensionality information than projections originating from smaller number of neurons and so needing some compression of the information send though he pathway. Here we have sought to determine the pathways that ensure the global efficiency of the graph. If someone considers the relative strength of connection as the compliance to information transfer then we are able to estimate the conductivity trough any possible pathway between a pair of areas. The pathway with highest conductance will be the one requiring less hops and using projections with high compliance. The global efficiency is the sum of the conductance between all pairs of areas, where the maximum resistance come from the weakest links. We tested the effect of attacking the graph by removing connections, starting with the weakest ones (Figure 3A). This does not show an effect on global efficiency until 81% of pathways (containing 7% of total neurons) have been removed. Hence the efficiency of the network is assured by the remaining 19% of pathways exhibiting the highest weights (93% of the cortical projection neurons). These pathways with the highest FLN that ensure the global efficiency, have a mean projection distance of 14mm, considerably shorter than the 38mm of the connections that do not contribute to global efficiency. The network formed by 19% pathways that confer efficiency, constitute a backbone of the graph. It is the minimal set of connections that provide unaffected global efficiency. Interestingly, given the large average path length (3.7 hops) and the diameter of the graph (9 hops!) the efficiency backbone does not seem to correspond to a small world architecture. A complementary measure of efficiency is the local efficiency [29] which is the summed conductance between all the areas connected to an area X, after removal of area X. It is like assessing how easily you can travel between the satellites of a town, without using routes passing through the town. Again this is averaged across the entire graph. Local efficiency evolves differently with weak link removal (Fig 4A). Whereas global efficiency shows a very modest decline with weak link removal, local efficiency shows a gradual increase, peaking in the region just prior to the breakdown of the global backbone. The differential responses of the local and global efficiencies are predicted by the EDR but not by the CDR, this shows that the geometry and weight configuration (in other words the physical embedding) has a particular significance in the efficiency configuration of the network. Further the differential response of the local and global efficiencies suggests interesting dynamics of the system. The effect of weak pathway removal is one way of examining how threshold changes in the network will influence information flow. High activity levels in the network could raise neuron response threshold [30-32].

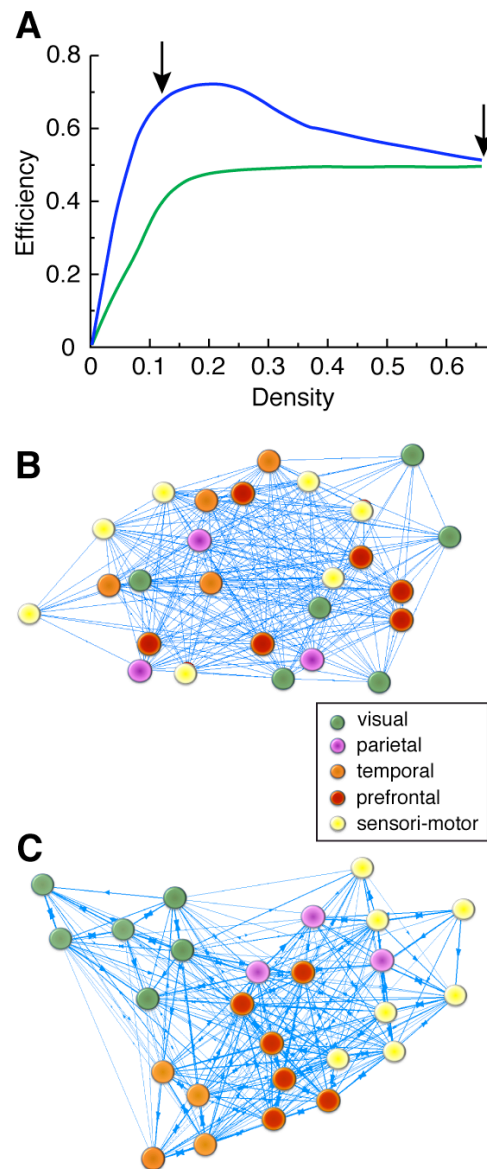


Figure 3 Efficiency of the cortex. A) Effect of removal of weak projections on efficiency. B) Kamada-kawai plot of the cortical graph unweighted. C) Weighted plot of the graph with the same algorithm converging in layout representing functional clusters.

This suggests that activity dependent increases in threshold [30] could lead to a small decrease in global efficiency that is off-set by a large increase in local efficiencies, as has been suggested in the local microcircuit [33]. In this way the control of assembly dynamics in the cortex will have a spatial component in large part due to the spatial and weight characteristics of the cortical network described here. A simple way to illustrate the role of connection weight and distance is to plot the graph either using a binary or weighted, adjacency matrix. When weights are not taken in to account the algorithm converges to a layout where there is no biologically relevant node clustering (Fig. 4B). Remarkably when the weighted matrix is provided to the algorithm it converges to areal groupings that strongly reflect the functional lobes (Fig. 4C). This is

highly illustrative of the link between connection weight and distance that we reveal in the EDR.

3. Conclusion

The novel anatomical connectivity data, including the strengths of connections and spatial information suggest a revision of the cortical network given by previous studies. In particular, the newly uncovered anatomical connections lead to a very strongly connected inter-areal network (over 66% of the possible connections exist). In the light of such high density the small-world like properties of the graph (average directed path length = 1.34 and diameter = 2) are not significant. Neither can the network be described as scale-free in terms of its binary connectivity, given that the number of nodes is small and given their non-power-law degree distributions.

With a density of over 66%, binary features of the cortex, such as small world properties and hubs provide little functional insight, given that non sparse graphs can hardly be rewired in a manner not to express short path and high clustering. Instead, the range of weights of connection and distance must be examined. Doing so reveals a strong regularity of the cortex, where each area has strong connections with its neighbors, and where weights of connections fall off exponentially with distance to give place to weak, mid to long distance projections. These latter connections greatly contribute to linking areas standing on very distant levels of the cortical hierarchy and yet appear to make only a poor contribution to the global efficiency of the cortex. We see a dichotomy between the circuit of few very strong connections and the myriad of weak links that do not provide channels broad enough to transfer detailed, extensive fine grain information.

The out-standing reason why interareal connectivity does not correspond to a small world network is that the density of the graph is way too high. Lock 100 people into a room and shortly they will all know each other, leading to a social graph of 100% density, with path length of 1 hop and a single large cluster. Small world properties only become interesting when the number of nodes is large and the number of links is small.

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