Accepted Manuscript

Hundreds of brain maps in one atlas: Registering coordinate-independent primate neuro-anatomical data to a standard brain

Gleb Bezgin, Vasily A. Vakorin, A. John van Opstal, Anthony R. McIntosh, Rembrandt Bakker

PII: S1053-8119(12)00394-1
DOI: doi: [10.1016/j.neuroimage.2012.04.013](https://doi.org/10.1016/j.neuroimage.2012.04.013)
Reference: YNIMG 9400

To appear in: *NeuroImage*

Accepted date: 7 April 2012

Please cite this article as: Bezgin, Gleb, Vakorin, Vasily A., van Opstal, A. John, McIntosh, Anthony R., Bakker, Rembrandt, Hundreds of brain maps in one atlas: Registering coordinate-independent primate neuro-anatomical data to a standard brain, *NeuroImage* (2012), doi: [10.1016/j.neuroimage.2012.04.013](https://doi.org/10.1016/j.neuroimage.2012.04.013)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Hundreds of brain maps in one atlas: registering coordinate-independent primate neuro-anatomical data to a standard brain

Gleb Bezgin^{a,b,*}, Vasily A. Vakorin^a, A. John van Opstal^b, Anthony R. McIntosh^{a,e}, and Rembrandt Bakker^{b,c,d}

^a*Rotman Research Institute of Baycrest Centre, University of Toronto, Toronto, Ontario, Canada M6A 2E1*

^b*Donders Institute for Brain, Cognition and Behaviour, Centre for Neuroscience, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands*

^c*Institute of Neuroscience and Medicine (INM-6), Research Center Jülich, Germany*

^d*Department of Biology II, Ludwig-Maximilians-Universität München, Germany*

^e*Department of Psychology, University of Toronto, Canada*

*Corresponding author. Present address: Rotman Research Institute of Baycrest Centre, University of Toronto, 3560 Bathurst Street, Toronto, Ontario, Canada M6A 2E1.

E-mail address: gbezgin@rotman-baycrest.on.ca

Abstract

Non-invasive measuring methods such as EEG/MEG, fMRI and DTI are increasingly utilised to extract quantitative information on functional and anatomical connectivity in the human brain. These methods typically register their data in Euclidean space, so that one can refer to a particular activity pattern by specifying its spatial coordinates. Since each of these methods has limited resolution in either the time or spatial domain, incorporating additional data, such as those obtained from invasive animal studies, would be highly beneficial to link structure and function.

Here we describe an approach to spatially register all cortical brain regions from the macaque structural connectivity database *CoCoMac*, which contains the combined tracing study results from 459 publications (<http://cocomac.g-node.org>). Brain regions from 9 different brain maps were directly mapped to a standard macaque cortex using the tool

Caret (Van Essen and Dierker, 2007). The remaining regions in the *CoCoMac* database were semantically linked to these 9 maps using previously developed algebraic and machine-learning techniques (Stephan et al., 2000; Bezgin et al., 2008). We analysed neural connectivity using several graph-theoretical measures to capture global properties of the derived network, and found that Markov Centrality provides the most direct link between structure and function. With this registration approach, users can query the *CoCoMac* database by specifying spatial coordinates. Availability of deformation tools and homology evidence then allow one to directly attribute detailed anatomical animal data to human experimental results.

Keywords: Brain atlas; Structural connectivity; Primate brain; Tract tracing; Animal model; Network analysis

1. Introduction

An important challenge in modern neuroscience is to understand the relation between structure and function of the human brain. Currently, most structure-function information in humans is obtained from non-invasive neuroimaging studies, and in recent years many labs have generated huge amounts of spatiotemporal neuroanatomical data. Several coordinate-based mapping techniques have been developed to cope with these large data sets (Derrfuss and Mar, 2009; Fox et al., 2005; Marcus et al., 2007; Nielsen, 2009; Van Essen, 2009; Wilkowski et al., 2010). Using these tools, neuroscientists can compare measured activation in a particular brain region with other neuroimaging studies. Typically, spatial reference to active regions is made with respect to well-recognizable landmarks, like gyri or sulci (e.g., superior temporal gyrus, Sylvian fissure, etc.). For example, the postcentral gyrus in primates (including humans) is known to represent the somatosensory cortex (Whitsel et al., 1969), the occipital cortex corresponds to the primary visual areas, whereas the precentral gyrus mainly incorporates the primary motor cortex (von Bonin and Bailey, 1947). Yet, many cortical topographies cannot be readily assigned to a specific function. For example, the fusiform gyrus in humans is involved in a multiplicity of higher functions, such as face (Haxby et al., 2000) and word (Xue et al., 2010) recognition. As a consequence, topographic assignment is not always informative about the functional role of a particular brain area, which may be partially due to the poor and highly variable spatial relationship between cortical cytoarchitectonics and topological organisation (Amunts et al., 2007). The variability increases with more convoluted brains, and for macaques and humans there are ongoing efforts to document the uncertainties in the form of probabilistic maps. Another strong motivation to identify cytoarchitectonic regions is the vast body of literature on the structural connectivity between brain regions. The results of these studies have been collated in databases for the Macaque (*CoCoMac*; Stephan et al., 2001) and rat (*BAMS*; Bota and Swanson, 2010).

Although the detailed anatomy of the human brain is still poorly understood, there exist many homologies with the brains of non-human primates. Thus, a viable route to enhance the functional-anatomical framework in humans would be to map human brain regions to areas that have been well studied in invasive monkey experiments. In the context of anatomical connectivity between regions, invasive axonal tract-tracing studies (Köbbert et al., 2000) provide more precise information on axonal connections than tract-imaging techniques in the human brain, such as DTI (Le Bihan, 2003). Animal studies provide information on direction and extent of connecting axonal fibre bundles, and often include details such as laminar patterns of origin and termination (Felleman and Van Essen, 1991) or fractions of labelled neurons (Markov et al., 2011). These details are important to interpret functional activations observed in human neuroimaging (Krumnack et al., 2010).

1.1 Primate tracing and mapping studies

Macaque tract-tracing and architectonic mapping studies have been performed for more than a century. Cajal (1894) was the first to successfully apply the Golgi staining method to distinguish individual neurons and neuronal types. Brodmann investigated the macaque (1905) and human (1909) cortex and proposed a subdivision based on cytoarchitectonic characteristics. Even today, Brodmann's map, consisting of 52 distinct regions, is frequently used as an anatomical reference for functional neuroimaging studies. A strong increase of axonal tract-tracing studies emerged after discovering powerful functionalities with horseradish peroxidase and other substances that allowed efficient anterograde and retrograde neural tracing (see, e.g., Mesulam, 1982).

Whereas cytoarchitectonic studies frequently cover the entire cortex (e.g., von Bonin and Bailey, 1947; Brodmann, 1905, 1909; Paxinos et al., 2000, 2008; Vogt and Vogt, 1919), multiple tracer injections would obfuscate each other. Therefore, axonal tract-tracing studies typically focus on particular subsystems of the brain (e.g., frontostriatal connections: Ferry et al., 2000; visual cortex: Felleman and Van Essen, 1991; parietal

cortex: Pandya and Seltzer, 1982; auditory cortex: Hackett et al., 1998; cingulate cortex and thalamus: Vogt et al. 1987). Present day tract tracing studies deliver fine detail, introducing mesoscale (e.g., laminar patterns), and even microscale (e.g., neuronal extensions, synaptic weights, dendritic spines) features.

Combining these different studies, however, is a major research effort, as micro-, meso and macroscale features vary tremendously in nomenclature and how they are described in different studies. The *CoCoMac* database (methodology: Stephan et al., 2001; current online version: <http://cocomac.org>; Kötter, 2004; forthcoming online version: <http://cocomac.g-node.org>; see Materials and Methods) is such an effort, by accumulating data and related metadata on cortical and subcortical regions, their parts and the connections between them. *CoCoMac* is currently becoming a community project, allowing users to enter new data. This will be of increasing value, as modern tracing experiments are more advanced and provide finer detail on neuronal connectivity patterns than earlier studies (Gerbella et al., 2010; Markov et al., 2011).

The core output of *CoCoMac* has the form: “region A has an axonal projection of strength K to region B”. We have developed a technique for registering the anatomical regions in *CoCoMac* to spatial coordinates, so that we can transform the previous statement to “voxel (x,y,z) is part of a region A, which has an axonal projection of strength K to region B, which covers a set of voxels $\{(x,y,z)\}_B$ ”. Our main initial assets were: (1) the *CoCoMac* database, constantly populated by new tract tracing studies, and (2) the surface-based registration tool *Caret* provided by the Van Essen lab (Van Essen and Dierker, 2007). *Caret* contains a number of widely used brain maps that are registered to the cortical surface of a standard brain. The registration procedure involves the following. *CoCoMac* links regions to connectivity, whereas *Caret* links regions to coordinates. The remaining effort is to link regions in *CoCoMac* to regions in *Caret*. The brain maps that come with *Caret* already overlap with many of the regions described in *CoCoMac*. To further improve the coverage we extended *Caret* with the “Regional Map”, which is a rather coarse map of gross anatomical features that is defined for both human and non-human primates (Kötter and Wanke, 2005; Bezgin et al., 2008). For those regions in *CoCoMac* that do not

directly map to one of the nine atlases in *Caret*, we used *CoCoMac*'s mapping system. This uses statements from the literature that describe how newly delineated regions relate to regions in older atlases. By combining and chaining such statements, almost all cortical regions in *CoCoMac* could be linked to one of the *Caret* maps. In this paper, we describe the spatial registration procedure in detail and explore its use: we project connectivity-related statistics onto the cortical surface, and show an application in neuroimaging data analysis.

2. Materials and methods

2.1 The CoCoMac database

The *CoCoMac* database (<http://cocomac.org>, redeveloped at <http://cocomac.g-node.org>) is a neuroinformatics resource containing information about axonal tract tracing studies, currently covering 459 publications, culminating in 3279 tracer injections and 43746 labelled sites where injected tracer was found after an incubation time. As of December 2011, the total number of brain regions has reached 8396. This very high number of brain regions is a consequence of the *CoCoMac* design philosophy to consider every region in every publication as new, unless it is specifically equated to a region in a previous publication. *CoCoMac* deals with these duplicate brain regions using a (re)mapping technique called ORT (Objective Relational Transformation; Stephan et al., 2000), which uses chains of relational mapping statements (“region *A* in publication *X* is equal to region *B* in publication *Y*”) to map a brain region from its original map into a user-specified map. Note that the words ‘atlas’ and ‘parcellation’ are often used instead of ‘map’; here, we prefer to use the term ‘map’, particularly if the parcellation only covers a part of the brain (or a part of the cortex).

The amount of data in *CoCoMac* is such that for a majority of region pairs, multiple injections are available to establish their connection strengths and consistencies. To this end, a new, efficient implementation of ORT has been developed that also takes care of inconsistencies in the mapping procedure: conflicting mapping statements can arise when different studies do not agree on the definition of a brain region, or when too many (imprecise) statements are chained together. A separate development effort involves the creation of intuitive visualisation widgets, essential to quickly navigate through the database and to draw scientific insights from the large pool of data (Bezgin et al., 2009; Modha and Singh, 2010; <http://scalablebrainatlas.incf.org/cocomac>).

In each tracing study entered in *CoCoMac*, details about the locations of tracer injections and labelled sites are provided. Occasionally, the laminar structure of the latter is described – i.e., which cortical layers contain most of the label caused by a given injection. Given the large number of brain maps in the database, it is hard to make an estimate of the overall distribution of these quantities across the brain. This study shows for the first time how much redundancy there is in the database, and how it is distributed over the brain. It does so by projecting a multitude of brain maps onto a standard brain surface, resulting in spatial representations of nearly all cortical brain regions in *CoCoMac*.

2.2 *Caret* and the F99 standard brain

Functionality to register a multitude of brain maps to a standard Macaque coordinate space is provided by the *Caret* software of the Van Essen lab (Van Essen et al., 2001; Van Essen and Dierker, 2007). The standard Macaque brain used in *Caret* is called F99, it is based on an individual macaque monkey MRI, from which a cortical surface mesh has been extracted (Van Essen, 2004). Registration of brain maps is done by drawing its regions as two-dimensional shapes on the cortical surface. *Caret* comes with eight different brain maps that are registered to the F99 surface. Conversion of surface coordinates to voxel coordinates is possible by assigning a constant thickness to the cortical surface.

The eight Macaque brain maps in *Caret* already cover many regions defined in *CoCoMac*. We have registered one additional brain map to the F99 surface, the Regional Map (RM). This is a map with a special status in *CoCoMac*. It does not originate from one of the publications that make up *CoCoMac*, but it was specifically designed to contain regions that can easily be located in both macaque and human brains. Here we provide a brief description of each of these maps, together with their abbreviations as they appear in *CoCoMac*:

1. The Regional Map (RM, Kötter and Wanke, 2005), drawn on the F99 template by Gleb Bezgin under supervision of Prof. Dr. Rolf Kötter (Bezgin et al., 2008; Bezgin and Kötter, unpublished data). This map represents a cortical parcellation taking into account both functional (e.g., primary auditory cortex) and topographic (e.g., dorsolateral prefrontal cortex) regions which can be identified in the brain of any primate (including human) in the least ambiguous way possible.
2. LV00, a whole cortex parcellation made by Lewis and Van Essen in 2000 (Lewis and Van Essen, 2000a; Lewis and Van Essen, 2000b). Both of these studies investigated architectonic subdivisions and axonal connectivity in the macaque cortex, respectively, with an emphasis on parietal and occipital cortices responsible for visual, sensorimotor and multimodal processing.
3. UD86, a parcellation of visual areas from primary to MT, made by Ungerleider and Desimone in 1986 (Ungerleider and Desimone, 1986a; Ungerleider and Desimone, 1986b). Both studies investigate connections of early visual cortical areas to the superior temporal sulcus, as well as intracortical connections of the area V5, also known as MT.
4. FV91, a systematic analysis of preceding studies on macaque cortical anatomical connectivity by (Felleman and Van Essen, 1991). This was, to our knowledge, the first attempt to systematically collate a bulk of primate tract tracing studies in one coherent resource. A particular emphasis was put on the visual system, whose connections were also analysed in the context of their laminar patterns, and the visual hierarchy was proposed on the basis of these patterns. Altogether, this study can be regarded as a hybrid between a paper and a database.
5. B05, Early cytoarchitectural study on macaque cortex by (Brodmann, 1905). It investigates histological localisation in non-human primates, serving as a predecessor for Brodmann's study in 1909 on higher primates and human.

6. BB47, advanced study on the cortical cytoarchitecture on *Macaca Mulatta*, independent of Brodmann's study (von Bonin and Bailey, 1947). The whole macaque cortex study, investigating details of connectional patterns, including laminar structure.
7. FÖAP00, a study on connections from the prefrontal cortex to the striatum in the macaque (Ferry et al., 2000). This study does not specify its own parcellation of the prefrontal cortex, but adopts one from the study by (Carmichael and Price, 1994). The striatum is not included in our spatial map, as we deal only with cortical structures in our study.
8. PHT00, the first stereotaxic atlas of the macaque cortex; it is the most fine-grained parcellation in this list, having 175 regions that cover the entire cortex (Paxinos et al., 2000). The original paper atlas consists of 151 pages, taking every tenth section of the dissected brain, providing specific "stereotaxic" spatial coordinates which are commonly utilised by neurosurgeons to enable higher precision in scalpel and electrode penetrations.
9. PG91, a study on cytoarchitecture of the macaque prefrontal cortex (Preuss and Goldman-Rakic 1991). It compares the frontal architectonics of *Macaca* to that of *Galago*, using myelin- and Nissl-stained material.

2.3 Area ranking systems

CoCoMac contains 459 brain maps with nearly 8400 brain regions. The 9 brain maps registered to the F99 surface have a direct relation to 519 *CoCoMac* regions. However, many regions in *CoCoMac* are redundant: they are delineated in a paper, with the notion that they are actually the same as an equivalent region in an earlier paper. Using the redeveloped ORT routines, we found that a large majority of the *CoCoMac* cortical regions can be equated to a region in one of the 9 registered maps. Once a *CoCoMac* region is linked to the F99 surface, all its injections, labelled sites and derived measures can be assigned to a set of vertices of the

F99 surface. This opens a way to display cortical distributions of all kinds of information that was previously only accessible by brain region name. Not only simple statistics, such as the number of injections in a brain region, but also the results of advanced graph-theoretical analyses can be plotted as a function of location in the brain. We have employed multiple measures for global network analysis, including PageRank, Markov Centrality, and Betweenness Centrality (Freeman, 1978). The latter measure is the fraction of all shortest paths in the network that pass through a specified node (or edge). In this manuscript, we discuss node betweenness, not edge betweenness.

Markov Centrality (MC) appeared to be the most relevant measure needed for our purposes (see Results for more detail). MC is one of the node importance measures which is not yet commonly used for brain network analyses. In this approach, the network is viewed as a stochastic process where parameters are conditioned only on the present state of the system. This is known as a Markov process (White and Smyth, 2003). The MC measure can be interpreted as the amount of time that some imaginary token doing random walks on the network spends on a particular node. More formally: first, the mean first passage time between nodes s and v is obtained:

$$m_{sv} = \sum_{n=1}^{\infty} n f_{sv}^{(n)} \quad (1)$$

where n is the number of steps taken, m_{sv} represents expected number of steps until first arrival at the node v starting at the node s , and $f_{sv}^{(n)}$ stands for the probability that a given chain first comes to the state v in exactly n steps. This mean first passage time can be represented as a matrix:

$$M = (I - Z + EZ_{dg})D \quad (2)$$

where I is the identity matrix, E is the matrix containing all ones, D is a diagonal matrix where each element in the diagonal is reciprocal of the stationary distribution $\pi(u)$ of a node u , and Z is given by

$$Z_{dg} = (I - A - e\pi^T)^{-1} \quad (3)$$

where A is the network adjacency matrix, e is a column vector of all ones, and π is a column vector of the stationary probabilities. The importance of a node v is the inverse of the average of the corresponding column in M :

$$I(v) = \frac{n}{\sum_{u \in N} m_{uv}} \quad (4)$$

where N is the set of all n nodes in the graph.

One of the ways to define stationary distribution $\pi(u)$ is using PageRank, another measure of node importance, originally developed by the Google founders (Brin and Page, 1998). In the context of the World Wide Web applications, this algorithm measures the likelihood that a person randomly clicking on links will arrive at a particular web page. This fraction is measured by first transforming the graph into a first-order Markov chain where the transition probability of going from node u to all other n nodes in the graph is derived iteratively:

$$\pi(u) = \frac{1-d}{n} + d \sum_{v \in M(u)} \frac{\pi(v)}{L(v)} \quad (5)$$

where d is a heuristic value called the damping factor and, following a number of evaluations, is usually set to 0.85; $M(p_i)$ is the set of nodes that link to u , $L(v)$ is the number of all out-edges on node v .

If v has no out-edges in the original graph then 0 is used instead of $1/L(v)$. Once the Markov chain is created for each pair of nodes, the stationary probability of being at each node (state) is computed using an iterative update. This method is guaranteed to converge if the Markov chain is ergodic, i.e., aperiodic and positive recurrent.

The rationale for using PageRank in brain connectivity analysis and in conjunction with Markov Centrality in particular is the assumption that neuronal activity is to a large extent mediated by the underlying anatomy, and the probability of arrival at a particular anatomical region following a random walk on all regions (which is the meaning of PageRank in this context) is an important functional property of a given structural network.

The main rationale in applying Markov Centrality to analyse the brain's anatomical network is that this measure directly reflects the stochastic nature of brain's dynamics, exhibiting such phenomena as stochastic resonance (Benzi et al., 1981), emerging from random walks on the given anatomical network; complex dynamics are typically mediated by a structural substrate which is accordingly complex. Representing the brain network as a stochastic system helps identify brain regions and connections which are functionally important.

For calculating the graph-theoretical measures described above, we used the tool ConJUNGtion (Cortical Network JUNG-based visualisaTION) software under development, adapted from the JUNG toolkit (Madadhain et al., 2005), and the Brain Connectivity Toolbox (Rubinov and Sporns, 2010).

3. Results

3.1 Primary results

We linked all 519 regions of the nine brain maps registered to the F99 standard brain to the matching brain areas in *CoCoMac*. In addition, we also included all areas in *CoCoMac* that have equivalence statements to any of these 519 regions. This covers 67.5% of all regions (90.9% of all iso- and 85.6% of all allocortical regions) in *CoCoMac*. Remaining cortical areas had no mapping statements associated with other areas; therefore we can conclude that the given nine maps provided a linkage to all information on cortex in the database. Next we visualised primary statistics of the data in *CoCoMac* as distributed across the cortical sheet. The selected statistics are: (1) the number of injections; (2) the number of labelled sites reported in anterograde experiments (in these experiments, labelled sites are axon terminals); (3) the number of labelled sites reported in retrograde experiments (in these experiments, labelled sites are cell bodies); and finally (2) and (3) repeated, but now counting only those labelled sites for which laminar patterns have been reported (Fig. 2).

Fig. 2 shows the general cortical coverage that *CoCoMac* provides. Note that a large number of injections appears in visual areas, whereas less, but sufficient coverage is found e.g. at insular and somatosensory cortex. Qualitative visual inspection suggests that some of the distributions shown in Fig. 2 may be strongly correlated, for example the similarity (apart from a scaling factor) between A (injections) and F (labelled sites, anterograde) is striking. We investigate this quantitatively in Fig. 3. Indeed the linear fit of labelled sites, anterograde vs. injections has a much higher goodness-of-fit ($R^2=0.77$) than that of labelled sites, retrograde vs. injections ($R^2=0.36$), and even higher than that of labelled sites, anterograde vs. injections, anterograde

($R^2=0.59$, data not shown). Figure 3 also shows that of all labelled sites, about 25% has the laminar pattern specified, both in the retrograde (Fig. 3C) and anterograde (Fig. 3D) case.

In addition to the nine brain maps (Fig. 1), *Caret* contains a tenth map which specifies the cortical lobe that each of the F99 surface nodes belongs to: either the frontal, temporal, parietal, occipital or limbic lobe. Figure 4 shows the averaged statistics for each of these lobes. It shows that occipital and temporal lobes host relatively more injection sites and reveal more labelled sites than the other three lobes, whereas retrogradely labelled sites appear predominantly in the temporal and frontal lobes (Fig. 4). See Discussion for more detail on this issue.

3.2 Statistical evaluations of overall connectivity data

We next derived *CoCoMac*'s connectivity information for the different F99 overlays. Characteristic for maps covering the whole cortex (RM, LV00, FV91, B05, BB47 and PHT00, see Fig. 1), the highest Markov Centrality was typically found for the prefrontal cortex, though on average the most significant hubs were revealed in frontal, temporal and parietal lobes (Fig. 5). Importantly, the notion of "hub" usually refers to an area with a high node degree (Kaiser et al., 2007); in this study, we refer to regions with high Markov Centrality as to "hubs", given a high correlation between node degree and Markov Centrality across our data ($R^2 = 0.93$).

Hub dominance in frontal, temporal and parietal lobes is consistent with previous findings in both macaque and human (Kaiser et al., 2007; Buckner et al., 2009; Modha and Singh, 2010; van den Heuvel and Sporns, 2011).

Particularly low Markov Centrality appears to be in the occipital cortex, especially V1, likely because V1 mainly acts as a transfer hub for information coming from the thalamic part of the visual system, which is not a part of the network graph. Although the variability of Markov Centrality ranks (or any of the other measures) for the majority of areas within each cortical lobe was rather high due to the fact that each lobe spans a large number of regions, the general tendency of hub dominance in frontal (F), parietal (P) and temporal (T) lobes resulted to be consistent (Fig. 6).

Only the FV91 map showed, on average, a relatively lower MC value for the temporal lobe, which is due to an incomplete coverage of this region by that study (note the high variability). As evidenced in Fig. 5c, one of the highest rank values appeared on the temporal pole, which corroborates the general trend of hub dominance observed in the other maps. Although the PageRank values (not shown) were highly correlated with Markov Centrality ratings, the propensity of PageRank hub dominance in the F, P and T lobes is much lower than Markov Centrality. For example, the average PageRank for the occipital lobe in the LV00 map is higher than the one for the frontal lobe in the same map (this is also the case for the node degree measure). Betweenness Centrality appears to be rather low in the frontal lobe, and higher in the parietal and limbic lobes, although these observations are inconsistent between maps. Of these three network measures, the Markov Centrality distribution is most in line with previous findings (Buckner et al., 2009; Modha and Singh, 2010; van den Heuvel and Sporns, 2011). To provide some more intuitive graph-theoretical measures, we also checked RM distributions across lobes for Network Participation Indices (NPIs, Kötter and Stephan, 2003; see Table 1).

4. Discussion

There have been several earlier attempts to summarise and visualise the *CoCoMac* database to make it more accessible to the general neuroscientific community. For example, the *CP3D* project (Bezgin et al., 2009) and the follow-up project *Scalable Brain Atlas* (<http://scalablebrainatlas.incf.org/cocomac>) utilised the stereotaxic atlas of the Rhesus monkey brain from Paxinos et al. (2000). It was one of the first attempts to register *CoCoMac* data with the real brain space. The main differences of *CP3D* compared to the F99 representations described here are that (i) the Paxinos et al. (2000) atlas contains not only cortical structures, but also subcortical nuclei, and (ii) the Paxinos data are volumetric and not surface-based. The approach presented here is the first study of this kind in registering many cortical maps onto one standardised surface to enable visualisation of different properties of the anatomical database in a systematic way. The advantage of this technique is that surfaces are more flexible than volumes in that they can be easily flattened to make the deep sulci visible (Van Essen and Dierker, 2007), and registration of cortical data on surfaces is technically easier and more intuitive from the user perspective.

In a recent study Modha and Singh (2010) constructed a large hierarchical network from all available regions in *CoCoMac*, and visualised and analysed the emerging network using various ranking systems, including PageRank and Betweenness Centrality. Although the mapping procedures used gross simplifying assumptions with regard to the identity of similarly named brain regions, it has produced a visually very attractive way to depict the entire *CoCoMac* network in one figure. Nevertheless, due to its complexity, the resulting graph still remains hard to decipher (see Fig. 1 in Modha and Singh, 2010). For this reason, we here attempted to link rank data to a real brain space, as such an approach captures the essential properties of the network (i.e., graph theoretical measures such as Markov Centrality), rather than the network itself. One of the reasons why MC measures are more consistent across lobes than other measures lies in the nature of MC; it represents a

physically/biologically inspired model of propagation through a network, so that nodes with high degree will have neighbours with high MC rating as well, since the probability of a large propagation towards immediate node neighbours is high.

Another important contribution of this study to a database of tracing experiments is a straightforward statistical representation of original data. Several peculiarities encountered in this study (such as higher correlation between injections and anterogradely labelled sites, than correlation between anterograde tracer injections and all anterogradely labelled sites) were previously observed in tracing experiments on other species. For example, Barbaresi et al. (1994) performed antero- and retrograde tracing experiment on the cat, and found out that anterograde labelling is mainly revealed in regions homotopic to those injected (periaqueductal gray matter, in case of that study). In contrast, retrograde labelling primarily incorporated commissural fibers, and rarely ended at homotopic locations. This observation in cat might explain the observed aforementioned difference in correlation values of the monkey data. Another potential reason for this might be a notion that anterograde transport has better terminal resolution than retrograde transport (Gibson et al., 1984), and anterogradely labelled regions may therefore be localised more reliably. Many injections are bidirectional, hence the higher correlation found with the full set of injections, rather than their retro- and anterograde subsets, on the one hand, and retrograde labelled sites on the other hand (Fig. 3).

The main rationale for this study, however, is not merely a visualisation of certain brain properties, but also a linkage between a pool of spatiotemporal neuroimaging data on the one hand and a large set of coordinate-independent axonal connectivity data from primate experiments on the other hand. An example shows how this is achieved: the nearest proximity of a particular location specified in a neuroimaging experiment result is identified and linked to a homologous brain region specified in *CoCoMac*. The interspecies mapping functionality is provided by *Caret* (see Fig. 7).

For illustrative purposes, we here associated MNI (Montreal Neurological Institute template) coordinates from the study of Buckner et al. (2009) with the MNI representation of the Regional Map (Table 1).

Further, we can visualise a connectivity graph resulting from this study; a simple visual inspection of Fig. 8 points out to a qualitative correspondence between the whole cortical network (Fig. 8a) and the sub-network revealed by Buckner et al. (Fig. 8b). Moreover, three functional hubs represented in Table 2 are also among major hubs in the RM structural matrix shown in Fig. 8. Further quantitative analyses will provide more detail on this issue.

Using this functionality, we can compare structural with functional connectivity matrices (e.g. with macaque resting state fMRI data; Hutchison et al., 2011), estimate the directional influence of one region over another (Deco et al, 2011), constrain effective connectivity models with ground truth anatomical connectivity information provided by either diffusion tensor imaging (DTI) data (Stephan et. al, 2009), or axonal tract tracing studies, such as ones in *CoCoMac*.

5. Conclusions and perspectives

In this study, we developed a concept of mapping the *CoCoMac* connectivity database, representing 459 tract-tracing studies from macaque monkey cortex, to a standardised spatial template (here: F99). To summarise, we achieved the following goals:

- We linked the entire subset of the *CoCoMac* database concerning isocortex and allocortex to the F99 template, and performed an intuitive visual analysis of the dataset.
- This mapping functionality enables the retrieval of structural connectivity such as laminar patterns (where available) for specified cortical coordinates.
- We analysed connectivity data on cortex using several approaches for network analysis, spanning from simple participation indices to measures commonly used for ranking internet pages. Among these, Markov Centrality resulted to be the most robust measure.
- The utility of spatial topological properties in the connectivity analysis enabled, in contrast to non-spatial graph-theoretical analysis (cf. *CP3D* connectivity analysis features, Bezgin et al., 2009)
- We have provided tools for the users to re-generate data from this study (with up-to-date *CoCoMac* entries) – see Appendix / Information sharing statement.

One of the future perspectives would be to extend the use of this method also to subcortical structures. A current limitation, however, is the lack of coordinate data on the fine subdivisions of subcortical nuclei. Indeed, coordinates for the representations of thalamus, hypothalamus, amygdala, basal ganglia and other subcortical structures are available as various templates used for neuroimaging data analysis, but there are no data of the laminar and directional connectivity details on those structures from invasive animal studies.

A second short-term perspective is to implement a query system for *CoCoMac* based on the specification of coordinates, and to embed it into the *CoCoMac* interface. That would allow specification of average coordinates and spatial extent on each of the templates for each database entry on the cerebral cortex (both isocortex and allocortex, and prospectively subcortical nuclei). This will be applicable to human templates as well, given known homologies between human and non-human primates, and the availability of deformation tools, such as *Caret* (Table 1 and Fig. 7 illustrate the first steps towards this possibility).

The linkage between invasive monkey tract-tracing results and human DTI (Diffusion Tensor Imaging) data will be an important asset for evaluating the plausibility and identifying the directionality of DTI tracts on the one hand, and informing tract-tracing data with tract trajectory and capacity information on the other hand. Specifically, this approach is to be utilised by a modeling initiative called *The Virtual Brain* (<http://www.thevirtualbrain.org/>).

Acknowledgements

GB and RM acknowledge McDonnell Baycrest grant 737100401. RB is supported by the German INCF Node (BMBF grant 01GQ0801), the Helmholtz Alliance on Systems Biology, JUGENE Grant JINB33, the Next-Generation Supercomputer Project of MEXT, Japan, EU Grant 269921 (BrainScaleS). We thank David Van Essen, Donna Dierker, John Harwell, Stan Gielen, Alfi Afadiyanti, Jimmy Shen, Kelly Shen. Thanks to Rolf Kötter and his family.

References

1. Amunts, K., Schleicher, A., Zilles, K., 2007. Cytoarchitecture of the cerebral cortex – more than localization. *NeuroImage* 37, 1061-1065.
2. Barbaresi, P., Minelli, A., Gazzanelli, G., Malatesta, M., 1994. Commissural connections of the cat periaqueductal gray matter studied with anterograde and retrograde tract-tracing techniques. *Neuroscience*. 60, 781-99.
3. Benzi, R., Sutera, A., Vulpiani, A., 1981. The Mechanism of Stochastic Resonance. *J. Phys. A* 14, 453-457.
4. Bezgin, G., Wanke, E., Krumnack, A., Kötter, R., 2008. Deducing logical relationships between spatially registered cortical parcellations under conditions of uncertainty. *Neural Networks* 21, 1132-1145.
5. Bezgin, G., Reid, A.T., Schubert, D., Kötter, R., 2009. Matching spatial with ontological brain regions using Java tools for visualization, database access, and integrated data analysis. *Neuroinformatics* 7, 7-22.
6. Bonin, G.V., von, Bailey, P., 1947. The neocortex of *Macaca mulatta*. The University of Illinois Press, Urbana, Illinois.
7. Bota, M., Swanson, L.W., 2010. Collating and Curating Neuroanatomical Nomenclatures: Principles and Use of the Brain Architecture Knowledge Management System (BAMS). *Front. Neuroinform.* 4:3.
8. Brin, S., Page, L., 1998. The Anatomy of a Large-Scale Hypertextual Web Search Engine. Proceedings of the 7th international conference on World Wide Web (WWW). Brisbane, Australia. pp. 107–117.
9. Brodmann, K., 1905. Beiträge zur histologischen Localisation der Grosshirnrinde. Dritte Mitteilung. Die Rindenfelder der niederen Affen. *Journal für Psychologie und Neurologie* 4, 177-226.
10. Brodmann, K., 1909. Vergleichende Lokalisationslehre der Grosshirnrinde. *The Journal of Nervous and Mental Disease* 37, 783-784.
11. Buckner, R.L., Sepulcre, J., Talukdar, T., Krienen, F.M., Liu, H., Hedden, T., Andrews-Hanna, J.R., Sperling, R.A., Johnson, K.A., 2009. Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. *J. Neurosci.* 29, 1860-73.
12. Carmichael, S.T., Price, J.L., 1994. Architectonic subdivision of the orbital and medial prefrontal cortex in the macaque monkey. *J. Comp. Neurol.* 346, 366-402.

13. Deco, G., Jirsa, V.K., McIntosh, A.R., 2011. Emerging concepts for the dynamical organization of resting-state activity in the brain. *Nat Rev Neurosci.* 12, 43-56.
14. Derrfuss, J., Mar, R.A., 2009. Lost in localization: the need for a universal coordinate database. *NeuroImage* 48, 1-7.
15. Felleman, D.J., Van Essen, D.C., 1991. Distributed hierarchical processing in the primate cerebral cortex. *Cerebral Cortex* 1, 1-47.
16. Ferry, A.T., Öngür, D., An, X., Price, J.L., 2000. Prefrontal cortical projections to the striatum in macaque monkeys: evidence for an organization related to prefrontal networks. *J. Comp. Neurol.* 425, 447-470.
17. Fox, P.T., Laird, A.R., Fox, S.P., Fox, P.M., Uecker, A.M., Crank, M., Koenig, S.F., Lancaster, J.L., 2005. BrainMap taxonomy of experimental design: description and evaluation. *Human Brain Mapping* 25, 185-198.
18. Freeman, L.C., 1978. Centrality in social networks: conceptual clarification. *Soc. Netw.* 1, 215-239.
19. Gerbella, M., Belmalih, A., Borra, E., Rozzi, S., Luppino, G., 2010. Cortical connections of the macaque caudal ventrolateral prefrontal areas 45A and 45B. *Cerebral Cortex* 20, 141-68.
20. Gibson, AR, Hansma, DI, Houk, JC, Robinson, FR., 1984. A sensitive low artifact TMB procedure for the demonstration of WGA-HRP in the CNS. *Brain Res.* 298, 235-41.
21. Hackett, T.A., Stepniewska, I., Kaas, J.H., 1998. Subdivisions of auditory cortex and ipsilateral cortical connections of the parabelt auditory cortex in macaque monkeys. *J. Comp. Neurol.* 394, 475-95.
22. Haxby, J.V., Hoffman, E.A., Gobbini, M.I., 2000. The distributed human neural system for face perception. *Trends Cogn. Sci.* 4, 223-233.
23. Heuvel, M.P., van den, Sporns, O., 2011. Rich-club organization of the human connectome. *J. Neurosci.* 31, 15775-86.
24. Hutchison, R.M., Leung, L.S., Mirsattari, S.M., Gati, J.S., Menon, R.S., Everling, S., 2011. Resting-state networks in the macaque at 7 T. *Neuroimage* 56, 1546-55.
25. Kaiser, M., Martin, R., Andras, P., Young, M.P., 2007. Simulation of robustness against lesions of cortical networks. *Eur. J. Neurosci.* 25, 3185-92.
26. Kleinberg, J., 1999. Authoritative sources in a hyperlinked environment. *Journal of the ACM* 46, 604-632.

27. Köbbert, C., Apps, R., Bechmann, I., Lanciego, J.L., Mey, J., Thanos, S., 2000. Current concepts in neuroanatomical tracing. *Progress in Neurobiology* 62, 327-351.
28. Kötter, R., 2004. Online retrieval, processing, and visualization of primate connectivity data from the CoCoMac database. *Neuroinformatics* 2, 127-144.
29. Kötter, R., Stephan, K.E., 2003. Network participation indices: characterizing component roles for information processing in neural networks. *Neural Networks* 16, 1261-75.
30. Kötter, R., Wanke, E., 2005. Mapping brains without coordinates. *Phil. Trans. R. Soc. B* 360, 751-766.
31. Krumnack, A., Reid, A.T., Wanke, E., Bezgin, G., Kötter, R., 2010. Criteria for optimizing cortical hierarchies with continuous ranges. *Front Neuroinform.* 4:7.
32. Le, Bihan, D., 2003. Looking into the functional architecture of the brain with diffusion MRI. *Nature Reviews Neuroscience* 4, 469-480.
33. Lewis, J.W., Van Essen, D.C., 2000a. Corticocortical connections of visual, sensorimotor, and multi-modal processing areas in the parietal lobe of the macaque monkey. *J. Comp. Neurol.* 428, 112-137.
34. Lewis, J.W., Van Essen, D.C., 2000b. Mapping of architectonic subdivisions in the macaque monkey, with emphasis on parieto-occipital cortex. *J. Comp. Neurol.* 428, 79-111.
35. Madadhain, J., Fisher, D., Smyth, P., White, S., Boey, Y.B., 2005. Analysis and visualization of network data using JUNG. *Journal of Statistical Software* 10, p. 1-35.
36. Marcus, D.S., Olsen, T.R., Ramaratnam, M., Buckner, R.L., 2007. The Extensible Neuroimaging Archive Toolkit. An informatics platform for managing, exploring, and sharing neuroimaging data. *Neuroinformatics* 5: 11-33.
37. Markov, N.T., Misery, P., Falchier, A., Lamy, C., Vezoli, J., Quilodran, R., Gariel, M.A., Giroud, P., Ercsey-Ravasz, M., Pilaz, L.J., Huissoud, C., Barone, P., Dehay, C., Toroczkai, Z., Van Essen, D.C., Kennedy, H., Knoblauch, K., 2011. Weight consistency specifies regularities of macaque cortical networks. *Cerebral Cortex.* 21, 1254-72.
38. Mesulam, M. Marsel, 1982. *Tracing Neural Connections with Horseradish Peroxidase*. Chichester: John Wiley.
39. Modha, D.S., Singh, R., 2010. Network architecture of the long-distance pathways in the macaque brain. *PNAS* 107, 13485-13490.
40. Nielsen, F.Å., 2009. Lost in localization: a solution with neuroinformatics 2.0? *NeuroImage* 48, 14-17.

41. Pandya, D.N., Seltzer, B., 1982. Intrinsic connections and architectonics of posterior parietal cortex in the rhesus monkey. *J. Comp. Neurol.* 204, 196-210.
42. Paxinos, G., Huang, X-F., Toga, A.W., 2000. *The Rhesus Monkey Brain In Stereotactic Coordinates*. Academic Press, San Diego.
43. Paxinos, G., Huang, X-F., Petrides, M., Toga, A.W., 2008. *The Rhesus Monkey Brain In Stereotactic Coordinates*. Academic Press, San Diego.
44. Preuss, T.M., Goldman-Rakic, P.S., 1991. Myelo- and cytoarchitecture of the granular frontal cortex and surrounding regions in the strepsirrhine primate Galago and the anthropoid primate Macaca. *J. Comp. Neurol.* 310, 429-474.
45. Rubinov, M., Sporns, O., 2010. Complex network measures of brain connectivity: uses and interpretations. *NeuroImage* 52, 1059-1069.
46. Stephan, K.E., Kamper, L., Bozkurt, A., Burns, G.A., Young, M.P., Kötter, R., 2001. Advanced database methodology for the Collation of Connectivity data on the Macaque brain (CoCoMac). *Phil. Trans. R. Soc. Lond. B* 356, 1159-1186.
47. Stephan, K.E., Tittgemeyer, M., Knösche, T.R., Moran, R.J., Friston, K.J., 2009. Tractography-based priors for dynamic causal models. *Neuroimage* 47, 1628-38.
48. Stephan, K.E., Zilles, K., Kötter, R., 2000. Coordinate-independent mapping of structural and functional data by objective relational transformation (ORT) *Phil. Trans. R. Soc. Lond. B* 355, 37-54.
49. Ungerleider, L.G., Desimone, R., 1986. Cortical connections of visual area MT in the macaque. *J. Comp. Neurol.* 248, 190-222.
50. Ungerleider, L.G., Desimone, R., 1986. Projections to the superior temporal sulcus from the central and peripheral field representations of V1 and V2. *J. Comp. Neurol.* 248, 147-163.
51. Van Essen, D.C., Dierker, D.L., 2007. Surface-based and probabilistic atlases of primate cerebral cortex. *Neuron* 56, 209–225.
52. Van Essen, D.C., 2009. Lost in localization – but found with foci?! *NeuroImage* 48, 14-17.
53. Van Essen, D.C., Lewis, J.W., Drury, H.A., Hadjikhani, N., Tootell, R.B., Bakircioglu, M., and, Miller, M.I., 2001. Mapping visual cortex in monkeys and humans using surface-based atlases. *Vision Research* 41, 1359-1378.

54. Van Essen, D.C., 2004. Surface-based approaches to spatial localization and registration in primate cerebral cortex. *NeuroImage (Supplement: Mathematics in Brain Imaging)* 23, s97-s107.
55. Vogt, B.A., Pandya, D.N., Rosene, D.L., 1987. Cingulate cortex of the rhesus monkey: I. Cytoarchitecture and thalamic afferents. *J. Comp. Neurol.* 262, 256-70.
56. Vogt, C., Vogt, O., 1919. Ergebnisse unserer Hirnforschung. 1.-4. Mitteilung. *J Psych. Neurol.* 25, 279–461.
57. Walker, A.E., 1940. A cytoarchitectural study of the prefrontal area of the macaque monkey. *J. Comp. Neurol.* 73, 59–86.
58. White, S., Smyth, P., 2003. Algorithms for estimating relative importance in networks. *International Conference on Knowledge Discovery and Data Mining, Proceedings of the ninth ACM SIGKDD international conference on Knowledge discovery and data mining* 2, 266 – 275.
59. Whitsel, B.L., Petrucelli, L.M., Werner, G., 1969. Symmetry and connectivity in the map of the body surface in somatosensory area II of primates. *J. Neurophysiol.* 32, 170-183.
60. Wilkowski, B., Szewczyk, M., Rasmussen, P.M., Hansen, L.K., Nielsen, F.Å., 2009. Coordinate-based Meta-analytic search for the SPM Neuroimaging Pipeline - The BredeQuery Plugin for SPM5. In *Proceedings of HEALTHINF.*, 11-17.
61. Xue, G., Mei, L., Chen, C., Lu, Z.L., Poldrack, R.A., Dong, Q., 2010. Facilitating memory for novel characters by reducing neural repetition suppression in the left fusiform cortex. *PLoS One.* 5, e13204.

Figure captions

Figure 1. The brain maps from Caret which have representations in CoCoMac, used for linking the entire database to spatial coordinates of the F99 macaque template. Colours are randomly assigned to regions by Caret. Columns display the maps in lateral, medial and ventral views, respectively.

Figure 2. Distributions of cortical data in CoCoMac. A) overall injections; B) injections of retrograde tracers; C) injections of anterograde tracers; D) labelled sites; E) sites labelled by retrograde tracers; F) sites labelled by anterograde tracers. Data are displayed on an inflated surface representing the right hemisphere of the F99 macaque template. Top: right lateral view. Bottom: right medial view, upside down. Colour code represents number of occurrences, values are thresholded for visualisation convenience.

Figure 3. Correlations between cortical distributions of CoCoMac data. Axes represent the number of occurrences. The highest correlation displayed here is between injections and anterogradely labelled sites (panel B). As expected, a high correlation was also observed between overall labelled sites and those labelled sites which contain laminae data ($R^2 = 0.8$, data not shown).

Figure 4. Overall distributions of injections and labelled sites across cortical lobes. Abbreviations of lobes: F=frontal, T=temporal, P=parietal, O=occipital, L=limbic. Y axis represent the number of occurrences. Majority of retrogradely labelled sites are found in the frontal and temporal lobes, whereas other quantities appear predominantly in the occipital and temporal lobes. A) injections; B) injections of retrograde tracers; C) injections of anterograde tracers; D) labelled sites; E) sites labelled retrogradely; F) sites labelled anterogradely.

Figure 5. Distributions of Markov Centrality (MC) ranks for six F99 maps that cover the entire cortex. A) RM; B) LV00; C) FV91; D) B05; E) BB47; F) PHT00 (cf. Fig. 1). Finer maps (B, C and F) have more gaps in the connectivity

measures than the coarser maps (A, D and E), although main hubs appear in similar locations in all of them (frontal, parietal and temporal lobes – see section 3.2 for more details). Markov Centrality values form a probability density function across areas within each map, so that the total sum of these values (as shown on colour bars) is 1.

Figure 6. Distributions of Markov Centrality ranks for six F99 maps covering the whole cortex, across cortical lobes as obtained from Caret. Standard error bars are defined as in Fig. 4. Note the scale difference.

Figure 7. Regional Map representations on macaque F99 (A, B, C) and human MNI (D, E, F) templates. Views, from left to right: lateral, medial and ventral. Sizes on panels C and F are specified on the basis of F99 and MNI templates data. Labels are described in appendix; note that topographic assignments originate from the macaque cortex, but can appear not confined to the same topography in the human cortex (e.g., human homologue of macaque TCs occupies most of the lateral part of temporal cortex in human).

Figure 8. RM network and its sub-network related to the study by Buckner et al. A) The whole cortex network overlaid on top of the MNI template. Vertices are sized according to their degree. B) The sub-network described in Buckner et al. study. Vertically stretched vertices have higher in-degree, whereas horizontally stretched vertices have higher out-degree. Note that the medial side vertices are displayed on the lateral side. Visualisation enabled by the ConJUNGtion software (see methods).

Table 1. NPI values, as defined by Kötter and Stephan (2003) for RM across cortical lobes. Density measure is identical to node degree; symmetry signifies a fraction of reciprocal connections of a node; transmission is a fraction of all outgoing connections.

NPI	value	F	T	P	O	L
Density	mean	0.801	0.873	0.854	0.584	0.737
	std	0.044	0.019	0.037	0.065	0.087
Symmetry	mean	0.892	0.927	0.919	0.911	0.761
	std	0.041	0.011	0.018	0.021	0.096
Transmission	mean	0.49	0.494	0.507	0.491	0.462
	std	0.018	0.004	0.005	0.008	0.051

Table 2. An example of CoCoMac data utility in neuroimaging analysis. Three RM regions with the highest Markov Centrality in different lobes are chosen; they appear as major hubs in the Buckner et al. (2009) study. The first two columns represent data produced by our procedure, whereas the rest of the table contains information from Buckner et al. (2009). Combining neuroimaging experimental results with structural connectivity in CoCoMac provides additional analysis possibilities.

RM hub	RM MC rank	Lobe	x	y	z	Topography	Intensity
PFCvl	0.0327	frontal	-42	54	-4	Left orbitofrontal	1.07
TCc	0.0314	temporal	-62	-14	-24	Left middle/inferior temporal	0.87
PCi	0.031	parietal	-42	-62	50	Left inferior/superior parietal lobule	1.39

Fig. 1

Fig. 2

Fig. 3

Fig. 4

Fig. 5

Fig. 6

Fig. 7

Fig. 8