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Online retrieval, processing, and visualization of primate connectivity data from the CoCoMac database

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Abstract

Connectivity is the key to understanding distributed and cooperative brain functions. Detailed and comprehensive data on large-scale connectivity between primate brain areas have been collated systematically from published reports of experimental tracing studies. Although the majority of the data have been made easily available for online retrieval, the multiplicity of brain maps and the precise requirements of anatomical naming limit the intuitive access to the data. The quality of data retrieval can be improved by observing a small set of conventions in data representation. Standardized interfaces open up further opportunities for automated search and retrieval, for flexible visualization of data, and for interoperability with other databases. This article provides a discussion and examples in text and image of the capabilities of the online interface to the CoCoMac database of primate connectivity. These serve to point out sources of confusion and failure, and demonstrate the automated interfacing with other neuroinformatics resources that facilitate selection and processing of connectivity data, for example, for computational modelling and interpretation of functional imaging studies.

Introduction

Information on anatomical connections between brain regions has become a highly valued resource in systems neuroscience since this information is useful to put constraints on possible interpretations of functional data as obtained from multi-site recording or neuroimaging techniques. Models based on detailed anatomical data, for example, make better predictions of topographical activation patterns than those based on general assumptions of regular neighbourhood or random connectivity (Kötter & Sommer, 2000); also anatomical models provide a basis for structural equation modelling and its extensions to infer the causal effects underlying correlated functional signals (McIntosh & Gonzales-Lima, 1994; Büchel & Friston, 1997; Friston et al., 2003). In particular, as the conceptual emphasis is shifting from spatially segregated to interactive and integrative processing (Friston, 1995; Kötter & Stephan, 2003) knowledge of the anatomical routes of information transfer is of paramount importance.

Obtaining the necessary information at the required level of detail is still a complicated and tedious process. The most extensive and detailed information on regional interconnections has been obtained from tracing studies in the brains of mammals, in particular rats, cats and monkeys. Due to the invasive and time-consuming experimental procedures, however, the results are gathered incrementally and scattered across hundreds of separate research publications from the second half of the 20th century. Over this period the available techniques have improved to deliver more specific, more detailed and more complete results. In addition, the partitioning of brain regions has become more sophisticated and diverse as many different subjective criteria are being applied. Finally, the correspondence between microstructurally identified brain regions and gross anatomical landmarks holds only at a coarse level (e.g. Amunts et al., 1999) leading to uncertainties when comparing individual maps or idealized schemes from tracing studies with the voxel-based data sets obtained by neuroimaging.

All these complicating issues need to be addressed by compilations of connectivity data. Whereas the first comprehensive literature reviews published in the 1990es already focussed on well defined species (Felleman & Van Essen, 1991; Young, 1993; Scannell et al., 1995, 1999; Burns & Young, 2000) the more intricate complications could only be efficiently addressed with the development of advanced neuroinformatics tools and algorithms (Stephan et al., 2000; Stephan et al., 2001; Burns, 2001; Kötter, 2001) that allowed us to keep track of thousands of heterogeneous details and still extract the gist of characteristic features in a transparent, reproducible and flexible way. We face further challenges, however, when trying to reconcile 1) the anatomist's distinguishing of microscopic details with the imager's need for less finely grained, but accurate information, 2) the comprehensiveness of textual lists with the intuitiveness of images and 3D representations, and 3) the notation in microstructural partitioning schemes with the application to spatial coordinate systems (tracing data have only in rare cases been referenced to the latter, e.g. Bjaalie et al., 2000; representations of data from Lewis & Van Essen, 2000b in Caret framework).

This paper explores these challenges in more detail using as an example interfaces of the CoCoMac database, the "Collation of Connectivity on the Macaque brain", to illustrate current possibilities and limitations in the systematic retrieval of connectivity information between brain regions. Three types of approaches are considered in the following order: 1) search for relevant publications, 2) retrieval of mapping information, 3) evaluation of connectivity data. This order follows the process of data extraction and processing from published tracing data to the listing of connections, where each new step builds on the previous and thus is more comprehensive and more complicated. Following this track helps to understand the philosophy of the database design and is important for making optimal use of the interface. The three approaches are arguably relevant to different user groups: The literature search is the first choice if you are interested in tracing details and want to check on the contents of particular publications or the work of a particular research group; the mapping information is the choice for those concerned with brain mapping even if they are not working with connectivity data, at all; finally connectivity has the largest scope of users including neurologists, neuroanatomists, neurophysiologists, computational modellers and – most frequently – researchers involved in functional brain imaging. The reader who is solely interested in the retrieval of connections may jump directly to the connectivity section and follow the cross-references to earlier sections if necessary to clarify concepts that had been introduced elsewhere.

The CoCoMac database

The CoCoMac database has gradually developed since 1997 with the aim to obtain an overview of the large-scale wiring of the primate cerebral cortex that could be used for systems analysis and computational modelling. This information is in principle available from experimental tracing studies, but the data are scattered across hundreds of individual research reports. By contrast, recent advances, such as spatially registered tracing and diffusion-weighted imaging data, have not yet generated comparable amounts of data. Therefore, CoCoMac was designed as a literature database to organize the wealth of published tracing data on the macaque monkey brain in an objective, detailed and coherent fashion. Building on experiences with previous data collections (Felleman & Essen, 1991; Young, 1993; Scannell, 1995; Burns, 1997) we realized very early that such a database had to provide full transparency all the way from the published datum to the final retrieved output if it was to stand the scrutiny of neuroanatomists and to survive the requirements of incremental data acquisition and the changing views on cortical partitioning schemes (Stephan et al., 2001). The adherence to the transparency principle is a particular advantage of CoCoMac. It had us a face major challenges, however, concerning the integration of redundant or contradictory published (primary) data, and the transformation of the integrated primary data from various partitioning schemes into a coherent brain map. Integration and transformation are effected by several methods, including the ORT (Objective Relational Translation) procedure, which is presented in detail elsewhere (Stephan & Kötter, 1998; Stephan et al., 2000).

CoCoMac has a clear focus on connectivity data from the brains of adult primates of the genus macaca. The most prominent member of this genus is the species Rhesus monkey (Macaca mulatta), but other frequently investigated species are the closely related Cynomolgus monkey (Macaca fascicularis), the pig-tailed macaque (Macaca nemestrina) and the Japanese macaque (Macaca fuscata). Data collation is carried out by a group of highly trained and closely interacting individuals in the course of their research projects. It progresses by functionally related regions and comprises already most of the cerebral cortex as well as its thalamic and amygdalar afferents.

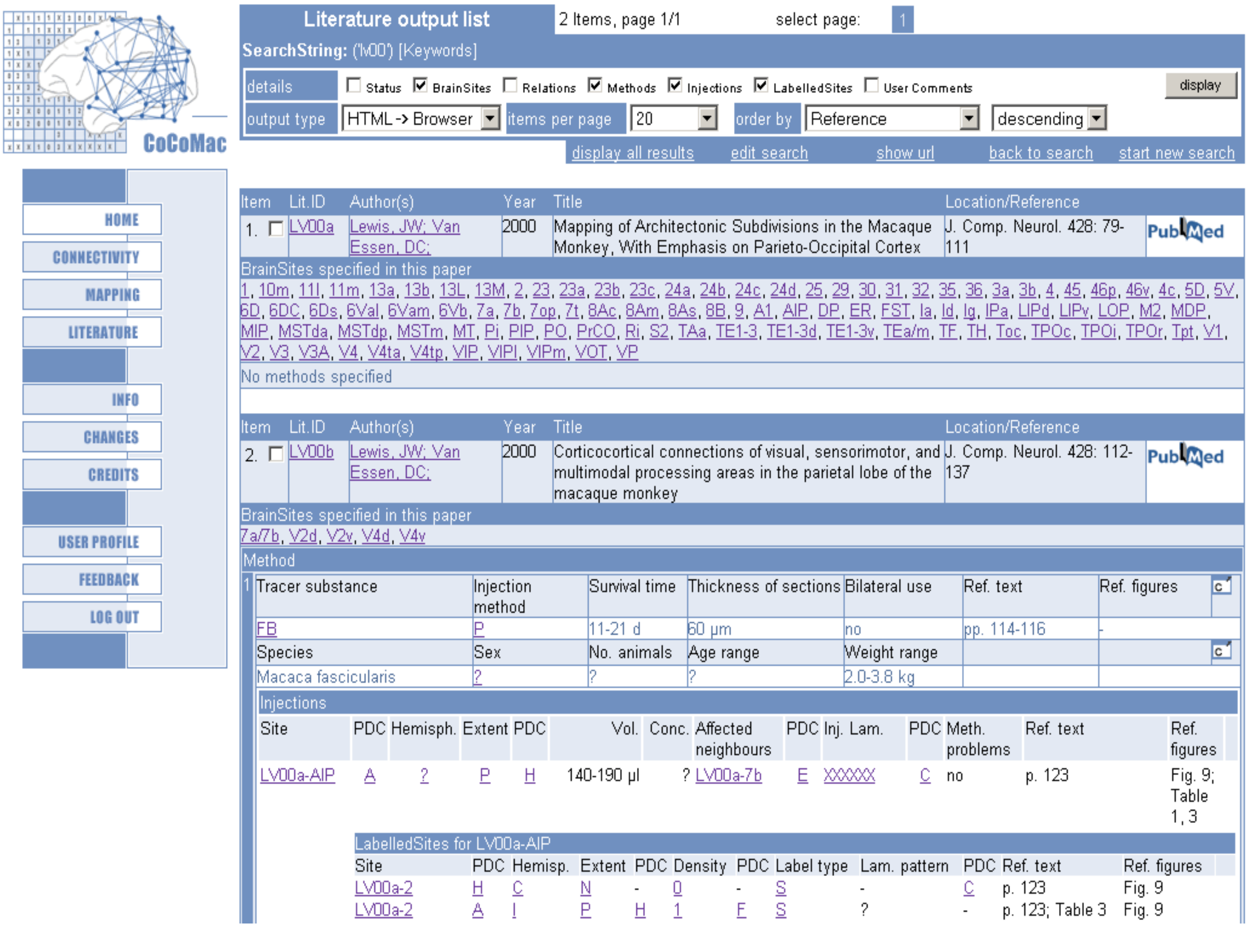
Over the last years we have developed an online-interface for the CoCoMac database, which provides public access to large parts of the CoCoMac database (for a first introduction to the retrieval of literature data see Kamper et al., 2002). Access is gained via the internet at http://www.cocomac.org, is free of charge but requires registration. The registration information helps us to keep track of the user community, which is useful to prioritize further steps of data collation and software development. After successful login the home page offers a quick and simple keyword search as well as essential information on the main menu. The simple keyword search facility is a combined shortcut to the keywords searches in each of the three data categories literature, mapping or connectivity, which are explained in the relevant sections below. The menu buttons are self-explanatory and include an INFO button, which delivers basic information to orient the novice user.

This paper provides a more extensive presentation of the concepts behind the online-interface of CoCoMac with the intention that users obtain a better understanding of its strengths and limitations so that they can optimise their searches, obtain the desired results and integrate the online interface with their own neuroscience or database projects.

Literature

As CoCoMac is a collation of data from the published literature the most immediate impression is gained by inspecting what data have been extracted from individual publications. Selecting the "Literature" access one can search the database for relevant articles not only by the usual bibliographic descriptors but also according to contents-related criteria, such as particular brain maps or sites, certain general classes of brain sites, the presence of mapping or tracing related details, and the use of specified tracer substances.

One important aspect of data representation in CoCoMac concerns the acronym that identifies a publication (LitID) or a brain map. Each collated article is uniquely referred to by the sequence of initials of the authors' surnames followed by the last two digits of the year of publication. If there is more than one article that would be abbreviated in the same way then these are distinguished by a suffix a, b, etc. For example, we extracted data from the two companion articles published by Lewis & Van Essen in 2000 (Lewis & Van Essen, 2000a, b) resulting in the LitIDs LV00a and LV00b (Fig. 1). If the authors define a partitioning scheme (a "BrainMap") in that publication, the same acronym also serves to identify the particular set of brain sites regarded.



Literature output list 2 Items, page 1/1 select page: 1

SearchString: ('lv00') [Keywords]

details ☐ Status ☑ BrainSites ☐ Relations ☑ Methods ☑ Injections ☑ LabelledSites ☐ User Comments

output type HTML -> Browser items per page 20 order by Reference descending

Item	Lit.ID	Author(s)	Year	Title	Location/Reference
1. ☐	LV00a	Lewis, JW; Van Essen, DC;	2000	Mapping of Architectonic Subdivisions in the Macaque Monkey, With Emphasis on Parieto-Occipital Cortex	J. Comp. Neurol. 428: 79-111

BrainSites specified in this paper

1, 10m, 11l, 11m, 13a, 13b, 13L, 13M, 2, 23, 23a, 23b, 23c, 24a, 24b, 24c, 24d, 25, 29, 30, 31, 32, 35, 36, 3a, 3b, 4, 45, 46p, 46v, 4c, 5D, 5V, 6D, 6DC, 6Ds, 6Val, 6Vam, 6Vb, 7a, 7b, 7op, 7t, 8Ac, 8Am, 8As, 8B, 9, A1, AIP, DP, ER, FST, Ia, Id, Ig, IPa, LIPd, LIPv, LOP, M2, MDP, MIP, MSTda, MSTdp, MSTm, MT, Pi, PIP, PO, PrCO, Ri, S2, TAa, TE1-3, TE1-3d, TE1-3v, TEa/m, TF, TH, Toc, TPOc, TPOi, TPOr, Tpt, V1, V2, V3, V3A, V4, V4ta, V4tp, VIP, VIPl, VIPm, VOT, VP

No methods specified

Item	Lit.ID	Author(s)	Year	Title	Location/Reference
2. ☐	LV00b	Lewis, JW; Van Essen, DC;	2000	Corticocortical connections of visual, sensorimotor, and multimodal processing areas in the parietal lobe of the macaque monkey	J. Comp. Neurol. 428: 112-137

BrainSites specified in this paper

7a/7b, V2d, V2v, V4d, V4v

Method

1

Tracer substance	Injection method	Survival time	Thickness of sections	Bilateral use	Ref. text	Ref. figures
FB	P	11-21 d	60 µm	no	pp. 114-116	-

Species	Sex	No. animals	Age range	Weight range
Macaca fascicularis	?	?	?	2.0-3.8 kg

Injections

Site	PDC	Hemisph.	Extent	PDC	Vol.	Conc.	Affected neighbours	PDC	Inj. Lam.	PDC	Meth. problems	Ref. text	Ref. figures
LV00a-AIP	A	?	P	H	140-190 µl	?	LV00a-7b	E	XXXXXX	C	no	p. 123	Fig. 9; Table 1, 3

LabelledSites for LV00a-AIP

Site	PDC	Hemisp.	Extent	PDC	Density	PDC	Label type	Lam. pattern	PDC	Ref. text	Ref. figures
LV00a-2	H	C	N	-	0	-	S	-	C	p. 123	Fig. 9
LV00a-2	A	I	P	H	1	F	S	?	-	p. 123; Table 3	Fig. 9

Figure 1.

We distinguish three ways of referring to specific brain sites (Stephan et al., 2001): If the authors report their own microstructural investigations to specify the extent of the brain sites then the report gives rise to a new brain map. Well known examples are the "classic" brain maps specified in the books by Brodmann in 1909 (B09) and von Bonin & Bailey in 1947 (BB47). Of the two articles mentioned in the preceding paragraph the first one defines a brain map referred to as LV00a. Lewis & Van Essen adopt this partitioning scheme when describing the results of their tracing experiments in LV00b. Thus, LV00b describes the locations of the tracer injections and the labelled sites with reference to cortical areas in the map LV00a, which we classify as a case of specific adoption. Consequently, a literature search for LV00a with the criterion “LitID” will bring up LV00a, whereas the same search term with the criterion “BrainMap” delivers the article LV00b because this article uses the map LV00a. As the user can imagine certain brain maps are more commonly used than others - also across research groups - to describe the locations identified in tracing studies. These are helpful maps to remember when searching for connectivity data: Commonly used maps are FV91 (Felleman & Van Essen, 1991) for visual, PS82 (Pandya & Seltzer, 1982) for parietal, HSK98a (Hackett et al., 1998) for auditory, VPR87 (Vogt et al., 1987) for cingulate, or W40

(Walker, 1940) for prefrontal cortex. Finally, there are publications that mention brain sites whose definitions cannot be attributed to specific microstructural investigations. In this case of unspecific adoption we would create a brain map for the LitID concerned and use additional information to infer the mapping of those brain sites to the brain sites of other partitioning schemes (see section Mapping below).

Every brain map is made up of one or more structures, which we call “BrainSites”. A list of all BrainSites specified in a publication can be obtained by ticking the corresponding box in the details of the literature output list (see Fig. 1). BrainSites fall into different classes (areas, nuclei, layers, columns, neuronal populations etc.), which invoke different concepts and require different treatments by the database tools. Although any such classification has a degree of arbitrariness (and for consistency in the database we classified all amygdaloid structures as nuclei), the search criterion “BrainSiteClass” can be useful to identify reports that deal, for example, only with isocortex, allocortex, nuclei or their layer subcompartments.

Publications represented in the CoCoMac can be divided into those that describe the delineation and mapping of microstructural partitions of the brain, on the one hand, and those that report the results of tracing experiments with reference to such partitions, on the other hand. Therefore, the literature search interface offers a search by DataType, which allows a limitation of the search to reports whose mapping and/or connectivity data we extracted. Note that from a minority of papers we did not extract all the presented data yet, in particular if these data concerned subcortical structures that were not among our research priorities.

Concerning tracing studies a particularly interesting piece of information is the TracerSubstance used, which includes a range of tracers with anterograde (e.g. tritiated amino acids) or retrograde (e.g. rhodamine-coupled latex microspheres) or bidirectional (e.g. horseradish peroxidase) transport properties. The direction of transport is important for the type of label that we encounter at the labelled sites: Anterograde tracers label axonal terminals ("T") whose density is difficult to quantify, whereas retrograde transport labels cell bodies (somata, "S"), which can be counted to obtain quantitative data. Note in this context that information on laminar specificity of projections is usually only obtained for the labelled but not the injected brain sites. To obtain comprehensive laminar information of a projection it would, therefore, usually be necessary to combine information from an anterograde and a retrograde tracing experiment investigating the same projection.

At present we do not offer search criteria such as MacaqueSpecies, AnimalGender or Hemisphere, although we provide this information with the retrieved output. Hemisphere and fibre course (ipsilateral, contralateral) can be specified, though, when searching for connections derived from the tracing data (see section Connectivity below).

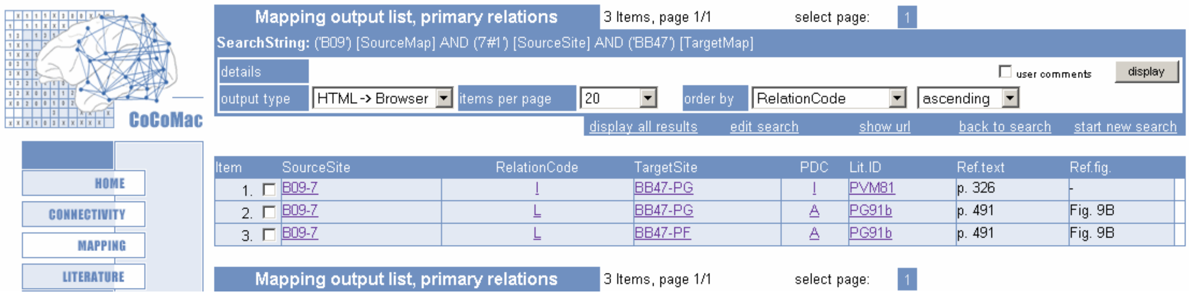
The initial output of any literature search is a bibliographic list of relevant publications. The header and footer of this list provide tick boxes to display further details on all or (after ticking at least one of the boxes next to the item numbers) on the selected items. Available details include the list of BrainSites, mapping information, the tracing methods, injection and labelled sites, as well as information on the status of data collation and proofreading and any user comments. A default set of pre-selected details is displayed by clicking on the LitID or the authors of an individual article: these details include status, methods and injection sites. Further details can then be obtained by altering the selected details or by clicking the icons labelled “LS” to obtain the list of labelled sites for a specific tracer injection, or the icons “C” to view the data collator’s comments. Note that we have implemented a hierarchical proofreading schedule to verify correct data extraction and database entry; its progress divided into mapping and connectivity data can be inspected by choosing the display option “Status”.

The detailed output lists contain many other pieces of information that are documented in help windows that open by clicking on the respective item. In a certain operating system-associated browser the relevant information shows up conveniently as a fly-out and in the status line when the mouse curser is moved over the item. A detail that requires further explanation is indicated by the acronym PDC for “Precision of Description Code”. Five such code categories indicate the data collators' standardised assessments of the precision with which the respective data were presented in the evaluated article. The categories are Site/ Location (how precisely a BrainSite was specified in text or figures), Extent (how well the coverage of the BrainSite with label was described), Laminae (how precisely the laminar pattern of tracer injection or label was presented), Mapping (precision of describing the relation between two BrainSites; see section Mapping below) and Density (precision in specifying the amount of transported label; see section Connectivity below). These PDCs must not be confused with an assessment of the correctness or scientific value of the collated data; as external observers we have to remain neutral apart from the limitation that the published material does not allow us to evaluate objectively the quality of the experimental work. What we see, however, is the descriptions in words and pictures whose precision we assess systematically according to pre-defined criteria.

Mapping

The question into how many structures the brain should be divided and where their precise borders are has been heavily debated for more than a century and is still not solved satisfactorily (see, for example, Stephan et al., 2000). Although parcellation-based frameworks need not be concerned with precise spatial locations, the debate concerns the specification the sites of tracer injection and transported label in the tracing experiments. Since we encounter many different names and definitions of brain structures and cannot unambiguously resolve uncertainties about their relationships we need to be very specific about which brain structure is being referred to. For our purpose, every brain structure can be uniquely addressed by its acronym and the brain map that it belongs to. Thus, we distinguish an area MT (middle temporal) as identified by Lewis & Van Essen (2000a) from e.g. MT defined by Desimone & Ungerleider (1986) or by Cusick et al. (1995) in that we precede each one with the BrainMap identifier (see chapter Literature) and a hyphen to become LV00a-MT, DU86-MT and CSCG95-MT, respectively. Since the BrainMap refers to a specific publication it is even possible to keep track of different definitions given by the same author. For example, Brodmann (1905) showed a rostral cingulate area 25 in his map of the cercopithecus monkey from 1905 (B05-25), which is clearly completely different from the subcallosal area 25 that he designated in 1909 (B09-25) after gaining further experience from the comparison of a large range of mammalian species (Brodmann, 1909).

While precision is a desirable feature it must be asked whether the policy described above artificially inflates the number of brain maps and obscures the important distinctions of some subsets of them. To answer this question we need to consider how we know which definitions refer to BrainSites that are identical and which refer to different ones. In many cases there is no clear answer either way since precision is limited when comparing brain sites defined by subjective and method-dependent criteria in different brains. We can deal with this problem in the same way as proposed for the connectivity data: by assembling statements from the literature. In most cases, the authors of a mapping study offer comments on the relationship of their findings to the brain sites described by others. Where two brain sites are said to be identical it seems unnecessary to distinguish them even if they carry different names, which then become synonymous, e.g. areas 17, OC, and V1. We observe statements, however, that are either directly or indirectly contradictory (Fig. 2): For example, concerning Brodmann’s area 7 (B09-7) was said to be identical with von Bonin & Bailey’s area PG (BB47-PG) by Pandya et al. (1981, p. 326); but later Preuss & Goldman-Rakic saw B09-7 to comprise BB47-PG (and additionally BB47- PF) (Preuss & Goldman-Rakic, 1991, p. 491 and fig. 9B). Such discrepancies occur not only in the complicated parietal region, but even in the primary motor cortex: von Bonin & Bailey’s area FA (BB47-FA) was regarded as smaller than Brodmann’s area 4 (Matelli et al., 1985, p. 134) but later the two appeared identical (Matelli et al., 1986, p. 281; Matelli et al., 1991, p. 459). This illustrates the general complication that original statements are subject to controversies and revision. If we did not keep original statements separate then we would risk difficulties with accommodating new insights. Consequently, the output of a mapping search provides information on the logical relationships of brain structures. The mapping search offers specification of a BrainMap (which includes all the identified BrainSites), of a BrainSite acronym (regardless of the specific BrainMap) or the combination of the two. Both BrainMap and BrainSite acronym can be selected twice to retrieve specific relationships as in: ('BB47')[SourceMap] AND ('FA')[SourceSite] AND ('B09')[TargetMap] AND ('4')[TargetSite] where the sequence and allocation of source and target are irrelevant for the results obtained.



Mapping output list, primary relations — 3 Items, page 1/1

SearchString: ('B09') [SourceMap] AND ('7#1') [SourceSite] AND ('BB47') [TargetMap]

output type: HTML -> Browser; items per page: 20; order by: RelationCode; ascending

Item	SourceSite	RelationCode	TargetSite	PDC	Lit.ID	Ref.text	Ref.fig.
1. ☐	B09-7	I	BB47-PG	I	PVM81	p. 326	-
2. ☐	B09-7	L	BB47-PG	A	PG91b	p. 491	Fig. 9B
3. ☐	B09-7	L	BB47-PF	A	PG91b	p. 491	Fig. 9B

Mapping output list, primary relations — 3 Items, page 1/1

Figure 2.

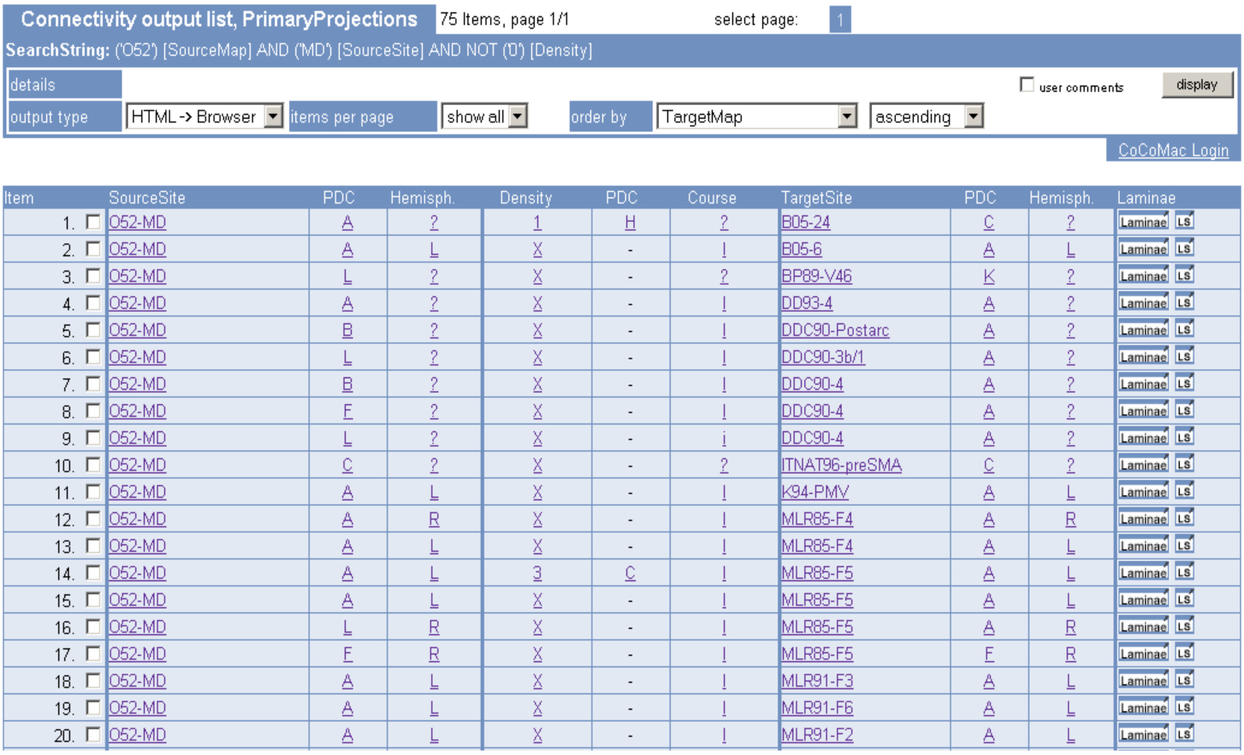
Concerning the type of mapping relationship we distinguish the following logical relationships (Fig. 2): Identity (I), substructure (S), larger structure (L) and overlapping structure (O). Additional RelationCodes are used to designate the special relationship between cortical areas and their layers: The degree of coverage with label (the “Extent”) seen in a cortical area depends on whether the structure is viewed as a three-dimensional object or in its surface projection. For example, total coverage of one layer and absence of label in all other layers translates into partial coverage of the area when it is regarded as a 3D object. The surface projection, however, would still show complete coverage of the area. To accommodate this distinction in the published data, we regard layers not simply as substructures (S) of areas, but they expand (E) to areas and, reversely, areas collapse (C) to layers to keep track of these special relationships. Thereby, we can consistently evaluate not only the logical relationships of cortical structures but also the extent of their labelling.

The resulting MappingOutputList (Fig. 2) provides, in addition, the data collators' assessments of the PDC (see section Literature) of this mapping relationship based on the available information in text (including tables) and figures of the original publication. The LitID references the publication where the mapping was described in the LiteratureOutput for more detailed inspection.

Finally, the search can be carried out on the so-called PrimaryRelations, which comprise all original statements on the mapping of BrainStructures collated from the literature. Alternatively, the search can be limited to the IntegratedPrimaryRelations, which are a subset of the PrimaryRelations such that redundant and contradictory data have been sifted with the result that only the most precise statement (according to the PDC for the Mapping) is kept.

Connectivity

Information on the presence or absence, and on the density (strength) or laminar specificity of a projection is the natural focus of interest in a connectivity database. The available search options are relatively easy to explain following the introduction to literature and mapping data above. As opposed to the direction of mapping, however, the orientation of projections is very important. Thus, a search has to distinguish between the source structure that emits efferent projections, and the target structure that receives afferent projections. Both source and target structure can be specified in terms of the BrainMap, the BrainSite acronym, or their combination. For example, a query that specifies the same BrainMap as source and target retrieves all available information on projections within this BrainMap, e.g. ('HSK98a')[SourceMap] AND ('HSK98a')[TargetMap] lists all connectivity information described within the auditory cortex as partitioned by Hackett et al. (1998). If we select a specific source structure then we retrieve the list of its targets, such as in ('O52')[SourceMap] AND ('MD')[SourceSite] AND NOT ('0') [Density], which features the (cortical) target structures that are known to receive afferents from the thalamic mediodorsal nucleus in the map of Olszewski (1952) (Fig. 3).



Connectivity output list, PrimaryProjections 75 Items, page 1/1 select page: 1

SearchString: ('O52') [SourceMap] AND ('MD') [SourceSite] AND NOT ('0') [Density]

Item		SourceSite	PDC	Hemisph.	Density	PDC	Course	TargetSite	PDC	Hemisph.	Laminae
1.	☐	O52-MD	A	?	1	H	?	B05-24	C	?	Laminae LS
2.	☐	O52-MD	A	L	X	-	!	B05-6	A	L	Laminae LS
3.	☐	O52-MD	L	?	X	-	?	BP89-V46	K	?	Laminae LS
4.	☐	O52-MD	A	?	X	-	!	DD93-4	A	?	Laminae LS
5.	☐	O52-MD	B	?	X	-	!	DDC90-Postarc	A	?	Laminae LS
6.	☐	O52-MD	L	?	X	-	!	DDC90-3b/1	A	?	Laminae LS
7.	☐	O52-MD	B	?	X	-	!	DDC90-4	A	?	Laminae LS
8.	☐	O52-MD	F	?	X	-	!	DDC90-4	A	?	Laminae LS
9.	☐	O52-MD	L	?	X	-	i	DDC90-4	A	?	Laminae LS
10.	☐	O52-MD	C	?	X	-	?	ITNAT96-preSMA	C	?	Laminae LS
11.	☐	O52-MD	A	L	X	-	!	K94-PMV	A	L	Laminae LS
12.	☐	O52-MD	A	R	X	-	!	MLR85-F4	A	R	Laminae LS
13.	☐	O52-MD	A	L	X	-	!	MLR85-F4	A	L	Laminae LS
14.	☐	O52-MD	A	L	3	C	!	MLR85-F5	A	L	Laminae LS
15.	☐	O52-MD	A	L	X	-	!	MLR85-F5	A	L	Laminae LS
16.	☐	O52-MD	L	R	X	-	!	MLR85-F5	A	R	Laminae LS
17.	☐	O52-MD	F	R	X	-	!	MLR85-F5	F	R	Laminae LS
18.	☐	O52-MD	A	L	X	-	!	MLR91-F3	A	L	Laminae LS
19.	☐	O52-MD	A	L	X	-	!	MLR91-F6	A	L	Laminae LS
20.	☐	O52-MD	A	L	X	-	!	MLR91-F2	A	L	Laminae LS

Figure 3

The latter example can be extended to illustrate the power of combining mapping and connectivity information: The mediodorsal nucleus is composed of subnuclei (magnocellular, parvocellular, etc.) that have specific cortical targets. These subnuclei are evaluated in addition to MD by ticking the EXTend option L, which means that we extend the source specification (O52-MD) to include all subnuclei of which the MD nucleus specified in Olszewski's map is a larger structure (see RelationCodes in section Mapping above). Now the retrieved list contains 25 further connections that result from inclusion of the subnuclei of the MD nucleus in the map of Olszewski (1952) using the Boolean AND condition.

The list of known connections comprises projections with different connection densities (corresponding to the experimentally determined amount of label on a rank order scale: 1 weak/sparse; 2 moderate; 3 strong/heavy; X existing label of unspecified density) including evidence for the absence of connections (0). The search criterion "Density" allows the user to exclude evidence of absence (by deselecting Density=0; see section Automated search and retrieval) or to extract only the strongest connections (by selecting only Density=3). The latter restriction is very useful as a rational criterion for selecting a reduced set of projections to be used in Structural Equation Modelling, where the number of connections (of either orientation) in the anatomical model must be smaller than the number of coefficients in the pairwise correlation/ covariance matrix (McIntosh & Gonzales-Lima, 1994; Backhaus et al., 2000; Friston et al., 2003).

Other important search criteria are the Hemisphere (Left or Right or Unknown location of Source or Target) and (Ipsilateral, Contralateral or Unknown) Course of the fibres. It must be realized that the majority of published tracing studies omit information on the investigated hemisphere, which reflects the limited number of hemispheres available in any single study and the (unproven) belief that lateralization, which is well documented in humans and great apes, does not play a role in the macaque brain. Most studies, however, investigate ipsilateral projections in either hemisphere, and very little is known about homotopic or heterotopic contralateral projections.

Among the search criteria is the option to specify a keyword. It is highly seducing to type a word or set of words and simply click the Search button without thinking about the retrieval strategy behind this option, even more since this is the first option encountered after logon to CoCoMac. The problem with this keyword criterion is that it is hard for us as the database providers to retrieve adequate output even when the intention of the search term can be guessed at; much worse is problem that the user has no way to assess the logic behind the retrieved results and to know whether all relevant data were obtained. In general, what this facility does is to search the full names of BrainSites for perfect matches, to identify the corresponding BrainSite acronyms and to retrieve database information for all brain sites that map with an “identity (I)"-relationship to the identified BrainSite. Occasional problems encountered with this keyword facility are absence of any results because the terms typed are incompatible with the contained data or their representation. For example, it is hard to disambiguate lists of terms that include both source and target sites; therefore the keyword entry must refer only to one brain structure. Also, colloquial terms such as “BA” or “Brodmann’s area”, or “Broca’s area” (a concept from clinical observations on the human brain) are not represented in the database, even though the terms “Brodmann” or “area 44”, respectively, retrieve relevant content as the user can ascertain. Functional terminology is not commonly used in anatomical publications and may produce no results, as will terms such as “barrel cortex”, which apply to rodents but not to primates. If no relevant data are returned then the user cannot know whether the data are missing or whether the search term missed the target. The answer may be found, however, by searching the literature with the keywords since the keyword facility in the literature category has access to all terms in the title and abstract of publications and retrieves all articles that list this combination of terms. From the details in the retrieved articles a list of applicable BrainMaps or BrainSites can be assembled.

As with the mapping search, the connectivity search can be carried out on all PrimaryProjections including redundant and contradictory data, or on the IntegratedPrimaryProjections, which represent an integrated subset of projections that are the best according to a pre-defined set of criteria. The procedure for choosing IntegratedPrimaryProjections is documented more fully in Stephan et al. (2001) and includes an appraisal of the PDCs of injected and labelled sites, the direction transport of the tracer, and the extent of coverage of the injected site by the tracer injection.

Other database contents

There is more content in the CoCoMac database than can be retrieved through the online interface despite the already extensive information provided. Interesting aspects are, for example, the method used for delineation of BrainSites, details on radioactive tracers employed, and quantitative data on connection densities, such as total number of labelled neurons in a BrainSite or the percentage of labelled cells in a BrainSite with respect to the total number of labelled neurons resulting from that injection. Since less than 5% of collated articles provide quantitative data, the implementation of a user interface for these data had low priority. Further information of interest includes visual representations of brain maps, and some of these are being re-drawn for representation in Catacomb and CARET (see section Graphical display of connectivity data).

The main menu of the online interface, however, contains further items (Fig. 1) that list changes to the contents or design of the database with time stamps so that recent additions can be monitored. Users are encouraged to add comments to all database output so that the community can benefit from external opinions on the representation or interpretation of the data (see the concept of the "Faculty of 1000" at PubMedCentral). Comments added to specific items are available whenever the item is retrieved again choosing the Display option “user comments” (Figs. 1-3). Independent of specific contents, feedback - including bug reports and suggestions - is most welcome and can be given through the corresponding menu item.

Every version of the CoCoMac database is archived. Although older database versions are not available online anymore it is in principle possible to reconstruct any query results if the date and time of retrieval is known. Thus, it is recommended that users note the date of database upload shown on the login page and the search string that produced the results that they want to refer to. The contents of the search strings is listed at the top of each OutputList, and the full query can be referenced and bookmarked after clicking “Show URL” from the OutputList. When using data from the CoCoMac database then it would be adequate to reference the source referring to http://www.cocomac.org or to the present article.

Automated search and retrieval

The online interface is conceptually a separate entity from the database and the query engine. It has two functions in interfacing with the user:

1) to aid the user in constructing the desired search query, which is then passed on to the query engine, and
2) to display the retrieved data in the form of textual output lists.

Both functions, query construction and display of results, can alternatively be carried out by other means including automatic generation of query strings and further processing of the returned results. This opens up many opportunities for interactions with other databases, visualization and modelling tools.

Query construction is a relatively straightforward process: Every query constructed in the online interface (and additional queries) can be expressed as a parameterized URL string that is a concatenation of the address of the server site, the search engine, a list of parameters, and the actual search string. If the output is HTML directed to the browser then the only differences to the manual output are the absence of the menu on the left and the additional CoCoMac login button, which allows the user to continue with a manual search under his own login (see Fig. 3). Alternatively, XML output can be obtained (Fig. 4) that is formatted according to the CoCoMac XML schema, which is available for inspection, download, and validation of XML files at http://www.cocomac.org/cocomac.xsd.

The full syntax of these http strings is documented at http://www.cocomac.org/cocomac_URLsearch.html. Here are sample strings for queries replicating examples from the sections above. The sample username and password shown below are to be replaced by the user's personal username and password:

The default view of the contents from the paper by Lewis & Van Essen (2000b) can be obtained by composing the following URL string and pasting it into the address field of your browser:

http://cocomac.org/URLSearch.asp?user=cocomac&password=cocomac&Search=Literature&OutputType=HTML_Browser&SearchString=('LV00b')[LitID]

From the section on Mapping the following URL string retrieves the contradictory statement on the mapping between von Bonin & Bailey's area PG and Brodmann's area 7:

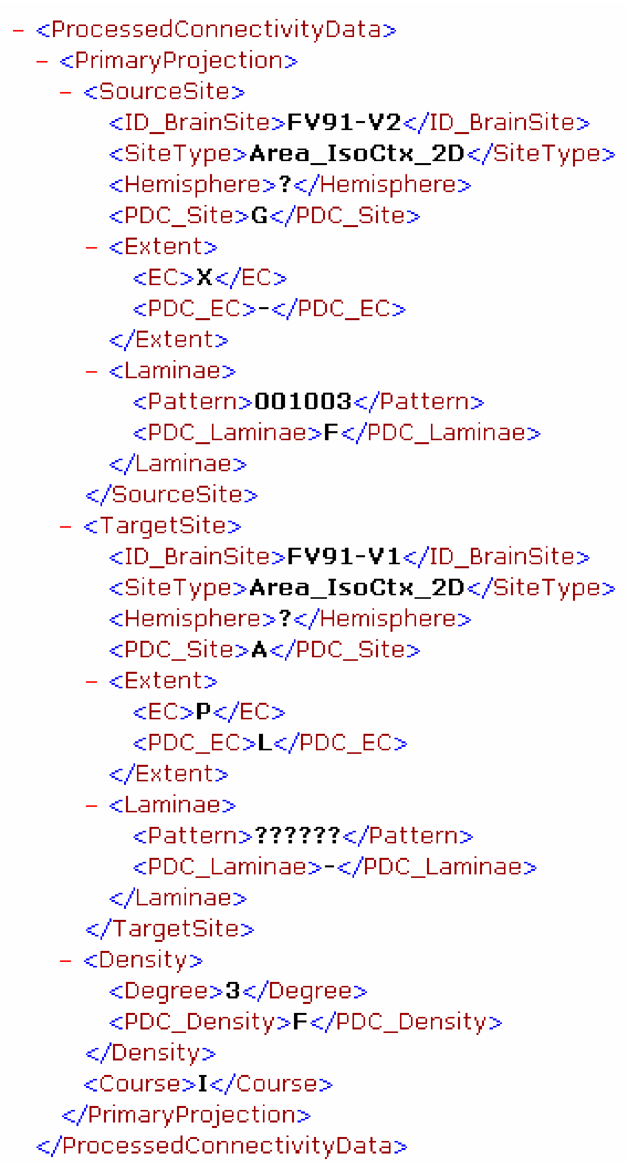
http://cocomac.org/URLSearch.asp?user=cocomac&password=cocomac&Search=Mapping&DataSet=PRIMREL&OutputType=HTML_Browser&SearchString=('BB47')[SourceMap]AND('PG')[SourceSite]AND('B09')[TargetMap]AND('7')[TargetSite]

Finally, here is a more complicated example with the retrieval of connectivity data limited to non-absent efferents from thalamic nucleus MD and its subnuclei in the map of Olszewski formatted such that all items go on one page and are ordered by the TargetMap (shown in Fig. 3):

http://cocomac.org/URLSearch.asp?user=cocomac&password=cocomac&Search=Connectivity&DataSet=PrimProj&OutputType=HTML_Browser&ItemsPerPage=All&SortBy=TargetMap&SearchString=('O52')[SourceMap]AND('MD' EXT 'L')[SourceSite]AND NOT ('0')[Density]

Finally, below is a very comprehensive example that retrieves all 843 projections noted in the map of Felleman & Van Essen (1991) and displays them in XML format for further processing (data snippet of a projection from V2 to V1 shown in Fig. 4):

http://cocomac.org/URLSearch.asp?user=cocomac&password=cocomac&Search=Connectivity&DataSet=PrimProj&OutputType=XML_Browser&SearchString=('FV91')[SourceMap]AND('FV91')[TargetMap]



```
- <ProcessedConnectivityData>
  - <PrimaryProjection>
    - <SourceSite>
        <ID_BrainSite>FV91-V2</ID_BrainSite>
        <SiteType>Area_IsoCtx_2D</SiteType>
        <Hemisphere>?</Hemisphere>
        <PDC_Site>G</PDC_Site>
      - <Extent>
          <EC>X</EC>
          <PDC_EC>-</PDC_EC>
        </Extent>
      - <Laminae>
          <Pattern>001003</Pattern>
          <PDC_Laminae>F</PDC_Laminae>
        </Laminae>
      </SourceSite>
    - <TargetSite>
        <ID_BrainSite>FV91-V1</ID_BrainSite>
        <SiteType>Area_IsoCtx_2D</SiteType>
        <Hemisphere>?</Hemisphere>
        <PDC_Site>A</PDC_Site>
      - <Extent>
          <EC>P</EC>
          <PDC_EC>L</PDC_EC>
        </Extent>
      - <Laminae>
          <Pattern>??????</Pattern>
          <PDC_Laminae>-</PDC_Laminae>
        </Laminae>
      </TargetSite>
    - <Density>
        <Degree>3</Degree>
        <PDC_Density>F</PDC_Density>
      </Density>
      <Course>I</Course>
    </PrimaryProjection>
  </ProcessedConnectivityData>
```

Figure 4.

These examples can be adapted to suit individual needs and, in fact, the http queries can be automatically generated within programmes that would thereby interface with CoCoMac-Online to send a query. The resulting output is either displayed in a browser window or, alternatively, can be processed further usually using the XML-output option. Useful cross-links would include interfaces with databases of further data modalities, with digital atlasses, with statistical analysis and computational modelling tools. Two examples are given in the following section.

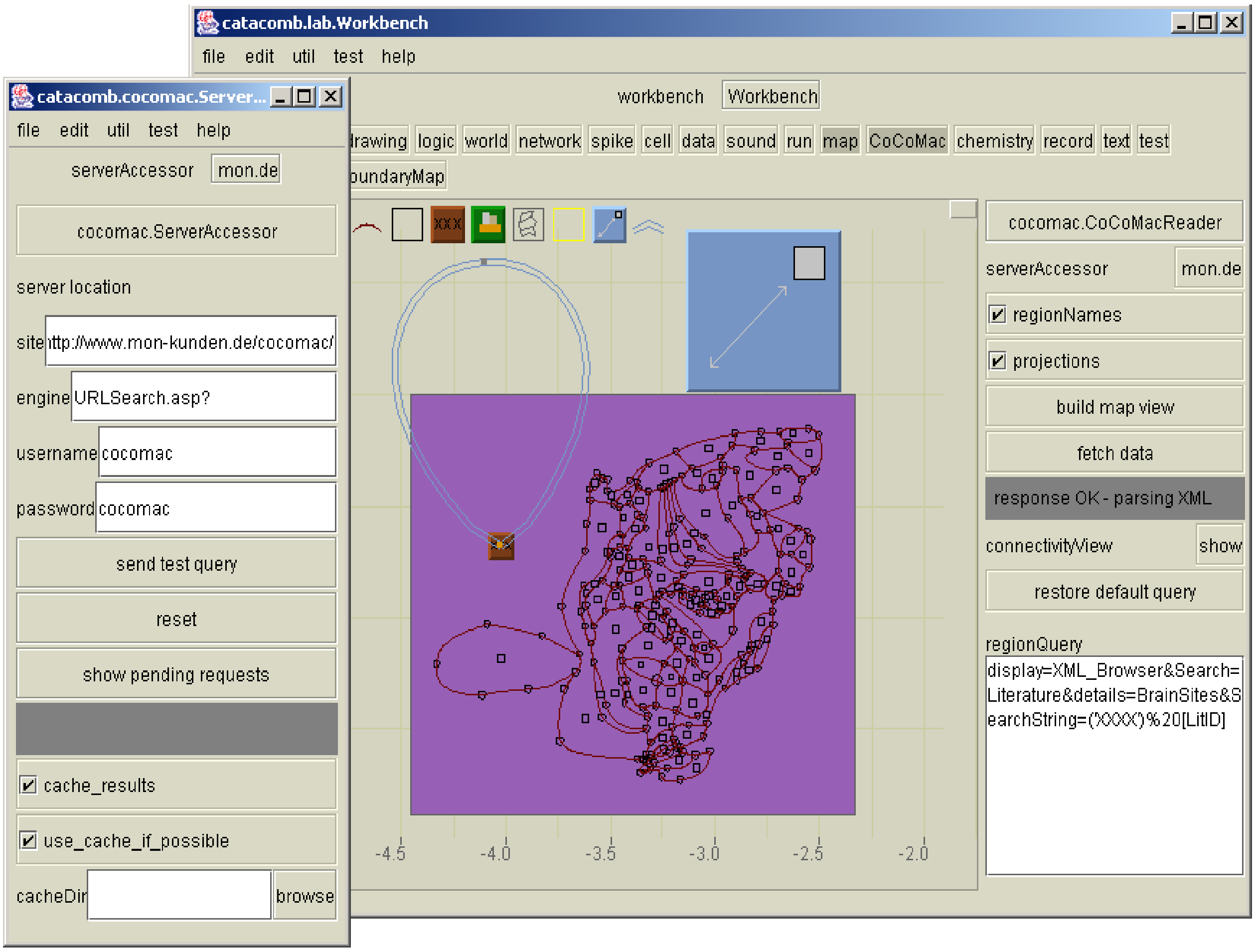
Graphical display of connectivity data

As soon as large numbers of connections between several areas are listed as text it would be far more intuitive and convenient if these could be displayed graphically. Since the spatial position and course of the fibres is not documented we have two basic options to display the connections:

1) We can follow the anatomical images, which show the label obtained from a specific tracer injection in sections or in a surface projection on a schematic brain.
2) We can draw oriented lines that link source areas with target areas in an idealized non-spatial manner.

Both options have been implemented: The first is available as part of the Caret software developed by the Van Essen lab (http://brainmap.wustl.edu/vanessen.html) and highlights the areas that are connected to a chosen area in the map of Felleman & Van Essen (1991) both in the flat map and in the fiducial surface representation of the macaque cerebral cortex.

The second option has been developed in collaboration with Robert Cannon as part of his Catacomb Workspace (Cannon et al., 2003). This JAVA-based tool was designed as a simulator of integrate-and-fire models with many extensions including a CoCoMac-specific part consisting of a map, a connector and a server accessor (Fig. 5). The server accessor generates a URL search as described above, parses the retrieved XML output and displays the connectivity information superimposed on maps that are drawn using the built-in map maker. Information and example maps can be downloaded from http://www.cocomac.org/catacomb.



serverAccessor mon.de

site ttp://www.mon-kunden.de/cocomac/

engine URLSearch.asp?

username cocomac

password cocomac

☑ cache_results

☑ use_cache_if_possible

cacheDir

serverAccessor mon.de

☑ regionNames

☑ projections

response OK - parsing XML

connectivityView

regionQuery
display=XML_Browser&Search=Literature&details=BrainSites&SearchString=('XXXX')%20[LitID]

Figure 5.

The main advantage of the display option implemented in the Catacomb Workspace is that it can present the connections between multiple areas simultaneously (Fig. 6). The particular set of areas can be selected by mouse clicks, for example, in accordance with the mapping of significantly activated areas in functional imaging experiments. Depending on whether PrimaryProjections or IntegratedPrimaryProjections are retrieved the representation will show all available data including redundant and contradictory information (Fig. 6) or only one projection that represents the most precise among the available data. Further options include the display of all afferents and/ or all efferents of the selected area(s) and the display of six-tiered colour bars representing the density values for each isocortical layer at the source and target of each connection.

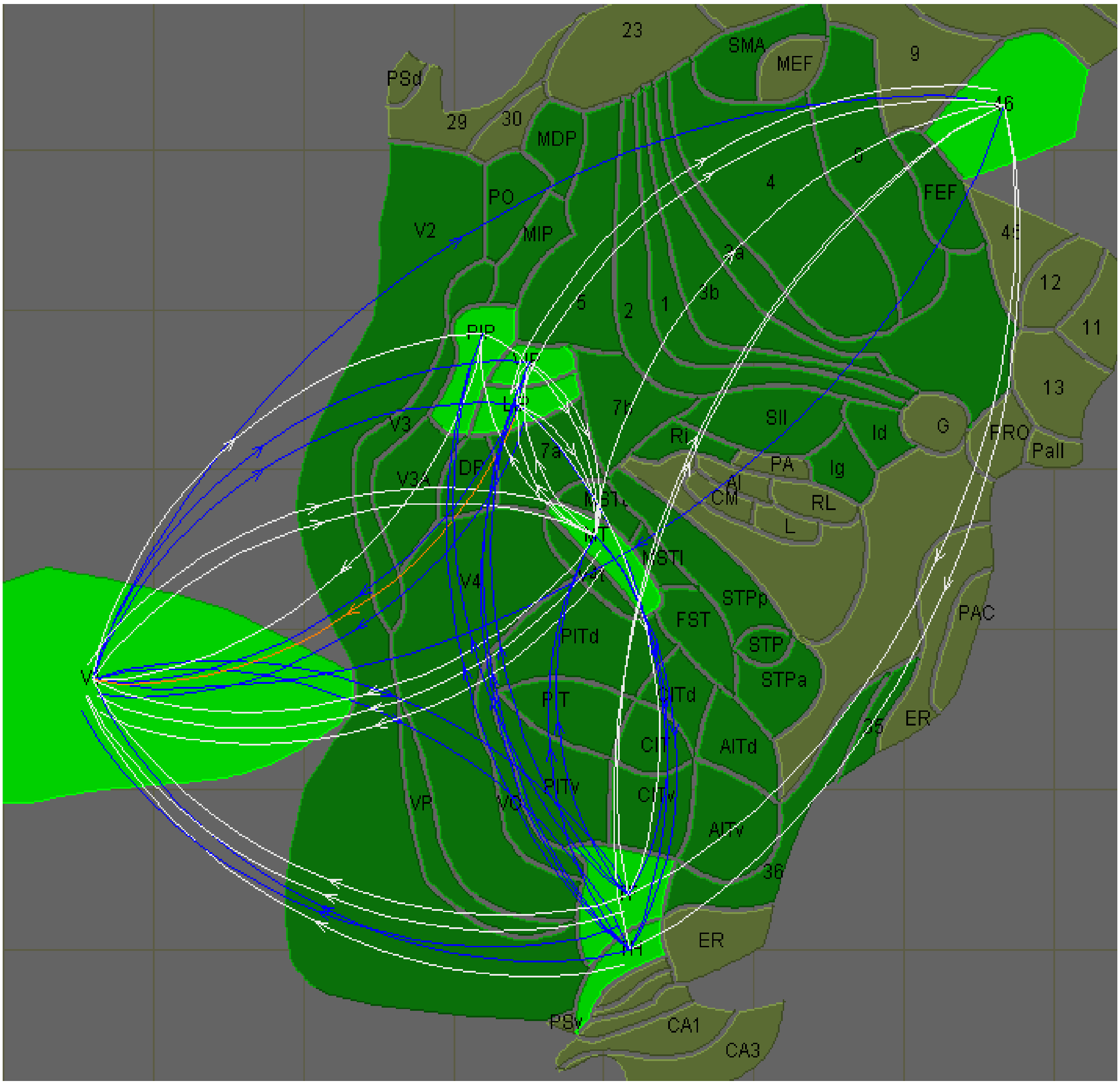


Figure 6.

Conclusions and perspectives

Information about the large-scale connectivity between brain regions is a valuable resource both for top-down descriptive modelling of functional data, such as those obtained with functional imaging techniques, and for bottom-up mechanistic modelling that constructs more complex models from detailed anatomical, biochemical, and physiological information. Such connectivity data are in principle available, but they are dispersed across hundreds of experimental reports whose interpretation requires neuroanatomical background knowledge and has a limited spatial resolution due to the lack of coordinate notations and the subjectivity of microstructural delineations. The CoCoMac database contains most of the published material on intra-cortical connectivity and presents it in a systematic and precise fashion. Remaining limitations result mainly from the confusing number of brain maps and the varying nomenclature of brain structures. As a consequence of the simultaneous collation of mapping information these problems are now systematically being addressed and have already led to the development of algorithmic transformation procedures, such as ORT (Stephan et al., 2000). Although this transformation process is fully documented and controlled by user-defined parameters, it is a complex multi-stage procedure whose understanding requires considerable familiarity with details of neuroanatomical data and their representation in the database. To complement older brain maps with controversial partitioning schemes and recent brain maps that are mostly limited to particular cortex regions we are taking steps to provide data in the comprehensive map of the first stereotaxic macaque atlas that comprises a cortex parcellation (Paxinos et al., 2000) and in an abstract map that refers to relatively large but less controversial topographic brain regions ("Regional Map") that will also facilitate cross-species comparisons. For retrieval purposes it would further be useful to link all BrainSites to a widely used ontology of macaque brain structures, such as the NeuroNames nomenclature (Bowden & Dubach, 2002), which has its conceptual counterpart in the implementation of a “General Map” in the CoCoMac system. Still the calculation of comprehensive connectivity matrices and the optimization of free-text interfaces is a time-consuming and tedious task that would benefit from dedicated software engineering work but is outside the scope and funding for scientific research projects. In the meantime, it seems important to convey the essential database concepts and retrieval options to make the search for relevant connectivity data more efficient, more versatile, and more rewarding.

As a result of the data collation for the CoCoMac database some surprising omissions became evident in the published data, which could be easily mended by attentive experimenters, referees and journal editors: In particular, essential descriptive information on the number and gender of investigated animals and the identity of the right or left hemisphere is frequently missing even in contemporary reports published in highly respected journals. From the viewpoint of the computational modeller it would be desirable to have more quantitative statements on the number of axons, their length and diameter, as well as the size of the connected brain structures to be able to constrain models in more detail and to test specific hypotheses of area interactions. For the purpose of interindividual and cross-species comparisons the time consuming and technically demanding process of three-dimensional registration of tracing data including the course of the fibre pathways will be essential. In this context, the validation of diffusion-weighted imaging (dMRI) data on the macaque brain against the battery of tracing data contained in a connectivity database, such as CoCoMac, could lead to a much better understanding of the conclusions that can be drawn from these convenient and non-invasive imaging methods. Finally, the spatial comparison of connectivity data with a wealth of other structural as well as functional data (as started with the CARET software) will open up rational ways of addressing questions of brain structure-function relationships. Already at the current level of detail connectivity databases provide for far more systematic and exhaustive ways of specifying the anatomical basis of functional activations than the apparently haphazard references commonly encountered in the specification of anatomical models for Structural Equation Modelling.

Given the conceptual importance of connectivity data it is likely that more accurate data and better tools will soon be created to register spatially and to compare connectivity data, and that connectivity data can be displayed, analyzed, and integrated with other data modalities using a variety of add-on tools and compatible software. Particularly promising fields include the systematic selection of connectivity data for the construction of descriptive and mechanistic models that will help to explain the spatial and temporal properties of large-scale activation patterns in the brain.

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Figure legends

Figure 1. Main menu of the online database after login (left) and Literature output list (right) for data collated from the two companion papers by Lewis & Van Essen (2000a, b). The two papers were retrieved using keywords, and the display options selected include details of brain sites, methods, injections and labelled sites.

Figure 2. Mapping output list after a manual search for mappings of area 7 in the map of Brodmann in 1909 to the map specified by von Bonin & Bailey in 1947. According to Pandya et al. (1981) Brodmann's area 7 is identical with von Bonin & Bailey's area PG, whereas Preuss & Goldman-Rakic (1991) regard Brodmann's area 7 to consist of areas von Bonin & Bailey's areas PG and PF.

Figure 3. Connectivity output list after URLsearch for existing connections from Olszewski's mediodorsal thalamic nucleus. Only the first 20 of 75 items are shown.

Figure 4. Snipped of the XML output from the CoCoMac online interface following retrieval of all connectivity data between the areas listed by Felleman & Van Essen (1991). This particular piece of output specifies a projection from area V2 to area V1 with a specific laminar pattern of origin (weak from layer 3 and strong from layer 6) (Rockland & Van Hoesen, 1994).

Figure 5. View of the Catacomb Workbench after loading the pre-configured components for retrieving connectivity data for the map by Felleman & Van Essen, 1991 using the files available from http://www.cocomac.org/catacomb.

Figure 6. Display of projections in the Connectivity Viewer of the Catacomb Workspace. Data are shown only for the light green set of selected areas that includes primary visual cortex (V1), the middle temporal area (MT), several intraparietal areas (PIP, VIP, LIP), inferotemporal areas TH and TF, as well as dorsolateral prefrontal area 46. Dark green fields identify non-selected areas with connection data attached but not shown. The grey-olive colour marks areas presented in the scheme by Felleman & Van Essen (1991) but not used to display connectivity data. Existing connections are shown in light grey, absent connections in dark blue. The orange projection from LIP to V1 is specified to be of medium strength. Note the absence of direct projections from V1 to area 46 and the contradictory data on the presence (Rockland & Van Hoesen, 1994) or absence (Felleman & Van Essen, 1991, Table 3) of projections from TH and TF to V1.