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Original Article

Integrating Databases and Expert Systems for the Analysis of Brain Structures

Connections, Similarities, and Homologies

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Abstract

The NeuroHomology Database system (NHDB) combines databases related to brain structures from different species with different knowledge management systems (KMSs) for systematization, evaluation and processing neurobiological data. Special attention is assessment of similarity of data from different species as a basis for exploring *neural homologies*. NHDB includes modules that handle brain structure and connectivity data, as well as inference engines for evaluation of the stored neurobiological information. The *spatial inference engine* evaluates the possible topological relations between cortical structures in different neuroanatomical atlases. The *connectivity inference engine* evaluates the reliability of information pertaining to fiber tracts as those are reflected in the literature. The *inference engine for translation of neuroanatomical connections* in different atlases evaluates the probability of existence of connections of interest in different parcellation schemes. Finally, the *similarity inference engine* calculates the overall degree of similarity of pairs of brain structures from different species by taking into account a set of eight criteria. We present examples of search for information in NHDB system, inferences of relations between cortical structures from equivalent neuroanatomical atlases, reconstruction of functional networks of brain structures from data collated from the literature, translation of connectivity matrices in equivalent parcellation schemes, and evaluations of similarities of brain structures from humans, macaques and rats.

Index Entries: Online database systems; inference engine; knowledge management systems; brain similarities; homology; hodology.

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Introduction

To address the problem of heterogeneity of information within and across different levels of the organization of the nervous system (Arbib and Bischoff-Grethe, 2001; Burns, 2001a), we designed the NeuroHomology Database system (NHDB) to combine databases related to brain structures from different species with knowledge management systems (KMSs) for systematization, evaluation and processing the neurobiological information, including assessment of *neural similarities*, in part as a basis for exploring neural homologies. In addition, NHDB includes modules that handle brain structure and connectivity data, as well as inference engines for evaluation of the stored neurobiological information.

- The *spatial inference engine* evaluates the possible topological relations between cortical structures in different neuroanatomical atlases.
- The *connectivity inference engine* evaluates the reliability of information in the literature pertaining to fiber tracts.
- The *inference engine for translation of neuroanatomical connections* in different atlases evaluates the probability of existence of connections of interest in different parcellation schemes.
- The *similarity inference engine* calculates the overall degree of similarity of pairs of brain structures from different species by taking 8 criteria into account.

The inference engines for evaluation of connectivity information and for computation of the overall degree of similarity can be customized by users according to their expertise. Here we describe the main aspects of each inference engine and provide a series of examples of the type of information and relations which can be extracted through their use. NHDB system can be used to retrieve brain structures and fiber tracts reports as collated from the literature. NHDB also can be used for evaluation of the strengths of neuroanatomical connections as reported by different authors, reconstruction of connectivity matrices of structures of interest, translation of connectivity information in equivalent parcellation schemes, and for evaluation of neural similarities between brain structures in different species.

We briefly present NHDB user interfaces in the context of the functionality of each of the inference engines. The description and the functionality of these inference engines and NHDB web interface are described elsewhere (Bota, 2001, Bota and Arbib, 2002).

NHDB has, at present, two online, fully searchable versions: NHDB-I and NHDB-II.

- NHDB-I system is designed in Microsoft Access and uses the WebMerger CGI parser engine as a web interface and can be accessed at the URL: http://brancusi.usc.edu/scripts/webmerger.exe?/database/homologies-main.html
  both for search of neurobiological information and for insertion of new data.
- NHDB-II system is designed in Informix 4.0 and uses the Illustra parser engine as a web interface. It can be accessed at the URL: http://java.usc.edu/neurohomologies/apb/webdriver?MIval=homologies-main.html.

NHDB-I contains a knowledge base that allows the insertion of neurobiological data from the cellular to the structural level of the nervous system and has inference engines for evaluating the reliability of the connectivity information and for evaluating the similarity of brain structures from different species. In what follows, we will use NHDB-I or NHDB-II when we refer to properties of a specific implementation, and NHDB alone when we refer to general properties of the database and inference engine design. NHDB-I currently contains information on brain structures, neuroanatomical connections, and similarities between brain structures from three species (genera): humans, macaques, and rats. These data were collated

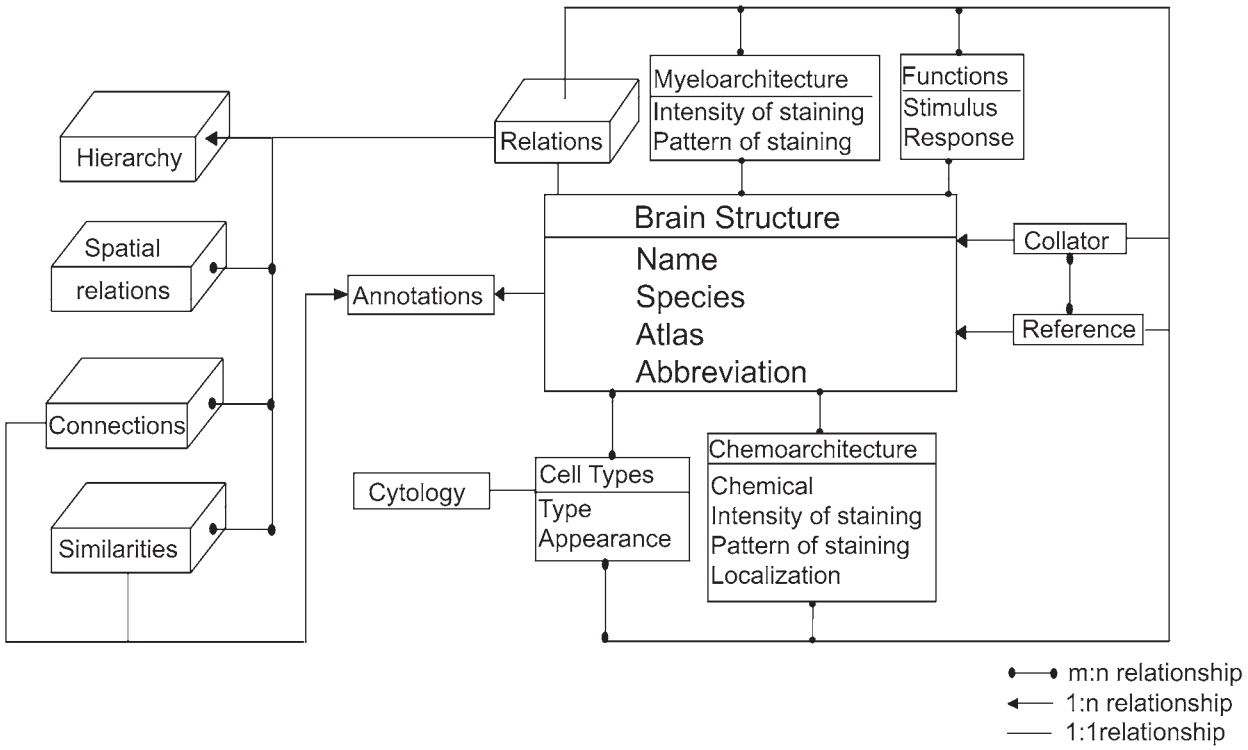


Fig. 1. The object-relationship schema of the main parts of NHDB. The object "Brain Structure" uniquely defined by the attributes "Name," "Species," and "Atlas" is associated in NHDB to five submodules: "Cell Types," including "Cytology," "Chemoarchitecture," "Myeloarchitecture," "Functions," and "Relations." Each of these submodules is described in detail in the Materials and Methods part of this paper. The objects "Collator" and "Reference" are modeled in 1:n relationships with "Brain Structure" since the attribute "Atlas" refers to a single reference and a brain region record associated to an atlas can be inserted by a single collator. Details about the structures of the objects "Collator" and "Reference" are provided in Materials and Methods. Each record of brain structures, connections or similarities can be associated to many annotations (1:n relationship) inserted by collators.

from more than 100 references from which we extracted more than 150 reports of brain structures in different parcellation schemes, more than 1200 reports of neuroanatomical connections, and about 100 established similarities between brain structures from rats, macaques, and humans. NHDB-II contains about 300 reports of brain regions and more than 800 topological relations established between brain structures in different neuroanatomical atlases for macaques and rats as well as several reports of cell types.

The General Structure of NHDB

Data in the system are grouped in three major classes: bibliographical data, experiment-related data, and results of running the inference engines. Data in the first two classes are inserted or interpreted by collators from the inspected literature. Each such datum is supported by citations from the associated references.

The structure of NHDB is centered on the object "Brain Structure." A part of the brain can be described according to a number of cri-

Table 1. The Main Components of NHDB and Their Information Content

Brain Structure	information about brain structures as collated from the literature
Cytology	information about the cell types that are found in different brain nuclei
Chemoarchitecture	information about the chemicals associated with specific brain nuclei
Myeloarchitecture	information about the myeloarchitectural organization of the associated brain nuclei
Functions	information about functions of brain structures
Annotations	parts of text describing brain structures in associated references, or comments inserted by users
Collator	information about the individuals who are allowed to insert data in the public part of NHDB
Name	the name of the collator
Address	the email and the surface addresses of the collator
Organization	the institution to which the collator belongs
Reference	
Journal	basic information on journal articles
Books	basic information on books
Book Chapter	basic information on book chapters
PhD Thesis	basic information on PhD theses
MSc Thesis	basic information on MSc Theses
Conference	basic information on a reference published in a conference proceedings
Unpublished	basic information on a reference which was not published in one of the above categories at the time of collation
Collator inference	information which is inferred from one or more references. It is specific to the Homologies module
Hierarchy	establishes relations between brain structures in the same species and neuroanatomical atlas, organizing those in trees of superstructures and substructures
Spatial relations	contains the inference engine for relating brain structure from the same species and the same or different neuroanatomical atlases, based on qualitative spatial relations
Connectivity	evaluates relations between brain structures in the same species and parcellation scheme, defined by neuroanatomical tracts
Similarities	evaluates the similarity relations between brain structures from different species as found or inferred from literature

Components in italics are described in this article.

teria: superficial features, relative or absolute position, cytoarchitectonics, myelo- or chemoarchitecture, hodology (the specific patterns of afferent and efferent connections), or functionality. In NHDB, a recorded brain structure is uniquely defined by its name, species that was investigated, and the neuroanatomical atlas used to identify it. Only the combination of all three attributes assures the uniqueness of any report on a brain structure. The neurobiological information which is collated from the literature is stored in NHDB in a set of tables which are linked by relationships of types 1:1, 1:n, or m:n.

The object-relationship schema (OR) schema of the Brain Structures part of NHDB is presented in Fig. 1. Each of the objects and relations shown in the figure is usually captured in more than a single table. The list of the main components of NHDB system is provided in Table 1. In the following sections we will describe the main components of the NHDB system. The purpose of the Similarities component is to evaluate the similarity between brain structures from different species. Since there are multiple criteria of similarity, similarity is a matter of degree, rather than a binary relation. As is well-known, brain regions may be similar because of their shared relation to a brain region of a shared ancestral form (homology) or through a process of convergent evolution (homoplasy). The reader new to these distinctions may consult the subheading "Similarities: Homologies, and Homoplasy." The bottom line is that similar regions may be more or less homologous. Nonetheless, the search for homologies is a major motivation for NHDB, and is the reason for calling it the *NeuroHomology Database*. However, understanding the similarity of brain regions is important for neuroscience even when regions are not homologous since these similarities may provide data crucial for generalization of computational modeling across regions and species.

Similarities: Homologies and Homoplasies

The concept of homology is central in comparative biology. It expresses the existence of typical and specific correspondences between parts of members of natural groups of living organisms (Nieuwenhuys, 1998). The term was first introduced by Owen in 1849, who defined a *homolog* as "the same organ in different animals under every variety of form and function" (Butler and Hodos, 1996). This definition was given before Darwin's theory of evolution, and thus the modern concept of homology was changed by evolutionary biology and genetics (Butler and Hodos, 1996). Accordingly, the concept of *homology* was defined in terms of "continuity of information," inheritance of features from a common ancestry, or phyletic continuity. The advent of cladistics helped in distinguishing homologous from homoplasic structures (i.e., those structures that present a high degree of resemblance but do not share a common ancestor) (Wake, 1994; Kaas, 2002). Examples of cladograms of different parts of the vertebrate brain that have been offered by a series of authors are: the visual system and the somatosensory system across mammals (Kaas, 1995; Krubitzer and Kaas, 1993; Northcutt and Kaas, 1995; Krubitzer, 1995), the basal ganglia across vertebrates (Reiner et al., 1998; Medina and Reiner, 1995), the dorsal pallium of aminotes (Butler, 1994a), and the dorsal thalamus of jawed vertebrates (Butler, 1994b).

The study of homologies at the neural level poses further difficulties because the comparison of feature can be performed across different levels of organization of the central nervous system and also because of the lack of data characteristic to extinct species. While the general criteria for establishing neural homologies were laid out by Campbell and Hodos (1991), there is no general consensus

over the relative importance of each of the comparison criteria.

Thus, while the search for homologies is a primary motivation for NHDB, we stress that when the *similarity inference engine* calculates the overall degree of similarity of pairs of brain structures from different species, a high degree of similarity is no guarantee of homology. On the other hand, those who seek to understand the brain and its evolution should realize that homology itself is not usefully treated as a binary concept except at the grossest level, such as identifying visual cortex across mammalian species. The key to evolution is *change*, and a structure in an ancestral species may be duplicated in more recent species, and these duplicates may have adapted in subtle or dramatic ways to the ecological niches of the new species. Thus, even if genetic analysis were to establish that two brain regions were homologous in that they were related to a common ancestral form—and future "editions" of NHDB must certainly incorporate such data—it would still be important to have access to a measure of similarity such as that computed by NHDB which, drawing our attention to data associated with lowering the degree of similarity, would constrain too facile an assumption that homology guarantees similarity across all criteria. Indeed, from the perspective of computational and comparative neuroscience, declared homologies may be the start, rather than the end, of the search for similarities that will guide the understanding of brain mechanisms across diverse species.

Materials and Methods

Brain Structures

Each brain region in NHDB is captured in a unique "hierarchy path" which lists the volumetric brain parts which contain it (Bota and Arbib, 2001). The hierarchy path for each brain structure is established on the basis of the reference that describes it, or inferred on the basis of a commonly used frame of reference (i.e., neuroanatomical atlas). For example, the hierarchy path of the dorsal part of the lateral intraparietal area (LIPd) in the macaque cortex in NHDB-I, as inferred from the combination of the brain hierarchy provided by Bowden and Martin (1997) and the information collated from Lewis and Van Essen (2000b) is:

Brain/Forebrain/Telencephalon/Cerebral cortex/Parietal lobe/

Inferior parietal lobule/Intraparietal sulcus/LIP

The "Hierarchy" submodule has two components: the *hierarchy level* and the *hierarchy path*, where the hierarchy level is the number of structures in the hierarchy path. The hierarchy level can in principle take any positive integer value; however, we have set it to a maximal value of 16. Indeed, the smallest subdivisions of the rat central nervous system, those belonging to the lateral septum, have hierarchy level 11 (Swanson, 1992).

Annotations: Any brain structure may be associated with a set of annotations. We consider two types of annotations:

Clumps, i.e., an extract from the cited reference that refers directly to the object brain structure, or that supports any attribute of the brain structure.

Other annotations can be comments, or statements related to the associated brain structure. Annotations can be inserted by both collators and users of the database.

Whenever a record is retrieved from the database, the associated set of annotations can be inspected, too.

Collator and References: A collator can insert information related to many brain nuclei in the database, while information related to a single brain structure can be inserted by different collators. Similarly for references: information about a given brain structure can be found in different references

Table 2. The Set of Spatial and Morphological Characters Considered for Each of the Elements of a Cell Class Allowed in the Object-Relationship Schema of Cell Types in NHDB

Cell elements	*Cell*	*Apical*	*Basal*	*Oblique*	
Features	*body*	*dendrite*	*dendrite*	*dendrite*	*Axon*
More than one element	no	yes	yes	yes	no
Size	yes	no	no	no	no
Position in associated structure	yes	no	no	no	no
Length	no	yes	yes	yes	yes
Shape	yes	no	no	no	no
Thickness	no	yes	yes	yes	yes
Orientation	yes	yes	yes	yes	yes
Synapse	yes	yes	yes	yes	yes
Synapse type	yes	yes	yes	yes	yes
Spines	yes	yes	yes	yes	yes
Branches	no	yes	yes	yes	yes
Collaterals	no	no	no	no	yes
Target	no	no	no	no	yes
Type of target (inside or outside of the associated structure)	no	no	no	no	yes
Myelin	no	no	no	no	yes
Special character	yes	yes	yes	yes	yes
Plexus	no	no	no	no	yes

and a single report can contain data related to many brain structures. The classes of references supported in the database are "the usual"—articles, books, chapters of books, articles presented in conferences, Master's and PhD theses—as well as metadata or summaries inferred by the collator from more than one reference. An additional type of reference, "unpublished report," is specific to the personal profiles option and will be discussed in the following.

Chemoarchitecture, cell types (cytology), myeloarchitecture, and functionality are the attributes of a brain structure to which we now turn.

Chemoarchitecture and Myeloarchitecture

Chemoarchitecture refers to that set of chemicals which is specific to the brain structure. The properties of any chemoarchitectonical component are the intensity and pattern of staining, and its localization within the structure. The values that can be taken by the intensity of staining are qualitative: "none," "weak," "moderate," "strong," or "unknown." The patterns of staining and localization within the structure are extracted from the associated references. The myeloarchitecture of a given brain structure has as properties the intensity and pattern of staining of the myelinated axons within the structure of interest. The

intensity of staining can take the same values as for the chemoarchitecture and the possible values of pattern of staining are "radial," "transversal," "mixed," or "unknown."

Cell Types (Cytology)

We have designed a specific database structure to capture the characteristics of neural cells, as described in Golgi staining. The Nissl description of brain structures provides an insufficient description of neural cell classes and subclasses. We do however capture the Nissl description of cell types identified in brain regions in the associated basic descriptions in NHDB-II and as a similarity criterion in NHDB-I.

Our database schema for neural cell types is general enough to allow the insertion of information pertaining to any class or subclass of neurons, being based on those morphological characteristics which can be used to define a generic neural cell. Some morphological features of neural cells, such as the first or second order dendrites, were not considered. Nevertheless, the database schema allows coding of a wide range of spatial and morphological features and is readily extensible to meet further needs.

The database schema for a cell class allows the insertion of information related to a cell body, an axon and a variety of dendritic systems including apical, basal, and oblique dendritic systems. The features that have to be taken into account in order to describe the cell body, the dendritic system and the axon of a cell type are listed in Table 2.

Each of the morphological elements of the object "cell type" (i.e., the cell body, the axon and the dendritic systems) has the attribute "special character" which can include any distinctive feature of the morphological element. For example, the apical dendrite of the pyramidal cell in the mammalian neocortex has as special character the terminal tuft (Nieuwenhuys, 1998; Jones, 1990a,b; Jones and Hendry, 1990).

The possible values for any type of dendrite are "yes," no," not known" and the number of types of dendrites for each type of neural cell as described in the associated reference.

The object-relationship schema of the dendritic system does not address the classification of the dendrites in first-order, second-order, and third-order components, but considers the secondary and tertiary dendritic components as "branches."

The object-relationship schema of the axon makes the distinction between collaterals, branches and plexus. The collaterals are considered as the principal divergent components from the axon. Under the concept of "branches" we have considered all those higher order specializations that diverge from collaterals. The term "plexus" refers to the specific mode of termination of an axon.

Functionality

The attribute "Functions" of an object in "Brain Structures" refers to neurophysiological responses of its cellular components, or behavioral correlates of the brain nucleus. The functionality of a brain structure is given the fields "stimulus" and "response." By "stimulus" we refer to any type of employed perturbation (e.g., from neurophysiological stimulations of single neurons, to lesions, to temporary inactivation of brain structures by using local cooling techniques, to the action of specific drugs), and by "response" we refer to any type of change of activity recorded from the individual cells, or behavioral alterations due to lesions of brain structures.

Relationships of Brain Structures

The object "Brain Structures" can be found in three types of relationships: "Spatial Relations," "Connectivity," and "Similarities" (Fig. 1). Each of these relationships is repre-

Table 3. The Geographical Cardinal Directions as Used in the Geographical Information Systems (GIS) Framework and Their Counterparts Adopted in NHDB

Geographical cardinal direction	*Corresponding neuroanatomical direction in NHDB*
North	Rostral
Northeast	Rostro-medial
East	Medial
Southeast	Caudo-medial
South	Caudal
Southwest	Caudo-lateral
West	Lateral
Northwest	Rostro-lateral
Same	Same

Since the qualitative spatial reasoning implemented in NHDB is applied to 2D objects, the neuroanatomical directions ventral and dorsal are interpreted as lateral and medial, respectively.

sented by a knowledge base that contains the specific relations between brain structures and their associated properties, and an inference engine that evaluates new relations from the data contained in the knowledge base.

Spatial Relations Between Cortical Structures

"Spatial Relations" refers to the qualitative topological and directional relations between different brain structures in the same or different neuroanatomical atlases as found or inferred from the literature, or established from unrelated information by running the topological inference engine.

Different brain parcellation schemes have been provided by researchers for a number of mammalian species since the first complete cortical maps have been provided by Brodmann and Campbell in 1905. The existence of many maps for a single species can be a major source of confusion and debate for neuroanatomists and leads to problems of identification and assignment of different properties to specific brain regions.

Our spatial inference algorithm is applied for processing topological relations between cortical structures from different neuroanatomical atlases. Since the topological inference engine is accessible on the web and should therefore be able to process queries from multiple users in a short amount of time, we approximate cortical structures as 2D convex objects. Nevertheless, the topological inference algorithm can be adapted for concave 2D structures (Papadias and Sellis, 1994). The qualitative spatial relations are collated or interpreted from the inspected neuroanatomical atlases.

The algorithm is based on the eight possible topological relations between a pair of 2D objects defined by Egenhofer and Franzosa (1991):

$$U = \{d, m, o, cv, cvBy, co, isCo, i\}$$

namely, disjoint (d), meet (m), overlap (o), covers (cv), is covered by (cvBy), contains (co), is contained, or inside (isCo), and identical (i). Composition of topological relations need not yield an unequivocal answer (Egenhofer and Franzosa, 1991). Therefore, to reduce the number of possible topological outcomes, additional qualitative information should be used. We use the cardinal directions between two 2D objects as given by Papadias and Sellis

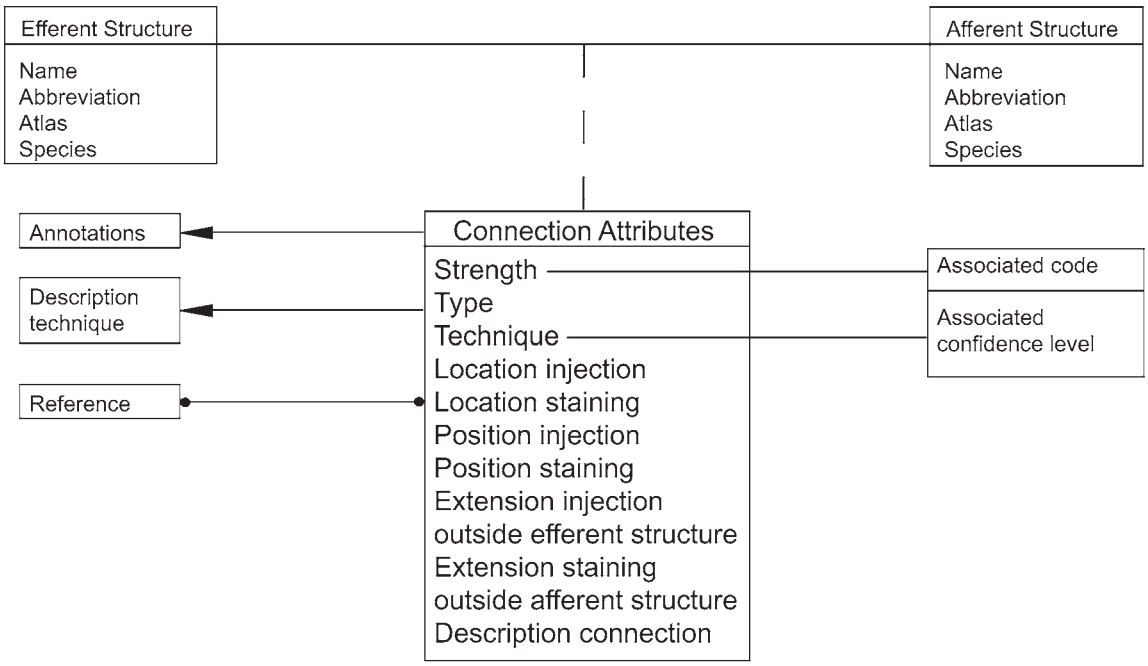


Fig. 2. The object-relationship schema of the Connections module of NHDB.

(1994) and Sharma (1996), namely

$$D_n = \{N, NE, E, SE, S, SW, W, NW, Same\}.$$

The eight cardinal directions are used whenever the two related objects are either in a "disjoint" or "meet" topological relation. The directional relation "Same" is applied whenever the related objects have a common interior. In order to apply the qualitative spatial reasoning to infer spatial relations between cortical structures, we have replaced the geographical cardinal directions with the relative directions used in neuroanatomy, as shown in Table 3. The general description of our algorithm to infer new topological relations by combining topological and directional data is provided in Appendix 1 (for the full description of the spatial algorithm, *see* Bota, 2001).

The knowledge base associated with "Spatial Relations" stores topological and directional relations between brain structures as found or inferred from the associated references, as well as new directional relations found by running the spatial inference engine. The spatial relations between two cortical structures are inferred only once, namely when the query for establishing these is run for the first time. The result is recorded in the knowledge base of "Spatial Relations" and is retrieved whenever identical queries are run by users. We also allow the inferred spatial relations to be changed by collators whenever more precise information is found in the inspected literature. Thus, collators can update any inferred topological information that exists in the knowledge base of NHDB. In this situation, all those relations which have been inferred on the basis of the previous update are deleted from the system and new queries have to be run.

Connectivity Issues

The neuroanatomical connections inserted in NHDB are relations between pairs of brain structures in the knowledge base. The object-relationship schema of the NHDB

Table 4. The Proposed Values of the Connections Confidence Levels as Reflected From the Literature and Encoded in NHDB

Expression used to describe a connection and found in the associated reference	*Interpretation in NHDB*	*Associated confidence level*
"contrary to previous reports, we did not find connection Y"	not found	–1
"no connection was found between structures X and Y"	none	0
"light," "sparse" connection	light	1
connection "X is stronger than Y" and Y "is light"	light/medium	2
"the labeling is moderate"	medium	3
"X is stronger than Y" and X "is moderate"	medium/strong	4
"strong labeling," "strong connection"	strong connection	5
"very strong labeling," "very strong connection," or "X is stronger than Y" and X "is strong"	very strong connection	6

"Connections" module is shown in Fig. 2. "Connection strength" refers to the density of staining of a neuroanatomical connection. The method of assignment of the associated connection confidence level is an adaptation of the approach used in the NeuroScholar database (Burns, 1997). We allow the connection confidence level to take any integer value between –1 and 6, with the assignment of a specific value to the strength of a connection as summarized in Table 4.

Connection type: the major neurotransmitter (dopaminergic, cholinergic) or functionality (inhibitory, excitatory), as described in the inspected reference. The set of neurotransmitters which is specific to a given neuroanatomical projection can be stored in the chemoarchitecture part of NHDB.

Technique: the specific tract-tracing method used to reveal the neuroanatomical connection. As was the case for strength of connection, we associate a confidence level with each of the techniques that was used to investigate a given connection. The assignment of a confidence level to each technique takes into account the relative advantages and limitations of each of the tract-tracing methods used by neuroanatomists to reveal connections between brain structures (Bota and Arbib, 2001; Bota, 2001).

Location injection/staining site: the topological positions of the injection site and of the terminal field, respectively, in the related brain nuclei.

Position injection/staining: code for the relative sizes of the injection site and of the terminal field within the associated structures. The allowed values of these attributes are "small," "moderate," "big," and "not reported."

Extension injection/staining: Information about the extension of the injection site and of the terminal field outside the associated structures. The allowed values of these attributes are "none," "small," "moderate," "big," and "not reported."

The attributes **Description technique** and **Description connection** allow the collator to insert information related to the specific protocol which was used and to the revealed neuroanatomical tract.

The knowledge base of the Connections module of NHDB is augmented with two

inference engines for processing the information inserted in it.

Inference Engine for Evaluating the Reliability of Information Regarding the Strength of a Connection

The inference engine we describe in this subheading aims to address the problem of contradictory results of tract tracing experiments. The sources of contradictory results of tract tracing experiments are the relative advantages of the techniques which were employed and in the spatial features of the injection site: the size of the injection relative to the target area and the extension of the injection outside the borders of the target region. Thus, the evaluation of connection confidence level (CCL) is a function of the density of labeling assessed by the authors of the collated references, the technique confidence level, the size of the injection in the brain region of interest, and the extension of the injection outside of the injection site. For each of the three variables that determine CCL we assess distributions of "votes" or weights over the set of the possible strengths. For simplicity reasons the first two connection strength codes shown in Table 4 are considered identical. The connection confidence level, the size of the injection and the extension of injections outside of the target area are considered independent. The evaluated strength of a connection for a single report is assessed as the product of these three variables:

$$V(CCL=c)=V(c/T=t)V(c/S=s)\times V(c/O=o) \quad \text{[Eq. 1]}$$

The weight of CCL to take the value c is the product of the confidence level of the technique t to reveal a projection with the strength c, the weight of c to be obtained when the injection has the size s, and the weight of c when the extension of the injection outside of the target region is o. The sum of votes over the set of all possible strengths for any value of T, S, or O is equal to 1.The value of CCL is determined by the maximal number of votes or weights over the set of possible strengths. If the set of connection strengths has more than one value with the maximal weight, then the inference engine assesses the highest value as CCL.

If there are more reports associated to a given projection, then the connectivity inference engine evaluates CCL as the maximal sum of the votes over the set of possible strengths.

We describe now the assumed distributions of weights for each of the variables that determine the CCL over a set of tract tracing reports.

In order to evaluate the technique confidence level, we investigated the advantages and the limitations for each commonly used tract-tracing technique in neuroanatomy: The details of tract-tracing techniques (Skirboll et al., 1989; Sawchenko et al., 1990; Gerfen and Sawchenko; 1984, Sawchenko and Swanson, 1981; Llewellyn-Smith et al; 1992; Smith, 1992) which were considered when evaluating the technique confidence levels were:

the mechanism of incorporation of chemicals by neurons,

the trans-synaptic labeling,

the labeling of damaged or intact fibers of passage,

the difficulty of evaluation of the number of labeled cells.

Table 5 summarizes the default values of the confidence levels associated with each of the considered tract tracing techniques. The procedure of assignment of technique confidence levels over the set of strengths follows the analysis of tract tracing data presented in Bota et al. (2003) and takes into account the possible overstaining that can be elicited when using a specific tract-tracing technique. Formally, the distribution of V(c/T) over the set of possible strengths is

Table 5. The List of Some of the Techniques Used in Neuroanatomical Experiments and Encoded in NHDB

Technique	*Interpretation in NHDB*	*Default confidence level*
degeneration study	degeneration	0.15
any radioactive tracer	radioactive tracer	0.3
not specified	N/A	0.3
horseradish peroxidase	HRP	0.5
HRP enhanced with WGA or WGA-CBT	HRP-WGA; WGA-CBT	0.7
the above category associated to gold	HRP-WGA/gold; WGA-CBT/gold	0.8
any retrograde fluorescent tracer	retrograde tracer	0.8
the above category associated to Phaseolus vulgaris leucoagglutinin (PHAL)	retrograde tracer/PHAL	0.9
PHAL	PHAL	0.9

$$V(x \mid c, T) = \begin{cases} t & \text{if } x = c \\ \dfrac{1-t}{3} & \text{if } x = c-1 \text{ or } x = c-2 \\ \dfrac{1-t}{12} & \text{otherwise} \end{cases}$$

where c is the strength reported in the associated reference, t is the technique confidence level as represented in Table 5 and employed in the associated references and c–1 and c–2 represent the next two lower possible strengths. If no connection is reported between two brain regions, then this may be interpreted that the employed technique is not sensitive enough to reveal the existing projection and the distribution shown in Eq. 2 is changed only towards higher possible strengths.

Thus, if a given paper reports a strong connection between two regions and the technique which was used is HRP, then the connectivity inference engine assigns the probability of 0.5 for "strong," probability of 0.16 for "moderate/strong" and "moderate," respectively, and 0.04 for the remaining strength possibilities.

For example, if a paper reports a moderate projection between two brain regions and the employed technique consisted of radioactive amino acids, then the distribution of the V(x/c, T) over the set of possible strengths, calculated according to Eq. 2 is shown in Table 6. If the employed technique does not have a high confidence level, the next two lower strengths have the weights close to that assigned to the reported strength and therefore a lighter projection than reported is possible.

The reported strength of a neuroanatomical connection may be determined by the size of the injection in the brain region of interest. A neural connection between two regions which is reported to be a weak in a given reference, may have a different strength reported in another paper, even though the same tract tracing technique was employed, but the sizes of injection sizes differ. The distribution of V(c/S) over the set of possible strengths assigns values for each of those in such a way that stronger connections than reported are

Table 6. The Technique Weights Assigned by the Connectivity Inference Engine for Staining With Radioactive Amino Acids

Strength	*None*	*Light*	*Light/ Medium*	*Medium*	*Medium/ Strong*	*Strong*	*Very Strong*
V(x/c, T)	0.06	0.23	0.23	0.3	0.06	0.06	0.06

more likely for small injections and the reported strength has a higher weight for moderate and big sizes of the marker injection in the region of interest. As for the assignment of technique weights distribution, the next two higher connections than the reported one will have a higher weight assigned.

Table 7 summarizes the proposed distribution V(c/S). If the injection size is not specified in the associated report then all the possible strengths will be assigned the same probability equal to 1/7. If the reported connection is very strong then the assigned weight to this value will be 0.9 and the other possible strengths will have an equal weight of 0.1/6.

The reported strength of a neuroanatomical projection may also be determined by the size of injection outside of the region of interest. If a big portion of the injection is found outside of the target structure, then the actual connection may be weaker than the reported one, since the neurons from the neighboring structures may participate to it. Thus, whenever a connectivity report is associated to a big extension of the injection outside the border of area of interest, those strengths which are lighter than the reported one are more likely because of the contamination of the neighboring areas.

Table 8 summarizes the distribution V(c/O) proposed by us. If the extension of injection outside of the target structures is not specified in the associated report then all the possible strengths will have assigned the same probability and equal to 1/7. If no connection is reported between two brain regions then the probability assigned to this value will be 0.9 and the other possible strengths will be an equal probability of 0.1/6.

Inference Engine for Translating Connectivity Information Between Parcellation Schemes to Different Neuroanatomical Atlases

The inference algorithm for translation of connectivity data between parcellation schemes in different neuroanatomical atlases is based on the spatial inference reasoning presented in Appendix 2. This inference algorithm evaluates the indices of translation of the injection site and of the terminal field (IT_I or IT_T) of any tract tracing experiment in the target structures from the new parcellation scheme.

Based on these indices, the inference engine computes the probability of translation of the connections in the new atlas B, for a given pair of structures Z and W, found in it. We adapt here a probabilistic approach of translating tract tracing experiments in different parcellation schemes because the implemented qualitative inference algorithm does not always yield unequivocal results. Therefore, the result of the qualitative inference engine may be a set of topological relations, all considered equally possible.

Any neuroanatomical connection found in a given parcellation scheme and translated in a second cortical map will preserve its original strength only when both degrees of translation are equal to one. Otherwise, the confidence level of the translated connection will be smaller than one, meaning that it is possible that other cortical structures which are adjacent to the structures Z and W in parcellation B may participate in it.

Table 7. The Proposed Distribution of Weights Over the Set of Strengths for the Injection size V(c/S)

Possible Strengths *Injection size*	*c*	*c+1*	*c+2*	*Remaining strengths*
small	0.1	0.45	0.25	0.2/4
moderate	0.3	0.3	0.2	0.2/4
big	0.65	0.15	0.2/5	0.2/5

Degrees of Similarity

The relationship "Similarities" shown in Fig. 1 is not directly based on genetic or other data relevant to establishing an evolutionary relationship of brain structures. Thus (recall "Similarities: Homologies and Homoplasies") the algorithm for comparison of neural characters across species does not establish homologies between different brain regions, but does provide a general assessment of the similarity of a pair of brain regions based on the available information. Our evaluation of the similarities between two brain structures from different species takes into account eight different criteria: relative position, cell types (cytoarchitecture), chemoarchitecture, afferent and efferent connections, myeloarchitecture, functionality, and superficial appearance. The inference engine for evaluating the "similarities" of brain regions does not return a binary "yes" or "no" to the question "Are these two brain structures from different species similar?" but instead takes the data available on these eight criteria for the two brain structures and returns a measure of similarity which we call the degree of similarity between the brain structures.

The object-relationship schema of the "Similarity" part of NHDB is shown in Fig. 3. Each of the criteria is associated to specific attributes that are recorded in the knowledge-base of NHDB, as shown in Fig. 3. To compute the overall degree of similarity (ODS) between a pair of brain structures from two different species, we first compute an index of similarity (IS) for each of the considered criteria.

The IS for relative position, afferent and efferent connections, chemoarchitecture and cytoarchitecture are smooth functions of the common characteristics and take values between 0 and 1. The indices of similarity for gross appearance, myeloarchitecture and functionality are considered as taking a fixed value if there is information pertaining to them, otherwise are zero. We have set the default value for any of these indices of similarity to 1. Nevertheless, users are allowed to customize the similarity inference engine by changing the values of any of these indices, from zero to one, increment of 0.25.

The general formula for evaluation of IS with respect to relative position, hodology, chemoarchitecture and cytoarchitecture uses a sigmoid function a s given in equation 3:

$$IS = \frac{2}{1+\exp(-\alpha * f(N)/N_t)} - 1 \qquad (3)$$

where f(N) is a function of the number of common characters for each of the considered criterion and recorded in the knowledge base of NHDB, N_t is the maximal number of possible common features for each of the considered criteria and α is a parameter for adjusting the slope of the sigmoid. Whenever the number of common characters is zero then f(N)=0, and the index of similarity will be equal to zero. Conversely, if f(N)= N_t the exponential will tend to zero and IS will be equal to one.

The general formula for f(N) for any of the similarity criteria that are smooth functions of the related characters, is given by equation 4:

Table 8. The Proposed Distribution of Weights Over the Set of Strengths for the Contamination Size V(c/O)

Possible Strengths *Injection sizes*	*c*	*c–1*	*c–2*	*Remaining strengths*
none	0.9	0.1/6	0.1/6	0.1/6
small	0.55	0.25	0.2/5	0.2/5
moderate	0.25	0.25	0.25	0.25/4
big	0.15	0.30	0.30	0.15/4

$$f(N) = \sum_{i=1}^{n} a_i * c_i \quad (4)$$

where a_i is a parameter associated to the type of common characters, as reflected from the investigated literature and inserted in the knowledge base of NHDB, c_i is the i^{th} common character, and n is the number of the common characters retrieved from NHDB and related to the evaluated similarity criterion. The parameter a_i can take values between zero and one and depends both on the type of common characters and on the accuracy of the related information. The dependence of a_i on the type of common characters is specific to each of the considered criteria and the accuracy of information is related to the comparison of the common patterns of afferent and efferent connections of the compared brain structures. The most complex computation of the parameter a_i is for evaluation of the IS for common afferent and efferent connections. In this case, a_i is a function of the types of the compared neuroanatomical projections, and of the degrees of similarity of the compared structures, computed independent of the compared connections. The full discussion of the proposed formalism for evaluating the parameters a_i depending on the type of the associated similarity criterion is presented in Bota (2001). A further important aspect of the evaluation of the degree of similarity between brain structures from different species is related to the problem of *recursion*, namely that the degrees of similarity for relative position and hodology depend not only on the number of common neighbors or afferent, or efferent structures, respectively, but also on how similar the related nuclei have been judged to be—and vice versa. If there is no related information in the knowledge base of NHDB, the computation of IS associated to each of these criteria will depend on a bias parameter which represents an *a priori* evaluation of how similar are the related structures, spatially and/or by neuroanatomical fiber tracts.

A source for the bias parameters is given by the phylogenetic trees constructed by using different set of characters. In this sense, we propose that the bias is computed as an inverse function of the number of nodes on the phylogenetic tree that separate the two compared species. The phylogenetic tree we used to calculate the bias is a composite of those provided by Purvis (1995), Carroll (1988), Johnson et al. (1994), and Kirsch and Johnson (1983). Thus, whenever there is no information associated to the sets of structures which are related spatially or by neuroanatomical connections with the compared brain structures, we use the bias as a prior degree of similarity to calculate the IS for criteria of relative position and hodology. For example, if one wants to compare a pair of brain regions in the macaque and rat, then the prior is evaluated between the genus Macaca and the subfamily Murinae. Otherwise, we use the degrees of similarities between each of the pairs of brain structures from the related

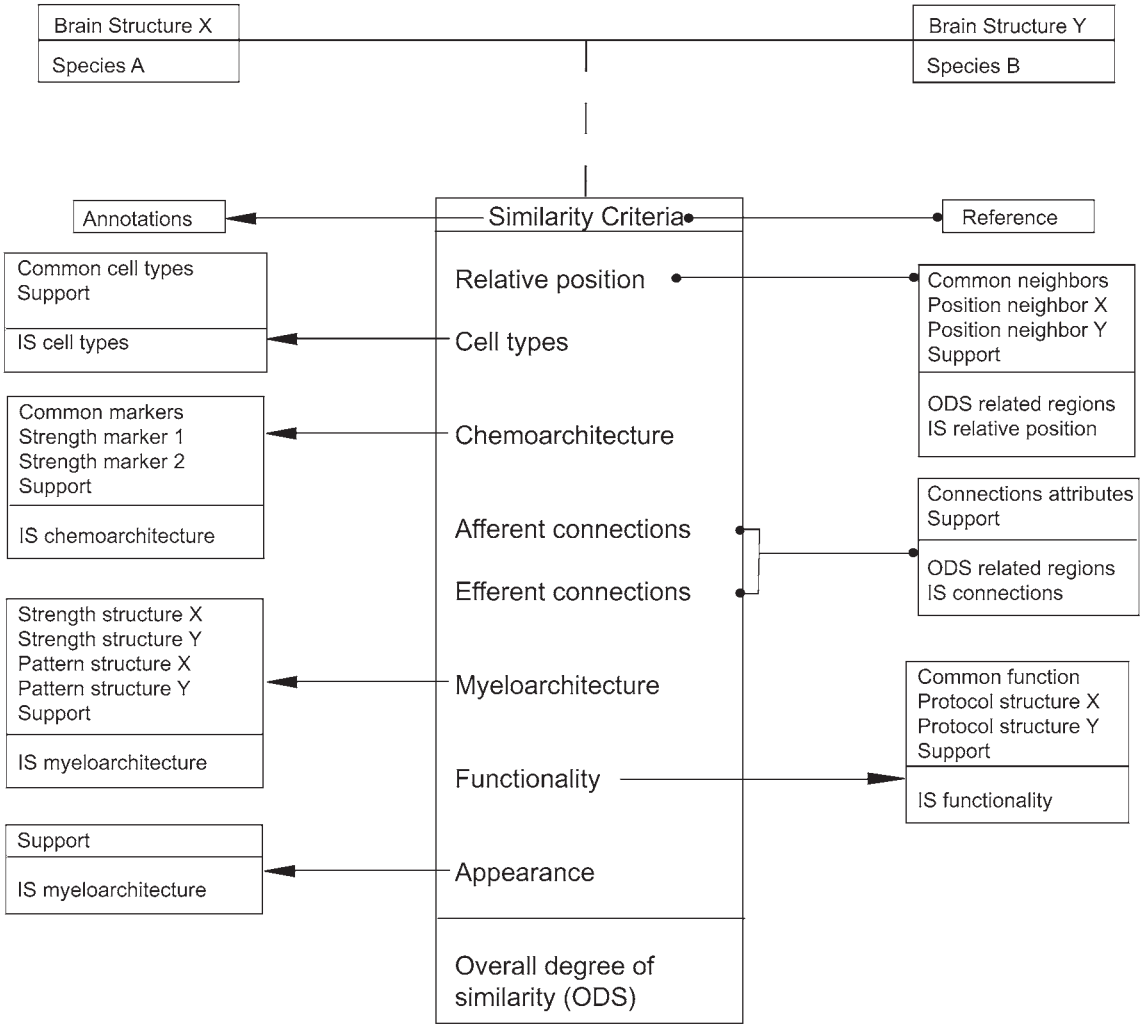


Fig. 3. The object-relationship schema of the Similarities module of NHDB.

sets, which were previously calculated by using the knowledge inserted in NHDB.

Results

As noted in the Introduction, NHDB has at present two online, fully searchable versions, NHDB-I and NHDB-II. NHDB-I contains a knowledge base of neurobiological data from the cellular to the structural level of the nervous system, the inference engine for evaluating the reliability of the connectivity information, and the similarity inference engine. Despite its capabilities, NHDB-I does not address the problem of translation of the neurobiological data in different parcellation schemes, nor does it contain a scheme for encoding the cellular level of the nervous system. NHDB-II contains the knowledge base for essential aspects of cytology of brain structures as well as inference engines for evaluation and for translation of connectivity information. Our goal is to transfer all the information currently in NHDB-I to NHDB-II. Meanwhile, each version contains links to the other.

In terms of the user interface, NHDB contains three interconnected modules, Brain

Data retrieved

All brain areas for species (genus) Human

Click on *ID* to see all the associated annotations
Click on *Hierarchy* to see the hierarchy path
Click on *Author* to see details
Click on *Collator* to see details

ID	Author	Name of brain structure	Species (strain)	Hierarchy	Description	Collator	Inserted on:
504	Bowden & Martin, 1995	Precentral sulcus	Human	4	Landmark structure of the lobe.	Mihail Bota	17 July 2000 12 38
493	Bowden & Martin, 1995	Inferior temporal sulcus	Human	4	A superficial structure within the temporal lobe.	Mihail Bota	2 July 2000 14 40
505	Bowden & Martin, 1995	Area 44	Human	5	This area occupies the pars opercularis of the inferior frontal gyrus, and it is thought to constitute the larger part of Broca's area.	Mihail Bota	17 July 2000 13 03

Fig, 4. A typical result of search in records of the Brain Structures Module of NHDB.

Structures, Connections, and Similarities, which can be accessed independently. We have designed the web interface in independent parts to allow queries from a larger category of users. A user who wants to find if there is any similarity between two structures X and Y from different species can also inspect the definitions of X and Y found in different sources, as well as the pattern of connectivity of these two structures.

The Brain Structures Module

Searches of the Brain Structures module can be extended or made more specific. One type of extended search can be made using a word or phrase from the description of entered brain structures. Another can be made by the name of an author of an article inserted in the database. The search of brain structures can be more specific, by using any combination of three possibilities of search: search by abbreviations of brain structures, by superstructure, and by species.

A typical result of a search performed in the Brain Structures module is shown in Fig. 4. Regarding the details of the neural cell types associated to brain structures and recorded in the knowledge base of NHDB, an example of result of search for pyramidal cells in area 8A in the macaque is shown in Fig. 5. The full description of the user interface of the Brain Structures module can be found in Bota (2001).

Relating Cortical Structures in Different Atlases

Whenever users access the records of brain structures, they can also inspect the possible topological relations established between the searched structures and other cortical regions by running the spatial inference engine, as exemplified in Fig. 6.

Moreover, the possible topological relations between cortical structures established by the topological inference engine can be used to construct graph representations of the spatial relationships between cortical structures of interest. An example of a graph representing the possible topological relations between six cortical structures of the macaque brain revealed in three different parcellation schemes in presented in Fig. 7.

The results presented in Figs. 6 and 7 were inferred using the topological and directional relations collated from the literature and inserted in NHDB and provided in Table 9. The remaining topological relations shown in Figs. 6 and 7 were inferred by running the topological inference engine.

Cell body details

Cell type	Found in layer	Soma shape	Soma size	Orientation soma	Has spines	Type of synapse	Has synapse
pyramidal	III	vertically elongated	big	vertical up	few	symmetric	moderate

Axon details

Cell type	Axon is myelinated	Direction	Thickness	Length	The target is	Target inside of area?	Special feature
pyramidal	yes	vertical down	moderate	long	not known	No	none

Axon changes direction	Second direction	Collaterals	Length collaterals	Direction collaterals	Thickness collaterals	Branches	Length branches	Direction branches	Plexus?	Plexus number	Size plexus
not known	none	few	short	vertical down	thin	few	short	vertical down	No	none	none

ID	Cell morphology	Collator	Reference	Inserted on:
76	Layer III contains small, medium and large neurons	Mihail Bota	Petrides & Pandya	06/20/2001
77	A typical pyramidal cell	Mihail Bota	Petrides & Pandya	06/20/2001

Fig. 5. Cell body and axon details of a pyramidal cell record associated with area 8A in the macaque (the retrieved records are shown in the inset), collated from Petrides and Pandya, 1999. User can also inspect online the information about the dendritic systems of the retrieved cell types (not shown in this figure).

The Neuroanatomical Connections Module

The Neuroanatomical Connections module can also be searched online in several different ways, from general to specific (i.e., by afferent or efferent structures and by species). A typical search result is shown in Fig. 8.

Evaluating Connectivity Reports From Literature

As shown in Fig. 8, users may not only inspect the details of each of the connectivity reports that are retrieved by queries, but also can evaluate online the connection confidence levels from the information retrieved from the knowledge base of NHDB. The connectivity inference engine evaluates CCL over all retrieved reports that are associated with the searched pair of structures, and the connection confidence level for each of the associated references. The example shown in Fig. 8 is the result of a search for connections between cortical areas LIPd and 7a in NHDB. The evaluated connection confidence level indicates that overall there is a strong connection between these two regions. However, the connection confidence levels evaluated for the references differ owing to differences in the employed techniques and the features of the injections performed in the structures of interest. The evaluated connection confidence level for the reports collated from Andersen et al. (1990) shows that the connection between LIP and 7a is a moderate-strong one, while that of reports collated from Lewis and Van Essen (2000a,b) shows a strong connection between these two regions. The difference in evaluations is related to differences in techniques and in the size of the injection outside of the region on interest: one report from Andersen et al. was interpreted as having an injection site with a big extension outside of the boundary of LIPd. As described in Materials and Methods, the algorithm for evaluation of CCL assigns a higher weight to weaker strengths when neighboring regions are also stained and the employed technique is prone to overstaining. Therefore, the algorithm for computing of CCL evaluates

Hierarchy tree: Forebrain/Telencephalon/Frontal Lobe

Related brain structures

Brain structure	Atlas	Relation with F4
F5	Matelli	meet
FBA	von Bonin	meet
FCBm	von Bonin	identical
4c	Barbas	overlap
6va	Barbas	disjoint
6vb	Barbas	disjoint
6Va	Goldman-Rakic	overlap
6Vb	Goldman-Rakic	overlap
4c	Vogt	overlap
PRCO	Goldman-Rakic	disjoint
6aav	Vogt	disjoint
6ba	Vogt	overlap

Name of brain structure (approximate): F4

Submit Reset

meet	overlap	is covered	is contained		
meet	overlap	is covered	is contained	identical	
covers	contains				
meet	overlap	is covered	is contained		
meet	overlap	is covered	is contained		
is covered	is contained	identical			

Fig. 6. A typical result of search in the Brain Structures module of NHDB. The search for information was performed by partial match of names of brain regions. The result of the query is shown in the inset. Users can access additional information, such as the established set of topological relations between the retrieved structure and other nuclei. Brain structures 6aav and 6ba atlas Vogt refer to the regions 6aav and 6ba, same parcellation scheme. See Table 9 for the collated topological and directional relations.

the projection reports according to the accuracy of experiments.

The inference engine for evaluation of tract-tracing reports can also be used for reconstruction of the connectivity matrices of structures of interest from the information in the NHDB knowledge base. An example of such a reconstruction of the pattern of connectivity of two cortical areas in the macaque posterior parietal cortex (PPC) is shown in Fig. 9.

The patterns of connectivity of areas 7a and 7b shown in Fig. 9 were reconstructed from 294 reports collated or inferred from the neuroanatomical literature. In this reconstruction, we were interested in the sensory inputs from the visual and somatosensory areas and outputs to the frontal/prefrontal cortices, cingulate areas and areas from the hippocampal formation, the projections from other structures of the macaque PPC to areas 7a and 7b, as well as visual and somatosensory inputs to the efferent areas of 7a and 7b from the PPC. The parcellation scheme used in our reconstruction was a composite one, obtained by combining alternative cortical maps. We evaluated the OCL for each of the connections between 7a or 7b and any of the afferent or efferent structures and we classified all the connections with OCL>1 in one of the following three categories: strong, medium/strong, and weak/medium connections.

The reconstructed patterns of connectivity of the areas 7a and 7b of the macaque PPC are in accord with the hypothesis of Lewis and Van Essen (2000b): the higher the degree of connectivity with the sensory areas, the high-

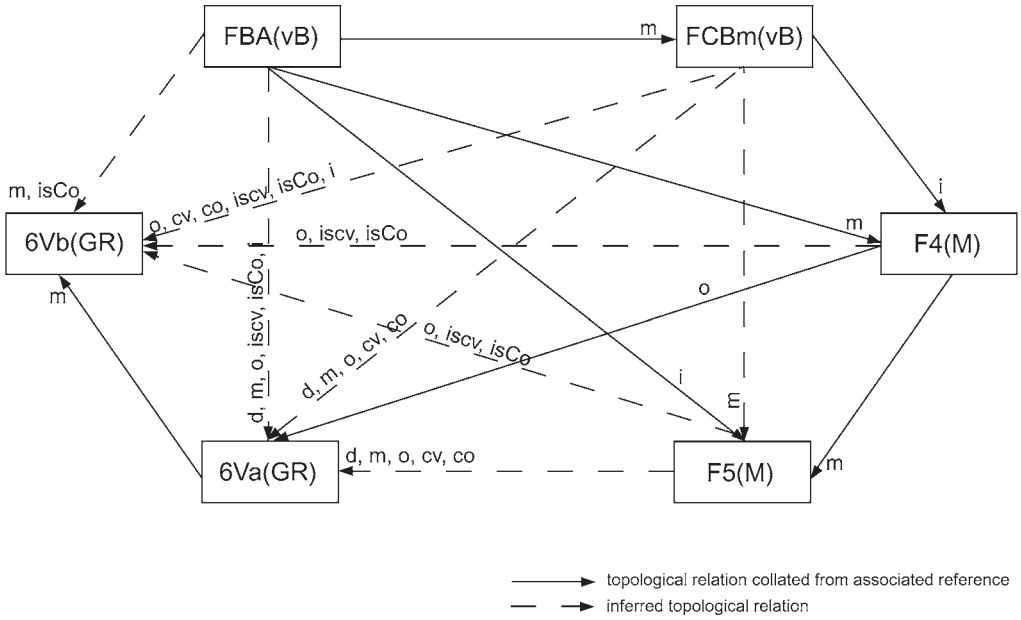


Fig. 7. The diagram of the inserted and inferred topological relationships between the areas that make up the macaque ventral premotor cortex in three parcellation schemes. In this example, six relations were inserted by the collator and the remaining relations were inferred by running the spatial inference engine, as well as the complementary relations between any pair of brain structures. *See* Table 9 for the collated topological and directional relations.

er the degree of connectivity with frontal and prefrontal areas. As shown in Fig. 9, area 7a receives visually related input from more areas than 7b and projects to more frontal/prefrontal areas. Further differences between the reconstructed patterns of connectivity of areas 7a and 7b are given by the projections toward the hippocampal cortices, cingulate cortices, and the afferents from other structures of the macaque PPC. Area 7a sends moderate/strong and weak/moderate projections to the entorhinal cortex, the CA1 field, parahippocampus, perirhinal cortex, and the parasubiculum, while area 7b does not send any major projections towards these cortical structures. As for the hippocampal and parahippocampal cortices, area 7a projects towards the cingulate regions while 7b does not present major outputs towards these areas. Regarding the afferent projections from other areas of the macaque PPC, our areas of interest, area 7a appears to receive major connections from all PPC structures, except area AIP, while the only major PPC input for area 7b is from area VIP.

One should mention that the patterns of connections shown in Fig. 9 may change whenever new evidence is inserted in the knowledge base of NHDB. As an example, new experiments may reveal connections from area 7b toward the hippocampal and parahippocampal cortices. Regarding those, Ding et al. (2000) report a light projection and no connections toward the presubiculum, parasubiculum, and entorhinal cortex. Since we took only the major projections into account in our reconstruction, the connection between 7b and the CA1 field of the hippocampus was not included in the reconstructed pattern of connectivity of 7b. Nevertheless, the interested user can inspect the complete pattern of connections of 7b

Table 9. The Collated Topological and Directional Relations of Cortical Areas That Make Up the Macaque Ventral Premotor Cortex and Defined in Different Parcellation Schemes

Related cortical regions	*Collated topological relation*	*Collated directional relation*
6Va(GR)→4c(B)	co	same
6Va(GR)→6Vb(GR)	m	medial
6Va(GR)→PrCO(GR)	d	medial
6Va(GR)→F4(M)	o	same
6Vb(GR)→PrCO(GR)	m	rostro-lateral
PrCO(GR)→4c(V)	d	rostro-lateral
PrCO(GR)→FCBm(vB)	d	rostro-lateral
F4(M)→4c(V)	o	same
F4(M)→FCBm(vB)	i	same
F5(M)→F4(M)	m	rostral
F5(M)→FBA(vB)	i	same
FBA(vB)→FCBm(vB)	m	caudal
FBA(vB)→4c(B)	o	same
FBA(vB)→6va(B)	o	same
FCBm(vB)→6vb(B)	o	same
4c(B)→6va(B)	m	lateral
4c(B)→6vb(B)	d	medial
4c(B)→4c(V)	i	same
6vb(B)→4c(V)	d	lateral
4c(V)→6aαv(V)	m	lateral
4c(V)→6bα(V)	d	caudo-medial
6aαv(V)→ 6bα(V)	m	caudo-lateral

Related regions: FBA and FCBm, atlas von Bonin (code vB, von Bonin and Bailey, 1947), F4 and F5 atlas Matelli (code M, Matelli et al., 1985), 6Va, 6Vb and PrCO, parcellation Goldman-Rakic (code GR, Cavada and Goldman-Rakic, 1989a; Cavada and Goldman-Rakic, 1989b), 4c, 6va, 6vb, parcellation Barbas (code B, Barbas and Pandya, 1987), 4c, 6aαv, and 6bα parcellation Vogt (code V, Vogt and Vogt, 1919, Matelli et al., 1991).

(including the weak connections), as well as those of other cortical areas of the macaque PPC, as reconstructed from the information in NHDB, in Bota (2001).

Translating Connections in Different Parcellation Schemes

Users can perform online translations of the connectivity matrices of structures of interest by running the inference engine for translation of connectivity information in different neuroanatomical atlases. An example of translation of the connection between areas AIP and F2 (Matelli et al., 1998) to areas AIP and 6Ds in the parcellation scheme defined by Lewis and Van Essen (2000a) is shown in Fig. 10.

The output of the inference engine for translation of the connectivity information includes the inferred topological relations of the injection site and terminal field in the new

Summary of projections from LIP to 7a, species Macaca.

ID	Author	Efferent structure	Afferent structure	Abbreviation efferent structure	Abbreviation afferent structure	Species (genus)	Technique	Strength of connection	Description connection	Collator
285	Andersen et al., 1990	Lateral intraparietal area	Area 7a	LIP	7a	Macaca	radioactive aminoacids	strong	The injection of tritiated aminoacids into area LIP produced label in a large number of extrastriate cortical areas including areas MT, MST, DP, PO, 7a, V4, V3A, V3d, V3v, and TEO. Area 7a was most densely labelled in layers IV and IIIb, followed by I, followed by II and by IIIb. This pattern suggests that area 7a must stay above area LIP in cortical processing.	Mihail Bota
967	Lewis & van Essen	LIP	7a	LIP	7a	Macaca	retrograde tracer	strong	Table 3. Page 351	Mihail Bota
968	Lewis & van Essen	LIP	7a	LIP	7a	Macaca	retrograde tracer	medium	Table 3. Page 351	Mihail Bota
1148	Andersen et al., 1990	Lateral intraparietal area	Area 7a	LIP	7a	Macaca	radioactive aminoacids	medium/ strong	The injection of tritiated aminoacids into area LIP produced label in a large number of extrastriate cortical areas including areas MT, MST, DP, PO, 7a, V4, V3A, V3d, V3v, and TEO. Area 7a was most densely labelled in layers IV and IIIb, followed by I, followed by II and by IIIb. This pattern suggests that area 7a must stay above area LIP in cortical processing.	Mihail Bota

Overall results

The evaluated connection confidence level is **strong**
The most reliable technique(s) is(are): **retrograde tracer**
The projection with the highest strength is **strong**

Evaluation of each of the associated references

Associated reference	Number of reports	Evaluated strength
Andersen et al., 1990	2	moderate-strong
Lewis & van Essen	2	strong

Fig. 8. Users can access connectivity information in NHDB as well as evaluate connection confidence levels. The search was performed by the abbreviations of the efferent and afferent structures, respectively.

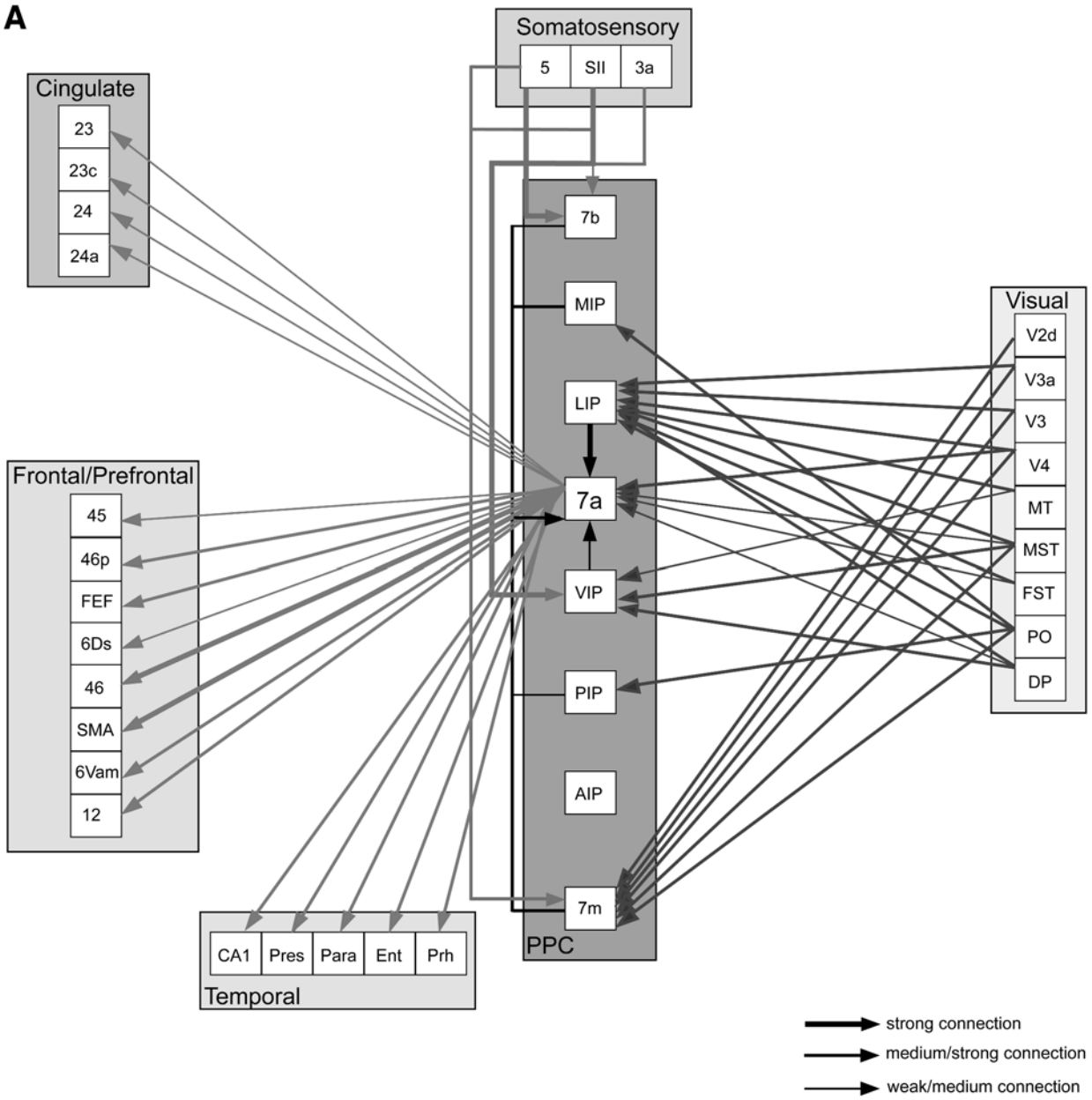
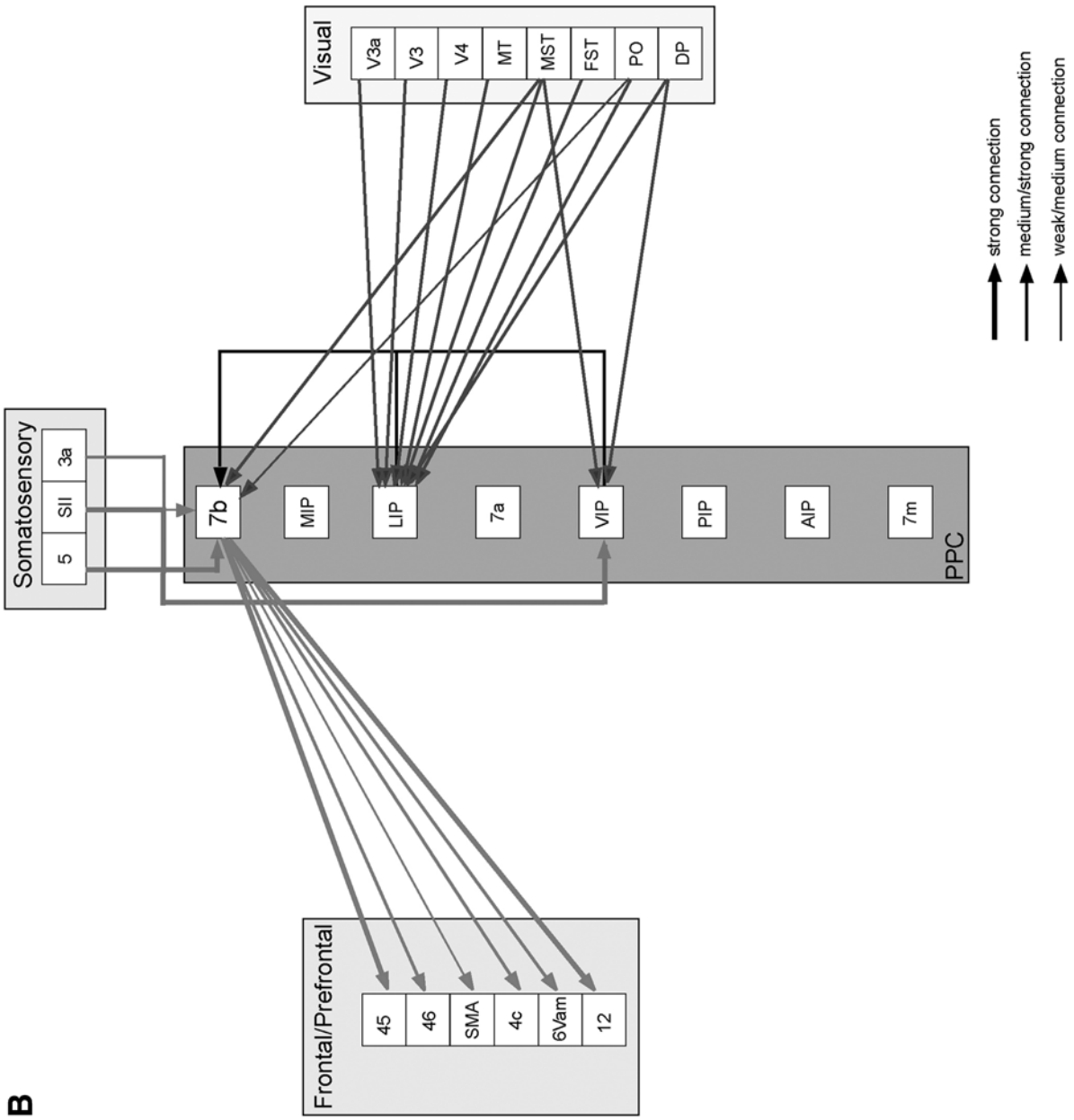
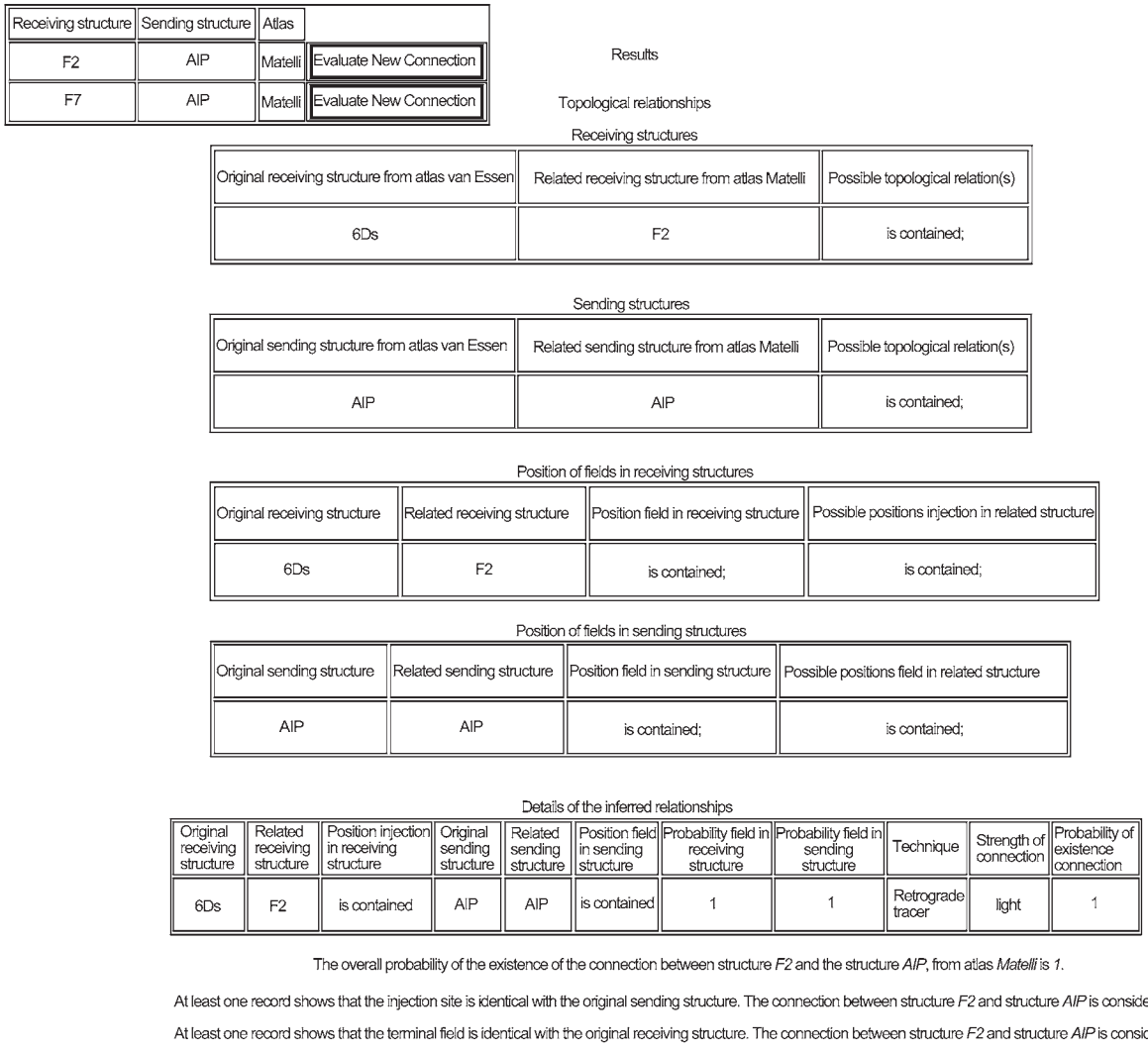


Fig. 9. The reconstructed patterns of connectivity of: **(A)** areas 7a and **(B)** 7b from the macaque PPC, from the set of connectivity reports stored in NHDB.


B
Visual
V3a
V3
V4
MT
MST
FST
PO
DP
Somatosensory
3a
SII
5
7b
MIP
LIP
7a
VIP
PIP
AIP
7m
PPC
Frontal/Prefrontal
45
46
SMA
4c
6Vam
12
strong connection
medium/strong connection
weak/medium connection



Receiving structure	Sending structure	Atlas	
F2	AIP	Matelli	Evaluate New Connection
F7	AIP	Matelli	Evaluate New Connection

Results

Topological relationships

Receiving structures

Original receiving structure from atlas van Essen	Related receiving structure from atlas Matelli	Possible topological relation(s)
6Ds	F2	is contained;

Sending structures

Original sending structure from atlas van Essen	Related sending structure from atlas Matelli	Possible topological relation(s)
AIP	AIP	is contained;

Position of fields in receiving structures

Original receiving structure	Related receiving structure	Position field in receiving structure	Possible positions injection in related structure
6Ds	F2	is contained;	is contained;

Position of fields in sending structures

Original sending structure	Related sending structure	Position field in sending structure	Possible positions field in related structure
AIP	AIP	is contained;	is contained;

Details of the inferred relationships

Original receiving structure	Related receiving structure	Position injection in receiving structure	Original sending structure	Related sending structure	Position field in sending structure	Probability field in receiving structure	Probability field in sending structure	Technique	Strength of connection	Probability of existence connection
6Ds	F2	is contained	AIP	AIP	is contained	1	1	Retrograde tracer	light	1

The overall probability of the existence of the connection between structure *F2* and the structure *AIP*, from atlas *Matelli* is *1*.

At least one record shows that the injection site is identical with the original sending structure. The connection between structure *F2* and structure *AIP* is considered to exist.

At least one record shows that the terminal field is identical with the original receiving structure. The connection between structure *F2* and structure *AIP* is considered to exist.

Fig. 10. The result of the translation of a connectivity report between AIP and 6Ds in parcellation Van Essen to the pair AIP, F2, parcellation Matelli.

parcellation scheme and the calculation of the degrees of translation, and of the confidence level for existence of the connection between AIP and 6Ds, according to equations A2–A4 from Appendix 2.

As for the inference engine for evaluation of neuroanatomical connections, the outputs of the inference engine for translation of the connectivity information can be used to evaluate patterns of connectivity in different atlases. An example of reconstruction of connectivity patterns in different atlases is shown in Fig. 11.

Figure 11 compares the reconstruction of the connectivity matrices of the three premotor structures (F4, F5, and F7) with three areas from the macaque intraparietal sulcus (AIP, LIP, and VIP) in the parcellation scheme proposed by Matelli et al. (1985) with the patterns of connectivity of these structures, according to Luppino and Rizzolatti (2000). The reconstructed patterns of the efferent projections of AIP, LIP, and VIP to F4, F5, and F7 (Fig. 11, right) were obtained by translating the connectivity reports collated from multiple

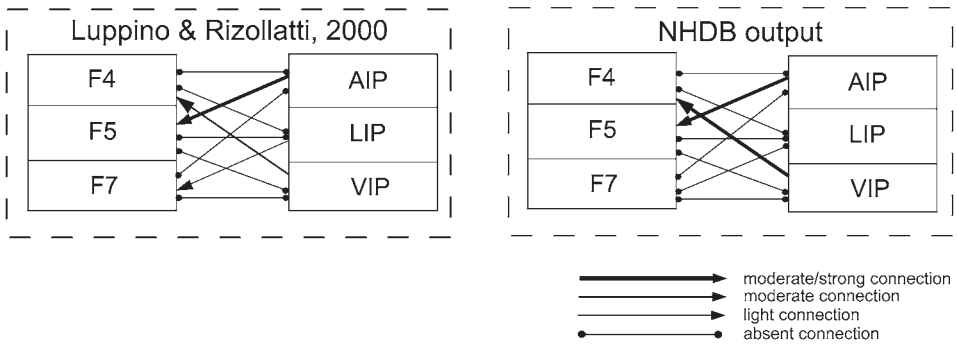


Fig. 11. The comparative reconstruction of the patterns of connectivity of areas AIP, LIP, and VIP with the premotor areas F4, F5, and F7, parcellation Matelli (Luppino & Rizzolatti, 2000; Matelli and Luppino, 2000) and the result of translation of connections identified in the parcellation schemes Van Essen, Goldman-Rakic, and Andersen to parcellation Matelli. See text for details.

sources (Lewis and Van Essen, 2000a; Lewis and Van Essen, 2000b; Cavada and Goldman-Rakic, 1989a; Cavada and Goldman-Rakic, 1989b; Preuss and Goldman-Rakic, 1991; Andersen et al., 1990) to the parcellation scheme proposed by Matelli. The collated or inferred topological relationships between the premotor and parietal areas in parcellation Matelli and their counterparts in the other considered atlases are listed in Table 10.

Details of the computational approach can be found in Bota (2001). Comparing the result of the translation of the connectivity data collated from the above sources to the parcellation scheme proposed by Matelli, with the pattern of connections proposed by Luppino and Rizzolatti one should observe that the overlap between the two sets of connectivity matrices is seven connections (present and absent) out of nine. The differences between our reconstruction and the results of tract tracing experiments of Luppino and Rizzolatti are related to the connection between LIP and F7 (light connection for Luppino and Rizzolatti and absent in our reconstruction) and between VIP and F4 (moderate connection as collated from Luppino and Rizzolatti and moderate/strong in our reconstruction). The differences in terms of strengths of connections between our reconstruction and the experimental data from Luppino and Rizzolatti are mainly owing to the difficulties in evaluating the initial topological relationships between the different parcellation schemes, and of the extents of the injection sites and terminal fields. Nevertheless, if we take into account only the existence or absence of the neuroanatomical tracts AIP, LIP, and VIP, and F4, F5, and F7, then our reconstruction matches eight of nine possible connections.

The Similarities Module

The information existent in the Similarities part of NHDB can be inspected online in two ways: browsing all the similarities in the knowledge base at a given moment or searching the system by abbreviations of brain structures and species.

The information that is retrieved when browsing the similarities existent in the database includes the abbreviations of the compared brain nuclei, the associated species, the common features, the reference and the colla-

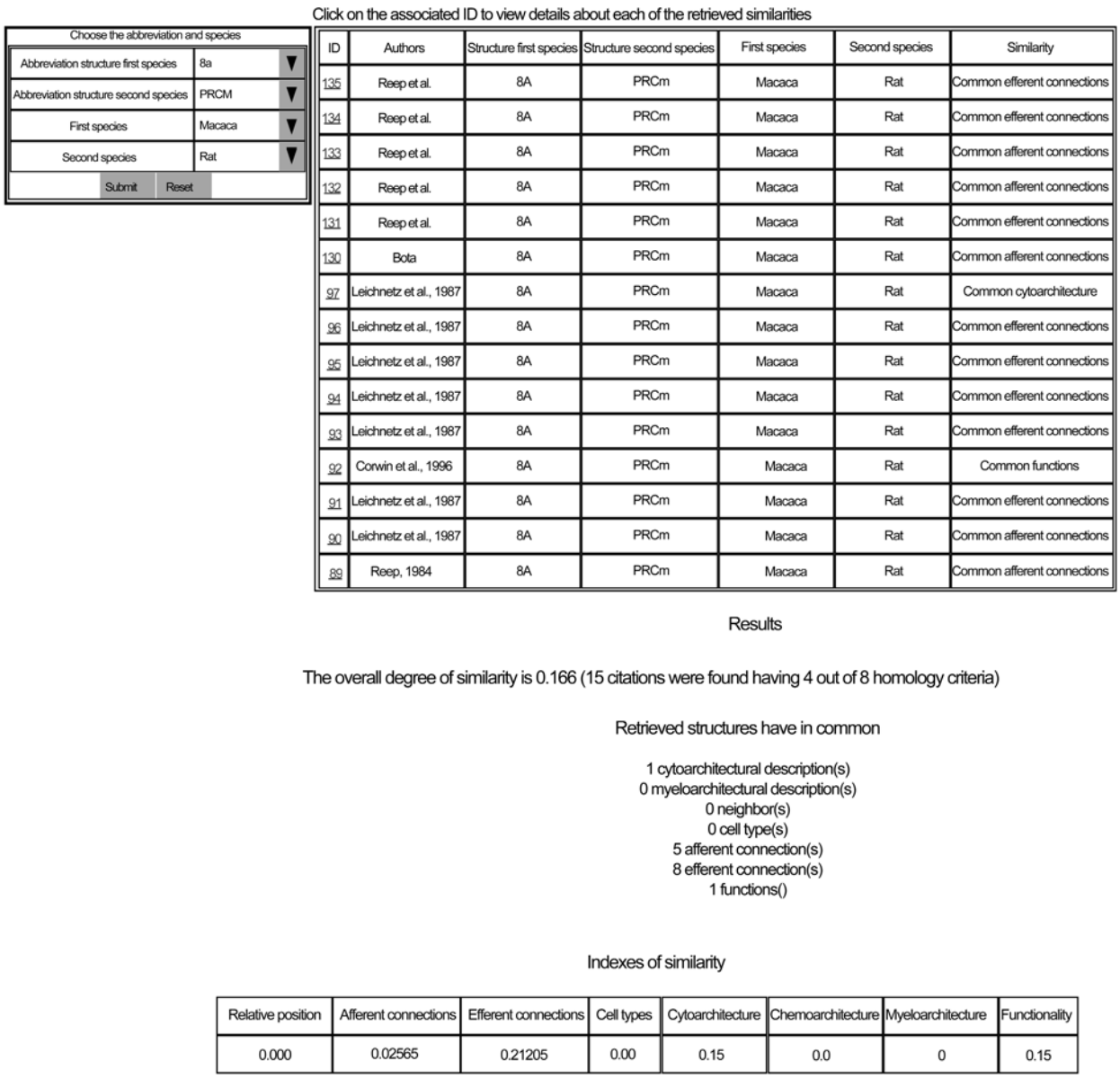
Table 10. The Topological Relationships Between the Cortical Structures Defined in Parcellations Van Essen (code vE, Lewis and Van Essen, 2000a; Lewis and Van Essen, 2000b), Goldman-Rakic, (code GR, Cavada and Goldman-Rakic, 1989a; Cavada and Goldman-Rakic, 1989b; Preuss and Goldman-Rakic, 1991), Andersen (code A, Andersen et al., 1990), and Matelli (code M, Matelli et al., 1985; Luppino and Rizzolatti, 2000; Matelli and Luppino, 2000) and Used for Translation of Connectivity Information.

Related cortical regions	*Collated topological relation*
F4(M)→6Va(GR)	o
F4(M)→6Vb(GR)	o
F4(M)→6Val(vE)	o
F4(M)→6Vam(vE)	m
F4(M)→4c(vE)	co
F5(M)→6Va(GR)	o
F5(M)→6Vb(GR)	o
F5(M)→6Val(vE)	o
F5(M)→6Vam(vE)	o
F5(M)→4c(vE)	m
F5(M)→6(A)	o
F7(M)→6D(GR)	o
F7(M)→6Ds(vE)	co
PF(M)→7b(GR)	isCo
PF(M)→7b(vE)	isCo
PF(M)→7b(A)	o
PG(M)→7a(GR)	isCo
PG(M)→7a(vE)	isCo
PG(M)→7a(A)	isCo
PFG(M)→7b(GR)	o
PFG(M)→7b(vE)	o
PFG(M)→7b(A)	o
PFG(M)→7a(GR)	o
PFG(M)→7a(vE)	o
PFG(M)→7a(A)	o
PGM(M)→7m(GR)	i

tor, as well as the calculated ODS. As for the other modules of NHDB, users can access details of the associated references and of the collator, and insert personal annotations to each of the retrieved entries.

The second option of accessing the comparative data allows the user to evaluate ODS from the information related to the searched structures and species and existent in NHDB, according to equations 6 and 7. An example of search of similarities and evaluation of ODS for area 8A in the macaque and the precentral medial cortex (PrCM) in the rat is shown in Fig. 12.

The result of the query shown in the inset of Fig. 12 returns all the records existent in the



Choose the abbreviation and species

Abbreviation structure first species	8a
Abbreviation structure second species	PRCM
First species	Macaca
Second species	Rat

Submit Reset

Click on the associated ID to view details about each of the retrieved similarities

ID	Authors	Structure first species	Structure second species	First species	Second species	Similarity
135	Reep et al.	8A	PRCm	Macaca	Rat	Common efferent connections
134	Reep et al.	8A	PRCm	Macaca	Rat	Common efferent connections
133	Reep et al.	8A	PRCm	Macaca	Rat	Common afferent connections
132	Reep et al.	8A	PRCm	Macaca	Rat	Common afferent connections
131	Reep et al.	8A	PRCm	Macaca	Rat	Common efferent connections
130	Bota	8A	PRCm	Macaca	Rat	Common afferent connections
97	Leichnetz et al., 1987	8A	PRCm	Macaca	Rat	Common cytoarchitecture
96	Leichnetz et al., 1987	8A	PRCm	Macaca	Rat	Common efferent connections
95	Leichnetz et al., 1987	8A	PRCm	Macaca	Rat	Common efferent connections
94	Leichnetz et al., 1987	8A	PRCm	Macaca	Rat	Common efferent connections
93	Leichnetz et al., 1987	8A	PRCm	Macaca	Rat	Common efferent connections
92	Corwin et al., 1996	8A	PRCm	Macaca	Rat	Common functions
91	Leichnetz et al., 1987	8A	PRCm	Macaca	Rat	Common efferent connections
90	Leichnetz et al., 1987	8A	PRCm	Macaca	Rat	Common afferent connections
89	Reep, 1984	8A	PRCm	Macaca	Rat	Common afferent connections

Results

The overall degree of similarity is 0.166 (15 citations were found having 4 out of 8 homology criteria)

Retrieved structures have in common

1 cytoarchitectural description(s)
0 myeloarchitectural description(s)
0 neighbor(s)
0 cell type(s)
5 afferent connection(s)
8 efferent connection(s)
1 functions()

Indexes of similarity

Relative position	Afferent connections	Efferent connections	Cell types	Cytoarchitecture	Chemoarchitecture	Myeloarchitecture	Functionality
0.000	0.02565	0.21205	0.00	0.15	0.0	0	0.15

Fig. 12. The result of searching for similarities between area 8A in the macaque and PrCM in the rat, in NHDB-I. See text for details.

knowledge base of NHDB and related to similarities between areas 8A and PrCM. The retrieved information includes the summary of the fulfilled criteria, the values of indices of similarity associated to each criterion, and the calculated ODS. As in the case of evaluation of connections confidence levels, users have the possibility of customizing the similarity inference engine by changing the maximal number of the common characters for similarity criteria of hodology, relative position, cell types and chemoarchitecture, and/or the values of IS for appearance, myeloarchitecture and functionality criteria. Users are also allowed to

change the confidence levels of the tract-tracing techniques that were used to reveal common patterns of afferent and efferent connections. Users can access the interface for customization of the similarity inference engine through the button "Recalculate," shown in Fig. 12.

As for the inference engines for connectivity reports, the outputs of the similarity inference engine can be used to compare any number of pairs of brain structures from different species.

Discussion

In this article we have described the structure of the KMS NHDB and the main aspects of online searching and processing of neurobiological information existent in the system. Even though we did not describe in full details the inference algorithms encoded in NHDB, the most important aspects of each of those were provided, as well as a number of case studies of inference of topological relations between cortical structures in different parcellation schemes, evaluating neuroanatomical connections, and of neural similarities as reflected from the literature. NHDB includes a series of important features:

a) unique identification of brain structures according to three different attributes,
b) flexible handling of neurobiological information ranging from functional aspects of brain nuclei to morphological and spatial features of neural cell types,
c) realistic representation of connectivity information as collated from the literature,
d) a comprehensive approach to comparative neurobiological data, and
e) flexible user interfaces designed for some of the inference engines of NHDB, allowing them to customize the process of evaluation of information.

The identification of brain structures by three attributes (name, species, and atlas) in the knowledge base of NHDB ensures the uniqueness of each of records and the proper representation of properties of any of those. The unique identification of records of brain structures in NHDB also allows the association to each of those of a non-contradictory hierarchy tree. The object-relationship structure of NHDB accommodates the storage and retrieval of a series of attributes and relations of brain structures, as reflected from the literature, ranging from the cytology of brain nuclei to their functionality. Therefore, NHDB is not restricted to a single aspect of neurobiological information, but can be used to inspect data pertaining to several levels of organization of the central nervous system. An important part of NHDB is dedicated to the representation of fiber tracts which are seen as relations between brain structures. Each report of neuroanatomical connections can be described in terms of 13 attributes, ensuring a realistic representation of connectivity information as collated from the literature.

A crucial module of NHDB deals with the representation and processing of comparative neurobiological information. The eight criteria which are taken into account to evaluate the similarities between brain nuclei from different species are the most important ones across different schools of comparative neurobiology (Butler and Hodos, 1996; Campbell and Hodos, 1970; Campbell and Hodos, 1991; Hall, 1994; Nieuwenhuys, 1998; Northcutt, 1984, Striedter, 1999, Wiley, 1981).

Therefore, the structure of the Similarities module of NHDB allows the storage and retrieval of comparative neurobiological information from different sources and related to several levels of organization of the central nervous system.

NHDB is not only a data repository which can be queried online by members of the neu-

roscientific community. It also contains a series of inference engines for evaluation of the neurobiological information. In this sense, the spatial inference engine is used to infer new relations between cortical structures from unrelated information and users can inspect the possible topological relations between structures in different atlases. The inference engine for evaluation of neuroanatomical connections computes the overall confidence levels of fiber tracts by taking into account the connection strength as reported in the associated references, the techniques which were used in each of the experiments, as well as the most important characteristics of the injections in the regions of interest. Users can access this inference engine online and evaluate the confidence levels of connections of interests. The connectivity inference engine is not meant to replace the expertise of neuroanatomists, but the proposed algorithm is an approximation of the process of evaluation of tract-tracing results from the literature. Since the results of the connectivity inference engine depend on the accuracy of data provided in the collated references, users can compare the outputs of the inference engine with the textual information extracted from the inspected articles. This enables the users to combine the experimental results with the results of the inference engine and therefore to better assess the strength of projections between regions of interest. The outputs of the inference engine for evaluation of the connectivity information also can be used to reconstruct the patterns of connectivity of structures of interest, as exemplified in this article. Thus, the results of the inference engine for evaluation of neuroanatomical connections can be used to reconstruct functional networks of brain structures of interest, and it may be a starting point for design of new neuroanatomical experiments.

The inference engine for translation of connectivity information in different atlases computes the probabilities of existence of fiber tracts of interest for each of the pairs of structures that are topologically related in the knowledge-base of NHDB. The similarity inference engine computes the overall degree of similarity of pairs of brain structures from different species from the comparative data existent in NHDB.

Moreover, NHDB can be used by the members of the neuroscientific community as a repository of personal insertions of connectivity reports or results of searches of reports of connections in the public part of the system, as well as an environment for sharing connectivity information (readers can find the description of this additional module in Bota, 2001 and Bota and Arbib, 2002).

NHDB shares many common features with two online KMS, the Neuroscholar (Burns, 1997; Burns, 2001a; Burns, 2001b; Burns et al., 2003) and CoCoMac systems (Stephan et al., 2001) in terms of representation of brain regions and connectivity information but it has also several features which make it specific. The structure of NHDB allows the integration of hierarchically organized brain records with connectivity, cytoarchitectural, myeloarchitectural and functional data. Moreover, the Similarities module of NHDB, which is unique to this system, allows users to browse and evaluate neural similarities taking into account eight criteria, as well as to customize the evaluation algorithm. Other KMSs which are available online and share similar features with NHDB are the BrainInfo (Bowden and Martin, 1995; Bowden and Martin, 1997; Bowden and Dubach, 2002; Bowden and Dubach, 2003) and the NeuronDB (Marenco et al., 1999) systems.

Finally, we propose in this article not only a KMS for handling of information, but also several novel computational algorithms for processing and evaluation of the neurobiolog-

ical data as reflected from the literature. The spatial inference algorithm implemented by us is similar with other computational frameworks proposed by other research groups for relating cortical structures in equivalent parcellation schemes (Stephan et al., 2000a,b). The spatial inference algorithm presented by us has the advantages of using the complete set of topological relations that exist between 2D objects and the qualitative directional relations that can be established between cortical structures. The probabilistic approach adopted here is motivated by the fact that the qualitative spatial algorithm does not yield unequivocal topological configurations between the structures of interest. The inference engine for evaluation of connectivity information is similar to that implemented in Neuroscholar and to the precision of descriptions codes (PDC) implemented in CoCoMac. We however, extend these approaches by introducing the concept of technique confidence level and evaluate the connection confidence level by taking into account two more characteristics of any tract tracing experiment: the size of injection relative to the region of interest and the size of the injection outside the target region. Therefore, the connectivity inference engine is novel both in terms of the variables which are processed and in the method employed. The inference engine for translation of connectivity information in different parcellation schemes is novel in that it proposes a probabilistic approach of the problem of evaluation of fiber tracts in equivalent atlases. Most importantly, we propose a novel approach of the comparison of neural structures in different species.

Turning from similarity to homology, we stress that the question of whether two brain structures are homologous should take into account the constellation of attributes that can be related to an evolutionary perspective (Hall, 1994; Nieuwenhuys, 1998). Also, the existence of homology at one level does not imply necessarily the existence of homology at other levels and two brain structures can be similar according to a series of criteria, but dissimilar with regard of other criteria. Therefore, the discussion of whether two brain structures are homologous should be shifted to how homologous they are. Moreover, the discussion of whether two brain regions are truly homologous or homoplasic should be based on the cladistic analysis of the similar characters. In this case, the indices of similarity defined in this article can provide an indication of how close two brain structures are, according to the associated criteria, and the degree of similarity can be seen as an overall measure of closeness of pairs of neural structures from different species. The values of the evaluated degree of similarity are meaningful when they are compared with the individual IS and across pairs of brain regions from different species. A higher degree of similarity for a given pair of regions, compared with other pairs may be an indication that this pair shares more common characters and further investigation may reveal whether those are homologous or homoplasic. Therefore, the results of the similarity inference engine should be taken as indications of how close different pairs of regions are, depending on the amount and quality of data inserted in the system.

The limitations of NHDB result mainly from the fact that the neurobiological information which is inserted in its knowledge-base has to be interpreted by collators from the inspected literature (Stephan et al., 2001). In this sense, the accuracy of insertion of the topological relations between cortical structures from different parcellation schemes depends on the expertise of collators and therefore the incorrect interpretation of information from collated references can lead to insertion of erroneous relations, which will

lead to false spatial inferences and translations of neuroanatomical connections in different atlases. However, NHDB contains a module for updating the knowledge base, accessible to registered collators (Bota, 2001). A further limitation of the KMS described in this article is related to the fact that neither the reconstruction of the connectivity patterns of brain structures of interest nor the translation of those in different parcellation schemes is performed automatically—users have to perform queries for each of the connections that will be included in the reconstructed patterns. Also, the evaluation of the similarities between brain structures in different species is not performed automatically from the unrelated information existent in NHDB, but the individual similarities between the pairs of brain structures are inserted and depend on the expertise of the collator. As future work merges the two separate but connected database systems NHDB-I and NHDB-II into a new integration of NHDB, we plan to integrate the information from both current versions and add new tools to address such deficiencies.

Nevertheless, NHDB already provides a valuable computational environment for searching, sharing and evaluating neurobiological information. We thus invite the members of the neuroscientific community to search NHDB-I and NHDB-II and to participate in our efforts to populate them with yet more neurobiological information.

Notes

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Appendix 1. The Spatial Inference Algorithm

The inference algorithm of new spatial relations from unrelated information is based on the algorithm proposed by Sharma (1996).

His algorithm uses three types of spatial reasoning: homogeneous, heterogeneous and mixed.

Qualitative homogeneous reasoning refers to the inference of new spatial relations from spatial relations of the same type.

Qualitative heterogeneous spatial reasoning is the inference of new spatial relations from qualitative spatial relations of different types. In this case, heterogeneous spatial inference extracts topological relationships from a combination of topological and directional information.

Mixed spatial reasoning extracts one type of qualitative spatial information from other types of spatial information, e.g., extracting topological information from from directional information or extracting directional relationships from topological information.

For each of the three types of spatial reasoning, a specific rule of composition of spatial relations is defined. The general case of inferring spatial relations between 2D objects is when we consider two objects, A and B, having the topological and directional relations t_j and d_i, respectively, and B and C, spatially related by t_j and d_j, and we have to infer the possible topological and directions between A and C, $\{t_k\}$ and $\{d_k\}$, by using the combined spatial reasoning.

Formally, the topological and directional relationships that are obtained by using the combined spatial reasoning are given by

$$\{t_i ;_{t1} t_j\} \wedge \{t_j ;_{t2} d_j\} \wedge \{d_i ;_{t2} t_j\} \wedge \{d_i ;_{t3} d_j\} \rightarrow \{t_k\} \quad \text{(A1)}$$

$$\{d_i ;_{d1} d_j\} \wedge \{t_j ;_{d2} d_j\} \wedge \{d_i ;_{d2} t_j\} \wedge \{t_j ; d3\ tj\} \rightarrow \{d_k\}$$

$$k=1, ..., 8$$

where $;_{t1}$ and $;_{d1}$ are the rules of compositon for homogeneous reasoning for topological and directional relations, respectively, while ;t2 and $;_{d2}$ are the rules of composition for heterogeneous reasoning for topological and directional relations, respectively, $;_{t3}$ and $;_{d3}$ are the rules of composition of the mixed reasoning for topological and directional relations, respectively, and the sign "^" stands for the operation of conjunction.

Combined spatial reasoning exploits all the possible combinations between topological and directional relationships that can be specified between objects, in order to reduce the number of possible inferred relationships. Thus, combined spatial reasoning, as proposed by Sharma, can be used to infer topological and directional relationships between 2D objects when the outcome of the homogenous spatial reasoning is equivocal.

In order to apply the combined spatial reasoning to infer spatial relations between cortical structures, we extended the inference algorithm proposed by Sharma, by imposing the constraint on non-contradiction (the result of the inference should not be the null set ϕ) and generalizing the rules of inference in equation A1. Thus, we allow the evaluation of topological and directional relations between cortical structures from sets of spatial relations between structures, previously inferred. In the following we briefly describe the process of inference of topological relations in NHDB. The reader can inspect the full description of the spatial inference engine implemented in NHDB in Bota, 2001.

Assuming that the set of topological relations between two cortical structures A and B is $\{a_r\}$ and between B and C is $\{b_s\}$ with r, s=1, .., 8, then the process of inference of new topological relations, implemented in NHDB, is as follows:

for r=1:a_1
for s=1:b_1
$t_r ;_t t_s \rightarrow \{t_a\}$
next r
next s
$\{t_{ACt}\}=\wedge_{a1,b1} \{t_{asr}\}$
where a=1...8

The set of relations $\{t_a\}$ is obtained by applying the topological inference to any two relations of the sets associated to the spatial relation between A and B, and B and C, respectively. This process is repeated for all elements "a_1" and "b_1." By running this iterative algorithm, we obtain the set of sets of all possible relations between A and C. The number of elements of the set of sets of the topological relations between A and C is equal with product between "a_1" and "b_1." Finally, the set of homogeneous topological relations between A and C, $\{t_{ACt}\}$, is obtained by applying the conjunction operation over the set of sets of topological relations obtained by running the iterative algorithm presented above.

The same algorithm is applied for the heterogeneous and mixed topological inferences, as well as for the directional relationships between A and C. We finally obtain four sets of topological and directional relations, respectively The last step of the algorithm is to apply equation A1 to the sets of all possible topological and directional relationships and the outcome is the inferred spatial relationships between A and C.

All these operations run under the constraint of non-contradiction. If any of the operations described above yields an empty relation, it will be discarded.

Appendix 2. The Inference Algorithm for Translation of Connectivity Information in Different Parcellation Schemes

Any neuroanatomical connection between two brain structures, **X** and **Y**, identified in a parcellation scheme can be approximated as a relation between an injection site **I**, and a terminal field **T**. The injection site in structure **X** and the terminal field in structure **Y** are approximated as 2D objects, being in a topological relationship with **X** and **Y**, respectively. The topological relations between **X** and the injection site **I** and **Y** and the terminal field **T**, respectively, are inserted in the knowledge base of NHDB as found or interpreted from the associated reference. Considering the structures **X** and **Y** in a given parcellation scheme **A**, the problem that has to be solved is the translation of the injections site **I and of the terminal field** T from parcellation **A** in another atlas, **B**. In other words, one has to translate the objects **I** and **T** in a second pair of cortical structures **Z** and **W**, identified in **B**. The inference algorithm for translating the connectivity information in equivalent neuroanatomical atlases works under the assumption that the topological relations between the structures **X** and **Z**, and **Y** and **W**, respectively, are known. Assume that the set of topological relations between **X** and **Z** is $\{t_{xz}\}$ and between **Y** and **W** is $\{t_{yw}\}$, and both are recorded in the knowledge base of NHDB as results to previous runs of the inference engine for spatial relations between cortical structures. Knowing the topological relation between **X** and **I**, t_1, and **Y** and **T**, t_2, then the sets of the possible topological relationships between **I** and **Z**, $\{t_{ZI}\}$, and **T** and **W**, $\{t_{WT}\}$, respectively, are obtained by iteratively applying the inference algorithm presented in Appendix 1. Generally, the topological relations between the **I** and **Z**, or **T** and **W** in the parcellation scheme B can have a number "n_1" and "n_2" of possible outcomes where n_1 and n_2 take integer values between 1 and 8. The existence of a connection between **Z** and **W** in **B** is ensured if the interiors of **I** and **T** have a non-empty intersection with the related structures. This means that **I** and **T** have to be in any of the following topological relations with **Z** and **W**, respectively: o, cv, co, isCo, cvBy, i. If **I** and **T** are identical, covered or contained by **Z** and **W**, respectively, then we are sure that **I** and **T** are translated integrally in the related structures in **B**. However, if **I** or **T** overlap, contain, or cover **Z** or **W**, respectively, then the strength of the translated connection or even the connection itself, can be due to those parts of **I** and **T** that are outside of the related brain structures. Since the algorithm for inference of the topological relations between 2D structures does not provide any information about the sizes of the interiors of the objects being in relations o, cv, co, then in the case of translating of a neuroanatomical connection in different parcellation schemes, the neurons that send the axons, or the cells that receive the tracts can be either in the common interiors, or outside of the boundaries of **Z** or **W**. In this situation, we propose as qualitative measure of the degrees of translations of the interiors of **I** and **T** in **Z** and **W** respectively, two indices of translation, IT_i and IT_t, given by the equations:

$$IT_I=(k_I+ext*l_I)/n_1 \qquad IT_T=(k_T+ext*l_T)/n_2 \qquad \text{(A2)}$$

where k_I and k_T are the numbers of occurrences of the topological relations i, isCo, cvBy between **I** and **W** and **T** and **Z**, respectively, ext=0.5, l_I and l_T are the number of outcomes for the topological relations o, cv, co and n_1 and n_1 are the total numbers of topological outcomes for **I** and **W** in **T** and **Z**, respectively. The parameter ext is seen as an uncertainty factor and takes value 0.5 because it is equally probable that the connection arises from the

common interiors of **I** and **Z**, or **T** and **W**, or from the interiors of **I** or **T** which are outside of **Z** and **W**, respectively.

Since we approximate a neuroanatomical connection as a relation between an injection site and terminal field and the topological relations between the **I** and **X**, and **T** and **Y** as independent events, we define the degree of translation DT of a connection from parcellation **A** to parcellation **B** as the product of the indices of translation of the injection site in **Z** and of the terminal field in **W**:

$$DT = IT_I \times IT_T \quad \text{(A3)}$$

The degree of translation, DT, can be interpreted as the probability of existence of the connection between **Z** and **W** in atlas **B**. DT is equal to 1 only when both the interiors of I and the T are inside of the interiors related structures in **B**. Otherwise, the degree of translation is smaller than 1, meaning that the translated connection can appear due axonal projections not only between the efferent and afferent structures in **B**, but also from the adjacent structures. The degree of translation is equal to zero when either of the indices of translations is equal to zero.

Since the connection confidence level depends on how probable a connection is in a given parcellation scheme, we evaluate the confidence level of the translated connection, CCL, as the product of the initial confidence level (in parcellation **A**) and the probability (the degree of translation DT) of the connection in parcellation **B**:

$$CCL = DT \times C \quad \text{(A4)}$$

where C is the connection strength as originally stated in the related references or inferred by the collator.

The inference engine for translation of the connectivity information contains an additional rule for establishing the existence of a connection between **Z** and **W** in **B**: if either IT_I or IT_T is equal to one and the other index of translation is greater than zero, then the connection is considered to exist. Conversely, if either of the indices of translation is equal to zero, then the result of the inference engine will indicate that there is no connection between **Z** and **W**.

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