CHAPTER 6.4

The NeuroHomology Database

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6.4.1 Introduction: The Definition of the Concept of Homology in Neurobiology

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, 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, 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 relation to "continuity of information," inheritance of features from a common ancestry, or phyletic continuity.

When discussing homologies at the level of the nervous system, one has to distinguish three levels of organization (Striedter, 1999):

1. Hierarchy of cellular aggregates, composed of major brain regions, brain nuclei, and nuclear subdivisions
2. Hierarchy of cell types, including major types and subtypes
3. Hierarchy of molecules grouped into families and superfamilies.

Even though specific homologies between two species can be identified at each level of organization of the nervous system, it is not necessarily true that a homology at a level will transcend it or imply a homology that is specific for another level. As an example, Reiner (1991) considers that the dorsal cortex of reptiles is homologous to mammalian neocortex, but the reptilian neocortex does not have cells specific to the mammalian neocortex. Due to the great complexity of the task of finding homologies between two species at each level of organization of the nervous system, we will mainly discuss in the following those that are characteristic of the hierarchy of cellular aggregates in adult organisms.

The process of definition of homology at the level of brain structures is not a direct one; rather, it implies a process of inference from distinct clusters of attributes. Thus, the concept of *degree* of homology is more appropriate to use when discussing homologies of brain structures across species. If one wants to define and evaluate the degree of homology between two brain structures from two species, then it has to correlate with what makes a given brain structure distinguishable from other structures. To define a neural structure, neuroscientists use numerous attributes, including gross morphology, relative location, cytoarchitecture, types of cell responses to different ways of stimulation, and function (Bowden and Martin, 1997).

In this sense, Bowden and Martin (1997), using a unified dictionary for human and monkey brain structures (*Nomina Anatomica*), established homologies between monkey and rat brain structures based on their morphology (gross and Nissl stain appearance). Bowden and Martin consider that at least 84% of the primary

landmark structures of the macaque brain have morphologic homologs in the rat, excluding the cortex. The status of another 8% of brain structures is unclear, so it is possible that as many as 92% of macaque brain structures have morphologic homologs in rat. At the cortical level the rats lacking the cortical sulci, have no morphological equivalents of about 25 cortical gyri of the macaque cortex. At the subcortical level, the structures of the macaque brain that do not have morphological homologs are the level of subdivisions of the thalamus (mainly the pulvinar nucleus), the striatum, and the lateral ventricle. This way of defining homologies between rat and monkey brain structures is incomplete. Areas that are morphologically homologous are not necessarily homologous from the functional point of view, or areas that are not homologous according to their morphology can be homologous according to other criteria.

A more complete way of defining homologies between two brain structures has to take into account as many attributes as possible. In this sense, following Butler and Hodos (1996) and Nieuwenhuys *et al.* (1998), we identified eight criteria that can make a brain area distinguishable and can be used to evaluate the degree of homology between two brain structures. These eight criteria are the morphology of cells within a brain structure, the relative position, the cytoarchitecture, chemoarchitecture (neurotransmitters and enzymes that are found within a brain structure), myeloarchitecture, afferent and efferent connections (hodology), and function. Accordingly, we take into account all these identified attributes when evaluating the degree of homology of a pair of brain structures from two species.

The first criterion, that of *morphology of neurons*, refers to the hierarchy of cell types within the nervous system. As an example, the structure of pyramidal neurons of cerebellum is a constant feature across tetrapods (Striedter, 1999). The principal type of cell in the lateral, basal, and accessory basal nuclei is a "pyramidal" neuron (Price *et al.*, 1987). This structure was found to be common for basolateral nuclei across species. In cat, these cells are called P cell, while in rat and mouse, about 70% percent of the basolateral nuclei are made of pyramidal cells. A similar type of cell was recognized in the opossum amygdala. Moreover, the principal cell type of the human basolateral amygdala appears to be a pyramid-like cell (Price *et al.*, 1987).

The criterion of *relative position* refers to the position of a brain structure, relative to other brain nuclei or to brain landmarks. As examples of homologies based on relative position we consider the periamygdaloid cortex which occupies the ventral surface of the amygdala in rat, cat, and monkey (Price *et al.*, 1987) and the retrosplenial cortex in the monkey and human which includes areas 29 and 30 and is buried in the callosal sulcus (Vogt, 1993).

The criterion of *cytoarchitecture* refers to the appearance of brain structures in Nissl staining. In this sense, Krieg's parietal Area 1 in rat cytoarchitectonically resembles Area 1 in humans, due to the fact that cells in layers IV and VI are noticeably sparse (Krieg, 1947). In rat and rabbit, the anterior cingulate cortex is agranular, and the posterior cingulate cortex has a dysgranular component, with layers II and III poorly differentiated, a thin layer IV, and a prominent layer V (Vogt, 1993). A poor differentiation of the anterior cingulate cortex is characteristic for monkeys and humans, too (Vogt, 1993).

The criterion of *chemoarchitecture* of brain structures refers to specific neurotransmitters and enzymes that are found within these structures. One example of homology based on chemoarchitecture is the case of the accessory basal nucleus of amygdala in rat and cat and the basomedial nucleus in monkey. Even though this nucleus of amygdala has different sizes and appearances across species, it lightly stains for acetylcholine esterase (AChE) in monkey, cat, and rat (Price *et al.*, 1987). The same situation is found for the magnocellular portion of the basal nucleus of amygdala; it is that part of the basal nucleus of the amygdala that stains most intensely for AchE in rats, cats, and monkeys.

The method of staining of myelin of axons is used not only for identification of specific areas, but also as a criterion of homology. Accordingly, the distinction between the lateral intraparietal area (LIP) and the ventral intraparietal area (VIP) can be made on the basis of difference in myelin staining. VIP appears to be highly myelinated, while the myelin stain in LIP is light (Colby *et al.*, 1988). Examples of homologies established on the basis of *myeloarchitectonics* include area DM that appears to be a visual area in all nonhuman primates (Krubitzer and Kaas, 1993) and the cerebellum in avians and mammals (Feirabend and Voogd, 1986).

The homology criteria of *common afferent and efferent connections* have a particular importance. This is due to the fact that the pattern of connectivity of a brain structure can be directly related to the function of that brain structure, and the pattern of afferences and efferences, respectively, establish the position of that brain structure in the hierarchy of processing information by the brain. In many cases, a pair of structures from two different species can be remotely related in terms of relative position and cytoarchitecture but can share a common pattern of connections. This is the case of the rat and monkey prefrontal cortices. The existence of rodent prefrontal cortex is still under debate, but if one follows the definition of the prefrontal cortex as that cortex that receives input from the mediodorsal nucleus of thalamus, then several prefrontal cortices can be identified in the rat (Kolb, 1990). Based on the fact that MD projects in primate brains mainly to the prefrontal cortices, one can assume that the prefrontal cortices in rat and monkey are homologous with respect to the input from MD.

Another case of defining and finding homologies of a brain structure is that of the rodent posterior parietal cortex (PPC). In rodents, PPC is distinguished from the adjacent areas on the basis of thalamic inputs: it receives inputs exclusively from the laterodorsal (LD) and lateral posterior (LP) thalamic nuclei (Chandler *et al.*, 1992; Corwin and Reep, 1998). Regarding the putative homology between the rodent PPC and the monkey PPC, one can note that the monkey PPC receives thalamic connections from the pulvinar nucleus and from LP. Corwin and Reep consider that the existence of a pulvinar-LP complex is recognized across mammalian species that lack a pulvinar, and it is likely that the LP is a homologous structure of the pulvinar nucleus. Corwin and Reep conclude that the monkey and rat PPC have a common thalamic input. The patterns of connections for rat and monkey PPC bring more information in favor of the existence of homology between these two areas. In both species, the PPC has extensive connections with the prefrontal cortices (Corwin and Reep, 1998); therefore, one can assume the existence of homology between the rat and monkey posterior parietal cortices.

The homology criterion of *function* is not considered to be a proper one by all schools of comparative neuroanatomy. As an example, de Beer defines the homology between two organs on the basis of their characteristics (what they are) and not what they do (Nieuwenhuys *et al.*, 1998). On the other hand, Campbell and Hodos (1970) include the physiological data and behavioral changes resulting from stimulations and lesions as information that has to be used in establishing the homologies between two brain structures. The homology criterion of function depends in fact on the above-discussed criteria. Thus, if two brain structures have common cell types, present common chemo-and cytoarchitectonical characteristics, and common connectivity patterns, then one should expect that those two brain structures have the same function or related functions. Accordingly, we follow the definition given by Campbell and Hodos and consider the function as a homology criterion. A typical example is the primary visual area (area 17). In each major branch of mammalian species, area 17 can be delimited on the basis of myelo-(heavy myelination) and cytoarchitecture (the presence of a granular layer IV), the presence of a single and systematic visuotopic map, a well-defined pattern of subcortical afferents, small receptive fields relative to the extrastriate areas, and the presence of many orientation-selective neurons with simple receptive fields; therefore, one should expect that area 17 has the same function across species.

The discussion of the homology criteria that can be established between pairs of brain structures across species indicates that two brain structures are homologous within a certain degree. Discussion about whether two brain structures are homologous should take into account the constellation of attributes that define those. Also, the existence of homology at one level does not necessarily imply the existence of homology at other levels; therefore, the discussion of whether two brain structures are homologous should be focused on the degree of homology. The degree of homology can take a maximal value, when all the homology criteria are fulfilled, and a minimal value, when none of the homology criteria is fulfilled.

6.4.2 Theory of Degrees of Homology

The degree of homology is calculated on the basis of the number of fulfilled homology criteria for each retrieved reference and of the number of retrieved references. As described earlier, we have taken into account eight criteria to define a homology between two brain structures in different species. Due to the fact that the literature on the homologies at the level of neural systems is not in agreement when stating the hierarchy of importance of the criteria that are used to establish a homology between two brain structures, we have considered that all criteria have the same weight. This can be seen as a limitation of the formalism proposed, but it is a result of the heterogeneity found in the literature dedicated to comparative neuroanatomy.

We have inserted data found in literature that explicitly states homologies between brain structures for humans, monkeys, and rats. That is, if a reference states a homology between two brain structures for a pair of species, then the criteria that are fulfilled are recorded in the database. In order to compute the degree of homology between two brain structures, we have assigned an index for each considered criterion. Thus, for any given pair of brain structures from two different species, the indexes for those criteria that are fulfilled in each inserted reference will take value 1; otherwise, the value will be zero. The query for homologies for two brain structures from two different species will retrieve all the references in the database that refer to the searched pair. Accordingly, the query will retrieve all the associated indexes to the homology criteria and will evaluate the number of indexes that have value 1. If two references have a number of common criteria that are fulfilled, then the indexes do not change their values. The degree of homology is then calculated as the sum of all indexes retrieved from all references related to the searched pair of brain structures and divided by the total number of criteria of homology (8). The degree of homology increases only if the number of fulfilled criteria is increased in all searched papers and remains constant if the same criteria are found in any number of entries. Thus, the database tries to maximize the degree of homology for any pair of brain structures that are inserted in it, regardless of the number of papers that cite that pair as being homologous.

We have chosen this way of computing the degree of homology making the following assumption: the process of establishing homologies between brain structures from different species is an incremental one. That is, with the development of neuroanatomical and neurophysiological techniques, more homology criteria can be investigated and more accurate answers can be given to the question of whether two brain structures fulfill a given set of criteria. Another reason for choosing the above-mentioned method of computing the degree of homology is related to the redundancy found in the literature. One reference can establish that a number of homology criteria are fulfilled and also can cite other sources for extending the number of criteria or in support of the findings described in the reference.

6.4.3 The NeuroHomology Database: Description

The NeuroHomology Database is designed in Microsoft® Access and uses the WebMerger CGI parser engine as a Web interface. NeuroHomology is a knowledge-based summary database and contains three interconnected modules: *Brain Structures, Connections*, and *Homologies*. In Fig. 1 we show the modules and relationships that are contained in the database. Descriptions of each module of the database will be provided in later sections of this chapter. The conventions that are used to express relationships between entities and objects are as following:

1. A unidirectional connection denotes a 1-to-*n* relationship. This is the case of the relationship between Brain

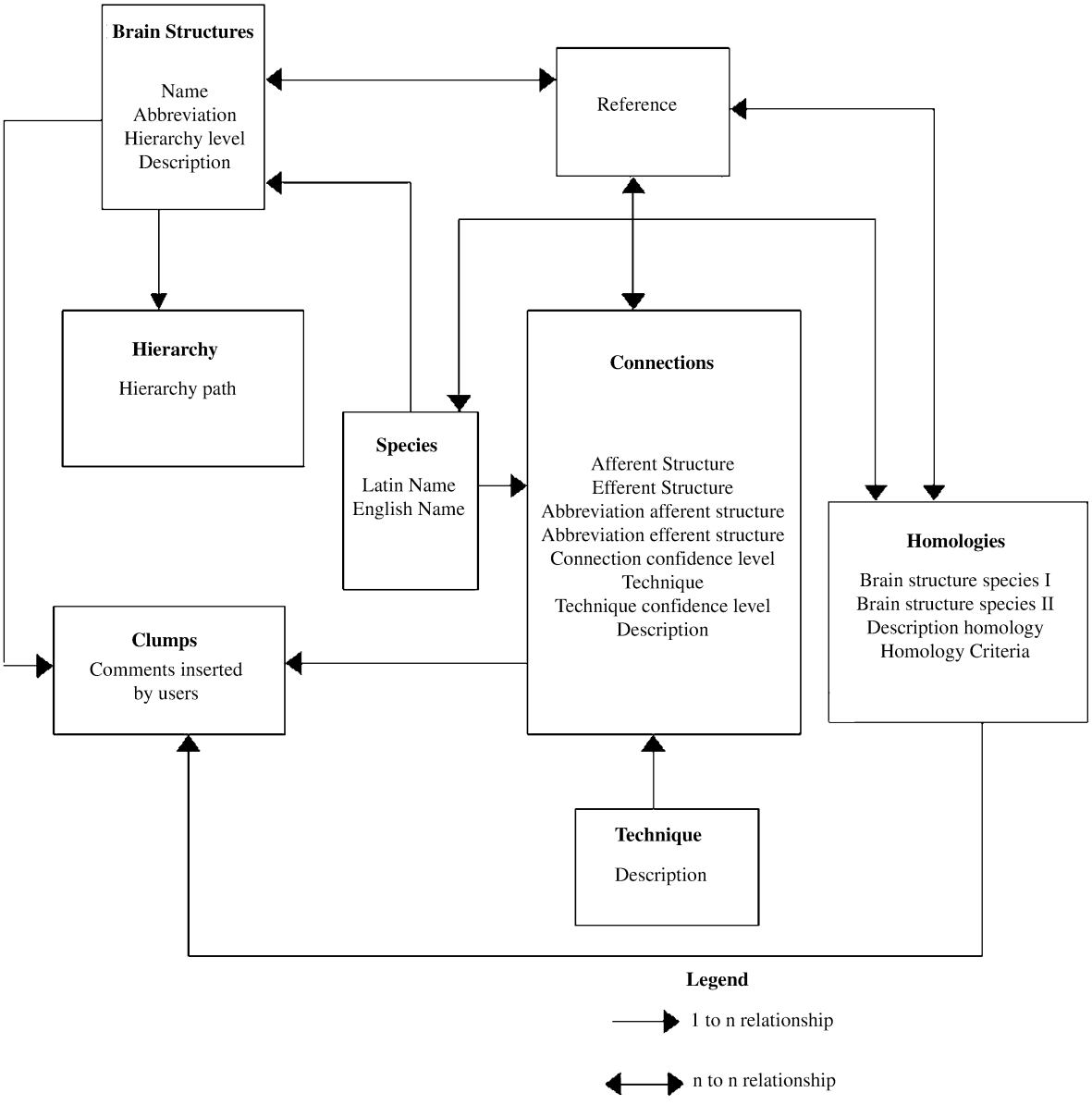

Figure 1 Schematic of the NeuroHomology Database structure.

Structures and the Hierarchy module. One brain structure (one entry in the database) has a single hierarchy path, but one hierarchy path can be common to a number of brain structures that have the same degree of specialization.

2. A bidirectional connection denotes an *n*-to-*n* relationship. This is the case of the relationship between references and any of the three entities. One reference can refer to many brain structures, and a brain structure can be defined in a number of different papers.

The parts of the NeuroHomology Database—Brain Structures, Connectivity Issues, and Homologies—can be accessed independently. We have designed the Web interface in independent parts to answer to queries from a larger category of users. In this way, a user who wants to find if there is any homology between structures X and Y from two different species can also find the definitions of structures X and Y according to different sources, as well as the afferents and efferents of these two structures.

6.4.4 The NeuroHomology Database: Brain Structures

The Brain Structures part of the NeuroHomology Database has brain structures as objects, as found in the literature. The description of a brain structure is taken as it is from the inserted papers. When searching the neuroanatomical literature, one can find brain structures defined on the basis of the topological or topographical position or on the basis of chemoarchitecture or myeloarchitecture. Usually, those brain structures that cannot be distinguished from the neighbors on the basis of gross appearance are defined according to other criteria. As can be seen in Fig. 2, PPC is defined in three sources on different grounds: morphological appearance and relative position. The description for each entered brain structure is the minimal one that can be found in the paper that describes it. To ensure a proper definition of a brain area, we seek to insert in the database those research papers that define brain structures according to at least one criterion. Each brain structure is captured in a hierarchy of brain superstructures. In this way, the hierarchy path that is assigned to a brain nucleus shows the successive specializations of brain superstructures that lead to that brain nucleus. The hierarchy path for each brain structure is established on the basis of the paper that describes it. Generally, a hierarchy path contains volumetric superstructures up to the level where a superstructure is defined by other criteria.

As an example, the lateral intraparietal area (LIP) in the macaque brain is defined by Felleman and van Essen (1991) on a myeloarchitectonical basis. The level of hierarchy for LIP is 5, so the hierarchy path is "Forebrain/Telencephalon/Cerebral Cortex/Parietal Lobe/Intraparietal Sulcus." Thus, area LIP has the hierarchy path determined only on volumetric structures, but this structure is defined on the basis of the criterion of myeloarchitecture. A similar situation is that of the lateral intraparietal area-ventral part (LIP-v). Felleman and van Essen (1991) define this region from LIP as being the target of the input from area MT. Accordingly, the

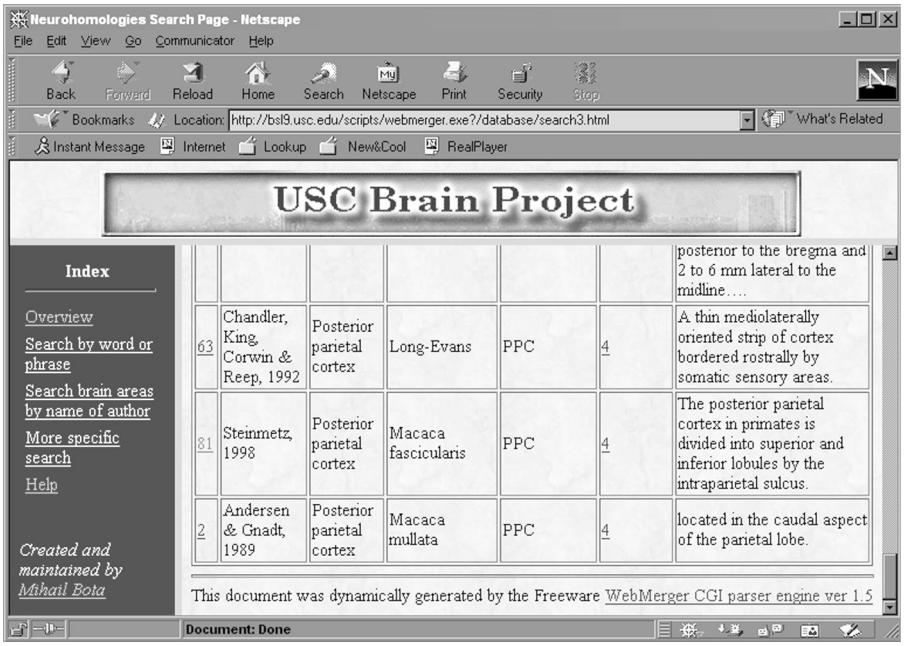

Figure 2 The result of a query using the abbreviation of a brain structure. The searched abbreviation was PPC. The user can compare definitions of brain areas with the same denomination, but in different species.

hierarchy level of this area is 6, and the hierarchy path is "Forebrain/Telencephalon/Cerebral Cortex/Parietal Lobe/Intraparietal Sulcus/LIP."

A possible source of confusion may arise from the use of different names for the same structure and from definitions of brain structures that are defined on different criteria and partially overlap. In this situation, the user has the possibility of searching by superstructure. The search by superstructure will return all the brain structures that exist in the database and are under it. The user then can compare the criteria that were used to define structures that are identical in terms of localization in the brain but have different names or areas that partially overlap. This is the situation for area 7a defined by Cavada and Goldman-Rakic (1989a,b) and area PG defined by Pandya and Seltzer (1982). Both sources describe the same part of the macaque parietal lobe but use different names. Whenever possible, we have used the Latin name for species (genus, or strain). If the Latin name is not available (as in the case of different strains of rats), we have used the English name.

The search of the Brain Structures can be extended or made specific. The brain structures that can be found in the database are regardless of species; in this way, the user is able to compare definitions of brain structures that have the same name in different species. Fig. 2 gives comparative definitions of brain structures in *Macaca fascicularis*, *Macaca mulatta*, and the Long-Evans rat. One type of extended search can be made using a word or phrase from the description of entered brain structures. Another possible extended search can be made by the name of an author of an article in the database. This type of query will retrieve the names of authors that partially or totally match the searched string, together with the names, abbreviations, and hierarchies of brain areas that have been investigated by them and the descriptions of brain areas that are associated with the retrieved brain structures.

The search of brain structures can be more specific, by using any combination of three search possibilities: by abbreviations of brain structures, by superstructure, and by species. The page that contains these search options is shown in Fig. 3. The user is offered seven different combinations for searching the Brain Structures part of the NeuroHomology Database. By clicking on only one of the three checkboxes, the user can perform a more general search. The search will be narrowed if two out of three or all three checkboxes are used. In the case of search by species, a more general search can be done if the name of the family of species (i.e., "Macaca") or the generic name for a strain (i.e., "rat") is searched for. This type of search will return all records that have those species under the same genus. As an example, searching by the species "Macaca" will result in all the entries that contain as species *Macaca fascicularis*, *Macaca fuscata*, *Macaca nemestrina*, *Macaca mulatta*, etc. In the same way, if one searches by the species "rat," then the result will include all records that contain the strains Albino rat, Sprague-Dawley rat, Long-Evans rat, etc. A narrower search can be performed if strings such as

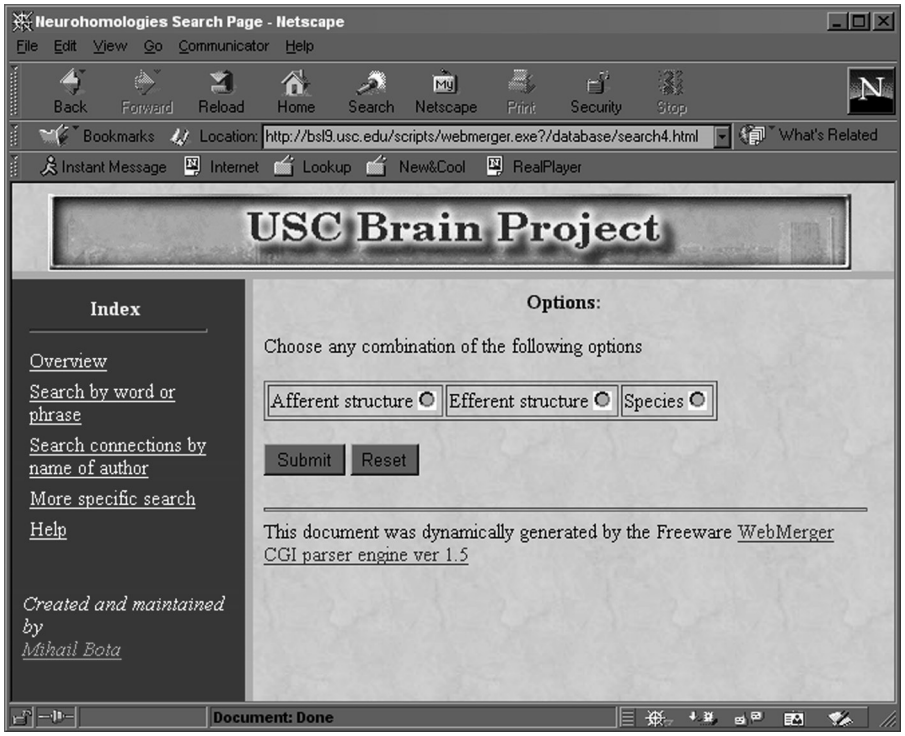

Figure 3 Annotations can be associated to any retrieved information. The user can inspect the associated annotations that were entered previously.

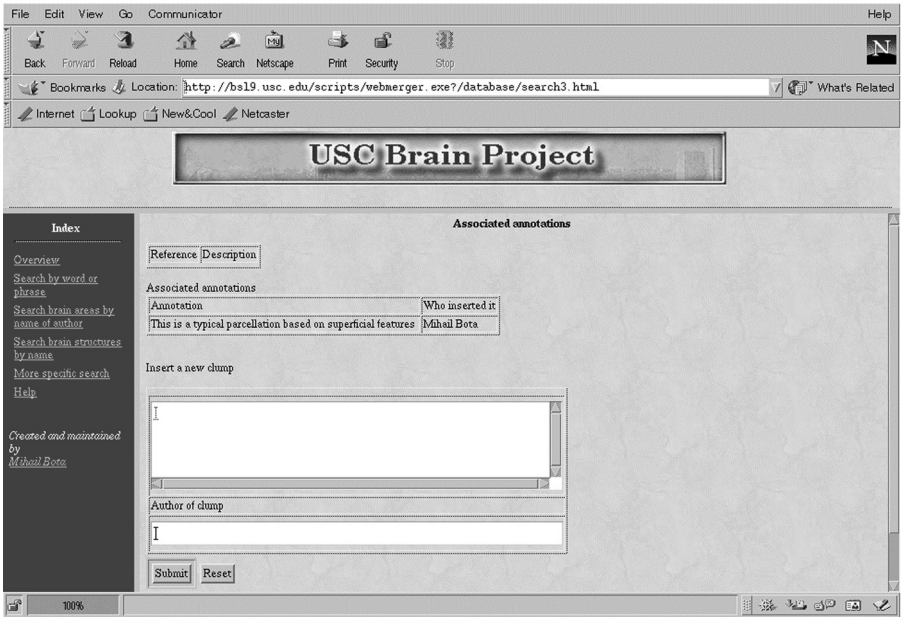

Figure 4 The window for a specific search of Brain Structures. The user can choose any combination of the three options for searching: by abbreviation of brain structure, name of superstructure, and species.

"nemestrina," or "Albino" are entered in the query. This type of search will result only in entries that belong to *Macaca nemestrina* or Albino rat, respectively. The most specific search is made if all three possibilities are chosen. In this case, the result will be restricted to a given species and will contain a single brain structure with at least one definition. In other words, the query will return those structures that have the same abbreviations, are under the same superstructure, and can be found in a single species. That is, a single structure will be retrieved having at least one definition from at least a single source.

In this way, the user can begin with a broad search of brain structures by using a word or phrase from the descriptions of brain structures or by author, choosing the appropriate option from the menu of the search page, or the user can narrow subsequent searches in order to inspect brain regions for a given species as specializations of a specific superstructure. Another specific feature of the NeuroHomology Database is associating new annotations (comments) with any retrieved entry (Fig. 4). By clicking on the ID that is associated with each retrieved entry, the user can inspect the annotations entered by previous users, and this function also allows the user to add new comments to the selected entry.

6.4.5 NeuroHomology Database: Connectivity Issues

The Connections part of the NeuroHomology Database has brain structures related by connections as objects. A typical result of a search of Connections contains the sources that discuss the retrieved connection; the species (strain); the afferent, efferent, and abbreviations of structures as found in the reference; the type of connection (excitatory/inhibitory or in terms of neurotransmitters); the technique that was used; the connection confidence level; the technique confidence level; and a description of the connection as found in the reference. The field "Technique" contains the specific technique that was used (e.g., "injection with tritiated amino-acids" or "PHAL"). By clicking on this field, the user has the option of inspecting the procedure that was followed and its description in the inserted paper. The evaluation of the connection confidence level was inspired by the confidence level used in the NeuroScholar Database (Burns, 1997). We considered five possible integer values for the connection confidence level: the maximum value is 3 and the minimum is -1. The assignment of a specific value for connection confidence level is the result of interpretation of the data from an article by the collator.

The value of -1 is used for an assertion such as "contrary to previous studies, we did not find the connection between area X and Y in the inserted article." A value of 0 is considered when no connection was found between two brain structures. A value of 1 is found when expressions such as "light connection," "light labeling," "sparse labeling," or "few cells were labeled" are found in the description of the connection. We consider that a connection has a confidence level of 2 when in the description of the connections statements such as "moderate staining" or "moderate labeling" are found. Finally, a value of 3 is assigned to those connections that are described as having "dense labeling" or "dense

staining" attributes or the connection is "strong" or "dense."

Due to the fact that a number of sources describe connections as one relative to the other, we assigned values for connection confidence level as follows. If the confidence level for a connection was already assigned, then the confidence level for a connection that is discussed relative to the first one will be increased by 1 if the connection is "stronger" or the injection produced a "stronger" or "heavier" "labeling" or "staining." Conversely, a connection that is discussed relative to another will have a confidence level decreased by 1 if it is described as having "lighter" or "fewer" cells "labeled" or "stained."

We also assigned a confidence level for the technique that was used to investigate a given connection. The confidence levels can take values between 1 and 3. In order to evaluate the technique confidence level, we investigated the advantages and limitations for each commonly used technique for labeling brain connections. In this sense, we have taken into account the following tract-tracing techniques: injections with tritiated amino acids, horseradish peroxidase (HRP) alone or conjugated to wheat-germ agglutinin (WGA) or cholera toxin (CBT), fluorescent dyes, combinations of retrograde fluorescent markers and antigens, and *Phaseolus vulgaris* leuco-agglutinin (PHAL). The limitations of tract-tracing techniques that were taken into account when evaluating the technique confidence level were the mechanism of incorporation of chemicals by the neurons, the trans-synaptic labeling, the labeling of damaged or intact fibers of passage, and the difficulty of evaluating the number of labeled cells (Gerfen and Sawchenko, 1984; Llewellyn-Smith *et al.*, 1992; Sawchenko and Swanson, 1981; Sawchenko *et al.*, 1990; Skirboll *et al.*, 1989; Smith, 1992).

Injections with tritiated amino acids can lead to trans-synaptic labeling; the degree of staining is time dependent, and the degree of opaque grains on the sensitive film can be influenced by the background radioactivity. Moreover, the axonal trajectories are difficult to trace, and the axonal and terminal labeling fields are difficult to discriminate (Gerfen and Sawchenko, 1984). Therefore, we assigned a value of 1 to this technique. The HRP technique is successfully used for both retrograde and anterograde labeling and does not lead to trans-synaptic labeling but is taken up non-specifically by the axons, dendrites, and cell bodies of neurons (Llewellyn-Smith *et al.*, 1992). Moreover, HRP is taken up by fibers of passage (Gerfen and Sawchenko, 1984). Accordingly, we assigned the value of 1.5 to the technique.

In the case of combination of HRP with WGA or CBT, the binding process is more specific. These specific uptake mechanisms make WGA-HRP and WGA-CBT more sensitive retrograde tracers than free HRP. On the other hand, just as for HRP, these techniques are prone to label fibers of passage (Gerfen and Sawchenko, 1984). Thus, we assigned the value of 1.75 for each of these techniques. One improvement to the WGA-HRP and WGA-CBT techniques is that of adding gold to these tracers; the cut or damaged axons do not take up these tracers, although they are taken up by the fibers of passage and axon terminals. Accordingly, we assigned the value of 2 to this tract-tracing technique.

One widely used group of techniques for retrograde staining of neural connections employs such fluorescent markers as rhodamine beads, fast blue, Fluoro-Gold, and propidium iodide (Kuypers *et al.*, 1979; Skirboll *et al.*, 1989). Each of these markers has its own advantages and limitations. As an example, fast blue and Fluoro-Gold are taken up by fibers of passage, and these dyes are not very useful for studying neurons with small projection fields; staining with rhodamine beads has disadvantages regarding evaluating the number of cells that are labeled (Skirboll *et al.*, 1989). For all these techniques and the combinations of those with antigens we assigned the value of 2.5; however, if the source mentions that no fibers of passage were labeled, and the number of labeled neurons could be evaluated, then the confidence level increases to 3.

The last discussed tract-tracing technique is that of PHAL. The principal advantages of this anterograde labeling technique include the clarity and completeness of labeling of neurons at the site of injection and of their axons; the tracer is not taken up by fibers of passage, and the results of injections into pairs of adjacent cell groups show that the anterogradely filled fibers and the terminal fields arise strictly among cell groups in which the labeled cells are seen (Gerfen and Sawchenko, 1984; Smith, 1992). Moreover, the fibers that are morphologically distinct, the collateral branches, and terminal specializations can be easily visualized (Gerfen and Sawchenko, 1984). For all these advantages, we assigned the value of 3 to PHAL. Also, reports of using combinations of PHAL as an anterograde staining technique with retrograde tracers that state that no fibers of passage were labeled will have the confidence level of 3. In conclusion, by evaluating the relative advantages and limitations of each widely used tract-tracing technique, we have offered a partial quantification of the reliability of results obtained using each technique.

The search of the Connections part of the NeuroHomology database is analogous to that of the Brain Structures. As in the case of Brain Structures, the search can be broad, or it can have different degrees of specificity. The broad search can be made by a word or phrase from the description of a connection or by the name of an author. Also, as for Brain Structures, the user can insert comments to any retrieved entries. A search can be narrowed by using a combination of three additional possibilities: afferent structure, efferent structure, and species (Fig. 5).

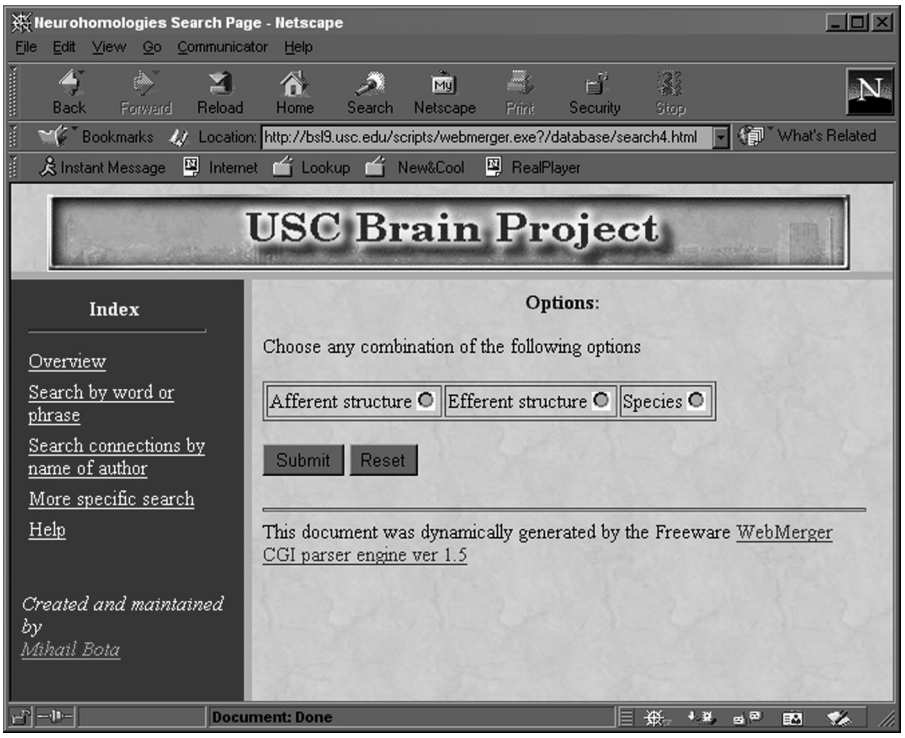

Figure 5 The window for specific search of Connections. The user can choose any combination of options for searching by afferent structure, efferent structure, and species.

A third degree of confidence, that of combined confidence level, is computed for the narrowest query: search by afferent structure and by efferent structure and by species. For each entry that has a pair of structures, the searched afferent and efferent brain nuclei, and for the searched species, the connection confidence level and technique confidence levels are calculated. The combined confidence level for each retrieved entry is calculated as following:

$$CC = CCL^{*}TCL/\max(TCL) \qquad (1)$$

where *CC* is the combined confidence level, *CCL* is the connection confidence level, and *TCL* is the technique confidence level. The value of *max(TCL)* is 3. In this way, the strength of the connection is weighted with the relative confidence of the technique. The minimum value of *CC* is -1, and the maximum value is 3. For a single retrieved entry, a value of *CC* smaller than that of *CCL* is an indication of the fact that the retrieved connection could have another confidence level if a more reliable technique is used. If there is more than one entry for a given connection, then an overall confidence level is computed as the average of combined confidence levels for all retrieved entries. The overall confidence level shows how a connection is reflected in a number of papers, taken together. The overall confidence level should be interpreted in correlation with overall confidence levels for each individual paper. As an example, if, in one paper, a connection is described as being "strong" and the technique that was used was injection with tritiated amino acids, then the connection confidence level will be 3 and the technique confidence level will be 1, with the combined confidence level being 1. If, in a second paper, the same connection is described as being "sparse" and the technique was PHAL, then the second confidence level will be 1 and the technique confidence level will be 3, with the second combined confidence level being 1 again. The overall confidence level for both entries will be 1, indicating the fact that the connection is possibly "sparse" and the results obtained by using the PHAL technique are more reliable. Therefore, one can conclude that the degree of reliability of the strength of a specific connection is increased not only by the specific technique that was used, but also by the number of entries found in the database that are related to it. On the other hand, an entry that states that there is no connection between two structures, contrary to the previous studies, will decrease the overall confidence level. A special case would be that of two entries, both with the same technique confidence level but one with a connection confidence level of 1 and one with -1. The overall confidence level in this case would be equal to zero, meaning that there is no connection between those two structures. This result can be an indication that further studies might be needed to elucidate the existence of that connection or that more data should be entered in the database.

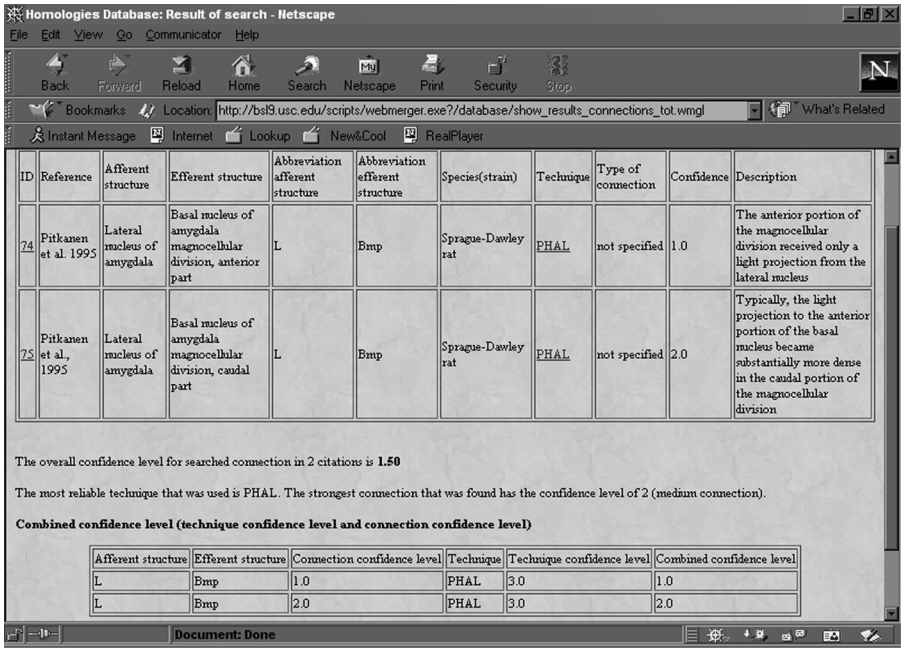

Figure 6 The result of a search of connections between the lateral nucleus of amygdala and basal nucleus of amygdala magnocellular division. For each search by afferent and efferent structures and by species, the combined confidence levels and the overall confidence level are calculated (see text for details).

Another example is shown in Fig. 6, which shows two entries for connections from the rat lateral nucleus of amygdala (L) to the basal nucleus of amygdala, magnocellular division (Bmp), as found in Pitkanen *et al.*, (1995), who follow the terminology and parcellation defined by Reep *et al.*, (1987) for amygdala. The authors dissociate between the anterior and caudal parts of Bmp, based on the density of afferents from L, but do not provide distinct abbreviations for these two parts. Thus, the anterior part of Bmp receives a light projection from L (the confidence level has the value 1), while the caudal part receives a more dense projection (we assigned a value of 2 to this connection). Both connections have been traced using PHAL (technique confidence level 3). As can be seen in Fig. 6, the connection confidence level is identical with the combined confidence level; therefore, the reliability of the connections is maximal. On the other hand, the overall confidence level for both entries is 1.5, suggesting that the connection between L and Bmp as an individual nucleus is between a light and a medium one. This result can be interpreted as follows: if one considers the Bmp as an individual nucleus, then the connection from L to Bmp is between light and medium. On the other hand, this interpretation is a simplistic one, and the topography of projections from L to Bmp, as suggested by Pitkanen *et al.*, is lost. In this situation, based on the afferents from L, one can propose a further dissociation of Bmp into an anterior and caudal part, seen as distinct substructures. This suggestion can be seen as a prediction for future experiments to establish the possible subparcellation of Bmp according to different criteria; therefore, by providing the above-described confidence levels, we offer a way for evaluating different results of tract-tracing experiments. By using the overall confidence level for a number of entries, we offer an overall view of the connections between brain structures as reflected in the literature. Moreover, as we saw above, we can offer predictions for future experiments to elucidate the existence of connections between two brain structures that retrieve two contradictory entries with the same confidence level or the existence of brain nuclei as distinct structures on the basis of their connectivity patterns.

6.4.6 The NeuroHomology Database: Homologies

As described earlier, we have identified eight criteria to define a homology between two brain structures: cell morphology, relative position, cytoarchitecture, chemoarchitecture, myeloarchitecture, afferent and efferent connections, and function. We use these eight criteria to evaluate a degree of homology between two brain nuclei. The Homologies part of the NeuroHomology database can handle data about brain structures from any species; however, due to the fact that the Homologies are seen as a tool for computational neuroscientists and we focus on models of brain structures for humans, monkeys, and rodents, the database contains human/rat, human/monkey, and monkey/rat homologies.

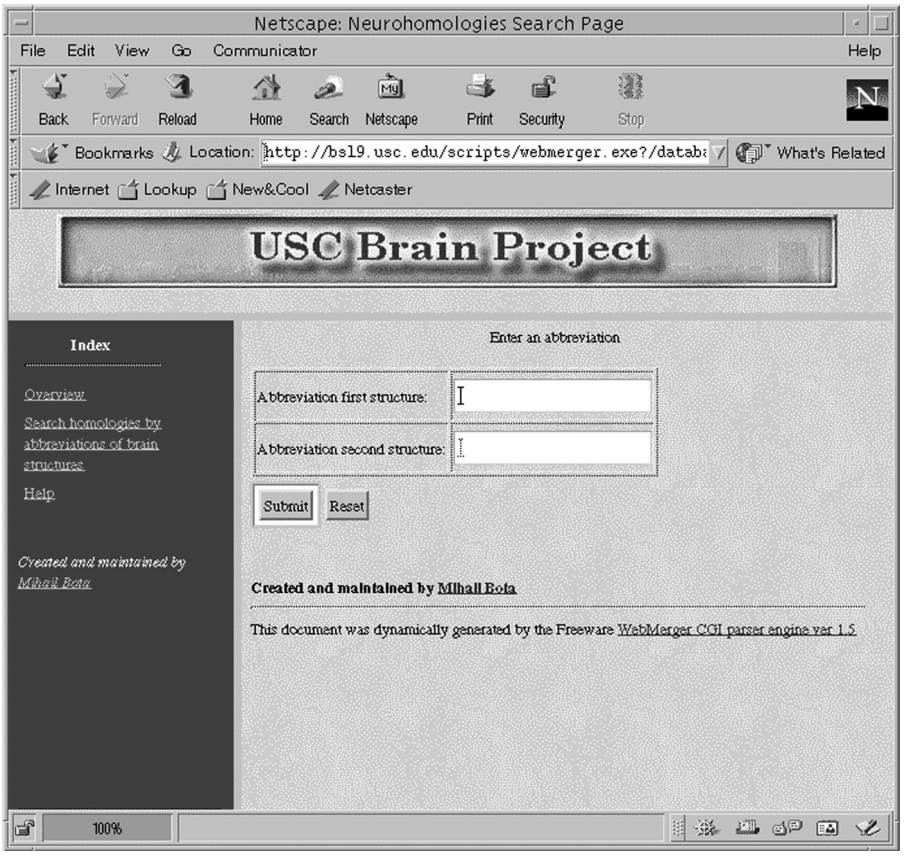

Figure 7 The window for a specific search of homologies. The user can search homologies between brain structures in different species by abbreviations of structures.

The search of the Homologies database can be made by abbreviations of brain structures that are considered to be homologous (Fig. 7). The user can enter in the fields "Abbreviation first structure" and "Abbreviation second structure" the abbreviations for two brain structures from two different species. The result of a search will retrieve all the homologies that are retrieved by the homology inference engine of the database that was described in a previous section, with regard to the searched pair of brain structures. An example of a typical search is shown in Fig. 8. The situation shown in Fig. 8 is the result of a search for homologies between the monkey frontal eye fields (Fef) and the rodent medial agranular cortex (PrCm). The abbreviations of structures are entered as found in the entered sources. The user can inspect all the details of any retrieved entry by clicking on the cited reference. The result will be eight different tables containing information about each homology criterion. Associated with each entry is a short description of the homology, which is inserted by the collator. The user can enter and inspect additional annotations that are attached to each investigated entry.

In the case of homology between Fef and PrCm, the degree of homology is 0.13, while in the case of homology between the rodent L and monkey L (Fig. 9), the degree of homology is 0.5, with four criteria (afferent connections, relative position, cytoarchitecture, and chemoarchitecture) being fulfilled in five retrieved entries. Each entry that is shown in Fig. 9 refers to a different citation of fulfilled criteria of homology.

The user can investigate each entry by clicking on the "Reference" field. A typical example is shown in Fig. 10. The example shown in Fig. 10 involves the homologies between monkey PPC and rat PPC. This page shows the details of the homologies found in the citation Reep *et al.* (1994). The user can further investigate the details of the afferents and efferents by clicking on the abbreviations of efferent and/or afferent brain structures.

Separately, we calculate the common afferent and efferent connections for each homologous pair of brain structures (as shown in Fig. 9). In this way, the user can evaluate the relative importance of common patterns of connectivity in evaluating the degree of homology. A second reason for showing the common afferent and efferent connections, as reflected by the data in the database, is related to the functionality of brain areas. Two brain structures that share a common pattern of connectivity are likely to have the same position in the hierarchy of processing of information in the central nervous system and to have common functions. Moreover, the computational neuroscientists who use the NeuroHomology Database can evaluate the degree of reliability to model

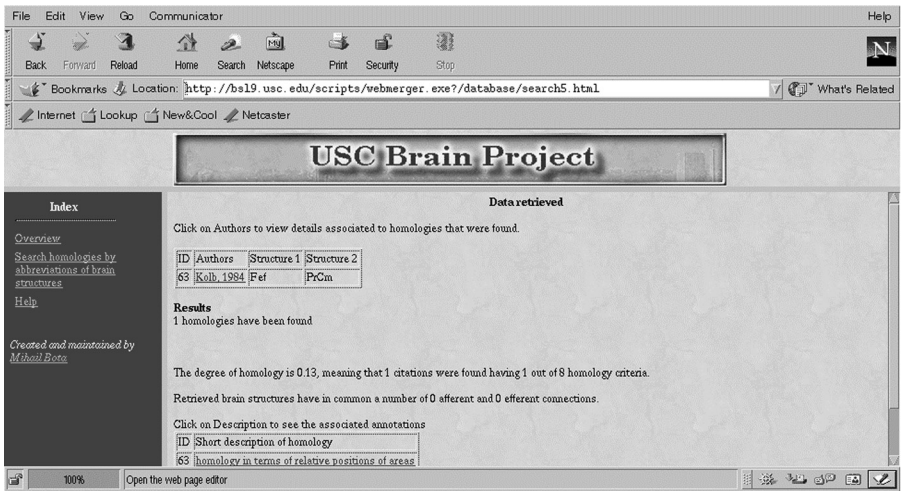

Figure 8 The result of a search of homologies between primate Fef and rodent PrCm (see text for details).

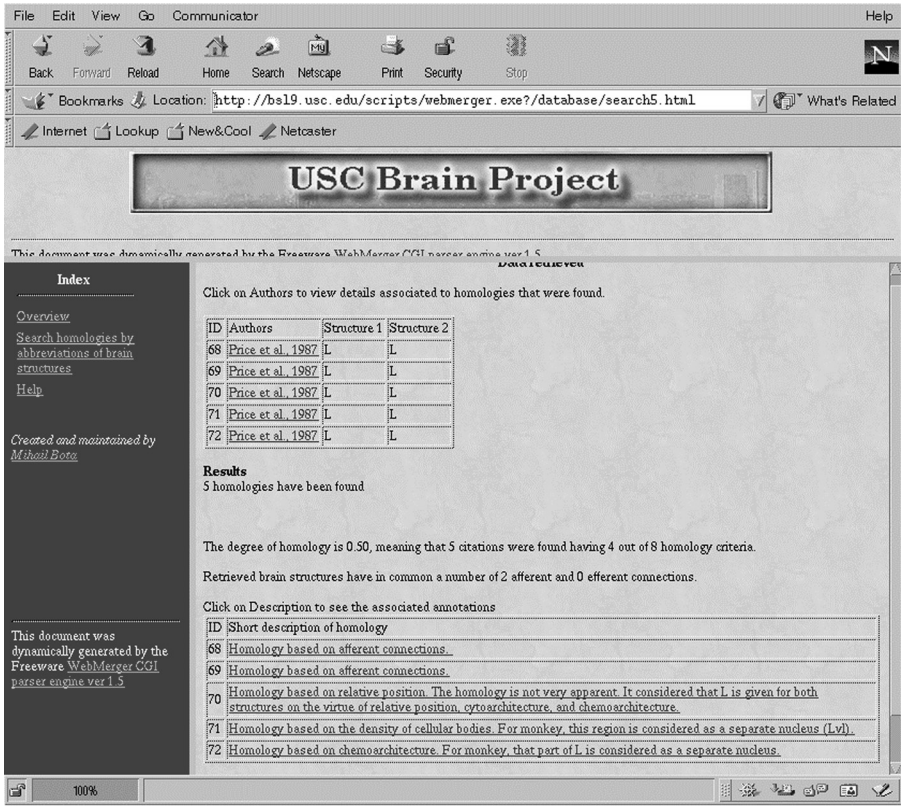

Figure 9 A query for homologies between monkey lateral nucleus of amygdala (L) and rodent L retrieved five different entries. The homology criteria that are fulfilled are afferent connections, relative position, cytoarchitecture, and chemoarchitecture (staining for AchE).

neural systems from one species by using data from other species.

6.4.7 Conclusion and Future Development

The NeuroHomology Database is a knowledge-based summary database that contains homologies between brain structures for human/monkey, human/rat, and human/rodent species. The database can be used for searching brain structures and connections as interpreted from the literature. We have proposed a way to quantify the degrees of confidence of connections and staining techniques that are used. We also have proposed a method for computing the overall confidence level for a number of entries related to a single connection; based on it, the user can evaluate the reliability of the searched connection as reflected in the literature.

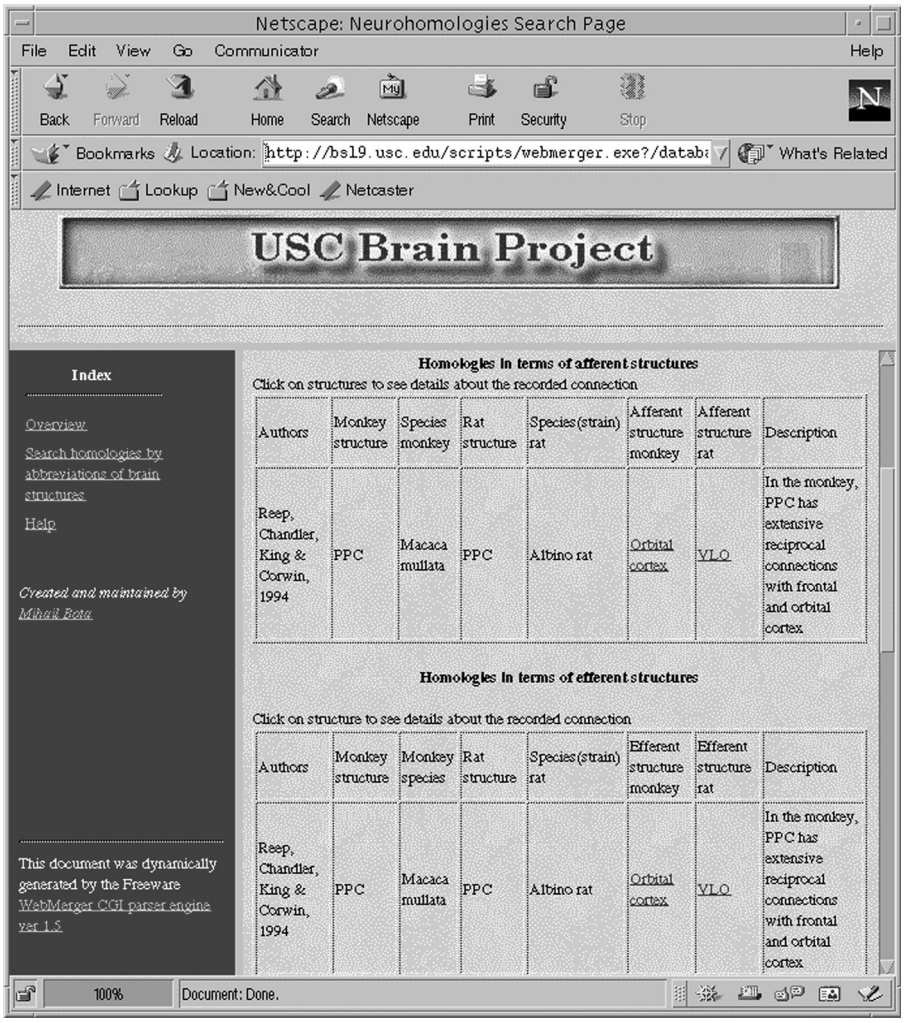

Figure 10 The details of an entry retrieved by the search for homologies between *Macaca mulatta* PPC and Albino rat PPC.

Related to homologies between brain structures, we propose that the homology between two structures from different species can be better described by the degree of homology computed by taking into account the criteria described earlier. In this way, we can offer a quantitative measure of the homology between two brain structures. The NeuroHomology Database is the first attempt to systematize the literature on homologies between brain structures. Therefore, the usefulness of the NeuroHomology Database can be threefold: (1) as a tool for systematization of existing information about homologies at the level of the central nervous system that could be of special interest for comparative neuroanatomists; (2) as a tool for neuroscientists who study a brain structure in a given species and want to compare their findings with those that are characteristic of a possibly homologous structure from another species; and (3) for computational neuroscientists that can evaluate the degree of reliability to model brain structures from one species by using experimental data or characteristics of brain structures from other species. The future development of the NeuroHomology Database will be focused on two main directions: (1) further refinement of the existent criteria of homology and insertion of new criteria, and (2) extension of the NeuroHomology Database with electrophysiological information and linking it to the BMW database.

Related to the first direction of development, the criteria of relative position and cytoarchitecture will be refined. The relative position will be considered in both topological and topographical terms. The criterion of cytoarchitecture will make the dissociation between the layers of the isocortex and allocortex on one hand, and the appearance of subcortical nuclei. Related to this direction of development is the issue of assigning specific weights for each criterion taken into account. As stated in a previous part of this chapter, we consider in the current version of the NeuroHomology Database that all criteria have the same importance in establishing a degree of homology, each having the same weight. A more accurate and realistic way of calculating the degree of homology for a pair of brain structures from two species would be to assign specific weights for each considered criterion. In the first part of this chapter, we

restricted our discussion to the homology of brain structures at the level of hierarchy of cellular aggregates. Future development of the NeuroHomology Database will be also be in the direction of establishing homologies at the levels of hierarchies of brain cells and their subtypes and molecules. To do so, special work will be devoted to add the homologies at the level of gene expression. The homology criterion will include in this way the ontogenetic similarities in different species.

The second line of development, which is related to the first one, is the incorporation of electrophysiological data at the cellular level and the connection of the NeuroHomology Database with the BMW database. In this way, the Brain Structures part of the NeuroHomology Database will describe more accurately a brain structure, and a link with the BMW database will be possible. The user will be able to inspect both the neuroanatomical and neurophysiological properties of a brain structure in a given species and the computational models/modules that are associated with that structure or model some features of it.

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