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DATABASE AND TOOLS FOR ANALYSIS OF TOPOGRAPHIC ORGANIZATION AND MAP TRANSFORMATIONS IN MAJOR PROJECTION SYSTEMS OF THE BRAIN

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Abstract—Integration of dispersed and complicated information collected from the brain is needed to build new knowledge. But integration may be hampered by rigid presentation formats, diversity of data formats among laboratories, and lack of access to lower level data. We have addressed some of the fundamental issues related to this challenge at the level of anatomical data, by producing a coordinate based digital atlas and database application for a major projection system in the rat brain: the cerebro-ponto-cerebellar system. This application, Functional Anatomy of the Cerebro-Cerebellar System in rat (FACCS), is available via the Rodent Brain WorkBench (http://www.rbwb.org/). The data included are x,y,z-coordinate lists describing exact distributions of tissue elements (axonal terminal fields of axons, or cell bodies) that are labeled with axonal tracing techniques. All data are translated to a common local coordinate system to facilitate across animal comparison. A search capability allows queries based on, e.g. location of tracer injection sites, tracer category, size of the injection sites, and contributing author. A graphic search tool allows the user to move a volume cursor inside a coordinate system to detect particular injection sites having connections to a specific tissue volume at chosen density levels. Tools for visualization and analysis of selected data are included, as well as an option to download individual data sets for further analysis. With this application, data and metadata from different experiments are mapped into the same information structure and made available for re-use and re-analysis in novel combinations. The application is prepared for future handling of data from other projection systems as well as other data categories.

Key words: 3-D reconstruction, cerebro-cerebellar, database, data sharing, neuroinformatics, pontine nuclei.

Topographic organization is a general feature of brain architecture, critical for appropriate information processing and normal functioning of the nervous system. Brain maps identified with use of electrophysiological methods often display spatial orderliness (see, e.g. Mountcastle, 1957; Woolsey, 1958; Woolsey and Van der Loos, 1970; Welker, 1971, 1976; Kaas et al., 1979; Donoghue and Wise, 1982; Chapin and Lin, 1984) and order is typically found also in the projection systems that connect the various divisions of the brain (see, e.g. Deschenes et al., 1998; Zaborszky et al., 1999; Chesselet, 2000; Schmahmann, 2000; Swanson, 2000; Leergaard and Bjaalie, 2002; Dum et al., 2002; Leergaard, 2003; Kelly and Strick, 2004). But topographic maps in different interconnected brain regions are often organized according to different principles. The spatial organization characteristics for the individual maps presumably provide different opportunities and restrictions for information processing occurring at the respective levels of the brain circuits. For example, map elements that are remotely located in one map may be co-located in another map, allowing integration of new combinations of information (Bjaalie and Brodal, 1989; Leise, 1990; Nelson and Bower, 1990; Brown, 1992; Flaherty and Graybiel, 1993; Alloway et al., 2000; Hoffer and Alloway, 2001; Brown et al., 1998; Schwarz and Thier, 1999; Leergaard et al., 2004).

One of the largest projection systems in the brain is the pathway connecting the cerebral cortex with the cerebellum (for review, see Voogd, 1995). This pathway is interrupted by a major intercalated structure, the pontine nuclei. The first link in this pathway, the corticopontine projection, originates in a large number of cortical areas, whereas the second link, the pontocerebellar projection, reaches virtually all parts of the cerebellar cortex. The principles of topographic organization in this pathway have been outlined in most detail for the corticopontine projection, where topography has been demonstrated at multiple levels, across regions of the cortex, across areas, and also across subdivisions of a single area (for reviews, see Brodal and Bjaalie, 1992; 1997; Schmahmann and Pandya, 1997; Ruigrok, 2004; Bjaalie and Leergaard, 2005). Fundamental principles of organization have been outlined in particular detail for the projections originating in the rat somatosensory cortex (reviewed in Leergaard, 2003).

The map transformations that occur in the cerebro-ponto-cerebellar pathway are substantial (Fig. 1). Thus, the continuous and relatively simple maps found in the cerebral cortex (Welker, 1971; Hall and Lindholm, 1974; Chapin and Lin, 1984) are transformed to discontinuous and complex, patchy maps in the cerebellar cortex (Shambes et al., 1978; Bower et al., 1981; Bower and Kassel, 1990). The pontine nuclei are also known to dis-

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Abbreviations: BDA, biotinylated dextran amine; FACCS, Functional Anatomy of the Cerebro-Cerebellar System in rat; FR, rhodamine-conjugated dextran amine, FluoroRuby; MI, primary motor cortex; Pha-l, *Phaseolus vulgaris*-leucoagglutinin; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; 3-D, three-dimensional.

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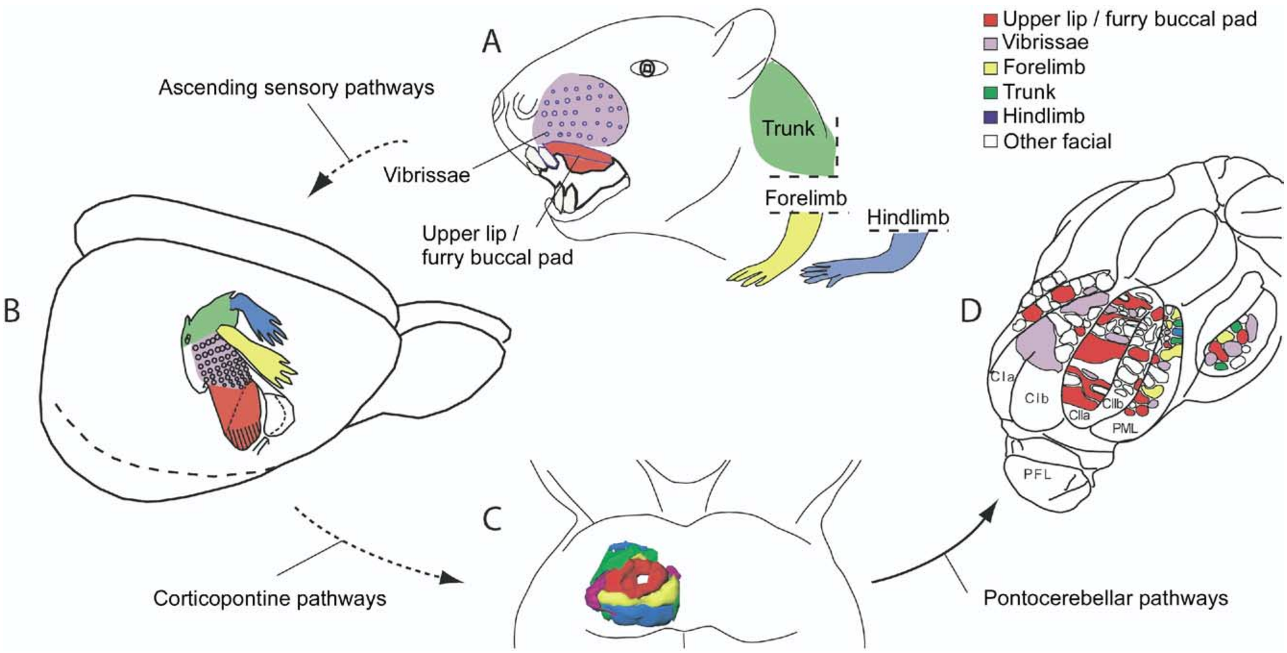

Fig. 1. Map transformations in the rat somatosensory system. Sensory information from the body surfaces on the left side (A) is orderly projected through ascending pathways and represented in a somatotopic map in the right primary somatosensory cortex. The essentially 2-D cortical somatotopic brain map (B) is projected to the cerebellum (D) by way of the pontine nuclei (C). In the right pontine nuclei (C), the cortical map is transformed into a more complex 3-D map. The cerebellar cortex (D), in turn, contains an even more complex map referred to as a fractured map. Reprinted from Bjaalie and Leergaard, 2005, with permission.

play a well-organized representation of the cerebral cortical map, and the principles of organization of this pontine map have been gradually modified with increasing access to more refined neural tracing data (Nyby and Jansen, 1951; Brodal, 1968, 1978; Hartmann von Monakow et al., 1981; Wiesendanger and Wiesendanger, 1982; Mihailoff et al., 1985; Schmahmann and Pandya 1989, 1991, 1993; Panto et al., 1995; Schwarz and Thier, 1995, 1999; Leergaard et al., 1995, 2000a,b, 2004; Schmahmann et al., 2004).

As the multiple divisions of the cerebro-cerebellar system (Fig. 1) are studied, data are accumulated with reference to regions, areas and sub-areas of the cerebral cortex (sites of origin of the corticopontine projections), to sub-volumes of the pontine nuclei (terminal fields of corticopontine projections and neurons of origin of pontocerebellar projections), and to regions, stripes, zones, and patches of the cerebellar cortex (targets of the pontocerebellar projections). Detailed features of the spatial organization of this system are thus collected across different laboratories and different studies within a laboratory.

A problem with data published in the traditional journal format relates to the limitations imposed by presentation of results in the form of text and illustrations. The lower level data are generally not made available. Further, differences in data presentation and data formats used in different laboratories typically make comparisons of data across studies and laboratories difficult. Needless to say, this hampers the establishment of comprehensive resources that efficiently bring together results and allow full use of the data accumulated (Chicurel, 2000; Koslow, 2000; Amari et al., 2002; Bjaalie, 2002; Martone et al., 2004; Bjaalie and Leergaard, 2005). This observation is valid for data collected from the cerebro-cerebellar system as well as for data from most other systems of the brain.

To address the challenge of managing spatial distribution data from the brain, we have developed a database that allows users to query, retrieve, visualize, and analyze different combinations of data sets. The application is built around the analysis of the rat cerebro-cerebellar system, but its overall structure and tools could equally well be used for the study of other projection systems. First, we have employed a standardized coordinate system (Brevik et al., 2001) for presentation of the data on topographical distribution (locations of terminal fields of axons and distributions of neurons of origin) within the pontine nuclei. The data are coordinates describing the distribution of the elements labeled with axonal tracing techniques, following injections in the cerebral cortex or cerebellum. All data are transformed to the standardized coordinate system. Second, we have developed a database architecture based on a relational database system that is flexible and scalable and allows future expansion, to include other data modalities and other brain systems. Using Java-based tools in the application, it is possible to view and analyze any combination of available data sets, in order to reveal shape and distribution of the labeled elements. Analytical methods include re-slicing at user-defined section thicknesses and section angles, creation of atlas-style presentation diagrams of the selected data sets, and mathematical analysis of overlap and segregation between the selected data points.