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ORIGINAL ARTICLE

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Organization of identified fiber tracts in the rat fimbria-fornix: an anterograde tracing and electron microscopic study

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Abstract The fimbria is a major route for afferent and efferent fibers of the hippocampal formation. However, little is known about the intrinsic organization of the fimbria-fornix complex. In this study, the anterograde tracer *Phaseolus vulgaris*-leucoagglutinin (PHAL) was used to analyze the ultrastructure and topography of identified fiber tracts within the fimbria-fornix. Septo-hippocampal fibers are loosely distributed throughout the fimbria-fornix. Commissural fibers cross the midline in the ventral hippocampal commissure and form a tight fiber bundle in the fimbria. Crossed entorhino-hippocampal fibers cross the midline in the ventral hippocampal commissure rostral to the commissural fiber bundle, and crossed entorhino-entorhinal fibers pass through the dorsal hippocampal commissure. This suggests a topographical organization of fiber tracts within the fimbria-fornix that reflects the laminar organization of the hippocampal target structure: fibers of the diffusely terminating septo-hippocampal projection are loosely distributed throughout the fimbria-fornix, while those projections that are known to terminate in specific laminae of the hippocampal formation (commissural projection, crossed entorhino-hippocampal projection) form fiber bundles within the fimbria and the ventral hippocampal commissure.

Key words *Phaseolus vulgaris*-leucoagglutinin · Hippocampus · Septum · Entorhinal cortex · Limbic system · Fimbria

Abbreviations *A* Astrocyte · *CA1, CA3* hippocampal subfields · *CC* corpus callosum · *D* dendrite · *DG* dentate gyrus · *DHC* dorsal hippocampal commissure · *Fi* fimbria · *LS* lateral septal area · *LV* lateral ventricle · *O* oligodendrocyte · *SFO* subfornical organ · *VHC* ventral hippocampal commissure

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Introduction

The major afferent and efferent fiber bundles of the hippocampal formation pass through the fimbria-fornix. Although the areas of origin of these projections as well as their target areas have been described in detail (see Amaral and Witter 1995 for review), only a few studies have addressed the intrinsic organization of these axon bundles (Wyss et al. 1980; Deller and Nitsch 1995) or their glial framework (Suzuki and Raisman 1992; Suzuki and Raisman 1994) within the fimbria-fornix itself. This is surprising, since the experimental transection of the fimbria-fornix is a common neuroanatomical approach for connectivity studies (e.g., Frotscher and Zimmer 1983; Leranth and Frotscher 1983; Seress and Ribak 1984; Deller and Leranth 1990) as well as studies that focus on re- and degenerative changes occurring in the hippocampus or the septal nuclei (e.g., Raisman 1969; Raisman and Field 1973; Koliatsos et al. 1989; Buchan and Pulsinelli 1990; Li et al. 1992; Naumann et al. 1992). Similarly, electrophysiological stimulation of the fimbria or the ventral hippocampal commissure has been used to analyze the functional significance of the commissural (e.g., Finnerty and Jefferys 1993) and the septo-hippocampal (e.g., Lamour et al. 1984; Dutar et al. 1986) projections, and embryonal transplants have been placed into the fimbria-fornix to investigate axonal regeneration and reorganization within the white matter (Brook et al. 1993; Raisman et al. 1993).

Recently, we have demonstrated that a precise transection of the rostral fornix interrupts the connection between the septum and the hippocampus while leaving the commissural projections intact (Deller and Nitsch 1995). This approach was possible only after the exact position of commissural fibers within the ventral hippocampal commissure became known (Deller et al. 1995).

In the present study, we investigated the major afferent and efferent fiber tracts of the hippocampal formation that run in the fimbria-fornix. First, we investigated the ultrastructure of the fimbria and described the arrangement of fibers and glial cells within this central fi-

ber pathway. With the help of the anterograde tracer *Phaseolus vulgaris*-leucoagglutinin (PHAL) that allows for the direct visualization of fiber tracts within the fimbria-fornix, we then analyzed the major afferent and efferent fiber systems of the hippocampal formation and characterized their relative positions within the fimbria-fornix. This detailed description of the structural organization of the fimbria-fornix may provide a basis for precise and localized manipulations of this pathway in future experimental studies.

Materials and methods

Animals

Adult Sprague-Dawley rats (250–350 g) housed under standard laboratory conditions were used in this study. Surgical procedures were performed under anesthesia with a combination of ketamine, xylazine, and acepromazine (ketamine 62.5 mg/kg body weight, xylazine 16.7 mg/kg body weight, acepromazine 6.25 mg/kg body weight). Several groups of animals were used in these experiments:

1. Unoperated controls (*n* 5) to study the normal anatomy of the fimbria-fornix.
2. Animals with PHAL injections into the medial septum/diagonal band complex (MS/DB; *n* 12; coordinates from bregma according to Paxinos and Watson 1986: AP –0.2 to +0.8; L 1.0; V –6.8, pipette angled inwards by 11°) to label the septo-hippocampal projection.
3. Animals with PHAL injections into the hilar area of the dentate gyrus and/or area CA3 of the hippocampus (*n* 12; coordinates from bregma: AP –6.3; L 4.7; V –5.8, and AP –3.8; L 1.6; V –3.8) to label the commissural projections.
4. Animals with PHAL injections into the entorhinal cortex (*n* 12; coordinates from bregma: AP –8.5; L 3.8–4.5; V –5.8, and AP –8.6; L 5.0–6.0; V –5.8) to label the crossed entorhino-hippocampal and entorhino-entorhinal projections.

PHAL iontophoresis and PHAL immunocytochemistry

PHAL injection and immunostaining procedures have been described in detail elsewhere (e.g., Gerfen and Sawchenko 1984; Deller et al. 1995). The 36 experimental animals received a iontophoretically delivered deposit of PHAL (2.5% in 10 mM phosphate buffer, pH 7.8; Vector Laboratories, Burlingame, Calif., USA) into the respective areas (see above) via a stereotaxically positioned glass micropipette with a tip diameter between 15 and 30 µm. A positive current of 5 µA was applied for every other 5 s for 20–30 min. After a survival time of 10 days following the injection of the anterograde tracer, the rats were deeply anesthetized with an overdose of Nembutal and were transcardially perfused with a fixative containing 4% paraformaldehyde, 0.08% glutaraldehyde, and 15% picric acid in 0.1 M phosphate buffer (PB, pH 7.4). Animals not injected with PHAL were transcardially perfused with a fixative containing 4% paraformaldehyde and 1% glutaraldehyde in 0.1 M PB. The brains were removed, postfixed for 2 h in glutaraldehyde-free fixative, and cut as frontal or horizontal sections (100 µm) on a vibratome.

Immunocytochemistry was used to visualize PHAL-containing axons. Free-floating sections were incubated for 2 days at 4 ° C in biotinylated goat anti-PHAL (1:400, Vector Labs.), 1% normal horse serum, and 0.1% NaN_3 in 0.1 M PB. For light microscopy, the antibody solution also contained 0.5% Triton X-100. After rinsing in PB, the sections were incubated in the intensified avidin-biotin-peroxidase complex (ABC-Elite, Vector Labs.) for 3 h. Following three subsequent washes, the sections were immersed in a Nickel/DAB solution (0.05% 3,3' diaminobenzidine, 0.02% nickel ammonium chloride, 0.024% cobalt chloride, 0.001% H_2O_2) for 5–10 min, which resulted in deep-blue labeling of PHAL-containing fibers. Sections were placed on gelatin-coated slides, dehydrated in ethanol, mounted in Eukitt and examined under the light microscope. Camera lucida drawings were made of defined sections of the fimbria-fornix. These drawings were superimposed and a synopsis of the different fiber tracts in the fimbria-fornix was made (Fig. 8).

Selected sections of control and experimental animals were embedded for electron microscopy and serially sectioned on a Reichert Ultracut. Ultrathin sections were mounted on single-slot grids coated with Formvar film, stained with lead citrate, and studied in a Zeiss EM 110.

Results

Control animals

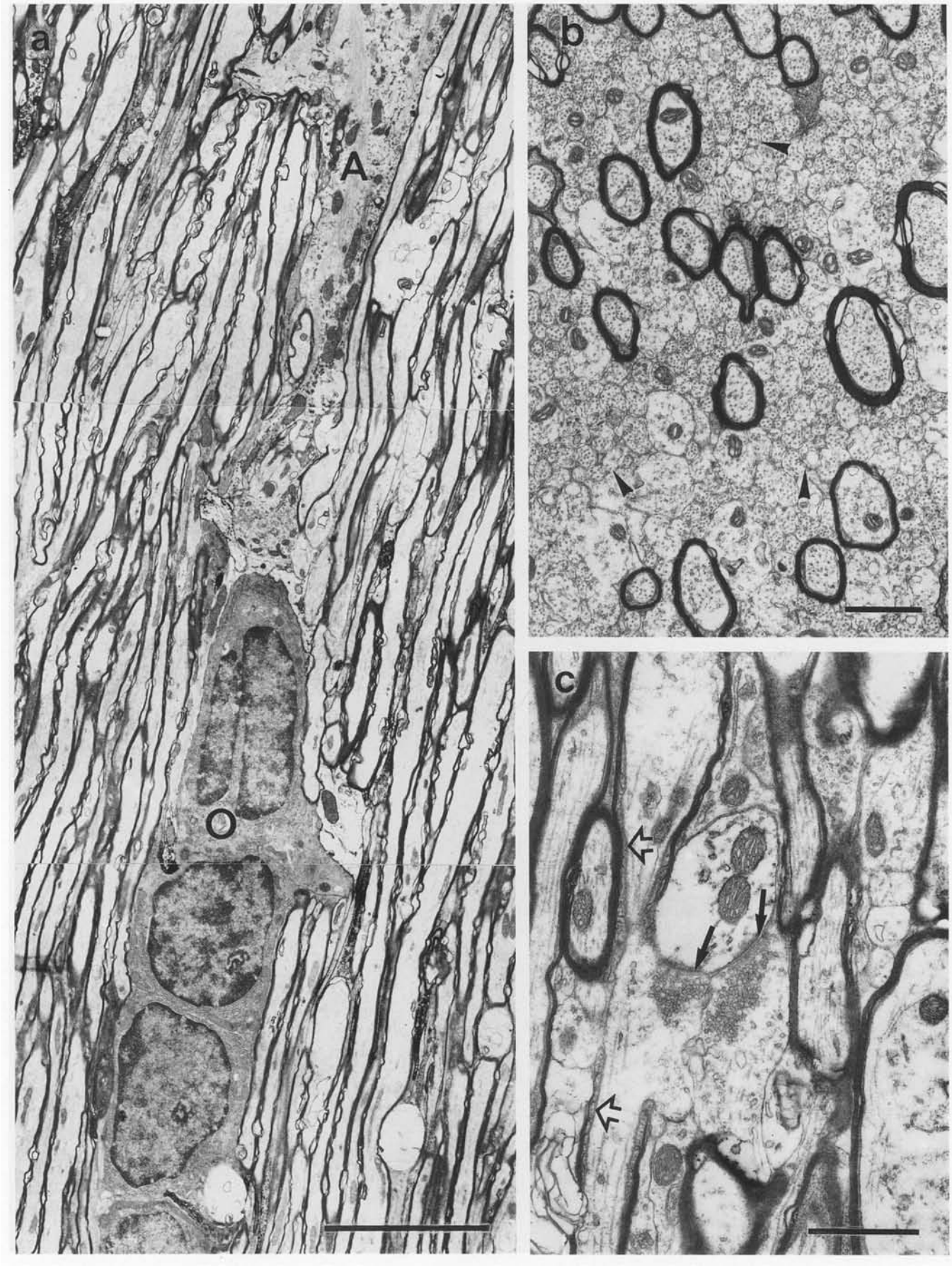
The ultrastructure of the normal fimbria was analyzed in untreated control animals. Sections of the dorsal and the caudal portions of the fimbria were used for these investigations.

Myelinated and unmyelinated axons were unevenly distributed within the fimbria. In most areas myelinated axons dominated (Fig. 1a), while in some areas unmyelinated axons were more numerous (Fig. 1b). Oligodendrocytes appeared to "line up" in parallel with the fiber course, and solitary astrocytes could be found in their vicinity (Suzuki and Raisman 1992; Fig. 1a). Only in portions of the fimbria close to the hippocampus or the midline and the triangular septal nucleus (TS) were dendrites also observed (Figs. 1c, 2). Some of these dendrites were contacted by an axon forming a typical en passant synapse (Fig. 1c). Other dendrites were the targets of numerous boutons (Fig. 2a), some of which contained dense core vesicles (Fig. 2b). In most cases, the dendrites were found in the dorsal portion of the fimbria.

Animals with PHAL injections into the MS/DB

After PHAL injections into the MS/DB (Fig. 3a), PHAL-labeled septal fibers were found in all hippocampal subfields and laminae (Fig. 3b). In the fimbria-fornix, PHAL-labeled fibers were loosely distributed and could be followed on their way to the hippocampus. In the fornix, septo-hippocampal fibers spare the ventral hippocampal commissure (Fig. 3c, d), where the commissural

Fig. 1a–c Ultrastructure of the rat fimbria. **a** Electron micrograph of a longitudinal section of the fimbria. An astrocyte (*A*) and several oligodendrocytes (*O*) are arranged in a row between numerous myelinated and unmyelinated axons. **b** Electron micrograph of a transverse section of the fimbria. Note the variation in diameter of the myelinated axons and the intermingled clusters of unmyelinated fibers (*arrowheads*). **c** Electron micrograph of an en passant synapse within the fimbria. The *arrows* point to the synaptic clefts. The synapse is formed at a node of Ranvier with the dendrite of an unidentified target neuron. The two *open arrows* indicate the unmyelinated portion of the axon. *Bar* 5 µm in **a**, 0.5 µm in **b**, 1 µm in **c**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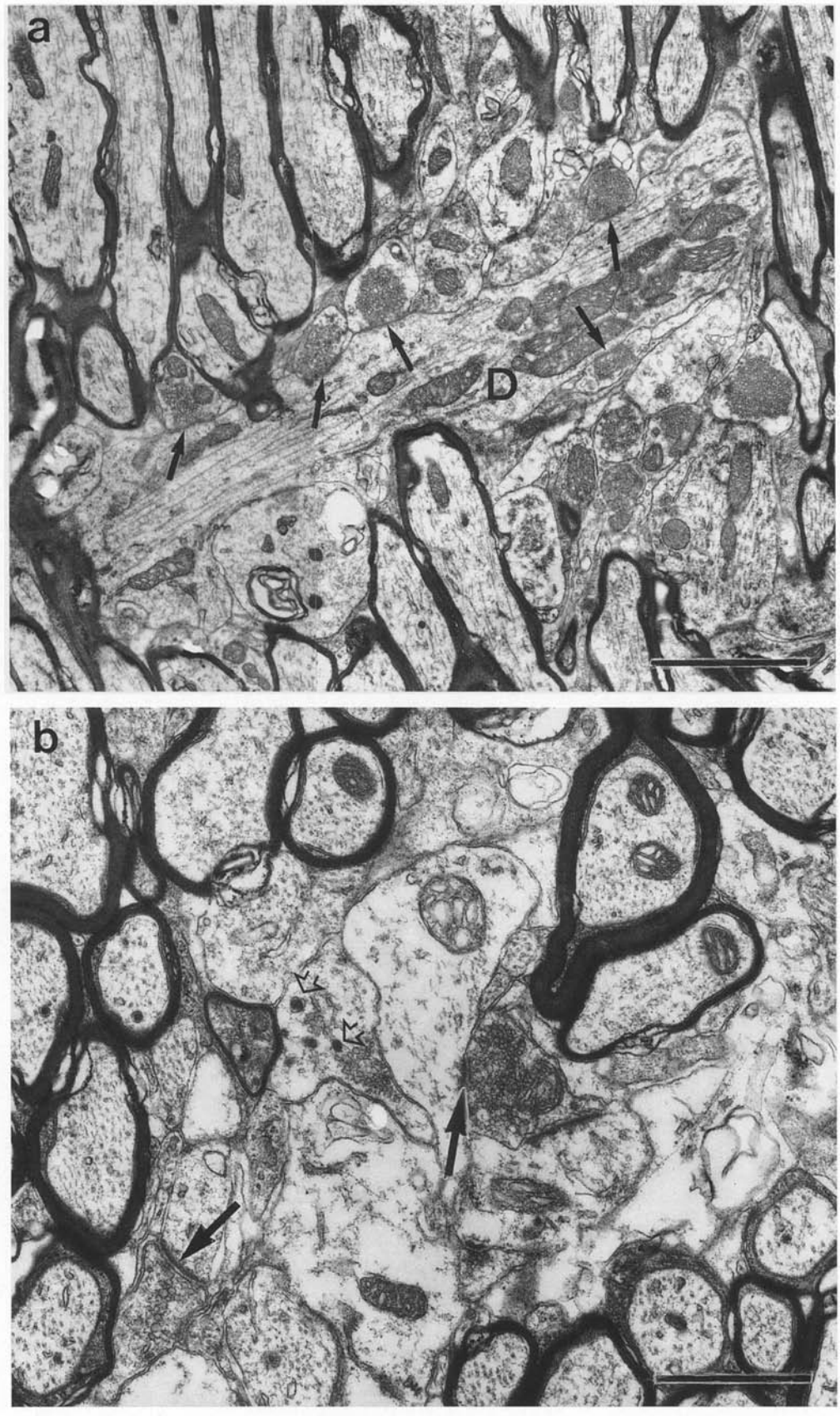
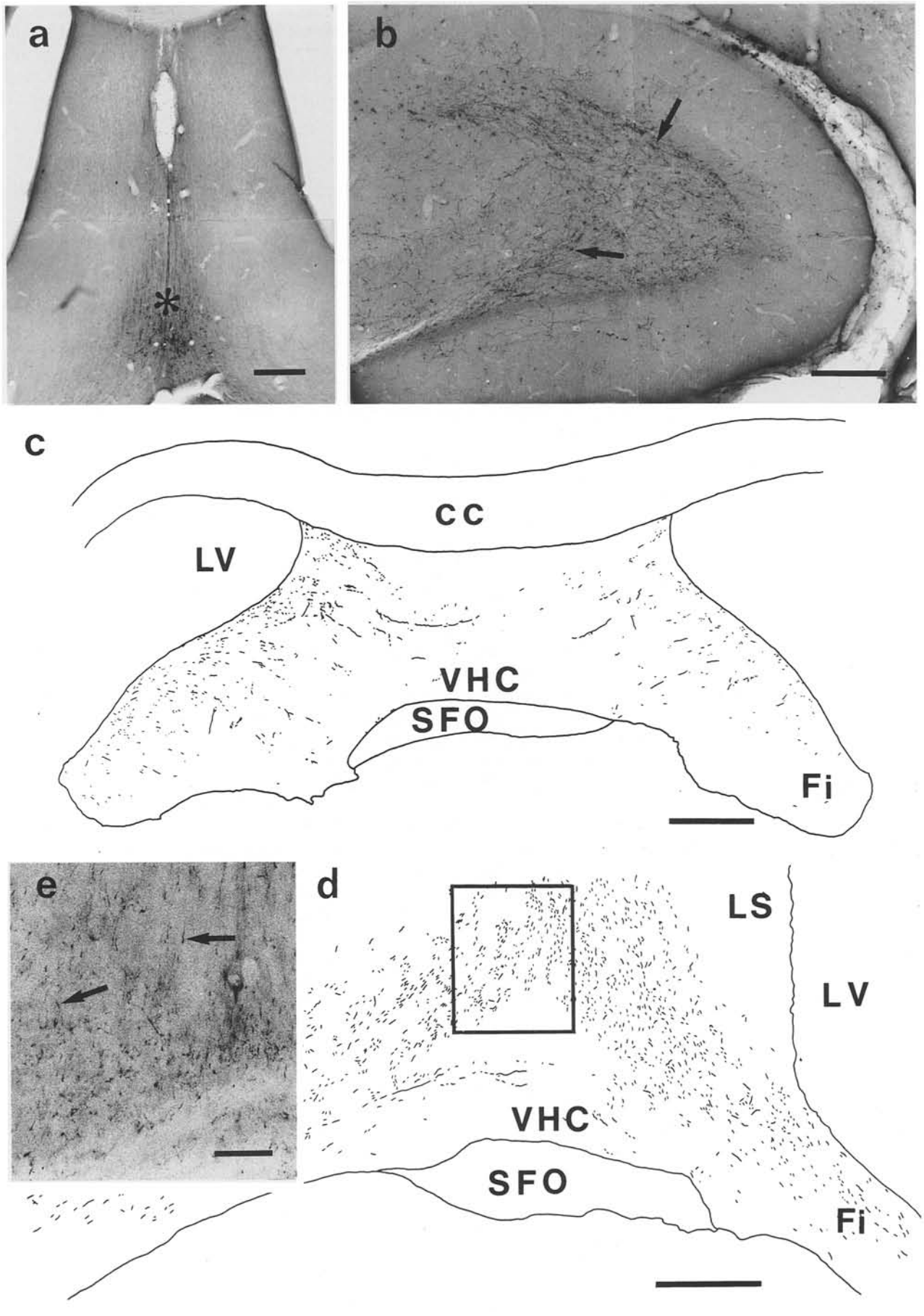


Fig. 2a,b Ultrastructure of synapses in the fimbria. **a** Electron micrograph of the dorsal fimbria. Several axon terminals form synapses with a dendrite (*D*) of an unidentified target neuron. The *arrows* point to the synaptic clefts. **b** Electron micrograph of the caudal (posterior) fimbria. Numerous axon terminals form synapses with dendrites. The *bold arrows* indicate the synaptic clefts. One terminal contains dense core vesicles (*open arrows*). *Bar* 2 μm in **a**, 1 μm in **b**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and crossed entorhinal fibers cross the midline (see below). Septo-hippocampal fibers were more numerous close to the ventricular surface of the fimbria-fornix (Fig. 3c). In horizontal sections, PHAL-labeled septo-hippocampal fibers could only be followed for short distances, indicating that these fibers leave the horizontal plane of sectioning. In the fimbria, PHAL-labeled septo-hippocampal fibers could be followed to the hippocampal formation. Septo-hippocampal fibers were loosely distributed within the fimbria (Fig. 4a, b), but showed a preference for the ventricular side of the fimbria. Electron microscopy revealed small unmyelinated (Fig. 4c), medium-sized myelinated (Fig. 4d), and large (Fig. 4e) myelinated PHAL-labeled septo-hippocampal fibers in the fimbria.

Animals with PHAL injections into the contralateral hippocampus

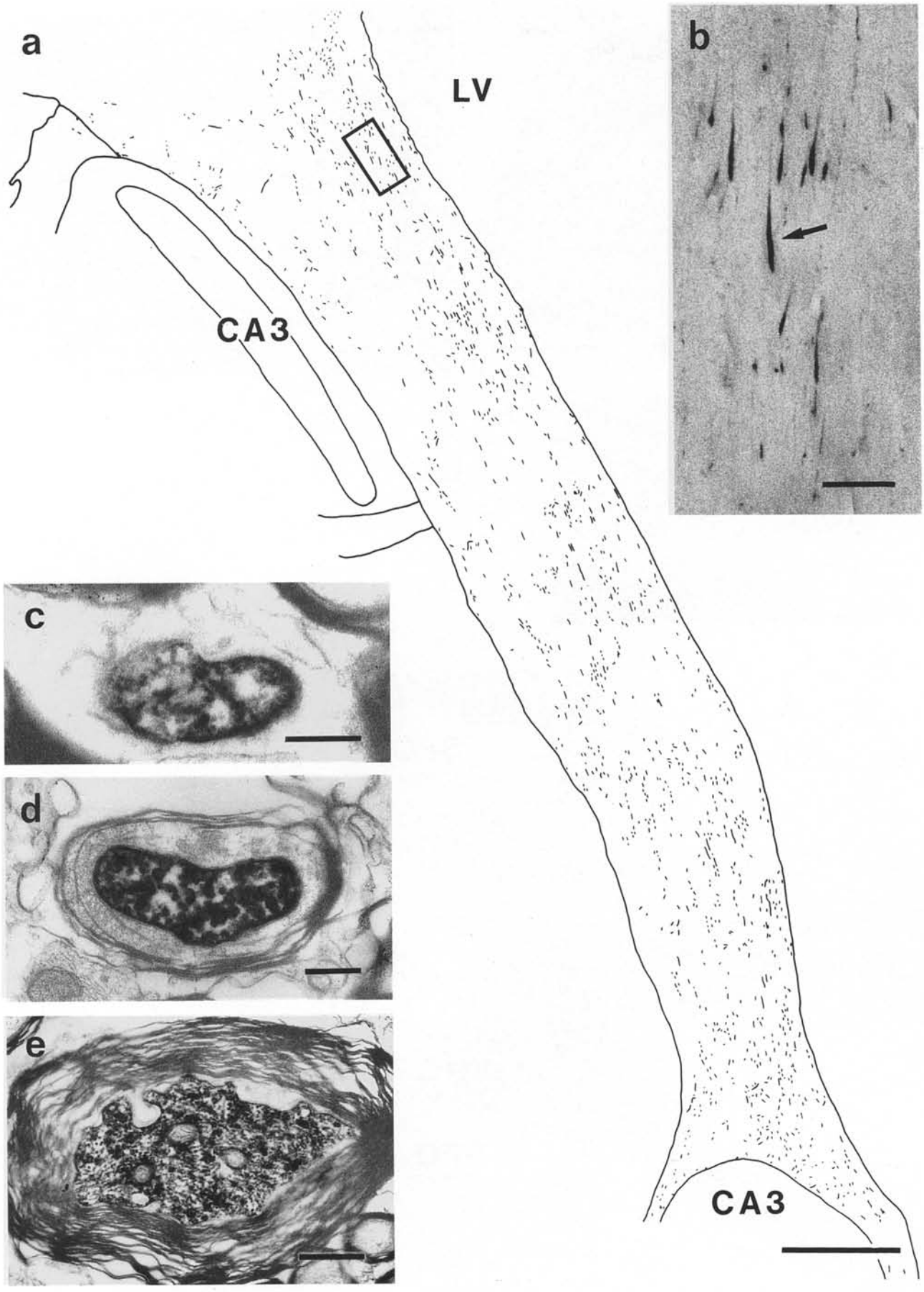
In this group of animals, the PHAL deposit covered the dentate gyrus, area CA3, or both hippocampal subfields (Fig. 5a). In the contralateral hippocampus, the commissural projections to the dentate gyrus and hippocampal subfields CA3 and CA1 could be observed (Fig. 5b). In the fornix, the commissural fibers were located in the ventral (Fig. 5c) and caudal (Fig. 5e) portion of the ventral hippocampal commissure, as could be seen on frontal and horizontal sections through the fornix, respectively. Commissural fibers displayed numerous varicosities (Fig. 5d, f). Together with the commissural projection, the hippocampo-septal projection was also labeled (Fig. 5e). After PHAL injections that also covered CA3 neurons, hippocampo-septal fibers could be observed on both sides of the midline (Fig. 5e), and these fibers terminated in the lateral septal area (data not shown; see also Deller et al. 1995). PHAL injections that were restricted to the hilus showed only a weak and predominantly ipsilateral hippocampo-septal projection to the medial septal area (Alonso and Köhler 1982; Gaykema et al. 1991; Deller et al. 1995). In the fimbria, PHAL-labeled fibers formed a tight bundle close to the pial surface on both the injection side (Fig. 6a, b) and the contralateral side (Fig. 6c, d). Close to the midline, collaterals branch off the commissural fiber bundle and turn rostrally towards the septum. For this reason, PHAL-labeled fibers can be found throughout the septal portion of the fimbria after large PHAL injections into area CA3 of the hippocampus. The commissural fiber bundle, however, stays together and crosses the midline in the ventral hippocampal commissure (see above).

Animals with PHAL injections into the contralateral entorhinal cortex

The cells of origin of the crossed entorhino-dentate projection located in layer II of the medial entorhinal cortex (Steward and Scoville 1976; Wyss 1981), and the cells of origin of the crossed entorhino-hippocampal projections located in layer III of the medial entorhinal cortex (Steward and Scoville 1976; Wyss 1981) took up the tracer (Fig. 7a). PHAL-labeled fibers could be found in the contralateral hippocampus (data not shown; see Deller et al. 1996) and the contralateral entorhinal area (entorhino-entorhinal projection, Fig. 7b). In the fimbria, the entorhino-dentate and entorhino-hippocampal projection pass through the ventral hippocampal commissure (Fig. 7c; see Amaral and Witter 1995), while the entorhino-entorhinal projection can be followed into the dorsal hippocampal commissure (Fig. 7d), the contralateral angular bundle and into the contralateral entorhinal cortex. In frontal sections of the fornix, crossed entorhino-dentate and crossed entorhino-hippocampal fibers can be found in the dorsal portion of the ventral hippocampal commissure, located dorsally to the commissural fibers (see above). In horizontal sections (shown in the synopsis, Fig. 8b), these fiber projections are located rostrally to the commissural fibers in the ventral hippocampal commissure. While most axons cross the midline in a straight line, numerous axons were found that leave the crossed entorhinal fiber bundle and turn rostrally towards the septal nuclei. Some fibers were observed that turned rostrally first, but eventually turned around and entered the contralateral fimbria (Fig. 8b). Thus, the crossed entorhino-hippocampal fiber projections occupy the rostrally and dorsally located portion of the ventral hippocampal commissure. In the fimbria, crossed entorhino-dentate and crossed entorhino-hippocampal fibers can be found in the middle of the fimbria and closer to the ependymal side of the fimbria. These fiber projections form a fiber

Fig. 3a–e The septo-hippocampal projection. **a** *Phaseolus vulgaris*-leucoagglutinin (PHAL) injection site in the medial septum/diagonal band complex. *Asterisk* indicates the injection site. **b** Septo-hippocampal PHAL-labeled fibers in the dentate gyrus (*arrows*). **c** Camera lucida drawing of a coronal section of the fornix and the ventral hippocampal commissure (*VHC*). Septo-hippocampal fibers are loosely distributed and spare the VHC. **d** Camera lucida drawing of a horizontal section of the fornix and the VHC. Septo-hippocampal fibers spare the VHC. *Framed area* illustrated in **e**. **e** Photomicrograph of the *framed area* shown in **d**. *Arrows* indicate PHAL-labeled septo-hippocampal fibers. *Bar* 500 μm in **a**, 200 μm in **b**, 400 μm in **c** and **d**, 100 μm in **e**

Fig. 4a–e Septo-hippocampal fibers in the fimbria. **a** Camera lucida drawing of a horizontal section through the fimbria. PHAL-labeled septo-hippocampal axons are loosely distributed throughout the fimbria, but show a preference for the ventricular side of the fimbria. *Framed area* shown at higher magnification in **b**. **b** Enlargement of the rectangle in **a**. *Arrow* points to a PHAL-labeled septo-hippocampal axon. **c** Electron micrograph of a small unmyelinated PHAL-labeled septo-hippocampal axon. **d** Electron micrograph of a medium-sized myelinated PHAL-labeled septo-hippocampal axon. **e** Electron micrograph of a large myelinated PHAL-labeled septo-hippocampal axon. *Bar* 400 μm in **a**, 30 μm in **b**, 0.2 μm in **c** and **d**, 0.5 μm in **e**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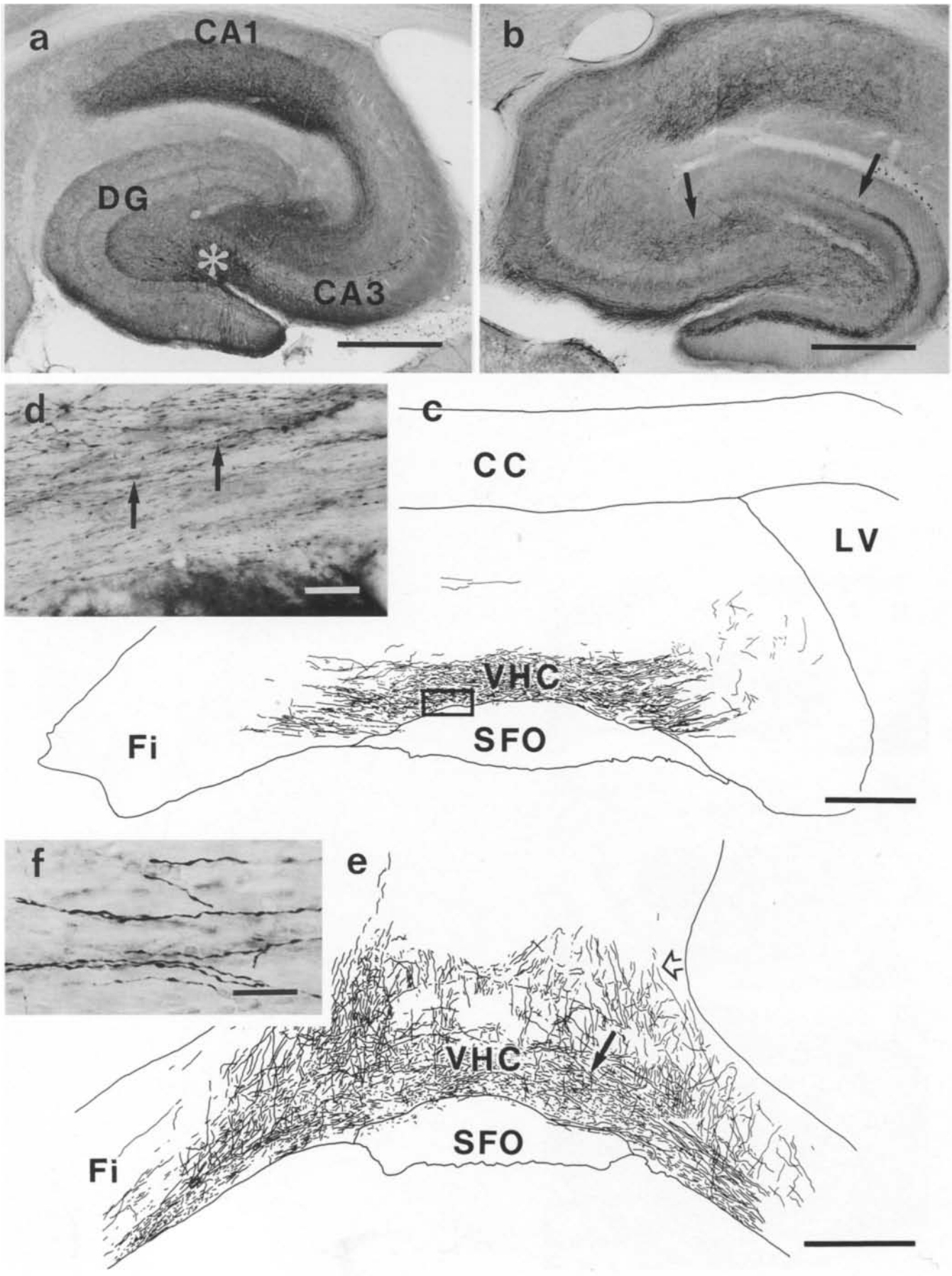
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bundle similar to the one shown for the commissural projection (Fig. 6). In the ventral portion of the fimbria, the crossed entorhino-dentate and crossed entorhino-hippocampal fibers are located laterally to the commissural fibers.

Discussion

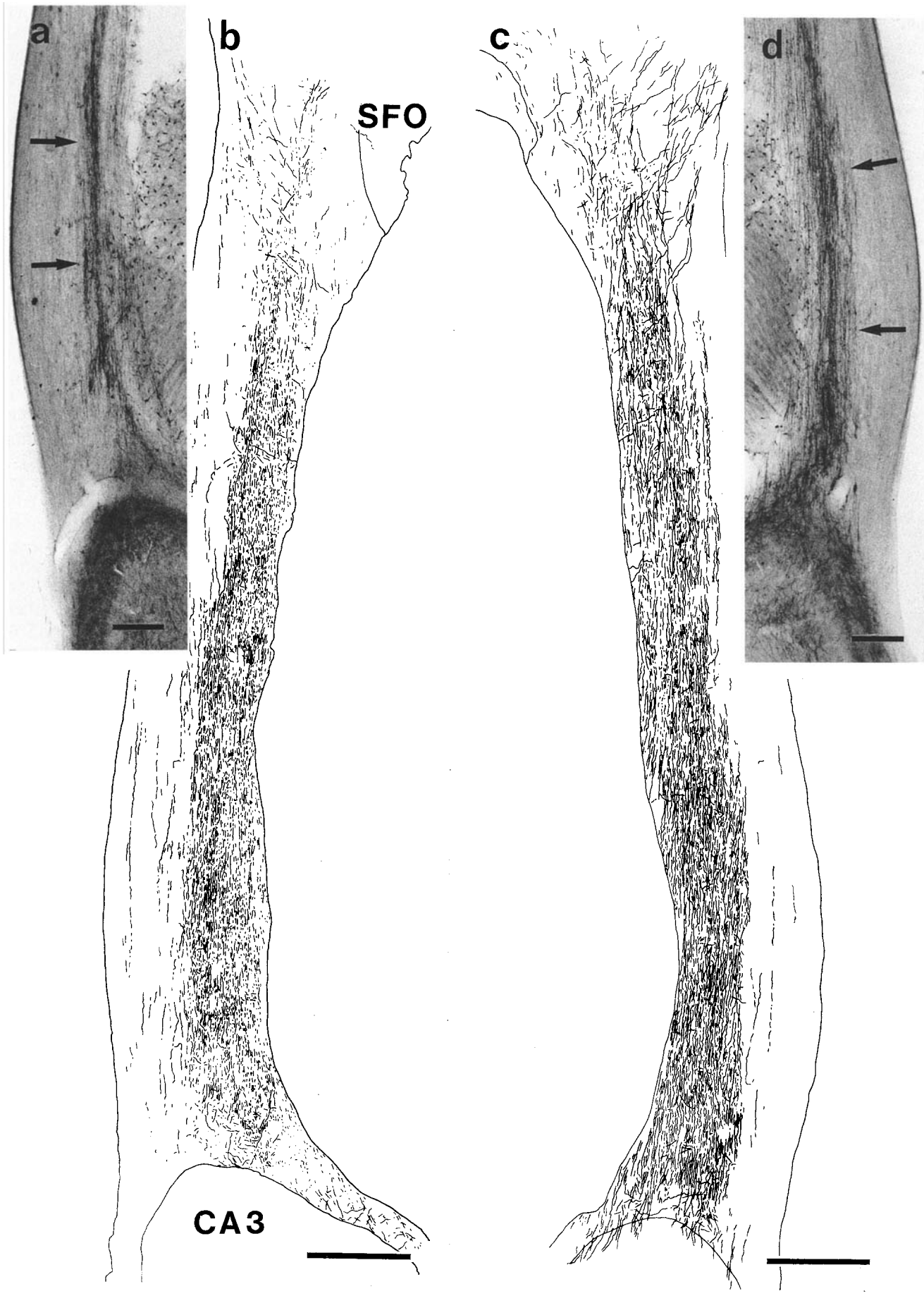
In the present study, fiber tracts within the fimbria-fornix were identified with the help of the anterograde tracer PHAL. Although this tracer is highly specific and reliable (Gerfen and Sawchenko 1984; Deller et al. 1994; Deller et al. 1995), it should be kept in mind that single tracer injections, as used here, only label portions of the total projection. Even in the case of very large injections, as demonstrated in Figs. 3a and 5a, some neurons are missed, and the axons of these neurons are not labeled. For this reason, we have made a large number of injections with different coordinates. The material shown in this study is representative of a large group of animals receiving similar PHAL-deposits into the same regions. The synopsis illustrating the relative position of fiber tracts within the fimbria-fornix (Fig. 8) includes the results of all animals of a group and thus appears to be a reliable map for the location of these fiber tracts within the fimbria-fornix. We will now discuss our findings with respect to the topography of the different fiber systems within the fimbria-fornix and with respect to the laminar organization of their target area.

The synopsis of all experimental groups is shown in Fig. 8 for a coronal section (Fig. 8a) and a horizontal section (Fig. 8b) through the fornix and the ventral hippocampal commissure: fibers that arise from the rostrally located septal nuclei enter the fimbria without reaching the ventral hippocampal commissure. In contrast, fibers that arise from within the contralateral temporal lobe (commissural fibers and crossed entorhinal fibers) cross the midline in the ventral hippocampal commissure. Some of these fibers leave the ventral hippocampal commissure and turn rostrally towards the septum. These fibers are collaterals of commissural axons, since the commissural and the hippocampo-septal axons are known to arise from the same neurons (Swanson et al. 1980). The remaining fibers cross the midline in a laminated fashion: commissural fibers are located caudo-basally, while entorhino-dentate and entorhino-hippocampal fibers are located rostro-dorsally in the ventral hippocampal commissure. This lamination continues into the fimbria, where commissural fibers are located subjacent to the pial surface while fibers from the entorhinal cortex are located laterally to this fiber bundle. In contrast, septo-hippocampal fibers can be found throughout the fimbria, even in those portions that are occupied by commissural or crossed entorhinal fibers. The observed variation in the size of septo-hippocampal axons (Fig. 4c–e) could be the electron microscopic correlate of the thick and thin septo-hippocampal axons described earlier by Freund and Antal (1988).

This organization of afferent fiber tracts to the hippocampus reflects their lamina-specific organization within the hippocampal formation (see Frotscher 1988, 1991, 1992; Amaral and Witter 1995 for reviews). Septo-hippocampal fibers are known to terminate diffusely within the dentate gyrus and Ammon's horn. Septal fibers can be found in all subfields and laminae of the hippocampal formation (e.g., Nyakas et al. 1987). In contrast, commissural fibers terminate in a laminated fashion. In the dentate gyrus, the majority of commissural fibers terminates in the inner molecular layer, while only very few fibers reach the outer molecular zone (Deller et al. 1995). In Ammon's horn, commissural fibers terminate primarily within the stratum radiatum of CA3 and CA1 (e.g., Swanson et al. 1978; Deller et al. 1994), and some fibers can be found in the stratum oriens (Deller et al. 1994). In contrast, the stratum lacunosum-moleculare is completely devoid of commissural fibers. Crossed entorhino-dentate and crossed entorhino-hippocampal fibers are also bound to specific hippocampal laminae: the former terminate within the outer two-thirds of the molecular layer, while the latter reach the stratum lacunosum-moleculare of CA1 (Steward 1976; Wyss 1981). Thus, our data suggest a topographical organization of fiber tracts within the fimbria-fornix system that reflects the laminar organization of the hippocampus: fibers of the diffusely terminating septo-hippocampal projection are loosely distributed throughout the fimbria-fornix, while those projections that are known to terminate in specific laminae of the hippocampal formation (commissural projection, crossed entorhino-hippocampal projection) form

Fig. 5a–f The commissural projection. **a** Horizontal section of the injection side. The injection site (*asterisk*) is located in the dentate gyrus and in CA3. **b** Horizontal section of the contralateral side. PHAL-labeled commissural fibers (*arrows*) can be seen in the dentate gyrus and in subfields CA1–CA3. **c** Camera lucida drawing of a coronal section through the ventral hippocampal commissure (*VHC*) and the fimbria. The PHAL-labeled fibers are located ventrally. *Framed area* shown at higher magnification in **d**. **d** Enlargement of the rectangle in **c**. *Arrows* indicate PHAL-labeled commissural fibers in the VHC. **e** Camera lucida drawing of a horizontal section through the VHC. The labeled fibers are located caudally. Hippocampo-septal fibers are turning rostrally towards the lateral septal area (*open arrow*). *Bold arrow* points to region shown at higher magnification in **f**. **f** Enlargement of the region indicated by the *bold arrow* in **e**. The undulating PHAL-labeled commissural axons show numerous varicosities. *Bar* 500 μm in **a** and **b**, 400 μm in **c** and **e**, 40 μm in **d**, 30 μm in **f**

Fig. 6a–d Commissural fibers in the fimbria. **a** Photomicrograph of a horizontal section through the fimbria on the injection side. *Arrows* point to PHAL-labeled commissural fibers. **b** Camera lucida drawing of the same section as in **a**. The PHAL-labeled commissural fiber bundle is located close to the pial surface of the fimbria. **c** Camera lucida drawing of a horizontal section through the fimbria on the contralateral side. The PHAL-labeled commissural fiber bundle is located close to the pial surface of the fimbria. **d** Photomicrograph of the same section as in **c**. *Arrows* point to PHAL-labeled commissural fibers. *Bar* 200 μm in **a** and **d**, 400 μm in **b** and **c**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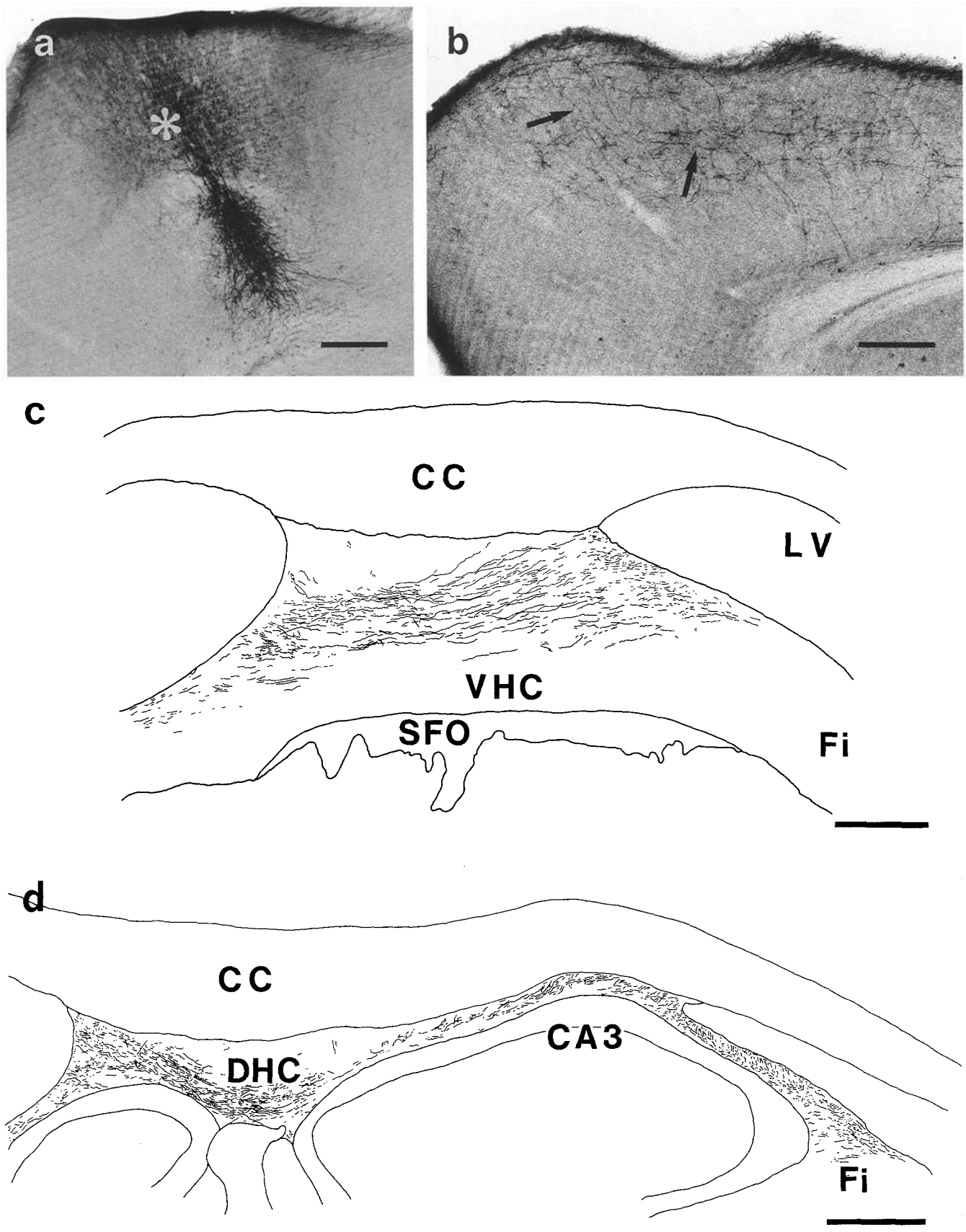

Fig. 7a–d Crossed entorhinal fibers (entorhino-hippocampal projection and entorhino-entorhinal projection). **a** Injection site (*asterisk*) located in the entorhinal cortex. **b** PHAL-labeled entorhino-entorhinal fibers (*arrows*) in the contralateral entorhinal cortex. **c** Camera lucida drawing of a coronal section through the ventral hippocampal commissure (*VHC*). PHAL-labeled axons are located dorsally. Note labeled axons close to the ventricular surface in the adjacent fimbria. **d** Camera lucida drawing of a coronal section through the dorsal hippocampal commissure (*DHC*). The PHAL-labeled fibers are located ventrally. Note labeled axons close to the ventricular surface in the adjacent fimbria. *Bar* 100 μm in **a** and **b**, 400 μm in **c** and **d**

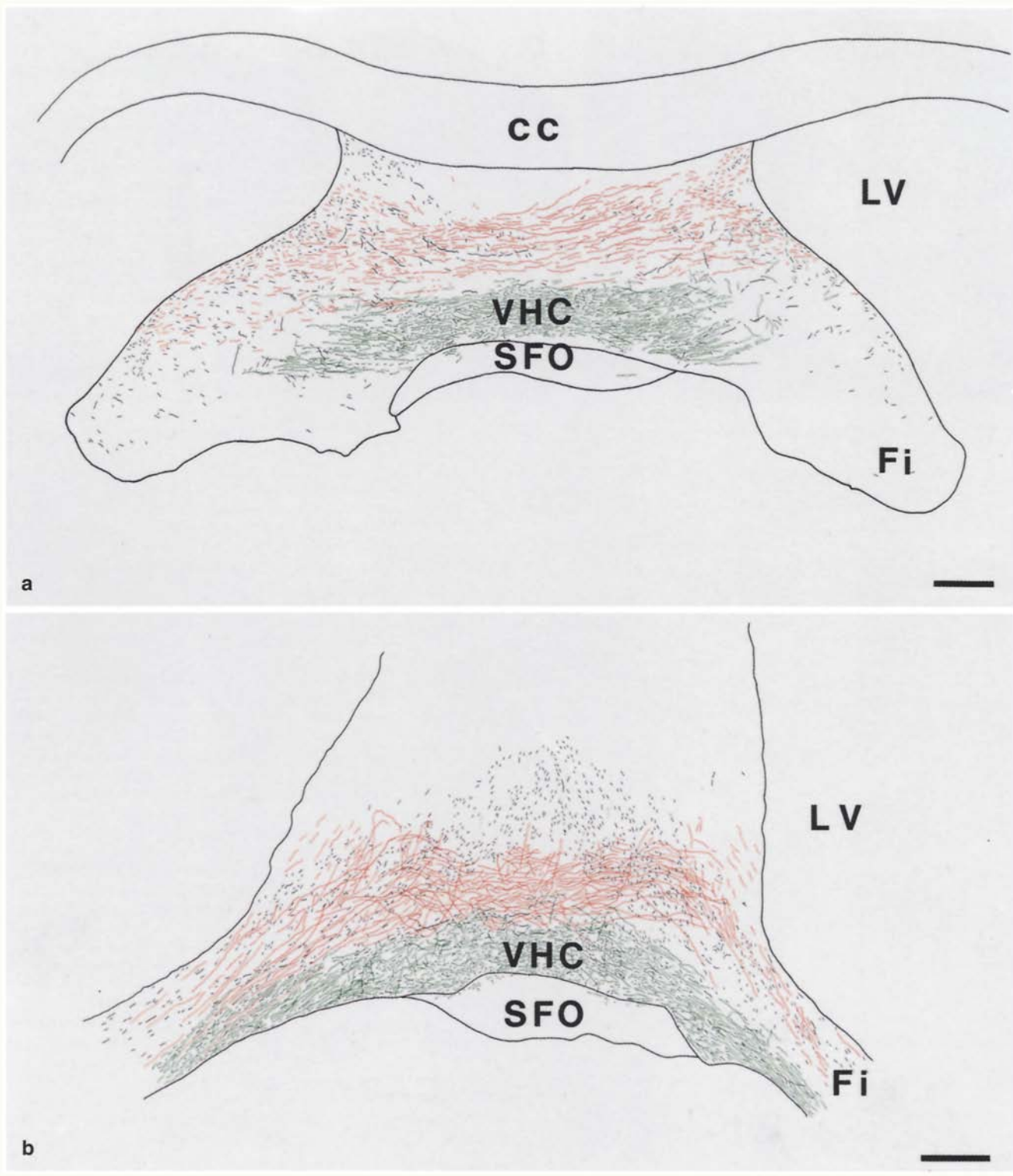

Fig. 8a, b Schematic drawing of fiber tracts in the fornix and the ventral hippocampal commissure (*VHC*). **a** Snyopsis of fiber tracts in a coronal section of the fornix and the VHC; **b** synopsis of fiber tracts in a horizontal section of the fornix and the VHC (septo-hippocampal fibers *black*, commissural fibers *green*, crossed entorhinal fibers *red*). *Bar* 250 μm in **a**, 280 μm in **b**

fiber bundles within the fimbria and the hippocampal commissures.

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