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Distinct Patterns of Neural Inputs and Outputs of the Juxtaparaventricular and Supraforical Regions of the Lateral Hypothalamic Area in the Male Rat

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Abstract

We have analyzed at high resolution the neuroanatomical connections of the juxtaparaventricular region of the lateral hypothalamic area (LHA_{jp}); as a control and comparison to this we also performed a preliminary analysis of a nearby LHA region that is dorsal to the fornix, namely the LHA supraforical region (LHAs). The connections of these LHA regions were revealed with a coinjection tract-tracing technique involving a retrograde (cholera toxin B subunit) and anterograde (*Phaseolus vulgaris* leucoagglutinin) tracer. The LHA_{jp} and LHAs together connect with almost every major division of the cerebrum and cerebrospinal trunk, but their connection profiles are markedly different and distinct. In simple terms the connections of the LHA_{jp} indicate a possible primary role in the modulation of defensive behavior; for the LHAs a role in the modulation of ingestive behavior is suggested. However, the relation of the LHA_{jp} and LHAs to potential modulation of these behaviors, as indicated by their neuroanatomical connections, appears to be highly integrative as it includes each of the major functional divisions of the nervous system that together determine behavior, i.e., cognitive, state, sensory, and motor. Furthermore, although a primary role is indicated for each region with respect to a particular mode of behavior, inter-mode modulation of behavior is also indicated. In summary, the extrinsic connections of the LHA_{jp} and LHAs (so far as we have described them) suggest that these regions have a profoundly integrative role in which they may participate in the orchestrated modulation of elaborate behavioral repertoires.

Keywords

Lateral hypothalamic area; Ingestive behavior; Defensive behavior

INTRODUCTION

The periventricular region and adjacent medial zone of the hypothalamus have a fairly well defined cytoarchitecture characterized by circumscribed nuclei whose function is to some extent understood. In comparison, the cytoarchitectural differentiations of the larger lateral zone are more subtle: they form mostly regions rather than nuclei and the connections and

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functions of these regions are understood with considerably less clarity. Nevertheless, novel findings in recent years have contributed to a rise of interest especially in the lateral hypothalamic area (LHA) segment of the lateral zone. Before reviewing these developments, it is useful to consider first why a clear understanding of the LHA has long remained so elusive.

One of the more apparent features of the LHA is its intricate relationship with the most differentiated fiber system of the central nervous system, the medial forebrain bundle (Nieuwenhuys et al., 1982). In fact, one of the earliest allusions to the LHA as a specific region was made in one of the earliest studies of the medial forebrain bundle, in the mole (Ganser, 1882), where the LHA was referred to as a bed (or interstitial) nucleus of the medial forebrain bundle. Following this pioneering reference to the LHA, the first specific description of an identified lateral hypothalamic area appears to be that given by Franz Nissl for the rabbit (Nissl, 1913). During this early period, a region of the hypothalamus that included the LHA was also referred to as the *substantia reticularis hypothalami* (Malone, 1910), that is, the rostral extension or end of the reticular formation. The wide variety of LHA neuron morphology that Malone described may have informed his description of the LHA as reticular in nature; in this respect it does appear quite fitting, although (perhaps unfortunately) this nomenclature was not widely adopted. The LHA was subsequently described by Elisha Gurdjian in the rat using classical neuronal staining methods (Golgi for neuron morphology, Nissl for cytoarchitecture, and Weigert for myelinated fibers) (Gurdjian, 1927), and later (also in the rat) with similar methods by Wendell Krieg (Krieg, 1932).

According to Gurdjian, the rat LHA extends caudally from the lateral preoptic area (with which it is continuous) to the rostral aspect of the mammillary body (practically the full rostral-to-caudal extent of the hypothalamus) and consists of a group of characteristic medium- and large-sized neurons, distributed along the course of the medial forebrain bundle, intimately associated with the medial hypothalamic nuclei, and showing no “peculiar arrangement” (Gurdjian, 1927). Gurdjian’s description was supplemented by Krieg who clearly thought of the LHA as an interstitial nucleus that would act as a relay station from which information travelling through the medial forebrain bundle might reach the medial zone nuclei of the hypothalamus (Krieg, 1932). This general understanding of the LHA has been more or less affirmed by a cluster of complementary studies ranging across a wide variety of mammalian species, including the following: human (Le Gros Clark, 1938; Nauta and Haymaker, 1969), monkey (Crouch, 1934; Papez and Aronson, 1934), dog (Rioch, 1929), cat (Rioch, 1929; Ingram et al., 1932; Valverde, 1965), rat (Szentagothai et al., 1968), mouse (Millhouse, 1969), opossum (Warner, 1929), armadillo (Papez, 1932), and wild boar (Solnitzky, 1939) (for further references see (Fulton et al., 1940; Geeraedts et al., 1990).

The existence of a general consensus on the extent of the LHA and its relation to the medial forebrain bundle contrasts with little consensus on how this largest hypothalamic component should be differentiated and subdivided. Historically, a principal reason for this lack of agreement relates to the cytoarchitecture of the LHA: it has a subtle heterogeneity in which regional borders are not easily discernable in common Nissl preparations. Nevertheless, at least one differentiation of the LHA has consistently been identified, and this is a “perifornical region” that, in general terms, is considered to surround the column of the fornix. In this view the perifornical region is defined primarily by the column of the fornix as a fiducial marker, rather than by its cytoarchitecture. Nevertheless, species in which a perifornical region of the LHA has been variously identified include the following: human (Le Gros Clark, 1938), monkey (Crouch, 1934; Papez and Aronson, 1934), dog (Rioch, 1929), cat (Rioch, 1929; Ingram et al., 1932), rat (Gurdjian, 1927) and wild boar (Solnitzky, 1939); for further references see (Fulton et al., 1940; Geeraedts et al., 1990).

A novel schema for subdividing the LHA in the rat based primarily on a fine-grained reanalysis of the cytoarchitecture was proposed recently (Swanson, 2004; Swanson et al., 2005). At least two developments are noteworthy for providing the impetus for this renewed interest: 1) LHA chemoarchitecture as revealed by the expression of melanin-concentrating hormone and the orexin/hypocretin peptides (Swanson et al., 2005; Hahn, 2009; see also de Lecea et al., 1998; Bittencourt et al., 1992), and 2) The identification of a topographically organized and highly restricted input to the subfornical region of the LHA (LHAsf) originating in the pontine nucleus incertus (Goto et al., 2001). Prior to the developments that led to the present schema for parceling the LHA, a comparably detailed account was suggested (Geeraedts et al., 1990), based on cytoarchitecture and its correspondence with the various components of the medial forebrain bundle (Nieuwenhuys et al., 1982; Veening et al., 1982).

Before the present study, the only systematic analyses of LHA projections with regard to current parcellations (Swanson, 2004) concerned the tuberal nucleus (Canteras et al., 1994), parasubthalamic nucleus (Goto and Swanson, 2004), and LHAsf (Goto et al., 2005), and no study has examined such connections with a co-injection methodology at high spatial resolution (i.e. mapped to numerous consecutive atlas levels). Nevertheless, several earlier studies of LHA connections are noteworthy for providing evidence that the LHA is regionally differentiated rather than relatively homogenous (Conrad and Pfaff, 1976b; Saper et al., 1979; Hosoya and Matsushita, 1980; Hosoya and Matsushita, 1981b; Veening et al., 1982; Luiten et al., 1987; Allen and Cechetto, 1992; Roeling et al., 1993a; Deller et al., 1994; Abrahamson and Moore, 2001; Yoshida et al., 2006). In the present study, two nearby regions of the LHA middle group are subjected to a high spatial resolution analysis of their macro connection pattern; as delineated by the new parcellation they are the LHA juxtaparaventricular (LHAjp) region of the medial tier, and LHA suprafornical (LHAs) region of the perifornical tier. The LHAjp was the primary target for analysis, while the nearby LHAs served as a comparison site and control.

Our decision to make the LHAjp the primary focus of this study was prompted largely by its close proximity to a critically important neuroendocrine, autonomic, and behavioral part of the hypothalamus, the paraventricular nucleus (PVH) -- physiologic control of PVH neurons by local populations of neurons lying laterally adjacent to the PVH (within the LHA) has been suggested (Boudaba et al., 1997). In addition, a previous PHAL study provided a rudimentary description of projections from a region of the LHA corresponding approximately to the LHAjp (Roeling et al., 1993b). Determining the connections of the LHAjp and LHAs also allows for comparison with the already published connections of the LHAsf (Goto et al., 2005) -- establishing collectively the connections of three nearby LHA regions that are respectively ventral (LHAsf), medial (LHAjp), and dorsal (LHAs) to the fornix. More generally, a better knowledge of the neural connections of the LHA is a highly desirable goal given the extensive evidence implicating it in control of several fundamental behaviors including: eating and drinking (Mogenson and Stevenson, 1967; Watts et al., 1999), foraging and exploration (Lammers et al., 1988b; Goto et al., 2005), sleep/wake states (Alam et al., 2002), defense and aggression (Lammers et al., 1988a; Lammers et al., 1988b; Hrabovszky et al., 2005), and social behaviors (Lammers et al., 1987; Roeling et al., 1990).

MATERIALS AND METHODS

2.1. Animals and surgical procedures

Combined PHAL + CTB injections were made in 81 adult male Sprague-Dawley rats (supplier Harlan; 300 – 350g). The animals were kept under conditions of controlled temperature (22° C) and illumination (12-hour light cycle) and had access to food and water *ad libitum*. Animal housing conditions and all experimental procedures were in accordance with current NIH Guidelines for the Care and Use of Laboratory Animals; in addition, all protocols were approved by the University of Southern California Institutional Animal Care and Use

Committee. Our method for the central co-injection of PHAL and CTB is the first reported use of this method in the rat, and follows its first application for central tract-tracing studies in the hamster (Coolen and Wood, 1998). The present co-injection method combines earlier separate methods for the central iontophoretic injection of PHAL (Gerfen and Sawchenko, 1984) and CTB (Luppi et al., 1990) in the rat.

For the surgical procedure, animals were anesthetized with an equal mixture (1ml/kg body weight) of ketamine (50mg/ml) and xylazine (10mg/ml), delivered intramuscularly. Under anesthesia they received a single stereotaxically placed iontophoretic injection of a mixture of 2.5% PHAL (Vector Laboratories, Burlingame, CA) and 0.25% CTB (List Biological Laboratories, Campbell, CA) prepared in 0.1M sodium phosphate-buffered saline, pH 7.4. The tracers were ejected from a glass micropipette (12–20 μ m tip diameter) by applying a positive current (5 μ A, 7 sec on/off intervals) for 5–10 min; the pipette was then left in place for 10 minutes before retraction. From 12 – 20 days later, the animals were anesthetized deeply with sodium pentobarbital (40 mg/kg body weight, intraperitoneal) and perfused transcardially with 150 ml ice cold 0.9% NaCl, followed by 300 ml ice cold 4% paraformaldehyde in 0.1 M borate buffer (pH 9.5).

2.2. Tissue processing and immunocytochemistry

The fixed brains were postfixed for 20 hours at 4°C in 4% paraformaldehyde in 0.1 M borate buffer (pH 9.5) containing 10% sucrose. Serial 30 μ m thick transverse-plane sections (one-in-five series) were cut on a sliding microtome. One complete series of sections was processed for immunocytochemical detection of PHAL; another series was processed similarly for detection of CTB; an intervening series was thionin-stained. Except for the series allocated to thionin staining, the sections were collected in an anti-freeze solution and stored at –20°C until further processing. The anti-freeze solution consisted of 30% ethylene glycol and 20% glycerol in 0.02M potassium phosphate buffered saline (KPBS).

Immunocytochemical method for detection of tracers—From anti-freeze solution sections were washed in 0.02M KPBS (6 changes over 2 hours). The series of sections that were allocated for detection of CTB were then treated to suppress endogenous peroxidase activity: they were washed in a solution of 70% methanol containing 0.3% hydrogen peroxide for 15 minutes, and then washed twice with 2 changes of 0.02M KPBS. Sections were treated to block non-specific antibody binding: for PHAL detection, the sections were washed in 0.02 M KPBS containing 0.3% Triton X-100 and 10% non-fat milk (10 minutes); sections for CTB detection were washed in 0.02 M KPBS containing 0.3% Triton X-100 and 2% donkey serum. Following these steps, the sections were transferred to 0.02M KPBS containing primary antibodies raised against either CTB (species: goat, dilution: 1:10,000, supplier: List Biological Laboratories) or PHAL (species: rabbit, dilution: 1:3,000, supplier: Dako, Carpinteria, CA); these solutions also contained either 10% non-fat milk and 0.3% Triton X-100 (for PHAL) or 2% donkey serum and 0.1% Triton X-100 (for CTB). Sections were incubated in primary antibody solution for approximately 60 hours (3 nights); they were placed on a rotating platform and maintained at 4°C.

Following the primary antibody, the sections were washed in 0.02M KPBS (8 changes over 2 hours), and then washed in either 2% goat serum with 0.3% Triton X-100 and (for PHAL) or 2% donkey serum with 0.1% Triton X-100 and (for CTB). The sections were then exposed to a biotinylated secondary antibody (90 min, diluted 1:1000): donkey anti-goat for CTB (Jackson Immunoresearch, West Grove, PA), goat anti-rabbit for PHAL (Vector). The secondary antibody solutions also contained either 2% goat serum and 0.3% Triton X-100 (PHAL sections) or 2% donkey serum and 0.1% Triton X-100 (CTB sections).

Following the secondary antibody (the solution was retained), the sections were washed in 0.02M KPBS (6 changes over 30 minutes) and exposed to an avidin-biotin-horse radish peroxidase complex (ABC reagent, Vector, dilution: 1 drop reagent A and B in 30ml for CTB; 3 drops reagent A and B in 30ml for PHAL) in 0.02M KPBS for 2 hours. The sections were then washed in 0.02M KPBS (5 changes over 20 minutes) and placed again in their respective recycled secondary antibody solutions for about 16 hours (overnight) under the same conditions as for the primary antibody. Following the second secondary antibody exposure, the sections were washed in 0.02M KPBS (6 changes over 30 minutes), and then exposed to freshly prepared ABC reagent for 90 minutes. They were then washed in 0.02M KPBS (6 changes over 30 minutes). In order to visualize CTB and PHAL, the sections were exposed to 0.05% 3, 3'-diaminobenzidine (DAB) with 0.005% hydrogen peroxide in 0.02M KPBS; in order to enhance the visualization of the CTB label, 0.1 % ammonium nickel (II) sulphate was also included in the reaction mixture. The reaction was monitored and reaction times were typically between 10–15 minutes for PHAL and between 4–8 minutes for CTB. The reaction was stopped by successive washes in 0.02M KPBS (8 changes).

The sections were then mounted on to glass slides, air-dried, dehydrated through an ascending series of alcohols, and cleared in xylene. Some sets of sections processed for PHAL were then rehydrated and treated with osmium tetroxide (0.008%, for 60 minutes) in order to enhance visualization of the DAB reaction product under dark field illumination. Following this treatment, the PHAL sections were washed for 2 hours in tap water, again dehydrated and cleared in xylene and then (as was the case for all other mounted sections) treated with DePeX mountant and cover-slipped.

Antibody specificity—In order to provide a measure of specificity for the polyclonal primary antibodies that we used to detect either CTB or PHAL, we applied these antibodies to brain tissue sections collected from animals in which no tracer was injected. Following this procedure, no specific labeling was seen. Similarly, specificity of the polyclonal secondary antibodies was indicated by the observed absence of specific labeling in tissue sections collected from animals that had received a tracer injection, to which the immunocytochemical method was applied with omission of the primary antibody step.

2.3. Analysis

Injection site maps—Sites of tracer deposition within the LHA were plotted with the camera lucida method and with reference to adjacent thionin stained sections. The plotted data was then transposed on to a series of computerized standard drawings of the rat brain (Swanson, 2004); this was done with the use of illustration software (Adobe Illustrator CS3).

Tracer maps—PHAL-labeled fibers and CTB-labeled neurons were plotted either with the aid of the camera lucida method and then transposed to a computerized standard series of rat brain atlas maps (Swanson, 2004) using illustration software (Adobe Illustrator CS3), or they were plotted directly on to the latter. As was the case for mapping the sites of the tracer deposits, an adjacent series of thionin stained tissue sections was used as an aid in determining the cytoarchitectural boundaries between brain regions. Parceling of the rat brain, terminology for describing morphological features of tracer-labeled axons and cell bodies, and mapping strategies and procedures follow Swanson (2004), unless indicated otherwise.

Photomicrography—Individual photomicrographs were taken with a microscope-mounted digital camera (Diagnostics Instruments Spot/Leica DMRE, or Hamamatsu Orca ER/Zeiss Axio Imager.Z1) at a resolution of 1 megapixel, and saved as 8-bit TIFF files. The acquired image files were opened in photo-editing software (Adobe Photoshop CS3) where they were composed (cropped, rotated) and adjusted (brightness, contrast and color balance).

RESULTS

3.1. Normal anatomy

In Nissl-stained material the LHAjp and LHAs are spatially separate and visually distinguishable regions with less distinct borders than generally associated with neuron populations called nuclei; they are readily identifiable in sections cut roughly through the center of their spatial extent (Fig. 1), but gradations rather than clear borders between adjacent regions are typical. The borders and features of the LHAjp and LHAs have been mentioned elsewhere (Swanson, 2004; Swanson et al., 2005; Hahn, 2009) but a more careful account is useful here for describing our experimental results.

3.1.1. Borders and cytoarchitecture of the LHAjp (Fig. 1A; see also Fig. 3)—The LHAjp is a hypothalamic region of moderate size situated at a rostral dorsomedial site within the hypothalamus; in relation to other parts of the LHA, the LHAjp forms a rostradorsal specialization of the medial tier (Swanson et al., 2005). In thionin-stained sections, the perikarya of LHAjp neurons stain with moderate intensity; cell bodies are medium-sized and have a somewhat regular round to oval shape. Overall the LHAjp has a rather uniform, if not homogenous, appearance.

Rostrally, the LHAjp appears at approximately the same level as the anterior parvicellular part of the PVH (PVHap), and from there it extends caudally to the level of the posterior magnocellular part of the PVH (PVHpm). Along the entire length of its rostral-caudal axis, the LHAjp apposes closely the column of the fornix; this apposition occurs with the medial, dorsomedial, and dorsal borders of the fornix. At its most rostral and most caudal, the LHAjp apposes the medial, dorsomedial, and dorsal aspects of the fornix, whereas at midrostrocaudal levels of the LHAjp, the apposition occurs predominantly with the medial border of the fornix.

Caudal to the level of its rostral end, the LHAjp extends medially until it comes to appose the distinct lateral border of the PVH, first at the level of the PVHap and then its caudal half. Ventrally, except for its rostral tip, the LHAjp apposes the rather distinct dorsal border of the anterior hypothalamic nucleus (AHN); at its rostral tip, the non-forniceal borders of the LHAjp are not easily discerned, but are nevertheless formed by neurons within a dorsal region of the medial preoptic nucleus (medial border), a ventromedial region of the rostral tip of the reticular nucleus of the thalamus (RT; dorsal and dorsolateral border), and a dorsomedial region of the interfascicular nucleus of the bed nuclei of the stria terminalis (BSTif; ventral border).

At a level just caudal to its rostral pole, the LHAjp forms an indistinct ventromedial border with the internuclear region situated between the PVH and AHN; also at this level the LHAjp is bounded distinctly by the thalamus: dorsomedially by the ventral part of the rostral division of the nucleus reuniens (REv), and dorsolaterally by the RT. At a midrostrocaudal level, the LHAjp continues to be bounded dorsomedially by the REv, while its dorsolateral border is formed by the medial tip of the rostral end of the zona incerta. The caudal end of the LHAjp is bounded dorsally by the zona incerta, and dorsolaterally by the dorsal zone of the anterior region of the LHA (LHAad); the border with the latter appears to occur slightly lateral to the fornix although it is not distinct.

Finally, an additional feature of the LHAjp, and one that provides a useful fiducial marker for this region, is the presence of a peculiar and neglected lateral wing of the dorsal zone of the medial parvicellular part of the hypothalamic paraventricular nucleus (PVHmpdl) (Simmons and Swanson, 2008) that penetrates the rostral half of the LHAjp, and in transverse section appears to bisect it. This lateral wing protrudes laterally from the PVH and then forms a rather narrow columnar arch that describes a lateral path through the LHAjp to the dorsal border of the fornix. At the dorsal border of the fornix, the PVHmpdl bulges slightly and extends rostrally

to the level of the PVHap. The perikarya of the PVHmpdl stain intensely, making this structure appear quite distinct in relation to the medially adjacent LHAjp with its lighter stained perikarya (Fig. 1A). In addition, the cell bodies in the PVHmpdl have a distribution that is particularly dense in relation to the cell bodies of LHAjp neurons, further distinguishing this structure from the LHAjp.

3.1.2. Borders and cytoarchitecture of the LHAs (Fig. 1B; see also Fig. 3)—The perikarya of the LHAs show variety in their type: some cell bodies stain intensely with thionin, and these are intermingled with a greater abundance of smaller more lightly stained neurons (Fig. 1B). As its name suggests the LHAs sits atop the dorsal aspect of the fornix. Beginning rostrally at a level immediately caudal to the PVH, it extends caudally, to the level of the caudal-dorsal border of the dorsomedial nucleus. Along its rostral-caudal axis, the LHAs extends laterally slightly beyond the width of the fornix to merge with the dorsal region of the lateral tier of the LHA (LHA_d); medially it merges principally with the juxtadorsomedial region of the medial tier of the LHA (LHA_{jd}), and at its most caudal extent it merges with a ventrolateral region of the posterior hypothalamic nucleus. The LHAs forms a distinct dorsal boundary with the ventral border of the zona incerta.

3.2. Neuroanatomical connections of the LHAjp and LHAs

From 81 combined PHAL and CTB tracer experiments we obtained 42 instances where the injection site included and was largely restricted to regions of the LHA medial and perifornical tiers; 22 of these included the region of the LHAjp, and 11 included the region of the LHAs. In describing these results, first we give an account of the experiments that we selected for analysis, and for those mapped out in detail, a description of the morphology of PHAL-labeled axons; we also give an account of the distribution of the PHAL-labeled axons and CTB-labeled perikarya with respect to their lateralization. We follow this with a brief description of the regions of most prominent anterograde and retrograde labeling obtained in these experiments from either the LHAjp or LHAs. This overview is followed by a complete description of the anterogradely-labeled projections, and then the sites of retrograde labeling, first for the LHAjp and then for the LHAs. In order to provide logical structure to our descriptions, the way in which we have organized our description of the efferent and afferent projections differs: our description of the efferent projections begins at the locus of the injection site, and is guided by the projections themselves; in contrast, our description of the retrograde labeling is organized according to a systematic hierarchy of cell groups and regions in the rat central nervous system (Swanson, 2004). To allow us greater focus on possible functional implications of these voluminous data in the Discussion, we make reference in the Results to previous tract-tracing studies that have a direct bearing on the present findings.

We reserved our most detailed analysis for two experiments where the site of tracer deposition was most restricted to the caudal end of the LHAjp (the level at which it presents at its fullest) and a midrostrocaudal portion of the LHAs: these were experiments LHA#22 (LHAjp) and LHA#11 (LHAs) (Figs. 2 and 3). Additional analysis was performed on five experiments out of the available set of 33 (22 including LHAjp and 11 including LHAs) where the injection site included and was most restricted to either the LHAjp or LHAs (Fig. 3). One of these experiments (LHA#62) was particularly useful because it was concentrated in the rostral half of the LHAjp, thus providing together with experiment LHA#22 (caudal end of the LHAjp) an overview of the total connections of the LHAjp (these findings are summarized at the end of the Results, and also represented graphically in Figs. 12 and 13 of our Discussion section). Plots of the anterograde and retrograde labeling obtained in experiments LHA#22 (LHAjp) and LHA#11 (LHAs) are shown in Figure 4; these data are also represented in summary form on a 'flat map' of the rat brain (Fig. 5). We also carried out a semi-quantitative analysis of the

labeling obtained in experiments LHA #22, LHA #11 and LHA #62; the results of this analysis are given in tabular form (Table 1).

Labeled fibers, whether projecting from the LHA_{jp} or LHAs, rarely had the sole appearance of fibers of passage; the latter were predominantly confined to clearly identifiable fiber tracts. This is an important observation in so far as it suggests that neurons of the LHA_{jp} and LHAs distribute broadly the signals they convey. Typically, labeled axons displayed numerous varicosities and formed numerous boutons of passage; in addition, their distribution was characterized by much convolution, often giving the appearance of a loose or more tightly woven mesh. Identified terminal fields, in addition to the presence of terminal boutons, also typically contained boutons of passage; furthermore, the terminal field in any given region showed much variation in the density of fiber labeling.

3.2.1. Summary of prominent neuroanatomical connections of the LHA_{jp} and LHAs

3.2.1.1. Anterograde tracing summary: Our analysis of PHAL-labeled axons traced anterogradely from neurons located predominantly within the caudal end of the LHA_{jp} (experiment LHA#22, Figs. 2A, 3) revealed projections to a diverse array of brain regions; most of them are within the diencephalon and prominent among them (in descending order) are the lateral habenula, dorsal preammillary nucleus, posterior and anterior hypothalamic nuclei, nucleus reuniens, and paratenial nucleus. In contrast, brain regions receiving prominent projections from neurons located predominantly within the LHAs (experiment LHA#11, Figs. 2B, 3) include those in the midbrain and hindbrain as well as the diencephalon; these are (in descending order) Barrington's nucleus, ventrolateral division of the periaqueductal gray (PAG), lateral parvicellular and forniceal parts of the hypothalamic paraventricular nucleus (PVH_{lp/f}), substantia innominata, and midbrain reticular nucleus (principally the retrorubral area).

3.2.1.2. Retrograde tracing summary: Perikarya retrogradely labeled from the LHA_{jp} were abundant (in descending order) in the subiculum and adjacent field CA1 of the hippocampal formation, lateral septal nucleus, anterior hypothalamic nucleus, and posterior hypothalamic nucleus. These findings contrast with retrograde labeling from the LHAs that was prominent (in descending order) in the anteromedial and fusiform nuclei of the bed nuclei of the stria terminalis, medial preoptic area, and posterior hypothalamic nucleus. Labeling from the LHAs within the hippocampal formation was very sparse, in marked contrast to abundant retrograde labeling from the LHA_{jp}.

3.2.2. Detailed description of the neuroanatomical connections of the LHA_{jp} and the LHAs

3.2.2.1. Projections from the LHA_{jp} (PHAL anterograde tracing): Axons arising from neurons located predominantly within the LHA_{jp} reach their projection targets via several different paths (Fig. 5). The principal routes of egress for fibers as they emerge from the LHA_{jp} are ventral, rostral, dorsal, and caudal; a relatively low abundance emerges laterally, and exceedingly few emerge medially to project into the adjacent PVH (Fig. 4T–W). In addition, there is a moderate contribution of fibers to the nearby column of the fornix, most of which appear to project rostrally (Fig. 4T–U). With regard to possible sources of LHA input to the PVH, it is noteworthy that a projection to the PVH from the LHA does have previous description (Watts et al., 1999;Csaki et al., 2000); however, the source of the projection identified in the earlier work was a region of the LHA caudal and lateral to the LHA_{jp}, corresponding approximately to the LHAd (Watts et al., 1999;Csaki et al., 2000).

Ventrally adjacent to the LHAjp, a plexus of terminal boutons, boutons of passage and fibers of passage is present within the central part of the AHN (Fig. 4U); the posterior part of the AHN receives a lesser input (Fig. 4T–U), and there is very little input to the AHN's dorsal (Fig. 4V) or anterior (Fig. Q–T) parts. Fibers enter the subparaventricular zone and internuclear regions dorsal and medial to the AHN (Fig. 4Q–V), but very few of these fibers continue on to enter the PVH or the periventricular nucleus; however, they do continue ventrally, to reach the anterior part of the VMH (Fig. 4U). In the vicinity of the anterior part of the VMH, fibers are distributed sparingly in the ventral zone of the juxtaventricular LHA (LHAjvv; Fig. 4U), in the retrochiasmatic area (Fig. 4T), and rarely in the anterior zone of the subfornical region of the LHA, or the subventromedial part of the tuberal nucleus (principally as fibers of passage; Fig. 4U). Farther rostral, scattered fibers continue on through the medial preoptic and anterior hypothalamic areas, and rostral internuclear regions (Fig. 4M–R); a very light grouping of terminal fibers is present in caudal levels of the anterodorsal preoptic nucleus (Fig. 4O).

The rostral projection from the LHAjp via the column of the fornix appears to generate a moderate terminal field in the lateral and (to a lesser extent) medial septal nuclei (Fig. 4F–O); fibers also extend to the septofimbrial (Fig. 4N–O) and diagonal band nuclei (Fig. 4H–M), although these are more sparsely populated with boutons. It is principally the rostral part of the lateral septal nucleus that is the major septal region recipient of projections from the LHAjp (Fig. 4F–N), and most prominent among the receiving rostral subdivisions are dorsal regions of the medial (LSr.m.d; Fig. 4J–L) and in particular the ventrolateral (LSr.vl.d; Fig. 4F–J) zones. In addition, a lower density of terminal fibers is distributed widely across the lateral septal nucleus, mostly within its rostral part. In all, a total of fourteen identified subdivisions of the lateral septal nucleus receive an input to a moderate or lesser degree. In general agreement with our findings, a moderate projection to lateral and a lesser projection to medial septal nuclei from a region of the LHA showing correspondence to the caudal end of the LHAjp has been described previously (Roeling et al., 1993b). In more specific agreement with our findings, a later study reported numerous back-labeled neurons in a perifornical region adjacent to the AHN (i.e., the LHAjp) following a deposit of the tracer fluorogold centered within the LSr.v (Risold and Swanson, 1997).

The axons that emerge laterally from the LHAjp are sparsely populated with boutons of passage; these fibers give rise to a comparatively minor projection whose fibers course rostral-caudal through LHA regions lateral to the fornix. This lateral projection field remains mostly within about the medial two-thirds of the lateral tier of the LHA; it extends caudally into the posterior group of the LHA. Its rostral course leads through the anterior group of the LHA, in the intermediate (LHAai) and ventral (LHAav) zones, to a light terminal field in the BSTif (Fig. 4Q–R), and a smattering of terminal fibers in the adjacent principal nucleus (BSTpr); in small amounts fibers also reach the lateral preoptic area (Fig. 4O–P). In addition to its rostrocaudal extension, a very few fibers from the lateral path appear to continue laterally before entering anterior parts of the medial amygdalar nucleus (Fig. 4S–T). At least one previous retrograde tracing study has described an output from the LHA to the BST (Weller and Smith, 1982); however, in that study (using horseradish peroxidase as the tracer) the particular LHA region that was the source of the output was not made clear, neither was it stated in which BST cell groups the injections were made. Similarly, in a previous PHAL study, a strong projection to the BST from the LHA was described (Roeling et al., 1993b), but the receiving BST cell groups were not identified, nor was the full extent of the PHAL injection sites in the LHA shown.

A moderate portion of the fibers that emerge dorsally from the LHAjp enter medial regions of the zona incerta and travel caudally within it, to the level of the posterior hypothalamic nucleus (Fig. 4 U–Y); most of these fibers are distributed rostrally within the zona incerta (Fig. 4 U–W). To reach the zona incerta, some of the fibers emanating from the LHAjp appear to traverse

the PVHlp as fibers of passage, passing perpendicular to it without giving rise to terminal boutons (Fig. 4V). Directly adjacent to rostromedial regions of the zona incerta, and dorsomedial to the LHAjp, a dense terminal field is present within the rostral division of the thalamic nucleus reuniens in its ventral (REv), anterior (REa), and lateral (REl) parts (Fig. 4R–U). This finding is consistent with a report showing very abundant retrograde labeling in what appears to correspond to dorsocaudal regions of the LHAjp following injection of the retrograde tracer fluorogold into the rostral division of the nucleus reuniens (McKenna and Vertes, 2004); earlier studies reported a similar finding (Risold and Swanson, 1995; Risold et al., 1997; McKenna and Vertes, 2004). Dorsal to the hypothalamic part of the third ventricle, some labeled fibers cross the midline and a light terminal field is present in the contralateral nucleus reuniens, approximately mirroring the fiber distribution on the tracer-injected side (Fig. 4R–U). Dorsal to the REa, a moderate terminal field is present in the paratenial nucleus (Fig. 4R–U); medial to the REa, numerous fibers extend caudally through rostral regions of the thalamic paraventricular nucleus (Fig. 4R).

At the level of the rostral division of the nucleus reuniens, numerous labeled fibers are apparent within the stria medullaris; these give rise to an extremely dense terminal field within the lateral habenula (Figs. 4V–BB, 6A, 7). Within the lateral habenula the terminal field is for the most part differentiated into a dorsal and a ventral portion, and except for the most caudal level most of the fibers are present within the medial half. Several previous tracing studies confirm an input to the lateral habenula from LHA regions including one corresponding to the LHAjp, in the rat (Conrad and Pfaff, 1976b; Herkenham and Nauta, 1977; Parent et al., 1981; Shinoda and Tohyama, 1987; Ray et al., 1992), cat (Parent et al., 1981), and monkey (Parent et al., 1981); in addition, in the rat, this projection may include an enkephalinergic component (Shinoda and Tohyama, 1987). Further consistent with our results, previous tracing studies have also revealed in the rat a projection to the paraventricular thalamic nucleus (PVT) (Conrad and Pfaff, 1976b; Chen and Su, 1990; Kirouac et al., 2006), paratenial nucleus (Conrad and Pfaff, 1976b; Chen and Su, 1990), and rostral division of the nucleus reuniens from the LHA region including the LHAjp (Conrad and Pfaff, 1976b).

As we have described, by far the major portion of thalamic input arising from the LHAjp is present within the lateral habenula, PVT, PT, and RE. Nevertheless, a minor portion of thalamic input, in the form of sparsely distributed fibers, is also present in the anteroventral (AV), anteromedial (AM), anterodorsal (AD), interanteromedial (IAM), interanterodorsal (IAD), central medial (CM), mediodorsal (MD) (rostrally), lateral dorsal (LD), and RT (dorsal part) thalamic nuclei (Fig. 4S–BB). Together, these findings of thalamic (including zona incerta) input from the LHAjp are in general agreement with an earlier less comprehensive PHAL study in the rat (Roeling et al., 1993b).

Several components of the LHA caudal to the LHAjp receive an input from its neurons. In particular, the LHAjd (immediately caudal to the LHAjp) receives an extensive input (Fig. 4V–W); a less extensive fiber field is present in the LHAjvd, LHAjvv, and ventral levels of the LHAs (Fig. 4U–Z). In the vicinity of the LHAs, there is a group of labeled fibers with terminals that forms a tight cluster adjacent to the fornix, within the LHAjvv, LHAjvd, LHAs, and posterior hypothalamic nucleus (Fig. 4Y–Z). Medial to the LHA, the dorsomedial and ventromedial nuclei of the hypothalamus receive a light input from the LHAjp; for the dorsomedial nucleus this is mostly within its anterior part (Fig. 4W), and for the ventromedial nucleus this is within its anterior and dorsomedial parts (Fig. 4U–W). A previous study of inputs to the dorsomedial nucleus using fluorogold found a low density of retrograde labeling in the region of the LHAjp (Thompson and Swanson, 1998). A very large projection reaches the posterior hypothalamic nucleus, and this extends dorsally and caudally mostly as fibers of passage, predominantly within medial regions (Fig. 4X–BB). A previous retrograde tracing study examining the afferent connections of the posterior hypothalamic nucleus showed a

notable absence of retrograde labeling in a region of the LHA corresponding to the LHAjp (Abrahamson and Moore, 2001); this result is consistent with our present finding of numerous fibers of passage within the posterior hypothalamic area, arising from the LHAjp.

At the level of the posterior hypothalamic nucleus a very dense terminal field is present in the dorsal premammillary nucleus (PMd) (Figs. 4BB, 6B), apparently arriving there via a caudal route within the fornix. This projection was of much higher magnitude from the caudal end of the LHAjp (experiment LHA#22) than from the rostral half of the LHAjp (experiment LHA#62). Furthermore, the projection to the PMd is strikingly bilateral, with fibers appearing to reach the contralateral side via a route across the midline dorsal to the third ventricle at the level of the PMd (Figs. 4BB, 6B); the terminal field within the PMd is denser medially than laterally. In addition to targeting medial regions of the PMd, a moderate density of labeled fibers continue on to form a bilateral terminal field within the body of the medial mammillary nucleus, noticeably limited to its ventral half (Figs. 4CC, 6C); some of these fibers appear to enter the principal mammillary tract and then continue rostrally through the mammillothalamic tract, contributing to the light anterior thalamic projection already described. Consistent with our results, a previous retrograde tracing study of the afferent connections of the PMd reported cells in a region corresponding to the caudal end of the LHAjp, and they also reported a significant amount of contralateral labeling (Comoli et al., 2000). However, the level of retrograde labeling they reported in the caudal end of the LHAjp does appear to be lower than might be predicted by the density of the terminal field we found in the PMd. This could be accounted for by the extent of the injection site that formed the basis of their primary analysis because it appeared to barely include the medial PMd region where we observed much PHAL labeling from the LHAjp. Another factor may be the difficulty in determining the boundary between the LHAjp and immediately adjacent LHAjd because a higher abundance of retrograde labeling was observed rostrally in the LHAjd from the PMd (Comoli et al., 2000). It is also possible that relatively few cells in the caudal end of the LHAjp send axons to the PMd that ramify there greatly.

Numerous ribbons of fibers ascend dorsally within the posterior hypothalamic nucleus and rostromedial division of the periaqueductal gray (PAGrm; Fig. 4BB-DD). Within the PAG, some of these fibers pass through the precommissural nucleus (Fig. 4CC-DD), giving off boutons of passage en passant; at these levels a very light projection extends dorsally into the medial pretecal area (Fig. 4DD-FF), and caudally into medial regions of the superior colliculus (Fig. 4DD-HH). Farther caudal, a light terminal field is present within predominantly rostral levels of the ventrolateral division of the PAG and (to a much lesser extent) its medial and dorsal subdivisions (Fig. 4GG-LL). Consistent with these results, a previous CTB study of the connections of the precommissural nucleus found a moderate amount of retrograde labeling in an LHA region corresponding to the caudal end of the LHAjp (Canteras and Goto, 1999a). An earlier study using horseradish peroxidase as the retrograde tracer reported a large input to the ventrolateral and (to a lesser extent) dorsolateral divisions of the PAG from the LHA as a whole (Beitz, 1982); however, further direct comparison with the earlier study and our present data is not possible because regional LHA parcellation was not specified (Beitz, 1982). No PHAL-labeled axons arising from neurons within the LHAjp were found to extend caudal to the PAG in the pontine central gray.

3.2.2.2. Sources of projections to the LHAjp (CTB retrograde tracing)

3.2.2.2. Sources of projections to the LHAjp (CTB retrograde tracing): 3.2.2.2.1. Cerebral cortex: A striking difference between the regions targeted by projections from the LHAjp just described, and the sources of its inputs that we now describe, is the existence of a massive direct input to this moderately sized medial tier LHA region from the cerebral cortex. The major source of this cortical input is hippocampal; a more moderate input comes from the

medial prefrontal cortex. Retrograde labeling in the hippocampal formation was localized mostly to the pyramidal layer of its intermediate region, and foremost among the sources of hippocampal input to the LHAjp was the subiculum. A moderate abundance was also present in field CA1 of the intermediate region. Labeling also reached to the dorsal or septal pole of the subiculum and field CA1, but not quite the ventral or temporal pole. In transverse Atlas Levels this translates to the presence of very abundant labeling caudally, with progressively less observed more rostrally (Fig. 4FF–LL; see also Fig. 8A, B). In addition, a small amount was present in the parasubiculum, and a very few labeled neurons were present in the presubiculum, medial entorhinal area, and hippocampal field CA3 (Fig. 4 JJ–OO). It is noteworthy that labeling in intermediate regions of the subiculum was by far the most abundant of any brain region.

The moderate amount of retrograde labeling present within the medial prefrontal cortex was the sum of a lower incidence of retrogradely labeled neurons in infralimbic (layers 5 and 6a), prelimbic (layer 5), and anterior cingulate (layer 5) areas (Fig. 4A–N); a small-moderate amount of cortical labeling was also present at an intermediate level in the ventral part of the retrosplenial area (layer 5) (Fig. 4FF–II). In addition to these cortical areas, a very low incidence of labeled neurons was also present in rostral levels of the secondary somatosensory area (layer 5; Fig. 4F) and the orbital area (medial, ventral, and ventrolateral parts; Fig. 4A–B); furthermore, a low incidence of retrograde labeling was found ventrally adjacent to the infralimbic area, in layer 2 of the dorsal part of the tenia tecta (Fig. 4F–G). Finally, within the cortical subplate, a very few cells were also present within the basolateral and basomedial amygdalar nuclei (Fig. 4Z, CC).

In comparing our data with the fruit of earlier work, we find that a fairly recent study of the hypothalamic projections of the subiculum showed essentially the same magnitude and distribution of retrograde labeling in the subiculum (and field CA1) as we observed following a deposit of CTB shown to include a region corresponding to the caudal end of the LHAjp (Kishi et al., 2000); in addition, in the same study, following an injection of PHAL at a site within the intermediate third of the subiculum, the authors describe a “dense plexus of labeled axons diverging from the postcommisural fornix...in an area between the PVH and fornix” (Kishi et al., 2000) -- i.e., caudally within the LHAjp. A dense terminal field in the region between the PVH and fornix arising from the intermediate third of the subiculum is also described in previous PHAL studies (Witter et al., 1990; Cullinan et al., 1993); an early study of the projections of the fornix in the rat using the degeneration method also indicated a projection to the region of the LHAjp (Nauta, 1956). Conversely, and also consistent with our results, several previous studies have shown that the ventral (temporal) and dorsal (septal) ends of Ammon’s horn and the subiculum project comparatively little to caudal regions of the LHAjp (Swanson and Cowan, 1975; Swanson and Cowan, 1977; Witter and Groenewegen, 1990; Canteras and Swanson, 1992a; Cenquizca and Swanson, 2006).

With regard to the moderate amount of retrograde labeling we found in the medial prefrontal cortex from the LHAjp, several previous tracing studies in the rat together provide a robust confirmation of the topography and magnitude of this projection, for example: (Hosoya and Matsushita, 1980; Luiten et al., 1987; Brittain, 1988; Sesack et al., 1989; Hurley et al., 1991; Floyd et al., 2001; Pajolla et al., 2001; Vertes, 2004; Gabbott et al., 2005). Projections from prefrontal cortex to the LHA have also been reported in species other than rat: thus, one previous study with PHAL in the rabbit described such projections, although these were reported to target an LHA region just lateral to the fornix (Buchanan et al., 1994); however, an earlier study in the cat (with autoradiographic tracing) described a projection from infralimbic and prelimbic areas to LHA regions including medial levels of the LHA (Room et al., 1985). Very dense projections to medial levels of the LHA from the medial prefrontal cortex have also been described with anterograde tracing methods in Old World (macaque) (Ongur et al., 1998;

Rempel-Clower and Barbas, 1998) and more recently New World (marmoset) (Roberts et al., 2007) monkeys.

The low incidence of labeling we found in the basomedial amygdalar nucleus is corroborated by a previous PHAL study of this region (Petrovich et al., 1996); however, we could not find a comparable previous study for the basolateral amygdalar nucleus. Finally, we found only one previous study in which the efferent connections of the rat ventral part of the retrosplenial area had been studied, and there no mention was made of a projection to the hypothalamus (van Groen and Wyss, 1990); furthermore, to our knowledge, no previous tracing study has examined possible hypothalamic projections of the tenia tecta. Our finding of a small amount of retrograde labeling in the ventral part of the retrosplenial area and dorsal part of the tenia tecta from the LHAjp therefore appears to be novel.

3.2.2.2.2. Cerebral nuclei

3.2.2.2.2. Cerebral nuclei: 3.2.2.2.2.1. Striatum: Aside from the extensive cerebral cortical input, the brain region showing the next most abundant retrograde labeling from the LHAjp was the lateral septal nucleus, where retrograde labeling was mostly present in the rostral part (Fig. 4F–N), with comparatively little in the caudal part (Fig. 4 H–O). The subdivision of the rostral part of the lateral septal nucleus showing most abundant retrograde labeling from the LHAjp was the dorsal region (and lateral and medial domains) of the ventrolateral zone (LSr.vl.d.l/m), this was followed by the dorsal region of the medial zone (LSr.m.d) and then the medial region (and dorsal domain) of the dorsolateral zone (LSr.dl.m.d). Two more subdivisions of the lateral septal nucleus showed a small amount of labeling; these were the medial zone (central region) of the rostral part (LSr.m), and the dorsal zone (rostral region) of the caudal part (LSc.d.r). A lower amount of retrograde labeling, ranging from a few to about 10 retrogradely labeled neurons was also present in the following lateral septal subdivisions (see table of abbreviations for explanation): LSc.d.d, LSc.d.v, LSc.v.i, LSc.v.l.d, LSc.v.l.v, LSc.v.m.d, LSr.dl.l.d, LSr.dl.l.v, LSr.dl.m.v, LSr.m.v.c. It is noteworthy that the two lateral septal regions showing most abundant retrograde labeling from the LHAjp were the same two regions with the most extensive terminal field arising from the LHAjp (principally from its rostral half), namely: LSr.vl.d.m/l (Fig. 4 F–J) and LSr.m.d (Fig. 4J–L).

Among the most prominent of studies that have examined the projections of the lateral septal nucleus, an extensive tract-tracing study in the rat stands out in which they were examined comprehensively (Risold and Swanson, 1997). It was shown in the previous study that a PHAL injection into either the region of the LSr.vl.d or LSr.m.d would give rise to a moderate terminal field in the LHA region situated between the fornix and PVH (Risold and Swanson, 1997). Similarly, injections of the retrograde tracer fluorogold into regions of the AHN that included a portion of the LHAjp at rostral (their experiment AH3) or caudal (their experiment AH1) levels, resulted in numerous back-labeled cells in the LSr.vl.d.l/m (their experiment AH3) (Risold and Swanson, 1997); these results are consistent with our present findings. A projection from the lateral septal nucleus to the LHA has also been described in several earlier tract-tracing studies in species including (for example) rat (Meibach and Siegel, 1977; Kita and Oomura, 1982; Deller et al., 1994), cat (Krayniak et al., 1980), and pigeon (Krayniak and Siegel, 1978); however, the opportunity for direct comparison of these earlier studies with our present findings is limited because none describe the detail of this projection with respect to the precise delineations we present here.

Apart from the substantial amount of retrograde labeling in the lateral septal nucleus, we found very little retrograde labeling from the LHAjp in any other striatal cerebral nuclei. Nevertheless, a small amount of retrograde labeling was present in the septofimbrial nucleus (Fig. 4N–R), and farther caudal a few cells were retrogradely labeled in the medial part of the central amygdalar nucleus (Fig. 4U); slightly more were back-labeled in anterior and (to a

lesser extent) posterior parts of the medial amygdalar nucleus (Fig. 4S–X). In agreement with the latter finding, a previous PHAL study of the projections from the medial amygdalar nucleus revealed a predominantly light projection to the vicinity of the LHAjp from its anterior (and to a lesser extent) posterior parts (Canteras et al., 1995).

3.2.2.2.2. *Pallidum*: Two pallidal regions showed some degree of retrograde labeling from the LHAjp, although this was not particularly abundant. A moderate amount of retrograde labeling was present in the diagonal band nucleus (Fig. 4J–M); a similarly moderate amount was divided between several of the bed nuclei of the stria terminalis (BST). Within the BST, retrograde labeling (although modest overall) was most abundant in its posterior division, in the interfascicular nucleus (BSTif; Fig. 4Q–R), followed by the principal nucleus (BSTpr; Fig. 4Q). A very few cells were also back-labeled in the anterior division of the BST, in its dorsomedial nucleus (BSTdm) and anteromedial (BSTam) areas (Fig. 4M–P). Few studies appear to have examined the projections of the diagonal band nucleus with respect to the LHA; however, in general agreement with our present findings, at least two previous retrograde tracing studies in the rat have described (at relatively low spatial resolution) an output from the diagonal band nucleus to the LHA (Shiosaka et al., 1980; Kita and Oomura, 1982). Conversely, at higher spatial resolution, and also in agreement with our findings, a moderate projection from the BSTif and (to a lesser extent) the BSTpr to the region of the LHAjp is confirmed in a previous PHAL study (Dong and Swanson, 2004b); an earlier autoradiographic study also reported a similar finding (Swanson, 1976). The very low incidence of back-labeling we found in anterior levels of the BSTam is also confirmed by a previous PHAL study of the BST that indicated a very light projection from the BSTam to the LHAjp (Dong and Swanson, 2006a). However, our finding of very few cells in the BSTdm back-filled from caudal levels of the LHAjp is somewhat at odds with the findings of a previous PHAL study that indicated a light to moderate projection from the BSTdm to the LHAjp (Dong and Swanson, 2006b).

3.2.2.2.3. Cerebrospinal trunk

3.2.2.2.3. Cerebrospinal trunk: 3.2.2.2.3.1. *Sensory System*: A small amount of retrograde labeling was present in regions classed as being part of the sensory system of the cerebrospinal trunk (although it should be noted that our analysis did not extend to the spinal cord), and most of this was within the thalamic paraventricular nucleus (PVT) at rostral levels (Fig. 4R–U). A very low incidence of labeling was also present at rostral levels within the anterior thalamic nuclei, the paratenial nucleus, and the central medial nucleus (Fig. 4 R–T). The only other regions of the sensory system we found to contain any retrograde labeling from the LHAjp were the viscerosensory-related caudal zone of the medial part of the nucleus of the solitary tract, and the lateral division of the parabrachial nucleus; however, the retrograde labeling in the latter two regions consisted of single isolated cells. Consistent with our findings, a very recent PHAL study of projections from the PVT shows a light input to the LHA region situated between the PVH and fornix (Vertes and Hoover, 2008); in contrast, a previous PHAL study of PVT output in the rat showed the region of the LHAjp to be almost devoid of labeled fibers (Moga et al., 1995), whereas labeling was reported to be more pronounced in more caudal LHA regions, ventral and lateral to the fornix (Moga et al., 1995). Nevertheless, an even earlier PHAL study did report a light terminal field in the region surrounding the magnocellular part of the PVH (which would include the LHAjp) (Puigbonet and Ciriello, 1991); furthermore, a later anterograde tracing study with DiI, also in the rat, identified broadly the LHA, and in particular its perifornical region, as one of the main efferent targets of the PVT (Arлуison and Derer, 1993). In addition, a previous HRP retrograde tracing study in the cat identified the PVT as a region that provides a light output to a region of the LHA that appears to include the LHAjp (Smith and Flynn, 1980).

3.2.2.2.3.2. Behavioral State System: There was very little retrograding labeling in regions that form part of the behavioral state system of the cerebrospinal trunk; most of this was present in the dorsal region of the LHA (LHAd; Fig. 4V–W); isolated cells were also present in the hypothalamic subparaventricular zone, the lateral part of the supramammillary nucleus, and the superior central nucleus of the raphé. One recent PHAL study that examined projections from the subforminal region of the LHA (Goto et al., 2005), also described the results of an injection that included (but was not restricted to) rostral levels of the LHAd; a moderate projection to the LHAjp was noted (Goto et al., 2005).

3.2.2.2.3.3. Motor System: The bulk of cerebrospinal trunk retrograde labeling from the LHAjp was present within components of the motor system (Swanson, 2004), yet overall this was moderate (at most) in comparison to the combined labeling in the cerebral cortex and cerebral nuclei. Much of the labeling was present within regions classed as part of a behavior control column, and foremost among these regions was the anterior hypothalamic nucleus (AHN), which contained a moderate to high abundance of retrogradely labeled perikarya; these were distributed between the central (AHNc; Fig. 4R–U) and anterior (AHNa; Fig. 4Q–T) parts of the nucleus. For our experiment LHA-22, most of the labeled cells were present in the AHNc; however, CTB injections that were concentrated in the rostral half of the LHAjp (e.g., experiment #LHA62, Fig. 3) produced a far greater abundance of labeling in the AHNa and AHNc overall, and proportionally most of this was in the AHNa (Table 1). Rostral to the AHN, a very small amount of labeling was widely distributed in the lateral part of the medial preoptic nucleus (MPNI). Consistent with the AHN retrograde labeling, a previous PHAL study of projections from the AHN in the rat described a dense input to a region corresponding to the LHAjp from the AHNc and AHNa (Risold et al., 1994); a similar finding was described in a more recent PHAL study in the golden hamster (Delville et al., 2000). A previous PHAL study of the projections from the MPN (Simerly and Swanson, 1988) showed in one experiment involving the MPNI the presence of a light fiber plexus in the vicinity of the LHAjp (Simerly and Swanson, 1988).

Caudal to the PVH, a moderate amount of labeling was present in the hypothalamic ventromedial nucleus (VMH; Fig. 4U–Y), and this was mostly within the dorsomedial (VMHdm) part; however, a smaller amount was also present in the ventrolateral (VMHvl) and central (VMHc) parts. Caudal to the VMH, a very small group of cells was back-labeled in the rostral tip of the ventral tegmental area (Fig. 4CC), and a few cells were back-labeled in the ventral premammillary nucleus (PMv; Fig. 4AA–BB). Our finding of retrograde labeling in the VMH from the LHAjp is largely in agreement with a previous PHAL study of projections from the VMH that reported a terminal field in this LHA region from the VMHc, VMHvl, and VMHdm, with the latter part providing the most robust input (Canteras et al., 1994). In addition, a previous study of projections from the PMv revealed a light terminal field through the vicinity of the LHAjp (Canteras et al., 1992); similar findings for the VTA do not appear to have previous report.

The superior colliculus contained a small amount of retrograde labeling from the LHAjp (Fig. 4II–LL); more specifically this was within its intermediate (most in sublayer c) and deep gray layers. This observation does not appear to have previous wide confirmation; however, in a brief report of a previous anterograde tracing study of the superior colliculus in the rat and rabbit using the autoradiographic method, a projection to the LHA is mentioned, although its detail is not described (Fallon and Moore, 1979). Several central gray regions contained a moderate amount of retrograde labeling. This was most abundant in rostral levels of the posterior hypothalamic nucleus (PH) and PAG (Fig. 4Z–HH). Within the PAG, most of the back-labeled cells were present within the rostromedial division (PAGrm); a small group of cells was also present in the adjacent precommissural nucleus of the PAG. By comparison to the PAGrm, a lesser amount of labeling was present within mostly rostral levels of the

ventrolateral division (PAGvl); a lower incidence was present in the dorsal (PAGd) division, and farther caudal within the pontine central gray (Fig. 4PP).

In agreement with our finding of moderate retrograde labeling in the PH from the LHAjp, a projection from rostral levels of the PH was shown in an earlier PHAL study to end partly in the vicinity of the LHAjp (Vertes et al., 1995). A previous PHAL study of the projections from selected PAG divisions described a high density of fibers within the LHA arising from rostral levels of the PAGvl (Cameron et al., 1995); these were shown mostly in an LHA region lateral to the fornix, however also shown, and consistent with our present results, was a lighter input to a region corresponding to the LHAjp (Cameron et al., 1995). Our finding of retrograde labeling in the precommissural nucleus (Fig. 4 CC–DD) is confirmed by a previous PHAL study that described an output from that region to the vicinity of the LHAjp (Canteras and Goto, 1999a). However, the density of the terminal field in the vicinity of the LHAjp shown in the previous study is higher than might be predicted by the relatively small amount of retrograde labeling we found in the precommissural nucleus; this may be accounted for by inclusion of PHAL-labeled perikarya in the subjacent PAGrm (Canteras and Goto, 1999a) where we also found cells retrogradely labeled from the LHAjp. In another previous PHAL study of projections from the PAG, a dense terminal field in the vicinity of the LHAjp was shown to arise from both the commissural nucleus and the PAGrm (Krout and Loewy, 2000).

A few parts of the hypothalamic periventricular region contained a moderate amount of retrograde labeling from the LHAjp; these were the medial preoptic area (MPO; Fig. 4N–R), and to a lesser extent the caudally continuous anterior hypothalamic area (AHA; Fig. 4Q–R). Besides the latter two regions, very little retrograde labeling was present elsewhere within the periventricular region -- a very small amount was present in the median preoptic nucleus, and a similarly small amount was present in the anterior and ventral parts of the dorsomedial nucleus. Few previous tracing studies have looked specifically at the connections of either the AHA or the MPO; however, a couple of early studies did examine the outputs of these regions in the rat with the autoradiographic tracing method (Conrad and Pfaff, 1976a; Conrad and Pfaff, 1976b). In agreement with our present results, the previous autoradiographic studies do show that the MPO (Conrad and Pfaff, 1976a) and AHA (Conrad and Pfaff, 1976b) both appear to generate a light projection to the hypothalamic region situated between the PVH and fornix; for the AHA, in addition to its efferent connections in the rat, similar findings with the autoradiographic method in another early study were reported for the cat and squirrel monkey (Saper et al., 1978). An extensive PHAL study of projections from the DMH showed few fibers within the region between the PVH and fornix, and these were described mostly as fibers of passage (Thompson et al., 1996); this is consistent with the very small amount of retrograde labeling we found within the DMH.

Several regions within the reticular formation (mostly in the rostral end, the LHA) were together retrogradely labeled to a moderately high extent. The highest abundance of this intra-LHA labeling was present within the LHAjvv (Fig. 4U–Y). In addition, a low-moderate amount of retrograde labeling was present in the LHAjd and LHAav; low amounts were also present in the LHAad, LHAai, subfornical region of the LHA, and more rostral levels of the LHAjp and LHAs. Elsewhere in the reticular formation there was relatively little retrograde labeling; nevertheless, a low incidence of labeled cells was present in the zona incerta (mostly in medial regions; Fig. 4 U–W) and in the lateral preoptic area (at rostral levels; Fig. 4 J–O). Isolated cells were also labeled in the retrochiasmatic area, midbrain reticular nucleus, and medial pretectal area. Finally, very little retrograde labeling was present in the neuroendocrine motor zone of the hypothalamic paraventricular nucleus (PVH; Fig. 4P–V), and the little that was present was mostly within its anterior parvicellular part (PVHa); a very few cells were also labeled in the dorsal zone of the medial parvicellular (PVHmpd), and periventricular (PVHpv) parts.

Very few studies have examined the connections of the zona incerta; however, in agreement with our results, one previous PHAL study of medial levels of the zona incerta in the rat did report a light projection in and around the LHAjp (Wagner et al., 1995). Similarly few studies have examined local projections from the PVH; nevertheless, one previous intracellular filling study showed boutons of passage on neuroendocrine CRH neuron axons in the region of the LHAjp (Rho and Swanson, 1987), and a PHAL study showed a few axons projecting from the PVHmpd to the LHA region just lateral to the PVH, that is, caudally in the LHAjp (Roeling et al., 1993b). At present, there exists no systematic study of intra-LHA connections. However, an already referred to recent study of the connections of the subfornical region of the LHA (Goto et al., 2005) did also include data from control injections within the LHAA/d and LHAjv regions, from which projections to the LHAjp were reported. With reference to the previous study (Goto et al., 2005), in further general agreement with our results, the projection to the LHAjp from a PHAL injection centered in the LHAjvv was reported to be dense, whereas that from a site including the LHAA/d was reported to be moderate; a light to moderately dense projection was reported to arise from PHAL injections centered in the subfornical region of the LHA.

3.2.2.3. Projections from the LHAs (PHAL anterograde tracing): A deposit of PHAL (experiment LHA#11) centered and mostly contained within midrostrocaudal levels of the LHAs (Atlas Level 29 in Swanson, 2004) labeled perikarya that were mostly restricted to this region (Figs. 2B, 3). The principal route of fiber egress from this LHA site was apparent from numerous fibers that fanned out laterally, heavily innervating the adjacent LHAd and reaching across its rostrocaudal extent, predominantly in the medial half (Figs. 4W–Y, 9A). The laterally emerging fibers also extended to several other LHA regions: a moderately strong projection coursed caudally into the LHAp (Fig. 4AA–BB), while a lighter projection coursed rostrally to innervate the LHAd and LHAai (Fig. 4 Q–U), and a light-very light projection reached the LHAav, LHAsfp, LHApc, LHAm, LHAvm, LHAvl, and preparasubthalamic nucleus (Fig. 4Q–BB). In addition to the laterally emerging fibers, a lesser projection emerged medially from the LHAs to innervate moderately the LHAjd and LHAjvd, and lightly the LHAjvv, LHAsfp, and LHAjp (Fig. 4W–Y); a light projection also extended throughout the rest of the LHAs. Furthermore, a sparse distribution of fibers with terminals was present at the level of the injection site in the contralateral LHAs, LHAd, and LHAjd, appearing to reach these regions via a route above the roof of the hypothalamic part of the third ventricle.

In addition to intra-LHA connections, certain medial and periventricular hypothalamic nuclei also received a moderate input from the LHAs. At the level of the injection site, a light innervation throughout the anterior part of the DMH was apparent (Fig. 4W–X); a very few fibers were also present within the posterior and ventral parts of the DMH caudal to the level of the injection site. A previous study of inputs to the DMH using fluorogold reported retrograde labeling in the LHA that was mostly medial and most abundant between the levels of the DMH and the caudal half of the PVH (Thompson and Swanson, 1998) that include the LHAs; retrograde labeling was shown caudally in the LHAs, although midrostrocaudal levels of the LHAs (Atlas Level 29) were not represented (Thompson and Swanson, 1998).

A smattering of fibers with few boutons was present in the VMH, and these were mostly rostral within the ventrolateral, central, and dorsomedial parts of the nucleus. Except for a very few fibers, most apparent as fibers of passage, there was no input to the arcuate nucleus. Perhaps most striking within the hypothalamus was a dense projection from the LHAs to the fornical (f) and lateral parvocellular (lp) parts of the PVH (Figs. 4V, 9A); this projection continued medially and rostrally within the PVH to innervate moderately the PVHmpd and PVHap (Figs. 4Q–V, 9A); much lighter innervation, consisting of few fibers, was also present in the PVHpm1, PVHpm, and PVHpv. It is noteworthy that the projection to caudal levels of the PVHmpd and PVHlp/f included a light contralateral component that was not apparent in other parts of

the PVH. The projection from the LHAs to the PVH contrasts with the very minor projection to the PVH from the LHA_{jp}, and this was restricted principally to the PVH_{ap}. A projection to the PVH from the LHAs has not been described previously; however, an earlier PHAL study of a region of the LHA lateral and rostral to the LHAs (corresponding approximately to rostromedial levels of the LHAd) did show a pattern of input to the PVH similar to that described here (Watts et al., 1999).

Dorsal to the LHAs (and LHAd) a relatively few fibers, with the appearance of fibers of passage, were present in the zona incerta (ZI); some of these reached medially into the adjacent LHA_{jd} and caudal end of the LHAs where they intermingled with the projection that emerged medially from the LHAs. This rather spare group of fibers continued medially, passing through the rostral third (or thereabout) of the posterior hypothalamic nucleus (PH), reaching the nucleus reuniens, and extending dorsally through midline nuclei of the thalamus, including more rostral levels of the central medial (CM) and intermediodorsal (IMD) thalamic nuclei (Fig. 4X–Z). In contrast to this light projection, a rather more substantial projection ascended through the PH and this consisted of many fibers of passage apparently on route to the PAG, as well as smaller terminal fibers with numerous boutons; some of the fibers ascending within the caudal half of the PH appeared to support a light projection to the more caudal levels of the CM and IMD (Fig. 4Z–BB).

Dorsal within the midline thalamus, numerous fibers coursed along the entire rostral-caudal extent of the PVT (Fig. 4Q–BB); this was a major projection target of the LHAs and the fibers appeared to enter the PVT via a caudal and a rostral route. Within the PVT the heaviest labeling was apparent as a terminal field in the caudal half (or thereabout) (Figs. 4Z–AA, 9B). A very light projection also reached rostral levels of the mediodorsal thalamic nucleus (medial part) and paratenial nucleus. There was also a very light projection via the stria medullaris to predominantly medial levels of the lateral habenula; this is in contrast to the projection to the lateral habenula from the LHA_{jp} that is extremely dense and more broadly distributed (Figs. 4V–BB, 6A, 7).

The lateral projection from the LHAs continued laterally through the LHA and gave rise to a robust plexus of fibers within the substantia innominata (SI), mostly in medial regions (Fig. 4J–W). This projection continued across much of the SI's rostral-caudal extent (except for the most rostral levels), amounting to a sizeable projection overall. The fibers of this projection appeared to include fibers of passage intermingled with smaller branched axons possessing numerous boutons; the terminal field was densest at the level of the anterior parvicellular part of the PVH (Fig. 4R–T), it thinned out more rostrally, and was thinnest more caudally. Dorsal to the SI, a few fibers entered and descended within the internal capsule. Consistent with our present findings, a previous retrograde tracing study of the afferent connections of the SI showed retrograde labeling in the LHA, including a region corresponding approximately to midrostrocaudal levels of the LHAs, following a deposit of the tracer WGA-HRP in medial regions of the SI at about the level of the anterior parvicellular part of the PVH (Grove, 1988b); it is also noteworthy that retrograde labeling was shown to be restricted lateral and dorsal to the fornix in the LHA and did not extend medial to the fornix in the LHA (Grove, 1988b), a result that would be predicted by our observed absence of a projection to the SI from the LHA_{jp}.

Adjacent to the pallidal cerebral nucleus of the SI there was a comparatively miniscule projection to the striatal cerebral central (CEA) and medial (MEA) amygdalar nuclei; this consisted of few fibers within the medial part of the CEA, and very few within the posterodorsal part of the MEA (Fig. 4U–X). However, despite the small size of this projection, it is in part confirmed by a previous study that showed a low incidence of retrograde labeling within a region corresponding to the LHAs following injection of HRP into the medial part of the CEA

of the rat and cat (Ottersen, 1980). Farther rostral, within the ventral striatum, a low incidence of labeled fibers was distributed sparsely at mid-caudal levels of the nucleus accumbens, within the medial or “shell” region, medial and proximal to the ventral tip of the lateral ventricle (Fig. 4H–J). This light projection is in accord with the results of an earlier study of nucleus accumbens inputs using the tracer fluorogold, in which a low incidence of retrograde labeling was observed in the LHAs following a tracer deposit in the “septal pole” of the accumbens shell (Brog et al., 1993).

Turning our attention to rostral hypothalamic projections from the LHAs, few fibers were present within the AHN, predominantly in its central part -- in marked contrast to the very dense projection to the AHN from the LHAjp. Ventral to the AHN, a low density of fibers was present within the subventromedial part of the tuberal nucleus and the retrochiasmatic area. At very rostral levels of the PVH, a low density of fibers was also present in a region of the medial preoptic area dorsal to the fornix; at this level fibers were also clearly present within the stria medullaris, and in addition a few fibers were visible within the column of the fornix. Ventral to the fornix there were few fibers within the anterior hypothalamic area and median preoptic nucleus, and very few within the medial-, anterodorsal-, or anteroventral preoptic nuclei; however, a moderate terminal field extended across the medial preoptic area and a light projection extended to the lateral preoptic area (Fig. 4 K–R).

Returning to the pallidum, several bed nuclei of the stria terminalis received an input from the LHAs. A very few fibers were present in the BSTif; similarly few were present in the BSTov, BSTrh, and BSTfu. A light projection was apparent in the BSTmg; a moderate terminal field was present in the BSTdm (Fig. 4 O–P), and a moderate to dense terminal field was present in the BSTal and BSTam (Fig. 4 L–P). In terms of overall density, the projections to the BST from the LHAs exceeded those from the LHAjp; more striking are the differences in target region -- the prime targets for the LHAjp being the BSTif and BSTpr. Also within the pallidum, a low density of predominantly fibers of passage was apparent within the diagonal band nucleus, and these fibers extended into the medial septal nucleus, giving rise to a fairly light terminal field.

Returning to the striatum, the projection to the lateral septal nucleus was sparse overall; this is in contrast to the lateral septal input from the LHAjp, which was more substantial overall, and preferentially targeted the LSr.m.d and LSr.vl.d.m. No single subdivision of the lateral septal nucleus received more than a light input from the LHAs, and this was present in the form of scattered fibers with boutons and fibers of passage rather than a well defined terminal field; nevertheless, these fibers did pass through at least fifteen different lateral septal subdivisions (Table 1). Finally, for the rostral projections of the LHAs, a very few fibers appeared to extend rostral from the lateral septal nucleus into the dorsal part of the tenia tecta, and could be followed no farther.

Shifting focus to the caudal hypothalamus, except for the already described labeling in the LHAp, and PH, there was no appreciable additional input from the LHAs; this contrasts with a massive input to the dorsal preammillary nucleus and a moderate input to the mammillary body from the LHAjp. However, at the level of the mammillary body, a moderate projection composed of fibers with boutons and fibers of passage was present in the rostral end of the midbrain ventral tegmental area (VTA; Fig. 4 CC–FF); this result is consistent with a recent study of VTA inputs using fluorogold that showed rather abundant retrograde labeling in a region corresponding to the LHAs (Geisler and Zahm, 2005). The projection from the LHAs via the LHAp to the PH and VTA, continued caudally along two broadly distinguishable routes: one route went principally via the PH to the PAG, other midline and dorsal regions of the midbrain, and dorsal regions of the rostral hindbrain; the second route, caudal to the VTA, described a mainly ventrolateral path through reticular nuclei of the midbrain and hindbrain,

but also extended to dorsal and medial regions of the hindbrain (Fig. 5). This dual descending route from the LHA has been described in similar terms previously (Saper et al., 1979; Hosoya and Matsushita, 1981b).

Considering first the ventrolateral descending route in more detail, this involved a robust projection to the midbrain reticular nucleus (MRN). This was most apparent as a dense net of axons with terminals in the retrorubral area (Fig. 4JJ–LL). Terminals and boutons of passage were also evident in moderate abundance in the parvocellular division (MRNp; Fig. 4LL–OO); fibers within the MRNm appeared to include fibers of passage. A small proportion of the MRN-projecting axons appeared to enter (and descend within) the medial lemniscus. Caudal to the MRN, a projection of moderate density extended caudally into the hindbrain through the pontine reticular nucleus; this then continued more thinly into the gigantocellular-, magnocellular-, and parvocellular reticular nuclei (Figs. 4PP–III, 5). A sparse lateral continuation of this projection extended to the inferior salivatory, oral part of the spinal trigeminal, and paratrigeminal nuclei; a medial branch extended very lightly to the nucleus raphé magnus and nucleus raphé obscurus (very few axons).

In addition to these projections, a dorsal offshoot of the descending reticular projection reached the nucleus of the solitary tract (NTS; Fig. 4BBB–JJJ). Labeling within the NTS included both rostral (“gustatory”) and caudal zones of the NTS; it was moderate in its medial part and of low density in its lateral and commissural parts; furthermore, a few labeled axons extended to the dorsal motor nucleus of the vagus nerve (DMX; Fig. 4FFF–JJJ). The most caudal extension of this descending path that we traced reached with very few fibers into the ventral and dorsal parts of the medullary reticular nucleus; at this caudal level a few fibers were also present within the fiber tracts of the medial lemniscus and the medullary pyramids. Given that several previous reports have identified projections from the LHA (including the region of the LHAs) to the spinal cord, it is likely that some of the fibers we identified in the caudal medulla descended farther (Hancock, 1976; Saper et al., 1976a; Hosoya, 1980; Swanson and Kuypers, 1980).

The second major descending route from the LHAs into the midbrain was apparent as a projection of numerous labeled fibers within the PH that entered and coursed dorsally within the rostromedial division of the PAG (Fig. 4CC–DD); a small proportion of these fibers reached the precommissural nucleus of the PAG, a more moderate proportion reached the commissural nucleus of the PAG (Fig. 4EE–HH), and a very few extended to the nucleus of the posterior commissure. A moderate density of fibers was also present in the medial division of the PAG. Most notable within the PAG, an extensive terminal field was present within its ventrolateral division (Figs. 4GG–PP, 9C); rostrally this was fairly sparse, but farther caudal it became extremely dense. A sparse distribution of labeled fibers with terminals was also present within the dorsal and dorsolateral divisions of the PAG (mostly caudally; Fig. 4OO–QQ). In addition, at the level of the commissural nucleus of the PAG, a sparse projection of fibers was apparent within the superior colliculus; this extended caudally and included the intermediate layer but was largely within the deep layer, mostly in its deeper regions (Fig. 4EE–OO). At the caudalmost level of the PAG, a very few fibers were also apparent within the inferior colliculus (Fig. 4QQ–RR).

Certain more ventral midline regions of the midbrain also received an input. A light projection of mostly fibers of passage was present within the rostral linear and interfascicular nuclei of the raphé as well as the rostral subnucleus of the interpeduncular nucleus. In association with the latter site, it is noteworthy that a few fibers could be traced caudally from more rostral levels within the fasciculus retroflexus. Farther caudal a light terminal field was present within the raphé’s caudal linear nucleus (Fig. 4KK–LL), and a moderate terminal field was present in the dorsal nucleus of the raphé (Figs. 4LL–NN, 9C). A very few fibers were also apparent

in the superior central nucleus of the raphé (medial part). A moderate density of fibers could be traced within the superior cerebellar peduncle, although their possible terminations within the cerebellum were not apparent. A few fibers were also observed within the medial longitudinal fascicle.

At caudal levels of the PAG, a moderate projection to a rather broad extent of the parabrachial nucleus (PB) became obvious (Fig. 4PP–TT); this appeared to involve a contribution of fibers from each of the two main descending routes. Across the PB, the central lateral part in particular appeared to be the major recipient, with a much lesser projection to the external lateral and ventral lateral parts. Also at this level, a moderate density of fibers was present in the pontine central gray, appearing to be mostly a continuation from the ventrolateral division of the PAG. The most striking feature in this dorsal region adjacent to the midbrain-hindbrain border was the existence of a highly targeted and extremely dense terminal field in Barrington's nucleus (Figs. 4RR–SS, 10).

There is a paucity of earlier reports at a high spatial resolution (i.e. mapped to numerous consecutive atlas levels) for projections to the midbrain and hindbrain from the LHA, let alone the LHAs. Nevertheless, the earlier studies deserve some mention, in so far as they provide a measure of corroboration for our findings. For example, with regard to the labeling we observed in the region of the NTS and the DMX, a previous anterograde tracing study described labeling in those regions following a deposit of tritiated amino acids into a region encompassing the column of the fornix at a caudal level of the LHA (Hosoya and Matsushita, 1981b). In addition, a more recent retrograde tracing study (Grove, 1988b) showed a clearly demarcated cluster of cells in the vicinity of the LHAs following a large deposit of the tracer WGA-HRP into a region that included the NTS and DMX (Grove, 1988a); retrograde labeling in the vicinity of the LHAs was also noted in an earlier HRP study of the DMX (ter Horst et al., 1984). Furthermore, an earlier study identified cells in the vicinity of the LHAs that projected to the region of the NTS or to the spinal cord, or (in a very few instances) to both (Swanson and Kuypers, 1980).

Also previously noted are clear projections from the caudal “perifornical LHA” (which includes the LHAs) to the region of the VTA (Saper et al., 1976b; Saper et al., 1979; Hosoya and Matsushita, 1981b), PAG (Saper et al., 1976b; Saper et al., 1979; Hosoya and Matsushita, 1981b; Beitz, 1982), dorsal nucleus of the raphé (Hosoya and Matsushita, 1981a; Hosoya and Matsushita, 1981b; Peyron et al., 1998), PB (Hosoya and Matsushita, 1981a; Hosoya and Matsushita, 1981b), and Barrington's nucleus in the rat (Allen and Cechetto, 1992; Semba and Fibiger, 1992; Valentino et al., 1994) and cat (Kuypers et al., 2006); projections reaching farther caudal have also been described to regions including the nucleus raphé magnus (Hosoya and Matsushita, 1981b; Hermann et al., 1997), as well as the pontine central gray, reticular nuclei of the pons and medulla, salivatory nuclei, and spinal cord (Hosoya and Matsushita, 1981a; Hosoya and Matsushita, 1981b). Taken together, our present data are in rather good agreement the findings of the earlier work.

3.2.2.4. Sources of projections to the LHAs (CTB retrograde tracing)

3.2.2.4. Sources of projections to the LHAs (CTB retrograde tracing): 3.2.2.4.1. Cerebral cortex:

In marked contrast to the abundant retrograde labeling in the cerebral cortex from the LHA_{jp}, what we see from the LHAs is of substantially reduced abundance, and often quite different in distribution. The difference in abundance is most apparent in the hippocampal formation where a very low incidence of back-labeled cells was present in essentially the same overall distribution pattern. This finding appears to be consistent with the results of a recent PHAL study of the hypothalamic targets of subicular projections in the rat (Kishi et al., 2000); specifically, a PHAL deposit within the intermediate third of the subiculum labeled very few fibers in the vicinity of the LHAs, although numerous fibers and terminals were present within the LHA region immediately medial to the LHAs (Kishi et al., 2000). In addition, no

input to the LHAs was reported from PHAL injections in the ventral end of the subiculum (Canteras and Swanson, 1992a).

Within the medial prefrontal cortex very few cells were back-labeled from the LHAs in the anterior cingulate area (layer 5 and 6a); this compares to a moderate amount of retrograde labeling in the anterior cingulate area from the LHA_{jp}. A small amount of labeling was present in the prelimbic area (layer 5, occasionally layer 6a and possibly occasionally layer 3), rather similar in amount, but somewhat more rostral in distribution, than that from the LHA_{jp}. A moderate amount of retrograde labeling was present in the infralimbic area (layer 5 and occasionally layer 6a) from the LHAs (Fig. 4D–E); this was about double the abundance of labeling seen in this region from the LHA_{jp}. Also different from the input to the LHA_{jp}, we did not find any cells back-labeled from the LHAs in the retrosplenial area, but we did find a moderate incidence of labeling in the agranular insular area (layer 5), divided mostly between its dorsal and posterior parts (Fig. 4E–I); a low incidence of labeling was also present in the ventral part of the orbital area and dorsal part of the tenia tecta (layers 3 and 4). Finally, within the cortical subplate, a very low incidence of labeling was present in the claustrum, dorsal part of the endopiriform nucleus, and (as was the case for the LHA_{jp}), the basolateral and basomedial amygdalar nuclei.

Previous reports corroborate our data for the labeling we found in the prelimbic (Sesack et al., 1989; Vertes, 2004; Yoshida et al., 2006) and infralimbic (Brittain, 1988; Hurley et al., 1991; Vertes, 2004; Yoshida et al., 2006) areas. Past studies that speak to projections from the insular region have not examined them at a high spatial resolution with respect to the LHA. Nevertheless, at least three previous studies in the rat indicate a projection from the agranular insular area to the vicinity of the LHAs (Hurley et al., 1991; Floyd et al., 2001; Yoshida et al., 2006). In further agreement with one of the previous studies (Hurley et al., 1991), the labeled neurons we found in the agranular insular area were restricted to layer 5. This is at odds with a more recent report indicating that cells retrogradely labeled from the LHA (including the LHAs) are present in layer 3 of the agranular insular area, at a level of occurrence described as “moderate to heavy” (Yoshida et al., 2006); in the same study the authors reported very heavy labeling in the claustrum from the LHA (including the LHAs) (Yoshida et al., 2006), whereas we noted very few cells. Finally, the retrograde labeling we found in the basolateral and basomedial amygdalar nuclei has some confirmation from a previous PHAL study in which projections from the basomedial amygdalar nucleus were described (Petrovich et al., 1996); these were found to include a low density of labeled fibers in the vicinity of the LHAs.

3.2.2.4.2. Cerebral nuclei

3.2.2.4.2. Cerebral nuclei: 3.2.2.4.2.1. Striatum: Overall, there was a moderate abundance of retrograde labeling in the striatum from the LHAs; most of this was distributed widely within the lateral septal nucleus (Fig. 4G–P). However, no single region of the lateral septal nucleus contained more than a low incidence of retrograde labeling from the LHAs, in marked contrast to retrograde labeling from the LHA_{jp}, which was abundant in several components of the lateral septal nucleus. Almost every recognized differentiation of the lateral septal nucleus contained some retrograde labeling from the LHAs, although the majority of labeled cells were in the rostral part. In general agreement with these findings, a comprehensive previous study of the connections of the lateral septal complex in the rat revealed relatively few projections to the vicinity of the LHAs from either rostral or caudal parts (Risold and Swanson, 1997).

After the lateral septal nucleus, the second most abundantly labeled striatal component was the lateral part of the central amygdalar nucleus (CEAL; Figs. 4U–V, 8D); however, although in terms of overall amount of labeling the CEAL ranked second to the lateral septal nucleus, as a single striatal nucleus it contained the highest density and abundance of retrograde labeling from the LHAs. Aside from the moderate amount of labeling in the lateral septal nucleus and

CEAl, there was comparatively little labeling in other striatal cerebral nuclei; this was present at a low incidence in the anterodorsal part of the MEA, septofimbrial nucleus, and septohippocampal nucleus; and at a very low incidence in the anterior amygdalar area, CEAm, CEAc, and posterodorsal part of the MEA (sublayer a). Our finding of densely grouped neurons back-labeled in the CEAl is consistent with a previous report of this following an injection of CTB into a region of the LHA that included (but was not restricted to) the LHAs (Yoshida et al., 2006) -- labeling was also reported in the CEAm and CEAc, albeit at a much lower amount (Yoshida et al., 2006). An earlier PHAL study of output from the CEAl reported “no significant projections” to the LHA (Petrovich and Swanson, 1997); however, the PHAL study described principally the connections of a posterior region of the CEAl, whereas the retrograde labeling we report in the CEAl from the LHAs is highly restricted to its rostral tip.

3.2.2.4.2.2. *Pallidum*: The most abundant retrograde labeling in the entire brain from the LHAs was present within pallidal cerebral nuclei. Foremost among the pallidal regions back-labeled from the LHAs was the bed nuclei of the stria terminalis (BST), where labeled cells were very numerous; in addition to the BST, a moderate amount of labeling was present within the substantia innominata (SI) -- the latter is consistent with previous studies of projections from the SI (Grove, 1988a). Labeling in the BST was most prominent in its anterior division, more specifically within the anteromedial area (BSTam; Figs. 4K–P, 8C), which contained the highest abundance of labeling of any single delineated brain region. Next to the BSTam, the BST fusiform nucleus (BSTfu) contained the second most abundant BST labeling (a more moderate amount but a much higher density) (Figs. 4M–N, 8C), followed by the caudal half or so of the anterolateral area (BSTal), which contained a moderate amount (Fig. 4O–P). Within the anterior division of the BST, a low incidence of labeling was also present in dorsomedial (BSTdm) and interfascicular (BSTif) nuclei; a very few cells were also present in magnocellular (BSTmg) and ventral (BSTv) nuclei. One component of the posterior division of the BST contained a low incidence of labeling, and this was the principal nucleus (BSTpr; Fig. 4Q); also within the posterior division of the BST, a very few cells were retrogradely labeled within the transverse nucleus (BSTtr). By comparison to the BST, labeling within the SI was of a lower density; nevertheless, this extended over much of the rostral-caudal extent of the SI and summated to a somewhat higher than moderate amount in total (Fig. 4K–T). Outside of the BST and SI, there was no other site within the pallidum that contained more than a very few isolated back-labeled cells; these sites were in essence the medial septal nucleus and its ventrolateral extension, the diagonal band nucleus.

Several comprehensive PHAL studies of projections from the BST have been published in recent years; these studies by Hong-Wei Dong and colleagues include the BST divisions where we report retrograde labeling from the LHAs, and thus they provide a very useful set of data with which to make comparisons to our present findings (Dong et al., 2001b; Dong and Swanson, 2004a; Dong and Swanson, 2004b; Dong and Swanson, 2006a; Dong and Swanson, 2006b; Dong and Swanson, 2006c). Beginning with the BSTam, where we found such a very high abundance of retrograde labeling from the LHAs, following PHAL deposits in either dorsal or ventral regions of the BSTam, Dong and Swanson reported a “dense terminal plexus” in the LHAs (Dong and Swanson, 2006a). In a separate PHAL study, a projection from the BSTfu to the LHAs is reported (Dong et al., 2001b); this is shown to be dense within rostral levels of the LHAs, and of much lower density caudally (Dong et al., 2001b). Also in their study of BSTfu projections, Dong et al. described the projections of the BST oval nucleus (BSTov) (Dong et al., 2001b); this is a useful comparison here because the BSTov is adjacent to both the BSTam and BSTfu and yet provides essentially no projection to the LHAs (Dong et al., 2001b), which finding is consistent with our noted absence of retrograde labeling in the BSTov from the LHAs. Finally among the sites we have identified as providing a moderate or higher input to the LHAs from the BST, the retrograde labeling we found in caudal levels of the BSTal is confirmed by a shown moderate projection from this BST region to the vicinity

of midrostrocaudal levels of the LHAs (Dong and Swanson, 2004a); in further agreement with our results, it is also noteworthy that a projection to the vicinity of midrostrocaudal levels of the LHAs from *rostral* levels of the BSTal appears to be of considerably lower magnitude (Dong and Swanson, 2004a).

We now compare our results with respect to the BST studies of Dong and colleagues for those BST regions where we have reported a low degree of retrograde labeling from the LHAs. To begin, the low incidence of labeling we saw in the BSTdm at first glance appears to contradict the report of an extremely dense terminal plexus in the LHAs following a PHAL deposit centered within the BSTdm (Dong and Swanson, 2006b). However, on closer examination, it is apparent that the PHAL deposit in the experiment used for the most detailed analysis included adjacent regions; in particular it included a region of the BSTam that, as we have already discussed, provides a major input to the LHAs -- this may account to some extent for the seeming discrepancy. A similar interpretive situation is presented by the results of a PHAL study of the BSTmg and BSTv, both of which regions are reported to generate a dense terminal field in the LHAs (Dong and Swanson, 2006c) -- recall we found very few back-labeled neurons in either region from the LHAs. In this instance, inclusion of the BSTam is also a distinct possibility given the combination of its direct proximity to the BSTv and BSTmg, and the difficulties inherent in distinguishing boundaries between these differentiations and the BSTam. Following this theme, the BSTtr is also reported to generate a rich terminal field in the LHAs (Dong and Swanson, 2004b) -- much more than one might expect given the very few cells we found in the BSTtr back-labeled from the LHAs. In this case, the unpredicted result may to some extent be explained by the inclusion of some dorsomedial regions of the SI directly adjacent to the BSTtr in the PHAL deposit used for the analysis (Dong and Swanson, 2004b) because we did overall find a moderate amount of retrograde labeling in this region of the SI. Another possibility in all these cases is that a relatively few neurons in the BSTdm, BSTtr, BSTv, or BSTmg give rise to a relatively dense terminal field in the LHAs. Finally, the results of a study of projections from the BSTif and BSTpr (Dong and Swanson, 2004b) indicate very little input to the LHAs; however, an earlier autoradiographic study of the preoptic region that included analysis of a control injection within the BSTif/pr is more in agreement with our findings in that it indicated a moderate projection to the vicinity of the LHAs (Swanson, 1976). Clearly, further experimentation will be required to clarify these discrepancies.

3.2.2.4.3. Cerebrospinal Trunk

3.2.2.4.3. Cerebrospinal Trunk: 3.2.2.4.3.1. Sensory System: We found a relatively low abundance of retrograde labeling from the LHAs in brain regions classed generally as part of the sensory system; nevertheless, this was more abundant than the retrograde labeling we found in these brain regions from the LHAjp, and its distribution was considerably more extensive. Essentially, the labeling was divided between three components of the sensory system: (1) Polymodal sensory -- paraventricular nucleus of the thalamus (PVT; Fig. 4Q–U), (2) Viscerosensory – lateral division of the parabrachial nucleus (PBl; Fig. 4PP–SS) and a caudal (gustatory related) region of the medial part of the nucleus of the solitary tract (NTSm; Fig. 4III), and (3) Humorosensory -- the subfornical organ (SFO; Fig. 4Q–R). In and of these regions, in descending order, labeling was most abundant in the PBl, followed by the SFO, PVT and then the NTSm. Within the PBl, most of the labeled cells were located in the ventral lateral part (PBlv); a lower incidence was present in the central- (PBlc), dorsal- (PBl d) and external- (PBLE) lateral parts -- a few cells were also noted in the medial part of the medial parabrachial nucleus (PBmm). However, most of the labeled cells in the PBlv were present contralateral to the injection site; this is noteworthy not only by comparison with the other PBl labeling (which was almost exclusively ipsilateral) but also for being the site of most numerous contralateral retrograde labeling from the LHAs. The low incidence of labeling within the PVT was confined to its more rostral levels; outside of the PVT, a few isolated cells were also noted

in the lateral dorsal, intermediodorsal, anterior reuniens, and parafascicular nuclei of the dorsal thalamus.

Two previous studies (one very recent) have examined in detail the output of the PVT (Moga et al., 1995; Vertes and Hoover, 2008); in neither of these is a projection to the vicinity of the LHAs described. Nevertheless, in the more recent study (Vertes and Hoover, 2008) a very few fibers were shown in the vicinity of the LHAs in the figures depicting the distribution of the PHAL labeling. Furthermore, in the earlier study (Moga et al., 1995) a low incidence of *retrograde* labeling in rostral levels of the PVT is shown following a large injection of fluorogold into caudal levels of the LHA that may have included some of the LHAs. Consistent with the labeling we observed in the lateral division of the parabrachial nucleus, a previous PHAL study revealed a moderately dense fiber plexus in the vicinity of the LHAs labeled from a PHAL injection that appeared to include the PBlv, PBlc, and PBld (Bester et al., 1997); in addition, a plexus of fibers was shown within the vicinity of contralateral midrostrocaudal levels of the LHAs. Further consistent with our findings, a PHAL deposit in a region corresponding to the PBle resulted in very few labeled fibers in the vicinity of the LHAs (Bester et al., 1997). In an earlier and lower spatial resolution PHAL study of the PBl, a “light density” of labeling was reported in the LHA but its distribution was not specified (Krukoff et al., 1993).

In agreement with the retrograde labeling we observed from the LHAs in the SFO, a previous PHAL study of the SFO described a dense plexus of fibers in the LHA and showed clearly that this involves the dorsal perifornical region of the LHA at a level that includes most of the LHAs (Swanson and Lind, 1986). An earlier anterograde tracing study using the autoradiographic method also reported a dense terminal field in the dorsal perifornical area (Miselis, 1981), although this was mapped to an apparently more rostral site than was the case in the more recent PHAL study. Finally, for caudal levels of the NTSm, a recent PHAL study reported a small terminal field in the vicinity of the LHAs following a deposit of PHAL that labeled cells within the caudal half of the NTS (Geerling and Loewy, 2006). A previous PHAL study of the NTS reported a similar finding (ter Horst et al., 1989) and also showed that the caudal, but not the rostral, half of the NTS projects to the vicinity of the LHAs -- consistent with our findings. Furthermore, our present finding and the earlier PHAL studies are all consistent with an earlier autoradiographic study of NTS outputs in which sparse and diffuse labeling in the vicinity of the LHAs was reported (Ricardo and Koh, 1978).

3.2.2.4.3.2. Behavioral State System: Retrograde labeling in regions of the behavioral state system from the LHAs was similar to the labeling we obtained in these regions from the LHAjp, both in terms of its low incidence and regional distribution. Thus, the dorsal region of the LHA (LHA_d) contained the most labeled cells (Fig. 4V–Z); a very low incidence of labeling was also present in the hypothalamic subparaventricular zone, lateral part of the supramammillary nucleus, and more caudally within the caudal linear nucleus and dorsal nucleus of the raphé, and the pedunculopontine nucleus. The labeling we found in the LHA_d from the LHAs concurs with the results of a recent PHAL study (already mentioned in reference to the LHAjp) that included results from a PHAL injection involving (but was not restricted to) rostral levels of the LHA_d (Goto et al., 2005); a moderately dense projection to the LHAs was noted (Goto et al., 2005).

3.2.2.4.3.3. Motor System: As with the LHAjp, the bulk of cerebrospinal trunk retrograde labeling from the LHAs was present within regions classed as part of the motor system (Swanson, 2004); however, this was more extensive than the labeling in these regions from the LHAjp and in fact constituted the greater part of all the retrograde labeling from the LHAs. The majority of the labeled neurons were distributed between four of the eight divisions of the motor system: (1) Behavior control column, (2) Central gray, (3) Hypothalamic periventricular

region, and (4) Motor related hypothalamic lateral zone (LZm) of the reticular formation. Among these divisions, most of the labeled cells were present within the hypothalamic periventricular region (in contrast to the LHA_{jp} from which most of the back-labeled cells were within the behavior control column), but numerous cells were also present within the behavior control column, central gray, and LZm. In addition to these, a relatively low incidence of labeling was present in the neuroendocrine motor zone; this is in stark contrast to the LHA_{jp} from which labeling in the neuroendocrine motor zone was essentially absent.

Beginning with the comparatively little amount of retrograde labeling in the behavior control column from the LHAs, the regions that nevertheless contained the most back-labeled cells were the AHN (central part) (Fig. 4R–U) followed by the MPN (medial and lateral parts) (Fig. 4O–Q). A lower incidence of labeling was present in the dorsomedial part of the VMH (Fig. 4V–X) and a very low incidence was present in the ventrolateral part, and in the anterior and posterior parts of the AHN; in addition, a very few isolated cells were present in the central parts of the MPN and VMH, dorsal and ventral premammillary nuclei, and VTA. Although not part of the behavior control column, it is noteworthy that similarly few back-labeled cells were also present within the hierarchically-adjacent motor related intermediate gray layer of the superior colliculus (sublayer c). At least two previous PHAL studies in the rat showed a light to moderate projection from the central part of the AHN to the region of the LHAs (Risold et al., 1994; Delville et al., 2000), and one previous PHAL study of the MPN showed a moderate projection to the vicinity of the LHAs following a deposit of PHAL that included the medial, lateral, and central parts of the MPN (Simerly and Swanson, 1988).

Within the central gray numerous cells were back-labeled in rostral levels of the posterior hypothalamic nucleus (PH; Fig. 4X–BB), and a comparatively moderate number were present in the PAG (Fig. 4CC–PP). Labeling within the PAG was for the most part the sum of two small and diffuse groups of cells in the PAG_{vl} and (to lesser extent) PAG_{rm}; a very low incidence was also present in the PAG_d and commissural nucleus. Farther caudal, a small group of cells was back-labeled (bilaterally) in the pontine central gray, and a small but densely clustered group of cells was present within the lateral tegmental nucleus (LTN). An earlier PHAL study of PH outputs described especially dense labeling in the “dorsal perifornical area” (including a region corresponding to the LHAs) (Vertes et al., 1995) resulting from a PHAL injection in rostral levels of the PH.

The third division of the motor system of the cerebrospinal trunk that contained abundant retrograde labeling was the hypothalamic periventricular region. About a third of all labeling in the hypothalamic periventricular region was within the medial preoptic area (MPO; Fig. 4M–R). Besides the MPO, the median preoptic nucleus (MEPO) ranked second and contained a moderately high amount of labeling (Fig. 4L–P). Farther caudal, the DMH also contained a moderately high amount of labeling (Fig. 4W–Z); most of this was present in the posterior and anterior parts, and a small amount was present in the ventral part. In addition to these cell groups, a low to moderate incidence of labeling was present in the anteroventral preoptic nucleus (AVP; Fig. 4L–O) and also distributed in the internuclear region of the hypothalamic periventricular region. Furthermore, a low incidence of labeling was present in anteroventral periventricular (AVPV) and parastrial (PS) nuclei, and a very low incidence was present in the anterior hypothalamic area (AHA), posterior part of the periventricular nucleus (PV_p), and anterodorsal preoptic (ADP) nucleus.

Consistent with the very abundant labeling we found in the MPO, a previous study of MPO outputs using the autoradiographic tracing method revealed a dense terminal field in the region of the LHAs following a large deposit of ³H-leucine that was restricted mostly to the MPO (Conrad and Pfaff, 1976a). Much more recently, projections from the MEPO to the vicinity of the LHAs were shown using PHAL (Uschakov et al., 2007). With regard to the DMH, a

previous PHAL study described and showed a dense plexus of terminal fibers and fibers with boutons of passage in the vicinity of the rostral half of the LHAs following a deposit of tracer that included both anterior and posterior parts of the DMH (Thompson et al., 1996). In an earlier PHAL study of the DMH a robust projection to the vicinity of the (principally) rostral half of the LHAs arising from the anterior and posterior parts of the DMH was also described (ter Horst and Luiten, 1986). A previous PHAL study of projections from several of the more rostral periventricular hypothalamic regions including the AVP, AVPV, PS, and MEPO showed relatively light inputs from these regions to caudal levels of the LHAs, although its mid and rostral levels were not shown (Thompson and Swanson, 2003). An earlier PHAL study of the AVPV in the female rat revealed a light projection to the vicinity of the LHAs that appeared to be more pronounced rostrally (Gu and Simerly, 1997).

The final division of the motor system of the cerebrospinal trunk that contained abundant labeling was the motor related hypothalamic lateral zone (LZm) of the reticular formation. Labeled cells in LZm were present almost exclusively within one of several regions of the LHA or the lateral preoptic area (LPO -- the rostral extension of the LHA). A moderate amount of retrograde labeling was present in the LPO (Fig. 4K–P); in the ventral (LHAav), dorsal (LHAad), and intermediate (LHAai) zones of the anterior region of the LHA (Fig. 4Q–V); and in the ventral zone (LHAjvv) of the juxtaventromedial region of the LHA (Fig. 4T–Z). A low incidence of labeling was present in the LHAjd and LHAvm, and a very low incidence was present in the LHAsfp, LHAjp, and retrochiasmatic area; few isolated cells were present in the zona incerta, tuberal nucleus, LHAjvd, and midbrain reticular nucleus (magnocellular part). In a previous retrograde tracing study of the LHA (Kishi et al., 2000), moderate labeling was shown in the LPO following an injection of CTB into a dorsal perifornical region that included the LHAs; labeling was also apparent in several other regions of the LHA, but this was not analyzed at a high resolution or with regard to the present LHA parcellation.

As was mentioned at the start of this final section of our results, one other division of the motor system, the neuroendocrine motor zone (NEM), contained a relatively low incidence of labeling. About half of the labeling within the NEM (a moderate amount) was present within the anterior parvicellular part of the paraventricular hypothalamic nucleus (PVHap; Fig. 4P–S); a low incidence was present in the arcuate nucleus (Fig. 4U–Y), a very low incidence in the PVH medial parvicellular part dorsal zone (PVHmpd), and a very few cells were present in adjacent periventricular regions: PVH periventricular part (PVHpv), and periventricular hypothalamic nucleus anterior (PVa) and intermediate (PVi) parts. Our finding of moderate retrograde labeling in the PVHap is consistent with the results of an earlier lower spatial resolution study in which labeling was described in the “parvocellular regions of the PVH” apparently including the PVHap and to a lesser extent the PVHmpd following a deposit of CTB into a dorsal perifornical region that included the LHAs (Yoshida et al., 2006).

3.3. Comparison with additional experiments (control injections)

It is not possible with current methodology to reproduce exactly the same placement and distribution of tracer injection across experiments, and even if it were possible it is likely that the resultant pattern of labeling obtained would in each experiment be somewhat different. The reasons for this variation may include normal variation between individual animals that manifests as differences that affect not only the tracer placement but also its spread and the resultant neuronal labeling. Among the most apparent sources of variation are differences in brain dimensions, differences in the position of Bregma relative to the brain, and differences in the particular distribution of neurons and their processes within the neuropil. Nevertheless, these limitations duly noted, a measure of control is provided by comparing the results of experiments that are optimal (i.e., most restricted to the target region of interest) with experiments that either overlap or are adjacent to the target region.

In this study the LHA_{jp} is the primary focus, and experiment LHA#22 was selected as optimal for the most detailed analysis, being mostly restricted to the LHA_{jp} and centered in the caudal end of this region where the LHA_{jp} presents at its fullest, laterally adjacent to the fullest extent of the PVH (Figs. 1, 2A, 3); an additional experiment (LHA#62) that was also quite restricted to the LHA_{jp} extended primarily over approximately the rostral half of this region (Fig. 3). As a nearby control region for experiment LHA#22, experiment LHA#11 was selected for being mostly restricted to a dorsal perifornical region within a topographically central zone (i.e., midrostrocaudal levels) of the LHAs (Figs. 1, 2B, 3). A related adjacent region control is provided by the already published connections of the subfornical region of the LHA (Goto et al., 2005) (see also Fig. 13). In addition to experiments LHA#22, LHA#62, and LHA#11, four additional experiments were selected for comparison that partially overlapped with either the LHA_{jp} or LHAs (Fig. 3). For further comparison, the connections of the adjacent juxtadorsomedial region of the LHA (LHA_{jd}) will be described in the next paper in this series.

In general terms, deposits of combined CTB and PHAL that included either the region of the LHA_{jp} or LHAs as described for experiments LHA#22 (caudal end LHA_{jp}) or LHA#11 (midrostrocaudal levels of LHAs) yielded a pattern of labeling that largely reproduced the pattern seen in those experiments as well as producing an additional data set presumably resulting from the inclusion of adjacent regions. It is not within the scope of this paper to present and compare the fully detailed results of our analysis for all of these experiments. However, as a prelude to further publications we summarize here some of the more striking observations. Much similarity was noted in the pattern of labeling obtained in experiment LHA#22 and that obtained in experiment LHA#34 (mostly restricted to the rostral half of the LHA_{jd}), indicating that the caudal end of the LHA_{jp} and directly apposed rostral end of the LHA_{jd} connect similarly with other brain regions (we intend to present this data in a subsequent paper). Furthermore, there do appear to be certain clear quantitative differences between the rostral and caudal halves of the LHA_{jp}, as evidenced by comparing experiments LHA#22 (caudal end of LHA_{jp}) and LHA#62 (rostral half of LHA_{jp}). It is important to note, however, that these differences—to be described next—are generally quantitative rather than qualitative; that is, they generally represent differences in magnitude rather than the presence or absence of a pathway.

The caudal end of the LHA_{jp} (experiment LHA#22) shows a substantially stronger projection to the following regions than the rostral half of the LHA_{jp} (experiment LHA#62): medial mammillary and dorsal premammillary nuclei, rostral division of the nucleus reuniens and perireuniens nucleus, paratenial nucleus, anterior and dorsomedial parts of the VMH, and lateral and medial parts of the MPN. Conversely a substantially stronger projection from the rostral half of the LHA_{jp} (experiment LHA#62) was noted in the following regions: medial preoptic area, medial septal nucleus, and LSr.dl.m.v. Retrograde labeling from the caudal end of the LHA_{jp} was substantially more abundant than from the rostral half in the following areas: dorsal third of the subiculum, RSPv, ACA, LSr.m, and LSr.m.d. Conversely, many regions showed substantially more abundant retrograde labeling from the rostral half of the LHA_{jp} than from the caudal end, as follows: Cerebral cortex -- ILA, PL, ventral third of the subiculum, TTd; Striatum -- LSc.v.l.d, LSr.dl.l.d, LSr.vl.d.l, LSr.vl.d.m; Pallidum -- BSTam/if/pr, SF, TRS, SI; Thalamus -- PVT; Hypothalamus -- AHNa/c/p, LHAav/jd/jvv, LPO, I, MEPO, MPNm, MPO, PH, PVHap, SBPV, VMHdm, VMHvl, ZI; Brainstem -- PAGvl, PRC. A fuller comparison of the inputs and the outputs of the rostral and caudal ends of the LHA_{jp} is presented in Table 1.

DISCUSSION

The data from these tract-tracing experiments reveal much complexity in the neural connections of the LHA (Table 1; Fig. 4), and they affirm a view of the LHA as an

heterogeneous region in terms of its neuronal structure -- a region in which discrete LHA parcels in close proximity to one another can have quite different patterns of connectivity. Here we have shown this to be the case for the regions we refer to as LHA_{jp} and LHAs, and this is underscored further by the recent description of axonal projections from the subjacent subfornical region of the LHA (Goto et al., 2005). The very different patterns of connections for the LHA_{jp} and LHAs have been indicated to some extent in previous studies as was presented in parallel with the description of the Results. In the following discussion we address additional extrinsic connections previously described and related to the present data; in relation to this, we also suggest some possible functional roles for the LHAs and LHA_{jp} that are indicated by the very different patterns of their neural connections. Before this in-depth discussion of the data, we discuss briefly the technical limitations of the tract-tracing technique that was used in these experiments.

4.1. Methodological considerations

The goal of these experiments was to determine and compare systematically at high spatial resolution the source of neural inputs to, and the axonal pathways and associated terminal fields generated by, two nearby regions of the LHA. In this we aimed to provide a firmer and more substantive basis for further critical and hypothesis driven study of these LHA regions. To this end we employed a dual tract-tracing strategy that involved coinjecting from a single micropipette a mixture of two sensitive tracers -- PHAL and CTB; both tracers have had wide application in central anterograde (PHAL, and to a lesser extent CTB) and retrograde (CTB) tracing studies since their introduction about 25 years ago (Luppi et al., 1987; Gerfen and Sawchenko, 1984). When delivered by iontophoresis using the method described here, there is no unequivocal evidence that PHAL is taken up by fibers of passage (bearing in mind that long dendrites often extend into certain fiber tracts, for example, in the spinal cord). Instead, it is taken up by dendrites and cell bodies and is transported exclusively anterogradely to reveal the morphology of labeled axons with the clarity of a Golgi preparation (Gerfen and Sawchenko, 1984).

In contrast to PHAL, the tracer CTB is transported anterogradely and retrogradely following central injection; however the axonal labeling CTB produces is of lower clarity than that achieved with PHAL and it does not confound analysis of the retrograde labeling. Retrogradely transported CTB typically distributes rather uniformly in the perikaryon to reveal the morphology of the cell body and (to varying degree) its dendrites. However, despite wide application, questions pertaining to the efficacy of CTB persist (as is the case more generally for most if not all tracers); thus, one early report indicated that CTB is not taken up by undamaged fibers of passage in the olivocerebellar pathway following iontophoretic injection of CTB into a region of the cat ventrolateral medulla they assumed contained the olivocerebellar pathway (Luppi et al., 1990). In contrast, as evidence of uptake by fibers of passage, in a later study iontophoretic injection of CTB in the ventrolateral medulla of the rat was reported to result in retrograde labeling in the contralateral inferior olive, and anterograde labeling in the cerebellum (Chen and Aston-Jones, 1995); whether or not this was due to uptake by damaged or undamaged fibers was not established. Consistent with the former claim, in this study, for every region we reported retrogradely labeled with CTB we found no example of a previously published PHAL report to contradict this by indicating a given projection was not present (where the resolution of the former study was sufficient to allow such analysis); furthermore, for every instance where a previous PHAL report was available, the findings were consistent with our results. However, these are not definitive controls and future studies to resolve questions of tracer efficacy remain a critical priority. In any event, it can be concluded with certainty that retrograde labeling reported here was due to the uptake of CTB by axons generating terminals within and/or passing through the injection site.

Questions of efficacy aside, there are two intrinsic limitations of the coinjection method, one general and one (in this study) related to the LHAjp and LHAs. First, as considered in the Results, different neuronal pathway tracers have different diffusion patterns when injected into nervous tissue -- i.e. their injection sites have different characteristics, even when the same volume is injected, or they are injected together; second, it is difficult to establish with precision the effective spread of a tracer in solution from the tip of an injector -- that is, the actual spatial dimensions of the region of the injection site that produces detectible labeling of neuronal inputs or outputs -- this is particularly so when the neural connections of the injected region are poorly understood (as is the case with the LHAjp and LHAs). The specific relevance of this for the present coinjections is that the volume of neuropil exposed to effective concentrations of the two tracers cannot be assumed to be equal, although central regions of the injection site obviously contain effective concentrations of both tracers. Nevertheless, in this regard it is also important to point out an essential difference between PHAL and CTB (when the latter is employed as a retrograde tracer). In the case of PHAL, although the effective spread has not been measured, the labeled perikarya at the site of injection can be identified and quantified to some extent; this is not the case for CTB where the particular axons that take up the tracer for retrograde transport have not been similarly identified.

With regard to the limitations of the coinjection method used in the present experiments as they apply to the LHAjp and LHAs, firstly these are two relatively diminutive, irregularly shaped gray matter regions -- features that imposed limits on how confined to these regions our injection sites could be. Secondly, in each of our experiments, in addition to the possibility of undetected effective spread of tracer beyond the regions of interest, we always found at least a few PHAL labeled perikarya outside of the LHAjp or LHAs; the latter may also be due to dendrites extending from neighboring regions in to the target region. Thus, we cannot rule out the possibility that some of the lighter labeling we report relates not the LHAjp or the LHAs but to adjacent nuclei or regions. An effective and standard way to address this issue is to examine retrogradely labeled neuron populations with an anterograde tracer, and anterogradely labeled terminal fields with a retrograde tracer (whether through new experiments or those previously published). Another consideration is that with the present method it is not possible to determine whether or not neurons retrogradely labeled from two different sites that are intermingled in a given region project to both sites -- a double retrograde method in a single animal would be necessary to address this. As a final point here, neuronal gene expression patterns restricted to or selective for all of the projection neuron populations in the LHAjp and LHAs have not yet been established. This precludes the use of genetic dissection methods for determining the global neuronal input/output relationships of these two cytoarchitecturally differentiable gray matter regions (see Luo et al., 2008).

4.2. Connectional and functional overview

The present results indicate that the primary connections of the LHAjp and LHAs are differentiable but very complex, involving together almost 250 other definable gray matter differentiations of the brain (Table 1) -- this equates to approximately half the total number (about 550) currently recognized in the rat brain as a whole (Table B in Swanson, 2004). To place these results into a meaningful context necessitates a discussion of the functional implications. However, given the magnitude of these results we take a conservative approach and limit our discussion to what is known at a basic level about the structure-function attributes of a selection of the neuron populations that project directly to, or receive direct inputs from, these two nearby LHA differentiations. A theoretical framework for this discussion is provided by a four subsystem structure-function network model of the nervous system (Swanson, 2003b; Swanson, 2004) -- with motor, sensory, cognitive, and behavioral state subsystems. A single page summary of our results in the context of this four subsystem model is presented in the form of a tree diagram (Fig. 12); this is also referenced in a circuit diagram (Fig. 13), and

these diagrams together with the summary ‘flatmap’ (Fig. 5) may be referred to as a guide throughout the following discussion.

One approach to the four subsystem model concerns cerebral hemisphere (cognitive) regulation of motivated behavior (Swanson, 2000) and argues for the existence of a triple descending projection from the cerebral hemispheres to the motor system, including a behavior control column located medially within the hypothalamus and midbrain. The projection comprises interconnected cortical excitatory, striatal inhibitory, and pallidal disinhibitory components. Generally, recipient regions of the behavior control column in turn project to midbrain regions where patterns of behavior are initiated; the latter project to motor pattern generator networks within the hindbrain and spinal cord, and it is the activity of these that are largely responsible for the activity of specific sets of motoneuron pools that effect the corresponding specific behaviors. Although the fine details and functional dynamics of the circuitry remain to be fully elucidated, this model, characterized by topographically based hierarchical, parallel, and network organizing principles, provides a useful conceptual frame of reference for the complex circuitry presented here.

4.3. LHAjp discussion: Connectional and functional considerations

With the wider vista in mind, if we now select as a starting point the source of the most abundant input to the LHAjp, this directs us to the cerebral cortex and in particular the hippocampal formation (HPF). Before proceeding, we address certain difficulties inherent in description of HPF topography and present a novel approach (Fig. 11). As is known, the longitudinal axis of the rat HPF is roughly “C”-shaped, with a dorsal or septal end and a ventral or temporal end (see Swanson and Cowan, 1977, their Figs. 1 and 2). However, beyond this basic distinction, several different qualitative and arbitrary descriptions exist. For example, the subiculum has been divided into dorsal and ventral halves (e.g., Swanson, 2004), or dorsal, intermediate, and ventral “parts” (e.g., Groenewegen et al., 1987; Kishi et al., 2000) or “zones” (Swanson and Cowan, 1977); Groenewegen (1977) further divided the intermediate part of the subiculum into dorsal and ventral “parts”.

Our current approach is to qualitatively divide the hippocampal region (Ammon's horn and dentate gyrus) along with the adjacent subiculum into approximate thirds to give dorsal, intermediate, and ventral volumes, with further specificity of description achieved by referring to dorsal and ventral halves (Fig. 11). Applying this model to our results we can say that retrograde labeling in the HPF from the LHAjp was most abundant within the intermediate third of field CA1 and the subiculum (caudal region of field CA1 and subiculum in transverse section); more specifically it predominated within the ventral half of the intermediate third of the subiculum (Fig. 4 HH–LL). Also noteworthy is an alternate collective parceling scheme for field CA1 and the subiculum proposed by Risold and Swanson (1996), who divided the longitudinal extent of these cortical areas into five sequential domains based on their predominant mode of topographically organized projection to the lateral septal nucleus, which in turn establishes topographically organized bidirectional connections with various parts of the hypothalamus. The topographic relation of these domains to LHA terminal fields will be dealt with in a subsequent paper.

4.3.1. LHAjp discussion: Hippocampal formation—A recent study examined in the rat the behavioral effects of bilateral excitotoxic (ibotenic acid) lesions of the HPF (Pentkowski et al., 2006). In that study it was reported that lesions of the ventral half of the intermediate third of the HPF (including at least dentate gyrus, Ammon's horn, and subiculum) were effective at reducing an unconditioned (innate) defensive emotional response to the odor, but not the sight, of a predator (in this case a cat). Conversely, in the same study lesions restricted to the dorsal third of the HPF (including Ammon's horn and subiculum) were without effect

on these measures of behavior; the effect of lesion of the subiculum and Ammon's horn in between was not assessed (Pentkowski et al., 2006). The authors went on to suggest an anxiolytic but not anti-fear effect of their effective lesions proposed to be consistent with a reduction in exploratory risk assessment behavior to the odor, but no attenuation of escape or freezing behavior to the presence of a clear visual threat (cat exposure). In an earlier study by a different group, bilateral excitotoxic combined lesion of the ventral half of the dentate gyrus, Ammon's horn, and subiculum resulted in rats that spent more time in the open arms of an elevated plus maze -- an effect that was mimicked by the potent anxiolytic drug midazolam (a benzodiazepine derivative and potentiator of GABAergic neurotransmission) (Kjelstrup et al., 2002); furthermore, when confined for short periods in a brightly lit room these rats were also reported to defecate with much reduced frequency and to have lower plasma corticosterone in comparison to rats with combined lesion of the dorsal half of the dentate gyrus, Ammon's horn, and subiculum (Kjelstrup et al., 2002).

Additional previous work has also implicated the ventral half of the intermediate third of the subiculum in defensive responses. For example, bilateral electrolytic lesion involving the ventral half of the intermediate third of the HPF (reported as 50 – 60% lesion of the “posteroventral hippocampus”, and shown to include the dentate gyrus, subiculum, and parts of parasubiculum and adjacent entorhinal area but not Ammon's horn) in the rat has been reported to elicit a “rage syndrome” (McGowan et al., 1972) akin to a classic report of such behavior resulting from lesion of the lateral septal nucleus (Brady and Nauta, 1953). Furthermore, bilateral electrolytic lesion of the ventral half of the intermediate third of the HPF (shown to include at least the dentate gyrus, subiculum, and entorhinal area) (Blozovski and Harris, 1986) or combined lesion of the intermediate third of the HPF (shown to include at least subiculum and dentate gyrus) (Kimrua, 1958) in the rat results in a deficit in the acquisition of a passive avoidance response (Kimrua, 1958; Blozovski and Harris, 1986). Also noteworthy is a recent report indicating a requirement for roughly the ventral (but not dorsal) half of field CA1 in the temporal processing of olfactory information (Hunsaker et al., 2008); whereas the entire field CA1 appears to be involved in the temporal processing of visual information (Hunsaker et al., 2008).

The examples given above, indicative of an established role for the HPF in processing emotional stimuli, echoes a classical view of the HPF that has positioned it as a central regulator of emotion (Papez, 1937) -- a view that led to the proposal of a more specific role for the HPF in behavioral inhibition (Gray, 1976; Gray, 1982). However, these views have to some extent been overshadowed by studies emphasizing a role for the HPF in spatial navigation, for examples see: (O'Keefe and Nadel, 1978) and learning and memory, for examples see: (Eichenbaum, 2000a; Squire et al., 2004). Together these differing roles speak to a broader integrative function for the HPF -- one in which the seamless integration of spatial information and emotional salience with mnemonic processes facilitates appropriate modulation of an animal's behavior. An integrative role for the HPF is not a novel idea; several studies, many of them recent, grapple with this notion from differing perspectives, for examples see: (Hirsh, 1974; Eichenbaum, 2000b; Dolan, 2002; Holscher, 2003; Bannerman et al., 2004; Erdi et al., 2005; Kulvicius et al., 2008).

It is evident there exists regional division of function within the HF, and most apparent is a graded dorsal and dorsal intermediate to ventral intermediate and ventral differentiation in which the dorsal regions have a role in spatial navigation that is not necessarily (directly) influenced by anxiety-related information, but may be influenced by other emotionally salient stimuli (Bannerman et al., 2004; Pentkowski et al., 2006; O'Mara, 2006; Engin and Treit, 2008); whereas ventral regions (and in particular the ventral- and ventral intermediate subiculum) appears not to have a primary role in spatial navigation, but a central role in the processing of anxiety-related information (Herman et al., 1998; Kjelstrup et al., 2002;

Bannerman et al., 2004; Pentkowski et al., 2006; O'Mara, 2006; Herman and Mueller, 2006; Engin and Treit, 2008), including involvement in an activation of the neuroendocrine response to stress (Herman et al., 1998; Kjelstrup et al., 2002). It is also of note that whereas glucocorticoid receptors are expressed throughout the HF, the ventral regions of Ammon's horn and subiculum are reported to express approximately 2½ times the number of glucocorticoid receptors than the dorsal regions (Reul and de Kloet, 1985). To what extent differing views of the HPF can be reconciled remains to be determined and the details of the topography have yet to be fully elucidated. Nevertheless, a demonstrated involvement of the ventral intermediate region of the HPF in defensive responses is consistent with a strong projection from this region to the LHA_{jp}, which as we shall now discuss, receives from and projects to several regions that are positively identified as components of a medial hypothalamic defensive behavior system.

4.3.2. LHA_{jp} discussion: The medial hypothalamic defensive behavior system

—The medial hypothalamic defensive behavior system was identified in the rat following studies in which rats were exposed to a cat (predator) in order to elicit innate defensive behavior. Brain regions showing increased neuronal activation associated with the defensive behavior (as determined by elevated numbers of Fos immunopositive neurons) were identified (Canteras et al., 1997; Canteras and Goto, 1999b). From this work three medial hypothalamic differentiations were identified for their especially elevated levels of Fos expression, these were the AHN, VMH_{dm}, and PM_d (Canteras et al., 1997); more recent work has confirmed these findings (Cezario et al., 2008). In another related study in which rats were exposed to the odor (but not the site) of a cat, regions corresponding to the AHN, VMH_{dm}, and PM_d also showed a marked increase in Fos expression (Dielenberg et al., 2001). In the present study we have shown for each of these three regions (AHN, VMH_{dm}, and PM_d) that they receive a projection from the LHA_{jp} (major to the AHN and PM_d and moderate to the VMH_{dm}) (Fig. 13); in addition, the LHA_{jp} also receives a major input from the AHN (Fig. 13). Furthermore, previous PHAL studies have revealed the AHN, VMH_{dm}, and PM_d to be highly interconnected (Canteras, 2002; Thompson and Swanson, 2003).

In the predator exposure defensive behavior model just described, bilateral chemical (excitotoxic: ibotenic- or N-methyl-D-aspartic acid) lesion of the PM_d results in a severe reduction of escape and freezing responses (Canteras et al., 1997; Markham et al., 2004; Blanchard et al., 2005; Cezario et al., 2008), as well as chronic docility and attenuated vocalization when the animals are handled (Canteras et al., 1997). Bilateral electrolytic lesion of the PM_d results in a similarly dramatic reduction in rat defensive behavior to the presence or odor of a cat (Blanchard et al., 2003; Blanchard et al., 2005). Most recently, blockade of glutamatergic neurotransmission (Canteras et al., 2008) or facilitation of GABAergic transmission (Cezario et al., 2008) within the PM_d was shown to result in essentially the same behavioral deficit as that resulting from PM_d lesion. Conversely, other studies have shown that PM_d electrical stimulation (Yardley and Hilton, 1986) or microinjection of a GABA_A receptor antagonist (bicuculline methiodide) into the vicinity of the PM_d (Di Scala et al., 1984) will elicit the expression of behaviors resembling those presented by an animal exposed to a predator.

Interestingly, the AHN is implicated in different types of defensive response. Thus, electrical stimulation studies in the rat have identified a region encompassing much of the AHN from which escape (Lammers et al., 1988b) or attack (Kruk et al., 1983; Lammers et al., 1988a; Dielenberg et al., 2001; Hrabovszky et al., 2005) behavior can be evoked. It is noteworthy that a region corresponding to the anterior part of the AHN in particular was identified in these studies (Kruk et al., 1983; Lammers et al., 1988a; Lammers et al., 1988b); this is notable because in the present study we found the anterior part of the AHN to be a site of very abundant retrograde labeling from the LHA_{jp} (in particular from the rostral half of the LHA_{jp}). More

apposite, a region corresponding to the LHAjp is identified as a site at which electrical stimulation will elicit bite attacks in male rats exposed to conspecifics (Kruk et al., 1983), or nonspecific jumps (Lammers et al., 1988b).

The hypothalamic PMd gives rise to very robust and topographically organized descending projections to the midbrain PAG; although our understanding of the topography is currently incomplete, in broad terms it is clear that the more ventral (or ventrolateral) PMd targets very heavily rostral levels of the PAGdl, whereas the more dorsal (or dorsomedial) PMd gives rise to a very light projection to rostral levels of the PAGdl, and a very dense projection to a dorsolateral region of the PAGvl (Goto et al., 2005; Motta et al., 2009). Recall that we found the LHAjp to also target the PAG lightly, principally to rostral levels of the PAGvl (Fig. 4 GG–II). A strong descending projection from the LHAjp to the PMd and then PMd to the PAG, and a more moderate projection from the LHAjp directly to the PAG, is in line with hierarchical control of defensive behavior suggested by early work in this field (Hunsperger, 1956; Fernandez de Molina and Hunsperger, 1962); it is also in line with a general model for the control of motivated behavior expressed more recently and emphasizing separate, hierarchically ordered regions for behavior control (hypothalamus) and behavior initiation (midbrain) (Swanson, 2000).

4.3.3. LHAjp discussion: Beyond the medial hypothalamic defensive behavior system—Thus far we have shown the LHAjp to be intimately connected to a proposed medial hypothalamic defensive behavior system, which itself is part of a behavior control column within the hypothalamus. According to our data several extra-hypothalamic regions are likely to influence this system via the LHAjp, and prominent among these regions are: in the cerebral cortex the HPF and prefrontal cortex, in the striatum the lateral septal nucleus, and (less prominently) in the pallidum the bed nuclei of the stria terminalis and diagonal band nucleus (Figs. 12, 13). In this way, with reference to the concept of a triple descending projection from the cerebral hemispheres to a behavior control column, we have shown for the LHAjp a direct descending input from the cerebral cortex (presumed excitatory), striatum (presumed inhibitory), and pallidum (presumed disinhibitory). Thus, in addition to medial hypothalamic nuclei, the LHAjp could also be considered an integral component of, or intimately related to, the behavior control column. In this context also worthy of note is a less prominent ascending projection within the cerebrospinal trunk from the rostromedial division, and (to a lesser extent) precommissural nucleus, of the PAG to the LHAjp (Fig. 4 CC–DD). Given the importance of the PAG for the expression of defensive behaviors (Bandler et al., 1985; Krieger and Graeff, 1985), and the strong descending projections from the PMd to the PAG (Goto et al., 2005), an ascending projection from the PAG to the LHAjp provides a direct route whereby activity of the midbrain behavior initiation region in the PAG could provide feedback to modulate activity of the LHAjp (and therefore the behavior control column).

The LHAjp may well be involved in the modulation of defensive behaviors. However, it is likely that the defensive responses in which it *may* participate are influenced quite differently by different sensory modalities. For example, shock-based fear conditioning to an otherwise innocuous odor will strongly activate the PMd (Canteras et al., 2008); conversely, PMd activation is not noted when the conditioned stimulus is auditory (Pezzone et al., 1992). In addition, PMd lesion, while effective at reducing defensive behavior to cat odor, appears to have little effect on freezing responses to electric shock or in the elevated plus maze (Blanchard et al., 2003). We cited an article at the start of this discussion indicating involvement of the ventral intermediate HPF in rat defensive responses to predator odor (Pentkowski et al., 2006), and we suggested that this may involve the LHAjp via the massive input it receives from the ventral half of the intermediate third of field CA1 and the subiculum. This in turn may influence activity of the medial hypothalamic defensive behavior system, which presumably would result in modulation of defensive behavior. Consistent with the latter, a

recent study showed an approximately 2.5-fold increase in Fos expression specifically within the LHA_{jp} following exposure to a live cat (Cezario et al., 2008). In the same study an approximately 8-fold increase in Fos expression in the PMd was noted -- it is suggested the PMd may act to amplify the signals it receives relating to defensive behavior (Cezario et al., 2008).

It is important to be clear that a possible role for the LHA_{jp} in the modulation of defensive behavior in response to olfactory cues does not preclude its possible involvement in other behaviors that may or may not also be susceptible to influence by olfactory cues. For example, grooming behavior has been reported to occur following injection of various neurochemicals into a region corresponding to or including the LHA_{jp}. These neurochemicals include adrenocorticotrophic hormone (ACTH) (Van Erp et al., 1991) and the ionotropic glutamate receptor agonists kainic acid (Roeling et al., 1990) and N-methyl-D-aspartic acid (NMDA) (Roeling et al., 1991); grooming behavior is also reported following electrical stimulation in the vicinity of the LHA_{jp} (Lammers et al., 1987). A further consideration is that grooming behavior may also be related to defensive behavior, in the form of displacement behavior -- the nature of which was so well described by Nikolaas Tinbergen in his classic studies of instinct (Tinbergen, 1951).

An understanding of any given brain region merits a consideration of the relations of its input-providing regions and recipient sites. For the LHA_{jp} we have thus far done this for regions that together constitute elements of a medial hypothalamic defensive behavior system. We now consider with respect to the LHA_{jp}, the relations and possible functional roles of additional hypothalamic and extra-hypothalamic sites that project to or receive from the region of the LHA_{jp}. Within the hypothalamus, in addition to the aforementioned regions, ventral levels of the medial mammillary nucleus (MM) receive a dense and strikingly targeted projection from the caudal end of the LHA_{jp} (Fig. 6C). The MM, as is the case for the LHA_{jp}, also receives a strong projection from the subiculum (Swanson and Cowan, 1975; Swanson and Cowan, 1977; Kishi et al., 2000) as does the PMd (Comoli et al., 2000). Moreover, the topography of this projection is noteworthy in that the dorsal half of the subiculum projects predominantly to the dorsal MM (Swanson and Cowan, 1975; Swanson and Cowan, 1977; Shibata, 1989; Kishi et al., 2000), whereas the ventral half of the subiculum projects predominantly to the ventral MM (Shibata, 1989; Kishi et al., 2000); a similar topography is also reported in the macaque monkey (Aggleton et al., 2005).

Thus the ventral half of the subiculum targets heavily ventral levels of the MM in addition to the LHA_{jp}. To what extent these projections arise from the same neurons remains to be determined. Nevertheless, this projection, together with a projection from the caudal end of the LHA_{jp} to ventral levels of the MM, places the LHA_{jp} as an intermediary within the classic loop alluded to earlier and originally described by James Papez (Papez, 1937). This loop (in essence: hippocampal formation > mammillary body > anterior thalamic group > medial isocortex > hippocampal formation) he proposed as an anatomical substrate for the processing of emotion. Although the basic anatomical loop described by Papez has essentially stood the test of time, it has undergone substantial refinement (Swanson and Cowan, 1975; Swanson and Cowan, 1977; Seki and Zyo, 1984; Shibata, 1989; Shibata, 1992; van Groen and Wyss, 1995; Dalgleish, 2004). Furthermore, the functional role attributed to "the Papez circuit" has undergone revision, with a more current emphasis placed on mnemonic processes relating to spatial navigation rather than emotion *per se* (Vertes et al., 2001; Vann et al., 2003; Vann and Aggleton, 2003; Vann and Aggleton, 2004). Nevertheless, our results together with recent work on hippocampal function (Herman et al., 1998; Pentkowski et al., 2006; O'Mara, 2006; Engin and Treit, 2008) suggest the "circuit for emotion" as conceived by Papez continues to provide a useful heuristic.

4.3.4. LHAjp discussion: Thalamus—Given our proposed involvement of the LHAjp in the modulation of defensive behaviors, a direct link between the LHAjp and the MM is interesting in so far as it provides a link between a region implicated in behavior (LHAjp) and one implicated in learning and memory (MM, via its projection to the anterior thalamic group). More specifically the MM via the mammillothalamic tract (mtt) is implicated in visuo-spatial learning -- this is disrupted by lesions of either the MM or the mtt (Vann et al., 2003; Vann and Aggleton, 2003). Recent work suggests a similar role for PMd (Cezario et al., 2008; Carvalho-Netto et al., 2008) that also projects massively to the anterior thalamic group (specifically to the AMv) (Canteras and Swanson, 1992b). In short, what we have identified is a direct input from the hippocampal formation to the LHAjp and an indirect route by which the neurons of the LHAjp may (via the MM/PMd as a component of the Papez circuit) influence activity of the hippocampal formation. In terms of possible function, in essence what is described thus far is a basic circuit including the LHAjp that may be involved not only in the emotive expression of a behavior but also in experience-dependent changes to that behavior, i.e. learning and memory.

If we now consider the connections of ventral regions of the MM to the thalamus and beyond in more detail, we see that it is principally a dorsorostral subregion of the anteroventral thalamic nucleus (AV) that is the thalamic recipient region from the ventral MM (Seki and Zyo, 1984; Shibata, 1992). The dorsorostral subregion of the AV in turn has bidirectional connections with intermediate to caudal levels of the dorsal part of the retrosplenial area (RSPd) (van Groen and Wyss, 1995; Shibata, 1998; van Groen and Wyss, 2003); it also projects prominently to the pre- and (to a lesser extent) postsubiculum (van Groen and Wyss, 1995). Recall that we found a low amount of retrograde labeling at an intermediate rostrocaudal level of the *ventral* part of the retrosplenial area (RSPv) from the LHAjp (Fig.4 FF-II). The RSPv has major bidirectional connections with the RSPd (in addition to the contralateral RSPv) (van Groen and Wyss, 1990; van Groen and Wyss, 2003). The RSPv also projects strongly to dorsal regions of the AV and more lightly to a dorsal region of the lateral dorsal (LD) and reticular (RT) nuclei of the thalamus (van Groen and Wyss, 1990; Shibata, 1998) (the latter two regions also receive a very light input from the LHAjp); the RSPv also receives a strong input from the AD (van Groen and Wyss, 1990; van Groen and Wyss, 1995).

As is the case with lesion of the MM or mtt (Vann et al., 2003; Vann and Aggleton, 2003), lesion of the AD or AV impairs spatial learning (Byatt and Dalrymple-Alford, 1996; van Groen et al., 2002a; Mitchell and Dalrymple-Alford, 2005), as does lesion of the LD (van Groen et al., 2002b). Lesion of the RSPd and RSPv impairs spatial learning also, and this is of much greater severity if the RSPd and RSPv are lesioned together rather than independently (Vann and Aggleton, 2002; van Groen et al., 2004). In addition to learning impairment, recent work indicates that retrosplenial area lesion also impairs spatial navigation that is reliant on directional cues (Pothuizen et al., 2008). Recent work also suggests related involvement of two additional thalamic regions that share a connection with the RSP, these are the rostral division of the nucleus reuniens together with ventral levels of the anteromedial thalamic nucleus (AMv) (Carvalho-Netto et al., 2008) -- recall that the AMv receives a massive input from the PMd (Canteras and Swanson, 1992b).

Combined lesion of the rostral division of the nucleus reuniens and AMv is reported to result in a “drastic reduction of contextual conditioned defensive responses” (Carvalho-Netto et al., 2008). It is salient to recall that the rostral division of the nucleus reuniens receives a dense projection from the LHAjp (Fig.4 R-U): the rostral division of the nucleus reuniens also has robust bidirectional connections with field CA1 and the subiculum (Wouterlood et al., 1990; McKenna and Vertes, 2004; Vertes et al., 2006) that, as we have shown, project strongly to the LHAjp. Recall too that the subiculum and field CA1 also target heavily ventral regions of the MM (Shibata, 1989; Kishi et al., 2000), RSPv (van Groen and Wyss, 1990), and PMd

(Comoli et al., 2000), and that lesion of the ventral half of the intermediate third of the HPF (including at least dentate gyrus, Ammon's horn, and subiculum) reduces a defensive response to a threat signified by an odor (Pentkowski et al., 2006). Given these functional data together with the connectional data, one could predict that lesion of the LHAjp may have an effect on spatial (contextual) learning and navigation, and especially in relation to defensive behavior that has an olfactory component.

4.3.5. LHAjp discussion: Theta rhythms—An additional functional perspective and higher order of integration is suggested by previous work indicating that the Ammonic theta rhythm (characteristic of locomotor and attentive behavior in rats and associated with mnemonic processes) resonates throughout structures of the Papez circuit (Vertes et al., 2004); this raises the intriguing possibility that neurons within the LHAjp (as a putative accessory component of the Papez circuit) might also show theta oscillations. In further support of this proposition, several hypothalamic sites have been identified for their responsiveness to stimulation of the rostral (oral) part of the pontine reticular nucleus (Vertes and Kocsis, 1997; Woodnorth et al., 2003), a brainstem site capable of eliciting the synchrony of hippocampal activity that is a necessary prerequisite for theta rhythm generation (Vertes, 1981; Vertes, 1982). Moreover, in addition to its classic association with locomotion in the rat (Vanderwolf, 1969), the hippocampal theta rhythm is also associated with other processes that may be predicted to have a bearing on defensive behavior. Thus, hippocampal mnemonic processes are affected by the theta rhythm (Staubli and Lynch, 1987; Huerta and Lisman, 1996; Vertes and Kocsis, 1997); environmental novelty appears to reduce its frequency (Jeewajee et al., 2008; Lever et al., 2009); while an increase in theta rhythm frequency (also associated with a heightened motivational-emotional state) is reported to correlate with an increase in the speed of locomotion (Slawinska and Kasicki, 1998; Jeewajee et al., 2008).

The possibility of a theta rhythm influence on defensive behavior involving neurons within the LHAjp is also likely to involve certain neuron types that have particular roles in spatial cognition; these are the so-called "head-direction" (Taube et al., 1990a), hippocampal "place" (O'Keefe and Dostrovsky, 1971), and (most recently identified) entorhinal area "grid" (Hafting et al., 2005) neurons. Head-direction neurons as a group include subtypes that respond to the present or anticipated facing direction subject to the influence of a present or previous environment (Taube et al., 1990a; Taube et al., 1990b; Chen et al., 1994a; Chen et al., 1994b; Muller et al., 1996; Taube, 1998). Complimentary to head-direction neurons, place and grid neurons respond essentially to a specific locus (place) and locus progression (grid). Together with head-direction neurons, these three neuron types collectively comprise central elements of a system for spatial cognition -- a system essential for most behaviors, not least defensive behavior.

Of further relevance, head-direction neurons are present and prominent in several regions associated with the classic Papez circuit, including some that have light direct connections with the LHAjp, these regions are: lateral mammillary nucleus, anterolateral and lateral dorsal thalamic nuclei, and postsubiculum and retrosplenial area (Taube and Bassett, 2003). Head-direction neurons are therefore in a position to be influenced by the hippocampal region theta rhythm (Vertes et al., 2004), as are place neurons (being intrinsic to Ammon's horn); whereas grid neurons in the entorhinal area are in a strong position to influence the Ammonic theta rhythm via the perforant and direct temporoalvear paths. Therefore, the neurons of the LHAjp are in a position to integrate and contribute to a temporally coded stream of information relating to spatial cognition, locomotion, and emotional salience. Furthermore, a link is indicated between the rhythmic processes (associated and coordinated with respiration) that shape the flow of information into the olfactory system and modulate other central rhythms, not least the hippocampal region theta rhythm, as means to facilitate perceptive behavior (Uchida et al., 2006; Kepecs et al., 2006; Grosmaître et al., 2007).

Returning to and extending further our discussion of the connections of the retrosplenial area with regard to connections of the LHA_{jp}, it is noteworthy that the RSP_v receives a major input from the ventral intermediate subiculum (van Groen and Wyss, 1990). Dorsal to the RSP_v, and adjacent to the RSP_d, the agranular part of the retrosplenial area (RSP_{agl}) also has relevance to this discussion given its strong bidirectional connections with the RSP_v (van Groen and Wyss, 1990; van Groen and Wyss, 1992; Risold et al., 1997). In addition, the RSP_{agl} has bidirectional connections with the adjacent anteromedial visual area (VIS_{am}), as well as more rostral parts of the medial isocortex including the anterior cingulate area (van Groen and Wyss, 1992; Risold and Swanson, 1995). As is the case for other parts of the retrosplenial area, the RSP_{agl} has major connections with the thalamus. Prominent among them are bidirectional connections with anterior and lateral groups, and the rostral division of the nucleus reuniens (van Groen and Wyss, 1992; Risold and Swanson, 1995).

The RSP_{agl} also projects to the superior colliculus (van Groen and Wyss, 1992), and this projection (in addition to its connections with the lateral group of the thalamus) identify it and the RSP_v and RSP_d with which it is intimately connected, as being in a position to influence eye movements and so have a role in visual attention. Strong indirect connections of the LHA_{jp} with the RSP (in addition to a minor direct input from both the RSP_v and superior colliculus) are therefore indicative of a possible role in visual attention. This certainly fits with our proposed involvement of the LHA_{jp} in the modulation of defensive behavior; in the context of the discussion so far, it also refines our understanding of a previously proposed hypothalamus-thalamus-cortical circuit for mediating pheromonal influences on eye and head movements (Risold and Swanson, 1995).

We have now identified and highlighted certain medial hypothalamic, thalamic (anterior and lateral groups, and nucleus reuniens), cortical (retrosplenial area and subiculum), and midbrain (periaqueductal gray) regions that by their interconnections and connections with the LHA_{jp}, together with some elucidation of their functional roles, provide the basis of a theoretical framework for understanding the position of the LHA_{jp} within a broader structural and functional network. However, several additional components of this network remain to be addressed in order to provide a more coherent framework. These components include four regions that we mentioned earlier in this discussion, namely: the medial prefrontal cortex, lateral septal nucleus (striatum), diagonal band nucleus and bed nuclei of the stria terminalis (pallidum). In addition to these, a projection to the lateral habenula is noteworthy. Before entering into this final phase of our discussion for the LHA_{jp}, it is apposite first to review briefly the principal neural pathways likely to be involved in the transmission of pheromonal information to the LHA_{jp} because this forms a basic starting point for the possible behavioral role we are emphasizing.

4.3.6. LHA_{jp} discussion: Olfactory system—Recent studies of the mouse olfactory system indicate that the odor sensing capabilities of the main and accessory olfactory epithelia overlap more than was previously thought (Trinh and Storm, 2004; Lin et al., 2004; Xu et al., 2005; Wang et al., 2006). Furthermore, recent studies also reveal more extensive overlap in the central projection fields of the main and accessory olfactory systems in rats and mice (Halpern and Martinez-Marcos, 2003; Pro-Sistiaga et al., 2007; Pro-Sistiaga et al., 2008) than was indicated in a previous classic work (Scalia and Winans, 1975). Nevertheless, the vomeronasal organ persists as a site that is specialized for the detection of pheromones (Halpern and Martinez-Marcos, 2003). In addition there exists a rostrocaudal differentiation within the accessory olfactory system, characterized by molecular and cytoarchitectural differences in the accessory olfactory epithelium (Jia and Halpern, 1996; Herrada and Dulac, 1997; Jia et al., 1997a) and accessory olfactory bulb (Jia and Halpern, 1996; Jia and Halpern, 1997; Jia et al., 1997a; Larriva-Sahd, 2008) and by differences in a subset of the central projections of rostral and caudal levels of the accessory olfactory bulb (Mohedano-Moriano et al., 2007).

Specifically, rostral (but not caudal) levels of the accessory olfactory bulb (AOB) appear to project to the bed nuclei of the stria terminalis, principal nucleus (BSTpr); whereas caudal (but not rostral) levels of the AOB project to dorsal levels of the anterior amygdalar area (AAA), deep levels of the bed nucleus of the accessory olfactory tract (BA), and the anteroventral part of the medial amygdalar nucleus (MEAav) (Mohedano-Moriano et al., 2007). In addition to segregated regions of termination, most of the amygdalar differentiations targeted by the AOB receive jointly from its rostral and caudal region; these differentiations are the MEAad, MEApv, MEApd, and cortical amygdalar nucleus (COA) (Scalia and Winans, 1975; Mohedano-Moriano et al., 2007).

To recap: we found the LHAjp to have a light bidirectional connection with the BSTpr and BSTif (Fig. 4Q–R), and a very light bidirectional connection with the MEAad (Fig. 4S–U). Thus, these two cell groups provide a possible direct link between the accessory olfactory system and the LHAjp. Further possible links, more substantial yet indirect, are provided by the connections of additional AOB-recipient parts of the medial and cortical amygdalar nuclei. Before describing these it is noteworthy that with the exception of the MEApd, subdivisions of the medial and cortical amygdala are highly interconnected (Canteras et al., 1995). The MEApd projects heavily to the BSTpr, while the MEApv and MEAad (and possibly MEAav) project heavily to the interfascicular nucleus of the BST (BSTif) (Dong et al., 2001a), which itself has a moderate bidirectional connection with the LHAjp (Dong and Swanson, 2004b) (and our results) and also projects to all components of the medial hypothalamic defensive behavior system (i.e., the AHN, VMHdm, and PMd) (Dong and Swanson, 2004b); the posterior part of the COA also sends a moderate projection to the BSTif (Dong et al., 2001a).

In addition to possible connections of the AOB with the LHAjp via the projections of AOB-recipient parts of the amygdalar region that project to the BSTif and BSTpr, there are also projections from the medial amygdalar nucleus to several other sites that strongly project to the LHAjp; these sites are principally within the cerebral cortex and hypothalamus. Specifically, the MEAad/v, MEApv, and MEApd all send a moderate projection to the ventral halves of the subiculum and field CA1 and the infralimbic area (Canteras et al., 1995). The MEAad/v and MEApv also project moderately to the prelimbic area (Canteras et al., 1995). All parts of the medial amygdalar nucleus also project to the entorhinal area (Canteras et al., 1995) that itself projects via the perforant and temporoalvear paths to the subiculum and CA1 (Wyss, 1981; Witter et al., 2000). Hypothalamic sites receiving a robust projection from the medial amygdalar nucleus and projecting to the LHAjp include, from the MEAad/v: AHNc, MPO, MPNl, PH; from the MEApv: AHNa/c, MPO, MPN, VMHdm, PH; from the MEApd: PH. The medial amygdalar nucleus also projects to the lateral septal nucleus; however, the principal projection is from the MEAad/v to the LSv (Canteras et al., 1995), which projects little to the LHAjp. Especially noteworthy is that the MEApv is specifically implicated in the processing of pheromonal odor related to defensive behavior (McGregor et al., 2004; Choi et al., 2005).

4.3.7. LHAjp discussion: Lateral septal nucleus—In reviewing centripetal pathways from the AOB to the LHAjp, we have identified certain regions and routes by which pheromonal information may influence the activity of neurons within the LHAjp; we have also touched on two of the principal regions projecting to the LHAjp that remain to be more fully discussed in terms of the functional implications. These regions are the lateral septal nucleus and the prefrontal cortex. The lateral septal nucleus appears to have a central role in defensive behavior. Classic studies describe a hyperdefensive behavioral response resulting from lesion to the lateral septal nucleus (Brady and Nauta, 1953; Brady and Nauta, 1955; Albert and Chew, 1980); this is illustrated well by a description of the hyperdefensive response in the rat following lesion of the lateral septal nucleus: “Immediately following recovery from the anesthetic, an explosive wildness and fierceness developed in these animals which made them virtually

impossible to handle without special precautions and which appeared to leave them hyper-reactive to all sensory stimulation, particularly tactual.” (Brady and Nauta, 1955). Of particular relevance to our present results, the region of the lateral septal nucleus that was identified as being mainly involved in producing the hyperdefensiveness was the “rostrolateral septal nucleus” (Albert and Chew, 1980); this would have included the region of the lateral septal nucleus that we have identified as having strong bidirectional connections with the LHAjp (LSr.vl.d.l/m).

One interpretation of the classic septal lesion studies is that the lateral septal nucleus provides a tonic behavioral inhibition. This interpretation is broadly consistent with an inhibitory role for the striatum, of which the lateral septal nucleus is a component (Swanson, 2000). Given a massive cortical excitatory (presumed glutamatergic) projection from Ammon’s horn and the subiculum to the lateral septal nucleus (Risold and Swanson, 1997), it is also consistent with a previously suggested role for the hippocampal formation in behavioral inhibition (Gray, 1976; Gray, 1982) and may account for the early report of “rage syndrome” following bilateral electrolytic lesion of the ventral half of the hippocampal formation (that appeared to include at least the subiculum and dentate gyrus as well as parts of the parasubiculum and adjacent entorhinal area) (McGowan et al., 1972). However, various studies of lateral septal function have produced equivocal results, some suggesting behavioral inhibition, others activation, for examples see: (Gray and McNaughton, 1983). Nevertheless, strong bidirectional connections of the rostral part of the lateral septal nucleus with the LHAjp are consistent with our proposed involvement of the LHAjp in defensive behaviors. Furthermore, this raises the possibility that the previous equivocal results on the effects of septal lesions may have resulted from differential disruption of either a descending inhibitory projection or a (possibly inhibitory) ascending projection involving the LHAjp, as this might be predicted to produce differential effects on defensive behavior.

In this context it is also noteworthy that the rostral part of the lateral septal nucleus projects massively to the AHN (Risold and Swanson, 1997), which in turn has very strong bidirectional connections with the LHAjp. In addition, the part of the lateral septal nucleus that provides the strongest projection to the AHN (LSr.vl.d) (Risold and Swanson, 1997) is the same part that has the strongest bidirectional connections with the LHAjp. This speaks to the topography of the projections, and our findings confirm and extend previous work that has elucidated a highly organized topography in the projections of hippocampal domains via the fimbria to the lateral septal nucleus and between the latter and the hypothalamus (Risold and Swanson, 1996; Risold and Swanson, 1997). Specifically, the region of the hippocampal formation that projects most strongly to the LHAjp (intermediate regions of field CA1 and subiculum) also projects most strongly to the part of the lateral septal nucleus (LSr.vl.d) that has the strongest bidirectional connections with the AHN (Risold and Swanson, 1997) and LHAjp. These findings are also well viewed in light of recent work on hippocampal theta oscillations in the freely moving rat where these oscillations (recorded as field potentials from CA1) are revealed as travelling waves that propagate roughly along the dorsal to ventral (septotemporal) axis of the hippocampal formation (Lubenov and Siapas, 2009); one would predict such a functional topography to be determined by the underlying structural topography within the HPF, and to extend to its inputs and outputs.

Integration of the function of the LHAjp and lateral septal nucleus and further evidence of a highly organized topography is indicated by much commonality in the connections of the LHAjp and LSr.vl.d (Risold and Swanson, 1997). These common connections differ in magnitude, nevertheless efferent targets of the LHAjp and LSr.vl.d include (in addition to the AHN): anterior part of DMH, dorsal premammillary nucleus and ventral regions of medial mammillary nucleus, paraventricular thalamic nucleus, paratenial nucleus and rostral division of nucleus reuniens, lateral habenula, superior colliculus, and ventrolateral division of PAG;

whereas projections to the LHAjp and LSr.vl.d come from (in addition to AHN, field CA1, and subiculum): dorsomedial part of VMH and the posterior hypothalamic nucleus (Risold and Swanson, 1997).

4.3.8. LHAjp discussion: Lateral habenula—The lateral habenula merits special attention for the dense terminal projection it receives from the LHAjp. Interest in the role of the lateral habenula has burgeoned as a result of recent evidence implicating this epithalamic structure in the processing of information relating to negative reward and motivation (Matsumoto and Hikosaka, 2007; Hikosaka et al., 2008; Matsumoto and Hikosaka, 2009). To elaborate: an increase in lateral habenula excitation correlates with an increase in perceived negative reward value, whereas an increase in perceived positive reward value correlates with an increase in lateral habenula inhibition (Matsumoto and Hikosaka, 2007; Hikosaka et al., 2008; Matsumoto and Hikosaka, 2009). Furthermore, excitation of lateral habenula neurons temporally precedes and correlates with inhibition of midbrain dopamine neurons (in the ventral tegmental area and compact part of the substantia nigra) (Christoph et al., 1986; Matsumoto and Hikosaka, 2007) and serotonergic neurons (in the dorsal nucleus of the raphé) (Wang and Aghajanian, 1977; Park, 1987). The dorsal (and median, that is superior central) nuclei of the raphé and ventral tegmental area receive a direct projection from the lateral habenula (Herkenham and Nauta, 1979; Araki et al., 1988; Kim, 2009), as does the cholinergic neuron-rich laterodorsal tegmental nucleus (Herkenham and Nauta, 1979; Cornwall et al., 1990; Semba and Fibiger, 1992; Kim, 2009) -- also recall we found the ventral tegmental area projects directly and lightly to the LHAjp. Thus the lateral habenula is in a position to possibly effect a broad modulation of behavioral state, consistent with a possible role for the LHAjp in defensive behavior via its projection to the lateral habenula.

With further regard to an association between the lateral habenula and our proposed involvement of the LHAjp in the modulation of defensive behavior, a recent study is noteworthy in which it was reported that chemical stimulation of the lateral habenula in the rat with kainic acid would facilitate inhibitory avoidance in an elevated T-maze paradigm (purported to be a measure of anxiety), while bilateral electrolytic lesion of the lateral habenula produced an opposite effect (Pobbe and Zangrossi, Jr., 2008); an effect of electrolytic lateral habenula lesion to reduce active avoidance also has previous report (Wilcox et al., 1986). Given a projection from the intermediate subiculum and field CA1 to the LHAjp and from the LHAjp to the lateral habenula, the effect of lateral habenula lesion has an intriguing parallel to the effect of ventral intermediate hippocampal formation lesions that include Ammon's horn and the subiculum because these also attenuate a defensive response (risk assessment) considered to be a measure of anxiety (Pentkowski et al., 2006). Clearly a neural mechanism for associating a defensive (or other) behavior with the negative reward value of that behavior in a particular context would have utility for reining in behavior that if left unchecked could lead to undesired outcomes.

A novel understanding of lateral habenula function shows its connections in a new light. In addition to the already mentioned ventral tegmental area and nuclei of the raphé, one of the more well described and major targets of medial regions of the lateral habenula (the principle habenula region targeted by the LHAjp) is the nucleus incertus (Herkenham and Nauta, 1979; Goto et al., 2001; Olucha-Bordonau et al., 2003). The nucleus incertus is a distinct cell group situated adjacent to the dorsal tegmental nucleus in caudoventral regions of the pontine central gray (Goto et al., 2001); its diverse connections are well and lengthily described (Goto et al., 2001; Olucha-Bordonau et al., 2003); suffice to say here that the connections of the nucleus incertus have been taken to indicate a general role for it in behavioral planning, attention, execution, and learning (Goto et al., 2001; Olucha-Bordonau et al., 2003). A more specific role for the nucleus incertus is suggested to be control of the hippocampal theta rhythm (Olucha-Bordonau et al., 2003); this related to our earlier proposition that the LHAjp may be

influenced by theta oscillations (Vertes et al., 2004). Indeed electrical stimulation of the nucleus incertus in the rat is reported to evoke a theta rhythm in the hippocampal formation (recorded as a field potential centered in CA1) (Nunez et al., 2006), whereas lesion of the nucleus incertus can disrupt this rhythm (Nunez et al., 2006). Also noteworthy is a prominent projection from the nucleus incertus to the supramammillary nucleus, and bidirectional connections between the nucleus incertus and the posterior hypothalamic nucleus, and medial septal complex (Goto et al., 2001) -- each of these regions are understood to have a prominent role in either the generation or modulation of the hippocampal theta rhythm (Bland, 1986; Kocsis and Vertes, 1994; Vertes and Kocsis, 1997; Kirk, 1998; Pan and McNaughton, 2004).

Another structure of importance in relation to the lateral habenula and nucleus incertus is the interpeduncular nucleus (IPN). The IPN receives a topographically distinct input from the habenula (predominantly medial but also lateral) (Kim, 2009) and it has massive bidirectional connections with the nucleus incertus (which also connects massively with the superior central or median nucleus of the raphé) (Goto et al., 2001). Lesion of the IPN was shown recently to disrupt the activity of head-direction neurons in the anterodorsal nucleus of the thalamus (Clark et al., 2009); the latter is significant given the parity, discussed earlier, between certain regions showing theta oscillations (Vertes et al., 2004) and containing head direction neurons (Taube and Bassett, 2003), and connecting with the LHAjp. Continuing this theme, it is noteworthy that lesion of the dorsal tegmental nucleus or lateral mammillary nucleus also disrupts the activity of head-direction neurons in the anterodorsal nucleus of the thalamus (Bassett et al., 2007). The dorsal tegmental nucleus receives an input to its capsule from the nucleus incertus, and a direct input from the lateral mammillary and interpeduncular nuclei (Goto et al., 2001). In addition, lesion (ibotenic acid) of the laterodorsal tegmental nucleus -- a site of cholinergic neurons that receives a direct input from the nucleus incertus (Goto et al., 2001) as well as from the lateral habenula (Herkenham and Nauta, 1979; Araki et al., 1988; Cornwall et al., 1990; Semba and Fibiger, 1992; Kim, 2009) -- attenuates locomotion induced by scopolamine (a muscarinic acetylcholine receptor antagonist); this attenuation of locomotion is likely to be due in part to disruption of a cholinergic projection from the laterodorsal tegmental nucleus to dopamine neurons in the ventral tegmental area (Brudzynski et al., 1988; Oakman et al., 1995; Kocsis et al., 2001) -- the ventral tegmental area is also implicated in theta rhythm modulation (Kocsis et al., 2001; Bassant and Poindessous-Jazat, 2001).

As a final consideration to round out this section of the discussion, it is noteworthy that the nucleus incertus targets heavily an LHA site, namely the subfornical region of the LHA (and in particular its anterior zone) (Goto et al., 2001), which itself shares many of the projection targets of the LHAjp (Goto et al., 2005; see also Fig. 13). A further level of integration is suggested by the very abundant expression of corticotropin-releasing hormone (CRH) type 1 receptor expression in the nucleus incertus (Chalmers et al., 1995), indicating that the nucleus incertus (and thus perhaps the theta rhythm) may be modulated by the stress-related neuropeptide CRH, as has been suggested (Goto et al., 2001; Olucha-Bordonau et al., 2003) and indicated (Chan et al., 2000; Bittencourt and Sawchenko, 2000; Tanaka et al., 2005). In summary, a connection between the LHAjp and nucleus incertus via lateral habenula may provide a route whereby negative reward (error correction) information associated with defensive behavior could influence simultaneously the activity of head direction cells, theta oscillations, and locomotion, which in turn would influence any activity of the LHAjp modulated by these other activities. Relating the above considerations to the flow of the discussion overall, the findings argue a possible role for the LHAjp in the contextual, behavioral state-dependent and experience-dependent modulation and modification of behavior.

4.3.9. LHAjp discussion: Medial prefrontal cortex—Now we turn to consider the interconnections of the medial prefrontal cortex (rostromedial isocortex) with respect to the LHAjp. Overall, the medial prefrontal cortex (including here the anterior cingulate, prelimbic,

and infralimbic areas) projects strongly to the LHAjp. Infralimbic and prelimbic areas project strongly to the rostral half of the LHAjp and lightly to the caudal end of the LHAjp; whereas the anterior cingulate area projects more strongly to the caudal end of the LHAjp and more lightly to the rostral half. The medial prefrontal cortex has a central role in diverse aspects of cognition and in that role is associated with several interrelated processes, broadly including: attention (especially visual) (Desimone and Duncan, 1995; Sarter et al., 2006), working memory (Repovs and Baddeley, 2006), decision making and goal directed behavior (Bechara et al., 1997; de Bruin et al., 2000), and visceromotor control (Neafsey, 1990) -- for further review see: (Bechara et al., 2000; Miller and Cohen, 2001; Dalley et al., 2004; Vertes, 2006; Robbins, 2007).

The distinct yet interrelated nature of these cognitive processes is reflected in the topographic organization of the medial prefrontal cortex. Possibly most evident is a graduated dorsal to ventral division (not unlike that for the hippocampal formation). In very broad functional terms, in the rat dorsal levels of the medial prefrontal cortex (including the anterior cingulate area and dorsal levels of the prelimbic area) is indicated to have primary role in cognitive processes associated with exteroception; whereas ventral levels of the medial prefrontal cortex (including ventral levels of the prelimbic area and the infralimbic area) is indicated to have a primary role in cognitive processes associated with interoception (Gisquet-Verrier et al., 2000; Heidbreder and Groenewegen, 2003; Vertes, 2006; Hoover and Vertes, 2007). These appellations are tentative and come with the caveat that there persists some lack of consensus regarding the organization, function, and nomenclature of the medial prefrontal cortex across species (Uylings et al., 2003). Nevertheless, given a stronger projection to the caudal end of the LHAjp from dorsal levels of the prefrontal cortex and a stronger projection to the rostral half of the LHAjp from ventral levels of the prefrontal cortex, this suggests that cognitive influences on any defensive behavior in which the LHAjp may participate is likely to be differentially modulated by different cognitive processes.

Most previous studies of prefrontal cortex connections have detailed the efferent projections, for example: (Room et al., 1985; Sesack et al., 1989; Hurley et al., 1991; Takagishi and Chiba, 1991; Buchanan et al., 1994; Ongur et al., 1998; Floyd et al., 2001; Chiba et al., 2001; Vertes, 2002; Gabbott et al., 2003; Vertes, 2004; Gabbott et al., 2005; Vertes et al., 2007); however, extensive studies of the afferent connections are also available (Audinat et al., 1988; Conde et al., 1990; Conde et al., 1995; Hoover and Vertes, 2007). From these studies it is clear that the anterior cingulate, prelimbic, and infralimbic areas are highly interconnected with one another, and with diverse regions of the cerebral cortex and cerebrospinal trunk. Of particular relevance to this discussion, beginning with the cerebral cortex, is a major input to the prefrontal cortex from field CA1 and the subiculum (Swanson, 1981). The graduated dorsal-to-ventral division of function within the medial prefrontal cortex referred to above is reflected in a dorsal-to-ventral gradation of this projection: retrograde tracing studies have revealed relatively moderate back-labeling in field CA1 and the subiculum from the anterior cingulate area that becomes progressively more abundant in transition through the prelimbic to the infralimbic area (Hoover and Vertes, 2007). Thalamic nuclei also project strongly to the prefrontal cortex, including three that receive a notable input from the LHAjp, i.e. anteromedial, paratenial, and reuniens nuclei (Vertes et al., 2006; Hoover and Vertes, 2007; Vertes et al., 2007; Vertes and Hoover, 2008); projections to the medial prefrontal cortex from the midbrain (ventral tegmental area and dorsal nucleus of the raphé) and pons (laterodorsal tegmental nucleus) are also prominent (Hoover and Vertes, 2007). In these connections, the areas of prefrontal cortex that project to the LHAjp receive major inputs from several regions that are, as we have discussed, either connected first order to the LHAjp or connected as second order regions that are likely to be instrumental participants in the elaborated functions of the LHAjp.

Major projections from the medial prefrontal cortex that relate directly to the interconnections of the LHA_{jp} (in addition to the direct LHA_{jp} projection already described) include pathways from the anterior cingulate area to the retrosplenial area (van Groen and Wyss, 1992; Risold and Swanson, 1995; Shibata and Naito, 2008) and anteromedial and lateral dorsal thalamic nuclei (Shibata and Naito, 2005) -- relating strongly, as discussed, to aspects of attention (especially visual), learning, and memory. Similarly, major projections from the prelimbic and infralimbic areas include those to the thalamic paratenial and reuniens nuclei -- the paratenial nucleus and rostral division of the nucleus reuniens receive a substantial projection from the LHA_{jp}. The paratenial and reuniens nuclei in turn project massively (predominantly rostral division of reuniens) to the hippocampal formation (as well as back to the medial prefrontal cortex), thereby forming a nodal point for the flow of information between the LHA_{jp} (our results), medial prefrontal cortex, thalamus, and hippocampal formation (Ohtake and Yamada, 1989; Wouterlood et al., 1990; Risold et al., 1997; Vertes, 2002; Vertes, 2004; Vertes et al., 2004; Vertes et al., 2006; Vertes, 2006; Hoover and Vertes, 2007; Vertes et al., 2007; Vertes and Hoover, 2008). Hippocampal formation projections from the nucleus reuniens appear to target all of field CA1 and the subiculum (Wouterlood et al., 1990; Risold et al., 1997; Vertes et al., 2006), whereas those from the paratenial nucleus are predominantly restricted to the ventral half of the subiculum (Vertes and Hoover, 2008).

The infralimbic (but not prelimbic) area also targets heavily the lateral septal nucleus, in particular its rostral part (Vertes, 2004) -- the same region of the lateral septal nucleus that has a strong bidirectional connection with the LHA_{jp}. The lateral septal projection of the infralimbic area has particular resonance with our discussion given a general function of 'cognitive affect' associated with this region of the medial prefrontal cortex, an association of the lateral septal nucleus with behavioral inhibition, and a suggested role for the LHA_{jp} in defensive behavior. Furthermore, with our emphasis on the potential contribution of an olfactory component to modulation of LHA_{jp} neurons, it is noteworthy that several olfactory-related structures receive differentiated projections from the pre- and (predominantly) infralimbic areas, these include: anterior olfactory nucleus, tenia tecta, and olfactory recipient parts of the amygdalar region and BST (Vertes, 2004). More generally the described interconnections of the LHA_{jp}, thalamus, and hippocampal formation with the prefrontal cortex, highlight certain routes that are likely to be central to the influence of cognitive processes on the activity of the LHA_{jp}.

Further noteworthy projections from the prefrontal cortex include a robust midbrain projection to differentiations of the PAG that receive (and to a lesser extent project to) the LHA_{jp}, namely the precommissural nucleus and ventrolateral division (Floyd et al., 2001; Vertes, 2004). In addition, prefrontal cortex projections to the PAG may also reflect a graduated dorsal to ventral division of the prefrontal cortex in that the anterior cingulate area and dorsal levels of the prelimbic area are reported to project preferentially to the dorsolateral division of the PAG, whereas ventral levels of the prelimbic area and infralimbic area may project preferentially to the ventrolateral division of the PAG (Floyd et al., 2001). With regard to our discussion of how cerebral oscillations (and in particular the hippocampal theta rhythm) may involve the LHA_{jp}, it is relevant to mention a robust projection to the supramammillary nucleus from the infralimbic area (Vertes, 2004). Also relevant is a strong projection from the infralimbic area to the diagonal band nucleus (NDB) -- the NDB projects moderately to, and receives lightly from, the LHA_{jp}; the NDB also has bidirectional connections with the nucleus incertus and both regions, along with the supramammillary nucleus, are implicated in modulation of the hippocampal theta rhythm (Bland, 1986; Kocsis and Vertes, 1994; Vertes and Kocsis, 1997; Kirk, 1998; Pan and McNaughton, 2004; Nunez et al., 2006).

We have to this point discussed principal connections of the LHA_{jp} with other brain regions, and certain of the interconnections of those regions as they relate to the place of the LHA_{jp}

within a structural network, and as they may relate in terms of some possible functions. There remain several further aspects of this for future discussion. One of the more prescient topics is the relation of the connections of the LHAjp to the connections of the nucleus accumbens -- we found essentially no direct connections of the LHAjp with the nucleus accumbens. A further future consideration, given our emphasis on defensive behavior, would be to consider how our findings relate to systems involved in other behaviors.

4.4. LHAs discussion: Connectional and functional considerations

In this study we set out primarily to present and discuss the connections of the LHAjp and we have included an analysis of the connections of the LHAs as a control for, and comparison, to the connections of the LHAjp, and to the already published connections of the subfornical region of the LHA (Goto et al., 2005). Our analysis is partial in so far as the experiment we selected for most detailed analysis (experiment LHA#11) is one in which the tracer deposit is sited within a central part of the LHAs -- it remains to be determined how the connections of these midrostrocaudal levels of the LHAs compare to its more peripheral levels. Nevertheless, the connections of the LHAs in so far as we have described them are quite different to those of the LHAjp, indicative of a very different functional role for the LHAs and underscoring the heterogeneity of the middle group of the LHA.

4.4.1. LHAs discussion: Cerebral cortex—The most obvious difference between the LHAjp and LHAs in terms of neural input is the (almost) absence of a projection to the LHAs from the hippocampal formation. In addition to this major difference, projections to the LHAs from other cortical areas are very different overall from those to the LHAjp: both LHA regions receive a moderate input from the infralimbic area, but input to the LHAs from the prelimbic area is considerably less than to the LHAjp; there is essentially no projection to the LHAs from anterior cingulate- or retrosplenial areas, and (unique to the LHAs) a moderate input from the agranular insular area. These differences immediately suggest a different functional perspective: they indicate the LHAs is not directly modulated by hippocampal mnemonic processes relating to either spatial navigation or stress (anxiety), and that prefrontal cortex influence on the LHAs is weighted more to cognitive processes associated with interoception. Also noteworthy is the absence of a projection from a mid rostrocaudal level of the LHAs (and also from the LHAjp) to regions of the cerebral cortex that have been shown in earlier retrograde tracing studies to receive considerable input from the LHA (Allen et al., 1991; Saper, 1985; Saper et al., 1986). Nevertheless, our data appears to be consistent with the earlier work in that cerebral cortical projections were not shown to arise from regions of the LHA corresponding to the LHAjp, or a midrostrocaudal level of the LHAs. In fact, the region corresponding to a mid rostrocaudal level of the LHAs was shown specifically to not be retrogradely labeled following injections of the retrograde tracers fast blue or diaminodiphenylamine yellow in (respectively) the infralimbic or insular areas (Saper et al., 1986).

4.4.2. LHAs discussion: Cerebral nuclei

4.4.2.1. Striatum: Connections of the LHAs with cerebral nuclei are also quite different from those of the LHAjp. Beginning with the striatum, a tightly circumscribed group of cells back-labeled in rostral levels of the CEAl is striking -- no such retrograde labeling was found from the LHAjp. Pallidal connections with the LHAs are overall considerably more pronounced than with the LHAjp, and the involved regions are mostly different. Foremost are strong bidirectional connections of the LHAs with the BST and the substantia innominata. The LHAs also projects moderately to the medial septal nucleus and diagonal band nucleus.

The projection to the LHAs from the rostral tip of the CEAl provides further evidence of interoceptive (viscerosensory) and also gustatory influence on the LHAs because the CEAl is highly connected with regions involved in these processes. These connections include

extremely dense projections to the rostral end of the CEAl from the gustatory/viscerosensory region of the insular area (McDonald et al., 1999) and projections to the CEA from the infralimbic area (Vertes, 2004). In addition, the CEA has predominantly bidirectional connections with (mostly) the anterior division of the BST (Dong et al., 2000; Dong et al., 2001a; Dong et al., 2001b; Dong and Swanson, 2003; Dong and Swanson, 2004a; Dong and Swanson, 2004b; Dong and Swanson, 2006a; Dong and Swanson, 2006b; Dong and Swanson, 2006c), parabrachial nucleus (prominently PBlc and PBle) (Veening et al., 1984; Bernard et al., 1993; Petrovich and Swanson, 1997), PAGvl (Rizvi et al., 1991), dorsal nucleus of the raphé (Rizvi et al., 1991; Peyron et al., 1998; Lee et al., 2007), ventrolateral medulla (Jia et al., 1992; Jia et al., 1997b; Viltart et al., 2006), and dorsal vagal complex (NTS and DMX) (Veening et al., 1984; Jia et al., 1997b; Viltart et al., 2006).

An identified role for rostral levels of the CEAl in the transmission of viscerosensory and gustatory information to the LHAs relates more generally to involvement of the CEA in autonomic control (Swanson and Petrovich, 1998); yet a more commonly ascribed (although not necessarily unrelated) role for the amygdalar region as a whole is in the expression of fear responses (Ledoux, 2000; Antoniadis and McDonald, 2001). In this, a clear and unequivocal understanding of the role of the amygdalar region remains somewhat elusive, not least because of poor consensus of definition of its parts (Swanson and Petrovich, 1998; Swanson, 2003a). Connected to this, a further confound relates to the different ways in which fear may manifest, with different somatic and autonomic effects possibly involving different parts of the amygdalar region. With regard to the CEAl, its connections are consistent with its involvement in the expression of conditioned fear (Petrovich and Swanson, 1997); however, excitotoxic lesion studies indicate that the CEA (all parts) is not involved in a commonly used model of fear conditioning in which an unconditioned noxious stimulus (footshock) is paired with a conditioned benign stimulus (tone) to produce a conditioned reflex motor response (freezing) (Koo et al., 2004). Nevertheless, the CEA appears to have a role in other somatic (e.g., exploratory behavior) (Moreira et al., 2007) and autonomic (e.g., cardiovascular) (Rooszendaal et al., 1990) responses associated with conditioned fear.

In fact, the projection from the CEA to the LHA (including the region of the LHAs but not the LHA_{jp}) is implicated specifically with changes in arterial pressure associated with conditioned fear (Ledoux et al., 1988). In addition, an inhibition of the CEAl (as evidenced by a decrease in cFos mRNA expression) occurs in models of unconditioned “fear” (environmental novelty, loud noise, and restraint) (Day et al., 2001; Day et al., 2005) and conditioned “fear” (footshock paired with light) (Day et al., 2008). Given that most, if not all, CEAl neurons express GABA (Day et al., 1999) it is likely that the neurons inhibited under these conditions are GABAergic; however, the projection targets of these neurons remain to be determined. Evidently, the full extent of responses (somatic or autonomic) associated with expressions of presumed fear and involving the CEA requires further clarification. Any role of the LHAs in these responses will have to take into account not only the direct projection from the CEAl to the LHAs but also the extensive intra- and inter-connections of amygdalar and BST nuclei, and the direct connections of the BST -- also a site of abundant GABAergic neurons (Stefanova et al., 1997; Day et al., 1999) -- with the LHAs.

4.4.2.2. LHAs discussion: Pallidum: With regard to the BST, the LHAs receives major input from the BST_{am} and BST_{fu} (the BST_{am} also receives a moderate input from the LHAs). Together, the BST_{am} and BST_{fu} are thought to be involved in a broad coordination of responses (autonomic, neuroendocrine, and somatic or behavioral) to homeostatic challenges -- in particular those relating to stress and energy balance (Dong et al., 2001b; Dong and Swanson, 2006a). Furthermore, previous work has described a projection to the BST_{am} (previously subdivided into anterodorsal and anteroventral parts) and BST_{fu} from the CEAl (Dong et al., 2001a). In the previous work a PHAL injection restricted principally to a mid

rostrocaudal level of the CEAl (experiment #12) labeled moderately the BSTam and densely the BSTfu (see their Fig. 7) (Dong et al., 2001a); however, projections from the rostral end of the CEAl (where retrograde labeling from the LHAs in our experiment LHA#11 was observed) were not examined in the previous study (Dong et al., 2001a). Nevertheless, in an earlier study a PHAL injection centered within rostral levels of the CEAl was reported to label varicose fibers within the BST (Grove, 1988b); the distribution of these fibers within the BST was not described in the text, but they were shown to be present within a region corresponding to the anterior division of the BST (see her Fig. 9) (Grove, 1988b).

In addition to strong inputs to the LHAs from the BSTam and BSTfu, a moderate combined input arises from the BSTal, BSTdm, BSTif, and BSTpr; the BSTal and BSTdm also receive a moderate projection from the LHAs, and the BSTif a light projection. The BSTal and BSTdm have extremely diverse neural output profiles indicative of equally diverse roles in coordinating responses to homeostatic challenges (Dong and Swanson, 2004a; Dong and Swanson, 2006b). For the BSTdm a role in responding to thirst and salt appetite is suggested to be foremost among its possible functions (Dong and Swanson, 2006b); the BSTam is suggested to have a central role in the coordination of visceral and somatic motor responses relating to ingestive (eating and drinking) behavior (particularly associated with noxious stimuli) (Dong and Swanson, 2004a). In contrast to the BSTam, BSTfu, BSTdm, and BSTal, the projections of the BSTif and BSTpr are consistent with a central role for these regions in reproductive and defensive behaviors (Dong and Swanson, 2004b).

Strikingly, combined projection profiles of the BSTfu, BSTam, BSTal, and BSTdm show extensive overlap with regions that are either a target of (or are targeted by) the LHAs (Dong et al., 2001b; Dong and Swanson, 2004a; Dong and Swanson, 2006a; Dong and Swanson, 2006b). This correlation is strengthened by including the projections of additional BST regions (notably the BSTov, BSTju, BSTrh, BSTmg, BSTad) that have little or no direct connection with the LHAs, but are nevertheless highly interconnected with other BST regions. The high degree of overlap in the terminal fields of these BST regions and the connections of the LHAs suggests a high degree of functional interrelation. Conversely, the main projection targets of the BSTif and BSTpr are to regions that connect with the LHAs relatively little, whereas the BSTif projects to regions with which the LHAjp has robust connections (Dong and Swanson, 2004b). Given a central role for the BSTif and BSTpr in defensive (BSTif) and sexual/reproductive (BSTpr) behaviors this suggests that the LHAs may not be directly involved in the control of these behaviors, but is nevertheless a recipient of information relating to them -- such integration has clear utility for the appropriate modulation of one behavior (such as ingestive) in response to changes in another (such as defensive or sexual/reproductive). It also alludes to a hierarchy of behavioral control.

The connection of the LHAs with the substantia innominata (SI) is bidirectional, with a strong projection to a mostly dorsal region at medial levels of the SI, and a relatively light input to the LHAs from a similar region. Relating this to what we have just discussed it is noteworthy that the dorsal/medial region of the SI appears to have rather similar projections to the CEAl and also to the BST regions associated with homeostatic processes relating to ingestive behaviors (Grove, 1988a). Furthermore, this region of the SI appears to receive abundant input from areas of the cerebral cortex involved in similar processes that connect directly or indirectly to the LHAs, notably the gustatory/viscerosensory part of the insular area and the infralimbic area (Grove, 1988b). It is also noteworthy that connections of the LHAs with the lateral septal nucleus are much reduced in comparison to the strong bidirectional connections of the lateral septal nucleus with the LHAjp; the LHAs sends a light projection to primarily the rostral part of the lateral septal nucleus and receives very little lateral septal input. Moderate projections from the LHAs to the medial septal complex provide a link to our earlier discussion with regard to possible theta rhythm influences on the LHAjp, in which the medial septal complex is known

to be critically involved (Bland, 1986; Kocsis and Vertes, 1994; Vertes and Kocsis, 1997; Kirk, 1998; Pan and McNaughton, 2004). It is also noteworthy that in the rat the medial septal nucleus, and especially the diagonal band nucleus (recipient of a moderate input from the LHAs), is a principal site of gonadotropin-releasing hormone neurons (Witkin et al., 1982; Merchenthaler et al., 1984; Wray and Hoffman, 1986) -- whether or not this projection has any influence on the reproductive function of the GnRH neurons remains to be tested.

4.4.3. LHAs discussion: Cerebrospinal Trunk

4.4.3.1. Sensory System: Outside of the cerebral cortex and cerebral nuclei, a major target of the LHAs within the sensory system of the cerebrospinal trunk is the thalamus, specifically the PVT; a lighter projection also reaches from the LHAs to the IMD and PT, and the PVT and IMD also provide a light input to the LHAs. The dorsal midline (including PT and PVT) and medial (including IMD) nuclei of the thalamus are thought to have a general role in awareness, and four different groupings of these nuclei have been suggested to include different aspects of awareness (Van der Werf et al., 2002). Based primarily on their connectivity, the PVT, PT, and IMD have been assigned to the same group that is thought to be involved in viscerosensory awareness (Van der Werf et al., 2002). The appropriateness of this designation is better understood in light of the projection targets of the PVT, PT, and IMD. Among the most pronounced connections of these thalamic structures are strong projections to the nucleus accumbens (Van der Werf et al., 2002; Ligorio et al., 2009); robust connections also exist with parts of the amygdalar region (including CEA), BST (anterior division) and cerebral cortex (including insular area, infralimbic area, and ventral levels of the prelimbic area) that have major association with visceral sensorimotor processing (Van der Werf et al., 2002). In passing, it is noteworthy that the IMD receives a significant input from the supramammillary nucleus that itself has a role in control of the theta rhythm (Vertes, 1992); in this context also noteworthy is an already discussed projection from the PT (itself a major target of the LHA_{jp}) to the ventral half of the subiculum (Vertes and Hoover, 2008).

Caudal to the thalamus and also within the sensory system, the LHAs has moderate bidirectional connections with the lateral division of the parabrachial nucleus, and projects to rostral (“gustatory”) and caudal (“visceral”) levels of the NTS_m; the LHAs also sends a very few fibers to the NTS_{co} and NTS_l and it receives a light direct input from caudal levels of the NTS_m. These connections indicate a role for LHAs in the modulation of ascending viscerosensory signals, in particular those relating to ingestive behavior -- this is also indicated by light projections from the LHAs to the rostral (oral) part of the pontine reticular nucleus (PRN_r) and very light projections to the oral part of the spinal trigeminal nucleus and to the paratrigeminal nucleus; the projection to the PRN_r is also noteworthy for the effect of electrical stimulation of this region (at the level of the locus ceruleus) to elicit synchronous hippocampal oscillations at theta frequency (Vertes, 1981; Vertes, 1982).

The projection from the LHAs to the parabrachial nucleus is moderate and extensive, targeting the medial and lateral divisions (most evidently the PB_{lc}). The LHAs also receives a moderate input from the PB, primarily from the PB_{lc} and PB_{lv}. It is noteworthy that among the connecting regions of the PB are several that we have already discussed in relation to their connections with the LHAs, namely: the insular area, CEA, BST, dorsal regions of the SI, and midline group of the thalamus (Bernard et al., 1993; Alden et al., 1994; Petrovich and Swanson, 1997; Dong et al., 2001b; Dong and Swanson, 2004a). The CEA and BST in particular receive a massive projection from the PB; with regard to the CEA, the CEAm is targeted principally by the PB_m and PB_{lv}, and the CEAl by the PB_{lc} and PB_{le} (Bernard et al., 1993). The major BST recipient site is the BST_{ov} (Alden et al., 1994), which in turn targets densely the BST_{fu}; other regions targeted strongly by BST_{ov} include the BST_{am}, dorsal regions of SI, CEAm, and PB (Dong et al., 2001b).

An additional part of the sensory system, the subfornical organ (SFO), is notable for providing an input to the LHAs. The SFO is a circumventricular organ extensively characterized for its humorosensory role in the homeostatic control of arterial pressure and plasma sodium ion concentration (Fitzsimons, 1998; Geerling and Loewy, 2008). More recent work indicates the SFO (and other circumventricular organs) may also have additional roles in energy and thermal homeostasis (Cairns et al., 2005; Fry et al., 2007; Smith et al., 2009). The means by which the SFO effects its homeostatic functions involves the widespread projections of its neurons to regions involved in cognitive, behavioral state, and motor-related processes (visceral, neuroendocrine, and somatic) (Miselis, 1981; Swanson and Lind, 1986). Our finding of retrograde labeling in the SFO from the LHAs is consistent with a putative role for the LHAs in processes relating to ingestive behavior -- this may relate in particular to the ingestion of water and salt, given an established role for the SFO in thirst and salt appetite (Fitzsimons, 1998; Geerling and Loewy, 2008); however, clearly other functions in which the SFO has a role may also influence the LHAs.

It is of particular note that one of the sources of direct neural (as opposed, say, to hormonal) input to the SFO is caudal levels of the NTSm (viscerosensory part) (Zardetto-Smith and Gray, 1987); because the NTSm (rostral and caudal levels) also receives a direct neural input from the LHAs, this identifies the LHAs as a site that is in a position not only to be directly influenced by the SFO but to potentially directly modulate that influence via a feedback projection to the NTS. The possibility of a modulatory feedback role for the LHAs is also indicated by the preceding discussion in this section; it would appear that this may well be far reaching, not only in terms of the topography, but also in terms of the functional processes that may be modulated.

4.4.3.2. LHAs discussion: Behavioral State System: The next major division of the cerebrospinal trunk to which the LHAs directly projects is the behavioral state system. Moderate projections reach from the LHAs to the SBPV and dorsal nucleus of the raphé, and moderate to strong projections extend across the LHAd; very light terminal projections also reach to the hindbrain regions of the nuclei raphé magnus and obscurus (very few fibers). The SBPV has very strong bidirectional connections with the suprachiasmatic nucleus (Watts et al., 1987; Moga and Moore, 1997; Krout et al., 2002b) and evidence from transneuronal tracing studies indicates that LHAs projections to the SBPV may include some that innervate neurons projecting to the suprachiasmatic nucleus (Krout et al., 2002b) -- this may therefore be a route whereby LHAs neurons could influence circadian rhythms. The region of the LHAd is implicated in control of ingestive behavior. For example, CRH gene expression is induced (and neurotensin gene expression is increased) in rostromedial levels of the LHAd concurrently with anorexia induced in rats that imbibe a supraphysiological saline solution (Watts, 1992; Watts et al., 1995; Kelly and Watts, 1998; Watts et al., 1999; Watts, 2001) or that are subject to dehydration resulting from water deprivation (Kelly and Watts, 1996). The anorexia occurring in rats that drink supraphysiological saline is also associated with changes to CRH or neurotensin gene expression in several other sites that either directly project to the LHAs (CEAl, BSTfu, PVH, RCH) (Watts, 1992; Watts et al., 1995; Kelly and Watts, 1998; Watts et al., 1999; Watts, 2001) or are in a position to influence strongly the LHAs (BSTov) (Watts et al., 1995).

Furthermore, three regions closely associated with ingestive behavior and fluid homeostasis that project to LHAs, namely the BSTfu, MEPO, and SFO, also project to rostromedial levels of the LHAd (Kelly and Watts, 1996). In addition, neurons retrogradely labeled with fluorogold in these regions from injections centered rostromedially in the LHAd show increased expression of the c-fos gene in rats that have received intraperitoneal injections of supraphysiological saline (Kelly and Watts, 1996). Intriguingly, no increase in cFos protein in the CEAl is apparent in the dehydrated condition, but a conspicuous increase is apparent in

this region following the re-presentation of water (Alan G. Watts, unpublished observation). In the previous study, fluorogold injections were centered in the component of the LHA in which CRH gene expression occurs in association with dehydration anorexia; this LHA component is located dorsal and lateral to the fornix between Atlas Levels 27 and 28 of Swanson (2004) and appears to include rostral levels of the LHAd and the rostral tip of the LHAs (Kelly and Watts, 1996). Inclusion of rostral levels of the LHAs due to spread of fluorogold tracer makes it likely that at least some of the fluorogold labeled neurons were retrogradely labeled from the rostral end of the LHAs in addition to the rostral end of the LHAd (Kelly and Watts, 1996). Furthermore, there does appear to be considerable overlap in the projection profiles of the LHAs (our data) and LHAd (Kelly and Watts, 1996; Kelly and Watts, 1998); this is consistent with an established role for the LHAd (and a proposed role for the LHAs) in processes relating to ingestive behavior. Additional studies will be required to clarify the similarities and differences between these two apparently interrelated LHA regions.

The dorsal nucleus of the raphé is a principal site of brain serotonergic neurons (Steinbusch, 1981) and projections from this region extend widely throughout the central nervous system (Vertes, 1991; Vertes and Kocsis, 1994), reflecting the wide ranging functions of this nucleus as they relate to the modulation of behavioral state and the maintenance of homeostasis (Michelsen et al., 2008). Consistent with this, diverse neural inputs to the dorsal nucleus of the raphé indicate a high degree of functional integration, as evidenced in a very recent analysis that employed a conditional viral transneuronal tracing methodology to reveal the sources of projections to cell groups containing serotonergic neurons -- in either the dorsal nucleus of the raphé or the nucleus raphé magnus (Braz et al., 2009). Prominent among the functions in which the dorsal nucleus of the raphé is implicated are: sleep (Imeri and Opp, 2009), anti-nociception/analgesia (Wang and Nakai, 1994; Millan, 2002), and temperature regulation (Hillegaart, 1991; Tao and Auerbach, 1995); prominent among the *dysfunctions* it is implicated in are major depression (Stockmeier et al., 1998; Michelsen et al., 2008) and Alzheimer's disease (Michelsen et al., 2008).

Projections from the LHAs target almost exclusively rostral levels of the dorsal nucleus of the raphé (Swanson rat brain Atlas Levels 44/45). Notable differences in the ascending projections of rostral and caudal levels of the dorsal nucleus of the raphé are reported to include comparatively little projection to the hippocampal formation from rostral levels, yet denser projections to the rest of the cerebral cortex (Vertes, 1991); descending projections of rostral levels are reported to be heavier and to show wider distribution than those of caudal levels to several parts of the medulla (Vertes and Kocsis, 1994). Aside from these differences, targets common to both rostral and caudal levels of the dorsal nucleus of the raphé include widespread regions of the cerebrum and cerebrospinal trunk (Vertes, 1991; Vertes and Kocsis, 1994).

Among the notable sources of neural input to rostral levels of the dorsal nucleus of the raphé is a recently clarified projection from the prefrontal cortex, in particular from regions that also project to the LHAs, prominently the infralimbic area and adjacent ventral levels of the prelimbic area, and the dorsal agranular insular area (Goncalves et al., 2009). Additional areas of the prefrontal cortex projecting to the LHAs and rostral levels of the dorsal nucleus of the raphé include those dorsal to the rostral pole of the nucleus accumbens corresponding to the TTd, ORBv, EPdm, and also the claustrum (Goncalves et al., 2009). Finally, although we have focused here on the dorsal nucleus of the raphé, it should be noted that the additional (behavioral state) parts of the raphé to which the LHAs projects very lightly (i.e., the nuclei raphé magnus and obscurus), are, like the dorsal nucleus of the raphé, also implicated in a diverse range of homeostatic autonomic functions in which serotonergic neurons appear to have a central role (Krowicki and Hornby, 1993; Hermann et al., 1997).

4.4.3.3 LHAs discussion: Motor system

4.4.3.3 LHAs discussion: Motor system: 4.4.3.3.1. Behavior Control Column: The LHAs has robust connections with numerous regions that are classified as part of the motor system of the cerebrospinal trunk. In line with our discussion so far, these connections indicate a similar primary role for the LHAs: control of somatomotor, autonomic, and neuroendocrine processes relating to ingestive behavior and more broadly to the maintenance of homeostasis. Beginning with regions of the motor system's behavior control column, sites receiving prominent LHAs input include the midbrain reticular nucleus (principally the retrorubral area and more moderately the parvicellular part) and VTA. The descending division of the PVH also receives a robust input; lighter projections reach to the anterior part of the VMH, central part of the AHN, and lateral part of the MPN.

The retrorubral area has an identified role in orofacial motor control associated with eating and drinking in the rat (Uchida et al., 2005), cat (Joseph et al., 1985; Arts et al., 1998), and monkey (Mora et al., 1977; DeLong et al., 1983). This effect appears to be under tonic GABAergic inhibition: a GABA_A receptor antagonist (bicuculline) will elicit repetitive jaw movements when applied directly to the retrorubral area; conversely, a GABA_A receptor agonist (muscimol) when applied to the same area will counteract this effect (Uchida et al., 2005). In addition to the identified input from the LHAs, the retrorubral area receives massive innervation from the anterior division of the BST, most prominently from the BSTrh (Dong and Swanson, 2003), and also from the BSTdm, BSTal, BSTfu, and BSTju (Dong et al., 2000; Dong et al., 2001b; Dong and Swanson, 2004a; Dong and Swanson, 2006b). Prominent projections also reach the retrorubral area from the dorsal nucleus of the raphé (Vertes, 1991), CEA (including its rostral levels) (Gonzales and Chesselet, 1990), and dorsomedial levels of the SI (Swanson et al., 1984). These are all regions that have substantial direct connections with the LHAs. In this context, also noteworthy is recent work documenting extensive projections to the retrorubral area from hindbrain adrenergic and noradrenergic neurons (Mejias-Aponte et al., 2009).

A main projection target of the retrorubral area (along with the VTA and substantia nigra with which it is closely associated) is the caudoputamen; additional projections also reach to the SI, CEA (Prensa and Parent, 2001), and hippocampal formation (Gasbarri et al., 1996). The retrorubral area (and adjacent components of the substantia nigra) also projects to the parvicellular reticular nucleus (PARN) and adjacent regions that contain orofaciopharyngeal motor pattern generators, see: (Dong and Swanson, 2003). Another structure with notable direct projections to the retrorubral area is the paraventricular nucleus (PSTN) (Goto and Swanson, 2004). The PSTN (a caudal and far lateral part of the LHA adjacent to the subthalamic nucleus) has striking relevance here because its projection profile identifies it as a region whose functions are likely to be very closely allied to those of the LHAs (as also appears to be the case for, collectively, the anterior division of the BST). In particular, the PSTN has massive projections to hindbrain regions directly involved in ingestive behavior and autonomic (in particular cardiovascular) control: these include parasympathetic preganglionic neurons in the medulla (in particular salivatory nuclei and DMX), and in the PB and NTS (Goto and Swanson, 2004).

Furthermore, the PSTN has ascending projections to many differentiations that also connect to the LHAs: thalamus (PVT, MDm), CEA (mostly CEAm and CEAc, but not CEAl), anterior division of the BST (mostly BSTam, BSTal, BSTrh, and BSTfu, and also BSTov and BSTdm), SI (heavier than that from the LHAs and mostly more dorsal and lateral), infralimbic and agranular insular areas, PB, and NTS (Goto and Swanson, 2004). Other PSTN connections of note are to cortical areas associated with hippocampal formation and the main olfactory system (postpiriform transition area, lateral entorhinal area, and posterior part of the basolateral amygdalar nucleus). The PSTN also projects to the striatal fundus (implicated in somatomotor

control), which in turn projects to the retrorubral area and substantia nigra (Shammah-Lagnado et al., 2001); for further discussion see (Goto and Swanson, 2004). Incidentally, we described a light projection to the rostral tip of the PSTN from the rostral half of the LHAs (it remains to be seen whether this topography extends caudally).

We have highlighted an indicated role for the retrorubral area of the MRN in rhythmic patterned orofacial movement; the parvicellular MRN (MRNp) is suggested to participate in a different rhythmic patterned movement, namely locomotion (Rye et al., 1988). The MRNp was identified previously as the midbrain extrapyramidal area (Rye et al., 1987); before that it had also been included as part of the (ventrally and laterally) adjacent pedunculopontine nucleus (PPN) (Swanson et al., 1984). The PPN as now defined is currently implicated in rhythmic activity pertaining to functions including paradoxical sleep, arousal, and cognition (Garcia-Rill, 1991; Steckler et al., 1994; Inglis and Winn, 1995; Winn et al., 1997). Nevertheless, participation of the MRNp in orofacial control (and possibly other functions attributed to the PPN) should not be ruled out; this assertion is supported by transneuronal (viral) tracing studies that have identified reticular formation components (including the region of the MRNp) that collectively provide input to trigeminal, facial, and hypoglossal motor nuclei that control jaw, facial, and lingual muscles (Fay and Norgren, 1997a; Fay and Norgren, 1997b; Fay and Norgren, 1997c) -- the integrated nature of the reticular formation cautions against overly reductionist interpretation.

Few studies have examined specifically the connections of the MRNp -- much attention has been focused on the PPN. Nevertheless, one study has described the afferent connections of the MRNp in comparison to those of the PPN, and this revealed the strongest source of neural input to the MRNp to be the lateral habenula (Steininger et al., 1992). Major inputs to the MRNp also arise from the vicinity of the LHAs (confirming our data), LHAd, dorsal nucleus of the raphé, PAGvl, lateral division of the PB, and several other brain parts that have connections with the LHAs (Steininger et al., 1992). Notably, a projection to the MRNp from a dorsomedial region of the SI that is bidirectionally connected with the LHAs has been independently described (Swanson et al., 1984; Groenewegen et al., 1993). The MRNp (but not the PPN) is also bidirectionally connected with the substantia nigra and internal segment of the globus pallidus (Rye et al., 1987). In essence, our data establish the presence of a projection to the MRNp from the LHAs and the broader connections of the LHAs. Together with the known connections of the MRNp, this suggests that it would be useful to reevaluate the MRNp with particular regard to its role in autonomic and behavioral state control relating to ingestive behavior.

The projection from the LHAs to the VTA indicates a direct influence on processes relating to positive reward and motivation, in which function the VTA is prominently implicated (Ikemoto, 2007); however, a more complex picture is evident when this is viewed in light of our earlier discussion on the projection of the LHA_{jp} to the lateral habenula (which also projects to the VTA), and the involvement of the lateral habenula in processes associated with negative reward (Matsumoto and Hikosaka, 2007; Hikosaka et al., 2008; Matsumoto and Hikosaka, 2009). Recent work has elucidated further the microcircuitry of the VTA, detailing intra-VTA connections and showing extensive and highly topographically organized connections with the adjacent retrorubral area and substantia nigra (Ferreira et al., 2008). The afferent connections of the VTA have also recently been reassessed and these confirm the VTA as a center where information relating to reward value (input from lateral habenula and nucleus accumbens) is integrated with information from a wide variety of brain parts whose overarching function relates most evidently to ingestive behavior and interoception (Geisler and Zahm, 2005; Zhou et al., 2009).

In line with these findings, and as is the case for the retrorubral area, extensive ascending catecholaminergic projections also reach the VTA (Mejias-Aponte et al., 2009). The VTA and retrorubral area (along with the substantia nigra) are further associated by their neurochemical architecture that includes the dopaminergic cell groups A8–A10 and by projections from all three regions to the subiculum and field CA1 (Gasbarri et al., 1994; Gasbarri et al., 1996; Gasbarri et al., 1997). The projections to the hippocampal formation are especially intriguing as they target regions (field CA1 and subiculum) that provide the strongest input to the LHAjp -- recall that the LHAjp targets strongly the lateral habenula that in turn targets the VTA. The retrorubral area, VTA, and substantia nigra could conceivably be a nodal axis for relating and integrating motivational or incentive value (positive or negative) associated with different modes or systems of behavior that involve different LHA components, for example, the LHAs (ingestive) and LHAjp (defensive).

The remaining part of the behavior control column to receive a strong input from the LHAs is the descending division of the PVH (lateral and forniceal parts); this clearly reveals the LHAs as being in a position to directly influence autonomic outflow (Sawchenko and Swanson, 1982). Conversely, lighter connections of the LHAs with the AHNc (bidirectional), MPNI (receiving), and VMHa (receiving) may indicate interoceptive and autonomic influence (via the LHAs) on processes that involve these regions. Given what is known about the roles and connections of the AHNc, MPNI, and VMHa, this suggests influence on processes relating to defensive (AHNc) (Risold et al., 1994; Canteras, 2002) and reproductive (VMHa and MPNI) (Saper et al., 1976b; Simerly and Swanson, 1986; Simerly and Swanson, 1988; Canteras et al., 1994) behaviors.

4.4.3.3.2 LHAs discussion: Central Gray: Several components of the central gray connect with the LHAs, although the pattern of interactions is quite different to those of the LHAs; in particular there is very little projection to the lateral habenula from the LHAs in comparison to the very dense terminal field in the lateral habenula from the LHAjp. Major LHAs targets in the central gray are the PAGvl (which also provides a light input to the LHAs) and Barrington's nucleus -- in fact these two regions receive the densest LHAs innervation in the entire brain. The LHAs also sends a substantial projection to the commissural nucleus of the PAG and to the posterior hypothalamic nucleus (which also provides a heavy input to the LHAs). We previously discussed the posterior hypothalamic nucleus in relation to possible influence of the LHAjp on the theta rhythm; the same could be true for the LHAs, and in addition the rather considerable input to the LHAs from the posterior hypothalamic nucleus suggests a more complex interaction with possible feedback. It is also noteworthy that the ascending and descending projections of the posterior hypothalamic nucleus target many of the regions that connect directly with the LHAs (Vertes et al., 1995; Vertes and Crane, 1996).

The PAG is implicated in the modulation of behaviors relating to defense and reproduction (Simerly and Swanson, 1986; Behbehani, 1995; Marson and Carson, 1999; Murphy and Hoffman, 2001; Marson and Murphy, 2006); in these functions it recruits (and is modulated by) components of the somatic and autonomic nervous systems -- in particular much attention has focused on its role in the modulation of nociception (Keay et al., 1994; Behbehani, 1995; Millan, 2002). A current understanding of the PAG describes its caudal half as being composed of topographically organized longitudinal columns or divisions (at least four have been identified), each of which participates in distinct (yet interrelated) aspects of behavioral control (Bandler and Shipley, 1994; Bandler and Keay, 1996; Floyd et al., 2000; Keay and Bandler, 2001). In addition to its established role in the modulation of defense- and reproduction-related behaviors, neural inputs to the PAG indicate that it is heavily influenced by processes relating to ingestive behavior; this is evident in the projection we describe to it from the LHAs, and more firmly by the input it receives from regions of the anterior division of the BST that are strongly implicated in ingestive behaviors (Dong et al., 2001b; Dong and Swanson, 2003;

Dong and Swanson, 2004a). Less clear at present is the extent to which (and also how directly) the PAG modulates ingestive behaviors; nevertheless, in this regard massive connections of the PAG with the VMH and DMH are noteworthy (Saper et al., 1976b; Canteras et al., 1994; Thompson et al., 1996; Thompson and Swanson, 1998).

The projection from the LHAs to the commissural nucleus of the PAG compares to the projection from the LHA_{jp} to the precommissural nucleus; while the connections of the latter have been studied specifically (Canteras and Goto, 1999a), the connections of the former PAG region have not. Nevertheless, on the basis of its connections and location, the precommissural nucleus is considered to be a rostral component of the PAG (Canteras and Goto, 1999a), and thus by definition a rostral extension of the caudally adjacent commissural nucleus. Functional correlates specifically for the commissural nucleus are not yet available; however, the precommissural nucleus has a similar pattern of connectivity to the PAG_{dl}, and like the PAG_{dl} it is suggested to have a positive role in defensive behavior (Canteras and Goto, 1999a; Schenberg et al., 2005).

In contrast to the commissural nucleus, much can be said about the connections and functional correlates of the PAG_{vl}. To begin with, in light of what we discussed in the previous section on the behavior control column, of particular note are projections from the PAG_{vl} to the PVH (its neuroendocrine and particularly its descending divisions) (Floyd et al., 1996), and GABAergic projections from the VTA and SN to the PAG_{vl} (and dorsal nucleus of the raphe) (Kirouac et al., 2004); indeed it has been shown that stimulation of the VTA/SN will elicit cardiovascular depressor responses that appear to be mediated by this projection (Kirouac et al., 2004). With regard to the role of the PAG_{vl} in defensive behavior, this is to some extent complimentary or opposite to that of more dorsal PAG divisions. Thus, dorsal levels of the PAG_{vl} have a role in increasing sympathetic and somatomotor activation that manifests as (for example) hypertension, tachycardia, and the classic freeze, flight or fight response; whereas ventral levels of the PAG_{vl} have a role in decreasing sympathetic and somatomotor activation that manifests as (for example) hypotension, bradycardia, quiescence, and anti-nociception (Carrive, 1993; Bandler and Keay, 1996; Brandao et al., 1999; Keay and Bandler, 2001). Further studies will be required in order to clarify how the LHAs projection to the PAG_{vl} may influence these responses. Nevertheless, a putative role for the LHAs in processes relating to ingestive behavior is evidently more compatible with the spectrum of functions attributed to the PAG_{vl} rather than to more dorsal divisions of the PAG.

Furthermore, the PAG_{vl} is identified specifically as a site that receives convergent nociceptive afferent information from deep somatic and visceral sources (Keay et al., 1994) -- it is therefore in a position to respond by influencing somatic, autonomic (and neuroendocrine) responses accordingly. This is particularly interesting in light of the afferent autonomic-related projections to the LHAs and the fairly recent clarification of a common afferent pathway (to the insula area) for conveyance of interoceptive information associated with autonomic motor control (with interoceptive broadly redefined to include essentially all bodily sensations distinct from the exteroceptive system sensations of mechanoreception and proprioception) (Craig, 2002, 2003). The data suggest a possible involvement of the LHAs in feedback (or feed forward) modulation of somatic and autonomic efferent and afferent (interoceptive) information at the level of the PAG; for further thoughts on this see (Bandler et al., 2000a; Bandler et al., 2000b). As an additional point of interest, direct involvement of the PVH is also predicted given the robust projection to the PVH (in particular its descending division) from the LHAs (present data) and a strong projection to the (predominantly ventrolateral division of the) PAG from the PVH (Larry Swanson and Paul Sawchenko, unpublished observations).

In this last part of the discussion on the connections of the LHAs with the central gray, the remaining site of major LHAs connectivity is Barrington's nucleus -- recipient of very dense

innervation from the LHAs (Fig. 10). In addition to a well established role in the control of micturition (Marson, 1997;Valentino et al., 2000), it is increasingly apparent that Barrington's nucleus is also implicated in far more diverse aspects of autonomic and behavioral control (Cano et al., 2000;Sved et al., 2002). Recent transneuronal tracing studies suggest the existence of multisynaptic projections from Barrington's nucleus to several organs and tissues besides the bladder, these include: the trachea (Haxhiu et al., 1993), kidney (Cano et al., 2000), spleen (Cano et al., 2000;Cano et al., 2001), pancreas (Loewy and Haxhiu, 1993), distal colon (Valentino et al., 2000), gonads (Marson et al., 1993;Marson, 1995;Marson and McKenna, 1996;Orr and Marson, 1998;Papka et al., 1998;Tang et al., 1999;Marson and Murphy, 2006), and brown adipose tissue (Cano et al., 2003). Furthermore, Barrington's nucleus is activated by a variety of stressors (Sved et al., 2002). Taken together, the current evidence indicates a novel possible influence of Barrington's nucleus on physiological responses to stress.

There are some functional correlates consistent with this idea. For example, neurons retrogradely and transneuronally labeled with pseudorabies virus in Barrington's nucleus from intercapsular brown adipose tissue show a marked increase in Fos expression in rats placed in cold environment (Cano et al., 2003). Related to this, recent work also reaffirms a previously suggested role for the PVH in control of thermogenesis via its influence on sympathetic nerves innervating brown adipose tissue (Madden and Morrison, 2009); this is also suggested by the results of transneuronal tracing studies (Cano et al., 2003). Previous anterograde tracing studies using the autoradiographic method established the existence of a projection from Barrington's nucleus to the intermediolateral cell column at sacral levels of the spinal cord (Loewy et al., 1979); this has been confirmed with retrograde tracing (fluorogold) methods (Valentino et al., 1995). In addition, projections to Barrington's nucleus from the PVH have been demonstrated with anterograde (PHAL) and retrograde (CTB) methods (Valentino et al., 1994). Also noteworthy is a demonstrated ascending projection to Barrington's nucleus (PHAL method) from the central gray at lumbosacral (but not thoracic) levels of the spinal cord (Wang et al., 1999).

This updated view of Barrington's nucleus indicates that the projection to it from the LHAs may be involved in the modulation of physiological responses to stress. This idea is reinforced by studies that have shown modulation in the expression of the stress-related peptide corticotropin-releasing hormone (CRH) in Barrington's nucleus under a variety of stressful conditions (Imaki et al., 1991; Imaki et al., 1992). It is also noteworthy that a population of CRH-expressing neurons in Barrington's nucleus projects to the PAGvl, DMX, and lumbosacral spinal cord (Valentino et al., 1995). Furthermore, because neural inputs to the LHAs indicate that it receives interoceptive afferent information, this affirms a possible function of the LHAs as a nodal point for interoceptive control (as we discussed in relation to its projection to the PAGvl). In addition, the realization of Barrington's nucleus as a link between autonomic innervation of the pelvic viscera and the prefrontal cortex has led to the suggestion that it may be involved in pelvic visceral dysfunctions (such as bowel disorders) that have comorbidity with psychiatric disorders (Pavcovich et al., 1998; Valentino et al., 1999; Cairns et al., 2005); the connections of the LHAs indicate that it may have a central place within this circuitry. This may also be the case for dysfunctions that relate to the more classic understanding of Barrington's nucleus as the pontine micturition center, such as urge incontinence or other stress-related bladder dysfunctions (Kuipers et al., 2006; Wood et al., 2009).

4.4.3.3 LHAs discussion: Hypothalamic Periventricular Region: Several parts of the hypothalamic periventricular region connect with the LHAs, most notably the medial preoptic area (MPO), median preoptic nucleus (MEPO), and dorsomedial hypothalamic nucleus (DMH). Less substantial connections were noted between the LHAs and the anterior hypothalamic area, anteroventral preoptic nucleus, and anteroventral periventricular nucleus

(AVP and AVPV, respectively), and periventricular internuclear area (I). Rather abundant retrograde labeling in the MPO, together with a moderate direct projection to this area from the LHAs, indicates interaction between the LHAs and an area that is thought to have a broad role in the initiation of motivated (goal-oriented) behavioral responses that involve the recruitment of autonomic, somatic, and endocrine components of the nervous system (Swanson and Mogenson, 1981). Motivated behaviors in which the MPO has been implicated include reproductive behavior (Balthazart and Ball, 2007), defensive behavior associated with male conspecific interactions (Motta et al., 2009), and behavioral responses associated with thirst and thermoregulation (Swanson and Mogenson, 1981). Intriguingly, one of the (anatomically and functionally) identified projections of the MPO is to the region of the MRNp that also receives an input from the LHAs (see earlier discussion); also, a proportion of the projecting neurons express galanin (Swanson et al., 1987). Furthermore, the same study indicated that some neurons projecting to the vicinity of the MRNp also send a collateral projection to a region centered caudally in the zona incerta -- it is apparent that this region may have included the LHAs (Swanson et al., 1987); the PAGvl is also heavily targeted by the MPO (Swanson et al., 1987).

The LHAs therefore connects with an area (the MPO) that appears to have broad scope of influence on behavior, from manifest locomotor behavior to endocrine and autonomic modulation; these compare to an indicated role for the LHAs in the control of a broad spectrum of ingestive-related processes. For the LHAjp we suggested that its projection to the BSTpr indicated an interaction between a system for defensive behavior (involving the LHAjp) and one for sexual/reproductive behavior (involving the BSTpr) -- an example of a possible neural substrate for inter-behavior modulation. In the case of LHAs the indicated interaction is between processes related to ingestive behavior, thermoregulation, and sexual behavior -- a role for the LHAs in control of reproductive behavior is also indicated by its projection to the AVPV. These very simple formulations draw attention to the fact that different modes of behavior necessarily modulate other modes of behavior -- one would predict the variety and scope of these interactions to be an emergent property of the underlying neurocircuitry. Drawing attention to the reality of interaction between different systems of behavior also reinforces the caution against assigning exclusive function to a given brain region.

The connection we found between the LHAs and the median preoptic nucleus (MEPO) -- moderate retrograde labeling and light projection -- is informed by our earlier discussion of an input to the LHAs from the SFO. The SFO and MEPO, and a second circumventricular organ -- the vascular organ of the lamina terminalis (OVLT), are highly interconnected (Miselis, 1981; Saper and Levisohn, 1983; Swanson and Lind, 1986; Kawano and Masuko, 2006); the functional significance of this has been demonstrated most clearly in relation to the MEPO as a downstream target of the SFO and OVLT and the actions of humoral angiotensin II on the SFO and OVLT to promote arterial pressure, plasma sodium ion homeostasis, and drinking (Fitzsimons, 1998). In addition to its role in cardiovascular and hydromineral homeostasis, the MEPO is also implicated in control of thermoregulation (Morrison et al., 2008) and sleep-wake states/arousal (Ushakov et al., 2007; Kumar et al., 2008). As we discussed for the MPO, these different functions may relate to inter-behavior modulation; for example, the influence of thermoregulatory or sleep/wake state on processes relating to ingestive behavior.

The remaining part of the hypothalamic periventricular region that has substantial connections with the LHAs is the DMH. Specifically, a light terminal field was apparent in the anterior part of the DMH, and a moderate abundance of retrograde labeling was present in the anterior, ventral, and posterior parts -- most of this was present as a cluster of neurons in a dorsolateral region of the posterior part of the DMH. The connections of the DMH and its parts have been studied comprehensively (ter Horst and Luiten, 1986; Thompson et al., 1996; Thompson and Swanson, 1998), although functional differences that may exist between its individual parts

have not. Nevertheless, much evidence points to a role for the DMH in the control of energy homeostasis, and in particular a more recently established role for the DMH to integrate control of energy balance with the circadian rhythm (Bellinger and Bernardis, 2002; Chou et al., 2003; Gooley et al., 2006; Gao and Horvath, 2008).

With a view to future clarification of differential function between the different parts of the DMH, it is noteworthy that the pattern of parabrachial nucleus innervation of the DMH (Thompson and Swanson, 1998) appears to be quite similar to the distribution of retrograde labeling in the DMH seen from the LHAs; the DMH also receives very dense innervation from the parastrial nucleus (Thompson and Swanson, 1998). What also sets these two nuclei, parabrachial and parastrial, apart is that their projection to the DMH includes a robust innervation of the posterior part, unlike several other regions that project to the DMH (Thompson and Swanson, 1998). The projection to the DMH from the parabrachial nucleus indicates a further potentially important route for influence of the latter structure on the LHAs, in addition to the direct bidirectional connections the parabrachial nucleus has with the LHAs, as discussed.

We also found a low-moderate amount of retrograde labeling in the parastrial nucleus (PS) from the LHAs. The PS is indicated to participate in several functions and has connections with several regions that we have already discussed with regard to the LHAs. Thus the PS receives inputs from the subfornical organ (Swanson and Lind, 1986), BST_{fu} (Dong et al., 2001b), BST_{mg} (Dong and Swanson, 2006c), and CEA (Tsubouchi et al., 2007); PS projection targets include the PVH (Thompson and Swanson, 2003; Tsubouchi et al., 2007), AVPV (Hahn and Coen, 2006), MEPO, MPO, and AVP (Thompson and Swanson, 2003); the PS is also reported to be sexually dimorphic (Del Abril et al., 1990). As a final point to round out this section, it is quite interesting that six highly interconnected regions (AVP, ADP, AVPV, PS, MEPO, and DMH), put forward as a putative substrate for a hypothalamic visceromotor pattern generator network (Thompson and Swanson, 2003), provide to a greater or lesser degree an input to the LHAs -- the LHAs is therefore in a position to integrate and send on the activity of this network.

4.4.3.3.4. LHAs discussion: Reticular Formation: The LHAs, as is the case for the LHA_{jp}, has substantial interconnections with other motor related parts of the hypothalamic lateral zone (Fig. 12); in addition, and unlike the LHA_{jp}, the LHAs sends substantial projections to parts of the reticular formation located in the midbrain and hindbrain that are involved in the control of visceromotor processes, in particular those related to ingestive behavior (Fig. 12). With regard to the hypothalamic lateral zone, of note is a relatively light bidirectional connection between the LHAs and LHA_{jp}. This connection and the connections of the LHAs with other regions of the hypothalamic lateral zone could provide a means for crosstalk between regions whose connections indicate a deeply integrative role -- this high-order crosstalk could be conceived as a form of meta-integration.

From midbrain to hindbrain, the first principal target of the LHAs within the reticular formation division of the motor system is the magnocellular part of the midbrain reticular nucleus (MRN_m); the light to moderate projection of fibers is distributed diffusely and appears to include fibers of passage that continue on to form a more evident terminal field in the MRN_p, as previously discussed. The sources of neural inputs to the MRN_m include several that together strongly implicate the MRN_m in the control of motor processes relating to ingestive behavior, these sources include a robust input from the midbrain dorsal nucleus of the raphé (Vertes, 1991), extrapyramidal area (corresponds to MRN_p), and parabrachial nucleus (Rye et al., 1988), and substantial though lesser input from the retrorubral area, pedunclopontine nucleus, and subceruleal region (corresponds to sublaterodorsal nucleus) (Rye et al., 1988); it is

noteworthy to recall that the LHAs projects to (or has bidirectional connections with) each of these regions.

Caudal to the MRN, the fibers that descend into and through the reticular parts of the hindbrain do so rather diffusely; although as a whole this amounts to a sizeable projection. These descending axons course with moderate abundance through pontine, gigantocellular, and paragigantocellular reticular nuclei; with moderate to light abundance through parvicellular and magnocellular reticular nuclei; and with light abundance through medullary reticular nuclei. A prominent subset of these fibers traverses the caudal (motor) part of the pontine reticular nucleus (PRNc), principally within its lateral half. The PRN, together with the other hindbrain parts of the reticular formation, sends massive and topographically organized projections to midline and intralaminar groups of thalamic nuclei (Krout et al., 2002a). These projections and the nuclei that generate them form a prominent part of the classically described reticular activating system that is capable of exerting a major influence on arousal (Gottesmann, 1999; Vincent, 2000). The LHAs is thus in a position to exert a modulatory low level influence on this system -- a possible gating mechanism.

To examine this possibility further we can take the PRNc as an example. The major thalamic targets of the PRNc include nuclei associated with motor responses to salient stimuli (parafascicular nucleus) and multimodal sensory processing (rhomboid nucleus) (Van der Werf et al., 2002; Krout et al., 2002a). Conversely, sources of substantial descending projections to the PRNc, in addition to the LHAs, include the precommissural nucleus of the PAG (Canteras and Goto, 1999a) and the dorsomedial and rhomboid nuclei of the anterior BST division (Dong and Swanson, 2003; Dong and Swanson, 2006b). Each of these cell groups (as appears to be the case for the LHAs) is considered to have very broad roles in the control of body homeostasis and behavior and, particularly in relation to ingestive behavior and energy balance (BSTrh and BSTdm) (Dong and Swanson, 2003; Dong and Swanson, 2006b), but also possibly in relation to defensive or reproductive behaviors (PRC) (Canteras and Goto, 1999a).

Although it is unclear what effect the LHAs may exert on the PRN (or on the other reticular formation nuclei it projects to), a clue to a possible role is indicated by studies that have identified the PRN for having a role in audiogenic stress (“startle”) responses (Koch, 1999). Given an indicated role for the LHAs in the modulation of autonomic responses to stress, it could be that its projection to the PRN (and other reticular nuclei) may be involved in modulating the responsiveness of the reticular activating system to external stressful stimuli (including auditory stimuli that generate a startle response) dependent on the current level of internal stress. Conversely, dysfunction of such a mechanism could contribute to an inappropriate increase or decrease in arousal.

4.4.3.3.5. LHAs discussion: Motoneuron Groups: The lowest level of the motor system hierarchy with which the LHAs has substantial connections, contains the motor neuron groups that collectively form the final common neuronal pathway for the expression of behavior and the control of vital functions. Two motoneuron groups are noteworthy for their connections with the LHAs: these are the parvicellular division of the neuroendocrine motor zone, and the parasympathetic division of the preganglionic motor neuron pools. More specifically, the LHAs sends a moderately strong projection directly to the anterior- and medial parvicellular (dorsal zone) parts of the hypothalamic paraventricular nucleus (PVHap and PVHmpd, respectively); it also receives a moderate input from the PVHap and a light input from the hypothalamic arcuate nucleus (ARH). A light projection also extends from the LHAs directly to the dorsal motor nucleus of the vagus nerve and to the inferior salivatory nucleus. These connections reinforce an indicated role for the LHAs as a broad modulator of processes relating to autonomic and neuroendocrine control, energy balance, and ingestive behavior.

5. Concluding remarks

In this paper we have described at length the first order connections of the LHA_{jp} and LHAs, two differentiable, nearby regions of the lateral hypothalamic area -- a region traversed by the medial forebrain bundle, which is arguably the most complex fiber tract of the central nervous system. Given their location, it is perhaps not surprising that the connections of the LHA_{jp} and the LHAs are revealed in their way to be similarly complex. However, this complexity is not without order; in fact a highly topographic organization is apparent in the connections of the LHA_{jp} and the LHAs. This is also true for the previously described connections of the subfornical region of the LHA (LHAs_f) (Goto et al., 2005). Furthermore, the regions targeted by the anterior zone of the LHAs_f (LHAs_{fa}) share much similarity with regions targeted by the LHA_{jp}; whereas the projection pattern of the posterior zone of the LHAs_f (LHAs_{fp}) is similar in many respects to that of the LHAs (Goto et al., 2005; see also Fig 13). It remains to be seen how the differences and similarities in the topography of LHA projections for these LHA regions compare to other LHA differentiations. Nevertheless, the pattern of LHA_{jp} and LHAs connections indicates a profoundly integrative role for these LHA regions in the coordination and appropriate modulation of behavioral expression and bodily homeostasis.

In this role, the connections of the LHA_{jp} associate it primarily with defensive behavior, whereas the connections of the LHAs associate it with ingestive behavior. Furthermore, essentially all functional components of a basic four subsystem plan for the nervous system appear to be engaged: cognitive, state, sensory, and motor (Swanson, 2000). In addition to their indicated association with a primary mode of behavior, the connections of the LHA_{jp} and LHAs also indicate a role in inter-mode behavioral modulation. Thus, for the LHAs a possible a role in generating visceral responses to cognitive stress is indicated; similarly, the LHA_{jp} may have a role in modulating sexual behavior in response to changes in defensive behavior. While these hypotheses remain to be tested, in overtly simple terms analogies could be drawn between these processes and the inhibition of motoneurons for antagonistic muscle groups during limb movement, or the lateral inhibition of photoreceptor cells that occurs in the retina. However, much remains to be learned about the functional operation of the LHA regions, and the neurochemistry of their connections. For example, subsets of neurons within several LHA regions express the peptides melanin concentrating hormone or hypocretin/orexin (Swanson et al., 2005; Hahn, 2009). Therefore, as a guide to a better understanding of the contribution of individual neuron types, and in order to establish more general organizing principles, it will be necessary to determine in their entirety the first order connections of all LHA regions -- a goal we are working toward.

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Abbreviations

AAA	anterior amygdalar area
ACAd	anterior cingulate area, dorsal part
ACAv	anterior cingulate area, ventral part
ACB	nucleus accumbens ("shell" region)
aco	anterior commissure, olfactory limb
act	anterior commissure, temporal limb
AD	anterodorsal nucleus thalamus

ADP	anterodorsal preoptic nucleus
AHA	anterior hypothalamic area
AHNa	anterior hypothalamic nucleus, anterior part
AHNc	anterior hypothalamic nucleus, central part
AHNd	anterior hypothalamic nucleus, dorsal part
AHNp	anterior hypothalamic nucleus, posterior part
Ald	agranular insular area, dorsal part
Alp	agranular insular area, posterior part
Alv	agranular insular area, ventral part
alv	alveus of fornix
AMd	anteromedial nucleus thalamus, dorsal part
AMv	anteromedial nucleus thalamus, ventral part
AONpv	anterior olfactory nucleus, posteroventral part
AP	area postrema
AQ	cerebral aqueduct
AQc	cerebral aqueduct collicular recess
ARH	arcuate hypothalamic nucleus
AT	anterior tegmental nucleus
AV	anteroventral nucleus thalamus
AVP	anteroventral preoptic nucleus
AVPV	anteroventral periventricular nucleus
B	Barrington's nucleus
BA	bed nucleus of the accessory olfactory part
BAC	bed nucleus anterior commissure
BLAp	basolateral amygdalar nucleus, posterior part
BMAa	basomedial amygdalar nucleus, anterior part
BSM	bed nucleus of the stria medullaris
BSTal	bed nuclei stria terminalis, anterior division, anterolateral area
BSTam	bed nuclei stria terminalis, anterior division, anteromedial area
BSTd	bed nuclei stria terminalis, posterior division, dorsal nucleus
BSTdm	bed nuclei stria terminalis, anterior division, dorsomedial nucleus
BSTfu	bed nuclei stria terminalis, anterior division, fusiform nucleus
BSTif	bed nuclei stria terminalis, posterior division, interfascicular nucleus
BSTmg	bed nuclei stria terminalis, anterior division, magnocellular nucleus
BSTpr	bed nuclei stria terminalis, posterior division, principal nucleus
BSTse	bed nuclei stria terminalis, anterior division, rhomboid nucleus

BSTtr	bed nuclei stria terminalis, posterior division, transverse nucleus
BSTv	bed nuclei stria terminalis, anterior division, ventral nucleus
C	central canal
CA1	field CA1, Ammon's horn
CA1so	field CA1, stratum oriens
CA1spd	field CA1, pyramidal layer, deep
CA1sps	field CA1, pyramidal layer, superficial
CA2sp	field CA2, pyramidal layer
CA3so	field CA3, stratum oriens
CA3sp	field CA3, pyramidal layer
cc	corpus callosum
cgg	genu of corpus callosum
CEAc	central amygdalar nucleus, capsular part
CEAl	central amygdalar nucleus, lateral part
CEAm	central amygdalar nucleus, medial part
cc	commissure of the inferior colliculus
cing	cingulum bundle
CL	central lateral nucleus thalamus
CLA	claustrum
CLI	central linear nucleus raphé
CM	central medial nucleus thalamus
COAa	cortical amygdalar area, anterior part
COApl	cortical amygdalar area, posterior part, lateral zone
COApm	cortical amygdalar area, posterior part, medial zone
COM	periaqueductal gray, commissural nucleus
CP	caudoputamen
cpd	cerebral peduncle
csc	commissure of the superior colliculus
CSl	superior central nucleus raphé, lateral part
CSm	superior central nucleus raphé, medial part
CUN	cuneiform nucleus
da	dopamine (cell group within zona incerta)
DCO	dorsal cochlear nucleus
df	dorsal fornix
DGlb	dentate gyrus lateral blade
DMHa	dorsomedial hypothalamic nucleus, anterior part

DMHp	dorsomedial hypothalamic nucleus, posterior part
DMHv	dorsomedial hypothalamic nucleus, ventral part
DMX	dorsal motor nucleus vagus nerve
DR	dorsal nucleus raphé
dscp	decussation of the superior cerebellar peduncle
DTN	dorsal tegmental nucleus
ec	corpus callosum external capsule
ee	corpus callosum extreme capsule
em	external medullary lamina thalamus
ENTl	entorhinal area, lateral part
ENTm	entorhinal area, medial part, dorsal zone
EPd	endopiriform nucleus, dorsal part
EW	Edinger-Westphal nucleus
fa	corpus callosum anterior forceps
FF	fields of Forel
fi	fimbria
fr	fasciculus retroflexus
FS	fundus of the striatum
fx	columns of the fornix
fxpr	precommissural fornix
GPe	globus pallidus, external segment
GPi	globus pallidus, internal segment
GR	gracile nucleus
GRN	gigantocellular reticular nucleus
gVIIIn	genu of the facial nerve
hbc	habenular commissure
HPF	hippocampal formation
I	internuclear area, hypothalamic periventricular region
IA	intercolated nuclei amygdala
IAD	interanterodorsal nucleus thalamus
IAM	interanteromedial nucleus thalamus
ICc	inferior colliculus central nucleus
ICd	inferior colliculus dorsal nucleus
ICe	inferior colliculus external nucleus
IF	interfascicular nucleus raphé
IG	induseum griseum

ILA	infralimbic area
im	internal medullary lamina thalamus
IMD	intermediodorsal nucleus thalamus
INC	interstitial nucleus of Cajal
int	internal capsule
IPNc	interpeduncular nucleus central subnucleus
IPNd	interpeduncular nucleus dorsomedial subnucleus
IPNi	interpeduncular nucleus intermediate subnucleus
IPNld	interpeduncular nucleus lateral subnucleus dorsal part
IPNli	interpeduncular nucleus, lateral subnucleus, intermediate part
IPNlr	interpeduncular nucleus lateral subnucleus rostral part
IPNr	interpeduncular nucleus rostral subnucleus
ISN	inferior salivatory nucleus
ivf	interventricular foramen
KF	Kolliker-Fuse subnucleus
LC	locus ceruleus
LD	lateral dorsal nucleus thalamus
LDT	laterodorsal tegmental nucleus
LGd	dorsal part of the lateral geniculate complex
LH	lateral habenula
LHAad	lateral hypothalamic area, anterior region, dorsal zone
LHAai	lateral hypothalamic area, anterior region, intermediate zone
LHAav	lateral hypothalamic area, anterior region, ventral zone
LHAad	lateral hypothalamic area, dorsal region
LHAjd	lateral hypothalamic area, juxtadorsomedial region
LHAjp	lateral hypothalamic area, juxtaparaventricular region
LHAjvd	lateral hypothalamic area, juxtaventromedial region, dorsal zone
LHAjvv	lateral hypothalamic area, juxtaventromedial region, ventral zone
LHAM	lateral hypothalamic area, magnocellular nucleus
LHAMo	lateral hypothalamic area, motor related
LHAp	lateral hypothalamic area, posterior region
LHApc	lateral hypothalamic area, parvicellular region
LHAs	lateral hypothalamic area, supraforaminal region
LHAsfa	lateral hypothalamic area, subforaminal region, anterior zone
LHAsfp	lateral hypothalamic area, subforaminal region, posterior zone
LHAsfp	lateral hypothalamic area, subforaminal region, premammillary zone
m	

LHAVl	lateral hypothalamic area, ventral region, lateral zone
LHAVm	lateral hypothalamic area, ventral region, medial zone
LP	lateral posterior nucleus thalamus
LPO	lateral preoptic area
LRNm	lateral reticular nucleus magnocellular part
LSc.d.d	lateral septal nucleus, caudal (caudodorsal) part, dorsal zone, dorsal region
LSc.d.l	lateral septal nucleus, caudal (caudodorsal) part, dorsal zone, lateral region
LSc.d.r	lateral septal nucleus, caudal (caudodorsal) part, dorsal zone, rostral region
LSc.d.v	lateral septal nucleus, caudal (caudodorsal) part, dorsal zone, ventral region
LSc.v.i	lateral septal nucleus, caudal (caudodorsal) part, ventral zone, intermediate region
LSc.v.l.d	lateral septal nucleus, caudal (caudodorsal) part, ventral zone, lateral region, dorsal domain
LSc.v.l.v	lateral septal nucleus, caudal (caudodorsal) part, ventral zone, lateral region, ventral domain
LSc.v.m.d	lateral septal nucleus, caudal (caudodorsal) part, ventral zone, medial region, dorsal domain
LSc.v.m.v	lateral septal nucleus, caudal (caudodorsal) part, ventral zone, medial region, ventral domain
LSr.dl.l.d	lateral septal nucleus, rostral (rostroventral) part, dorsolateral zone, lateral region, dorsal domain
LSr.dl.l.v	lateral septal nucleus, rostral (rostroventral) part, dorsolateral zone, lateral region, ventral domain
LSr.dl.m.d	lateral septal nucleus, rostral (rostroventral) part, dorsolateral zone, medial region, dorsal domain
LSr.dl.m.v	lateral septal nucleus, rostral (rostroventral) part, dorsolateral zone, medial region, ventral domain
LSr.m.d	lateral septal nucleus, rostral (rostroventral) part, medial zone, dorsal region
LSr.m.v.c	lateral septal nucleus, rostral (rostroventral) part, medial zone, ventral region, caudal domain
LSr.m.v.r	lateral septal nucleus, rostral (rostroventral) part, medial zone, ventral region, rostral domain
LSr.vl.d	lateral septal nucleus, rostral (rostroventral) part, ventrolateral zone, dorsal region
LSr.vl.d.l	lateral septal nucleus, rostral (rostroventral) part, ventrolateral zone, dorsal region, lateral domain

LSr.vl.d .m	lateral septal nucleus, rostral (rostroventral) part, ventrolateral zone, dorsal region, medial domain
LSr.vl.v	lateral septal nucleus, rostral (rostroventral) part, ventrolateral zone, ventral region
LSv	lateral septal nucleus, ventral part
LTN	lateral tegmental nucleus
MA	magnocellular preoptic nucleus
MARN	magnocellular reticular nucleus
mct	medial corticothalamic tract
MDc	mediodorsal nucleus thalamus, central part
MDl	mediodorsal nucleus thalamus, lateral part
MDm	mediodorsal nucleus thalamus, medial part
MDRN d	medullary reticular nucleus, dorsal part
MDRN v	medullary reticular nucleus, ventral part
MEAad	medial amygdalar nucleus, anterodorsal part
MEAav	medial amygdalar nucleus, anteroventral part
MEApd -a	medial amygdalar nucleus, posterodorsal part, sublayer a
MEApd -b	medial amygdalar nucleus, posterodorsal part, sublayer b
MEApd -c	medial amygdalar nucleus, posterodorsal part, sublayer c
MEApv	medial amygdalar nucleus, posteroventral part
MEex	median eminence external
MEin	median eminence internal
MEPO	median preoptic nucleus
MEV	mesencephalic nucleus of the trigeminal
MH	medial habenula
ml	medial lemniscus
mlf	medial longitudinal fascicle
MM	medial mammillary nucleus (body)
MMme	medial mammillary nucleus, median part
MO	secondary somatomotor area
moV	motor root of the trigeminal nerve
mp	mammillary peduncle
MPNc	central part

MPNI	medial preoptic nucleus, lateral part
MPNm	medial part
MPO	medial preoptic area
MPT	medial pretectal area
MRNm	midbrain reticular nucleus, magnocellular part
MRNp	midbrain reticular nucleus, parvocellular part
MS	medial septal nucleus
mtg	mammillotegmental tract
mtt	mammillothalamic tract
mtV	mesencephalic tract of the trigeminal nerve
MV	medial vestibular nucleus
NC	supraoptic nucleus, accessory supraoptic group, nucleus circularis
ND	nucleus of Darkschewitsch
NDB	diagonal band nucleus
NIc	nucleus incertus, compact part
NIId	nucleus incertus, diffuse part
NIS	nucleus intercalatus
NLOT	nucleus of the lateral olfactory tract
NPC	nucleus of the posterior commissure
NTB	nucleus of the trapezoid body
NTSco	nucleus of the solitary tract, commissural part
NTSI	nucleus of the solitary tract, lateral part
NTSmc	nucleus of the solitary tract, medial part, caudal zone
NTSmr	nucleus of the solitary tract, medial part, rostral zone
och	optic chiasm
opt	optic tract
ORBl	orbital area, lateral part
ORBm	orbital area, medial part
ORBv	ventral part
ORBvl	ventrolateral part
OT	olfactory tubercle
PA	posterior amygdalar nucleus
PAGd	periaqueductal gray, dorsal division
PAGdl	periaqueductal gray, dorsolateral division
PAGm	periaqueductal gray, medial division
PAGrl	periaqueductal gray, rostromedial division

PAGrm	periaqueductal gray, rostromedial division
PAGvl	periaqueductal gray, ventrolateral division
PAR	parasubiculum
PARN	parvicellular reticular nucleus
PAT	paratrigeminal nucleus
PBlc	parabrachial nucleus, lateral division, central lateral part
PBlD	parabrachial nucleus, lateral division, dorsal lateral part
PBlE	parabrachial nucleus, lateral division, external lateral part
PBlv	parabrachial nucleus, lateral division, ventral part
PBmm	parabrachial nucleus, medial division, medial medial part
pc	posterior commissure
PCG	pontine central gray
PF	parafascicular nucleus
PG	pontine gray
PGRNd	paragigantocellular reticular nucleus, dorsal part
PGRNI	paragigantocellular reticular nucleus, lateral part
PH	posterior hypothalamic nucleus
PIR	piriform area
PL	prelimbic area
pm	principal mammillary tract
PMd	dorsal premammillary nucleus
PMv	ventral premammillary nucleus
POR	superior olivary complex periolivary region
POST	postsubiculum
PPN	pedunculopontine nucleus
PPT	posterior pretectal nucleus
PPYd	parapyramidal nucleus, deep part
PR	perireuniens nucleus
PRC	periaqueductal gray, precommissural nucleus
PRE	presubiculum
PRNc	pontine reticular nucleus, caudal part
PRNr	pontine reticular nucleus, rostral part
PRP	nucleus prepositus
PS	parastrial nucleus
PSCH	suprachiasmatic preoptic nucleus
PST	preparasubthalamic nucleus

PSTN	parasubthalamic nucleus
PT	paratenial nucleus
PVa	periventricular hypothalamic nucleus, anterior part
PVHam	paraventricular nucleus hypothalamus, magnocellular division, anterior magnocellular part
PVHap	paraventricular nucleus hypothalamus, anterior parvicellular part
PVHdp	paraventricular nucleus hypothalamus, dorsal parvicellular part
PVHf	paraventricular nucleus hypothalamus, forniceal part
PVHlp	paraventricular nucleus hypothalamus, lateral parvicellular part
PVHmp d	paraventricular nucleus hypothalamus, medial parvicellular part, dorsal zone
PVHmp dl	paraventricular nucleus hypothalamus, medial parvicellular part, dorsal zone, lateral wing
PVHpm l	paraventricular nucleus hypothalamus, posterior magnocellular part, lateral zone
PVHpm m	paraventricular nucleus hypothalamus, posterior magnocellular part, medial zone
PVHpv	paraventricular nucleus hypothalamus, periventricular part
PVi	periventricular nucleus hypothalamus, intermediate part
PVp	periventricular nucleus hypothalamus, posterior part
PVpo	preoptic periventricular nucleus
PVT	paraventricular nucleus thalamus
py	pyramidal tract, crossed
RCH	retrochiasmatic area
REa	nucleus reuniens, rostral division, anterior part
REc	nucleus reuniens, caudal division, caudal part
REcd	nucleus reuniens, caudal division, dorsal part
REcm	nucleus reuniens, caudal division, median part
REcp	nucleus reuniens, caudal division, posterior part
REd	nucleus reuniens, rostral division, dorsal part
REl	nucleus reuniens, rostral division, lateral part
REm	nucleus reuniens, rostral division, median part
REv	nucleus reuniens, rostral division, ventral part
RH	rhomboid nucleus
RL	rostral linear nucleus raphé
RM	nucleus raphé magnus
RN	red nucleus
RO	nucleus raphé obscurus

RPA	nucleus raphé pallidus
RR	midbrain reticular nucleus, retrorubral area
RSPv	retrosplenial area, ventral part
RT	reticular nucleus thalamus
rust	rubrospinal tract
SBPV	subparaventricular zone
SCdg	superior colliculus, deep gray layer
SCdg	superior colliculus, deep gray layer
SCH	suprachiasmatic nucleus
SCig-a	superior colliculus, intermediate gray layer, sublayer a
SCig-b	superior colliculus, intermediate gray layer, sublayer b
SCig-c	superior colliculus, intermediate gray layer, sublayer c
scp	superior cerebellar peduncle
SCsg	superior colliculus, superficial gray layer
setv	ventral spinocerebellar tract
SEZ/ RC	subependymal zone/rhinocele
SF	septofimbrial nucleus
SFO	subfornical organ
SH	septohippocampal nucleus
SI	substantia innominata
SLD	sublaterodorsal nucleus
sm	stria medullaris
smd	supramammillary decussation
SMT	submedial nucleus of the thalamus
SO	supraoptic nucleus
SPFm	subparafascicular nucleus thalamus, magnocellular part
SPFpl	subparafascicular nucleus thalamus, parvicellular part, lateral division
SPVI	spinal nucleus of the trigeminal interpolar part
SPVom dmd	spinal nucleus of the trigeminal oral part middle dorsomedial part, dorsal zone
SPVovl	spinal nucleus of the trigeminal oral part ventrolateral part
st	stria terminalis
SUB- sp*	subiculum, pyramidal layer

SUMl	supramammillary nucleus, lateral part
SUMm	supramammillary nucleus, medial part
sup	supraoptic commissures
SUT	supratrigeminal nucleus
SUV	superior vestibular nucleus
tb	trapezoid body
TMd	tuberomammillary nucleus dorsal part
TMv	tuberomammillary nucleus ventral part
tp	thalamic peduncles
TR	postpiriform transition area
TRN	tegmental reticular nucleus
TRS	triangular nucleus septum
ts	solitary tract
tsp	tectospinal pathway
TTd	tenia tecta, dorsal part
TTv	tenia tecta, ventral part
TUi	tuberal nucleus, intermediate part
TUl	tuberal nucleus, lateral part
TUsv	tuberal nucleus, subventromedial part
TUte	tuberal nucleus, terete subnucleus
V3h	third ventricle, hypothalamic part
V3m	third ventricle mammillary recess
V3p	third ventricle preoptic recess
V3r	third ventricle periventricular recess
V3t	third ventricle, thalamic part
V4	fourth ventricle
VAL	ventral anterior-lateral complex of the thalamus
vhc	ventral hippocampal commissure
VL	lateral ventricle
VLP	ventrolateral preoptic nucleus
vlr	ventrolateral hypothalamic tract
VM	ventral medial nucleus of the thalamus
Vma	motor nucleus of the trigeminal, magnocellular part
VMHa	ventromedial nucleus hypothalamus, anterior part

*In Swanson (2004) the subiculum (SUB) is further divided into dorsal and ventral halves; for clarity of description we have omitted those subdivisions in this article (see discussion section 4.3.).

VMHc	ventromedial nucleus hypothalamus, central part
VMHdm	ventromedial nucleus hypothalamus, dorsomedial part
VMHvl	ventromedial nucleus hypothalamus, ventrolateral part
VPMpc	ventral posteromedial nucleus of the thalamus parvicellular part
VTA	ventral tegmental area
VTN	ventral tegmental nucleus
XII	hypoglossal nucleus
ZI	zona incerta

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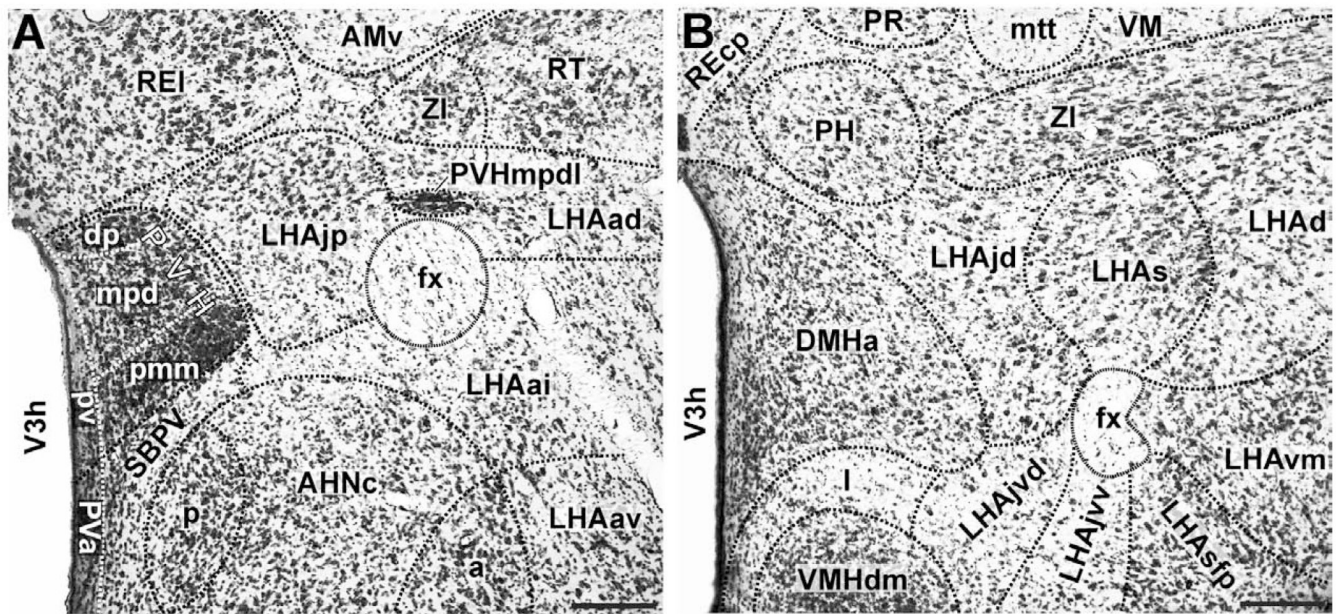


Figure 1. Representative photomicrographs of LHAs and LHAjp cytoarchitecture. (A and B) Brightfield photomicrographs of thionin stained transverse sections showing the cytoarchitecture and boundaries of the lateral hypothalamic area juxtaparaventricular region (LHAjp) at a caudal level (A) and the LHA supraforfornal region (LHAs) at a midrostrocaudal level (B). Boundaries of brain regions (dashed lines) and fiber tracts (finer dashed lines) correspond approximately to those delineated in an atlas of the rat brain (Swanson, 2004). A list of abbreviations used in this figure (and throughout this paper) is present from the second page of this paper. Scale bars = 100 μ m.

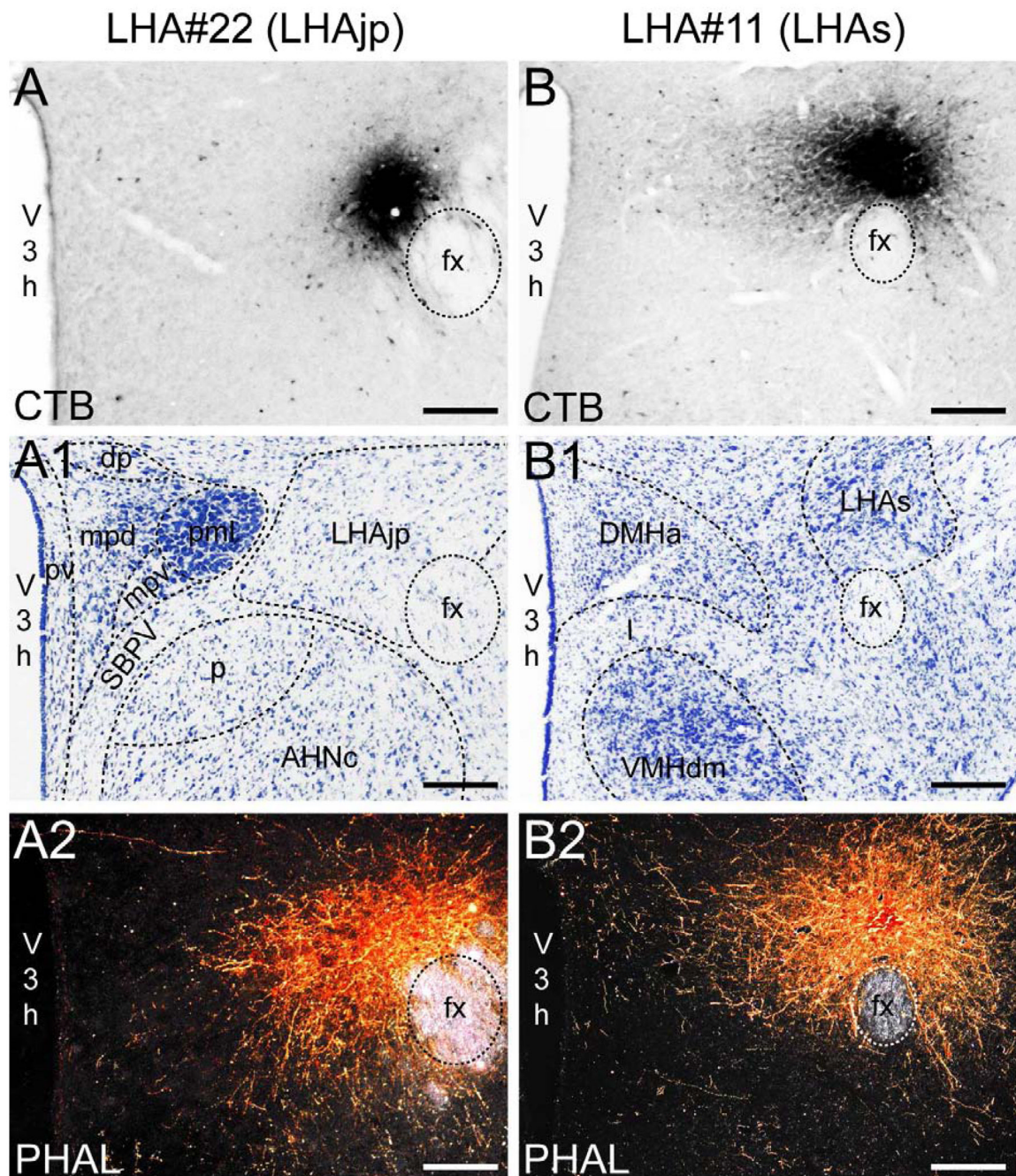


Figure 2.

Representative photomicrographs of PHAL and CTB injection sites. (A and B) Brightfield photomicrographs showing immunocytochemically identified deposits of cholera toxin B subunit (CTB) tracer for experiment LHA#22 within caudal levels of the lateral hypothalamic area juxtaparaventricular region (LHAjp) (A) and experiment LHA#11 within midrostrocaudal levels of the LHA supraforminal region (LHAs) (B). (A1 and B1) Thionin stained sections adjacent to the sections shown in (A, A2) and (B, B2). (A2 and B2) Darkfield photomicrographs showing immunocytochemically identified deposits of *Phaseolus vulgaris* leucoagglutinin (PHAL) tracer for experiment LHA#22 within caudal levels of the LHAjp (A2) and experiment LHA#11 within the midrostrocaudal levels of the LHAs (B2). Approximate boundaries of brain

regions (dashed lines) and fiber tracts (finer dashed lines) correspond to those delineated in an atlas of the rat brain (Swanson, 2004). Scale bars = 100 μm .

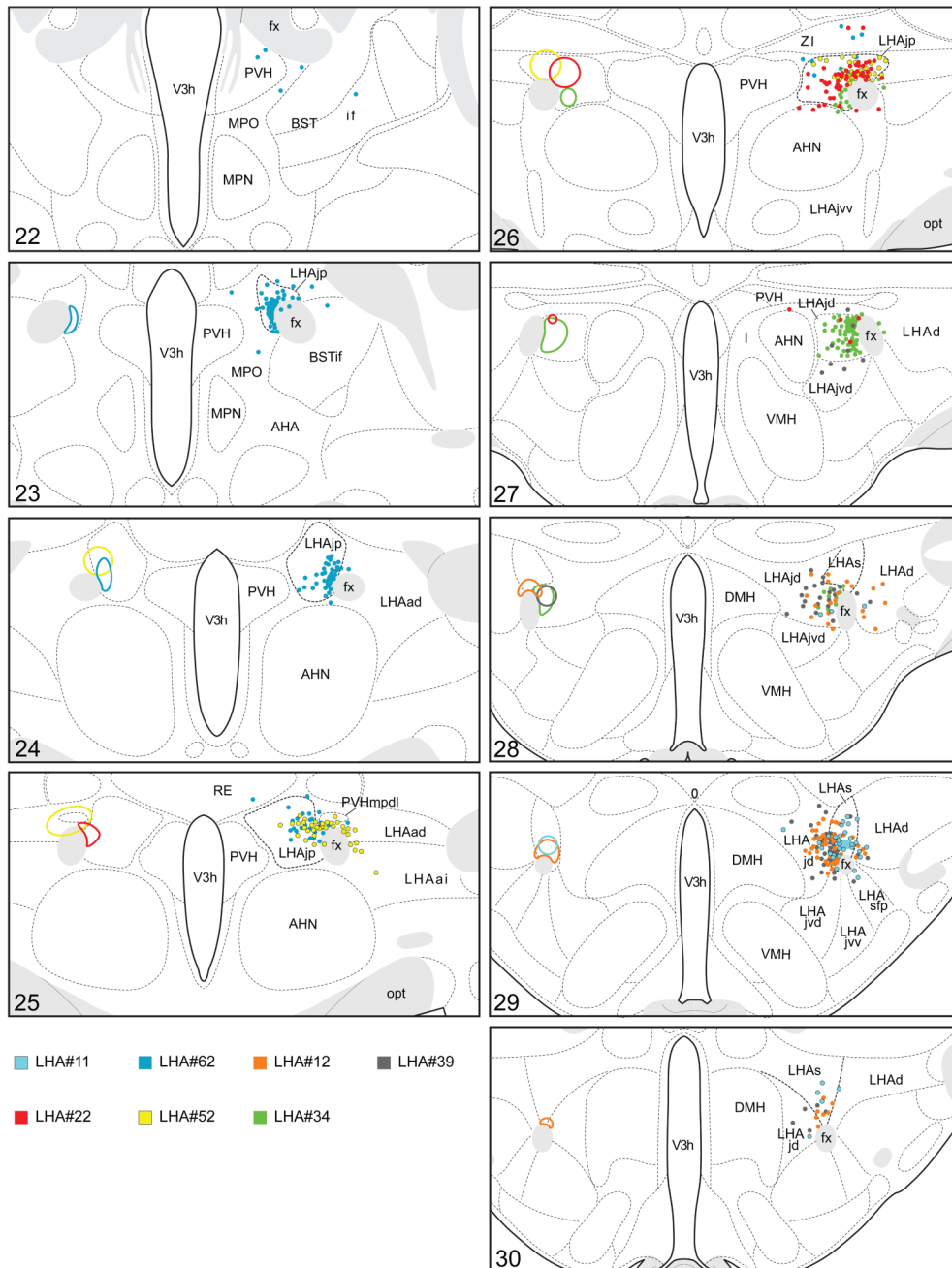
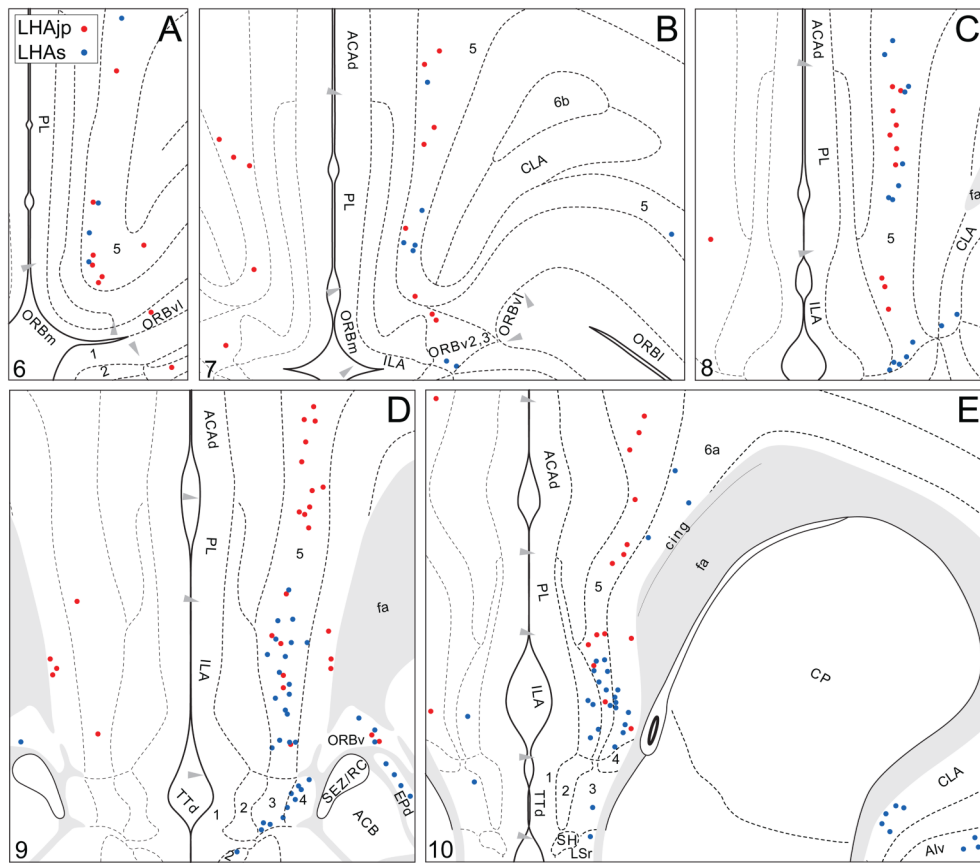
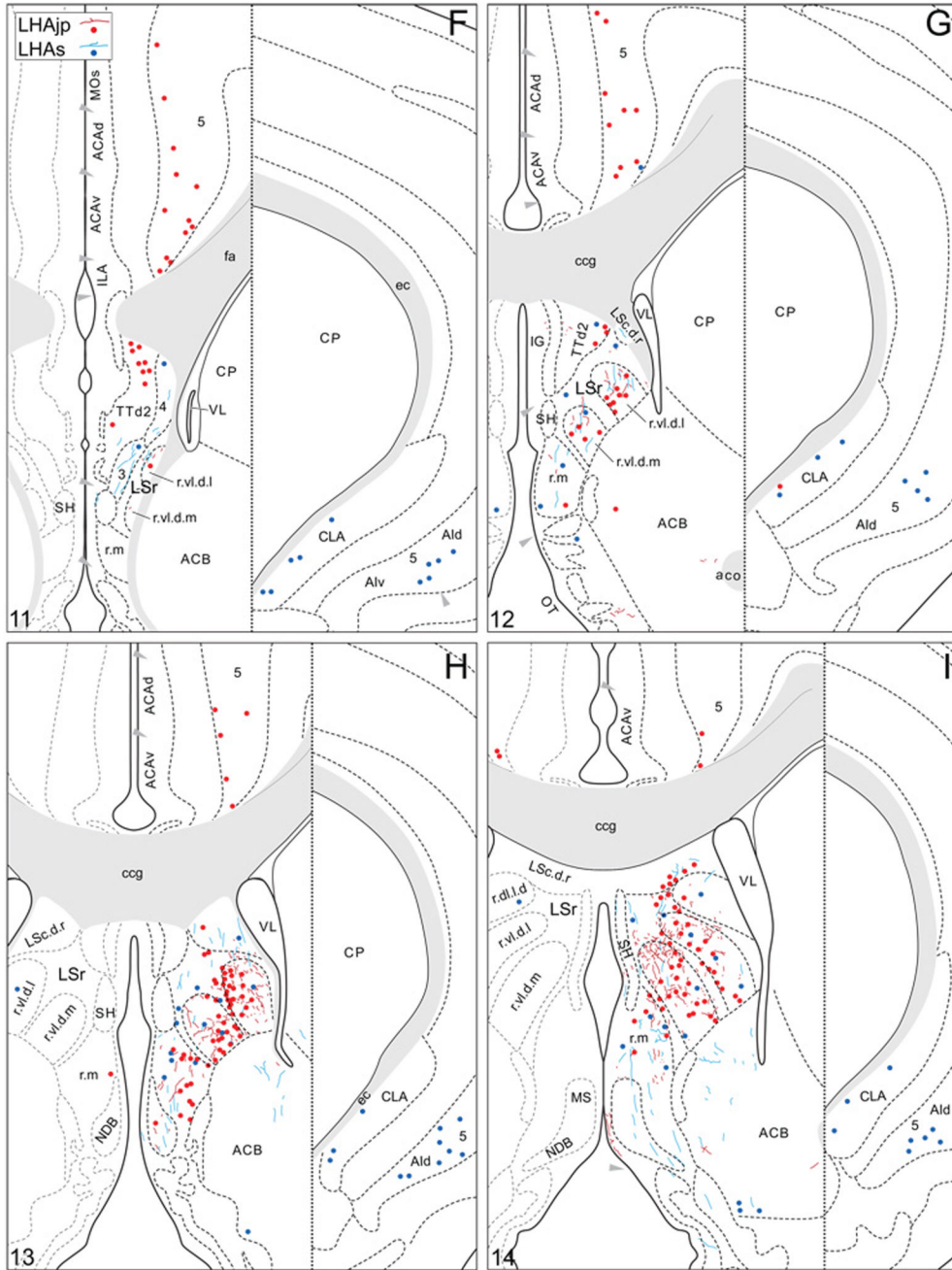


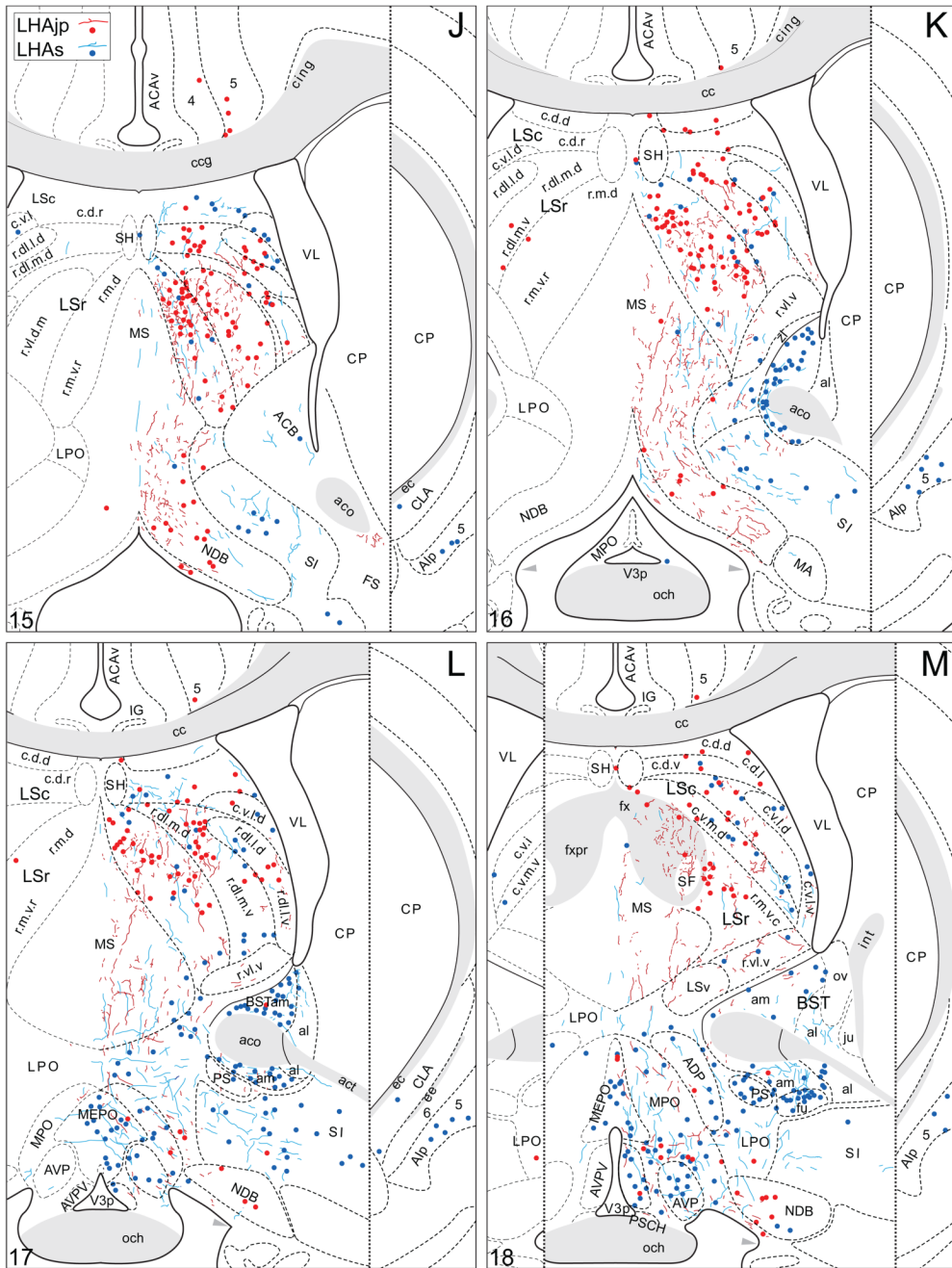
Figure 3.

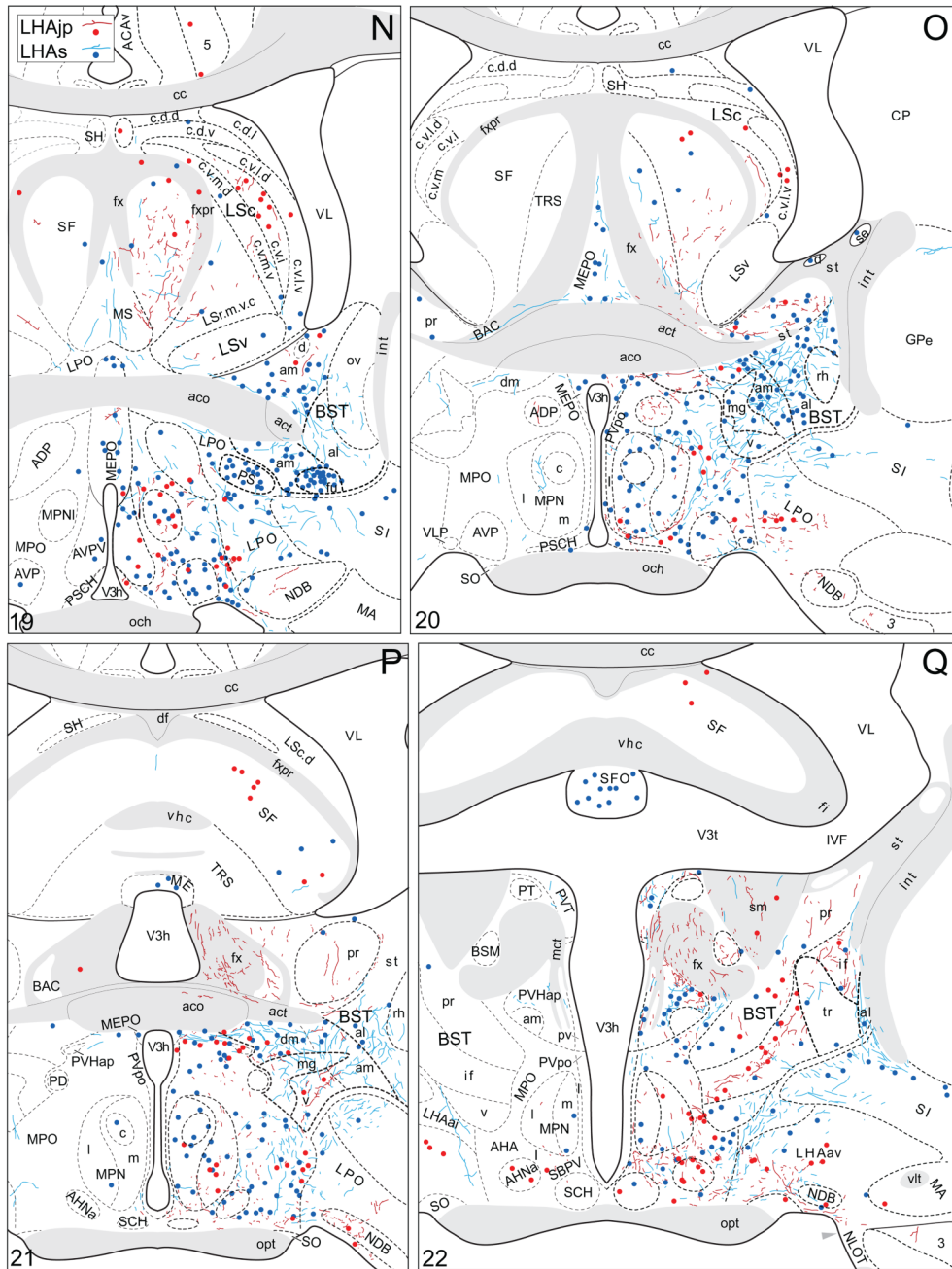
Plots of injection sites for representative experiments. The approximate extent of deposition sites for seven different tract-tracing experiments resulting from a combined injection of cholera toxin B subunit (CTB) and *Phaseolus vulgaris* leucoagglutinin (PHAL). The experiments presented involved either the lateral hypothalamic area juxtaparaventricular (LHAjp) or supraformal (LHAs) regions, or immediately adjacent regions, to a greater or lesser extent as shown. Each experiment is represented by a different color, with PHAL-labeled cells shown as colored dots and the approximate extent of each CTB deposit shown in colored outline. All injections were unilateral, but for clarity the CTB site outlines are transposed to the contralateral side of the atlas plates. These data were plotted with the aid of the camera

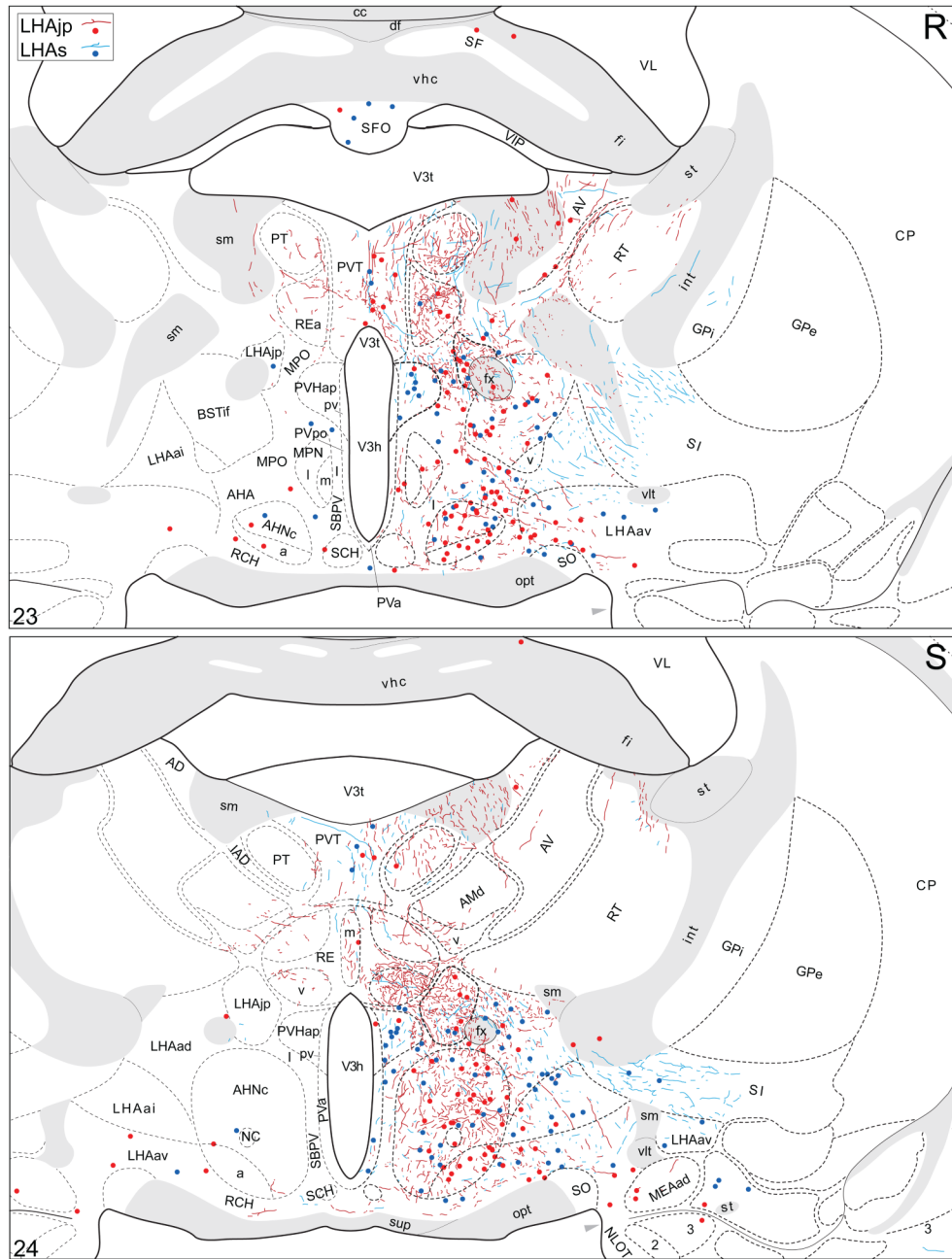
lucida method from tissue sections containing immunocytochemically detected PHAL and CTB, and with reference to an adjacent set of thionin stained sections; the plots were then transposed to corresponding atlas plates. Approximate boundaries of brain regions (dashed lines) and the shown fiber tracts (grayed areas) correspond to those delineated in an atlas of the rat brain (Swanson, 2004).

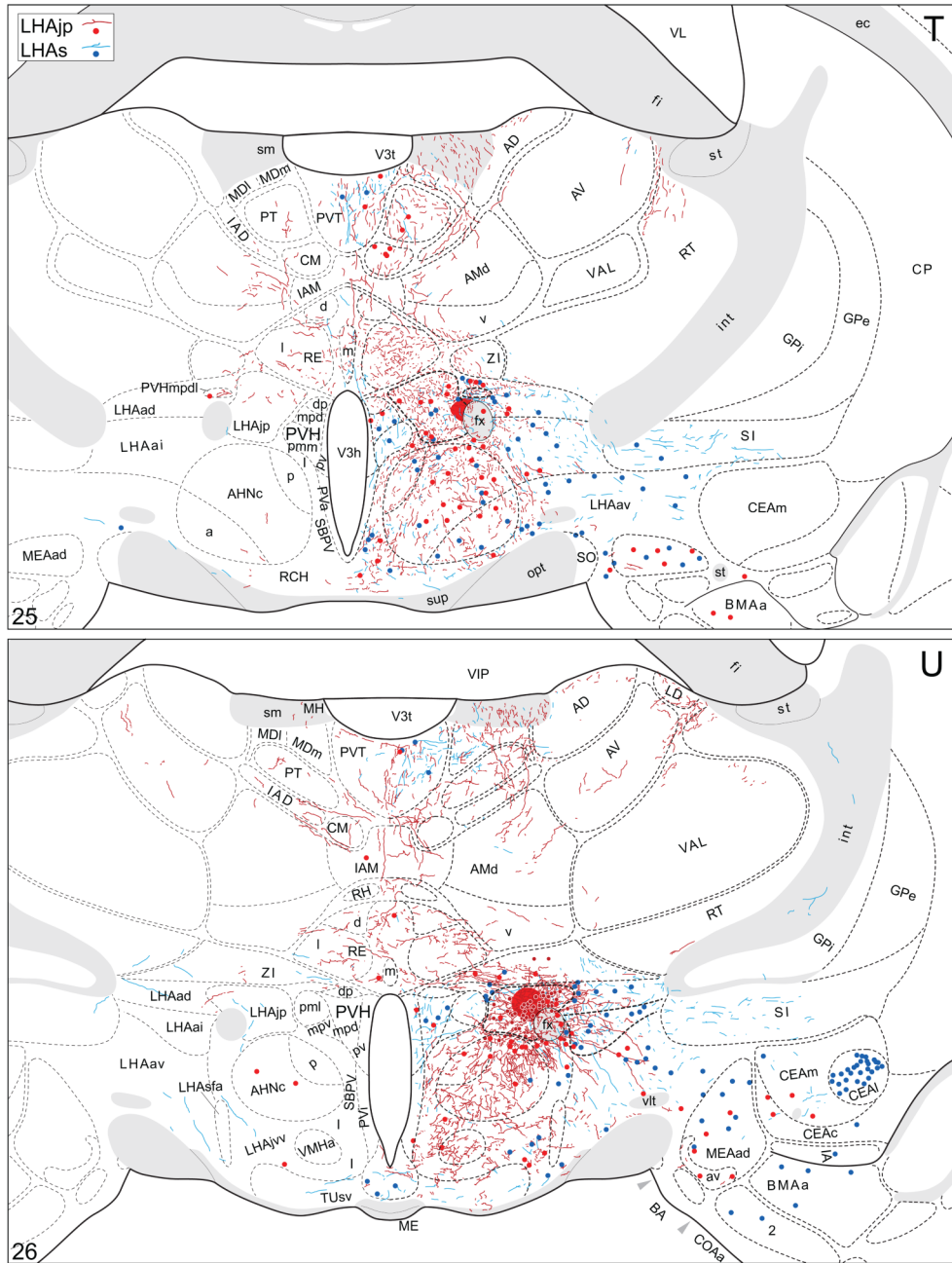


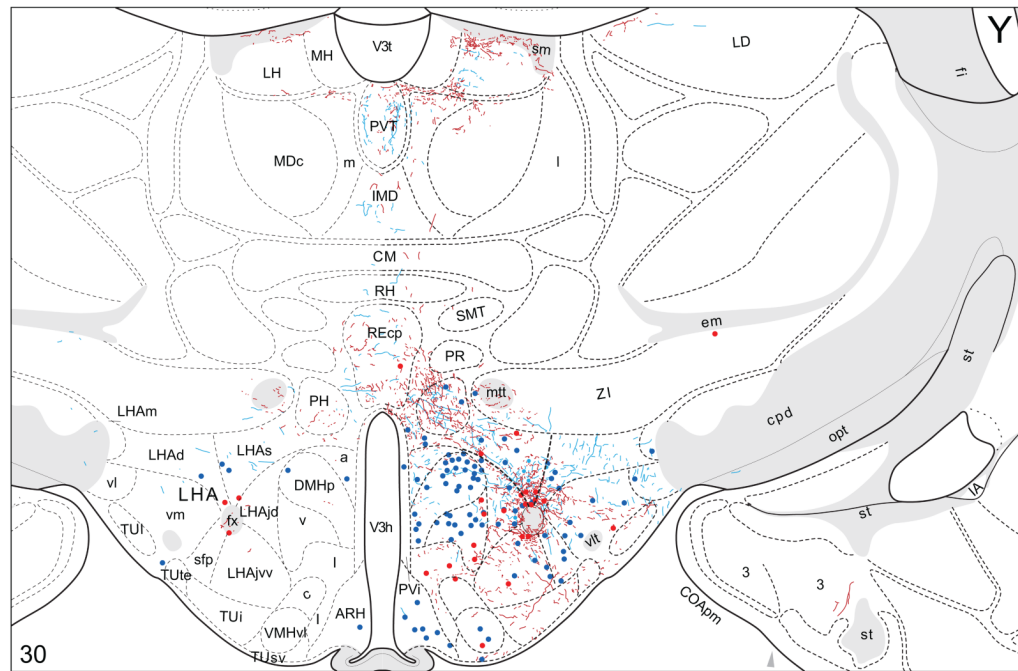
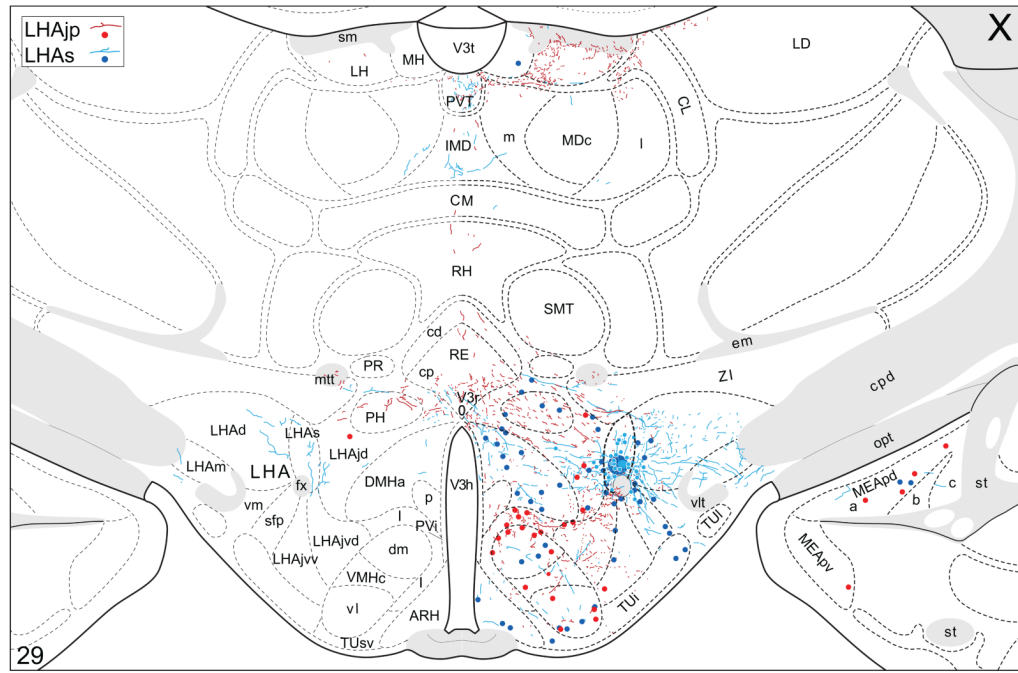


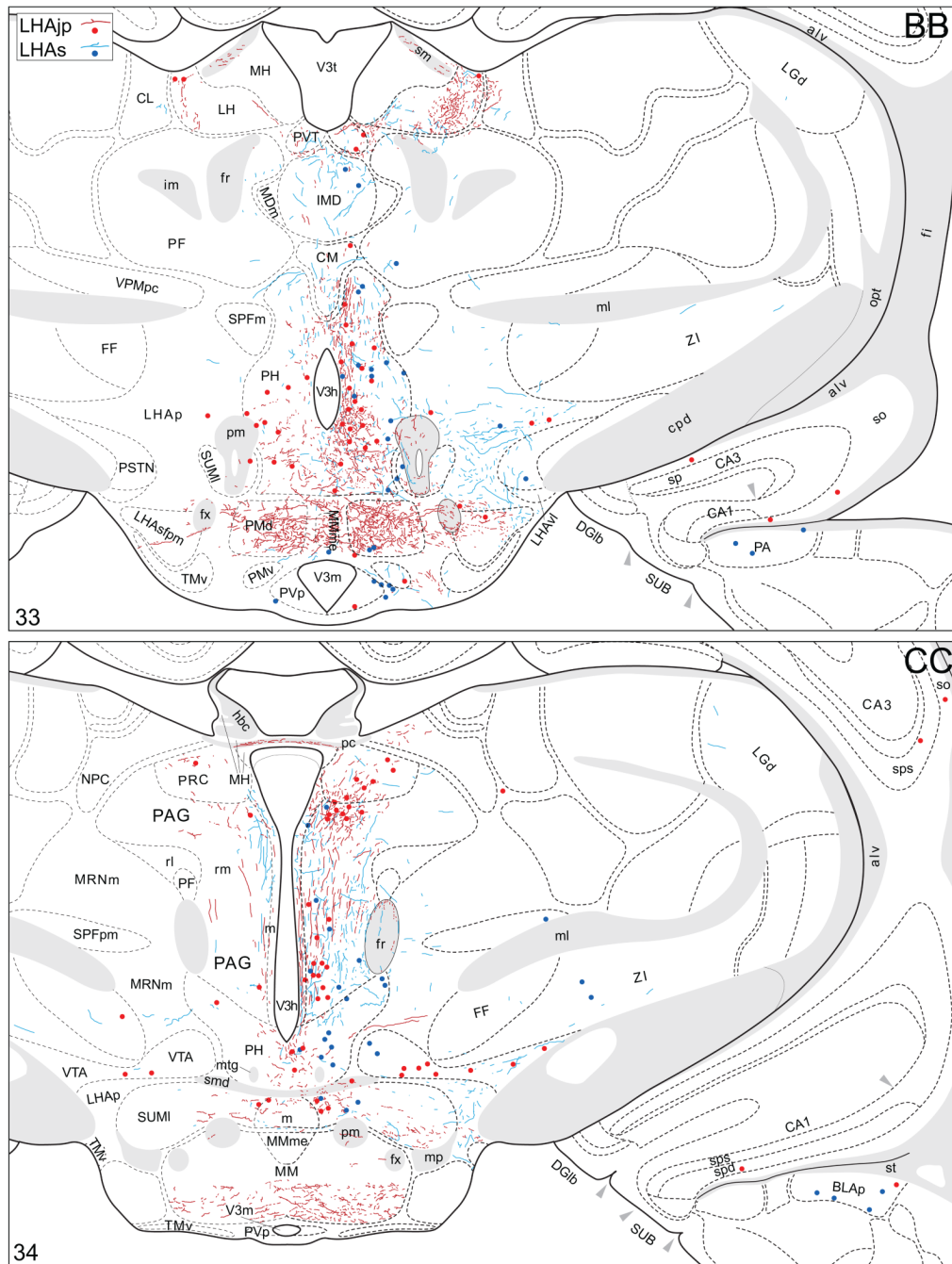


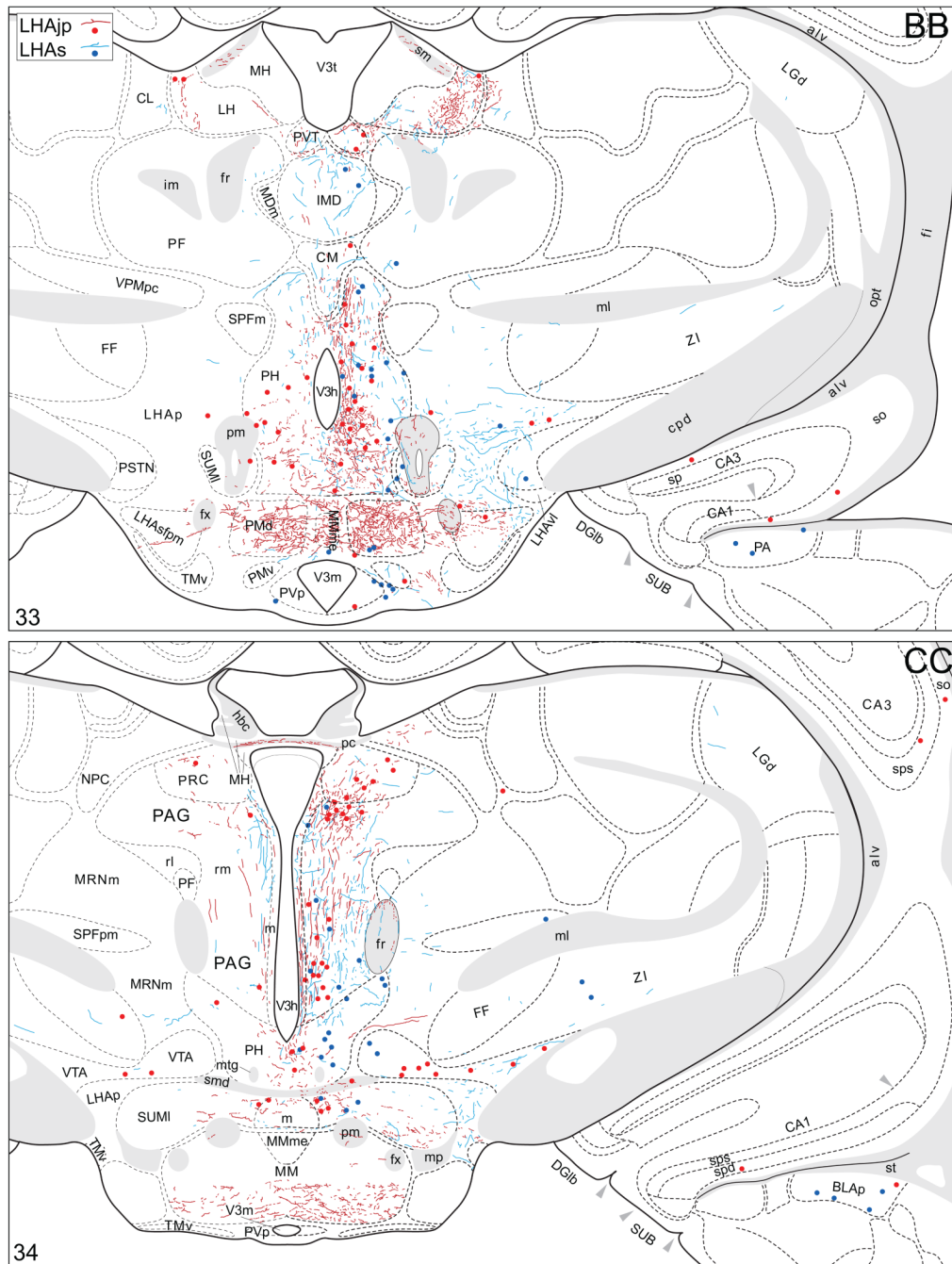


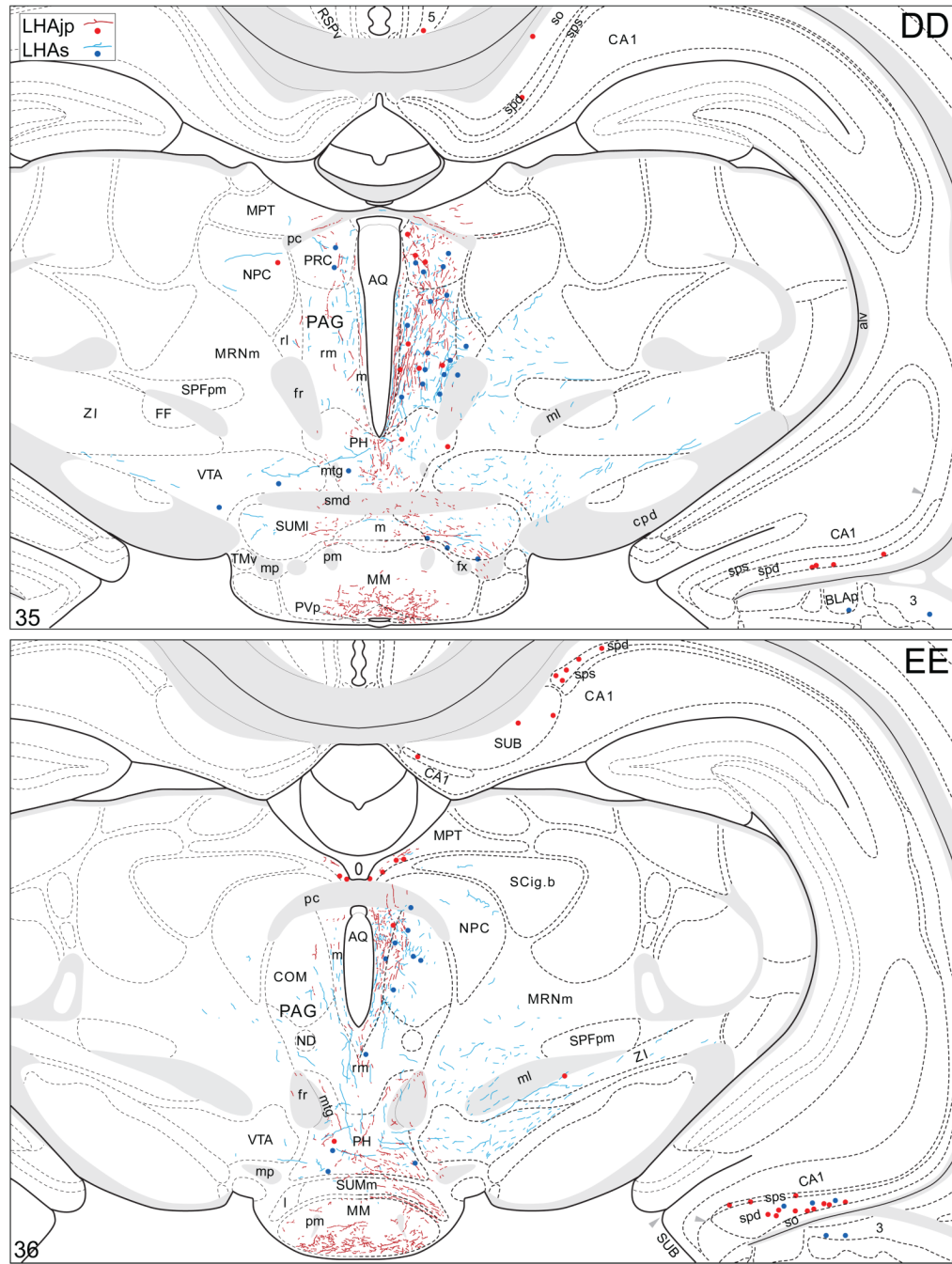


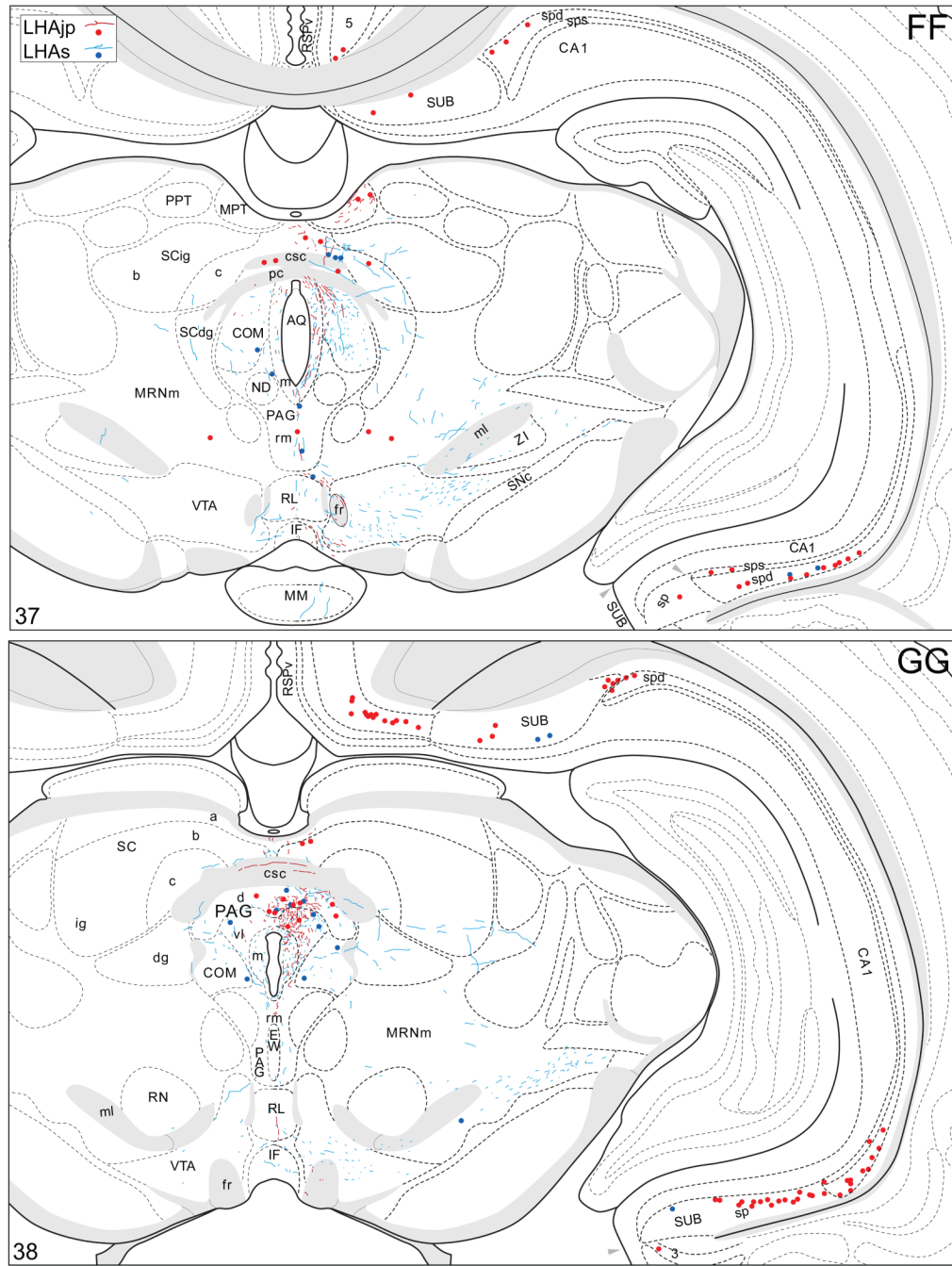


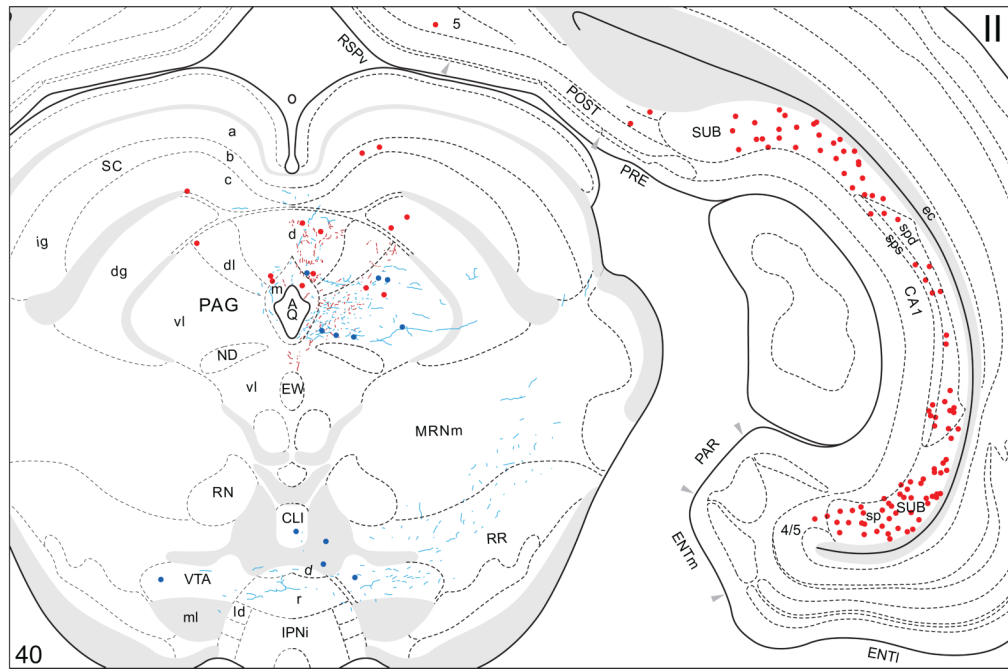
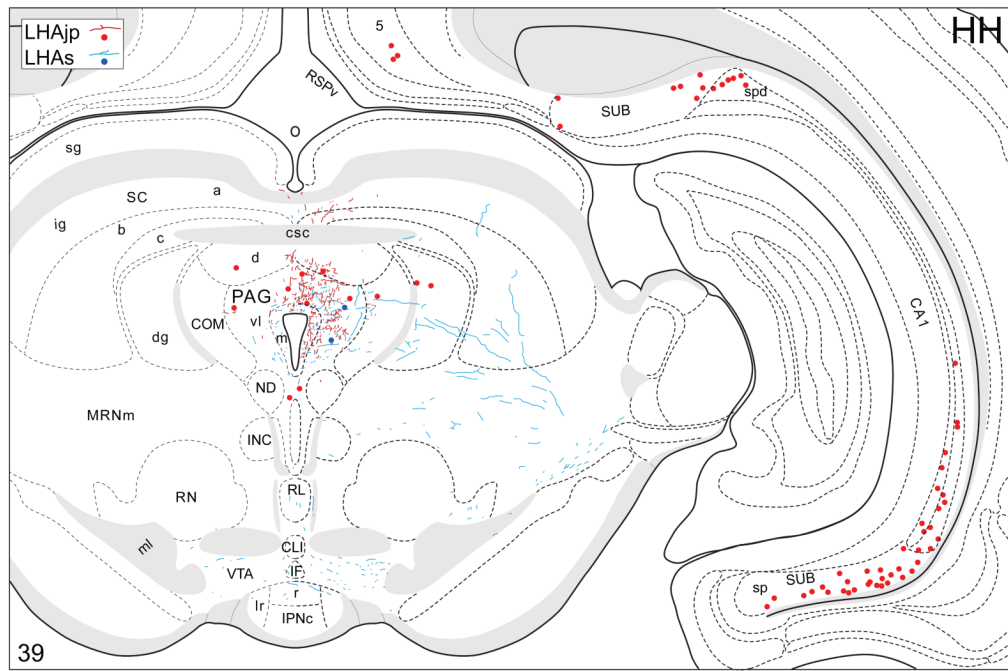


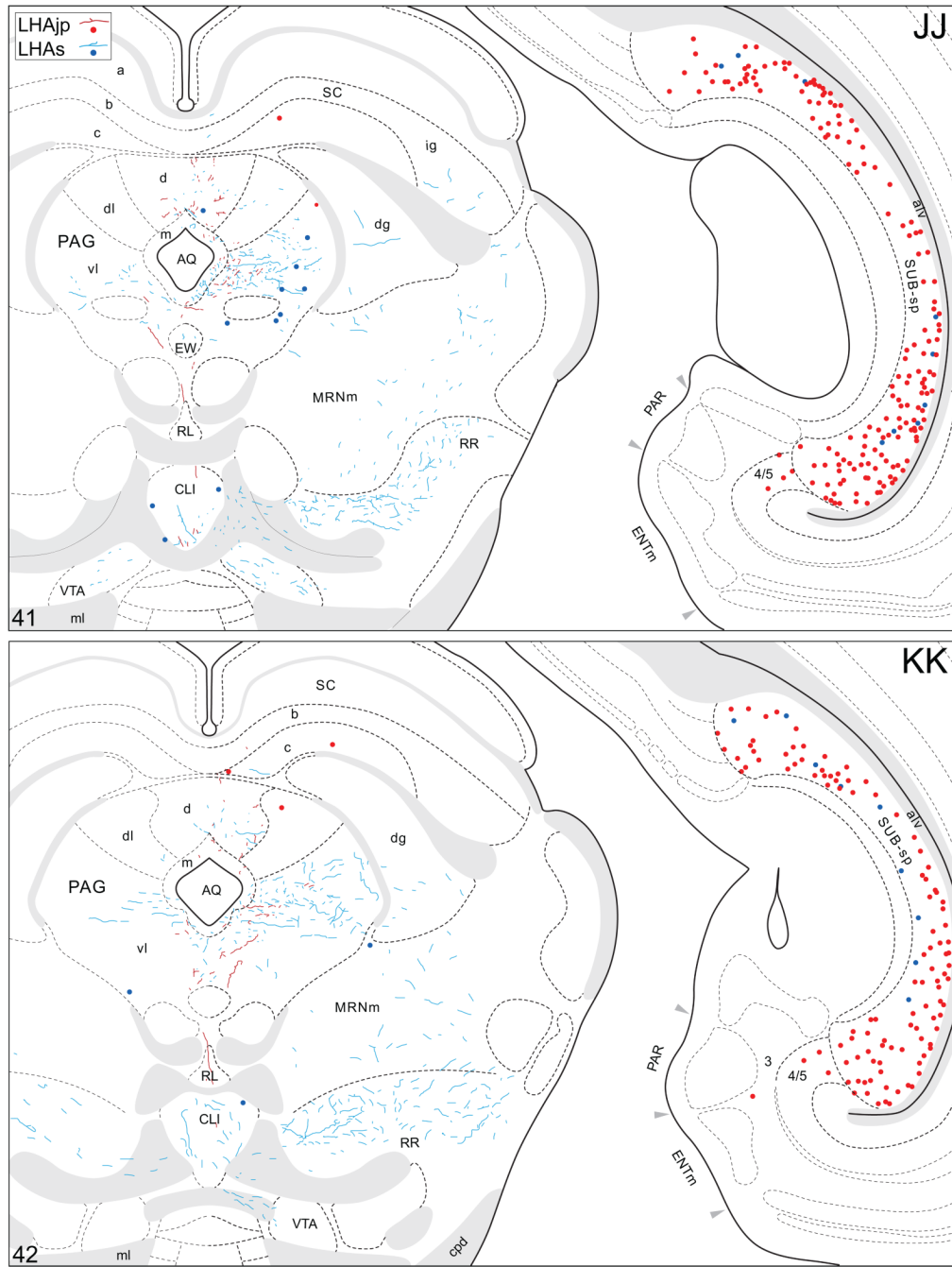


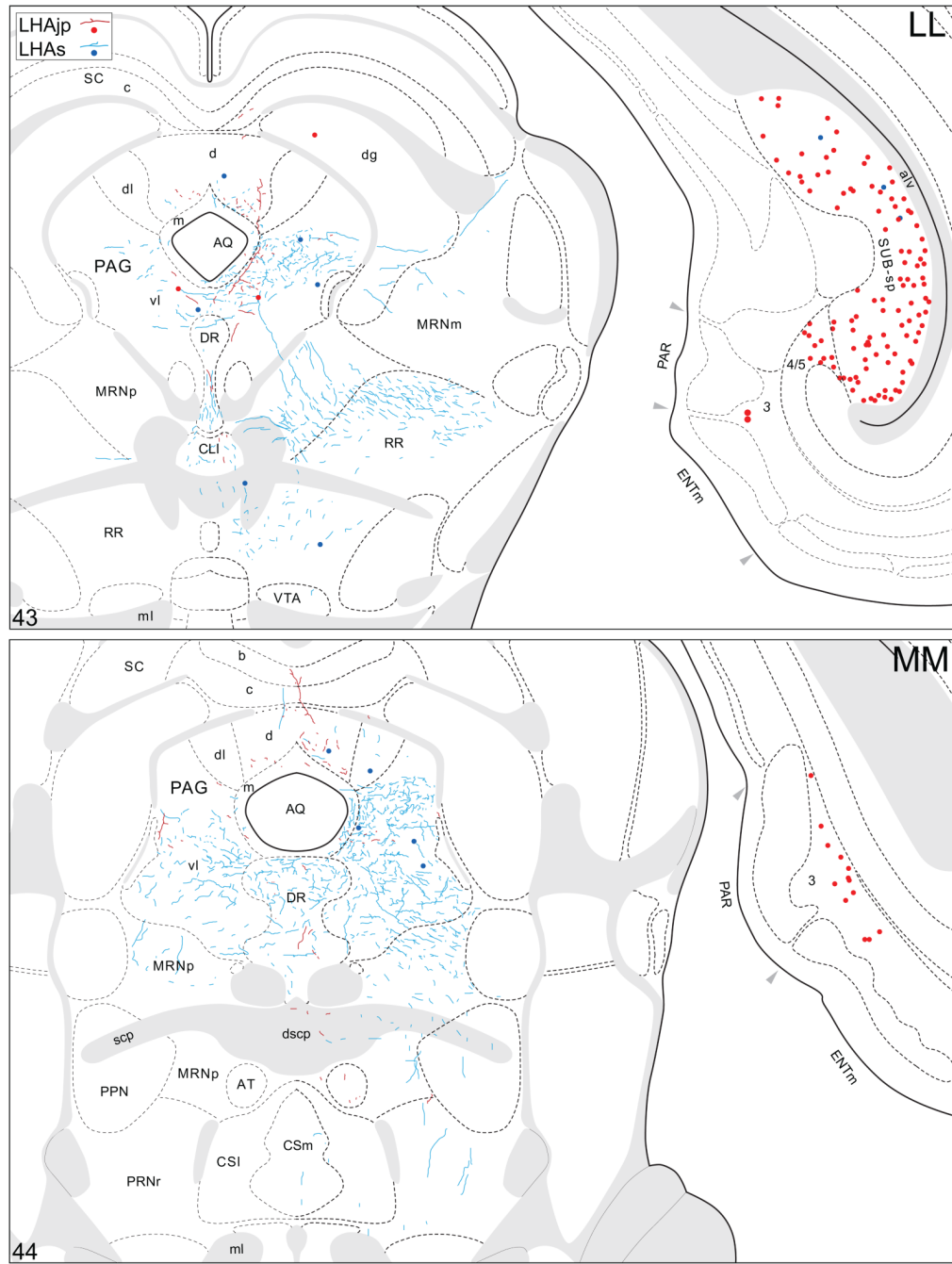


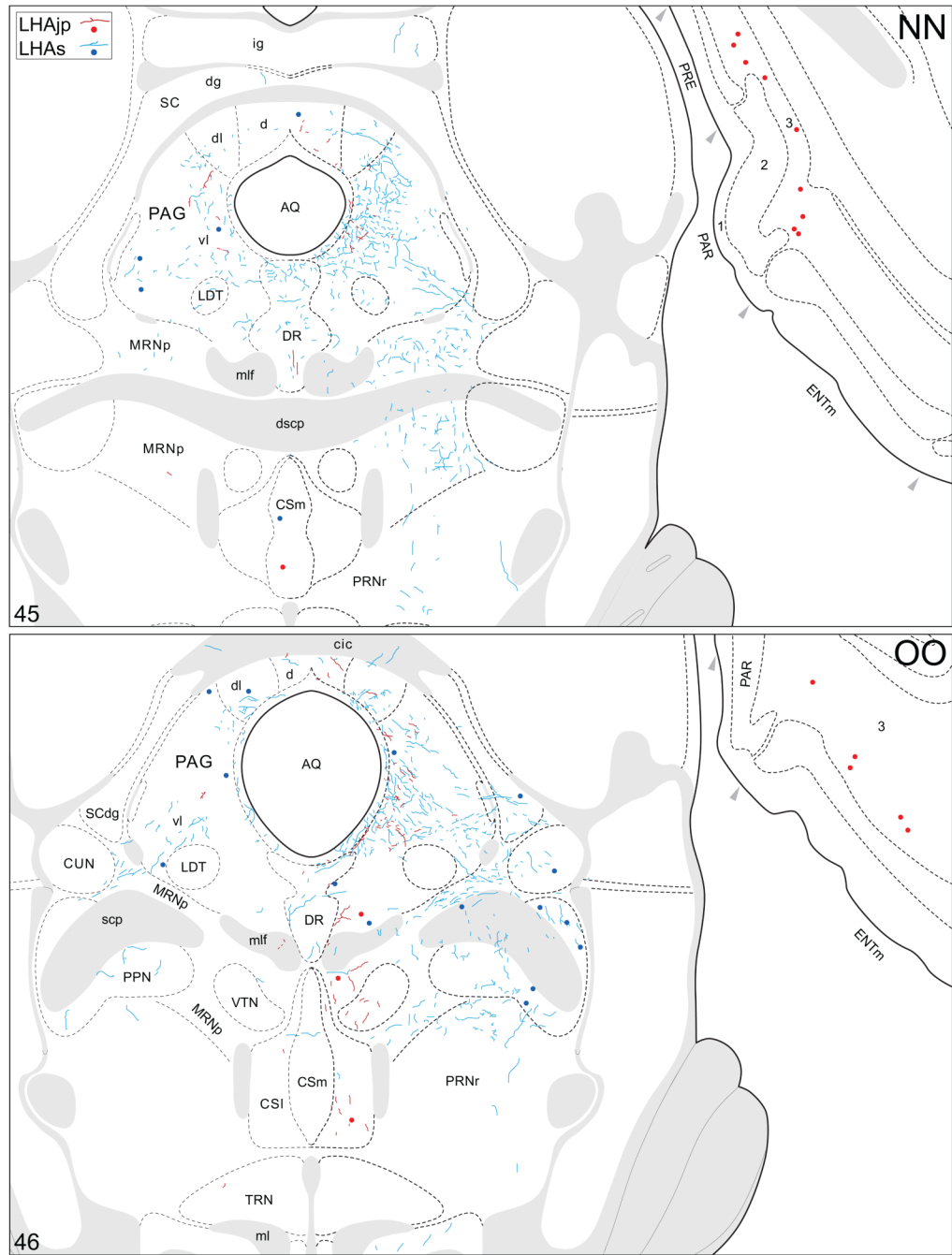


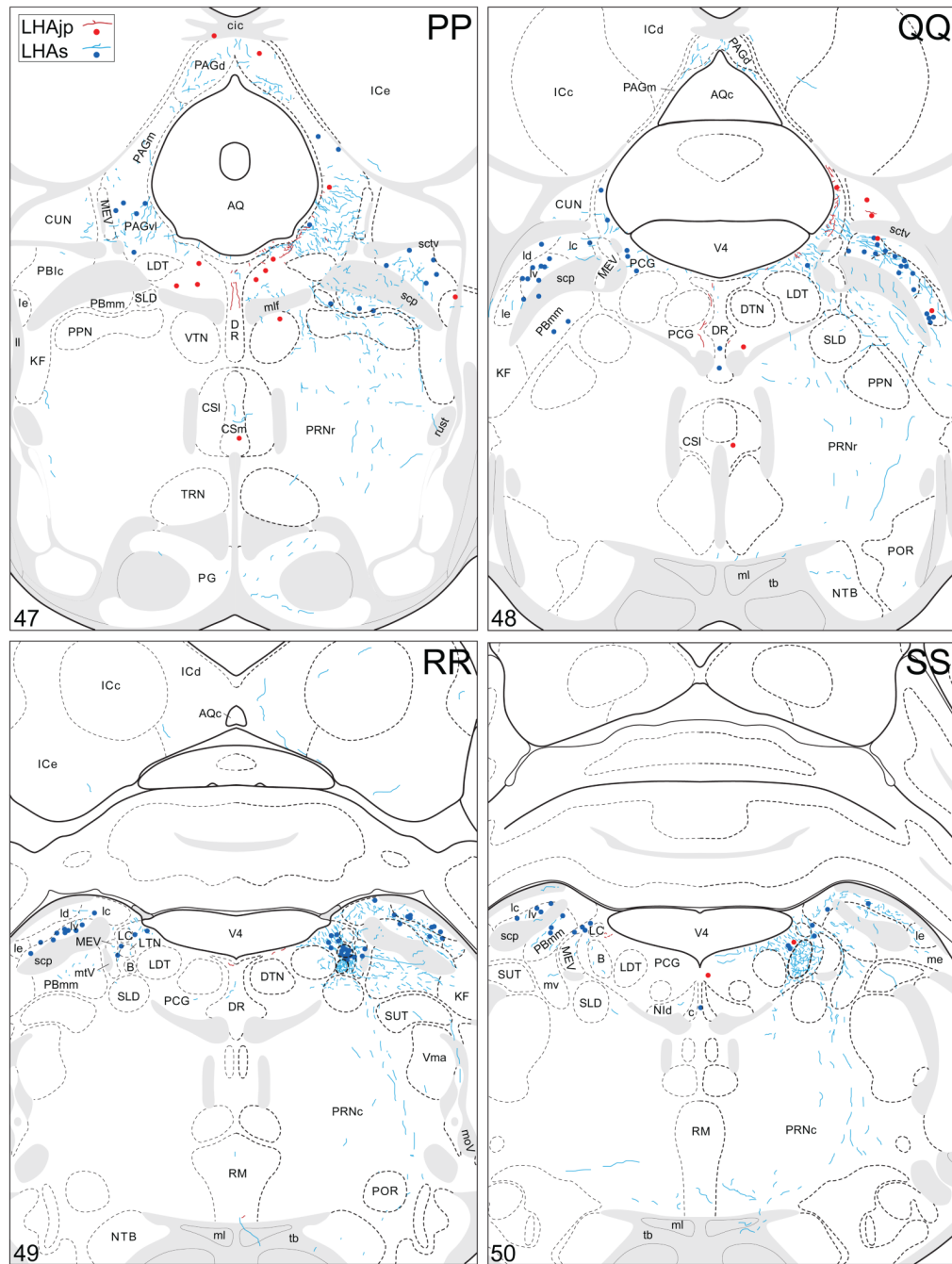


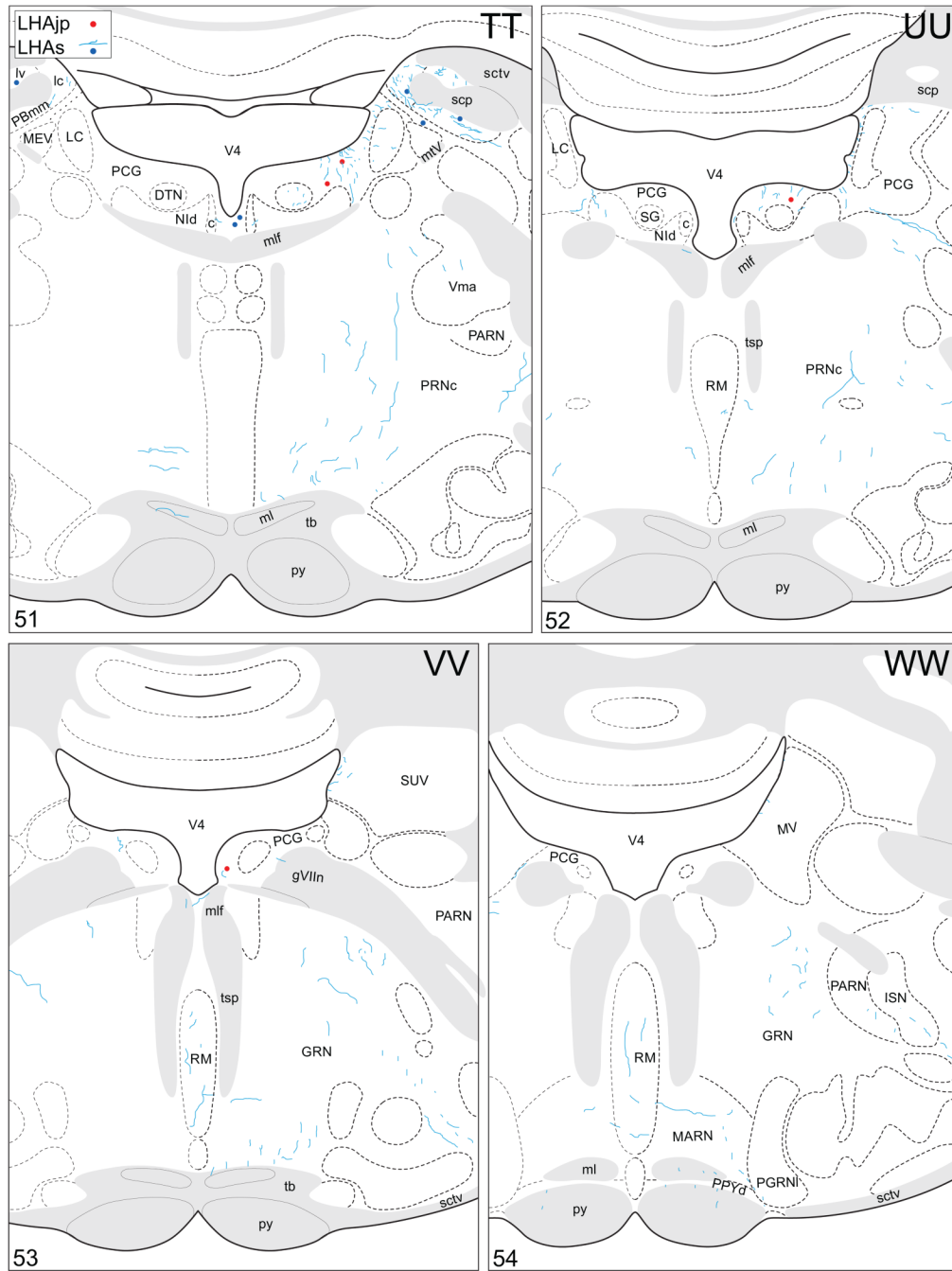


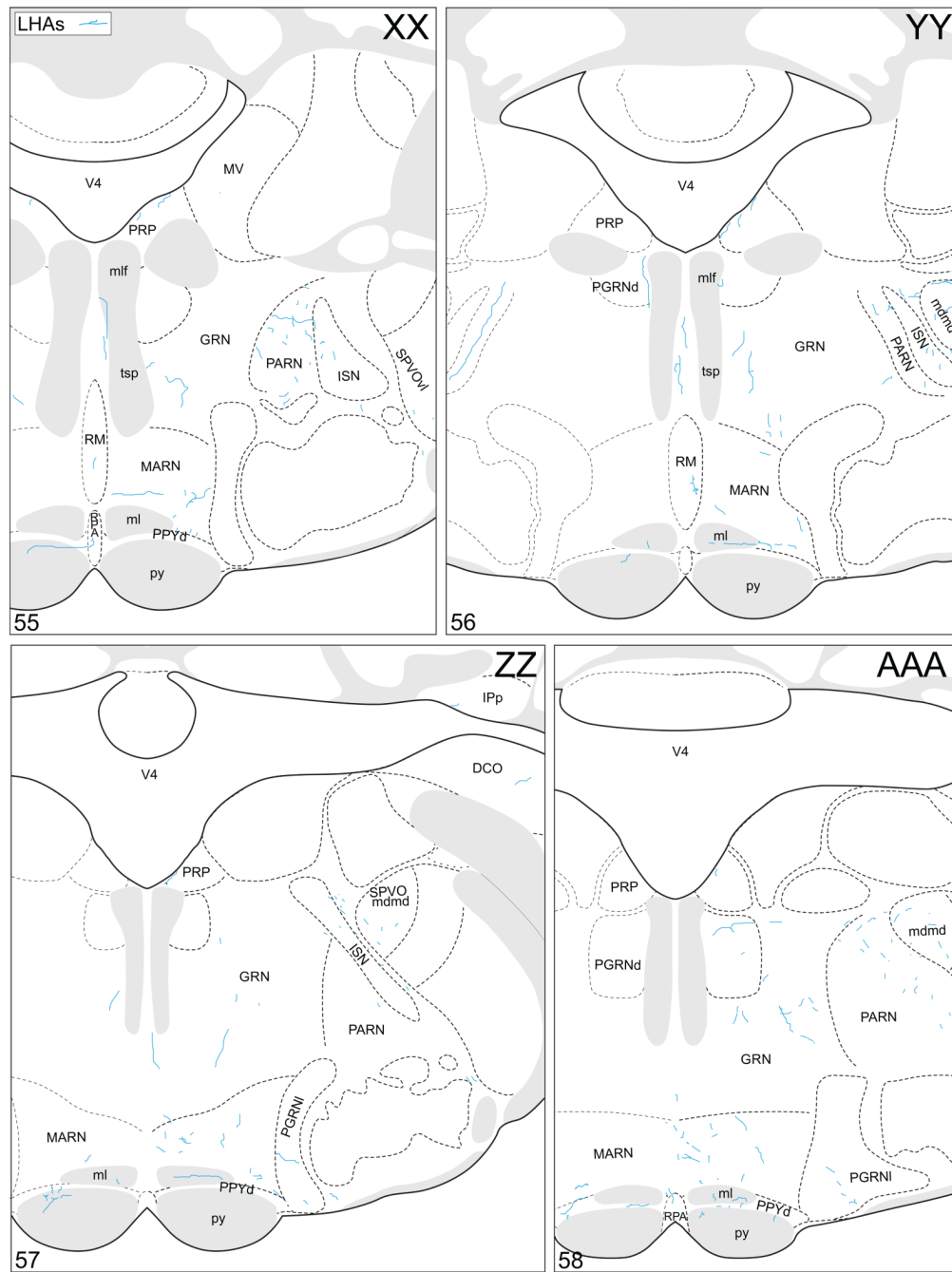


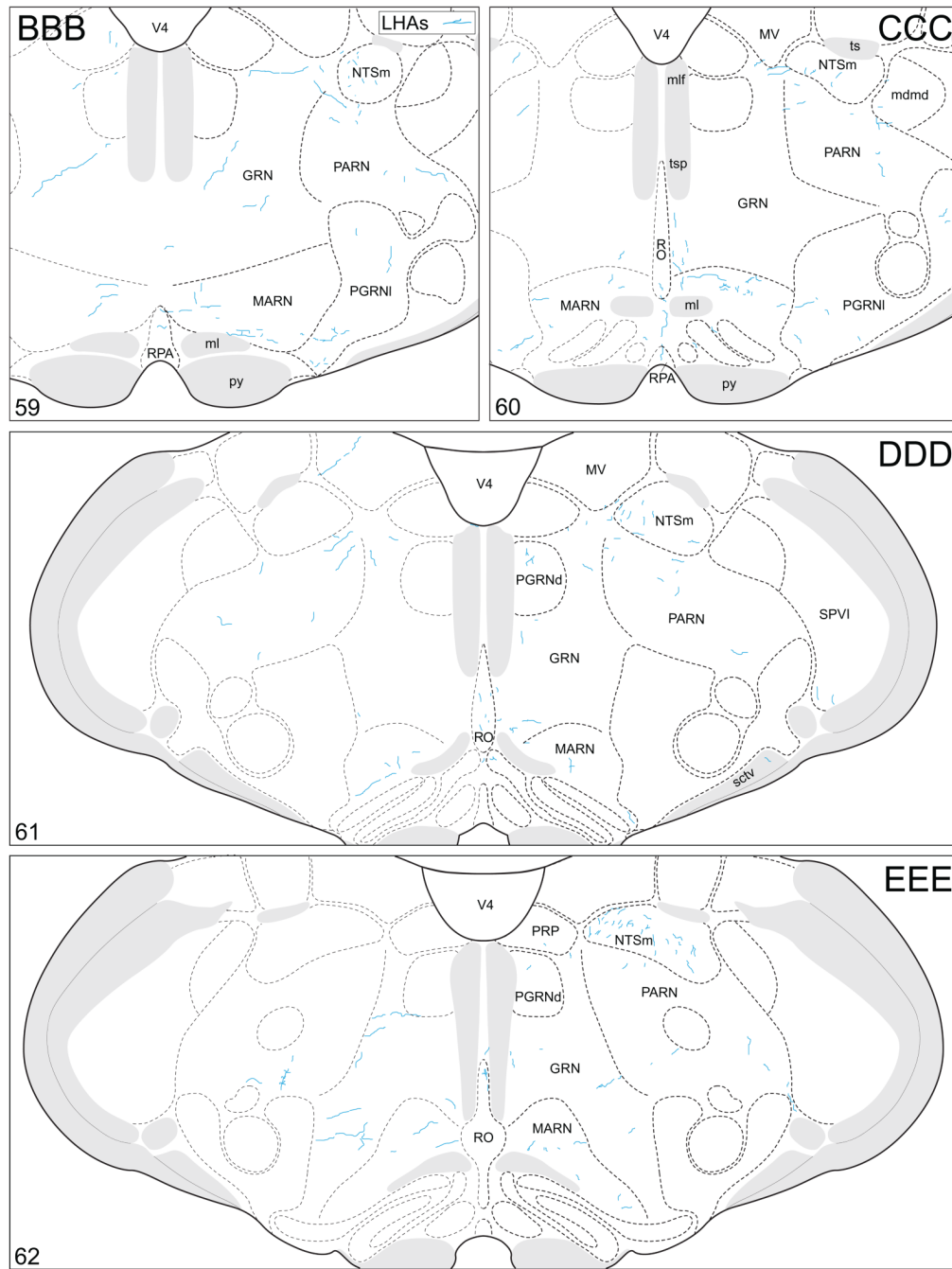












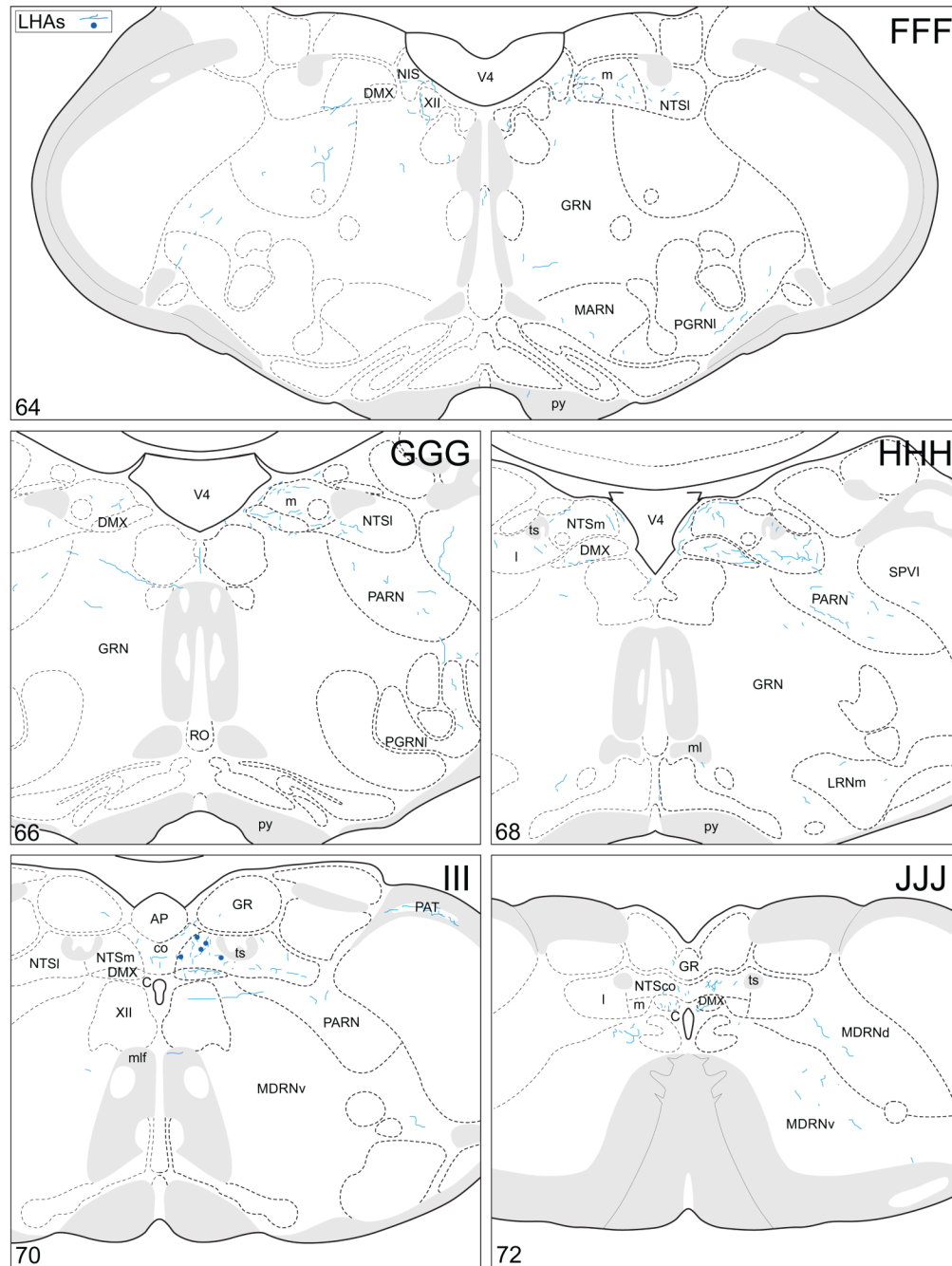


Figure 4.

Projections from and to the LHAjp and the LHAs. The distribution of *Phaseolus vulgaris* leucoagglutinin (PHAL)-labeled axons is represented by the colored lines (red = LHAjp experiment #22; blue = LHAs experiment #11). Cholera toxin B subunit (CTB) retrogradely labeled neurons are represented as colored dots with black outlines (red = LHAjp experiment #22; blue = LHAs experiment #11); one dot = one labeled neuron. The data is plotted onto a series of rat brain reference templates derived from Swanson (2004) and arranged from rostral to caudal (A-JJJ); atlas levels are indicated by a numeral in the lower left corner of each figure. PHAL-filled cells at the site of the injection sites are indicated by colored dots with a white outline (red = LHAjp experiment #22; blue = LHAs experiment #11); the approximate extent

of the visualized CTB injection site is indicated by a colored area with a black outline (red = LHAjp experiment #22; blue = LHAs experiment #11). It should be noted that in any given region where neurons retrogradely labeled from the LHAs and LHAjp are intermingled it is possible that a portion of them may project to both sites.

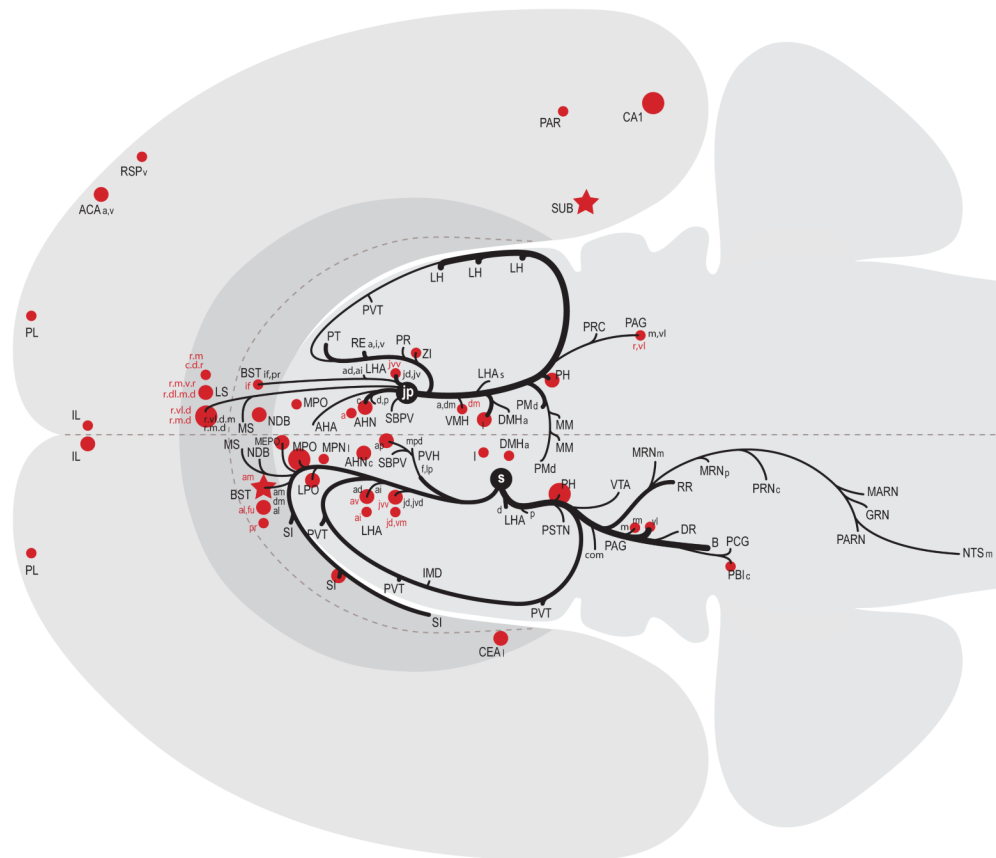
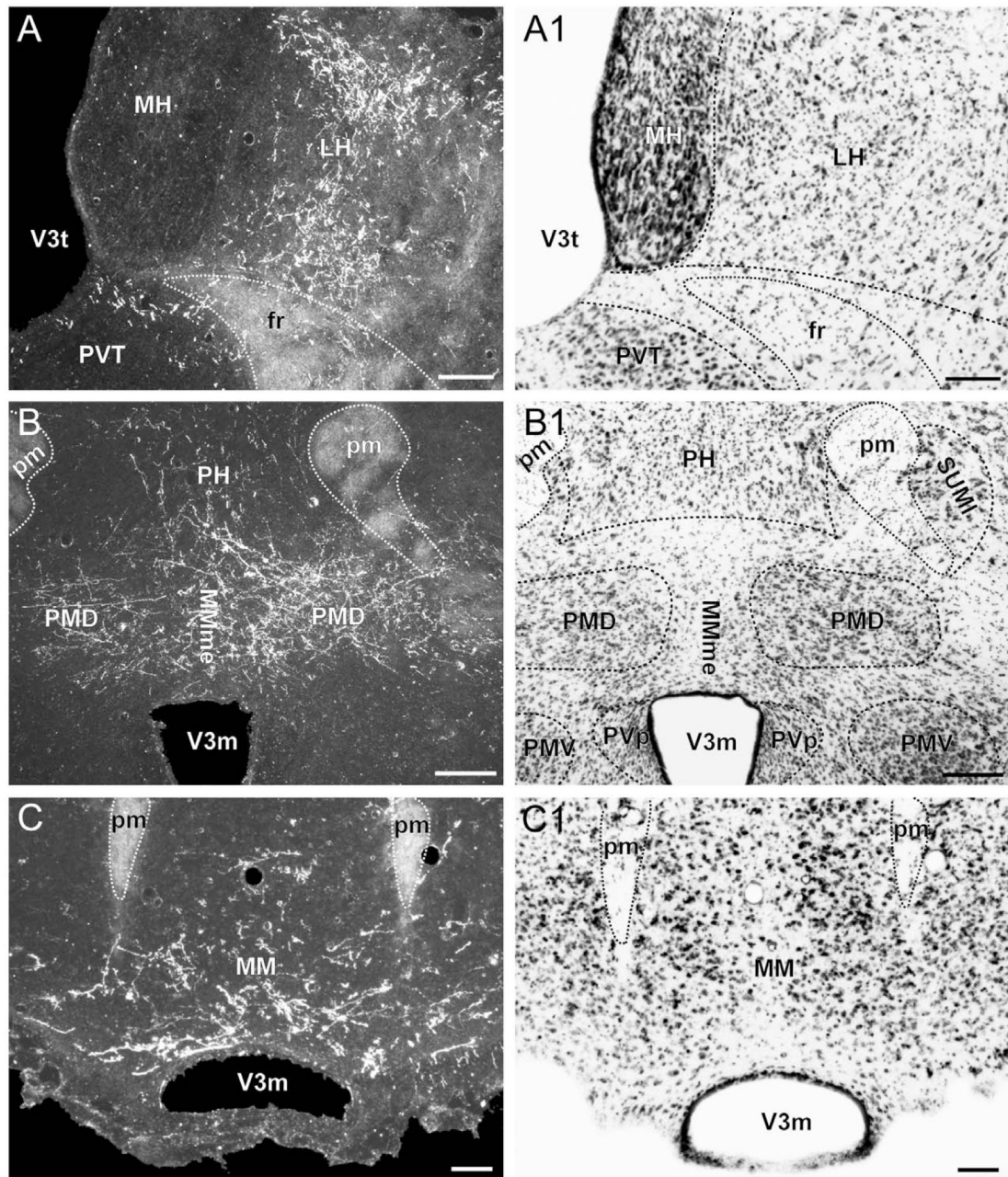


Figure 5. General organization of the principal projections from and to the caudal end of the LHAjp (experiment LHA#22) and midrostrocaudal levels of the LHAs (experiment LHA#11). Anterograde projections are indicated by black lines, retrograde labeling by red discs (or stars). The relative strength of each projection is indicated by the thickness of the black line/diameter of the red disc. Three levels are shown, and for the retrograde labeling a red star is used to indicate the site of most abundant retrograde labeling from the LHAjp or the LHAs. For regions that contained retrogradely labeled cells as well as anterogradely labeled fibers, red type is used to indicate particular subdivisions that were retrogradely labeled; black type indicates regions where anterograde-labeled projecting fibers were present. The flatmap is adapted from Swanson (2004).

LHA#22 (from LHAjp)

**Figure 6.**

(A to C) Representative darkfield photomicrographs showing axons immunoreactive for *Phaseolus vulgaris* leucoagglutinin (PHAL) tracer in several brain regions following a deposit of PHAL within caudal levels of the lateral hypothalamic area juxtaparaventricular region (LHAjp) (experiment LHA#22). (A1 to C1) Brightfield photomicrographs of adjacent thionin stained sections. Note the presence of substantial labeling in: (A) lateral habenula (LH), (B) dorsal preammillary nucleus (PMD), and (C) medial mammillary nucleus (MM). Approximate boundaries of brain regions (dashed lines) and fiber tracts (finer dashed lines) correspond to those delineated in an atlas of the rat brain (Swanson, 2004). Scale bars = 100 μm in (A) and (A1), 200 μm in (B) and (B1), and 50 μm in (C) and (C1).

LHA#22 (from LHAjp)

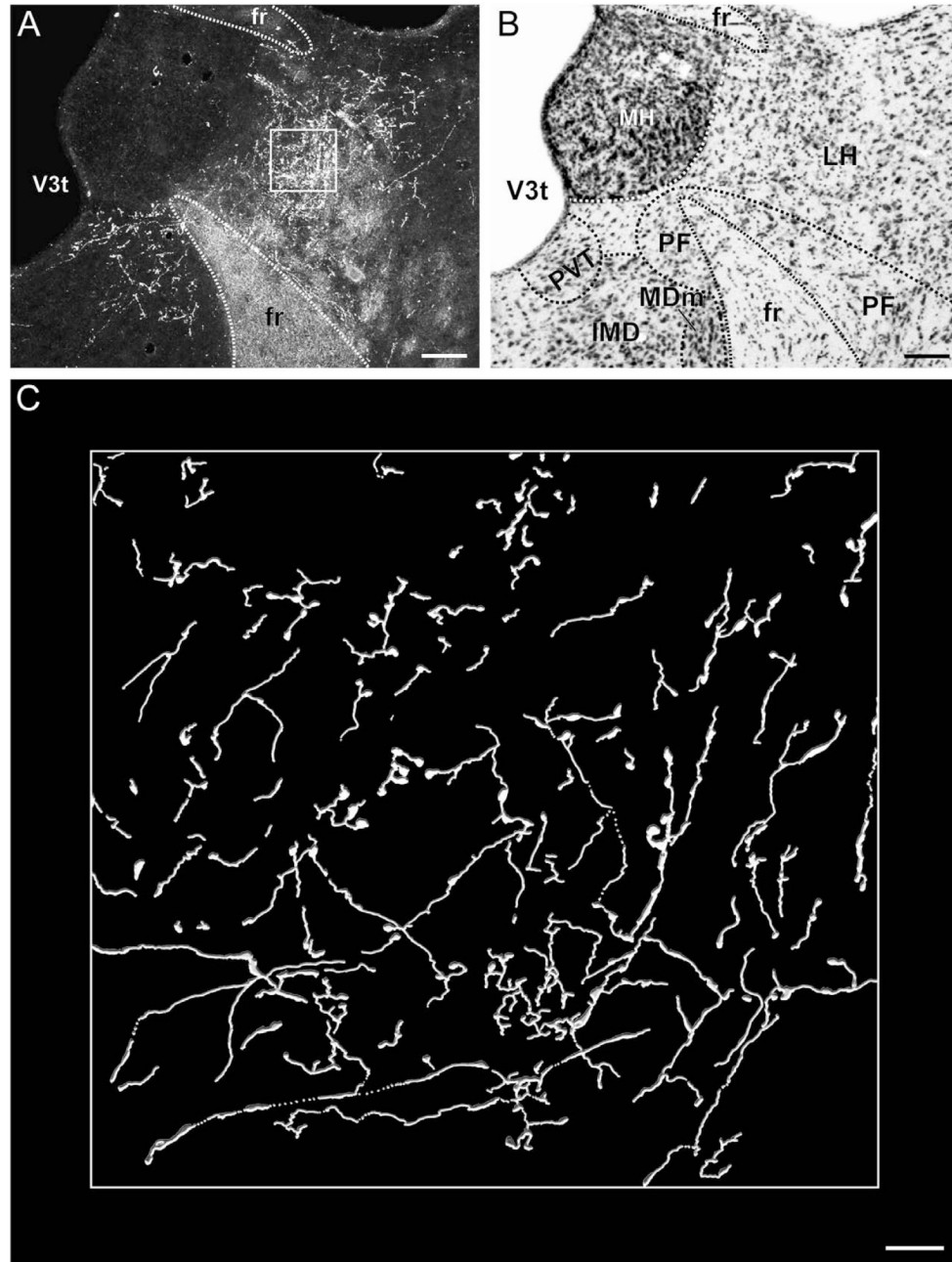


Figure 7. (A) Representative darkfield photomicrograph showing axons immunoreactive for *Phaseolus vulgaris* leucoagglutinin (PHAL) tracer in the region of the lateral habenula (LH) following a deposit of PHAL within caudal levels of the lateral hypothalamic area juxtaparaventricular region (LHAjp) (experiment LHA#22). (B) Brightfield photomicrograph of adjacent thionin stained section. (C) Digitally rendered camera lucida drawing of the area delineated by the white box in (A). Approximate boundaries of brain regions (dashed lines) and fiber tracts (finer dashed lines) correspond to those delineated in an atlas of the rat brain (Swanson, 2004). Scale bars = 100 μm in (A) and (B), 10 μm in (C).

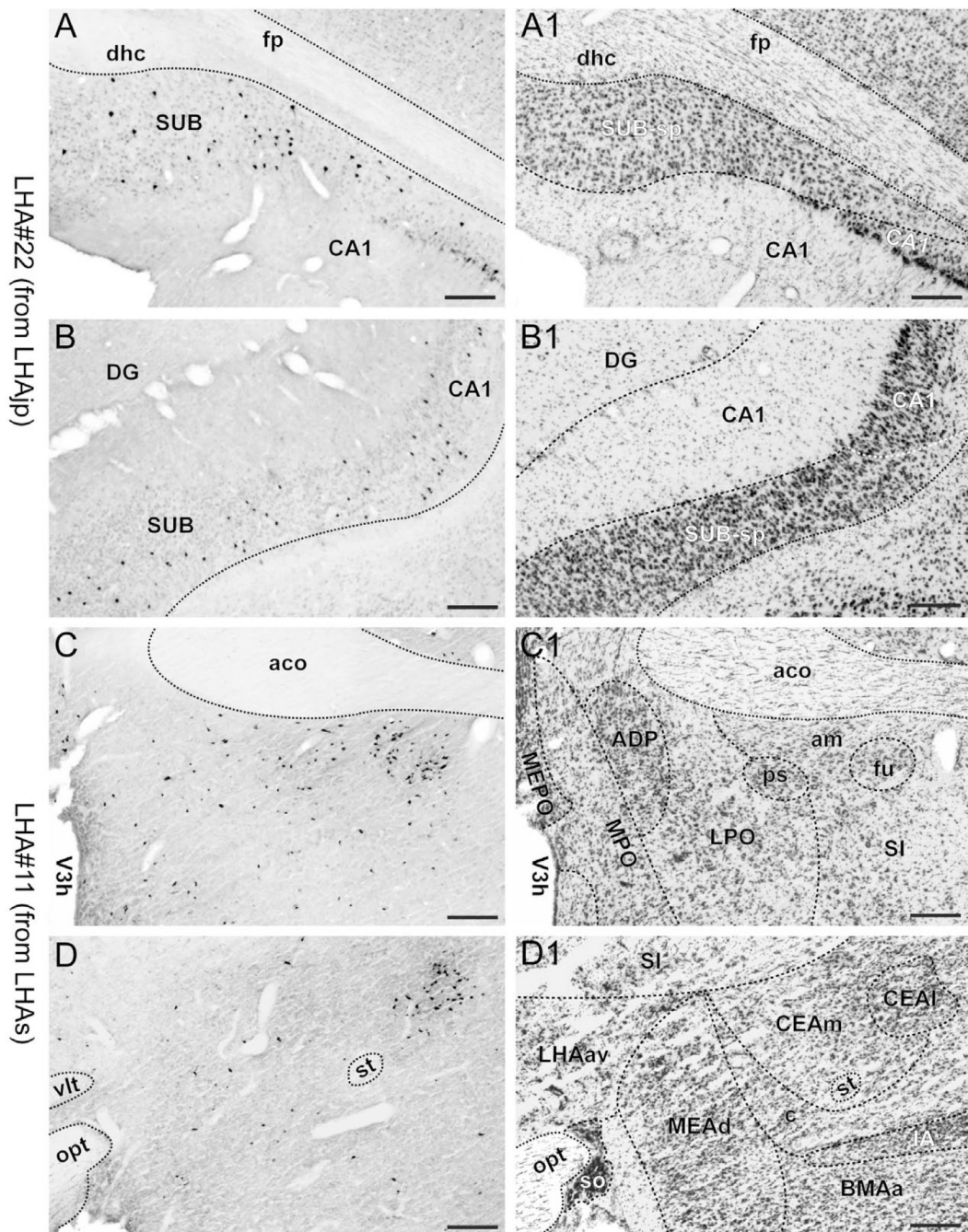


Figure 8.

(A to D) Representative brightfield photomicrographs showing perikarya immunoreactive for cholera toxin B subunit (CTB) tracer in several brain regions. (A1 to D1) Thionin stained sections adjacent to the sections shown in (A to D). Images (A) and (B) show retrograde labeling in the dorsal (A) and ventral (B) halves of the intermediate third of the subiculum resulting from a CTB deposit within caudal levels of the lateral hypothalamic area, juxtaparaventricular region (LHAjp) (experiment LHA#22). Images (C) and (D) show retrograde labeling in the region of the bed nuclei striata of the terminalis anteromedial area (BSTam) and fusiform nucleus (BSTfu) (C), and central amygdalar nucleus lateral part (CEAI) (D) resulting from a CTB deposit within midrostrocaudal levels of the lateral hypothalamic area, supraforminal region

(LHAs) (experiment LHA#11). Approximate boundaries of brain regions (dashed lines) and fiber tracts (finer dashed lines) correspond to those delineated in an atlas of the rat brain (Swanson, 2004). Scale bars = 100 μm .

LHA#11 (from LHAs)

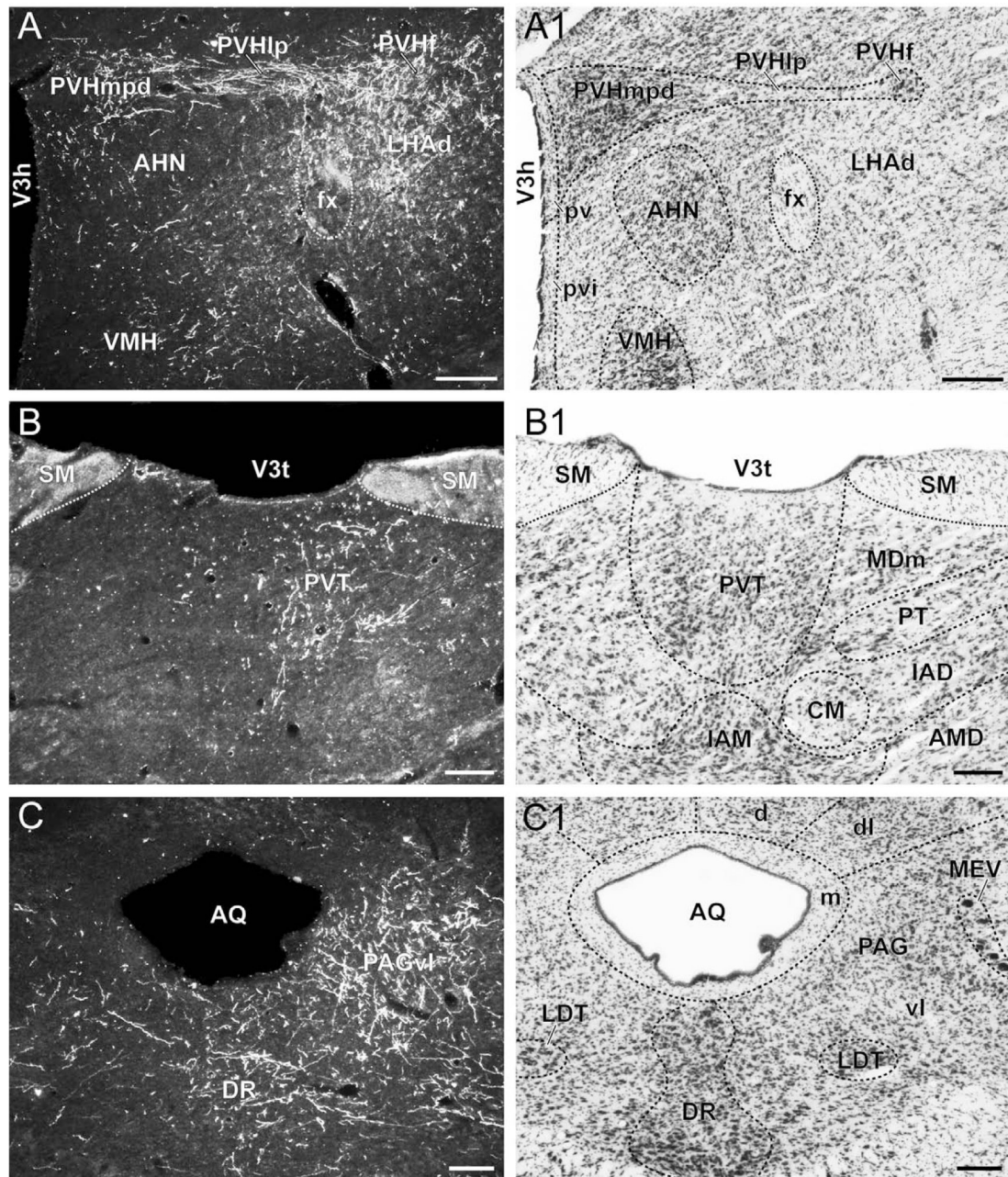
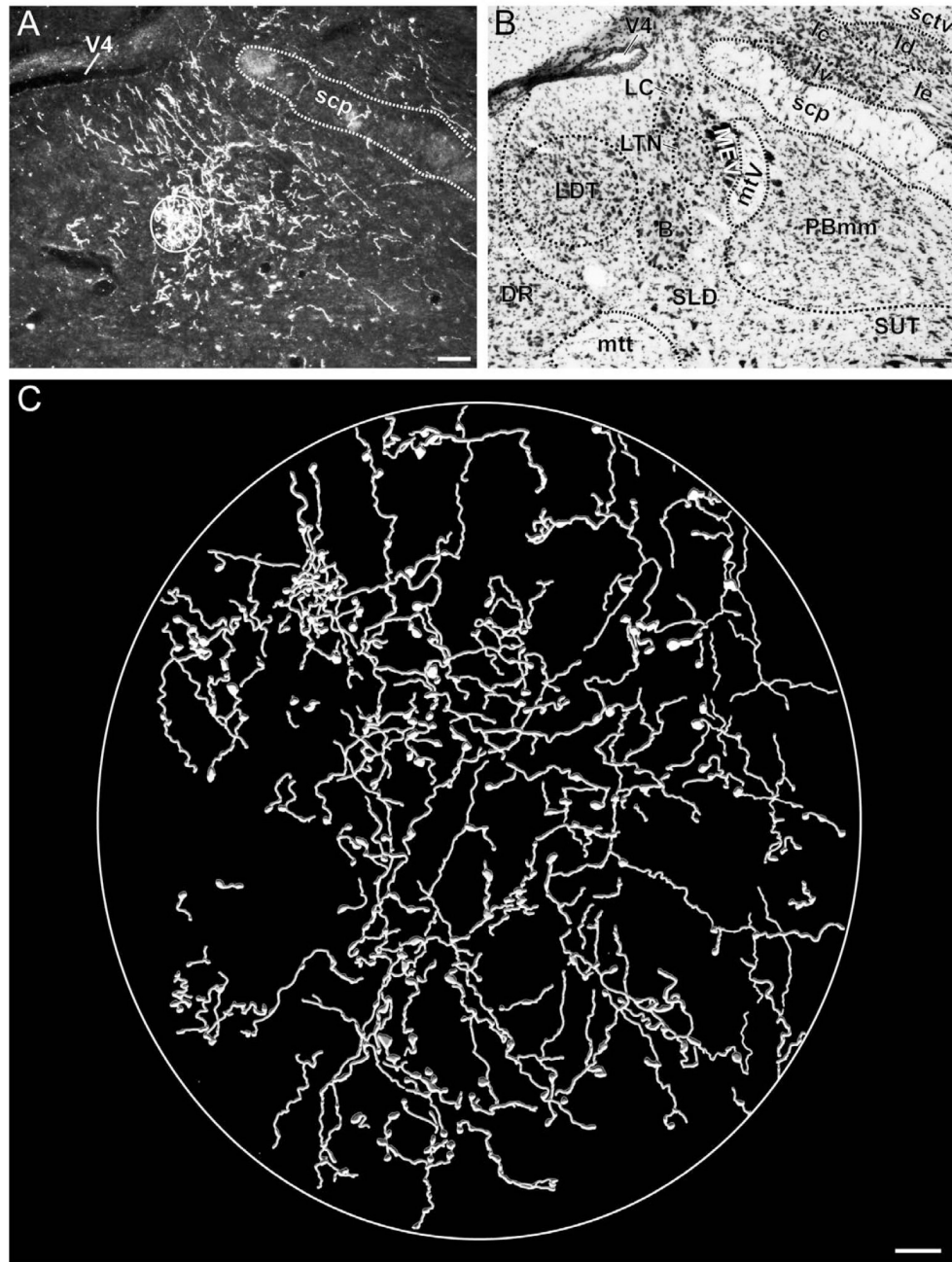


Figure 9.

(A to C) Representative darkfield photomicrographs showing axons immunoreactive for *Phaseolus vulgaris* leucoagglutinin (PHAL) tracer in several brain regions following a deposit of PHAL within midrostrocaudal levels of the lateral hypothalamic area supraforminal region (LHAs) (experiment LHA#11). (A1 to C1) Brightfield photomicrographs of adjacent thionin stained sections. Note the presence of PHAL-labeled fibers in: (A) LHA dorsal part (LHAAd) and paraventricular hypothalamic nucleus fornical (PVHf) and lateral parvicellular (PVHlp) parts, (B) paraventricular thalamic nucleus (PVT), (C) periaqueductal gray ventrolateral division (PAGvl) and dorsal raphé nucleus (DR). Approximate boundaries of brain regions (dashed lines) and fiber tracts (finer dashed lines) correspond to those delineated in an atlas of

the rat brain (Swanson, 2004). Scale bars = 200 μm in (A) and (A1), 100 μm in (B), (B1), (C) and (C1).

LHA#11 (from LHAs)

**Figure 10.**

(A) Representative darkfield photomicrograph showing axons immunoreactive for *Phaseolus vulgaris* leucoagglutinin (PHAL) tracer in the region of Barrington's nucleus (B) following a deposit of PHAL within midrostrocaudal levels of the lateral hypothalamic area supraforical region (LHAs) (experiment LHA#11, see Fig. 2). (B) Brightfield photomicrograph of adjacent thionin stained section. (C) Digitally rendered camera lucida drawing of the area delineated by the white oval in (A). Approximate boundaries of brain regions (dashed lines) and fiber tracts (finer dashed lines) correspond to those delineated in an atlas of the rat brain (Swanson, 2004). Scale bars = 100 μ m in (A) and (B), 10 μ m in (C).

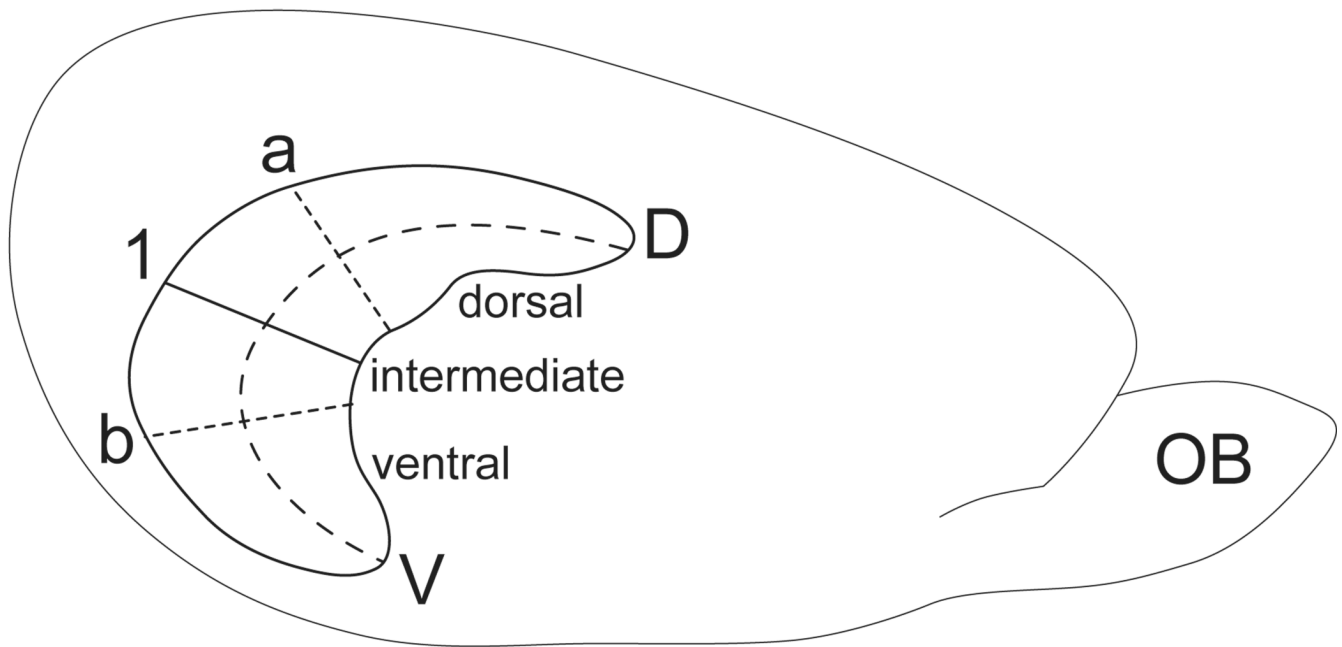


Figure 11.

A lateral view of Ammon's horn and the subiculum projected on the right cerebral hemisphere of the rat. The curved longitudinal axis of these parts of the hippocampal formation is indicated by a dashed line, with D at the dorsal or septal end and V at the ventral or temporal end. Dashed lines a and b are transverse to the longitudinal axis and divide qualitatively Ammon's horn and the subiculum into approximate dorsal, intermediate, and ventral thirds for descriptive purposes. The transverse solid line 1 divides qualitatively Ammon's horn and the subiculum into dorsal and ventral halves for descriptive purposes. OB, olfactory bulb (rostral end of cerebral hemisphere). Adapted from Swanson and Cowan (1977). It is noteworthy that the site of the most abundant retrograde labeling in this study identified a projection to the LHA_{jp} from the ventral half (predominantly) of the intermediate third of the subiculum.

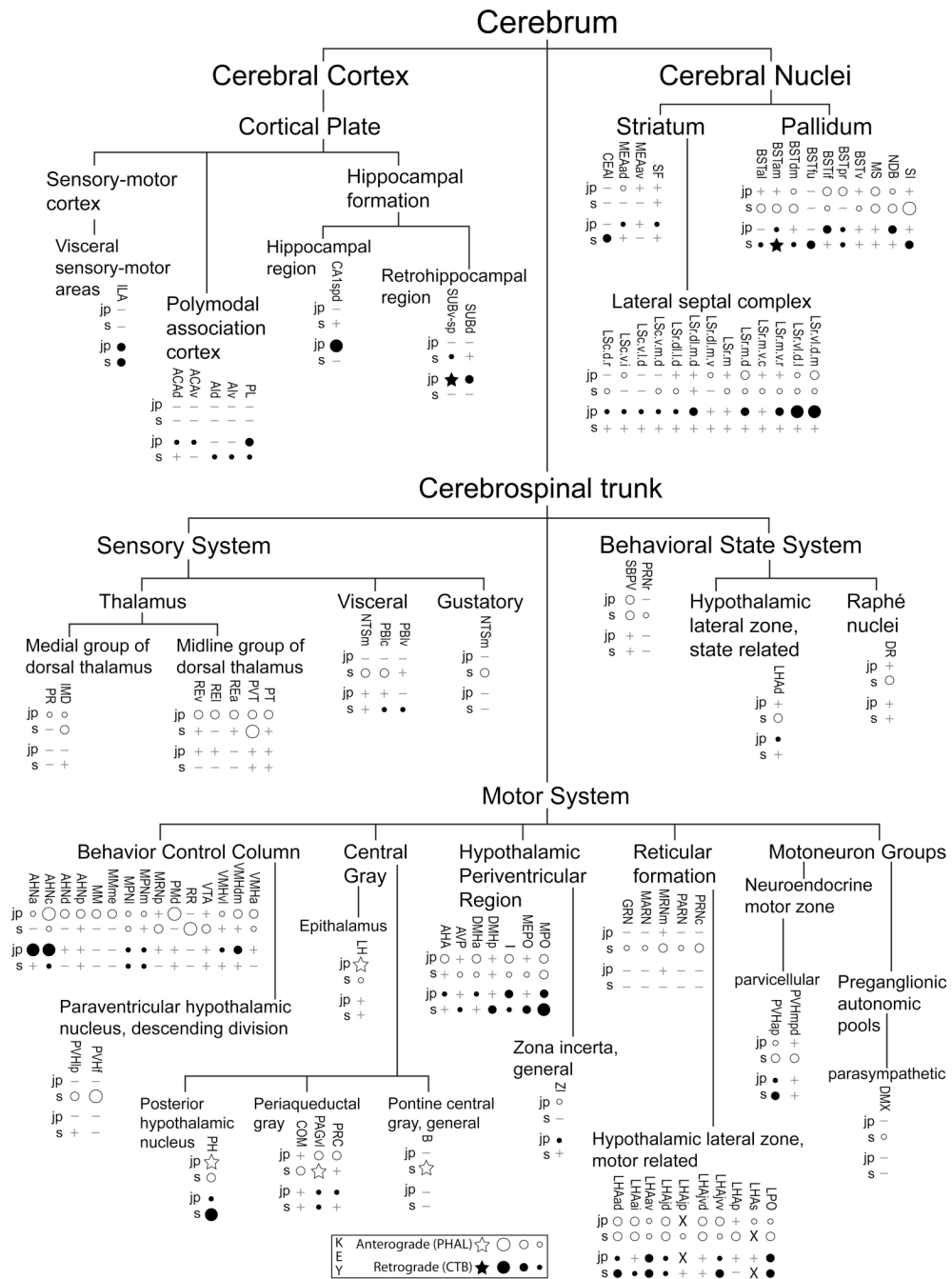


Figure 12. All regions of approximately moderate or higher anterograde (white-filled dots) and retrograde (black dots) labeling resulting from deposits of *Phaseolus vulgaris* leucoagglutinin (PHAL) and cholera toxin B subunit (CTB) within the lateral hypothalamic area juxtaparaventricular region (LHA_{jp}; combined analysis of caudal LHA_{jp} experiment LHA#22 and rostral LHA_{jp} experiment LHA#62) or LHA supraforaminal region (LHAs; midrostrocaudal level, experiment LHA#11) represented within a cerebral hierarchy. Regions in which the overall level of labeling amounted to approximately moderate (or above) are represented even if the constituent subregions contained a lower level of labeling (e.g., the MPN). For a more detailed comparison of the connections of caudal and rostral levels of the LHA_{jp} (for experiment LHA#22 and

LHA#62, respectively) and midrostrocaudal levels of the LHAs (for experiment LHA#11) see Fig. 4 and Table 1. The diameter of the round symbols corresponds to the relative abundance of labeling, 3 levels are represented: low, moderate and high. Stars indicate sites of highest abundance of labeling; “+” signs indicate the presence of labeling at a very low level; “-” signs indicate absence of labeling. “X” indicates the site of tracer injections.

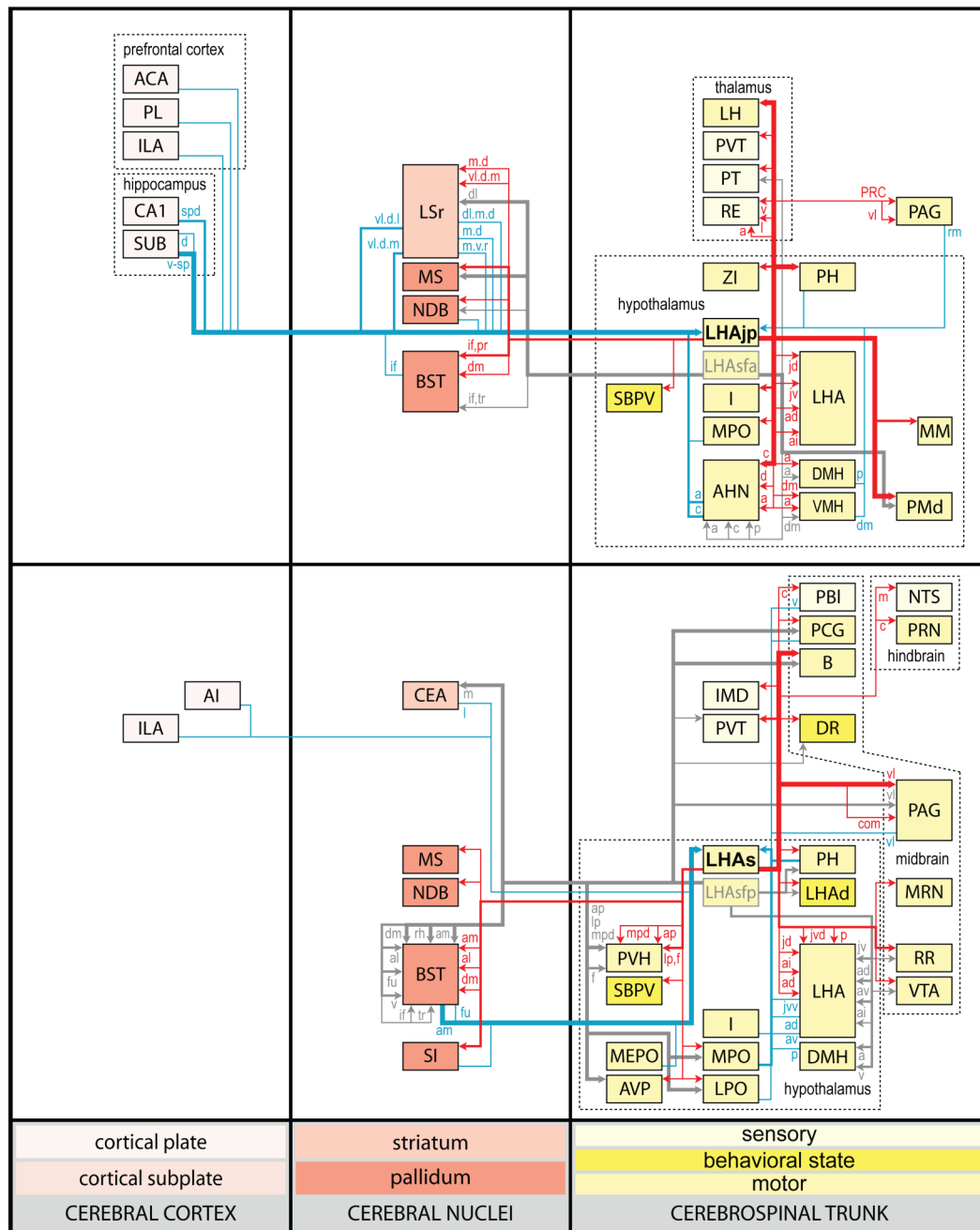


Figure 13. Summary diagram illustrating the major axonal inputs and outputs of the LHAjp (combined experiment LHA #22 and LHA #62) and midrostrocaudal levels of the LHAs (experiment LHA #11) represented within a cerebral hierarchy (see Swanson, 2004). Red lines indicate outputs and blue lines indicate inputs; directionality is also indicated by arrowheads. The thickness of each line corresponds to the relative magnitude of each projection. Small colored lettering indicates subdivisions of larger regions that are specifically targeted or that specifically provide an indicated input. For comparison, also shown (gray lines with gray arrow heads and gray lettering) are the previously published outputs of the LHA subformal region (LHAsf) (Goto et al., 2005); note the similarity between the outputs or projections of the posterior zone of the

LHAsf (LHAsfp) and midrostrocaudal levels of the LHAs, and the anterior zone of the LHAsf (LHAsfa) (Goto et al., 2005) and the LHAjp.

Table 1

Relative abundance of retrograde and anterograde labeling resulting from three separate experiments of combined cholera toxin B subunit (CTB) and *Phaseolus vulgaris* leucoagglutinin (PHAL) injections within the lateral hypothalamic area (LHA) of male rats; two of these were centered within the LHA juxtaparaventricular region (LHAjp, caudal = experiment LHA#22; rostral = experiment LHA#62), the other (experiment LHA#11) was centered within midrostrocaudal levels of the LHA supraformical region (LHAs) -- listed as "central LHAs" in column title for brevity. The relative abundance of labeling (retrogradely -- CTB -- labeled neurons or anterogradely -- PHAL -- labeled fibers) is represented by the following semi-quantitative grading schema: -- = absence of labeling; + = very low; ++ = low; +++ = moderate; ++++ = high; +++++* = very high; +++++ = region of highest amount of retrograde labeling for each experiment. Regions that contained PHAL-labeled axons with the appearance of fibers of passage, or regions that contained only a single CTB-labeled neuron, or PHAL-labeled fiber, are not included in the table (for further details see Fig. 4). The brain region hierarchy follows Swanson (2004).

CELL GROUP OR REGION	ANTEROGRADE (PHAL)			RETROGRADE (CTB)		
	rostral LHAjp (LHA#62)	caudal LHAjp (LHA#22)	central LHAs (LHA#11)	rostral LHAjp (LHA#62)	caudal LHAjp (LHA#22)	central LHAs (LHA#11)
1. Cerebrum						
1.1. Cerebral Cortex						
1.1.1. Cortical Plate						
Sensory-motor cortex						
Somatomotor areas						
secondary somatomotor area (MOs)	-	-	-	-	+	-
Visceral sensory-motor areas						
infralimbic area (ILA)	-	-	-	++++	++	+++
Olfactory areas						
anterior olfactory nucleus						
posteroventral part (AONpv)	-	-	-	+	-	-
tenia tecta						
dorsal part (TTd)	-	-	-	+++	++	++
ventral part (TTv)	-	-	-	+	-	-
piriform area (PIR)	-	-	-	+	+	-
postpiriform transition area (TR)	-	-	-	-	-	+
nucleus of the lateral olfactory tract (NLOT)	-	-	-	+	-	-
cortical amygdalar area						
anterior part (COAa)	-	-	-	++	+	+
posterior part						

	ANTEROGRADE (PHAL)			RETROGRADE (CTB)		
	rostral LHA#62 (LHA#62)	caudal LHA#22 (LHA#22)	central LHAs (LHA#11)	rostral LHA#62 (LHA#62)	caudal LHA#22 (LHA#22)	central LHAs (LHA#11)
lateral zone (COApl)	-	+	-	+	-	-
medial zone (COApm)	-	-	-	+	-	-
Polymodal association cortex						
anterior cingulate area						
dorsal part (ACA _d)	-	-	-	++	++	+
ventral part (ACA _v)	-	-	-	+	++	+
prelimbic area (PL)	-	-	-	++++	++	++
orbital area						
lateral part (ORB _l)	-	-	-	-	-	+
medial part (ORB _m)	-	-	-	-	+	-
ventral part (ORB _v)	-	-	-	+	-	+
ventrolateral part (ORB _{vl})	-	-	-	-	+	+
agranular insular area						
dorsal part (A _{ld})	-	-	-	-	-	+++
ventral part (A _{lv})	-	-	-	-	-	+
posterior part (A _{lp})	-	-	-	-	-	++
retrosplenial area						
ventral part (RSP _v)	-	-	-	-	++	-
hippocampal formation						
retrohippocampal region						
entorhinal area						
lateral part (ENT _l)	-	-	-	+	-	-
medial part, dorsal zone (ENT _m)	-	-	-	++	+	-
presubiculum (PRE)	-	-	-	+	+	-
parasubiculum (PAR)	-	-	-	-	++	-
subiculum						
pyramidal layer (SUB-sp)	-	-	-	++++*	++++*	++
hippocampal region						
Ammon's horn						
field CA1						

	ANTEROGRADE (PHAL)			RETROGRADE (CTB)		
	rostral LHA#62 (LHA#62)	caudal LHA#22 (LHA#22)	central LHAs (LHA#11)	rostral LHA#62 (LHA#62)	caudal LHA#22 (LHA#22)	central LHAs (LHA#11)
pyramidal layer						
deep (CA1spd)	-	-	-	+++++*	++++	+
superficial (CA1sps)	-	-	-	++++	++	-
stratum oriens (CA1so)	-	-	-	+	-	-
field CA2	-	-	-	+	-	-
pyramidal layer (CA2sp)						
field CA3						
pyramidal layer (CA3sp)	-	-	-	++	-	-
stratum oriens (CA3so)	-	-	-	+	+	-
1.1.2. Cortical Subplate						
Clastrum (CLA)	-	-	-	+	-	++
Endopiriform nucleus						
dorsal part (EPd)	-	-	-	+	-	+
Basolateral amygdalar nucleus						
posterior part (BLAp)	-	-	-	+	+	+
anterior part (BMAa)	-	-	-	+	+	+
Posterior amygdalar nucleus (PA)	-	-	-	+	-	-
1.2. Cerebral Nuclei						
1.2.1. Striatum						
Nucleus accumbens (ACB) ("shell" region)	-	-	+	+	+	+
Lateral septal complex						
lateral septal nucleus						
caudal (caudodorsal) part						
dorsal zone						
rostral region (LSc.d.r)	-	-	++	++	++	++
dorsal region (LSc.d.d)	-	-	-	-	+	-
lateral region (LSc.d.l)	-	-	-	+	-	-
ventral region (LSc.d.v)	-	-	-	+	+	+
ventral zone						
medial region						

	ANTEROGRADE (PHAL)			RETROGRADE (CTB)		
	rostral LHA#62 (LHA#62)	caudal LHA#22 (LHA#22)	central LHA#11 (LHA#11)	rostral LHA#62 (LHA#62)	caudal LHA#22 (LHA#22)	central LHA#11 (LHA#11)
dorsal domain (LSc.v.m.d)	-	-	+	++	+	+
ventral domain (LSc.v.m.v)	-	+	+	+	-	+
intermediate region (LSc.v.i)	-	+	-	+++	++	+
lateral region						
dorsal domain (LSc.v.l.d)	-	-	-	++	-	+
ventral domain (LSc.v.l.v)	-	+	+	++	+	+
rostral (rostroventral) part						
medial zone						
dorsal region (LSr.m.d)	+++	+++	+	+++	+++	+
ventral region						
rostral domain (LSr.m.v.r)	-	+	+	+++	+++	+
caudal domain (LSr.m.v.c)	-	+	+	++	++	+
ventrolateral zone						
dorsal region (LSr.vl.d)						
medial domain (LSr.vl.d.m)	+++	+++	+	++++	+++	+
lateral domain (LSr.vl.d.l)	++	+	+	++++	+++	+
ventral region (LSr.vl.v)	-	+	+	++	-	+
dorsolateral zone						
medial region						
dorsal domain (LSr.dl.m.d)	-	+	+	+++	+++	+
ventral domain (LSr.dl.m.v)	+++	-	-	++	-	+
lateral region						
dorsal domain (LSr.dl.l.d)	-	+	+	+++	++	++
ventral domain (LSr.dl.l.v)	-	+	+	-	+	-
ventral part (LSv)	+	+	-	+	-	-
septofimbrial nucleus (SF)	+	+	+	+++	++	+
septohippocampal nucleus (SH)	-	-	+	+	-	++
Anterior amygdalar area (AAA)	-	-	-	-	-	+
Central amygdalar nucleus						
medial part (CEAm)	-	-	+	-	+	+

	ANTEROGRADE (PHAL)			RETROGRADE (CTB)		
	rostral LHA#62 (LHA#62)	caudal LHA#22 (LHA#22)	central LHA#11 (LHA#11)	rostral LHA#62 (LHA#62)	caudal LHA#22 (LHA#22)	central LHA#11 (LHA#11)
lateral part (CEAl)	-	-	-	-	-	+++
capsular part (CEAc)	-	-	+	-	+	+
Medial amygdalar nucleus						
anterodorsal part (MEAad)	++	+	-	++	++	++
anteroventral part (MEAav)	-	+	-	-	+	-
posterodorsal part	-	-	-	+	+	+
sublayer a (MEApd-a)	-	-	-	+	+	+
sublayer b (MEApd-b)	-	-	+	+	-	-
sublayer c (MEApd-c)	-	+	-	+	-	-
posteroventral part (MEApv)	-	-	-	+	+	-
1.2.2. Pallidum						
Substantia innominata (SI)	-	-	+++	+	-	+++
Medial septal complex						
Medial septal nucleus (MS)	+++	+++	+++	++	+	+
Diagonal band nucleus (NDB)	++	+	+++	+++	+++	+
Triangular nucleus septum (TRS)	-	+	+	++	-	+
Bed nuclei of the stria terminalis						
Anterior division						
anterolateral area (BSTal)	-	+	+++	+	-	+++
anteromedial area (BSTam)	-	++	+++	+++	+	++++*
dorsomedial nucleus (BSTdm)	++	+	+++	+	+	++
fusiform nucleus (BSTfu)	-	-	-	-	-	+++
ventral nucleus (BSTv)	-	+	++	++	+	+
magnocellular nucleus (BSTmg)	-	-	++	+	-	+
Posterior division						
principal nucleus (BSTpr)	+++	++	-	+++	++	++
interfascicular nucleus (BSTif)	+++	++	+	+++	++	++
transverse nucleus (BSTtr)	-	-	-	+	-	+
dorsal nucleus (BSTd)	-	-	-	-	+	-
2. Cerebellum						
Cerebellum	-	-	-	-	-	-

	ANTEROGRADE (PHAL)			RETROGRADE (CTB)		
	rostral LHA#62 (LHA#62)	caudal LHA#22 (LHA#22)	central LHAs (LHA#11)	rostral LHA#62 (LHA#62)	caudal LHA#22 (LHA#22)	central LHAs (LHA#11)
3. Cerebrospinal Trunk						
3.1 Sensory System						
3.1.1. Thalamus						
Sensory-motor cortex related						
Ventral group of the dorsal thalamus						
subparafascicular nucleus thalamus						
magnocellular part (SPFm)	-	+	-	+	-	-
parvocellular part						
lateral division (SPFpl)	-	-	-	+	-	-
Polymodal association cortex related						
Lateral group of the dorsal thalamus						
lateral posterior nucleus thalamus (LP)	-	+	-	-	-	-
Anterior group of the dorsal thalamus						
anteroventral nucleus thalamus (AV)	-	++	-	+	+	-
anteromedial nucleus thalamus						
dorsal part (AMd)	-	+	-	-	-	-
ventral part (AMv)	-	++	-	-	-	-
anterodorsal nucleus thalamus (AD)	-	+	-	-	-	-
interanteromedial nucleus thalamus (IAM)	-	+	-	-	-	-
interanterodorsal nucleus thalamus (IAD)	-	++	-	-	-	-
lateral dorsal nucleus thalamus (LD)	-	+	-	-	-	-
Medial group of the dorsal thalamus						
mediodorsal nucleus thalamus						
medial part (MDm)	-	++	+	-	-	-
lateral part (MDl)	-	+	-	-	-	-
intermediodorsal nucleus thalamus (IMD)	-	-	++	-	-	+
perireuniens nucleus (PR)	-	++	-	-	-	-
Midline group of the dorsal thalamus						
paraventricular nucleus thalamus (PVT)	+++	+++	+++	+++	++	++
paratenial nucleus (PT)	++	+++	++	+	+	-

	ANTEROGRADE (PHAL)			RETROGRADE (CTB)		
	rostral LHA#62 (LHA#62)	caudal LHA#22 (LHA#22)	central LHAs (LHA#11)	rostral LHA#62 (LHA#62)	caudal LHA#22 (LHA#22)	central LHAs (LHA#11)
nucleus reuniens						
rostral division						
anterior part (REa)	++	++++	+	-	+	-
dorsal part (REd)	-	++	-	+	+	-
ventral part (REv)	-	++++	-	+	-	-
lateral part (REl)	++	++++	-	+	-	-
median part (REm)	-	+	+	-	-	-
caudal division						
caudal part (REc)	-	+	+	+	+	-
dorsal part (REcd)	-	+	-	-	-	-
median part (REcm)	-	+	-	-	-	-
Intralaminar group of the dorsal thalamus						
rhomboid nucleus (RH)	-	+	+	-	-	-
central medial nucleus thalamus (CM)	+	++	++	-	+	-
central lateral nucleus thalamus (CL)	-	+	+	-	-	-
parafascicular nucleus (PF)	-	-	-	+	-	-
Reticular nucleus thalamus (RT)	-	+	+	+	-	-
3.1.2. Visual	-	-	-	-	-	-
3.1.3. Somatosensory	-	-	-	-	-	-
3.1.4. Auditory	-	-	-	-	-	-
3.1.5. Gustatory	-	-	-	-	-	-
Nucleus of the solitary tract, medial part, rostral zone (NTSmr)	-	-	+++	-	-	-
3.1.6. Visceral						
Nucleus of the solitary tract						
commissural part (NTSco)	-	-	+	-	-	-
lateral part (NTSl)	-	-	+	-	-	-
medial part, caudal zone (NTSme)	-	-	+++	-	+	+
Parabrachial nucleus						
lateral division						

	ANTEROGRADE (PHAL)			RETROGRADE (CTB)		
	rostral LHA#62 (LHA#62)	caudal LHA#22 (LHA#22)	central LHA#11 (LHA#11)	rostral LHA#62 (LHA#62)	caudal LHA#22 (LHA#22)	central LHA#11 (LHA#11)
central lateral part (PBle)	-	-	+++	+	+	++
dorsal lateral part (PBld)	-	-	-	-	-	+
external lateral part (PBle)	-	-	+	-	-	+
ventral part (PBly)	-	-	+	-	-	+++
medial division						
medial medial part (PBmm)	-	-	++	-	-	+
3.1.7. Humerosensory						
Subformal organ (SFO)	-	-	-	-	-	++
3.2. Behavioral state system						
Suprachiasmatic nucleus (SCH)	-	-	-	+	-	-
Subparaventricular zone (SBPV)	+++	+++	+++	++	-	+
Hypothalamic lateral zone, dorsal region (LHAD)	-	++	+++	+	++	++
Supramammillary nucleus						
medial part (SUMm)	-	+	+	+	-	-
lateral part (SUMl)	-	++	+	+	+	+
Pedunculopontine nucleus (PPN)	-	-	++	+	-	+
Pontine reticular nucleus, rostral part (PRNr)	-	-	++	-	-	-
Raphé nuclei						
interfascicular nucleus raphé (IF)	-	+	-	-	-	-
interpeduncular nucleus						
lateral subnucleus						
intermediate part (IPNli)	-	-	+	-	-	-
rostral linear nucleus raphé (RL)	-	+	+	-	-	-
central linear nucleus raphé (CLl)	-	-	+	-	-	+
superior central nucleus raphé						
lateral part (CSI)	-	-	-	-	+	-
dorsal nucleus raphé (DR)	-	++	+++	+	-	+
nucleus incertus						
diffuse part (Nld)	-	-	-	+	-	-

	ANTEROGRADE (PHAL)			RETROGRADE (CTB)		
	rostral LHA#62 (LHA#62)	caudal LHA#22 (LHA#22)	central LHA#11 (LHA#11)	rostral LHA#62 (LHA#62)	caudal LHA#22 (LHA#22)	central LHA#11 (LHA#11)
nucleus raphé magnus (RM)	-	-	+	-	-	-
Locus caeruleus (LC)	-	-	+	-	-	-
3.3. Motor System						
3.3.1. Behavior Control Column						
Medial preoptic nucleus						
lateral part (MPNI)	++	+	-	++	++	++
medial part (MPNm)	-	+	+	++	+	++
central part (MPNc)	-	-	-	+	-	+
Anterior hypothalamic nucleus						
anterior part (AHNa)	++	+	-	++++	+++	+
central part (AHNc)	++++	++++	+	++++*	++++	+++
posterior part (AHNp)	+++	+++	+	++	+	+
dorsal part (AHNd)	++	++	-	+	-	-
Paraventricular nucleus hypothalamus, descending division						
dorsal parvocellular part (PVHdp)	-	+	-	-	-	-
lateral parvocellular part (PVHlp)	-	+	+++	-	-	+
forniceal part (PVHf)	-	-	+++	-	-	-
Ventromedial hypothalamic nucleus						
anterior part (VMHa)	+	++	+	+	-	-
dorsomedial part (VMHdm)	++	+++	+	+++	++	++
central part (VMHc)	++	++	+	++	++	+
ventrolateral part (VMHvl)	+	++	+	+++	++	+
Ventral premammillary nucleus (PMv)	-	-	+	+	+	+
Dorsal premammillary nucleus (PMd)	++	++++	-	+	-	+
Mammillary body						
medial mammillary nucleus	-	+++	-	-	-	-
body (MM)	-	+++	-	-	-	-
median part (MMme)	-	+++	-	-	-	-
Ventral tegmental area (VTA)	-	+	+++	++	++	+

	ANTEROGRADE (PHAL)			RETROGRADE (CTB)		
	rostral LHA#62 (LHA#62)	caudal LHA#22 (LHA#22)	central LHA#11 (LHA#11)	rostral LHA#62 (LHA#62)	caudal LHA#22 (LHA#22)	central LHA#11 (LHA#11)
Midbrain reticular nucleus, retrorubral area (RR)	-	-	++++	+	-	-
Midbrain reticular nucleus, parvicellular part (MRNp)	-	+	+++	+	-	-
3.3.2. Superior Colliculus, motor related						
Intermediate gray layer						
sublayer a (SCig-a)	-	+	-	-	-	-
sublayer b (SCig-b)	-	+	++	-	+	-
sublayer c (SCig-c)	-	+	+	+	+	+
Deep gray layer (SCdg)	-	-	+	-	+	-
3.3.3. Postcerebellar and Precerebellar Nuclei						
3.3.4. Vestibulomotor regions	-	-	-	-	-	-
3.3.5. Central Gray						
Epithalamus						
lateral habenula (LH)	++++	++++	++	-	-	-
Posterior hypothalamic nucleus (PH)	++++	++++	+++	++++	+++	++++
Periaqueductal gray						
precommissural nucleus (PRC)	+++	+++	+	+++	++	+
commissural nucleus (COM)	-	+	+++	+	-	++
rostromedial division (PAGrm)	-	+	++++	-	+++	++
rostrolateral division (PAGrl)	-	-	+	-	-	-
medial division (PAGm)	++	+++	+++	+	+	-
dorsal division (PAGd)	+	+	++	++	++	+
dorsolateral division (PAGdl)	-	-	+	++	-	-
ventrolateral division (PAGvl)	+++	+++	++++	+++	++	+++
nucleus of Darkschewitsch (ND)	-	-	+	+	-	-
Pontine central gray, general						
pontine central gray (PCG)	-	+	+++	+	++	+++
lateral tegmental nucleus (LTN)	-	-	+	+	-	++
Barrington's nucleus (B)	-	-	++++	-	-	-
3.3.6. Hypothalamic Periventricular Region						

	ANTEROGRADE (PHAL)			RETROGRADE (CTB)		
	rostral LHAjp (LHA#62)	caudal LHAjp (LHA#22)	central LHAs (LHA#11)	rostral LHAjp (LHA#62)	caudal LHAjp (LHA#22)	central LHAs (LHA#11)
Median preoptic nucleus (MEPO)	-	+	++	++	+	+++
Suprachiasmatic preoptic nucleus (PSCH)	-	-	-	-	-	+
Anteroventral periventricular nucleus (AVPV)	-	-	-	+	+	++
Anterodorsal preoptic nucleus (ADP)	-	+	-	+	+	+
Anteroventral preoptic nucleus (AVP)	-	-	+	+	-	+++
Parasubthalamic nucleus (PS)	-	+	-	-	-	++
Medial preoptic area (MPO)	+++	+	+++	++++	+++	++++
Anterior hypothalamic area (AHA)	+++	++	+	++	++	++
Dorsomedial hypothalamic nucleus						
anterior part (DMHa)	+++	++	++	++	+	++
posterior part (DMHp)	-	-	+	+	-	+++
ventral part (DMHv)	-	-	-	++	+	++
Periventricular hypothalamic nucleus, posterior part (PVp)	-	+	-	+	+	++
Internuclear area, hypothalamic periventricular region (I)	+++	++++	+	+++	++	+++
3.3.7 Reticular Formation						
Hypothalamic lateral zone, motor related						
lateral preoptic area (LPO)	++	+	+++	+++	++	++
lateral hypothalamic area, motor related (LHAMo)						
juxtaparaventricular region (LHAjp)	+++	+++	++	+++	+	++
juxtadorsomedial region (LHAjd)	++	+++	+++	+++	++	++
juxtaventromedial region						
dorsal zone (LHAjvd)	+++	+++	++	+	-	+
ventral zone (LHAjvv)	+++	+++	++	+++	++	+++
anterior region						
dorsal zone (LHAad)	++	+++	++	++	++	+++
intermediate zone (LHAai)	+++	++	++	+	++	+++
ventral zone (LHAav)	+++	++	++	+++	++	+++
retrochiasmatic area (RCH)	++	++	+	++	+	++

	ANTEROGRADE (PHAL)			RETROGRADE (CTB)		
	rostral LHA#62 (LHA#62)	caudal LHA#22 (LHA#22)	central LHA#11 (LHA#11)	rostral LHA#62 (LHA#62)	caudal LHA#22 (LHA#22)	central LHA#11 (LHA#11)
tuberal nucleus (TU)						
subventromedial part (TUsv)	-	+	+	+	-	+
intermediate part (TU _i)	-	+	-	+	-	+
lateral part (TU _l)	-	-	-	+	-	-
supraformical region (LHAs)	+++	+++	++	+	+	++
subformical region						
anterior zone (LHA _{sta})	-	-	-	+	-	+
posterior zone (LHA _{sp})	-	+	++	++	+	++
preammillary zone (LHA _{sfpm})	-	+	-	+	+	-
magnocellular nucleus (LHA _m)	-	-	+	-	-	-
parvocellular region (LHA _{pc})	-	-	+	-	-	-
ventral region						
medial zone (LHA _{vm})	-	+	+	+	-	++
lateral zone (LHA _{vl})	-	-	+	-	-	-
posterior region (LHA _p)	-	+	+++	-	+	-
preparasubthalamic nucleus (PST)	-	-	+	-	-	-
parasubthalamic nucleus (PSTN)	-	-	+	-	-	-
Zona incerta, general						
zona incerta (ZI)	++	+++	+	+++	++	+
pretectal region						
posterior pretectal nucleus (PPT)	-	-	-	+	-	-
medial pretectal area (MPT)	-	+	-	+	+	-
midbrain reticular nucleus, magnocellular part, general						
midbrain reticular nucleus, magnocellular part (MRNm)	-	+	+++	+	+	+
ventral tegmental nucleus (VTN)	-	+	-	+	-	-
cuneiform nucleus (CUN)	-	-	-	-	+	-
pontine reticular nucleus, caudal part (PRNc)	-	-	+++	-	-	-
gigantocellular reticular nucleus (GRN)	-	-	+++	-	-	-

	ANTEROGRADE (PHAL)			RETROGRADE (CTB)		
	rostral LHA#62 (LHA#62)	caudal LHA#22 (LHA#22)	central LHAs (LHA#11)	rostral LHA#62 (LHA#62)	caudal LHA#22 (LHA#22)	central LHAs (LHA#11)
paragigantocellular reticular nucleus (PGRN)						
dorsal part (PGRNd)	-	-	+	-	-	-
lateral part (PGRNI)	-	-	++	-	-	-
parapyramidal nucleus (PPY)						
deep part (PPYd)	-	-	+	-	-	-
magnocellular reticular nucleus (MARN)	-	-	+++	-	-	-
parvicellular reticular nucleus (PARN)	-	-	++	-	-	-
medullary reticular nucleus (MDRN)						
ventral part (MDRNv)	-	-	+	-	-	-
3.3.8. Motoneuron Groups						
Neuroendocrine motor zone						
magnocellular						
paraventricular nucleus hypothalamus, magnocellular division						
posterior magnocellular part						
medial zone (PVHpmn)	-	-	+	-	-	-
lateral zone (PVHpml)	-	++	+	-	-	-
parvicellular						
paraventricular nucleus hypothalamus, parvicellular division						
anterior parvicellular part (PVHap)	+	+	++	+++	++	+++
medial parvicellular part, dorsal zone (PVHmpd)	-	+	+++	+	+	+
periventricular part (PVHpv)	-	+	+	+	+	+
periventricular hypothalamic nucleus, anterior part (PVa)	-	-	-	+	-	+
periventricular hypothalamic nucleus, intermediate part (PVf)	-	+	-	+	-	+
arcuate hypothalamic nucleus (ARH)	-	+	-	+	-	++
Preganglionic autonomic pools						
parasympathetic						
inferior salivatory nucleus (ISN)	-	-	+	-	-	-

	ANTEROGRADE (PHAL)			RETROGRADE (CTB)		
	rostral LHA#62	caudal LHA#22	central LHA#11	rostral LHA#62	caudal LHA#22	central LHA#11
dorsal motor nucleus of the vagus nerve (DMX)	-	-	++	-	-	-