CHAPTER

16

Thalamus

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OUTLINE

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The thalamus of rats, like in most other vertebrate species, forms the largest part of the diencephalon. The diencephalon, situated between the cerebral cortex rostrally and the brainstem caudally, consists of several nuclear cell groups: the epithalamus, the dorsal thalamus, the ventral thalamus, and the hypothalamus. An alternative nomenclature for major subdivisions of the thalamus, based on the developmental genetic maps of Puelles and co-workers (see Chapter 1, *Gene Maps and Related Histogenetic Domains in the Forebrain and Midbrain*), is the thalamus (prosomere 2) for the dorsal thalamus, and the prethalamus (prosomere 3) for the ventral thalamus. Accordingly, these terms will be used (thalamus and prethalamus) to designate what has classically been referred to as the dorsal and ventral thalamus, respectively.

The (dorsal) thalamus has close connectional and functional relationships with the cortex and, to a lesser extent, with several forebrain structures including the basal ganglia and amygdala. The (ventral) prethalamus, ontogenetically originating from embryonic cells rostral to those forming the thalamus, is a heterogeneous collection of nuclei that would include the reticular nucleus (RT) and the ventral lateral geniculate nucleus. A discussion of the epithalamus (epiphysis, habenular complex, and stria medullaris) falls outside the scope of the chapter.

The thalamus forms a diverse and complex set of cytoarchitectonically, chemoarchitectonically, and hodologically distinct nuclei, their common characteristic being reciprocal connections with distinct parts of the cortex. Traditionally, the thalamus has been viewed as the final relay for extrinsic and intrinsic information channeled to the cortex. On the basis of the content of information reaching various thalamic nuclei through select inputs, as well as organizational aspects of thalamic projections to the cortex, thalamic nuclei have been characterized as specific versus nonspecific. Although this distinction (specific vs. non-specific) has become less sharply defined, the specific nuclei have traditionally encompassed sensory, motor, and associational nuclei of thalamus, whereas the "nonspecific" nuclei primarily consist of the midline and intralaminar nuclei of thalamus. A global view of thalamic function is that various streams of information channeled through the thalamus to the cortex are gated and modulated at the level of the thalamus. However, the precise nature and mechanisms of these gating and modulatory functions still remain largely elusive.

Main features of the prethalamus, exemplified by the thalamic reticular (RT) nucleus and the ventral lateral geniculate (VLG) nucleus, are that it distributes to the other thalamic nuclei, and unlike them, lacks projections to the cortex (Sherman and Guillery, 2006; Jones, 2007). While the reticular and ventral lateral geniculate nuclei have several characteristics in common, the VLG has a number of additional properties that distinguish it from RT and as such VLG will be discussed in conjunction with the lateral geniculate complex.

The present chapter will provide a general review of the functional anatomy of the thalamus, with emphasis on data obtained from studies in rats. For a further treatment of the thalamus, involving several species, the reader is referred to two excellent volumes on the thalamus: *Exploring the Thalamus and its Role in Cortical Function, 2nd edn*. (2006), by S. Murray Sherman and R.W. Guillery; and *The Thalamus, Volumes I and II* (2007), by the late Edward G. Jones.

Whereas the thalamus has been traditionally viewed as a "mere" gateway to the cortex, recent evidence indicates a much greater role for the thalamus in subcortical/cortical communication. As discussed herein, knowledge of the functional aspects of the thalamus has greatly expanded over the past decade—with much still to be discovered. The present chapter builds on previous comprehensive treatments of the thalamus in this series by Price (1995) and by Groenewegen and Witter (2004). This revised chapter aims to update knowledge of the anatomy of the rat thalamus within a functional context. In the first section, a number of issues of general interest on thalamic structure and function are discussed followed by a detailed description of different groups of thalamic nuclei. Emphasis is placed on those nuclei (or nuclear groups) for which recent research has yielded new data/insights, as is particularly the case for the midline and intralaminar nuclei of thalamus.

SOME GENERAL ASPECTS OF THALAMIC ORGANIZATION

The delineation of nuclei of the thalamus is primarily based on cytoarchitectonic, chemoarchitectonic, and

connectional features. The entire complex of nuclei, rostrally, laterally, and ventrally is "encapsulated" by the fibers of the external medullary lamina in which the RT is embedded. An internal medullary lamina separates dorsal and medial groups of the thalamus from ventral, lateral and posterior nuclei. Embedded in the internal medullary lamina are the intralaminar nuclei which, with some of the midline nuclei of thalamus, form a separate group based in part on their projections to the cortex as well as to subcortical sites prominently including the basal ganglia.

The caudal borders of the thalamus are less clearly defined; nuclei of the posterior thalamic complex merge with cell groups of the pretectum. In rats, as for some other species, the third ventricle does not extend dorsally from the hypothalamus through thalamus due to the merging of the two halves of the thalamus in the midline. The reticular thalamic nucleus, as part of the prethalamus, forms a thin sheet of neurons at the rostral and lateral borders of the thalamus, surrounded by fiber bundles of the internal capsule.

FUNCTIONAL SUBDIVISIONS OF THE THALAMUS

Classical Subdivisions

The classical categorization of thalamic nuclei is primarily based on the kinds and sources of information which are transferred through a particular thalamic nucleus (or group of nuclei) to the cortex. Traditionally, the thalamus has been divided into three anatomical/functional groups: the principal (or relay) nuclei, the association nuclei, and the midline and intralaminar nuclei (Price, 1995; Groenewegen and Witter, 2004). The main category is formed by the principal "relay" nuclei which receive specific sensory or motor information primarily through ascending pathways and transmit this information to discrete areas and layers of the cortex. The relay nuclei include: the lateral geniculate complex, medial geniculate nucleus, ventral posteromedial and posterolateral nuclei, posterior nucleus, ventral lateral nucleus, ventral anterior nucleus and the ventral medial nucleus. The "association" nuclei are a largely ill-defined group that essentially differ from principal nuclei in that they do not receive afferent information from primary sensory (e.g., retina) or motor sources and essentially do not target primary sensory and motor fields of the cortex. The association nuclei are thought to receive major afferents from layer 5 pyramidal cells of primary sensorimotor cortices and to relay this information to associational areas of cortex—hence association nuclei of thalamus.

Sherman and Guillery (2006) describe two basic types of thalamic relays, first and higher order relays, with the difference being that the first order relays receive, and then transmit, new (or previously unseen) information to the cortex; whereas higher order relays convey messages from one cortical area to another—or information that has already been processed by the cortex. In their view, this distinction precludes the need for the classification "association nuclei" of thalamus (see also below). In the classic tradition, the association thalamic nuclei include the mediodorsal nucleus (MD), the anterior nuclei (anterodorsal, anteroventral, and anteromedial), submedial nucleus, and the laterodorsal and lateral posterior nuclei (Groenewegen and Witter, 2004). The midline and intralaminar thalamic nuclei form a separate group primarily based on their: (1) distinct location along the midline and within the internal medullary lamina; (2) substantial distribution to subcortical as well as to cortical sites; and (3) seeming involvement in processes of arousal and attention. The intralaminar group consists of the central medial, paracentral, central lateral, parafascicular and subparafascicular nuclei, while the midline nuclei include the paratenial (PT), paraventricular (PV), rhomboid (RH) and reuniens (RE) nuclei—and in some classifications the intermediodorsal nucleus (IMD) (Groenewegen and Witter, 2004). As indicated, the reticular thalamic nucleus comprises a separate category in light of its position between (dorsal) thalamic nuclei and the cortex and its absence of cortical projections.

Non-Classical Subdivisions

An alternative classification might group thalamic nuclei according to their connections with sensorimotor systems or with the limbic system—and associated roles in sensorimotor or limbic functions. Like the previously described categorization, this classification might also yield three groupings of thalamic nuclei: sensorimotor nuclei of thalamus, limbic nuclei of thalamus, and thalamic nuclei that may bridge these two domains. While there is undoubtedly overlap in the anatomical/functional properties of these three groups (as for the classical divisions), the sensorimotor group would essentially consist of the principal thalamic nuclei; the "limbic group" would mainly include the anterior nuclei, MD, central medial nucleus and midline nuclei (PT, PV, RH and RE), and the sensorimotor/limbic "bridging nuclei" might consist of the submedial nucleus, the paracentral, central lateral, and parafascicular nuclei of the intralaminar complex, and the laterodorsal and lateral posterior nuclei of the lateral thalamus. This organization will be discussed in the chapter—and specifically the notion of the "limbic thalamus" (Bentivoglio *et al.*, 1991; Groenewegen and Berendse, 1994; Taber *et al.*, 2004).

CATEGORIZATION OF THALAMIC AFFERENTS AS "DRIVERS" OR "MODULATORS"

Before dealing with the structure, connections, and functional aspects of individual thalamic nuclei in later sections, it is important to briefly discuss the characterization of afferents to the thalamus as drivers or modulators (Sherman and Guillery, 1998, 2001, 2006). This classification provides a basis for distinguishing between afferents that carry specific information to the thalamus, which is subsequently transmitted to the cortex, and other systems that modulate the transfer of (specific) information from thalamus to cortex. Sherman and Guillery (2001, 2006) make a strong case for such an organization primarily based on first-order sensory thalamic nuclei such as the lateral geniculate nucleus, and suggest that these organizational principles can be extended to other (or higher order) nuclei of the thalamus (but see below). The designation of thalamic afferents as drivers and modulators involves several criteria including the site and mode of termination of afferent fibers, their ultrastructural characteristics, and physiological properties (see Table 7.1, pages 256, 257 of Sherman and Guillery, 2006). Primary sensory afferents to thalamus, whether of somatosensory, visual, or auditory origin, are similar with respect to their light microscopic appearance: relatively thick, richly branching terminal fibers with, in most cases, large boutons, although variable in shape and number. These fibers have been termed type II fibers and are considered to be "drivers" for the primary sensory relay nuclei. At the ultrastructural level, the driving afferents are associated with large terminals containing round vesicles (RL=round vesicles and large terminals). The RL-type terminals are often found in triadic arrangements; that is, they are presynaptic to dendrites of thalamic relay neurons as well as to axoniform dendrites of interneurons which in turn are presynaptic to dendrites of relay neurons. These triads regularly form part of glomerular structures containing various presynaptic and postsynaptic elements, typically ensheathed by astrocytic processes. A defining characteristic of "drivers" is that they rather faithfully transmit incoming signals through the thalamus to target neurons in recipient cortical zones. Accordingly, as noted by Sherman and Guillery (2006), drivers "can reasonably be regarded as bringing to the thalamus the message that is passed to cortex, whatever that message may prove to be" (p. 85). In general, driver inputs are excitatory and exert their effect mainly via ionotropic glutamate receptors (Sherman and Guillery, 2001, 2006).

By contrast, "modulators," as the term implies, represent thalamic afferents that modulate (or modify) information carried by the drivers to the cortex. Modulators have a different light microscopic appearance: fibers are thin and imbued with small, drumstick-like appendices strung along the extent of the fibers. They are categorized as type I thalamic afferents. In general, type I fibers more sparsely branch, contain fewer terminal-like structures, and distribute over wider regions than type II fibers. Ultrastructurally, type I fibers have small terminals with round vesicles (RS=round vesicles and small terminals). The receptive fields of type I afferents are generally wide and less defined than those of type II fibers, and instances in which type I fibers are glutamatergic, they probably exert effects primarily via metabotropic glutamatergic receptors.

Cortical afferents to a number of higher order thalamic nuclei are of the type II category indicating that these afferents serve as drivers for association thalamic nuclei. Whereas type I corticothalamic axons mainly derive from layer 6 of the cortex, type II corticothalamic fibers have been shown, in many cases, to arise from cells in cortical layer 5. However, the generality of this organization remains to be largely established, particularly for non-principal nuclei of the thalamus. Type I afferents to the thalamus of the "modulatory" category not only originate in the deeper layers of the cortex but also from a wide array of subcortical structures in the basal forebrain, diencephalon and brainstem (Sherman and Guillery, 2001, 2006).

The concept of drivers and modulators provides a challenging framework for the discussion and interpretation of thalamic structure and function. It serves as the basis for understanding what messages are transferred through the thalamus to the cortex and the systems modulating this flow of information. It further emphasizes that the sheer numbers or volume of afferents to the thalamus may not be the major factor in determining the precise nature of information transfer from the thalamus to the cortex. Specifically, for some systems numerically smaller inputs can exert a greater functional influence than more numerous ones (Sherman and Guillery, 2001, 2006). For instance, retinal afferents to the lateral geniculate nucleus (LGN) represent only about 7% of the total synapses on relay cells of LGN (Van Horn *et al.*, 2000). Despite this, it is clearly the case that retinal signals prevail over information carried by more numerous modulatory inputs to LGN. This, in part, owes to the fact that retinal fibers end as RL terminals on proximal dendrites of LGN neurons (Sherman and Guillery, 2006).

The driver/modulator concept, as briefly described, serves as a reference for the discussion of individual thalamic nuclei in subsequent parts of the chapter. As a general framework, however, some caveats should be addressed. The scheme (drivers/modulators) of Sherman and Guillery (2001, 2006) largely focuses on, and is generally applicable to, principal (relay) nuclei of the thalamus

and may be less relevant to other (or non-principal) nuclei of the thalamus. What probably distinguishes principal thalamic nuclei (e.g., visual, auditory, somatosensory) from other thalamic groups is the rather unambiguous ability to identify "driving" inputs to these nuclei—thereby allowing for a clear distinction between drivers and modulators. In this instance, modulators represent all other sources of input to the principal nuclei. Although in some cases, as noted previously, driving inputs to higher order thalamic nuclei originate from layer 5 cells of the cortex, for most thalamic nuclei the identification of "drivers" appears problematic—or has not even been attempted. In this regard, a main difficulty is the inability to precisely define the receptive fields of neurons in non-principal thalamic nuclei—to thereby determine the message(s) transmitted by these nuclei to the cortex. Sherman and Guillery (2006) addressed this issue as follows:

> Thus, for relay cells of the lateral geniculate nucleus, we can define drivers as primary transmitters of receptive field properties and modulators as inputs that do not provide the basic receptive field properties to the relay cell. This distinction may also serve for some of the other first order thalamic relays, such as the ventral posterior nucleus and the medial geniculate nucleus, where receptive field properties of the relay cells are well understood. However, this criterion will not serve to distinguish drivers from modulators in other thalamic nuclei where receptive field have not been defined. Examples include the medial dorsal nucleus, midline and intralaminar nuclei, much of the pulvinar and other nuclei (p. 258).

Although the authors proceed to describe several additional criteria for distinguishing drivers from modulators, the effectiveness of these criteria in differentiating drivers from modulators in non-principal thalamic nuclei remains to be determined.

RECIPROCITY OF THALAMO-CORTICOTHALAMIC RELATIONSHIPS

It is almost a dogma that the thalamo-corticothalamic relationships are organized such that each cortical area receiving an input from a specific thalamic nucleus faithfully reciprocates this input through a topographically organized cortical projection to that thalamic nucleus. Apart from the fact that relationships between the thalamus and cortex are not exclusively reciprocal (Hoogland *et al.*, 1987; Murphy and Sillito, 1996; Deschênes *et al.*, 1998; McFarland and Haber, 2002), it is far from clear what this reciprocity means and why corticothalamic fibers significantly outnumber their thalamocortical counterparts (Jones, 1985, 2007). With respect to the discussion of driver and modulatory inputs to the thalamus, it must be recalled that cortical outputs form a mixed population. Whereas most cortical afferents to primary relay nuclei are type I modulatory fibers, cortical inputs to higher order thalamic nuclei are type II fibers and thus may represent a main driving input to these nuclei (Sherman and Guillery, 2001, 2006). Driver inputs, by terminating on more proximal parts of dendrites of thalamic neurons, appear to exert a stronger influence on these cells than modulatory inputs which generally contact more distal parts of dendrites. Therefore, as Sherman and Guillery (2006) argue, it may not be the numbers that matter, but more the type and position of terminations on the dendritic tree.

Another approach to the issue of reciprocity has been set forth by Deschênes *et al.* (1998) in comparing the pattern and strength of cortical inputs to a particular thalamic nucleus with extra-thalamic projections to the nucleus. Deschênes *et al.* (1998) formulated the "rule of parity" which states that, "the distribution of corticothalamic projections across and within thalamic nuclei is determined by the branching patterns of the different classes of prethalamic afferents." In effect, corticothalamic projections may exceed thalamocortical projections but corticothalamic projections may largely match extra-thalamic inputs to particular thalamic nuclei.

In general, the rule of parity leads to reciprocity in the thalamocorticothalamic relationships, but this may not be true in all cases. Deschênes *et al.* (1998) based their hypothesis on the central organization of the vibrissal system of rats using the ventrobasal thalamic complex. The functional consequence of the rule of parity might be a negation of an exclusive feedback role for the corticothalamic system. Thus, depending on the behavioral context, either the corticothalamic or the thalamocortical system might play the dominant role. How and to what extent the varying roles of corticothalamic fibers are related to their origin from distinct layers of cortex remain to be established. Whether a rule of parity applies to all thalamic systems is unclear, but this hypothesis provides an important perspective on the bottom-up and top-down functional arrangements of the corticothalamic system. A likely consequence of nonreciprocity appears to be that the thalamus channels information between regions of the cortex as well as between cortical and subcortical structures (Guillery, 1995; McFarland and Haber, 2002; Sherman and Guillery, 2006). This may be a general principle of thalamocortical organization. As pointed out by Sherman and Guillery (2006), the thalamus is generally viewed as delivering information to the cortex and once information reaches the cortex the function of the thalamus is complete. The cortex then begins the important task of interpreting, organizing and acting on that information. But this "corticocentric" view of thalamocortical relationships may significantly underestimate the role of the thalamus in virtually all aspects cortical functioning—a full partner with the cortex.

LATERAL GENICULATE NUCLEUS

The lateral geniculate nucleus of rats is a relatively flattened, oval-shaped nucleus on the dorsolateral surface of the caudal thalamus. It is subdivided into dorsal (DLG) and ventral (VLG) lateral geniculate nuclei. The intergeniculate leaflet (IGL) is positioned between the DLG and the VLG. The DLG constitutes the main thalamic relay of visual information to the primary visual cortex. The VLG can be further divided into a lateral and medial division. The VLG shares a number of characteristics with the thalamic reticular nucleus, as its lateral part receives direct retinal input. The IGL constitutes a relay between the retina and the hypothalamus and is involved in circadian functions. (For a comprehensive treatment of the anatomical and functional aspects of the lateral geniculate complex, including the DLG, VLG, and IGL see *Visual System*, Chapter 30.)

Dorsal Lateral Geniculate Nucleus

The dorsal lateral geniculate nucleus (DLG) can be readily identified in Nissl-stained sections, in acetylcholinesterase-stained sections wherein the DLG shows moderate activity (Paxinos and Watson, 2014), and in serotonin stained tissue in which DLG shows very dense fiber labeling (Vertes *et al.*, 2010). The cytoarchitecture of the DLG of rats is rather homogeneous. The majority of dorsal lateral geniculate neurons are thalamocortical projection cells. Unlike most other principal thalamic nuclei of the rat, the DLG contains several types of interneurons, namely, GABAergic, NADPH diaphorase-containing neurons, and those co-expressing both substances (Ohara *et al.*, 1983; Jones, 1985, 2007; Gabbott and Bacon, 1994). In contrast to many other mammalian species, the rat DLG is not clearly laminated, although fiber bundles running in a ventrolateral to dorsomedial direction, parallel to the optic tract, impose a certain orientation on the neurons of the DLG. However, optic fibers from the ipsilateral and contralateral eyes in the caudolateral part of DLG remain segregated and create a "hidden lamination," with the lateral "outer shell" of DLG receiving input from the contralateral eye. The medial part of DLG, called the "inner core," consists of two regions: the most medial region receives input from the contralateral eye and the lateral region is innervated by the ipsilateral eye (Jones, 1985, 2007; Reese, 1988). Calcium-binding proteins are differentially distributed in fibers and neurons of the dorsal lateral geniculate nucleus. Whereas calretinin and parvalbumin are present only in fibers, calbindin D28K is also expressed in (inter)neurons, in particular in the outer shell (Luth *et al.*, 1993; Paxinos *et al.*, 1999). The plexus of calretinin fibers is most dense in the outer shell (Paxinos *et al.*, 1999). Parvalbumin fibers likely originate from the retina and the reticular thalamic nucleus, and calretinin fibers from the retina (Arai *et al.*, 1992; Luth *et al.*, 1993). Calbindin D28K-containing fibers may be derived from the superior colliculus (Lane *et al.*, 1997).

Afferent and Efferent Projections

The DLG forms the main relay between the retina and the primary visual cortex (area 17 or V1). The optic terminations in the DLG are retinotopically organized (Jones, 1985, 2007; Reese, 1988). The inner core receives, in its two ocular laminae, inputs from the contralateral nasal and the ipsilateral temporal retina, mapping the contralateral visual hemifield. The outer shell receives a projection only from the contralateral visual hemifield. These retinotopic maps in the contralateral and ipsilateral laminae of DLG are in complete register. Lines of projection are oriented rostroventromedially from the optic tract at the thalamic surface through the different laminae of DLG (Reese, 1988). Retinal inputs terminate as RL-type boutons, indicating that retinal fibers are the "drivers" of the DLG (Jones, 1985, 2007; Sherman and Guillery, 2001, 2006). The retinal afferents contact dendrites of both thalamocortical neurons and interneurons.

Cortical inputs to the DLG mainly derive from the primary visual cortex (area 17). The various cortical layers of the primary visual cortex have different projection patterns to the visual thalamus (Bourassa and Deschênes, 1995). Fibers originating in the upper part of layer 6 project to the DLG and terminate in rostrocaudally oriented bands or "rods" that run parallel to the lines of projection of retinal afferents. Neurons in the deeper part of layer 6 project to the lateral part of the lateral posterior thalamic nucleus and give off collaterals to the DLG, where they participate in the formation of the rods. Neurons in layer 5 of the visual cortex send projections to the brainstem, with collaterals to the ventral lateral geniculate nucleus, lateral posterior nucleus, and lateral dorsal thalamic nucleus (Bourassa and Deschênes, 1995). Layer 6 corticothalamic fibers send collaterals to the reticular thalamic nucleus but layer 5 axons do not. The fibers terminating in DLG that originate from layer 6 have small "en passant" varicosities which at the ultrastructural level show characteristics of the RS-type boutons and may be considered "modulators" (Jones, 1985, 2007; Bourassa and Deschênes, 1995; Price, 1995; Sherman and Guillery, 2001, 2006).

Subcortical inputs to DLG arise from the ventral lateral geniculate nucleus, reticular thalamic nucleus, superior colliculus, and several brainstem nuclei (Reese, 1988; Coleman and Mitrofanis, 1996; Moore *et al.*, 2000). The inputs from the superior colliculus terminate in the peripheral zone of the outer shell and are likely associated with the calbindin D28K-positive fiber plexus (Reese, 1988; Lane *et al.*, 1997). Brainstem afferents to

DLG originate from the some of the same nuclei giving rise to projections to the retina including the nucleus of the optic tract, pretectal nuclei, and the parabigeminal nuclei (Schmidt *et al.*, 1995; Born and Schmidt, 2007). A strong serotonergic input to DLG arises from the dorsal raphe nucleus (Papadopoulos and Parnavelas, 1990; Vertes, 1991; Waterhouse *et al.*, 1993; Vertes *et al.*, 2010). Noradrenergic afferents originate from the locus coeruleus, while the laterodorsal tegmental nucleus provides cholinergic input to the DLG (Papadopoulos and Parnavelas, 1990; Waterhouse *et al.*, 1993; Billet *et al.*, 1999).

The output of the DLG is mainly directed to the primary visual cortex (area 17), terminating in layer 4, whereas there are lesser inputs to layers 1 and 6 (Ribak and Peters, 1975; Jones, 1985, 2007). The peristriate area 18 also receives a weak projection from DLG (Sanderson *et al.*, 1991). The geniculocortical pathway uses glutamate as its neurotransmitter (Kharazia and Weinberg, 1994; Saez *et al.*, 1998).

Ventral Lateral Geniculate Nucleus

The VLG, like the reticular thalamic nucleus, is embryologically derived from the prethalamus (or ventral thalamus). Cytoarchitectonically, the VLG can be subdivided into a lateral, magnocellular part (VLGmc) and a somewhat smaller, medial parvicellular part (VLGpc). The two divisions are separated by a fiber-rich, cell-free zone (Jones, 1985, 2007). Neurons in the magnocellular part contain parvalbumin, nitric oxide synthase and enkephalin; those in the parvicellular part contain substance P and calretinin (Hermanson *et al.*, 1995; Harrington, 1997; Meng *et al.*, 1998; Jones, 2007).

Afferent and Efferent Projections

Afferents to the ventral lateral geniculate nucleus show a clear segregation between the medial VLGpc and the lateral VLGmc. The VLGpc receives extensive inputs from the brainstem, in particular from the reticular formation, the deep layers of the superior colliculus, the periaqueductal gray (PAG), parabrachial regions, the laterodorsal tegmental nucleus, the locus coeruleus, the substantia nigra-pars reticulata and deep cerebellar nuclei (Vaudano and Legg, 1992; Kolmac and Mitrofanis, 2000). The VLGmc receives strong projections mainly from the retina and layer 5 of the visual cortex (Hickey and Spear, 1976; Takahashi, 1985; Bourassa and Deschênes, 1995) but relatively few fibers from the brainstem (Kolmac and Mitrofanis, 2000). Immunohistochemical analysis has revealed a rich aggregate of serotonergic fibers in VLGmc, which are present, but not as dense, in the VLGpc (Vertes *et al.*, 2010).

Unlike the dorsal lateral geniculate nucleus, there are no projections from the VLG to the cortex. Instead, the VLG has rather extensive projections to the thalamus, comparable to those of the intergeniculate leaflet (see below). Thus, the medial, parvicellular part of the VLG projects to the parafascicular and lateral dorsal thalamic nuclei as well as to the reuniens (RE) and rhomboid nuclei (RH) of the midline thalamus (McKenna and Vertes, 2004). The lateral, magnocellular VLG sends fibers to the dorsal lateral geniculate and lateral posterior thalamic nuclei (Kolmac *et al.*, 2000; Moore *et al.*, 2000). Hypothalamic projections from the VLG reach the lateral and posterior hypothalamus and the perifornical area. The ventral lateral geniculate nucleus further distributes to the zona incerta, pretectal nuclei, deep and intermediate layers of the superior colliculus, dorsal and medial terminal nuclei of the accessory optic system, PAG, the peripeduncular region, and the accessory inferior olive (Moore *et al.*, 2000; Born and Schmidt, 2008).

Intergeniculate Leaflet

The IGL is a distinct, dorsoventrally narrow region lying between the dorsal and ventral lateral geniculate nuclei and extends virtually over the entire rostrocaudal length of the lateral geniculate complex (Hickey and Spear, 1976; Moore and Card, 1994). Like the ventral lateral geniculate nucleus, it is a derivative of the pre- (or ventral) thalamus. The borders of IGL can be readily identified by staining for glial fibrillary acidic protein (GFAP) or peptides like neuropeptide Y (NPY), substance P, and enkephalin, as well as the neurokinin-1 receptor. The IGL contains several types of small- to medium-sized neurons most of which have their dendritic arborizations within the nucleus (Moore and Card, 1994; Piggins *et al.*, 2001).

Afferent and Efferent Projections

The main sources of input to the intergeniculate leaflet are the retina and the contralateral IGL. Glutamatergic retinal fibers terminate as RL-type terminals and may be considered driving afferents to the IGL (Mikkelsen, 1992; Moore and Card, 1994). The neurons that give rise to the commissural connections contain enkephalin (Card and Moore, 1989). Further inputs to the IGL originate from the suprachiasmatic nucleus, posterior hypothalamic area, superior colliculus, and several brainstem nuclei, including the locus coeruleus, raphe nuclei, and the laterodorsal tegmental nucleus (Moore *et al.*, 2000; Vertes *et al.*, 2010). Orexinergic afferents from the hypothalamus make synaptic contacts with NPY containing IGL neurons (Nixon and Smale, 2005; Pekala *et al.*, 2011). There is a dense substance P-immunoreactive plexus in the intergeniculate leaflet (Piggins *et al.*, 2001).

The geniculo-hypothalamic tract represents the primary output of IGL and targets the suprachiasmatic nucleus and anterior hypothalamic regions. Neurons of IGL projecting to the suprachiasmatic nucleus contain

NPY (Card and Moore, 1989; Harrington, 1997; Morin, 2012). The IGL also distributes to the subcommissural organ and the pineal gland (Mikkelsen, 1994). Additional outputs include those to the midline thalamic nuclei, in particular, to the paraventricular, reuniens and rhomboid nuclei, as well as to the dorsal and lateral hypothalamus and zona incerta (Moore *et al.*, 2000; McKenna and Vertes, 2004). Brainstem targets are superficial layers of the superior colliculus, periaqueductal grey, and accessory optic nuclei (Moore *et al.*, 2000).

Functional Aspects of the Lateral Geniculate Complex

The DLG is the main thalamic gateway for the transfer of visual information from the retina to the cerebral cortex. The nucleus rather faithfully maps the external visual field onto the primary visual cortex (area 17, V1). The functional aspects of the DLG have been the subject of a vast body of literature and have recently been elegantly reviewed by others (e.g., Sherman and Guillery, 2001, 2006).

The functions of the VLG are less well-established. In view of its origin from the prethalamus, and some of its interconnections (rather extensive projections to the thalamus), the functions of the VLG might, in part, be compared with those of the reticular thalamic nucleus. However, the functional aspects of the VLG are probably much more diverse. Based on distinct differences in afferent and efferent projections, the medial and lateral parts of VLG (VLGpc and VLGmc, respectively) most likely have different, but related, functions. Whereas the VLGmc is more directly associated with the dorsal lateral geniculate nucleus and visual cortices, the VLGpc is closely linked with the hypothalamus, particularly the suprachiasmatic nucleus, and as such, may share functions with the IGL. The interconnections among VLG, SC, and pretectal nuclei may be involved in the control of visuomotor responses, whereas those with the hypothalamus may affect circadian rhythms (Harrington, 1997; Jones, 2007). The functional aspects of IGL have been studied in somewhat more detail. The retinal input to the IGL originates from a set of retinal ganglion cells that convey luminance information (Moore *et al.*, 1995). Subpopulations of IGL neurons projecting to either the suprachiasmatic nucleus or contralateral IGL show different firing characteristics in response to light and dark cycles (Błasiak and Lewandowski, 2013). Furthermore, the strong reciprocal connections of IGL with the suprachiasmatic nucleus as well as links with the dorsal raphe, lateral/posterior hypothalamus, and pineal gland fit well with a critical role for the IGL in circadian timing functions (Moore and Card, 1994; Harrington, 1997; Błasiak *et al.*, 2006; Pekala *et al.*, 2011; Błasiak and Lewandowski, 2013). While IGL projections to the suprachiasmatic nucleus provide an indirect means to influence autonomic and neuroendocrine circadian rhythms, IGL also directly connects with neuroendocrine cells in other parts of the hypothalamus (Horvath, 1998). The interconnections of IGL with the VLG, hypothalamus, and midline thalamic nuclei, including the paraventricular nucleus (PV), may contribute to their involvement in the circadian entrainment of food and energy regulation (for review, see Kelley *et al.*, 2005).

VENTRAL POSTERIOR COMPLEX

The ventral posterior complex (VP) of rats occupies an extensive area of the ventrolateral thalamus, positioned rostromedial to the medial geniculate complex and extending to the rostral third of the thalamus. The VP is bordered ventrally and laterally by the medial lemniscus and the reticular thalamic (RT) nucleus and dorsomedially by the posterior complex (PO) of the thalamus. Rostrally, PO is gradually replaced by the ventral lateral nucleus, located medial to VP. The ventral posterior complex is the main relay for various types of sensory information reaching the cortex and can be divided into three main parts: the ventral posterolateral nucleus (VPL) receiving somatosensory inputs from the spinal cord, the ventral posteromedial nucleus (VPM) receiving somatosensory inputs from the trigeminal system, and a small celled (or parvicellular) region medial to VPM/VPL, designated VPpc, which is the main thalamic relay for gustatory and visceral afferents.

The VPL and VPM are distinguishable not only by their connectivity but also on the basis of cyto- and chemoarchitectonics. In Nissl-stained material (Paxinos and Watson, 2014), VPM stands out by containing more densely packed cells than either VPL or PO, but VPM exhibits low levels of acetylcholinesterase (AChE) activity compared to moderate levels for VPL and the posterior complex. Most neurons in VPM and VPL are medium-sized thalamocortically projecting cells. In contrast to other species, there are reportedly no GABAergic neurons in the VP complex of rats (Harris and Hendrickson, 1987; Price, 1995; Sherman and Guillery, 2006). The neurons of VPL are arranged in rostrocaudal and dorsoventral rows that are roughly parallel to the external medullary lamina; the rows curve partially around the rostral pole of VPM (McAllister and Wells, 1981).

The VPM is largely organized into what are termed barreloids, first described in mice and later identified in rats (Van der Loos, 1976; Diamond *et al.*, 2008). Barreloids are aggregates or groupings of cells that represent individual whiskers at the level of the thalamus and can best be visualized using mitochondrial markers such as cytochrome oxidase (Land and Simons, 1985; Haidarliu and Ahissar, 2001; Diamond *et al.*, 2008; Bosman *et al.*,

2011). These microstructures are most apparent in young rats, but can also be demonstrated in adults. Whereas the barreloids of VPM convey information from single whiskers, the dendrites of neurons of barreloids may cross boundaries into neighboring barreloids thereby providing a neural substrate for cross-talk between barreloids (Desilets-Roy *et al.*, 2002). From the whiskers, information is first transmitted to barrelettes of the trigeminal nucleus, then to the barreloids of VPM, and finally to the barrels of the somatosensory cortex (S1). There is virtually a one-to-one relationship from individual whiskers to corresponding cortical barrels. Accordingly, the projections from the barreloids of VPM to the barrel cortex are strictly topographically organized (Lu and Lin, 1993; Land *et al.*, 1995). Thalamocortical axons from VPL/VPM terminate predominantly in layer 4 of the primary sensory cortex (S1) and use glutamate as a neurotransmitter (Kharazia and Weinberg, 1994). Apart from the main terminations in layer 4, VPM axons also branch to layers 1 and 5/6 of S1 (Lu and Lin, 1993; Zhang and Deschênes, 1998).

Afferent and Efferent Projections

The ventral posterolateral and ventral posteromedial nuclei receive main somatosensory inputs from the dorsal lamina of the spinal cord, dorsal column nuclei, and the trigeminal complex (Gauriau and Bernard, 2004; Tracey, 2004; Waite, 2004; see also *Somatosensory System*, Chapter 24).

Somatosensory projections are topographically organized such that afferents from the trunk and limbs terminate in VPL; those from the head terminate in VPM. Spinal and trigeminal fibers not only target VPL and VPM but also distribute to other thalamic nuclei including the posterior nucleus (see below), intralaminar nuclei and the submedial nucleus (SMT) of thalamus. Spinothalamic fibers conveying nociceptive signals to the thalamus originate from a relatively wide-ranging region of the spinal cord, most heavily from lamina 1 of the dorsal horn, and terminate as large boutons in VPL (McAllister and Wells, 1981; Burstein *et al.*, 1990; Dado *et al.*, 1994; Katter *et al.*, 1996; Kobayashi, 1998; Willis *et al.*, 2004). Nociceptive information also reaches VPL indirectly via several routes including from the caudal medullary reticular formation (Villanueva *et al.*, 1998). Afferents from the dorsal column nuclei to VPL also terminate as large boutons (McAllister and Wells, 1981; Villanueva *et al.*, 1998). VPL is reportedly divided into rostral, intermediate, and caudal zones, which are distinct, essentially non-overlapping, regions processing different types of modality specific information (Francis *et al.*, 2008). The rostral VPL mainly receives proprioceptive input, the intermediate VPL receives cutaneous afferents, and the caudal VPL processes nociceptive and visceral input. The receptive fields of the rostral and caudal VPL are broad, while those of the intermediate VPL (processing cutaneous information) are restricted and finely somatotopically organized with the forelimbs represented medially and the hindlimbs laterally (Francis *et al.*, 2008). Lemniscal, but also spinothalamic, fibers use glutamate as the neurotransmitter (De Biasi *et al.*, 1994). Spinothalamic fibers have also been shown to contain substance P (Battaglia *et al.*, 1992; Nishiyama *et al.*, 1995).

The spinal (SpV) and principal (PrV) nuclei of the trigeminal complex project to VPM and also to the medial part of the posterior nucleus (POm). The whisker-responsive regions of the SpV and PrV give rise to three (or possibly four) trigemino-thalamocortical pathways involved in the transfer information from the brainstem through the thalamus to the "barrels" of the barrel cortex—as well as to intervening septa between the barrels (Fig. 1) (Kim and Ebner, 1999; Pierret *et al.*, 2000; Urbain and Deschênes, 2007; Kichula and Huntley, 2008; Haidarliu *et al.*, 2008; Furuta *et al.*, 2009). The three major pathways are the lemniscal, the extralemniscal and the paralemniscal systems. The lemniscal system codes single whisker activity, with the other two essentially responsible for multi-whisker information. The lemniscal system originates from clusters of small neurons (barrelettes) of the PrV, which distribute densely to "core compartments" of single barreloids of the dorsomedial two-thirds of VPM (VPMdm) and from there to single barrels of S1. The extralemniscal system arises from inter-barrellete cells of the caudal part of the spinal interpolar trigeminal nucleus (SpV) which project to the ventrolateral sector of VPM (VPMvl) (or the "tail" of the barreloids), and then to the secondary somatosensory cortex (S2) and to the septa of S1. The paralemniscal system originates from the rostral part of the interpolar SpV which targets cells of the medial sector of the posterior nucleus (POm), and they, in turn, distribute to the septa and to all layers of the barrel cortex with a concentration in layers 1 and 5a (Petreanu *et al.*, 2009; Meyer *et al.*, 2010; Wimmer *et al.*, 2010). The POm input to the barrel cortex is substantial with 90-580 terminal boutons per neuron (Meyer *et al.*, 2010; Wimmer *et al.*, 2010).

In addition, a fourth ascending pathway for the vibrissa has been identified that originates from the dorsal part (or "head') of the barreloids and primarily distributes to the septa of the barrel cortex (Urbain and Deschênes, 2007). In contrast to the prevailing view that thalamic afferents to the septa essentially derive from the paralemniscal system (or POm) (Lu and Lin, 1993), Furuta *et al.* (2009) suggested that they originate from the head of the barreloids—and thus input to the septa, like that to the barrels, mainly arises from the lemniscal system.

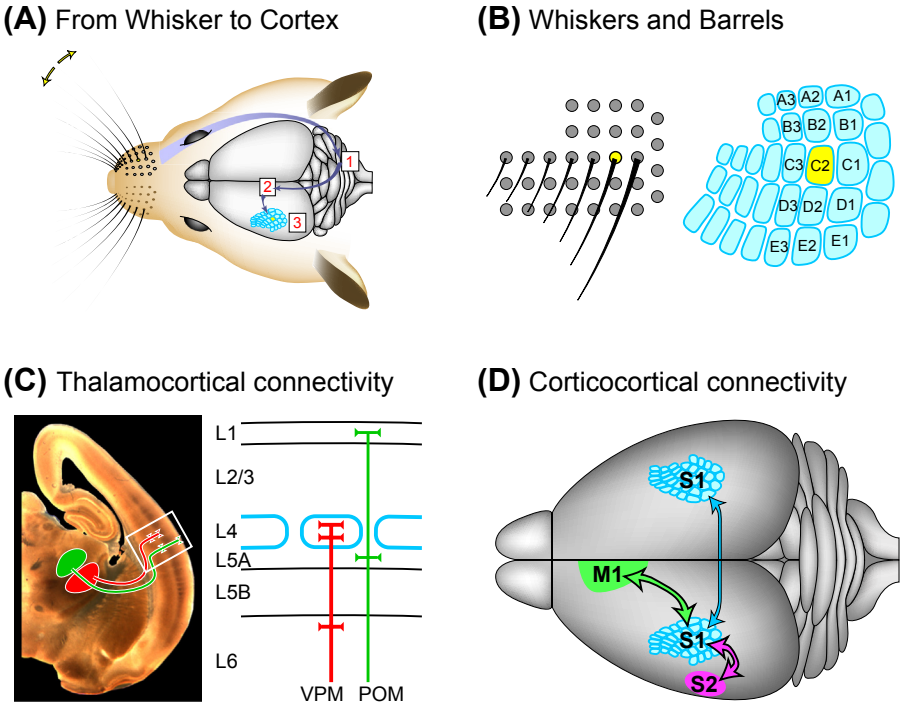

FIGURE 1 Synaptic pathways for processing whisker-related information in the barrel cortex of the rat. (A) Deflection of the whiskers evokes action potentials in sensory neurons of the trigeminal nerve, which release glutamate at a first synapse in the brainstem (1). Brainstem neurons send sensory information to the ventral posteromedial (VPM) and posterior (PO) nuclei of the thalamus (2), where a second glutamatergic synapse excites thalamocortical neurons projecting to the primary somatosensory barrel cortex (3). (B) The layout of whisker follicles (row C whiskers shown, left) on the snout of the rat with corresponding anatomical structures termed "barrels" in layer 4 of the primary somatosensory neocortex (right) which are arranged in a near identical pattern to that of the whiskers. The standard nomenclature for both whiskers and barrels consists of the rows A–E and the arcs 1, 2, 3, etc. The C2 whisker follicle and the C2 barrel are highlighted in yellow. (C) There are at least two parallel thalamocortical pathways for signaling whisker-related sensory information to the barrel cortex. Neurons in the VPM (red, left) are glutamatergic and signal information relating primarily to deflections of a single whisker. The axons of VPM neurons terminate predominantly in individual layer 4 barrels, with an additional innervation of layer 6 (right). Corticothalamic layer 6 neurons provide reciprocal feedback to the VPM (not shown). Neurons of the medial part of the posterior nucleus (POM) of the thalamus (labeled green, left) have broader receptive fields and axons which largely avoid the layer 4 barrels and primarily target layers 1 and 5A of the barrel cortex (right). Corticothalamic neurons in layer 5 provide a strong input to the POM (not shown). (D) Neurons in the barrel cortex are reciprocally connected to other cortical areas through long-range glutamatergic corticocortical synapses. Important pathways connect the primary somatosensory (S1) barrel cortex with the secondary somatosensory cortex (S2) and the primary motor cortex (M1) of the same hemisphere. Callosal projections are also present but less prominent. *From Petersen, C.C.H. (2007). The functional organization of the barrel cortex.* Neuron *56, 339–355.*

The three major thalamocortical pathways (paralemniscal, extralemniscal, lemniscal) serve different functional roles in the transfer of information from the whiskers to the somatosensory cortex (Williams *et al.*, 1994; Veinante and Deschênes, 1999; Pierret *et al.*, 2000; Ahissar *et al.*, 2000; Yu *et al.*, 2006). For instance, recordings from the three systems (POm/paralemniscal, VPMvl/extralemniscal, VPMdm/lemniscal) have shown that POm neurons encode whisker movements (whisking), VPMvl cells respond to contact (touch) information, and VPMdm cells respond to both contact and whisking (Yu *et al.*, 2006). Signals conveyed by the parallel systems are integrated at the barrel cortex for the detection, localization and identification of objects by the vibrissa (Ahissar and Arieli, 2001; Yu *et al.*, 2006; Alloway, 2008; Bosman *et al.*, 2011).

With respect to the barrel cortex, thalamic afferents appear to fairly selectively target either the septa or the barrels of the barrel cortex—indicating independent streams of processing from the thalamus to the barrel cortex (Shepherd and Svoboda, 2005; Alloway, 2008; Bokor *et al.*, 2008). Specifically, with some overlap, the extralemniscal and paralemniscal systems, responsive to multiple whiskers, distribute to the septa, whereas the lemniscal system, receptive to single whiskers, projects to the barrels of the barrel cortex (Derdikmann *et al.*, 2006; Yu *et al.*, 2006; Bokor *et al.*, 2008). This has led to the view that the septa mainly encode the kinetics of the whisker movements (e.g., frequency, amplitude), while the barrels process spatiotemporal information for object identification (Yu *et al.*, 2006). This is supported, in part, by the demonstration that the septa distribute to the motor cortex and to the contralateral septa (S1), thus possibly serving to coordinate bilateral whisker movements (Hayama and Ogawa, 1997; Chakrabarti *et al.*, 2008; Alloway *et al.*, 2004). The full range of vibrissal functions, however, requires an integration of the two

systems (septa and barrel) that is accomplished at several levels of the brain (Bosman *et al.*, 2011).

The VPL and VPM also receive afferents from other subcortical regions, among them a serotonergic input from the dorsal raphe nucleus, and GABAergic afferents from the RT of thalamus (Vertes, 1991; Cox *et al.*, 1996; Kirifides *et al.*, 2001). Some RT fibers distribute to VP as clusters while others have a wide and more diffuse pattern of termination. This indicates that inhibitory inputs from RT serve different roles in the ventrobasal complex (Cox *et al.*, 1996).

Corticothalamic projections to VPL and VPM are organized in a complex manner and generally reflect the hypothesized way in which afferents to the thalamus are organized as drivers and modulators (see *Some General Aspects of Thalamic Organization* above). Corticothalamic projections originating from pyramidal cells of the upper part of layer 6 (layer 6a) of the barrel cortex terminate exclusively in VPM where they arborize in long rostrocaudally oriented bands or "rods." A "rod" originating from a single barrel in the cortex can make contact with a series of barreloids that together represent an arc (column) of whiskers (Hoogland *et al.*, 1987; Bourassa *et al.*, 1995). Neurons in the deeper parts of layer 6 (layer 6b) of the barrel cortex primarily project to POm but also collateralize to VPM where they form rods (Bourassa *et al.*, 1995). Neurons in layer 6a of the interbarrel (septa) regions distribute to both VPM and POm, whereas those of layer 6b of septa terminate exclusively in POm (Wright *et al.*, 2000; Killackey and Sherman, 2003). All corticothalamic fibers originating in layer 6 send collaterals to the RT and possess long branches with numerous en passant boutons (Bourassa *et al.*, 1995; Levesque *et al.*, 1996; Wright *et al.*, 2000). Fibers originating in layer 5 of the barrel field distribute to POm but not to VPM—or to RT (Veinante *et al.*, 2000b; Killackey and Sherman, 2003). Layer 5 fibers terminate in clusters with large boutons in the posterior thalamic nucleus (Hoogland *et al.*, 1991; Bourassa *et al.*, 1995; Veinante *et al.*, 2000b). Interestingly, based on layer 5 barrel projections to POm, and return POm projections to septa of the barrel cortex (see above), Killackey and Sherman (2003) proposed that layer 5 "driving" inputs to POm would designate POm as a higher order thalamic nucleus and consequently its cortical target (septa of S1) as a higher order cortical area. Thus, as they state, S1 may represent a cortical mosaic; that is, "a true primary cortex (barrel cortex) and a higher order area (non-barrel cortex)" (Killackey and Sherman, 2003, p. 7383).

Functional Aspects

VPL and VPM are the primary thalamic relays for somatic sensation; that is, nociceptive and tactile/proprioceptive information from the body and head, respectively. In the rat, the barreloid region representing the whisker field occupies a large part of VPM, signifying the importance of the rodent whisker system for navigation and exploration. In part, this is an active process in which the whiskers are moved in exploratory activities. As described, the paralemniscal system plays a direct role in "whisking," whereas the lemniscal system conveys contact (touch) information (Pierret *et al.*, 2000; Yu *et al.*, 2006; Diamond *et al.*, 2008; Bosman *et al.*, 2011). For the whisker system to function as an integrated network, signals from different whiskers need to be integrated at several levels along the pathway from the periphery to the barrel cortex, and in particular, in VPM. This is indicated by the complex relationships that exist between the VPM and the barrel cortex, as well as by the actions of the reticular nucleus. For example, while as indicated, individual barreloids project to single cortical barrels, return projections from the cortex take the form of rods in VPM, "interconnecting" barreloids representing several or all whiskers in an arc (Hoogland *et al.*, 1987; Bourassa *et al.*, 1995). Further, the output from a row of cortical barrels converges onto common termination sites in the RT (Welker *et al.*, 1988), and RT sends at least two types of fibers having distinct terminal patterns to VPM which play a significant and differential role in the modulation of information at the level of the VPM (Cox *et al.*, 1996). Reticular projections to the barreloids are whisker-specific; that is, they target the barreloids of the (principal) whisker to which they are responsive (Desilets-Roy *et al.*, 2002).

Since there is extensive literature on electrophysiological and functional aspects of the thalamic relay of somatosensory information in relation to the whisker system, further elaboration on this subject is beyond the scope of this chapter. For a more comprehensive treatment of this subject, the reader is referred to several recent reviews: Petersen (2007), Alloway (2008), Diamond *et al.* (2008), Bosman *et al.* (2011) and Kleinfeld and Deschênes (2011).

POSTERIOR NUCLEUS

The posterior nucleus of thalamus (PO, or the posterior complex) is situated in the caudal part of the thalamus, bordered caudally by the pretectal nuclei. In its caudal aspect, PO is located medial to the medial geniculate nucleus; more rostrally this position is taken by the ventral posterior complex, particularly the ventral posteromedial nucleus. Dorsally, PO is mainly bordered by the lateral posterior nucleus and medially by the intralaminar nuclei. The posterior nucleus in rats is a heterogeneous area, particularly its caudal aspects. Within the region generally considered to include PO, several subnuclei have been identified on the basis of different staining patterns such as the ethmoid, scaphoid, and retroethmoid nuclei (Paxinos *et al.*, 1999). The PO appears

as a relatively cell-sparse area in Nissl-stained sections, standing out against the cell-dense ventral posteromedial nucleus, medially.

Afferent and Efferent Projections

PO consists of three main divisions: the lateral, intermediate, and medial divisions (Jones, 2007). The medial division (or POm), or whisker-related area, occupies a considerable portion of PO in rodents. Like the ventral posterior complex, PO receives significant input from the spinal cord and from the brainstem trigeminal complex (Cliffer *et al.*, 1991; Chiaia *et al.*, 1991a, 1991b; see also *Somatosensory System*, Chapter 24). However, most ascending projections from these systems are less dense and terminate in a more diffuse way in PO than in the adjacent ventral posterior nuclei (Chiaia *et al.*, 1991a; Villanueva *et al.*, 1998). Moreover, projections to PO from the spinothalamic tract and spinal trigeminal nucleus are more pronounced than those from the dorsal column nuclei or principal trigeminal nucleus (McAllister and Wells, 1981; Chiaia *et al.*, 1991a). As discussed, POm is part of the paralemniscal system; that is, one of three trigemino-thalamocortical pathways relaying vibrissal information from the periphery to the barrel cortex (Diamond *et al.*, 2008). POm receives afferents from the spinal trigeminal nucleus and projects to the septa as well as to layers 1 and 5a of the barrel cortex (Fig. 1) (Petersen, 2007; Petreanu *et al.*, 2009; Meyer *et al.*, 2010; Wimmer *et al.*, 2010).

Cortical projections to PO primarily arise from somatosensory areas S1 and S2, but additionally from the motor, premotor (frontal eye field) and insular cortices (Veinante *et al.*, 2000b; Guandalini, 2001). While S1 predominantly projects to dorsal parts of the posterior complex and S2 to more ventral and medial parts, there are substantial areas of overlap (Shi and Cassell, 1998b; Veinante *et al.*, 2000b). The corticothalamic S1 projections to POm predominantly originate from pyramidal layer 5 and layer 6 neurons; those of layer 5 are collaterals of axons distributing to the striatum and brainstem (Levesque *et al.*, 1996; Veinante *et al.*, 2000b; Killackey and Sherman, 2003). Layer 5 (or 5b) fibers to POm originate from both the barrels and septa of S1 and terminate on proximal dendrites of POm cells as large RL-type endings, thus considered "drivers" to POm cells (Sherman and Guillery, 2006). As discussed with respect to VP, this would designate POm as a "higher order" thalamic nucleus, or one that links primary with associational (or higher order) areas of the cortex (Killackey and Sherman, 2003; Sherman and Guillery, 2006).

Functional Aspects

While it is clear that PO receives inputs from various sensory modalities (somatosensory, auditory, visual, and vestibular) which likely converge onto some PO neurons, PO is dominated by the somatosensory modality. POm receives whisker-related information from the trigeminal complex and "driving" input from layer 5 cells of S1, and thus might be considered both a first and higher order thalamic nucleus (Sherman and Guillery, 2006). This, however, may be the case for most thalamic nuclei (see *Some General Aspects of Thalamic Organization* above).

The functional roles for POm have centered on its involvement in whisker behavior. As indicated, the whisker system not only provides information about passive movements of individual or groups of whiskers, but controls the active movements of whiskers (whisking) as an essential parts of exploratory behavior. POm appears to be intimately involved in "whisking," most likely its primary function in the whisker system. Specifically, POm cells respond to multiple whiskers (Veinante *et al.*, 2000a; Brecht and Sakmann, 2002; Yu *et al.* 2006; Bokor *et al.*, 2008), and as such would be poor candidates for discriminating spatiotemporal properties of individual whiskers, but would be well suited to track the synchronous movements of multiple whiskers—or whisking. In this regard, POm cells are reportedly strongly activated during free air whisking but unresponsive to vibrissal contact with external objects (Yu *et al.*, 2006). In addition, POm primarily targets the septa of the barrel cortex (Lu and Lin, 1993; Pierret *et al.*, 2000), and the septa (and associated structures) form part of a separate circuit within the barrel cortex responsible for encoding the kinetics of whisker movements (Kim and Ebner, 1999; Alloway, 2008). Finally, descending layer 5 corticothalamic S1 projections to POm (drivers) appear to provide feedback control over self-initiated whisker movements, possibly to fine tune these movements.

VENTRAL POSTERIOR PARVICELLULAR REGION

Gustatory and Visceral Nuclei

The ventromedial part of the ventral posterior complex is the relay for gustatory and visceral information from the periphery to the insular cortex (Norgren and Leonard, 1973; Cechetto and Saper, 1987; Lundy and Norgren, 2004). The medial part of VP appears to contain neurons that are smaller than those of other parts of VP, and has hence been designated the parvicellular ventral posterior nucleus (VPpc). There is some suggestion, however, that cells of this region are not smaller than other VP neurons but rather are more dispersed than those of the principal VP (Halsell, 1992). VPpc is bordered ventrolaterally by the medial lemniscus and extends medially just ventral to the parafascicular nucleus of thalamus, and more rostrally, ventral to the paracentral and central

medial nuclei. The VPpc is rostrally "replaced" by the ventromedial nucleus. The VPpc is a rather thin sheet of neurons and is generally divided into medial and lateral parts; that is, parvicellular parts of the VPM and VPL nuclei (Cechetto and Saper, 1987; Shi and Cassell, 1998a). The medial part of VPpc (or VPMpc) relays gustatory information (Cechetto and Saper, 1987; Lundy and Norgren, 2004) from the parabrachial complex to the gustatory cortex and hence constitutes the "gustatory thalamus" (Shi and Cassell, 1998a; Lundy and Norgren, 2004; Carleton *et al.*, 2010; Samuelson *et al.*, 2013). All sensory modalities for the oral cavity are represented in VPMpc (Carleton *et al.*, 2010).

Afferent and Efferent Projections

The major input to VPpc is derived from the parabrachial nucleus (Norgren and Leonard, 1973; Cechetto and Saper, 1987; Bester *et al.*, 1999; Krout and Loewy, 2000a; Lundy and Norgren, 2004). Other brainstem afferents to VPpc arise from specific parts of the spinal and principal trigeminal nuclei, as well as from the laterodorsal tegmental nucleus, locus coeruleus, solitary nucleus, A5 region, and the cuneate nucleus (Krout *et al.*, 2002). Subcortically, VPpc projects to the lateral and central nuclei of the amygdala, to the amygdalostriatal transition zone (dorsal to the central amygdaloid nucleus) and rostrally to ventral parts of the caudate-putamen. VPpc projections to cortex are primarily directed to granular and dysgranular areas of the posterior and parietal insular cortices; the anterior insular cortex receives only minor projections from VPpc (Kosar *et al.*, 1986b; Cechetto and Saper, 1987; Turner and Herkenham, 1991; Nakashima *et al.*, 2000). Projections from lateral parts of VPpc terminate more dorsally than those of the medial VPpc (or VPMpc) in the dysgranular insular (DI) cortex (Nakashima *et al.*, 2000). VPMpc fibers are mainly localized to caudal levels of DI, adjacent to the rhinal sulcus. VPMpc cells projecting to the insular cortex are separate from those projecting to the amygdala (Nakashima *et al.*, 2000). Cortical afferents to the VPpc primarily originate from the insular cortical areas to which it projects. The posterior granular and DI cortices mainly distribute to the medial VPpc, whereas the parietal insular cortex projects to the lateral part of VPpc (Shi and Cassell, 1998a, 1998b). The agranular insular cortices send few projections to VPpc (Shi and Cassell, 1998a).

Functional Aspects

The VPpc primarily serves to transfer gustatory and visceral information to the granular and dysgranular insular cortices. The insular cortices are situated between the olfactory cortex, ventrally, and the primary and secondary somatosensory cortices, dorsally. Combined anatomical and physiological studies have demonstrated that the gustatory area of the insular cortex is located mid-rostrocaudally along the length of the insular cortex, between the dorsal/ventral agranular insular cortices, rostrally, and the parietal insular cortices, caudally (Shi and Cassell, 1998a, 1998b). The VMPpc contains a heterogeneous population of cells responding to single or to multiple modalities of sensory stimuli. For example, a sampling of 115 cells of VMPpc showed that 23% of them responded to only one stimulus (unimodal neurons) such as touch, temperature or gustatory stimulation of the oral cavity, whereas 41% of cells responded to various combinations of these three modalities (Verhagen *et al.*, 2003). Regarding gustation, 9% of cells responded solely to gustatory stimuli, 33% to gustatory/touch and another 6% to all three modalities. In effect, then, about half of the population of VPMpc neurons responded to gustatory stimulation. It was further shown that inactivation of VPMpc with muscimol disrupted the taste-responsive activity of 66% of cells of the gustatory cortex (Samuelson *et al.*, 2013). Whereas there does not seem to be a topographical ordering of cell types in the VPMpc, those of the gustatory cortex observe a fairly strict dorsoventral topographic organization. Specifically, touch and temperature of the oral cavity are represented dorsally in the granular insular cortex, whereas taste is represented ventrally in the DI cortex and to a lesser extent in the agranular insular cortex (Kosar *et al.*, 1986a; Yamamoto *et al.*, 1988; Katz *et al.*, 2001). (For a more comprehensive review of the rat gustatory system including the role of the thalamus, see *Gustatory System*, Chapter 26.)

MEDIAL GENICULATE NUCLEUS

The medial geniculate nucleus (MG) forms the caudal extension of the thalamus and extends into the mesencephalon. The rostral part of MG is located ventromedial to the lateral geniculate complex. The MG is the principal auditory relay nucleus of the thalamus and consists of several subnuclei which have different functions within the auditory system. The MG can be divided into medial (MGm), ventral (MGv) and dorsal (MGd) divisions (Jones, 1985, 2007; Clerici and Coleman, 1990). The "auditory" thalamus further consists of a number of smaller nuclei that are positioned medial and ventromedial to the MG complex; that is, the suprageniculate nucleus (SG), the posterior limitans thalamic nucleus (PLi), the posterior intralaminar thalamic nucleus (PIL) and the lateral part of the parvicellular subparafascicular nucleus (SPF). A marginal zone (MGmz) "covers" dorsal, lateral, and ventral aspects of the MGd and MGv. (For an in-depth overview of the auditory thalamus, see *Auditory System*, Chapter 29.)

The MGd and MGv are separated by a midgeniculate bundle which is mainly derived from the inferior colliculus (IC). The MGv can be further divided into a

ventral and an ovoid part based on fiber architectonics and cytoarchitectonics (Clerici and Coleman, 1990). The main cell type in MGv is small to medium-sized and has bushy tufted dendrites forming fibrodendritic laminae that are oriented with respect to fiber bundles from the IC in a dorsolateral to ventromedial direction (Winer *et al.*, 1999a). In the oval part of the MGv, the orientation of cells and collicular afferents is more spiral-like (Clerici and Coleman, 1990). The MGd is rather heterogeneous in neuronal composition and can be subdivided into several subnuclei. Neurons of the MGd have radiating, "tufty" dendrites (Winer *et al.*, 1999a). The neuronal population of MGm is also heterogeneous, consisting of small to magnocellular neurons. Few interneurons (about 1%) have been identified in the MG complex, most of which are GABAergic (Winer and Larue, 1988; Winer *et al.*, 1999a).

Afferent and Efferent Projections

Ascending fibers to MG primarily originate from the IC. While the MGv is mainly targeted by the central nucleus of the IC, the MG complex as a whole receives fibers from the cortex of the IC. The MGm also receives input from the central nucleus of IC (Jones, 1985, 2007; LeDoux *et al.*, 1987). The central nucleus of the IC is strictly tonotopically organized, and the MGv transfers this highly organized information to the primary auditory cortex (AUD) of the temporal lobe (Winer *et al.*, 1999b). As such, the MGv, in particular the ovoid subnucleus, forms the main thalamic relay for the auditory area.

IC terminals in MG are variable in size and include small and large profiles, the larger ones being predominant in the MGv (Bartlett *et al.*, 2000). This heterogeneity in the morphology of the ascending colliculo-geniculate projections indicates a greater complexity in auditory pathways than those of other sensory thalamic nuclei. Furthermore, part of the collicular afferents to MGv and MGd appear to be inhibitory (Bartlett and Smith, 1999). Yet, the general organization of ascending driving inputs and descending modulatory cortical fibers seems also to apply to MGv. While MGv and MGd are devoid of return projections to IC, the inferior colliculus receives input from the MGm, the SG, the PIL and the subparafascicular nucleus (SPF) of the medial geniculate complex (Senatorov and Hu, 2002; Winer *et al.*, 2002).

The MG, as well as the SG and PIL, not only receives auditory information from the IC but is also contacted by fibers from the superior colliculus (Linke, 1999). In addition, the MGm receives direct projections from the dorsal cochlear nucleus, bypassing the IC. In view of the fact that the superior colliculus and the dorsal cochlear nucleus receive multimodal information, the medially located subnuclei of MG likely process more than auditory information (Malmierca *et al.*, 2002).

Corticothalamic fibers from the primary auditory (AUD) cortex and from secondary auditory areas (or auditory belt cortex), Te2 and Te3, terminate in different parts of the medial geniculate complex. AUD distributes to MGv in a topographical and tonotopic manner. The rostral AUD, which contains neurons that respond to high frequencies, sends projections to the ventral MGv, whereas AUD neurons with lower frequency characteristics, located more caudally in AUD, innervate the dorsal MGv (Shi and Cassell, 1997; Hazama *et al.*, 2004; Kimura *et al.*, 2005). AUD fibers also distribute to the auditory divisions of the thalamic reticular nucleus (Hazama *et al.*, 2004; Kimura *et al.*, 2005, 2012). Projections from AUD to MGd are modest and target its ventral aspect (Shi and Cassell, 1997; Hazama *et al.*, 2004; Kimura *et al.*, 2005).

The auditory belt cortex distributes most densely to MGd. The posterodorsal division of Te2 targets the rostral portion of MGd and the SG (Kimura *et al.*, 2004). Area Te3 projects densely to the dorsal part of MGd, directly adjacent to the lateral posterior thalamic nucleus which receives pronounced input from Te2 (Shi and Cassell, 1997, Kimura *et al.*, 2004). At the ultrastructural level, corticothalamic projections arising from the primary auditory cortex terminate as small and large ("giant") terminals in the MG complex. The smaller, most numerous corticothalamic terminals are present throughout the MG, the larger terminals are mainly found in the ventral part of MGd (Rouiller and Welker, 1991) and dorsal aspects of the marginal division (MGmz) (Bartlett *et al.*, 2000).

The output of MG is primarily directed to the primary and secondary auditory regions of cortex, with additional projections to adjacent areas of the temporal lobe, the basal ganglia and amygdala. MGv fibers mainly terminate in layers 3 and 4 of AUD, and less so in layers 1, 5, and 6 (Romanski and LeDoux, 1993; Cetas *et al.*, 1999; Winer *et al.*, 1999b, Smith *et al.*, 2012). The projections from MGv to the AUD are convergent, highly topographic, spatially focal, and originate from only one type of MGv neuron. With the exception of its caudal pole, MGv does not distribute outside the auditory region. Further, aside from a small percentage of MGv neurons which make synaptic contacts with GABAergic interneurons, most MGv fibers terminate on pyramidal cells (Vernby *et al.*, 2006; Smith *et al.*, 2012). MGd also distributes to layers 3 and 4 of AUD, but more heavily to the "auditory belt" cortex. More specifically, MGd neurons target posterodorsal and ventral components of these auditory regions, which lie immediately below the ventral division of AUD (Arnault and Roger, 1990; Winer *et al.*, 1999b; Kimura *et al.*, 2003, 2004, 2007a, 2010; Donishi *et al.*, 2006). MGd fibers primarily synapse on dendritic spines or shafts of pyramidal cells, with a few

contacts on GABAergic cells of the granular layer (Smith *et al.*, 2012). The projections from MGm to the cortex are divergent, similar to those of MGd. MGm neurons favor cortical areas Te2 and Te3, as opposed to the primary auditory cortex. Overall, projections arise from several types of geniculate neurons and largely terminate in middle cortical layers of these auditory zones (Roger and Arnault, 1989; Arnault and Roger, 1990; Winer *et al.*, 1999b; Kimura *et al.*, 2003).

All medial geniculate nuclei, except MGv, also distribute to temporal association areas such as the perirhinal cortex and to the amygdala. A common feature of the medially located MG, the SG, and the PIL is that each targets the upper part of layer 1 of temporal association cortices—in addition to more specific projections to deeper layers (Linke and Schwegler, 2000). SG also distributes to the medial agranular (frontal) cortex (AGm) (Kurokawa and Saito, 1995). Projections to the amygdala, primarily to the lateral nucleus and some to the basal nuclei, arise from the medially located MGm, the SG, and PIL, as well as from lateral parts of the parvicellular subparafascicular nucleus (LeDoux *et al.*, 1985, 1990; Turner and Herkenham, 1991; Namura *et al.*, 1997; Doron and LeDoux, 1999, 2000). In addition, medial subnuclei of the MG complex reciprocally connect with structures of the basal ganglia including caudal parts of the dorsal striatum, the amygdalostriatal transition zone and the posterior globus pallidus (Moriizumi and Hattori, 1992; Shammah-Lagnado *et al.*, 1996).

Functional Aspects

As evident from anatomical and physiological data, MGv is the main thalamic relay to the primary auditory cortex, subserving specific tonal analysis of sounds (LeDoux *et al.*, 1987; Romanski and LeDoux, 1993; Bordi and LeDoux, 1994a; Winer *et al.*, 1999b). The functions of the MGd are less clear, but are probably concerned with non-tonal aspects of sounds and integration with other sensory modalities. The projections from the IC to MGd stem from a region of the colliculus that is not tonotopically organized. Similarly, MGd projections to temporal cortices are also less strictly organized and mainly terminate in auditory association areas (LeDoux *et al.*, 1987; Clerici and Coleman, 1990). Reciprocal MGd connections with the posterodorsal division of Te2 suggest a role for MGd in the Te2 involvement in auditory spatial processing (Kimura *et al.*, 2004, 2010; Smith *et al.*, 2012). The superficial, dorsal region of MGd may be a visual-recipient rather than an auditory-recipient zone of the MG complex (Sun *et al.*, 1996; Shi and Cassell, 1997).

The MGm, like MGd, is not tonotopically organized and has multimodal connections with auditory and non-auditory structures (He, 2003). The functions of MGm, as well as those of SG, SPF and PIL, need to be interpreted in the context of their connections with temporal association cortices, the amygdala, and the basal ganglia. In fact, the relationship of these MG nuclei to the amygdala has been the focus of numerous studies examining their role in auditory-associated emotional responses. It is clear that these pathways connecting the auditory system with limbic regions of the brain participate in emotional and mnemonic aspects of sounds. The studies of LeDoux and colleagues have demonstrated that MGm, PIL and lateral part of SPF serve to link neutral stimuli (sounds) to emotionally negative (or noxious) events—underlying fear conditioning (LeDoux, 1993, 2000). The convergence of auditory and somatosensory information, as well as that from other sensory modalities, in MGm and associated medial auditory nuclei appears to provide the neuronal basis for such associations which are then behaviorally expressed in the amygdala (LeDoux *et al.*, 1987; Bordi and LeDoux, 1994a, 1994b; Linke *et al.*, 1999; LeDoux, 2000; Weinberger, 2011). In addition to the amygdala, MGm and PIL are critical for the expression of auditory fear conditioning (LeDoux, 2000; Maren *et al.*, 2001; Komura *et al.*, 2001; Parsons *et al.*, 2006; Han *et al.*, 2008; Orsini and Maren, 2009), in that lesions of these nuclei prevent auditory fear conditioning (LeDoux *et al.*, 1984, 1986; Campeau and Davis, 1995). The MGm and PIL have also been shown to be links in pathways leading to the neuroendocrine expression of audiogenic stress via the amygdala, and ultimately, the hypothalamic paraventricular–hypophysis axis (Campeau *et al.*, 1997; Campeau and Watson, 2000). Thus, the medially located nuclei of MG are important in associating auditory signals with other sensory events, and the "translation" of this information, via the amygdala and temporal association cortices, into behavioral and emotional responses (Lanuza *et al.*, 2008).

VENTRAL ANTERIOR AND VENTRAL LATERAL NUCLEI

While the ventral anterior (VA) and ventral lateral (VL) nuclei of primates are clearly separate and distinct groups (Jones, 2007), the VA and VL nuclei of rats are cytoarchitectonically similar and consequently are generally combined, with the designation the ventral anterior/ventral lateral (VA/VL) complex—or VAL (Swanson, 2004). The VA/VL complex occupies an extensive nuclear area located between the ventral posterior nuclei ventrolaterally, the posterior and lateral dorsal nuclei dorsally, and the intralaminar and anterior nuclei dorsomedially. Ventromedially, the VA/VL complex abuts the ventromedial nucleus. The VA/VL complex is a rather cell sparse region and contains relatively large neurons. In acetylcholinesterase-stained sections, VA/VL exhibits low activity and is therefore readily

delineated from surrounding nuclei such as the RT and the anterior complex (Paxinos and Watson, 2014).

Afferent and Efferent Projections

VA/VL receives afferents from three major sources: the substantia nigra-pars reticulata (SNr), the globus pallidus (GP), and the cerebellum. VA/VL is also reciprocally connected with somatomotor and premotor cortices. Additional subcortical inputs derive from the vestibular nuclei, the anterior pretectal nucleus, and the zona incerta (Shiroyama *et al.*, 1999; Barthó *et al.*, 2002; Bokor *et al.*, 2005; Giber *et al.*, 2008). Cerebellar inputs arise from deep cerebellar nuclei, primarily the lateral and interpositus nuclei (Angaut *et al.*, 1985; Sawyer *et al.*, 1994a, 1994b; Aumann *et al.*, 1994, 1996), while those of GP originate from the internal segment of GP (GPi)—or the rat homolog, the entopeduncular nucleus (EN) (Deniau and Chevalier, 1992; Deniau *et al.*, 1992; Sakai *et al.*, 1998; Sakai and Grofova, 2002; Sakai and Bruce, 2004; Kuramoto *et al.*, 2011).

There is a segregation of inputs to VA and VL in primates such that SNr projects selectively to VA, GPi to the oral (or anterior) part of VL, and the cerebellum to the caudal (or posterior) part of VL (Jones, 2007). A similar segregation of inputs exists for the rat; that is, major afferents to VA/VL terminate in discrete, essentially non-overlapping zones of VA/VL. Specifically, fibers from the basal ganglia (SNr and EN) distribute to rostromedial parts of VA/VL, whereas those from the cerebellum innervate caudolateral aspects of VA/VL (Angaut *et al.*, 1985; Deniau *et al.*, 1992; Sakai *et al.*, 1998; Bodor *et al.*, 2008; Kuramoto *et al.*, 2011). Within the rostromedial (or rostro-ventromedial) VA/VL, there is a further segregation of inputs from SNr and EN such that SNr fibers distribute virtually throughout the rostro-ventromedial VA/VL, while those of EN are mainly restricted to caudolateral parts of this region. SNr projections to VA/VL significantly outnumber those from EN (Kuramoto *et al.* 2011).

The terminal endings of basal ganglia (SNr and EN) and cerebellar fibers distributing to VA/VL are also distinctly different: SNr/EN boutons are mainly large and GABAergic, while cerebellar terminals are large and glutamatergic—VGLUT2 positive (Kha *et al.*, 2000, 2001; Bokor *et al.*, 2005; Lavallée *et al.*, 2005; Bodor *et al.*, 2008; Kuramoto *et al.*, 2011). Cerebellar terminals in VA/VL display properties of "drivers"; that is, they contain large round vesicles (or the RL type) interspersed with closely packed small round vesicles (Sherman and Guillery, 2006). This morphology is consistent with the excitatory nature of the cerebellothalamic projections to VA/VL (Sawyer *et al.*, 1994b). These large cerebellar originating terminals, however, make up a minority of presynaptic terminals in VA/VL, with the majority being of the RS-type originating from the cortex. While SNr/EN fibers to VA/VL also terminate as large boutons, they are GABAergic and hence by their inhibitory nature would not qualify as drivers, despite the fact that inhibition of SNr/EN cells (disinhibition) results in a pronounced excitation of thalamocortical VA/VL fibers—akin to driving (Sherman and Guillery, 2006).

In addition to basal ganglia and cerebellar afferents, VA/VL receives pronounced input from somatomotor cortices (M1, M2 and S1) as well as from frontal and parietal cortical areas. In particular, the rostromedial sector of VA/VL is targeted by fibers from the prefrontal cortex (Sesack *et al.*, 1989; Condé *et al.*, 1990; Reep and Corwin, 1999; Vertes, 2002). As indicated, cortical inputs are most likely the source of RS-type (modulatory) projections to VA/VL.

Comparable to the differential distribution of afferents to VA/VL, there appears to be a similar segregation of outputs from VA/VL to somatomotor cortices (Aldes, 1988; Yamamoto *et al.*, 1990; Aumann *et al.*, 1998; Mitchell and Cauller, 2001; Kuramato *et al.*, 2009; Hooks *et al.*, 2013). Using viral vectors to trace projections of single neurons of VA/VL, Kuramoto *et al.* (2009) described differing patterns of projections from two regions of VA/VL, namely, from a rostromedial area that receives inhibitory fibers from the basal ganglia, termed an inhibitory zone (IZ), and from a caudolateral region that receives excitatory cerebellar inputs, termed an excitatory zone (EZ) (Fig. 2). IZ neurons mainly terminate in layer 1 of somatomotor cortices and send collateral projections to the striatum. By contrast, EZ neurons distribute to middle cortical layers and do not branch to the striatum. Among other things, this suggests that the basal ganglia dominated region of VA/VL completes a loop with the striatum (striatum>SNr/EN>VA/VL>striatum) and also via collaterals, directly affects the cortex. Inhibitory (basal ganglia) and excitatory (cerebellum) regions of VA/VL modulate different lamina of the cortex—with likely differential effects on the output and function of the motor cortex (see below).

Functional Aspects

The VA/VL complex is the main motor thalamic relay to the cortex. As discussed, VA/VL receives major inputs from the basal ganglia (BG) and the cerebellum, which largely target non-overlapping regions of VA/VL. In addition, neurons from BG and cerebellar receptive zones of VA/VL distribute to separate lamina of the motor cortex: from the BG receptive region to layer 1 and from the cerebellar zone to deep layers, including layer 5. Based in part on these hodological differences, Kuramoto *et al.* (2009) proposed that the two main VA/VL thalamocortical systems serve different functions in motor control. Specifically, basal ganglia information

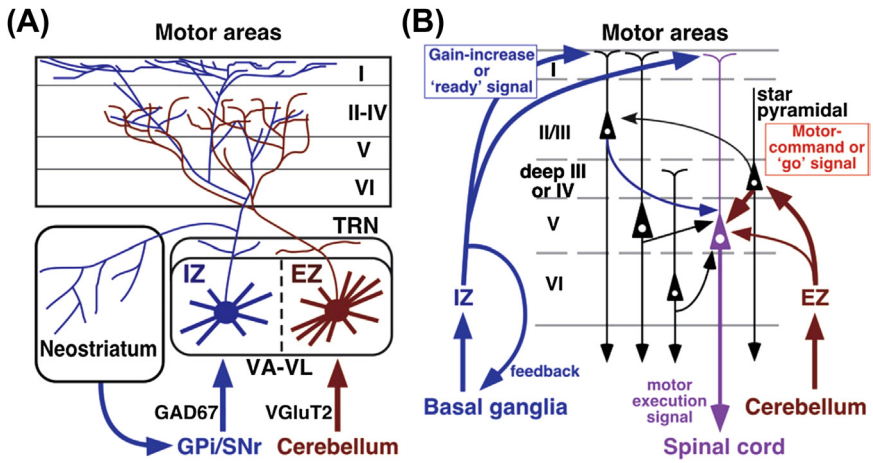

FIGURE 2 (A) Schematic diagram of motor thalamocortical projections. The rostromedial sector of the ventral anterior and ventral lateral (VA-VL) nuclei of thalamus mainly receives inhibitory inputs from the basal ganglia and has thus been designated the inhibitory zone (IZ), whereas the caudolateral VA-VL receives excitatory afferents from the cerebellum and has been termed the excitatory zone (EZ). IZ neurons send axons to the striatum (neostriatum) as well as to the cortex, whereas EZ neurons project selectively to the cortex. Furthermore, the main cortical target of EZ neurons is layers II-V of the motor cortex while that of IZ neurons includes layer I. (B) Function of IZ and EZ neurons in the context of motor execution. Basal ganglia information relayed through the IZ zone of VA-VL to distal apical dendrites of layer I of the motor cortex modulates the "gain" of layer V pyramidal cells, thereby producing a readiness signal for movement. By comparison, cerebellar signals relayed through the EZ zone of VA-VL to the basal dendrites/soma of layer IV/V cells serve as a motor command (or go signal) for the execution of movement. See text for further details. *From Kuramoto, E., Furuta, T., Nakamura, K.C., Unzai, T., Hioki, H., & Kaneko, T. (2009). Two types of thalamocortical projections from the motor thalamic nuclei of the rat: a single neuron-tracing study using viral vectors.* Cerebral Cortex *19, 2065–2077.*

relayed through VA/VL to the distal apical dendrites of layer 1 of the motor cortex modulates the "gain" of layer 5 pyramidal cells, thereby producing a readiness signal for movement. By comparison, cerebellar signals relayed through VA/VL to the basal dendrites/soma of layer 4/5 cells serve as a motor command (or go signal) for the execution of movement (Fig. 2). In this sense, the motor thalamus is critical both for preparing and initiating movements (Kuramoto *et al.*, 2009).

The thalamocortical and basal ganglia systems participate in a number of parallel, functionally segregated circuits (Deniau *et al.*, 1994, 1996; Groenewegen *et al.*, 1990, 1999; Haber and Calzavara, 2009). As will be discussed with other thalamic nuclei, there are multiple anatomical/functional loops linking the cortex, basal ganglia and thalamus. These parallel systems appear to consist of a main loop from the cortex to striatum to thalamus and back to the point of origin in the cortex, and a "secondary" loop from the basal ganglia to the thalamus and then directly back to the basal ganglia. Accordingly, the thalamus (or VA/VL) is pivotally positioned to modulate corticostriatal circuitry through multiple routes.

VENTRAL MEDIAL NUCLEUS

The ventral medial nucleus (VM) of thalamus is a rostrocaudally elongated nucleus located in the rostromedial part of the thalamus. Medially, VM can be clearly distinguished from the cell-sparse submedial nucleus. The mammillothalamic tract ascends just medial to VM. Dorsally and laterally, VM is bordered by VA/VL and more caudally by VPM and VPL. VM can be differentiated from these nuclei in Nissl-stained sections as it contains relatively small and densely packed neurons. In acetylcholinesterase-stained sections, the ventral medial nucleus exhibits low activity (Paxinos *et al.*, 1999). With respect to calcium-binding proteins, VM contains calbindin D28K-positive neurons throughout the nucleus, while calretinin-positive cells are restricted to its medial part (Arai *et al.*, 1994). A low density of calbindin D28K- and parvalbumin-positive fibers is present in the ventral medial nucleus.

Afferent and Efferent Projections

The ventral medial nucleus, along with VA/VL, comprises the motor thalamus. Major inputs to VM originate from the basal ganglia, mainly from the substantia nigra-pars reticulata (SNr) and to a lesser degree from the entopeduncular nucleus (EN) (Herkenham, 1979; Deniau *et al.*, 1992; Sakai *et al.*, 1998; Kuramoto *et al.*, 2011). Unlike VA/VL, VM receives few fibers from the cerebellum. Kuramoto *et al.* (2011) described the presence of large VGLUT2 terminals of cerebellar origin in VA/VL (see above), but failed to observe them in VM, and further showed that small to medium sized VGLUT2-containing varicosities in VM persisted after removal of cerebellar afferents to the thalamus suggesting a non-cerebellar origin. As discussed below, a likely source of excitatory (glutamatergic) input to VM is the

dorsal reticular nucleus of the medulla—which reportedly serves to relay nociceptive information to VM (Villanueva *et al.*, 1998). SNr and EN fibers to VM preferentially target medial parts of VM, while lateral regions are less densely innervated (Carter and Fibiger, 1978; Herkenham, 1979; Deniau *et al.*, 1994; Groenewegen *et al.*, 1999). Other subcortical projections to VM originate from deep layers of the superior colliculus, deep mesencephalic nucleus, PAG, raphe nuclei, the peripeduncular region, laterodorsal tegmental nucleus, locus coeruleus, the parabrachial region, and the trigeminal complex (Herkenham, 1979; Krout and Loewy, 2000a, 2000b; Krout *et al.*, 2001, 2002). Cortical afferents to VM arise from a rather extensive region of the frontal cortex including the primary and secondary motor cortices (Herkenham, 1979; Sesack *et al.*, 1989; Hurley *et al.*, 1991; Desbois and Villanueva, 2001; Vertes, 2002).

VM distributes fairly widely throughout the cortex, most heavily to rostral, frontal regions of cortex but less so to more caudal areas (Herkenham, 1979; Condé *et al.*, 1990; Reep *et al.*, 1996; Desbois and Villanueva, 2001; Hoover and Vertes, 2007). With respect to laminar organization, VM fibers terminate in superficial parts of layer 1 over widespread regions of the frontal cortex, with a concentration in somatomotor cortices (Herkenham, 1979; Arbuthnott *et al.*, 1990; Condé *et al.*, 1990, 1995; Reep *et al.*, 1994; Reep and Corwin, 1999; Desbois and Villanueva, 2001; Mitchell and Cauller, 2001; Hoover and Vertes, 2007).

Functional Aspects

While VM together with VA/VL constitute the motor thalamus, there are anatomical differences between VM and VA/VL signifying functional distinctions. For instance, unlike VA/VL, VM does not receive input from the cerebellum. Further, SNr differentially distributes to these two divisions of the motor thalamus. The dorsal SNr projects to VM, terminating on distal dendrites of VM neurons, whereas the ventral SNr targets VA/VL forming axosomatic synapses with VA/VL cells (Sakai *et al.*, 1998; Cebrian *et al.*, 2005; Gulcebi *et al.*, 2012). This arrangement has led to the proposal that ventral SNr afferents to VA/VL (axosomatic endings) would have a marked, direct effect on VA/VL neurons. By comparison, dorsal SNr terminals on thin, distal dendrites of VM neurons would exert a more modulatory influence on VM cells (Sakai *et al.*, 1998). Consistent with this, VM distributes to layer 1 over a large area of the frontal cortex, whereas the output of VA/VL is mainly bound for motor cortices to thereby exert a direct influence on motor activity (see above).

As such, VM might be viewed as playing a modulatory role in thalamocortical circuitry, and by virtue of distributing widely throughout the frontal cortex, appears positioned to influence multiple corticostriatal systems (Groenewegen *et al.*, 1999). VM may be a source of attentional effects on the cortex, and it is thus noteworthy that the dorsomedial SNr that targets VM receives strong input from nucleus accumbens which participates in attentional mechanisms (Deniau and Chevalier, 1992; Deniau *et al.*, 1994, 1996; Montaron *et al.*, 1996).

A proposed role for VM in attention gains further support from studies by Villanueva and co-workers describing the involvement of the lateral part of VM (VMl) in nociception (Villanueva *et al.*, 1998; Monconduit *et al.*, 1999, 2003; Desbois and Villanueva, 2001; Monconduit and Villanueva, 2005). Cells of the dorsal reticular nucleus of the medulla are activated by various types of nociceptive stimuli applied over the body, and this information is then transmitted to the lateral division of VM (VMl), and from there to an extensive region of the frontal cortex, most heavily to somatomotor cortices (Villanueva *et al.*, 1998; Monconduit *et al.*, 1999). Accordingly, through VMl, pain signals gain direct access to widespread regions of the cortex. This "fast" route for the transfer of nociceptive information to the cortex may prime the cortex for coordinated motor and behavioral responses to painful stimuli (Monconduit *et al.*, 1999; Monconduit and Villanueva, 2005).

MEDIODORSAL NUCLEUS

The mediodorsal nucleus (MD) of the thalamus is located medial and dorsal to the internal medullary lamina of thalamus and ventral to the stria medullaris/habenular complex. The paraventricular and intermediodorsal nuclei are situated between the left and right sides of MD. The mediodorsal nucleus is bordered rostrally by the paratenial nucleus (PT) and caudally by the parafascicular nucleus of the intralaminar thalamus. Therefore, MD is virtually "encircled" by midline and intralaminar nuclei with which it shares several connections. The MD in rats is divided into three segments: medial (MDm), central (MDc) and lateral (MDl) divisions, and generally a fourth part, lateral to MDl, termed the paralamellar MD (MDpl)—as it abuts the internal medullary lamina (Leonard, 1969, 1972; Krettek and Price, 1977; Groenewegen, 1988). Distinctions between segments are based on cytoarchitectonics and input–output relationships. The central segment is rich in myelinated fibers and, in that respect, stands out from the other segments. The lateral segment has the highest activity for acetylcholinesterase (Paxinos *et al.*, 1999). The differential distribution of calcium-binding proteins also confirms distinctions between segments. This is most apparent with respect to calbindin D28K, which is present in both cell bodies and fibers in the medial and lateral segments, but much less so in the central segment (Arai *et al.*, 1994). Stellate and fusiform cells make up the majority of the

neuronal populations of MD, both considered to be thalamocortical neurons (Kuroda *et al.*, 1992, 1998). Stellate cells are most abundant in MDc, whereas fusiform neurons are more numerous in MDm and MDl. Interneurons are very rare, if present, in the rat mediodorsal nucleus. Dendrites of stellate and fusiform neurons largely remain within the segment in which their soma resides, stressing the morphological distinction between the segments (Kuroda *et al.*, 1992). On the basis of differences in fiber densities and connections, Ray and Price (1992) further subdivided MDl into dorsal and ventral parts. In general, the rat MDm and MDc are thought to be homologous to the medial magnocellular segment of the primate MD, while the rat MDl is homologous to the primate parvocellular, lateral segment of MD.

Afferent and Efferent Projections

The different segments of MD are characterized by distinct input–output relationships. On the whole, MD is strongly reciprocally connected with the medial, orbital and insular prefrontal cortices (Krettek and Price, 1977; Reep and Winans, 1982; Groenewegen, 1988; Condé *et al.*, 1990; Ray and Price, 1992; Reep and Corwin, 1999; Vertes, 2002, 2004; Jasmin *et al.*, 2004; Gabbott *et al.*, 2005; Rotaru *et al.*, 2005; Hoover and Vertes, 2007, 2011). In fact, the prefrontal cortex of rodents was initially designated as a "MD projection cortex" (Leonard, 1969; Uylings and van Eden, 1990). As with other regions of the PFC (see below), connections between MD and the medial PFC (mPFC) are highly topographically organized such that medial to lateral segments of MD are mapped onto ventral to dorsal regions of the mPFC. Specifically, the medial part of MD (MDm) connects with the infralimbic cortex (IL) (Fig. 3), the lateral part of MDm and MDc with the prelimbic cortex and ventral anterior cingulate (AC) cortex, the MDl with the dorsal AC, and MDpl with the medial agranular (motor) cortex (AGm or M2) (Groenewegen, 1988; Ray and Price, 1992; Vertes, 2002; Hoover and Vertes, 2007). Similar to the mPFC, specific segments of MD connect with distinct regions of the orbital cortex. MDm is reciprocally linked to the medial orbital (MO) cortex, MDc to the lateral orbital cortex, MDl to the ventral (VO) and ventrolateral (VLO) orbital cortices, and ventral aspects of MDc and MDl to the dorsolateral orbital (DLO) cortex (Groenewegen, 1988; Ray and Price, 1992; Hoover and Vertes, 2011). With respect to the insular cortex, MDm interconnects with the dorsal (AId) and posterior (AIp) agranular insular cortices, and MDc with the ventral agranular insular cortex (AIv) (Groenewegen, 1988; Ray and Price, 1992; Jasmin *et al.*, 2004). While there is a clear segregation of inputs/outputs of the various segments of MD with subregions of the PFC, there is also fairly considerable overlap in these connections—likely signifying shared functional properties.

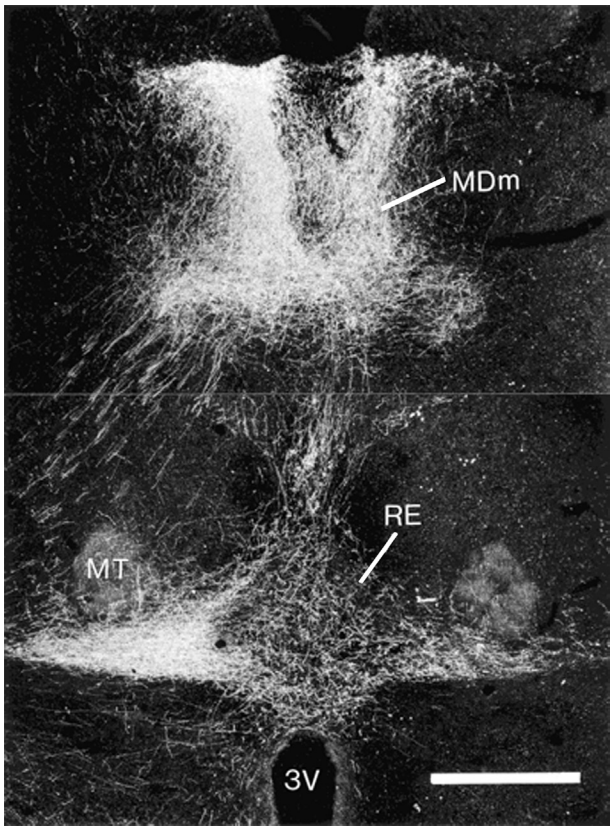

FIGURE 3 Darkfield photomicrograph of a transverse section through the diencephalon showing patterns of labeling at the midthalamus produced by an injection of the anterograde tracer, PHA-L, in the rat infralimbic cortex. Note the pronounced labeling in the medial division of the mediodorsal (MDm) nuclei, dorsally, and the nucleus reuniens (RE), ventrally. *Abbreviations*: MT, mammillothalamic tract; 3V, third ventricle. Scale bar=500 μm. *From Vertes, R.P. (2002). Analysis of projections from the medial prefrontal cortex to the thalamus in the rat, with emphasis on nucleus reuniens.* Journal of Comparative Neurology *442, 163–187.*

A seemingly unique feature of MD projections to the cortex is that they are virtually restricted to the PFC (orbitomedial and insular cortices) and only minimally extend to other regions of the cortex. In addition, whereas MD receives substantial subcortical inputs (see below), the subcortical projections of MD are limited and mainly directed to the dorsal and ventral striatum.

Most subcortical structures projecting to MD target specific segments of MD, but some (mainly of the brainstem) distribute throughout MD (Young *et al.*, 1984; Groenewegen, 1988; Kuroda and Price, 1991a, 1991b; Ray and Price, 1992; Vertes, 1991, 1992; Zahm *et al.*, 1996; Morin and Meyer-Berstein, 1999; Vertes *et al.*, 1999; Krout *et al.*, 2002; Tripathi *et al.*, 2012). As developed further below, MD is typically described as composed of three functional units: motor (MDl/MDpl), olfactory (MDc) and limbic (MDm), and with some overlap, subcortical inputs to MD reflect these functional divisions. Aside from sites projecting to all divisions of MD, afferents

to lateral segments of MD (MDl/MDpl) mainly derive from structures of the basal ganglia and the brainstem. These include the internal segment of the globus pallidus (GPi) and the substantia nigra-pars reticulata (SNr) of the basal ganglia, and the superior colliculus, pretectum, and acetylcholine-containing laterodorsal tegmental nucleus (LDT) of the brainstem. Inputs to MDc predominately originate from olfactory structures including the piriform cortex, endopiriform nucleus, olfactory tubercle, horizontal limb of diagonal band nucleus and the lateral preoptic area. Afferents to MDm arise from a greater number and more diverse set of structures than to the other divisions likely reflecting its involvement in limbic-associated functions. They include inputs from the nucleus accumbens/ventral pallidum, diagonal band nuclei, the anterior cortical, basal and accessory basal nuclei of the amygdala, the ventral tegmental area (VTA), the substantia nigra-pars compacta (SNc), the supramammillary nucleus, and the lateral entorhinal cortex (Groenewegen, 1988; Ray and Price, 1992; Vertes, 1992).

While the foregoing indicates a relatively clear segregation of inputs to separate segments of MD, the overlap indicates some integration across segments of MD. All divisions of MD receive common inputs from several sites including the reticular nucleus of thalamus, VTA, the mesopontine reticular formation, pedunculopontine tegmental nucleus, locus coeruleus, LDT, and the dorsal and median raphe nuclei of the brainstem (Groenewegen, 1988; Vertes, 1991; Vertes *et al.*, 1999; Krout *et al.*, 2002). The input-output relationships of MD appear so structured that separate segments/divisions of MD could function independently or as a whole dependent on task demands.

Functional Aspects

The different segments of the mediodorsal nucleus appear to serve distinct functions, but the "resolution" provided by behavioral studies using lesions or inactivation of MD is generally too coarse to reliably distinguish between different parts of MD. Furthermore, MD borders the midline and intralaminar thalamic nuclei and their possible involvement would also hinder the interpretation of lesion studies. Despite this, the functions of MD have been fairly extensively investigated and should be considered within the context of limbic and basal ganglia-thalamocortical circuits with which MD is linked (Groenewegen *et al.*, 1990; Deniau *et al.*, 1994; Zahm, 2000; Block *et al.*, 2007; Aggleton *et al.*, 2011; Mailly *et al.*, 2013). Specifically, the connections of MDm suggest a role in limbic-related functions, MDc in olfactory behaviors, and MDl/MDpl in motor functions.

The feature that most defines MD is its unique relationship with the prefrontal cortex and hence MD functions parallel those of the PFC. One function commonly associated with MD is behavioral flexibility—or the capacity to alter behavior to meet changing contingencies (McAlonan *et al.*, 1993; Hunt and Aggleton, 1998; Block *et al.*, 2007; Dolleman-van der Weel *et al.*, 2009). Rats with MD lesions (or inactivation) are unable to readily switch from one response to another in the face of changing task demands. Although several factors are likely involved, the deficit is generally attributed to perseverative responding, or maintaining a previously rewarded response strategy despite it being incorrect or unrewarded upon changed conditions. For example, Block *et al.* (2007) demonstrated that rats with bilateral MD lesions, or disconnecting MD from the mPFC, were unable to successfully switch from a "response" strategy (e.g., all right turns) to a visually cued strategy (or vice versa) on a four arm cross-maze. They postulated that MD "directs" the mPFC to switch strategies and the mPFC, in turn, suppresses incorrect responses in favor of correct ones to the new paradigm. Perhaps an even more striking example of failures in set shifting with MD lesions involved the use of a relatively undemanding reference memory task in the water maze (Dolleman-van der Weel *et al.*, 2009). MD lesioned rats were slow to acquire a water maze task, which reportedly was the result of "perseverance" of edge swimming (thigmotaxis) carried over from pretraining. These rats were also impaired in the change of task conditions in the probe test from a hidden platform to a visible one. In effect, even though the platform was visible, MD lesioned rats continued to search for the hidden platform—a clearly perseverative response. The deficits in switching strategies described with MD lesions are characteristic (or a hallmark) of dysfunctions of the prefrontal cortex (Ragozzino *et al.*, 1999; Birrell and Brown, 2000; Dias and Aggleton, 2000; Stefani *et al.*, 2003; Floresco *et al.*, 2006; Rich and Shapiro, 2009). This clearly points, then, to the interdependence of the two structures in these behaviors—or otherwise stated, the integrative actions of MD and the mPFC appear vital for flexible choice behavior.

In addition to a role in behavioral flexibility, the mPFC is an important component of an extended circuitry subserving recognition memory; that is, a circuitry which also includes the perirhinal cortex, hippocampus and MD (Ennaceur *et al.*, 1996; Norman and Eacott, 2004; Barker *et al.*, 2007; Barker and Warbuton, 2011; Cross *et al.*, 2012). Recognition memory involves the ability to identify stimuli based on previous experience with them, and judgments can be made using various types of information such as an object's characteristics (familiarity) or where (spatial location) or when (temporal order) it was encountered. Barker *et al.* (2007) examined the contribution of the mPFC to the different components of recognition memory showing that mPFC lesions spared single item recognition (novel object preference) as well as

object location (spatial displacement), but significantly disrupted associative object recognition (object in place task) and recency judgments (temporal order). With respect to MD, Cross *et al.* (2012) subsequently demonstrated that MD lesions (or disconnecting MD from the mPFC) produced the same types of recognition memory deficits as seen with mPFC lesions (Barker *et al.*, 2007); that is, intact single item recognition but marked impairments on associative recognition memory and recency discrimination. These findings suggest a conjoint action of MD and the mPFC in recognition memory.

As discussed, MDc is associated with the olfactory system. Unlike other sensory systems, olfactory information reaching the olfactory cortex is not first relayed through the thalamus but passes directly from the olfactory bulbs to the piriform cortex—and from there to orbital regions of the PFC (Price, 1990; Stevenson and Boakes, 2003). An alternate route to the orbital PFC involves the transfer of olfactory information from the piriform cortex (and other olfactory regions) to MD and then to the PFC. Since odors can be identified and differentiated at the piriform cortex, the olfactory path through MD undoubtedly serves other functions, prime candidates of which are olfactory attention and learning (for review, Tham *et al.*, 2009). While some reports found that rats with MD lesions could not effectively discriminate between olfactory stimuli, particularly if stimuli were novel or difficult to identify (Eichenbaum *et al.*, 1980; Staubli *et al.*, 1987), other studies failed to demonstrate this but rather showed that MD lesions significantly impaired olfactory learning (Slotnick and Kaneko, 1981; Lu and Slotnick, 1990; Koger and Mair, 1994; McBride and Slotnick, 1997; Zhang *et al.*, 1998). For instance, Slotnick and colleagues (Slotnick and Kaneko, 1981; Lu and Slotnick, 1990; McBride and Slotnick, 1997) demonstrated that rats with MD lesions could accurately detect and discriminate between odors, but were deficient in reversal tasks in which reward values for odors were reversed. Importantly, deficits were most severe with MDc lesions, were not seen with visual reversal tasks, and were equally pronounced following disconnection of MD from the orbital cortex as with bilateral MD lesions—thus directly implicating MD-orbital PFC connections in these effects.

On the human level, MD has been linked to processes of olfactory attention. Specifically, using fMRI techniques, Plailly *et al.* (2008) reported that subjects attending to odors (but not to tones) showed elevated activity selectively in a pathway from the piriform cortex to MD and from MD to the orbital PFC, while Tham *et al.* (2011a, 2011b) described a number of "attention-related" deficits in subjects with damage to MD including a reduced ability to detect the presence or absence of suprathreshold olfactory stimuli.

SUBMEDIAL NUCLEUS

The submedial nucleus (SM) is a relatively small nucleus in the mid-rostrocaudal part of the thalamus. SM is situated in between the RE and RH medially and VM laterally. This nucleus is also referred to as nucleus gelatinosus (Krieg, 1944; Jones, 1985, 2007). SM is relatively cell-sparse and stands out against neighboring nuclei in neurofilament-stained sections. Although there exists a light plexus of parvalbumin-positive fibers in SM, calcium-binding proteins are otherwise virtually absent from the nucleus (Arai *et al.*, 1994). In particular, calbindin D28K is conspicuously absent from SM making it readily identifiable in sections stained for this protein (Paxinos *et al.*, 1999). SM is generally divided into rostro-ventral and caudo-dorsal parts primarily based on the differential distribution of afferents to them: olfactory projections to the rostro-ventral SM, and somatosensory inputs to the dorsal SM (Yoshida *et al.*, 1992). The caudo-dorsal part of SM exhibits high acetylcholinesterase activity (Paxinos and Watson, 2014), most probably related to substantial cholinergic afferents from the laterodorsal tegmental nucleus (Yoshida *et al.*, 1992).

Afferent and Efferent Projections

Since the original description by Craig and Burton (1981) of afferents from the superficial layers of the spinal dorsal horn and spinal trigeminal nucleus to the submedial nucleus, SM has been associated with nociception and pain modulation (for review, Tang *et al.*, 2009). However, in addition to ascending somatosensory inputs, SM also receives projections from olfactory structures (Price and Slotnick, 1983; Yoshida *et al.*, 1992). Olfactory fibers mainly distribute to rostro-ventral parts of SM and derive from deep layers of the prepiriform cortex and endopiriform nucleus. Olfactory inputs originate from the same regions projecting to the central segment of MD (MDc), although those to SM arise from a more restricted area of the olfactory cortex. SM is strongly reciprocally connected with the ventral orbital cortex and to a lesser extent with other orbital areas: lateral (LO), ventral (VO) and medial (MO) orbital cortices (Yoshida *et al.*, 1992; Coffield *et al.*, 1992; Reep *et al.*, 1996; Hoover and Vertes, 2011). The dorsal peduncular cortex, ventral to the infralimbic cortex, and the dorsal subiculum are additional sources of cortical inputs to SM (Witter *et al.*, 1990; Yoshida *et al.*, 1992).

Subcortical fibers to SM originate from the diagonal band nuclei, the lateral hypothalamus, and reticular nucleus of thalamus of the forebrain, and from deep layers of the superior colliculus, reticular formation, parabrachial nuclei, laterodorsal tegmental nucleus, and the spinal trigeminal complex of the brainstem (Yoshida *et al.*, 1991, 1992; Krout *et al.*, 2001, 2002; Krout

and Loewy, 2000a). In view of SM's role in nociception, afferents from the trigeminal complex and dorsal horn of the spinal cord have received specific attention (Craig and Burton, 1981; Dado and Giessler, 1990; Yoshida *et al.*, 1991; Blomqvist *et al.*, 1992; Iwata *et al.*, 1992). In cats, trigemino- and spinothalamic afferents to SM are glutamatergic (Ericson *et al.*, 1995), whereas in rats, trigeminothalamic neurons appear to express substance P (Li, 1999). Trigeminothalamic fibers, originating from the caudal spinal trigeminal complex, terminate as RL-type terminals on dendritic protrusions forming glomeruli, surrounded by glial elements (Ma and Ohara, 1987; Ma *et al.*, 1988; Ericson *et al.*, 1996). There are additional "simple" boutons-en-passage of both trigeminal and spinal origin in the submedial nucleus, at least in cats (Ericson *et al.*, 1996). Cortical afferents most likely end as RS-type terminals, while some large boutons with flattened vesicles are also present (Ma *et al.*, 1988).

Functional Aspects

While SM is involved in multiple functions, it serves a major role in nociception—or more specifically is part of a neural circuitry that suppresses painful stimulation. As indicated, SM receives inputs from layer 1 of the dorsal spinal gray and the spinal trigeminal complex, and SM cells respond to noxious stimulation (Miletic and Coffield, 1989; Fu *et al.*, 2002). In a series of studies, Tang and colleagues provided evidence that SM is an integral part of an anti-nociceptive system that also involves the ventrolateral orbital cortex (VLO) and the periaqueductal gray (PAG) (for review, Tang *et al.*, 2009). Specifically, these structures are critical components of a pain modulatory network which when activated triggers a PAG-originating descending inhibitory system that suppresses nociceptive signals at the brainstem and spinal cord. Supporting this, single cells of SM and VLO respond to painful stimulation applied to an extensive area of the body indicating that they are not well suited to localize sources of pain, but rather encode affective dimensions of pain (Dostrovsky and Guilbaud, 1988; Kawakita *et al.*, 1993; Backonja *et al.*, 1994). Further, activation of SM or VLO raises the threshold for pain (less painful), whereas the suppression of SM/VLO lowers the threshold for pain (Roberts and Dong, 1994; Zhang *et al.*, 1995a, 1995b, 1996; Zhang *et al.*, 1997a, 1997b; Zhang *et al.*, 1998). Tang *et al.* (2009) proposed that local GABAergic neurons of SM and VLO tonically inhibit output cells of SM/VLO, and that various modulatory inputs to SM/VLO including serotonergic afferents, suppress GABAergic actions on SM/VLO cells (disinhibition) thus activating them and triggering a VLO-PAG descending anti-nociceptive system.

In addition to a role in nociception, SM, with links to VLO, appears part of an extended system subserving directed attention, alterations of which produce sensory neglect (Corwin *et al.*, 1994; Corwin and Reep, 1998; Reep *et al.* 2003; Cheatwood *et al.*, 2005; Reep and Corwin, 2009). In addition to SM and VLO, the system includes the medial agranular (motor) cortex, the posterior parietal cortex, secondary visual areas and the dorsocentral striatum. As described, SM receives a relatively diverse set of afferents from limbic-related regions of the brainstem and forebrain. Accordingly, through SM, multimodal affective information would reach VLO, and VLO could thus provide emotional input to a complex circuitry responsible for directed attention. Finally, the submedial nucleus, like the central part of MD, receives olfactory input and SM-orbital projections may complement those from MDc to the orbital cortex in its role in olfactory attention (Tham *et al.*, 2009).

ANTERIOR NUCLEI

Three distinct nuclei in the rostral one-third of the thalamus belong to the anterior complex of the thalamus: the anterodorsal (AD), anteroventral (AV), and anteromedial (AM) nuclei. The AM nucleus fuses medially to form the interanteromedial nucleus (IAM) which extends slightly caudal to the other anterior nuclei. In Nissl-stained sections, the anterodorsal nucleus is most conspicuous because of its large, darkly stained cells. The anteromedial and anteroventral nuclei have smaller and lighter staining neurons and, although the cell density in AV is lower than that of AM, in Nissl-stained sections the border between these nuclei is somewhat difficult to define. However, in sections stained for AChE, a clear distinction can be made between the anterior nuclei, the AM exhibiting the lowest and the AV the highest activity for this enzyme (Paxinos *et al.*, 1999). The anterior nuclei contain varying proportions of cells reactive for calcium-binding proteins but are not conspicuous in this regard for the thalamus. Neurons positive for calbindin D28K are present in AM but not in the other anterior nuclei. Within the anteroventral nucleus, a distinction can be made between ventrolateral (AVvl) and dorsomedial (AVdm) parts on the basis of calbindin immunoreactivity: AVvl (like AM) contains a moderately dense calbindin-positive neuropil; AVdm (like AD) virtually none (Arai *et al.*, 1994).

Afferent and Efferent Projections

Inputs to the anterior thalamic nuclei (ATh) predominantly derive from the medial prefrontal cortex, the anterior cingulate cortex, the secondary motor cortex (MO2 or AGm), the retrosplenial cortex (RS), the subicular domain of the hippocampus, and the mammillary bodies (Swanson and Cowan, 1977; Seki and Zyo, 1984; Witter *et al.*, 1990; Shibata, 1992, 1998; Hopkins,

2005; Shibata and Naito, 2005; Wright *et al.*, 2010, 2013; Yoder and Taube, 2011). Additional sources of input to the ATh include serotonergic fibers from dorsal and median raphe nuclei and cholinergic fibers from the lateral dorsal tegmental (LDT) and pedunculopontine tegmental (PPT) nuclei (Gonzalo-Ruiz and Lieberman, 1995; Gonzalo-Ruiz *et al.*, 1995; Vertes *et al.*, 2010). Reticular thalamic projections to ATh originate from the rostral, "limbic" portion of RT (Seki and Zyo, 1984; Shibata, 1992; Lozsadi, 1995).

The anterior nuclei, or more specifically AM, IAM and AV, receive relatively massive input from "limbic" and non-limbic regions of the PFC (Shibata, 1998; Hopkins, 2005; Shibata and Naito, 2005; Wright *et al.*, 2010, 2013). Limbic prefrontal projections mainly originate from the medial wall of the PFC—or the medial orbital cortex (MO), the infralimbic (IL) cortex (Brodmann's area 25), the prelimbic (PL) cortex (Brodmann's area 32) and the anterior (AC) cingulate cortex (Brodmann's area 24) (also see *Cingulate Cortex and Pain Architecture*, Chapter 21). The relative order of strength of PFC projections to ATh is AC>PL>MO>IL, and all areas appear to distribute more heavily to AM than to AV. AC gives rise to a pronounced and topographically organized set of projections to AM/AV such that anterior and posterior regions of AC innervate respective rostral and caudal zones of AM/AV (Shibata and Naito, 2005). Projections from the secondary motor cortex (M2) are about equally dense to AM/AV, and similarly topographically organized as those from AC. Prefrontal fibers (from all areas) to AM/AV predominantly arise from layer 6 cells; considerably fewer from layer 5 cells (Shibata and Naito, 2005; Petrof and Sherman, 2009). Even though PFC cells projecting to AM or to AV are largely intermingled, very few cortical neurons (about 1%) distribute, via collaterals, to both AM and AV (Wright *et al.*, 2013). Unlike AM/AV, there are only minor PFC (mPFC, AC and M2) projections to the anterodorsal nucleus.

As has been well established, the anterior thalamus is reciprocally connected with the retrosplenial cortex (RS) (Shibata, 1993a, 1998; Hopkins, 2005). The retrosplenial cortex consists of two major divisions, the granular (RSg) and dysgranular (RSd) cortices, and the granular cortex is further divided into a dorsal part *b* and a ventral part *a* (Van Groen and Wyss, 1992a, 2003). RS fibers more heavily target AM and AV than AD (Van Groen and Wyss, 1990a, 1992a, 2003; Shibata, 1998; Hopkins, 2005). The retrosplenial granular cortex (RSg) is the main source of projections to AV, whereas both divisions distribute fairly equally to AM (Wright *et al.*, 2013). RSg fibers to AV (and to AM) primarily originate dorsally in RSg—or in part *b* (Van Groen and Wyss, 2003). Unlike the prefrontal cortex (see above), there is an inverse topographic order to RSd/g projections to AM/AV: rostral RSd/g fibers terminate caudally in AM/AV and caudal RSd/g fibers rostrally in AM/AV (Shibata, 1998). Similar to the PFC, however, retrosplenial projections to AM and to AV arise from separate populations of RSd/g cells—mainly of layer 6 (Wright *et al.*, 2013). Although AD strongly targets the retrosplenial cortex (Shibata 1993a; Van Groen and Wyss, 1995), there are relatively weak return RS projections to AD, mainly originating from RSg (Shibata, 1998; Wright *et al.*, 2010).

The subiculum as well as the pre- and parasubiculum are also major sources of input to the anterior thalamus (ATh). Subicular fibers to ATh mainly arise from the dorsal presubiculum (or postsubiculum), the dorsal subiculum (SUBd) and the intermediate subiculum (point of convergence of the dorsal and ventral subiculum) (Groenewegen, 1987), and secondarily from the ventral subiculum (SUBv), presubiculum and parasubiculum (Van Groen and Wyss, 1990b, 1990c; Wright *et al.*, 2010, 2013). AM and AV receive projections from similar regions of the subiculum which differ from those distributing to AD. Afferents to AV and AM mainly originate from the dorsal, intermediate, and ventral subiculum and less so from the pre- and parasubiculum (Wright *et al.* 2010). By contrast, with the possible exception of the presubiculum, AD receives dense projections from all divisions of the subicular cortex, most prominently from the dorsal presubiculum. Finally, subicular cells projecting to ATh and to the mammillary bodies (MB) originate from separate populations of neurons: from deep layers of the subiculum to ATh and superficial layers to MB (Naber and Witter, 1998; Ishizuka, 2001; Wright *et al.*, 2010).

The mammillary bodies are the source of a pronounced and highly topographically organized set of projections to the anterior thalamus (Seki and Zyo, 1984; Hayakawa and Zyo, 1989; Shibata, 1992; Hopkins, 2005; Wright *et al.*, 2013). Proceeding medially to laterally in MB, the medial division of the medial MB mainly distributes to AM, the lateral division of the medial MB to AV, and the lateral mammillary nucleus to AD (for review, Hopkins, 2005). Very few MB cells distribute, via collaterals, to more than one anterior thalamic nucleus (Wright *et al.*, 2013).

Whereas AM and AV receive common sets of inputs, distinct from those of the anterodorsal nucleus (see above), AV and AD distribute to similar structures which differ from those targeted by AM (Shibata, 1993a, 1993b; Van Groen and Wyss, 1995; Van Groen *et al.*, 1999; Hopkins, 2005; Shibata and Honda, 2012). All three anterior thalamic nuclei, however, project to the retrosplenial cortex (Shibata, 1993a; Odagiri *et al.*, 2011). AM fibers spread widely throughout the cortex, notably to anterior as well as to posterior regions of cortex. Major targets are the secondary motor, anterior cingulate, and retrosplenial cortices (all divisions), and secondarily, the ventral orbital, perirhinal, medial and lateral entorhinal, and secondary visual (area 18b) areas. AM sends few fibers

to the subicular domain, mainly targeting the ventral subiculum (proper). By contrast with AM, the cortical projections of AD and AV are almost exclusively directed to the retrosplenial cortex and to the subiculum—with some additional fibers to the medial EC. With the exception of a minor AV projection to AC, there is an essential lack of AV (or AD) projections to rostral regions of cortex. AV distributes to both divisions of the retrosplenial cortex, but heavier to the granular cortex (RSg) (Odagiri *et al.*, 2011), whereas AD fibers appear confined to RSg. Although AD and AV distribute to all parts of the subicular domain densities differ across regions. Specifically, AD strongly targets the presubiculum and parasubiculum; by comparison, AV mainly projects to the ventral subiculum (all layers) and weakly to the parasubiculum.

Functional Aspects

The anterior thalamus is intimately connected with the hippocampus; that is, ATh receives direct as well indirect (mainly from the mammillary bodies) projections from the hippocampus, and in turn projects directly (to the subiculum) and indirectly (mainly via the retrosplenial cortex) to the hippocampus. As such, the anterior thalamus has been viewed as part of an extended hippocampal circuitry subserving similar (or nearly identical) types of functions as the hippocampus (Gaffan, 1992; Aggleton and Brown, 1999, 2006; Aggleton *et al.*, 2010). In humans, damage to the anterior thalamus produces profound memory deficits comparable to those seen with hippocampal lesions, including severe anterograde and graded retrograde amnesia. This so-called diencephalic amnesia has been linked to alterations of the mammillary bodies, the mammillothalamic tract, and the anterior thalamus (Von Cramon *et al.*, 1985; Harding *et al.*, 2000; Van der Werf *et al.*, 2000, 2003; Gold and Squire, 2006). Lesions of other nuclei of thalamus in humans affect cognitive processing but essentially not memory (Van der Werf *et al.*, 2003).

The effects of anterior thalamic (ATh) lesions have been extensively examined in rats and been shown to disrupt "hippocampal-dependent" memories for both spatial and non-spatial tasks (Byatt and Dalrymple-Alford, 1996; Sziklas and Petrides, 1999, 2007; Warburton *et al.*, 2001; Mair *et al.*, 2003; Moran and Dalrymple-Alford, 2003; Wolff *et al.*, 2008; Savage *et al.*, 2011; Moreau *et al.*, 2013). By contrast, lesions of thalamic nuclei adjacent to ATh, such as the mediodorsal or intralaminar nuclei, fail to disrupt performance on spatial memory tasks (Mitchell and Dalrymple-Alford, 2006; Wolff *et al.*, 2008; Moreau *et al.*, 2013). For example, Mitchell and Dalrymple-Alford (2006) described a double dissociation between the effects of ATh and intralaminar lesions such that only ATh lesions altered performance on spatial memory tasks, while intralaminar lesions produced impairments on a non-hippocampal-dependent egocentric working memory task.

Based in part on hippocampal output to ATh, it was originally thought that the ATh involvement in memory largely resulted from the effects of the hippocampus on the anterior thalamus (Gaffan, 1992; Aggleton and Brown, 1999). In this "hippocampal-centric" view, hippocampal-originating memories (or traces) were transferred from the hippocampus to the ATh (and to other subcortical structures) and the downstream sites (merely) passively responded to the information received from the hippocampus (Savage *et al.*, 2011). This notion, however, has gradually been modified in large measure by the demonstration that ascending (brainstem/diencephalic) systems can exert marked effects on memory, independent of the influence of the hippocampus. In this regard, a key finding was that destruction of a branch of the post-commissural fornix that selectively innervates the mammillary bodies produced very slight (or no) effects on tests of spatial memory (Vann *et al.*, 2011). By comparison, performance on these same tasks was severely altered following lesions of the mammillary bodies or the mammillothalamic tract (Sziklas and Petrides, 1993; Vann and Aggleton, 2003). These findings at least partially ruled out the actions of the hippocampus on the mammillary bodies on these tasks, and further pointed to a direct role for MB in spatial memory processing. Regarding possible "non-hippocampal" actions on MB in memory, the mammillary bodies are strongly reciprocally connected with the ventral tegmental nuclei (VTg) (of Gudden) of the brainstem, and ventral tegmental lesions have been shown to disrupt performance on various spatial learning tasks including delayed match to place in the water maze, T-maze alternation, and working memory tasks on the radial arm maze (Vann, 2009, 2010).

The hippocampus, anterior thalamus, mammillary bodies, and Gudden's tegmental nuclei constitute key elements of interconnected circuitry which in basic form was originally described by Papez's (Papez's circuit, 1937). More recently this system of connections has been shown to be organized as two parallel but segregated anatomical and functional networks—medial and lateral systems (Fig. 4) (Vann and Aggleton, 2004; Vertes *et al.*, 2004; Aggleton *et al.*, 2010). The medial system is comprised of the ventral tegmental nucleus (VTg), the medial MB, the anteroventral nucleus of thalamus, and the subiculum/retrosplenial cortex; the lateral system consists of the dorsal tegmental nucleus, lateral MB, the anterodorsal nucleus of thalamus, and the pre, para and postsubiculum (Fig. 4) (Vann and Aggleton, 2004; Vertes *et al.*, 2004; Aggleton *et al.*, 2010).

Functionally, the medial system has been identified a "theta system" or one in which cells of each structure fire rhythmically synchronous with the hippocampal theta rhythm (Kocsis and Vertes, 1994, 1997; Bland *et al.*, 1995;

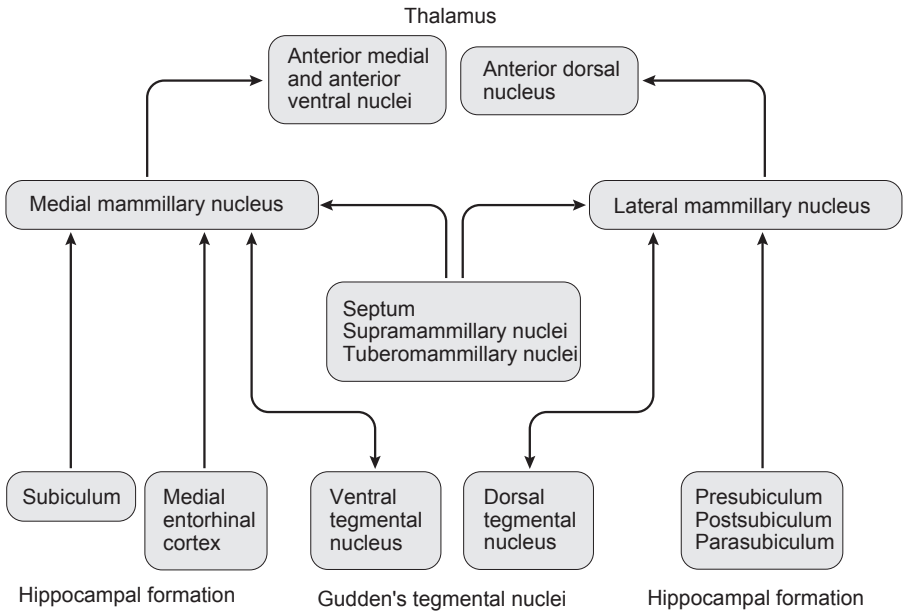

FIGURE 4 Schematic representation of the main nuclei and their interconnections associated with the medial mammillary theta system and the lateral mammillary head direction system. See text for further details. *From Vann, S.D., & Aggleton, J.P. (2004). The mammillary bodies: two memory systems in one?* Nature Reviews Neuroscience *5, 35–44.*

Kirk *et al.*, 1996; Bassant and Poindessous-Jazat, 2001; Kocsis *et al.*, 2001; Vertes *et al.*, 2001; Albo *et al.* 2003, 2011; Talk *et al.*, 2004; Tsanov *et al.*, 2011a, 2011b). For example, *all* cells of VTg were found to discharge rhythmically in bursts with theta, whereas 75% of those of AV were identified as "theta-rhythmic" neurons (Kocsis *et al.*, 2001; Vertes *et al.*, 2001; Albo *et al.*, 2003, 2011). The lateral system, on the other hand, consists of a well-defined head direction (HD) network—meaning that cells of structures comprising this system discharge selectively when a rat (or rat's head) is facing or oriented in a particular direction irrespective of a rat's location in its environment (Taube, 1995, 1998; Wiener and Taube, 2005). Lesions at each stage/nucleus of this ascending system disrupt HD activity at successive rostral stages demonstrating the importance of information transfer from lower to higher levels of the brain in the HD system (Bassett and Taube, 2005; Wiener and Taube, 2005).

While not fully resolved, it appears that these two apparently dissimilar systems (theta and HD) may serve complementary roles as their functions become integrated at successive rostral levels of the brain (Vertes *et al.* 2004; Aggleton *et al.*, 2010). In particular, it has been proposed that theta rhythmic activity (of the medial system) may promote and enhance the transfer of HD signals through the HD circuitry (Albo *et al.*, 2003, 2011; Vertes *et al.*, 2004). This may involve the unique properties of bursting neurons—or the theta bursting cells of the medial system. As described by Lisman (1997), burst discharges, relative to single spikes, represent a much more effective (or reliable) mode of communication between neurons. As was pointed out, there is a low probability that single presynaptic spikes can generate action potentials in postsynaptic cells (unreliable synapses), compared to a high probability that presynaptic bursts would drive postsynaptic neurons (reliable synapses). This "special" quality of bursting neurons has been well documented in several systems of the brain including the thalamus (Guido and Weyand, 1995; Fanselow *et al.*, 2001; Swadlow and Gusev, 2001). For example, ventrobasal thalamic neurons were shown to exert considerably stronger postsynaptic actions on cells of the somatosensory cortex when firing in bursts than tonically (Swadlow and Gusev, 2001). In an analogous manner, the theta burst firing of AV neurons could enhance the activity of target cells of the subiculum or retrosplenial cortex to thereby increase their responsiveness to other inputs, such as from HD cells of the anterodorsal thalamus—thus magnifying the influence of anterodorsal HD cells on subicular/retrosplenial neurons. It would appear that directional information is very critical for a rat (and other species) when engaged in locomotor/exploratory behaviors (theta states) and less so during non-locomotor activities such as grooming or consumatory acts (non-theta states) (Vertes and Kocsis, 1997; Vertes, 2005). Accordingly, theta burst firing may represent an important signal involved in the differential processing of HD activity under the two conditions (e.g., locomotion or grooming); that is, essentially only when HD activity is coupled with theta-rhythmic discharge is head direction information processed and used to guide spatial behaviors.

Whereas there is an almost complete segregation of theta and HD signals at lower levels of the brain (tegmental nuclei and MB), the two systems appear to converge at thalamocortical levels—with likely important functional consequences. In studies examining the discharge properties of AV neurons in behaving rats,

Aggleton and colleagues (Tsanov *et al.*, 2011a, 2011b) showed that 25–30% of AV neurons were "theta" cells, and about one-third of these, mainly of the medial AV, also exhibited directional properties. Specifically, these cells fired rhythmically (theta) and also responded to changes in head position and were thus termed "directionally modulated theta cells" Another population of AV neurons was identified as head direction cells and a subset of them (about 40%) showed theta rhythmicity, most evident when the rat was facing or heading in the preferred direction—or "head direction-by-theta cells." In effect, these findings strongly point to an integration of theta and directional signals within the anterior thalamus. The theta modulation of HD activity was proposed to represent "an oscillatory enhancement of the HD signal" (Tsanov *et al.*, 2011b).

Comparable to the integration of theta and HD signals at the thalamus, a class of neurons of the presubiculum and parasubiculum have been identified which code for location (place) and direction (HD) and are also theta modulated—theta modulated place by direction (TPD) neurons (Cacucci *et al.*, 2004). It was suggested that the likely source of theta rhythmicity to TPD cells was AV of the thalamus. In summary, the foregoing would indicate that the anterior thalamus is a vital hub in a hierarchically arranged system of connections serving a critical role in spatial navigation and hence in spatial learning/memory in rats.

LATERAL NUCLEI

The lateral thalamic complex consists of two structures, the laterodorsal (LD) and lateral posterior (LP) nuclei. The two nuclei constitute a large part of the dorsal surface of the thalamus, lateral to the habenular complex and, caudally, medial to the dorsal lateral geniculate nucleus (DLG). The LD stretches from the caudal part of the anterior thalamic complex to the rostral pole of DLG. The lateral posterior nucleus starts at mid-thalamic levels between the habenular complex, medially and the laterodorsal nucleus, laterally, and in the posterior direction, LP gradually replaces LD. Caudally, the lateral posterior nucleus is situated medial to DLG and in its most posterior extent, dorsal to the medial geniculate nuclei (Paxinos and Watson, 2014). In Nissl stained sections, the lateral nuclei appear rather homogeneous, but both LD and LP can be subdivided into several subnuclei, based on cytoarchitectonics and distinct patterns of connectivity with the cortex. These subdivisions can be recognized in acetylcholinesterase-stained sections showing some differences in staining intensity in the various subnuclei (Takahashi, 1985; Paxinos and Watson, 2014). Acetylcholinesterase activity in the lateral posterior nucleus is higher than that in the laterodorsal nucleus in which there is only moderate activity. While not throughout, the calcium-binding proteins, calretinin and calbindin D28K, are present in neurons in certain parts of LD and LP, while parvalbumin and the other two calcium binding proteins are present in fibers of both nuclei (Arai *et al.*, 1994; Paxinos *et al.*, 1999).

Afferent and Efferent Projections

Similar to the anterior thalamic nuclei, LD is strongly related to the retrosplenial cortex (Van Groen and Wyss, 1990a, 1992a; Shibata, 2000). The projections from different parts of the retrosplenial cortex, originating predominantly from layer 6, but also layer 5, distribute in a topographical manner to the various subnuclei of LD (Fig. 5) (Shibata, 2000; Shinkai *et al.*, 2005). Thus, a rostral-to-caudal axis in the retrosplenial cortex (area 29c–29a) corresponds to a ventromedial-to-dorsolateral axis of LD. In addition, cortical inputs to LD originate from visual areas 17 and 18, the presubiculum, entorhinal cortex, and the posterior parietal cortex (Thompson and Robertson, 1987a, 1987b; Reep *et al.*, 1994; Shibata, 1996; Shinkai *et al.*, 2005; Wright *et al.*, 2010). Prefrontal projections to LD mainly arise from the anterior cingulate (AC) and medial agranular (AGm) cortices (Sukekawa, 1988; Vertes, 2002; Shibata and Naito, 2005). AC distributes to dorsal and ventral medial parts of the medial LD, while AGm projects to lateral parts of this division of LD (Shibata and Naito, 2005).

Subcortical inputs to LD arise from the thalamic reticular nucleus, pretectal nuclei, intermediate layers of the superior colliculus, the ventral lateral geniculate nucleus, and trigeminal nuclei (Thompson and Robertson, 1987b; Coleman and Mitrofanis, 1996; Kolmac *et al.*, 2000; Bezdudnaya and Keller, 2008). The efferent projections of LD reach various limbic and visual cortical areas, including the anterior cingulate, retrosplenial and entorhinal cortices and the subiculum. These projections are topographically organized and originate from different subnuclei of the laterodorsal nucleus (Van Groen and Wyss, 1992b; Shires *et al.*, 2013). LD also sends projections to the striatum (Cheatwood *et al.*, 2003; Kamishina *et al.*, 2008).

The lateral posterior (LP) nucleus is reciprocally connected with a number of sensory and motor cortices, and to a lesser extent with "limbic" cortices. They include the medial agranular, anterior cingulate, occipital, posterior parietal, and temporal association cortices (Vaudano *et al.*, 1991; Reep *et al.*, 1994; Coleman and Mitrofanis, 1996; Shi and Cassell, 1997; Kolmac *et al.*, 2000; Shibata, 2000; Conte *et al.*, 2008; Kamishina *et al.*, 2009). These connections are highly topographically organized. For instance, the rostral ventromedial division of LP projects substantially to the medial agranular cortex, to the dorsomedial AC and to rostral aspects of the retrosplenial

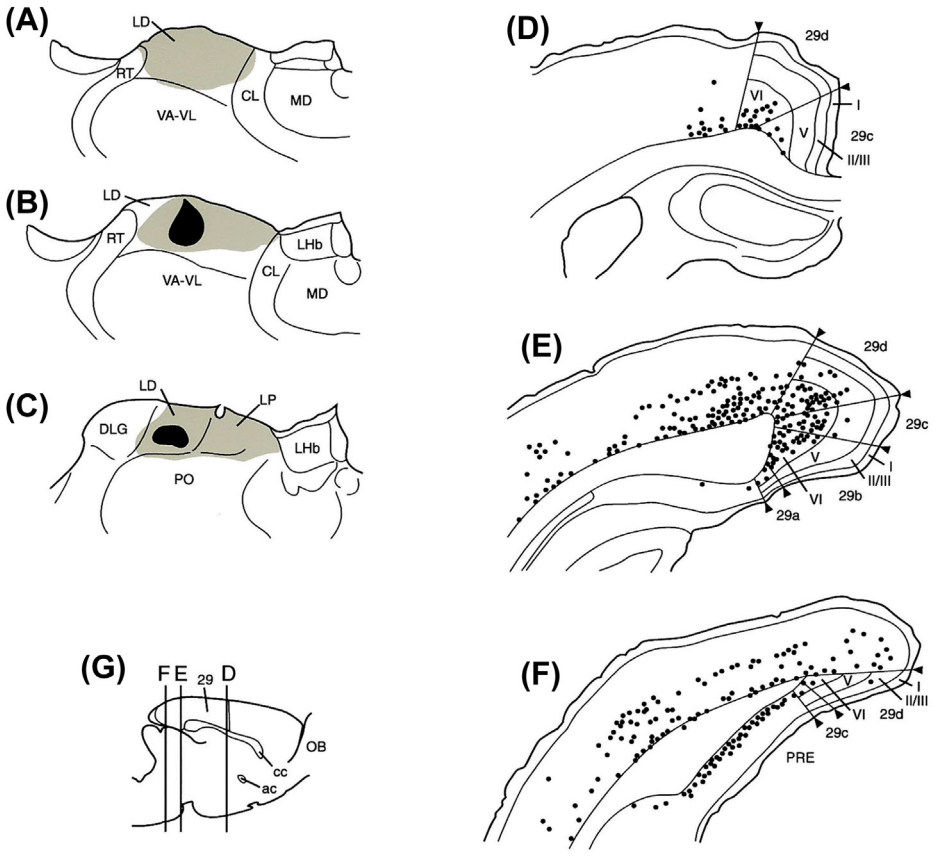

FIGURE 5 Pattern of projections of the retrosplenial cortex to the rat laterodorsal nucleus of thalamus. (A–C) Schematic representation of three rostrocaudally aligned transverse sections through the thalamus showing the site of injection of the retrograde tracer, cholera toxin B (shaded area) in the laterodorsal nucleus (LD) of thalamus. (D–F) Schematic representation of three rostrocaudally aligned transverse sections through the retrosplenial cortex showing the distribution of retrogradely labeled cells (dots) in the retrosplenial cortex following the injection in LD. (G) Sagittal section showing the anterior-posterior locations of the transverse sections of D–F. Note the pronounced numbers of retrogradely labeled neurons, mainly in layer 6 and to a lesser extent in layer 5, throughout the entire retrosplenial cortex (29a–29d) following the LD injection. *From Shibata, H. (2000). Organization of the retrosplenial cortical projections to the laterodorsal thalamic nucleus in the rat.* Neuroscience Research *38, 303–311.*

cortex (Kamishina *et al.*, 2009). In addition to the cortex, LP also distributes to the dorsal striatum and in a highly topographical manner (Erro *et al.*, 2002; Cheatwood *et al.*, 2003, 2005; Kamishina *et al.*, 2008). Specifically, fibers of the rostromedial part of medial LP project to the central region of the dorsocentral striatum, whereas those of the central part of medial LP target the dorsal sector of the dorsocentral striatum (Kamishina *et al.*, 2008). The LP receives dense projections from the temporal area Te2, an auditory and visual association area, but not from areas Te1 and Te3 (Shi and Cassell, 1997). Visual input to LP originates from both the primary visual cortex and the superior colliculus (Takahashi, 1985; Masterson *et al.*, 2009). Afferents from the primary visual cortex to LP mostly consist of collaterals of neurons in layer 5 that project to the brainstem (Bourassa and Deschênes, 1995). Tectal projections to LP include substance P containing cells targeting the lateral division of LP (Paul and Cox, 2010).

Functional Aspects

The laterodorsal and lateral posterior nuclei are considered "association" thalamic nuclei in that they do not receive direct motor or sensory inputs. However, a recent finding indicates that LD receives inputs from trigeminal nuclei relaying somatosensory information of the vibrissae (Bezdudnaya and Keller, 2008). In addition, LP and LD receive pronounced projections from cortical sensory, motor association, and limbic cortices. Based on strong relationships with cortical and subcortical visual structures, LP is often considered the visual association thalamus—much like the pulvinar of cats and primates (Jones, 1985, 2007). In humans and primates, damage to the pulvinar (i.e., lateral posterior nucleus) appears to produce spatial hemi-neglect, or the inability to attend or respond to sensory stimuli in the contralateral receptive field (see Reep and Corwin, 2009). In rats, LP has reciprocal and topographically organized connections with the dorsocentral striatum and with the posterior parietal and frontal cortices, including the medial agranular cortex. Damage to this network produces deficits in attention including multisensory neglect. LP appears positioned to serve a pivotal role in both visual and spatial attention (Burcham *et al.*, 1997; Reep *et al.*, 2004; Reep and Corwin, 2009).

In view of similarities in patterns of connections, the laterodorsal nucleus is strongly associated with the anterior thalamic complex and the head direction (HD) network (Taube, 2007). Similar to the anterior thalamus and postsubiculum, HD cells have been identified in LD (Mizumori and Williams, 1993). Additionally, LD is intimately tied to structures of the HD network, including the retrosplenial cortex and dorsal presubiculum.

However, the role of LD in head orientation, and thus in spatial navigation, appears to be different from that of the anterior thalamic nuclei and the pre- and parasubiculum. Lesions of the anterior thalamus in rats disrupt HD cell firing in the dorsal presubiculum and produce significant impairments in spatial navigation and mnemonic functions (Byatt and Dalrymple-Alford, 1996; Goodridge and Taube 1997; Mitchell and Dalrymple-Alford, 2006). By contrast, lesions of LD have no effect on HD cell firing in the dorsal presubiculum (Golob *et al.*, 1998). However, lesion and inactivation studies involving LD clearly demonstrate a role for the nucleus in spatial learning and memory. Disruption of LD produces impairments in spatial maze tasks (Mizumori *et al.*, 1994; Van Groen *et al.*, 2002), and these impairments are significantly augmented when lesions include both LD and the anterior thalamus (Wilton *et al.*, 2001; Van Groen *et al.*, 2002). LD may provide somatosensory-linked spatial information to the head direction network (Bezdudnaya and Keller, 2008).

INTRALAMINAR NUCLEI

The intralaminar nuclei of thalamus form a conspicuous collection of nuclei in the medial and dorsal part of the thalamic complex. The intralaminar thalamic nuclei (ILt) are located lateral to the mediodorsal nucleus and "embedded" within the internal medullary lamina. Several nuclei of the intralaminar complex have high activity for acetylcholinesterase (Paxinos and Watson, 2014). The intralaminar nuclei are made up of a rostral group, consisting of the central medial (CM), paracentral (PC), and central lateral (CL) nuclei. The caudal group is composed of the parafascicular–center median complex, which in rats consists of a single nuclear mass, hereafter referred to as the parafascicular (PF) nucleus. In addition, in the caudal one-third of the thalamus, the subparafascicular and PIL are considered part of the posterior intralaminar complex (see also the MGN section). In Nissl-stained sections, most of the intralaminar nuclei can be easily identified based on neuronal packing which is denser than that of adjacent thalamic nuclei (Paxinos and Watson, 2014).

The central medial nucleus can be clearly recognized as a centrally located group of large, deeply staining, flattened cells distinct from midline nuclei lying dorsal and ventral to it. Laterally, CM is continuous with the paracentral nucleus on both sides. In rats, the left and right sides of CM fuse to form a single, centrally positioned nucleus. The paracentral nucleus is a thin strip of cells that is continuous with CM, medially and with the central lateral nucleus, laterally. PC cells are difficult to distinguish from those of the CL, but appear more flattened. The paracentral nucleus lies in the anterior and middle portion of the internal medullary lamina, intercalated between MD and the ventral nuclei of thalamus. In the caudal PC, a distinct oval subnucleus can be recognized, the oval paracentral nucleus. The central lateral nucleus is the most dorsal component of the intralaminar nuclei, located posterior and dorsal to PC, and continuous with it. The CL is larger than PC but these nuclei share many connectional properties. Therefore, the central lateral and paracentral nuclei are often regarded as a single structure.

The parafascicular nucleus is a caudal component of the intralaminar complex. The PF stands out as a darkly staining nucleus, surrounding the fasciculus retroflexus. The lateral, larger part of the rat parafascicular nucleus, containing darker staining neurons than the medial part, is considered the equivalent of the primate center median nucleus, whereas the medial part of PF is homologous to the parafascicular nucleus (Jones, 1985, 2007). Ventrally, PF lies adjacent to the mesencephalon; dorsally it is bordered by CL and the habenular complex. The parafascicular nucleus lies lateral to the rostral extent of the periventricular gray matter. The subparafascicular nucleus (SPF) is a flat, horizontally oriented nucleus which stretches from just ventral to the parafascicular nucleus, rostromedially, and toward the posterior intralaminar and peripeduncular nucleus, caudolaterally. Neurons in the SPF have a horizontal orientation. Medially, the subparafascicular nucleus lies just dorsal to the medial lemniscus. SPF consists of a medial magnocellular part and a lateral parvocellular part (Faull and Mehler, 1985; LeDoux *et al.*, 1987; Coolen *et al.*, 2003a).

The principal neurotransmitters used by the intralaminar nuclei are excitatory amino acids (Hur and Zaborszky, 2005). Neurons containing calcium-binding proteins sparsely populate the intralaminar nuclei (Arai *et al.*, 1994; Coolen *et al.*, 2003a). Enkephalinergic neurons, as indicated by the presence of preproenkephalin mRNA, are present in CM and CL but to a much lesser extent in the paracentral and parafascicular nuclei (Hermanson *et al.*, 1995).

Afferent Projections

Main sources of input to the rostral intralaminar nuclei (CM, PC and CL) are subcortical structures, particularly of the brainstem and spinal cord. The following subcortical structures project to some or all nuclei of the rostral intralaminar complex: the mesencephalic, pontine, and medullary reticular formation, the serotonergic dorsal raphe, median raphe and raphe magnus, the cholinergic pedunculopontine (PPT) and laterodorsal tegmental (LDT) nuclei, the nucleus prepositus hypoglossi, the spinal trigeminal nucleus, the medial and lateral vestibular nuclei, several subnuclei of the parabrachial complex, the locus coeruleus, the nucleus incertus, distinct

regions of the periaqueductal gray, deep layers of the superior colliculus, the nucleus of Darkschewitsch, and the pars reticulata and pars compacta of the substantia nigra (Peschanski and Besson, 1984; Jones and Yang, 1985; Vertes *et al.*, 1986, 1999, 2010; Yamasaki *et al.*, 1986; Hallanger *et al.*, 1987; Vertes and Martin, 1988; Vertes, 1991; Villanueva *et al.*, 1998; Bester *et al.*, 1999; Groenewegen *et al.*, 1999; Shiroyama *et al.*, 1999; Goto *et al.*, 2001; Krout *et al.*, 2001; Olucha-Bordonau *et al.*, 2003). Using small injections of retrograde tracers in CM, PC, or CL, Loewy and colleagues (Krout and Loewy, 2000a, 2000b; Krout *et al.*, 2001, 2002) showed that each nucleus receives a different combination of inputs from various brainstem nuclei, as well as from subregions of these nuclei, suggesting a certain degree of specificity for the rostral intralaminar nuclei. In addition, the rostral intralaminar nuclei receive input from deep cerebellar nuclei, the supramammillary nucleus, zona incerta, and the reticular thalamic nucleus (Haroian *et al.*, 1981; Vertes, 1992; Kolmac and Mitrofanis, 1997; Power *et al.*, 1999; Power and Mitrofanis, 2001).

While cortical afferents to the intralaminar complex have not been examined *per se*, evidence gained from descriptions of cortical projections to thalamus shows that the PFC (or the mPFC) is a principal source of input to the rostral intralaminar nuclei (Reep *et al.*, 1987; Sesack *et al.*, 1989; Jasmin *et al.*, 2004; Vertes, 2002, 2004; Hoover and Vertes, 2011). Regarding the mPFC, ventral (or limbic) regions of the mPFC (i.e., IL, PL and AC) distribute strongly to CM but minimally to PC and CL, whereas the dorsally located AGm (or secondary motor cortex) exhibits the reverse pattern: pronounced projections to PC and CL and weak ones to CM (Vertes, 2002, 2004). By comparison, the orbital and insular cortices distribute moderately to the rostral intralaminar complex (ILt), with heaviest projections from the medial orbital (MO) cortex to CM (Shi and Cassell, 1998a; Jasmin *et al.*, 2004; Hoover and Vertes, 2011).

Subcortical inputs to the parafascicular nucleus are comparable to those to the rostral intralaminar nuclei (Haroian *et al.*, 1981; Cornwall and Phillipson, 1988; Lai *et al.*, 2000; Krout *et al.*, 2002; Van der Werf *et al.*, 2002). The lateral parafascicular nucleus receives relatively strong inputs from sensorimotor-related nuclei, such as the vestibular nuclei, spinal trigeminal complex, superior colliculus, substantia nigra-pars reticulata, and the entopeduncular nucleus (Shiroyama *et al.*, 1999; Gonzalo *et al.*, 2002; Krout *et al.*, 2002). The medial PF, on the other hand, primarily receives autonomic and visceral-related afferents, foremost among them, from the solitary nucleus, periaqueductal gray, and the parabrachial complex (Bester *et al.*, 1999; Krout *et al.*, 2000a, 2000b, 2002). As indicated, the subparafascicular nucleus (SPF) can be divided into a medial and a lateral part (Coolen *et al.*, 2003a) with each receiving a different set of afferents (Coolen *et al.*, 2003b). Thus, the medial SPF, characterized by galanin-immunoreactive fibers, receives inputs from lumbar spinothalamic neurons and visceral-related brainstem and forebrain regions. In contrast, the lateral SPF, containing calcitonin gene-related peptide (CGRP)-immunoreactive neurons and fibers, receives inputs from auditory- as well as visual-related brainstem and forebrain regions (LeDoux *et al.*, 1987; Coolen *et al.*, 2003b). The lateral subparafascicular nucleus is strongly related to the auditory thalamus, including the posterior intralaminar and medial geniculate nuclei.

Efferent Projections

The principal targets of the intralaminar nuclei are regions of the cortex and the dorsal striatum, with additional projections to the ventral striatum and to the amygdala. In general, fibers of the lateral (PC, CL) and caudal (PF) intralaminar nuclei innervate sensorimotor regions of the cortex and the dorsal striatum, whereas those of the central medial nucleus distribute over a much wider region of the forebrain to both limbic and non-limbic sites (Berendse and Groenewegen, 1990, 1991; Condé *et al.*, 1990, 1995; Su and Bentivoglio, 1990; Hicks and Huerta, 1991; Turner and Herkenham, 1991; Brog *et al.*, 1993; Reep and Corwin, 1999; Erro *et al.*, 2002; Van der Werf *et al.*, 2002; Jasmin *et al.*, 2004; Wang and Shyu, 2004; Hoover and Vertes, 2007; Vertes *et al.*, 2012). In this regard, the projections of CM more closely parallel those of midline thalamic nuclei (see below) than those of other intralaminar nuclei. Accordingly, the efferents of PC, CL and PF will be described as a group followed by a description of CM projections.

With some overlap, there is a medial to lateral gradient in the projections of PC/CL/PF to the dorsal PFC such that PC mainly targets the anterior cingulate (AC) cortex, CL the laterally adjacent secondary motor cortex (AGm), and PF the primary motor cortex (AG1) (Berendse and Groenewegen, 1991; Condé *et al.*, 1995; Reep and Corwin, 1999; Hoover and Vertes, 2007). More specifically, PC distributes primarily to the dorsal and ventral AC, and secondarily to AGm and to the caudally bordering retrosplenial (RS) cortex—with minimal projections to other cortical regions. CL mainly targets AGm, with additional projections to AGl, the primary and secondary somatosensory cortices, the retrosplenial cortex, and to occipital cortices. PF distributes almost exclusively to sensorimotor cortices, substantially to AGl, and less so to somatosensory cortices.

Similar to the output to the cortex, PC/CL/PF fibers project to separate but overlapping regions of the dorsal striatum but as a group encompass a wide expanse of the caudate-putamen (C-P). The rostral PC and the CL distribute to the dorsomedial and dorsolateral striatum, respectively, and hence as a pair, cover the entire

dorsal half of the striatum. PF fibers, on the other hand, terminate within a mid-dorsoventral zone of the lateral striatum, virtually throughout C-P. Although these intralaminar nuclei distribute to nucleus accumbens (ACC), projections are modest and selectively target the lateral core of ACC, with strongest projections from PC and medial PF to accumbens (Berendse and Groenewegen, 1990, 1991; Brog *et al.*, 1993; Erro *et al.*, 2002).

As demonstrated by Groenewegen and colleagues (Groenewegen *et al.*, 1999; Groenewegen and Witter, 2004), thalamocortical/thalamostriatal connections are highly topographically organized such the projections of individual thalamic nuclei reach specific regions of the cortex and the striatum which are, in turn, linked via corticostriatal projections. For instance, CL quite selectively targets the medial agranular cortex (AGm) and the dorsolateral quadrant of C-P, and AGm, in turn, distributes dorsolaterally in C-P (Berendse and Groenewegen, 1990, 1991; Wu *et al.*, 2009). As a result, CL is positioned to directly affect AGm as well as its target zone in the striatum. This appears to be a general pattern of organization of midline/intralaminar thalamo-corticostriatal systems.

Moreover, on the basis of single-cell tracing, Deschênes *et al.* (1996) showed that striatal and cortical projections from some caudal intralaminar nuclei arise from collaterals of the same neuron (see also Bubser and Deutch, 1998; Otake and Namura, 1998).

While, as indicated, the projections of the central medial nucleus differ from those of other intralaminar nuclei, similar to these nuclei, the main output of CM is to the cortex and to the dorsal striatum. By contrast with them, however, CM fibers distribute over much more extensive regions of both the cortex and striatum, and also terminate substantially in the ventral striatum (Fig. 6) (Van der Werf *et al.*, 2002; Vertes *et al.*, 2012).

Primary CM targets are anterior and posterior regions of cortex, the claustrum, the caudate-putamen, the nucleus accumbens, the olfactory tubercle, and the amygdala. There are distinct differences in projections from the rostral and caudal CM (Fig. 6) (Vertes *et al.*, 2012). The cortical projection of the rostral CM is virtually restricted to anterior regions of cortex, with fibers distributing to the AGm, AC, prelimbic, dorsolateral orbital, and dorsal agranular insular cortices. By contrast, the caudal CM mainly targets lateral and caudal structures of the cortex: the lateral and dorsolateral orbital cortices, dorsal and ventral agranular insular cortices, the gustatory/visceral cortex, primary somatosensory and motor cortices, and the perirhinal cortex. Subcortically, rostral CM distributes rostrocaudally throughout C-P, to the anterior core and shell of nucleus accumbens, and throughout the basal lateral nucleus (BLA) of amygdala. Caudal CM fibers, on the other hand, innervate lateral/ventrolateral regions of C-P and several nuclei

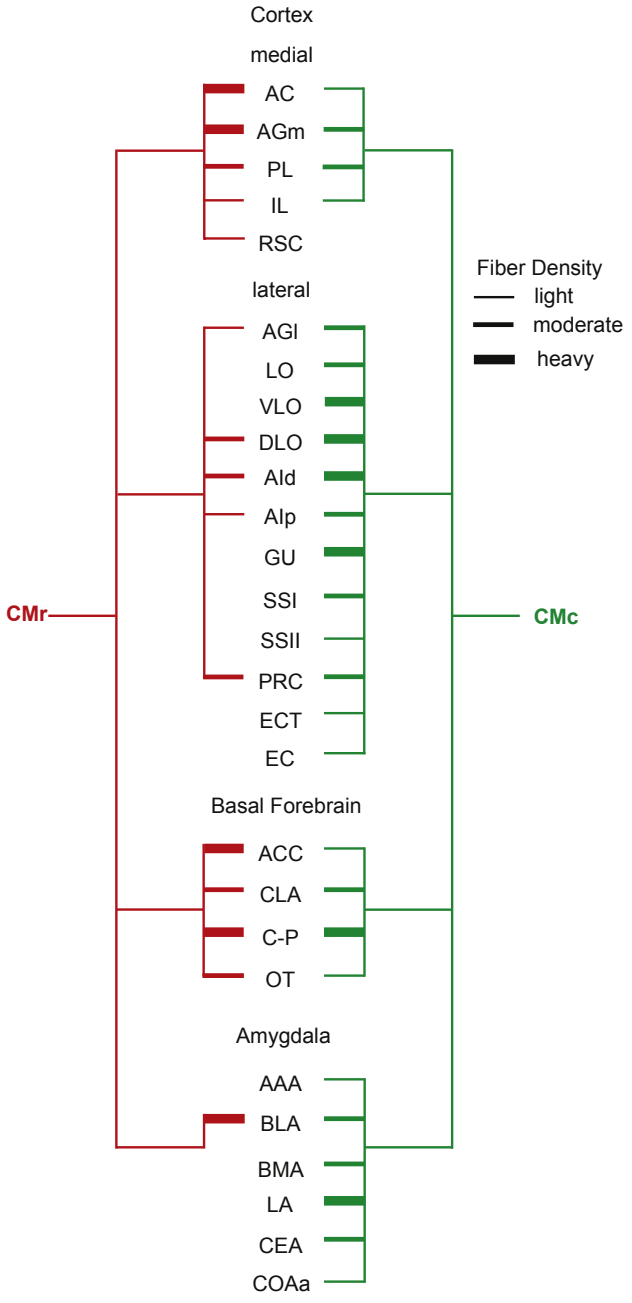

FIGURE 6 Summary diagram showing the pattern of projections of the rostral (CMr) and caudal (CMc) central medial nucleus of the thalamus to structures of the cortex (medial and lateral regions), the basal forebrain, and the amygdala. The relative density of projections to each structure is indicated by the thickness of the lines. See text for further details. *From Vertes, R.P., Hoover, W.B., & Rodriguez, J.J. (2012). Projections of the central medial nucleus of the thalamus in the rat: node in cortical, striatal and limbic forebrain circuitry.* Neuroscience *219, 120–136.*

of the amygdala including the anterior, lateral, central, medial, cortical, and basal nuclei. With the exception of nucleus accumbens, which receives input essentially only from the rostral CM, the rostral and caudal CM target the same structures but different parts of them. When outputs are combined, however, CM distributes

very widely over the cortex, to the entire dorsal striatum, to the anterior accumbens, and to most subnuclei of the amygdala (Vertes *et al.*, 2012).

Functional Aspects

Owing to the relatively small size of individual intralaminar nuclei, the complex configuration of these nuclei as a whole, and the intricate relationships of these nuclei to neighboring thalamic groups, it has been difficult to probe separate functions for each of the intralaminar nuclei. As such, when describing function, these nuclei are generally combined, and in some cases, the lateral MD is also included (Bailey and Mair, 2005; Mitchell and Dalrymple-Alford, 2005, 2006; Lopez *et al.*, 2009). As discussed, damage to the anterior thalamus (ATh) gives rise to deficits in (allocentric) spatial learning/memory which mimic those produced by lesions of the hippocampus. This is consistent with the strong anatomical links between these structures. Whereas the intralaminar nuclei lie caudally adjacent to the anterior thalamus, intralaminar projections significantly differ from those of the ATh. Specifically, ILt nuclei mainly target the striatum and dorsal/dorsolateral (motor) regions of cortex as opposed to hippocampal-related systems for the anterior nuclei. Based in part, however, on their close proximity to ATh, the functions of the intralaminar nuclei have often been compared to those of the anterior thalamus. Specifically, Mitchell and Dalrymple-Alford (2005) initially showed that ATh, but not intralaminar, lesions produced deficits on a spatial radial arm maze (RAM) task in rats. In a follow-up report, they described a double dissociation between the effects of lesions of the two thalamic regions; that is, only ATh lesions disrupted performance on the RAM task, whereas intralaminar lesions produced impairments on a non-hippocampal-dependent (egocentric) working memory task (Mitchell and Dalrymple-Alford, 2006). Consistent with this, Bailey and Mair (2005) demonstrated that intralaminar lesions produced essentially no impairments on a delayed nonmatching to sample RAM task which is sensitive to anterior thalamic or hippocampal damage (Mair *et al.*, 2003).

More recently, Hembrook and Mair (2011) compared the effects of intralaminar thalamic (ILt) lesions with those of the reuniens (RE) and rhomboid (RH) nuclei of the midline thalamus on a "win-shift" task (or a delayed non-match to sample RAM task), which is reportedly sensitive to both hippocampal and PFC damage, and on a visuospatial reaction time (VSRT) task used to evaluate lesions of the striatum and the dorsal frontal cortex (Burk and Mair, 2001; Mair *et al.*, 2002; Bailey and Mair, 2004). The effects of lesions of the two thalamic sites were doubly dissociated: RE/RH lesions disrupted performance on the win-shift task but not the VSRT task, while caudal intralaminar lesions altered behavior on the VSRT task but not on the win-shift task. Although as described, intralaminar lesions do not generally affect performance on spatial memory tasks, Cassel and colleagues (Lopez *et al.*, 2009) demonstrated some long-term effects of rostral ILt lesions on a (spatial) water maze task. Rats with intralaminar lesions showed no deficits on acquisition or on retention using a probe test 5 days post-acquisition, but were significantly impaired when tested 25 days post-acquisition, illustrating a loss of remote spatial memory.

MIDLINE NUCLEI

The midline nuclei are located medially in the thalamus as a relatively narrow band of nuclei that are distributed over the entire dorsal-to-ventral extent of the thalamus. The midline nuclei include the paraventricular, paratenial, reuniens, and rhomboid nuclei—and in some schemes, the IMD, which lies medially between the two halves of MD (Groenewegen and Witter, 2004). These nuclei occupy the midline of the thalamus from its very rostral tip to approximately two-thirds of the rostrocaudal length of the thalamus. The paraventricular nucleus (PV) is located medially, spanning the entire rostrocaudal length of the midline complex. PV lies directly ventral to the third ventricle, and dorsal and medial to the mediodorsal nucleus. Rostrally, it follows the surface of the massa intermedia and curves ventrally to form a wedge between the anterior poles of nucleus reuniens (RE) (Krieg, 1944). More caudally, PV curves slightly lateral, ventral to the habenula, and ends just rostral to the posterior commissure. The paratenial nucleus (PT) forms a slender, elongated nucleus located in the anterior part of the thalamus in close proximity and lateral to the paraventricular nucleus. At its posterior end, PT fuses with the mediodorsal nucleus. The PT, together with the mediodorsal and reuniens nuclei, are thought to originate from a common nuclear mass. The rhomboid nucleus (RH) is located ventral to the internal medullary lamina (Berendse and Groenewegen, 1990). At its rostral end, it merges with the anteromedial nucleus and has wing-like lateral extensions. The nucleus is easily distinguished by its conspicuous shape and its large and darkly staining cells.

The nucleus reuniens (RE) is located in the anterior two-thirds of the thalamus. Rostrally, it is divided into a left and a right component by the third ventricle; further caudally the two structures fuse and become a mass of cells on the midline of the thalamus, lying immediately dorsal to the third ventricle. The RE consists of a conglomerate of loosely packed cells (Jones, 1985, 2007; Risold *et al.*, 1997). The main mass of RE is bordered bilaterally by the perireuniens nucleus (or lateral wings of RE). The intermediodorsal nucleus (IMD) is located posteriorly, between the

left and right mediodorsal nuclei. An IMD is not recognized in all species, but has been defined in the rat (Jones, 1985; Berendse and Groenewegen, 1990). The midline nuclei use excitatory amino acids as a neurotransmitter (Hur and Zaborszky, 2005). In addition, calcium-binding proteins are present in both cell bodies and neuropil. Calretinin-positive neurons are present virtually throughout the midline nuclei, with a preference for PV and RE (Arai *et al.*, 1994; Paxinos *et al.*, 1999). Calbindin-positive neurons are predominantly located in the reuniens and intermediodorsal nuclei. Parvalbumin is conspicuously absent from the midline nuclei (Arai *et al.*, 1994). The neuropil of PV is very rich in neurotransmitters and neuropeptides, most of which are contained in afferent fibers. In addition, a subpopulation of PV neurons expresses preproenkephalin mRNA (Hermanson *et al.*, 1995).

Afferent Projections

The PV receives afferents from a wide array of cortical and subcortical sites (Cornwall and Phillipson, 1988; Sesack *et al.*, 1989; Chen and Su, 1990; Hurley *et al.*, 1991; Vertes, 1991, 1992, 2002, 2004; Otake and Nakamura, 1995; Otake *et al.*, 1995; Vertes *et al.*, 1995, 1999; Ruggiero *et al.*, 1998; Novak *et al.*, 2000; Krout *et al.*, 2002; Goto and Swanson, 2004; Peng and Bentivoglio, 2004; Kirouac *et al.*, 2005, 2006; Otake, 2005; Hoover and Vertes, 2011; Li and Kirouac, 2012). The main sources of subcortical input to PV are from structures of the brainstem and hypothalamus, with additional but more limited input from the bed nucleus of stria terminalis (BST) and parts of the amygdala. Similar to other midline nuclei (see below), PV receives projections from several nuclei/regions of the brainstem which include the ventral tegmental area (VTA), the pontomesencephalic RF, nucleus cuneiformis, nucleus of Darkschewitsch, the dorsal and median raphe nuclei, regions of the PAG, the parabrachial complex, LDT and PPT, the locus coeruleus and the solitary nucleus (Chen and Su, 1990; Takada *et al.*, 1990; Bester *et al.*, 1999; Krout and Loewy, 2000a, 2000b; Krout *et al.*, 2002; Li and Kirouac, 2012).

In a similar manner, PV receives a diverse and widespread set of hypothalamic projections from the tuberomammillary, supramammillary, dorsomedial, posterior, lateral and parasubthalamic nuclei of the hypothalamus, as well as from the medial preoptic area and diagonal band nuclei (Vertes, 1992; Vertes *et al.*, 1995; Goto and Swanson, 2004; Kirouac *et al.*, 2005, 2006; Menzie *et al.*, 2010; Li and Kirouac, 2012). In addition, PV is essentially unique among the midline nuclei in that it is in receipt of input from the suprachiasmatic nucleus and the intergeniculate leaflet (Moore *et al.*, 2000; Kawano *et al.*, 2001).

The other major source of afferents to PV is from the cortex, or more specifically from the mPFC and insular cortices (Groenewegen, 1988; Sesack *et al.*, 1989; Chen and Su, 1990; Hurley *et al.*, 1991; Vertes, 2002, 2004; Jasmin *et al.*, 2004; Hoover and Vertes, 2011; Li and Kirouac, 2012). Whereas fibers throughout the mPFC project to PV, there is a dorsal to ventral gradient in density such that AGm and AC distribute moderately, and PL and IL massively, to PV (Vertes, 2002, 2004; Li and Kirouac, 2012). Some inputs differentially favor anterior or posterior parts of PV (Li and Kirouac, 2012). Specifically, the ventral subiculum distributes more heavily to the anterior than to the posterior PV, whereas IL, PL and the posterior agranular insular cortex preferentially project to the posterior PV.

Compared to other midline thalamic nuclei, less is known about inputs to PT presumably owing to its small size and the difficulty in selectively targeting PT in tracing studies. Nonetheless, based on anterograde reports tracing projections to PT, an understanding of major sources of inputs to PT has emerged (Cornwall and Phillipson, 1988; Groenewegen, 1988; Sesack *et al.*, 1989; Chen and Su, 1990; Hurley *et al.*, 1991; Krout *et al.*, 2002; Vertes, 2002, 2004; Jasmin *et al.*, 2004; Hoover and Vertes, 2011). With some notable exceptions, PT and PV receive similar sets of projections. Like PV, brainstem inputs to PT mainly derive from the dorsal and median raphe, PAG, locus coeruleus, parabrachial complex, LDT, and the solitary nucleus. Forebrain structures distributing to PT include the ventral subiculum, the claustrum and suprachiasmatic nucleus, and less so, the lateral septum, diagonal band nuclei, BST, medial nucleus of amygdala, reticular thalamic nucleus, zona incerta and parts of the hypothalamus (Chen and Su, 1990).

As with PV, the PT receives substantial input from regions of the "limbic" cortex—or the medial, orbital, and insular PFC (Sesack *et al.*, 1989; Hurley *et al.*, 1991; Vertes, 2002, 2004; Jasmin *et al.*, 2004; Hoover and Vertes, 2011). PT is the recipient of numerous fibers from the ventral mPFC (IL and PL) but fewer from the dorsal mPFC (AC and AGm). In addition, PT is a prominent target of projections from the (rostral) agranular insular cortex and the medial (MO) and ventral (VO) orbital cortices (Jasmin *et al.*, 2004; Hoover and Vertes, 2011). PT appears to be an important site of convergence for fibers originating in IL, PL, MO, VO and the rostral insular cortex.

The RE of thalamus receives a wide array of afferents from the cortex, hippocampus, basal forebrain, amygdala, hypothalamus, and brainstem, with major inputs from the PFC and hippocampal formation (Herkenham, 1978; Sesack *et al.*, 1989; Witter *et al.*, 1990; Wouterlood *et al.*, 1990; Cullinan and Zaborszky, 1991; Hurley *et al.*, 1991; Canteras and Swanson, 1992; Vertes, 1991, 1992; Risold *et al.*, 1994, 1997; Canteras *et al.*, 1995; Vertes *et al.*, 1995; Naber and Witter, 1998; Canteras and Goto, 1999; Moore *et al.*, 2000; Krout *et al.*, 2002; Vertes, 2002, 2004; Jasmin *et al.*, 2004; McKenna and Vertes, 2004; Hoover and Vertes, 2011).

The main sources of brainstem afferents to RE are VTA, PAG, the medial and posterior pretectal nuclei, the superior colliculus, the precommissural and commissural nuclei, the nucleus of posterior commissure, the parabrachial complex, PPT, LDT, the dorsal and median raphe nuclei and nucleus incertus. Probably more so than other midline nuclei, RE also receives input from several subcortical forebrain structures including the claustrum, lateral septum, substantia innominata and medial/lateral preoptic nuclei of the basal forebrain, the medial nucleus of amygdala, the paraventricular and lateral geniculate nuclei of the thalamus, the zona incerta, and the anterior, ventromedial, lateral, posterior, supramammillary and dorsal premammillary nuclei of the hypothalamus (McKenna and Vertes, 2004).

Similar to cortical afferents to PV/PT, reuniens receives massive projections from the orbitomedial and insular PFC, but in addition receives very dense projections from the hippocampus, and to a lesser degree, from parahippocampal cortices. In particular, RE is targeted by the following cortical structures: AGm, AC, PL, IL of the mPFC, the dorsal and ventral agranular insular cortices, MO, the retrosplenial, ectorhinal and perirhinal cortices, and the subiculum of the hippocampus (Fig. 3) (Herkenham, 1978; Sesack *et al.*, 1989; Hurley *et al.*, 1991; Risold *et al.*, 1997; Vertes, 2002, 2004; McKenna and Vertes, 2004; Jasmin *et al.*, 2004; Hoover and Vertes, 2011).

The foregoing indicates that RE is a major site of convergence of a vast and diverse array of afferents largely, but not solely, originating from limbic-related subcortical and cortical structures. Accordingly, RE appears to represent a critical node in the integration and transfer of various types of limbic information to its main targets, namely, to the hippocampus and to the prefrontal cortex (see below).

Compared with other midline nuclei, much less is known about inputs to RH (Sesack *et al.*, 1989; Hurley *et al.*, 1991; Krout *et al.*, 2002; Vertes, 2002, 2004; McKenna and Vertes, 2004; Owens, 2005). Although there is some overlap, afferents to RH are distinct from those to RE—with a major difference being unlike RE, the RH receives significant input from non-limbic (sensory/motor) structures. As with other midline and intralaminar nuclei, the brainstem is a major source of afferents to RH, originating from such "limbic associated" sites as the VTA, PAG, PPT, LDT and the parabrachial nucleus, but also from "motor" nuclei including the substantia nigra-pars reticulata, mesencephalic RF, superior colliculus, and the anterior pretectal nucleus. In general, subcortical forebrain input to RH is not extensive, arising most heavily from the claustrum, substantia innominata, and zona incerta, and to a lesser extent from the posterior and lateral nuclei of the hypothalamus and parts of the amygdala.

Cortical afferents to RH originate from limbic and non-limbic regions of the cortex. While fibers throughout the medial wall of the PFC (or mPFC) distribute to RH, they arise most strongly from the dorsally located AGm and taper ventrally in the mPFC. In contrast to other midline nuclei, RH receives marked input from the primary motor cortex and the primary and secondary somatosensory cortices. Aside from inputs from parts of the insular and medial PFC, RH receives limited projections from "limbic" cortices, and notably few projections from the parahippocampal cortices and the hippocampus (McKenna and Vertes, 2004).

Efferent Projections

Although the midline and intralaminar thalamic nuclei are often discussed as a unit, their afferent and certainly their efferent projections differ. In general, the output of the intralaminar nuclei is fairly restricted and weighted to sensorimotor structures, whereas that of the midline nuclei is widespread with a concentration in limbic forebrain structures.

The PV distributes widely throughout the forebrain to cortical and subcortical structures, with virtually no projections to the brainstem (Berendse and Groenewegen, 1990, 1991; Meredith and Wouterlood, 1990; Su and Bentivoglio, 1990; Turner and Herkenham, 1991; Brog *et al.*, 1993; Condé *et al.*, 1995; Moga *et al.* 1995; Bubser and Deutch, 1998; Otake and Nakamura, 1998; Pinto *et al.*, 2003; Jasmin *et al.*, 2004; Peng and Bentivoglio, 2004; Parsons *et al.*, 2006, 2007; Hoover and Vertes, 2007; Shin *et al.*, 2008; Li and Kirouac, 2008; Vertes and Hoover, 2008). The principal targets of PV are the ventral mPFC (infralimbic, prelimbic and ventral AC cortices), AId, ventral subiculum of hippocampus, the claustrum, the lateral septum, the core and shell of nucleus accumbens (ACC), the olfactory tubercle (OT), bed nucleus of stria terminalis (BST), the medial, central, cortical and basal nuclei of amygdala, and the suprachiasmatic, arcuate, and dorsomedial nuclei of the hypothalamus. PV distributes particularly densely to the ventral mPFC, ACC, BST and the central, basal medial and basal lateral nuclei of amygdala (Fig. 7) (Li and Kirouac, 2008; Vertes and Hoover, 2008). In addition, the caudal, but not the rostral, PV distributes to the dorsal striatum, and the caudal PV is the source of strong projections to the mPFC and to the amygdala.

Compared to PV, much less attention has been paid to the efferent projections of PT, undoubtedly owing to its small size (Berendse and Groenewegen, 1990, 1991; Turner and Herkenham, 1991; Brog *et al.*, 1993; Condé *et al.*, 1995; Van der Werf *et al.*, 2002; Jasmin *et al.*, 2004; Hoover and Vertes, 2007; Vertes and Hoover, 2008). Nonetheless, the output of PT is pronounced and parallels that of PV (Vertes and Hoover, 2008). The main cortical targets of PT are the medial frontal polar, anterior cingulate, prelimbic, infralimbic, medial orbital, dorsal agranular insular, piriform and entorhinal cortices, and

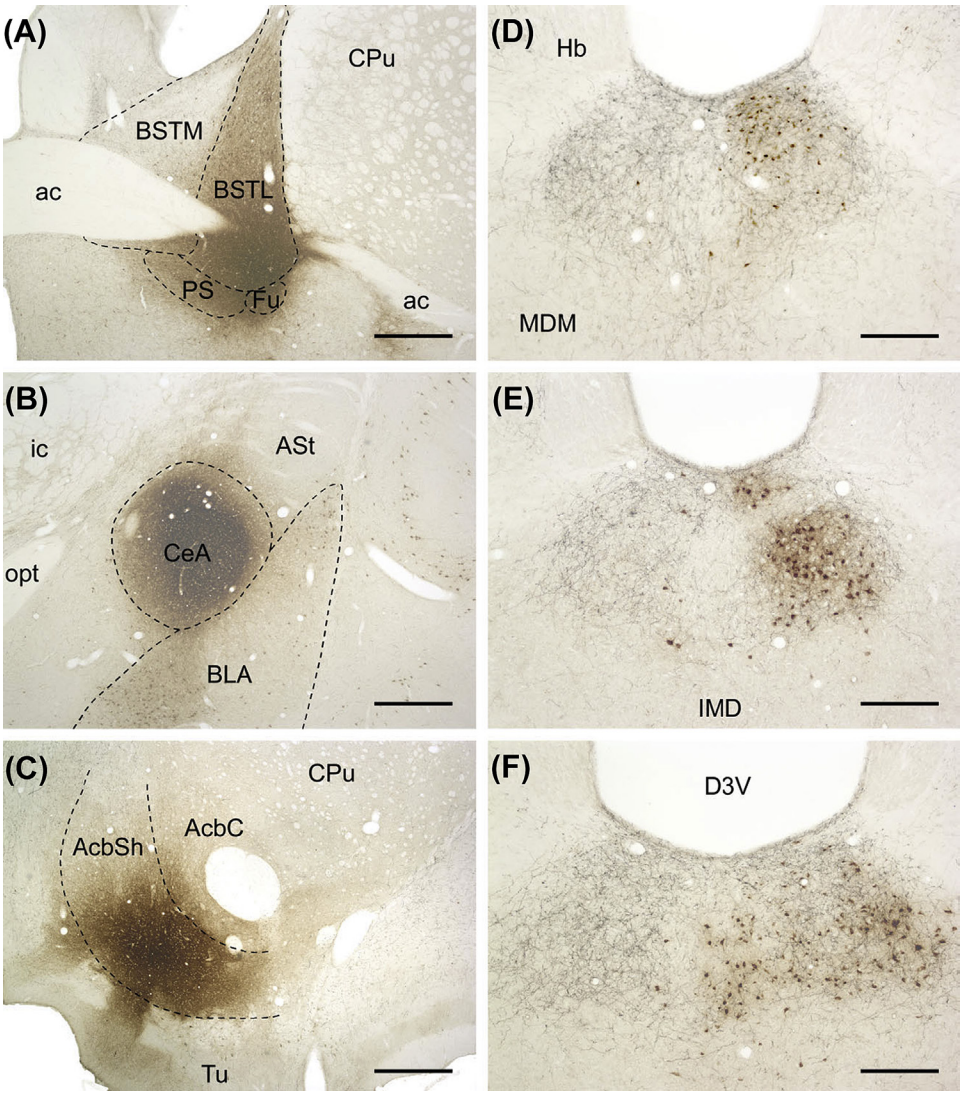

FIGURE 7 (A–C) Digital images showing sites of injection of the retrograde tracer, cholera toxin B, in the lateral bed nucleus of the stria terminalis (BSTL), the central nucleus of the amygdala (CeA), and the shell of the nucleus accumbens (AcbSh), respectively. (D-F) Digital images showing patterns of retrogradely labeled cells (brown) in the paraventricular nucleus of the thalamus corresponding to the three sites of injections (A-C): BSTL, CeA and AcbSh. Note significant numbers of labeled cells in the paraventricular nucleus, mainly ipsilateral to the injections, with each of the injections. Note further the presence of orexin-containing fibers (black) in the paraventricular nucleus (PV) which outline the boundaries of PV. Scale bars = 500 μm for A–C; 200 μm for D–F. See text for further details. *From Li, S., & Kirouac, G.J. (2008). Projections from the paraventricular nucleus of the thalamus to the forebrain, with special emphasis on the extended amygdala.* Journal of Comparative Neurology *506, 263–287.*

the ventral subiculum of the hippocampus. Principal subcortical sites of projection are the claustrum, the core and shell of ACC, the medial C-P, BST, and caudal parts of the central and basal nuclei of amygdala. PT also distributes lightly/moderately to the ventral orbital and perirhinal cortices, the dorsal subiculum, lateral septum, medial and cortical nuclei of amygdala, and the lateral hypothalamus (Vertes and Hoover, 2008).

There are some notable differences in the projections of PT and PV. In brief, the output of PT is more strongly weighted to (limbic) cortical than to subcortical structures, whereas the opposite is true for PV: subcortical greater than cortical. Specifically, PT distributes more widely throughout the cortex, and more intensely than PV to the MO, ventral mPFC, the lateral entorhinal cortex, the ventral subiculum, and the dorsal striatum. On the other hand, PV fibers terminate more heavily than those of PT in the BST, the central and basal nuclei of the amygdala and most of the hypothalamus. Both PT and PV, however, distribute massively to the nucleus accumbens (Vertes and Hoover, 2008).

The RE is the largest of the midline nuclei and the most thoroughly investigated, likely owing to the early demonstration that RE is a major source of input to the hippocampus (Herkenham, 1978). Although reuniens distributes to a few subcortical sites, it predominantly targets cortical structures (Herkenham, 1978; Ohtake and Yamada, 1989; Su and Bentivoglio, 1990; Wouterlood *et al.*, 1990; Wouterlood, 1991; Dolleman-Van der Weel and Witter, 1996; Risold *et al.*, 1997; Bokor *et al.*, 2002; Van der Werf *et al.*, 2002; Vertes, 2006; Vertes *et al.*, 2006, 2007; Hoover and Vertes, 2007, 2012; Cavdar *et al.* 2008; Varela *et al.*, 2014). These mainly include the medial and ventral orbital cortices, infralimbic, prelimbic and anterior cingulate cortices of the mPFC, the dorsal and ventral agranular insular cortices, rostral retrosplenial cortex, perirhinal cortex, medial and lateral entorhinal cortices, and the hippocampal formation. RE fibers distribute massively to the

hippocampus terminating selectively in the stratum lacunosum-moleculare (slm) of CA1 of the dorsal and ventral hippocampus as well as the molecular layer of the dorsal and ventral subiculum and the parasubiculum. RE axons form asymmetric (excitatory) contacts predominantly on distal dendrites of pyramidal cells in slm of CA1 and the subiculum (Wouterlood *et al.*, 1990). There is an absence of RE projections to CA2 and CA3 and to the dentate gyrus of the hippocampus. Subcortical projections of RE are limited and mainly directed to the claustrum and to the anterior pole of nucleus accumbens.

Examinations of the physiological effects of RE on the hippocampus and on the PFC have shown that RE exerts pronounced excitatory actions at CA1 of the hippocampus and at the mPFC (Dolleman-Van der Weel *et al.*, 1997; Bertram and Zhang 1999; Viana Di Prisco and Vertes, 2006). Dolleman-Van der Weel *et al.* (1997) demonstrated that RE stimulation produced large negative-going field potentials (sink) at slm of CA1 as well as paired pulse facilitation at CA1. Bertram and Zhang (1999) compared the effects of RE and CA3 stimulation on population responses (field EPSPs and spikes) at CA1 and reported that RE actions at CA1 were equivalent to, and in some cases considerably greater than, those of CA3 at CA1. They concluded that the RE projection to the hippocampus "allows for the direct and powerful excitation of the CA1 region. This thalamo-hippocampal connection bypasses the trisynaptic/commissural pathway that has been thought to be the exclusive excitatory drive to CA1." More recently, Viana Di Prisco and Vertes (2006) confirmed the excitatory effects of RE on the hippocampus, and further showed that RE stimulation produced large monosynaptically-elicited evoked responses dorsoventrally throughout the mPFC, with most pronounced actions (latency and amplitude) at the ventral mPFC—or at the prelimbic and infralimbic cortices.

The actions of RE on the hippocampus and the mPFC could involve a common group of RE cells with collaterals to both sites, or more likely separate populations of RE neurons. Relevant to this, recent studies (using double retrograde fluorescent techniques) have shown that approximately 5–10% of RE cells project, via collaterals, to both the hippocampus and the ventral mPFC (Fig. 8) (Hoover and Vertes, 2012; Varela *et al.*, 2014). Further, RE neurons projecting to one site or the other (non-branching) were shown to largely reside in separate regions of RE; that is, cells projecting to the mPFC were mainly localized to the perireuniens nucleus (or lateral wings of RE), while those distributing to the hippocampus were concentrated in the rostral pole of RE (Hoover and Vertes, 2012; Varela *et al.*, 2014). The issue, then, of the origin of RE cells that exert separate, as opposed to possibly combined, effects on the hippocampus and mPFC needs to be further investigated.

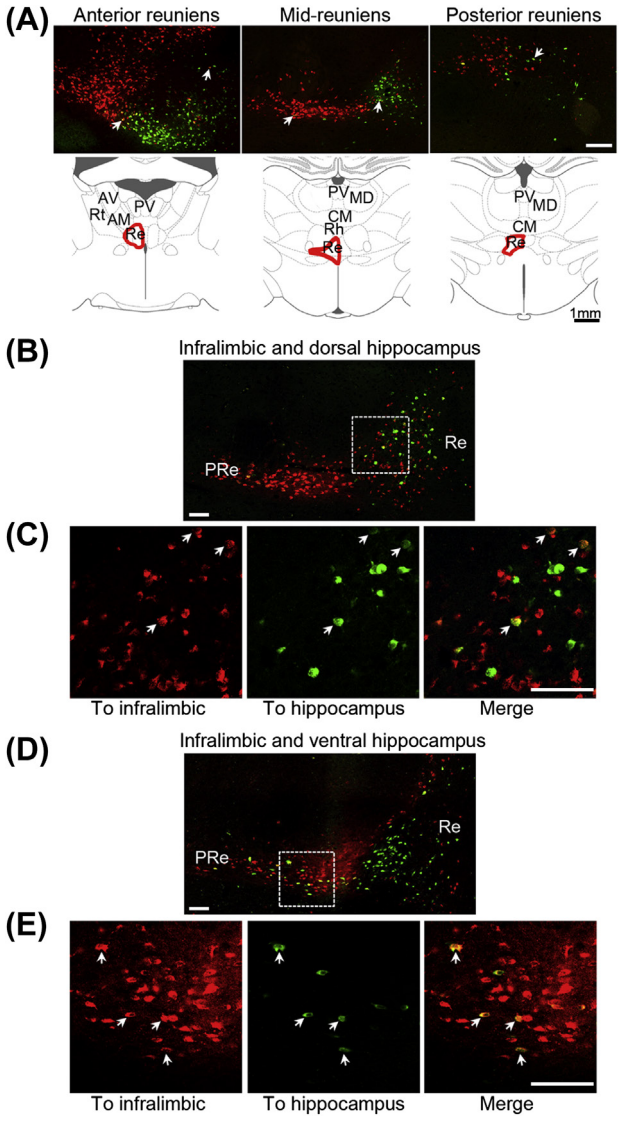

FIGURE 8 Single and double labeled cells in the nucleus reuniens (RE) of thalamus following retrograde fluorescent injections in the rat medial prefrontal cortex (mPFC) and the hippocampus. (A) Confocal microscope images at three rostrocaudal levels of nucleus reuniens (left to right) depicting the presence of labeled cells in RE following injections in the mPFC (red) or the hippocampus (green). White arrows denote double-labeled cells. (B) Confocal image showing labeled cells in nucleus reuniens following injections in the infralimbic cortex (red) and the dorsal hippocampus (green). (C) Enlargement of the boxed area in (B) depicting double-labeled cells (white arrows) in RE. (D) Confocal image showing labeled cells in nucleus reuniens following injections in the infralimbic cortex (red) and the ventral hippocampus (green). (E) Enlargement of the boxed area in (D) depicting double-labeled cells (white arrows) in RE. *Abbreviations*: RE, nucleus reuniens; PRe perireuniens nucleus. Scale bars for A=200 μm; for B–E=100 μm. *From Varela, C., Kumar, S., Yang, J.Y., & Wilson, M.A. (2014). Anatomical substrates for direct interactions between hippocampus, medial prefrontal cortex, and the thalamic nucleus reuniens.* Brain Structure and Function, *219, 911–929.*

While it is well recognized that the hippocampus gives rise to pronounced projections to the medial prefrontal cortex (Swanson, 1981, Ferino *et al.*, 1987; Jay and Witter, 1991;

Carr and Sesack, 1996; Hoover and Vertes, 2007), interestingly there are no return projections from the mPFC to the hippocampus (Laroche *et al.*, 2000; Vertes, 2004). The demonstration, however, of strong projections from the mPFC to RE and, in turn, from the RE to the hippocampus (Vertes, 2002; Vertes *et al.*, 2006) suggests that RE may be a main route for the transfer of information from the mPFC to the hippocampus—thus completing an important functional loop between these structures. Supporting this, mPFC fibers distributing to the RE have been shown to form asymmetric (excitatory) contacts on dendrites of RE cells projecting to the hippocampus (Vertes *et al.*, 2007).

Unlike RE, relatively few reports have described the efferent projections of RH (Ohtake and Yamada, 1989; Berendse and Groenewegen, 1990, 1991; Van der Werf *et al.*, 2002; Vertes *et al.*, 2006, Hoover and Vertes, 2007). In contrast to the cortical projections of RE which are largely restricted to "limbic cortices," those of RH distribute widely over the cortex to limbic and non-limbic regions. The cortical targets of RH are the medial orbital cortex, the AGm, AC, PL and IL of the mPFC, the posterior agranular insular, primary and secondary somatosensory, retrosplenial, posterior parietal, perirhinal, occipital, and temporal cortices, and the hippocampal formation. Similar to RE, RH fibers terminate within the slm of CA1 of the dorsal and ventral hippocampus as well as in the outer molecular layer of the dorsal and ventral subiculum. RH projections, however, to the hippocampus are less pronounced than those from RE.

The main subcortical termination sites of RH fibers are the claustrum, the dorsal striatum, the lateral septum, the core and shell of nucleus accumbens, the olfactory tubercle and the basal medial and basal lateral nuclei of the amygdala. Although present, RH projections to the striatum are restricted to medial aspects of C-P, and are much less abundant than those to the striatum from the central medial nucleus (see above). Consistent with diverse inputs to RH from limbic and non-limbic sites, RH fibers spread widely throughout the cortex to sensorimotor, associational and limbic regions of the cortex (Berendse and Groenewegen, 1991; Vertes *et al.*, 2006). Accordingly, RH seems well positioned to bridge the sensorimotor and limbic domains, possibly providing limbic support (emotional/cognitive) for goal directed behaviors.

Functional Aspects

Regarding function, the midline nuclei that have received the most attention are the PV and RE. Due in part to its close proximity to RE, the RH is often included with RE in behavioral studies.

The PV receives a wide array of afferents from arousal/attention-related sites of the brainstem and hypothalamus, including a major input from orexin-containing cells of the lateral hypothalamus (Peyron *et al.*, 1998). PV, in turn, projects to limbic subcortical and cortical sites including the mPFC, nucleus accumbens, BST, and the central and basal nuclei of the amygdala. Accordingly, PV is reportedly involved in a range of functions which would include stress and anxiety, feeding behavior, and drug seeking activities.

PV is activated by wide variety of stressors (e.g., fear/anxiety, immobilization, footshock) and hence appears to be responsive to stress, *per se*, independent of specific types of stressors (Chastrette *et al.*, 1991; Bubser and Deutch, 1999). PV has been shown to be instrumental in the adaptation to acute stressors following periods of chronic stress. For example, rats exposed to a repeated (chronic) stressor become habituated to that stressor, so that its re-introduction produces less of a response than the initial exposure. However, if a different stressor is introduced after habituation, the response to it is magnified, possibly signaling the presence of novel, potentially threatening, stimuli. PV appears to be involved in both processes: that is, adaptation to the original stressor and the heightened response to a novel stressor (Bhatnagar and Dallman, 1998; Bhatnagar *et al.*, 2002; Heydendael *et al.*, 2011). Specifically, posterior PV lesions block habituation to repeated restraint stress (Bhatnagar *et al.*, 2002) and c-fos expression in PV is significantly elevated when novel stressors are applied after a chronic stressor (Bhatnagar and Dallman, 1998).

Although more typically responsive to "negative" stimuli, PV cells are also activated by rewarding conditions and thus seem to generally encode emotionally salient events (Igelstrom *et al.*, 2010; Hsu *et al.*, 2014). Accordingly, PV serves a role in feeding behavior—which may be a model system for appetitive functions. In particular, c-fos levels in PV are enhanced in anticipation of feeding in food-deprived rats, and PV lesions attenuate anticipatory locomotor activity associated with feeding (Nakahara *et al.* 2004; Angeles-Castellanos *et al.* 2007). Kelley *et al.* (2005) advanced a model to account for the encoding of the incentive value of foods. Among other things, the model predicted when incentive values are high (very desirable foods), feeding would ensue even under sated conditions. The proposed circuit for this effect(s) was a hypothalamic-thalamic-striatal network of which PV served an integral role. PV was thought to be critically involved in the transfer of various types of affective/homeostatic information to the striatum in food seeking behavior, or as was stated: "PVT may act as an interface between signals related to arousal, energy balance, circadian or diurnal rhythms, and reward, and major striatal motor output systems" (Kelley *et al.*, 2005). Consistent with this, Choi *et al.* (2012) demonstrated that direct injections of orexin-A in PV produced a marked increase in dopamine release in the nucleus accumbens and elicited hedonic feeding—an overconsumption of palatable foods.

Similar to the reward circuit for food (Kelley *et al.*, 2005; Choi *et al.*, 2010, 2012), the postulated core circuitry for drug seeking behavior involves orexinergic projections from the lateral hypothalamus to PV and from PV to the nucleus accumbens (for review, Martin-Fardon and Boutrel, 2012). Regarding a role for PV in drug-seeking behavior, lesions or inactivation PV suppress drug-seeking activities (Hamlin *et al.*, 2009; James *et al.*, 2010; Marchant *et al.*, 2010), while cue-induced reinstatement of cocaine seeking behavior strongly correlates with c-fos activation in PV (James *et al.*, 2011). Further, injections of orexin-A in PV reinstated extinguished cocaine and sweetened condensed milk (SCM) seeking behavior (Martin-Fardon *et al.*, 2011). Finally, there may be a link between a PV involvement in stress/anxiety and in overeating and drug seeking behavior in that stress tends to exacerbate both behaviors (Martin-Fardon and Boutrel, 2012; James and Dayas, 2013).

The RE mainly targets the orbitomedial PFC, parahippocampal cortices and the hippocampus, whereas the RH also distributes (but less heavily) to these structures, and additionally to sensorimotor cortices, the nucleus accumbens, and parts of the amygdala (Vertes *et al.*, 2006). In contrast to the involvement of the dorsal midline thalamus in affective behaviors, the prominent (reciprocal) RE connections with limbic cortices, particularly the hippocampus and mPFC, points to a direct role in cognitive functions.

A number of studies have examined the effects of lesions (or inactivation) of RE on behavior, with many of them including RH with RE, together referred to as the ventral midline thalamus (Dolleman-van der Weel *et al.*, 2009; Davoodi *et al.*, 2009, 2011; Eleore *et al.*, 2011; Hembrook and Mair, 2011; Hembrook *et al.*, 2012; Loureiro *et al.*, 2012; Cholvin *et al.*, 2013; Prasad *et al.*, 2013). While a consensus has not been reached, it appears that RE is critically involved in behaviors that depend on interactions between the hippocampus and the mPFC. In an initial study, Dolleman-van der Weel *et al.* (2009) reported that rats with excitotoxic lesions of RE were comparable to controls in both the acquisition and retention of a water maze reference memory task. Specifically, on the probe test following acquisition, RE lesioned rats swam directly to the correct quadrant of the pool, but upon not finding the platform, immediately adopted a strategy of searching the entire pool for the platform. The deficit was described as non-mnemonic or a reduced ability to shift strategies—or adopting a much too flexible (or impulsive) pattern of behavior. In effect, the altered search strategy was viewed as a medial PFC rather than a hippocampal dysfunction. Subsequent studies have similarly shown that inactivation of RE/RH does not alter acquisition or retrieval on the standard water maze task (Loureiro *et al.*, 2012; Cholvin *et al.*, 2013). In accord with the findings of Dolleman-van der Weel *et al.* (2009), Prasad *et al.* (2013) showed that rats with RE lesions were unable to inhibit premature responses in a 5 choice reaction time task—an impulsive behavioral pattern characteristic of damage to the PFC (Chudasama *et al.* 2003).

In complementary reports, Mair and associates (Hembrook and Mair, 2011; Hembrook *et al.*, 2012) described the involvement of RE in tasks that depend on the interactions between the hippocampus and the mPFC. As previously discussed, Hembrook and Mair (2011) initially showed that RE/RH lesions produced no impairment on a visuospatial reaction time task sensitive to alterations of the striatum and motor cortex, but such lesions significantly altered performance on a win-shift radial maze task—or one that is affected by damage to the hippocampus or the mPFC (McDonald and White, 1993; Porter and Mair, 1997; Mair *et al.*, 1998). Hembrook *et al.* (2012) subsequently compared the effects of inactivation of RE/RH on performance on two tasks: (1) a delayed non-match to position (DNMTP) task in an operant chamber that is sensitive to lesions of the hippocampus or the mPFC; and (2) a variable choice radial maze delayed non-matching (VC-DNM) task that is affected by hippocampal but not by mPFC lesions (Porter *et al.*, 2000). RE/RH inactivation significantly disrupted performance on the DNMTP task but not on the VC-DNM task. The authors concluded that "RE and RH affect measures of spatial working memory that depend on interactions of between the hippocampus and mPFC, but not measures that depend on the hippocampus alone" (Hembrook *et al.*, 2012).

Using a different set of tasks, Cassel and colleagues similarly concluded that RE/RH selectively participates in functions requiring interactions between the hippocampus and the mPFC (Loureiro *et al.*, 2012; Cassel *et al.*, 2013; Cholvin *et al.*, 2013). Specifically, lesions of RE/RH had no effect on either acquisition or short-term retention (5 days post-acquisition) of a water maze task, but disrupted long-term retention (25 days) on the task (Loureiro *et al.*, 2012). As was pointed out, recent memory (5 days) involves the hippocampus, whereas remote memory (25 days) invokes both the hippocampus and the mPFC (Clark *et al.*, 2005; Broadbent *et al.*, 2006; Teixeira *et al.*, 2006; Lopez *et al.*, 2012).

In a subsequent report, Cholvin *et al.* (2013) compared the effects of inactivation of the hippocampus, mPFC or the RE/RH on a standard water maze (WM) task and on a double-H WM task that places demands on both the hippocampus (place identification) and the mPFC (strategy-shifting) for successful completion. Only hippocampal inactivation impaired performance on the standard WM task, whereas inactivation of the hippocampus, mPFC, or the RE/RH disrupted performance, and to a similar degree, on the double-H maze task. According to the authors, the hippocampus serves a recognized role in spatial memory,

the mPFC in set shifting, and RE/RH may act "as the coordinator of this processing" (Cholvin *et al.*, 2013).

RETICULAR NUCLEUS

The RT of the thalamus forms a thin neuronal sheet, positioned at the rostral, dorsolateral, lateral, and ventrolateral margins of the thalamus. The RT is strategically "placed" between the thalamus and the cerebral hemisphere, such that all incoming and outgoing fibers of the thalamus pass through it, most of which send collaterals to a restricted part of the reticular nucleus. Reticular thalamic neurons have a relatively extensive dendritic tree extending in a disk-like fashion in the same plane as the thin sheet formed by the RT (Jones, 1985, 2007; Spreafico *et al.*, 1991; Ohara and Havton, 1996). Frequent dendrodendritic junctions (i.e., synapses and puncta) have been noted in bundles of dendrites of RT neurons, indicating a special form of interneuronal communication within the reticular nucleus (Pinault *et al.*, 1997; Liu and Jones, 1999). Reticular thalamic neurons are all GABAergic and express parvalbumin, while a subset of RT cells contains calretinin (Mitrofanis, 1992; Lizier *et al.*, 1997). The RT in rats is a relatively well-developed nucleus that provides important GABAergic control of the thalamus, where in rats, GABAergic interneurons are relatively sparse (Price, 1995). The ventral lateral geniculate nucleus and the subgeniculate nucleus (ventral to VLG) form a dorsolateral and caudal extension of the caudal reticular nucleus and may be considered the "reticular" part of the visual thalamus. These nuclei are derived from the prethalamus embryonically, and their structural and connectional characteristics are very similar to those of RT (Jones, 1985, 2007). A specific visual sector of RT, however, also exists (Coleman and Mitrofanis, 1996).

During prenatal development, a considerable number of neurons exist within the internal capsule, laterally adjacent to the reticular nucleus, forming the so-called perireticular nucleus (Mitrofanis and Guillery, 1993). These neurons have been shown to project to the (dorsal) thalamus (Mitrofanis *et al.*, 1995), but probably not to the cortex (Coleman and Mitrofanis, 1999). The perireticular neurons are thought to play a role in guiding axons during development; the function of the relatively few surviving perireticular neurons in adulthood remains to be established (Amadeo *et al.*, 1998; Coleman and Mitrofanis, 1999).

Afferent and Efferent Projections

Unlike most other thalamic nuclei, RT does not project to the cortex but sends fibers almost exclusively to the thalamus (Vaccaro and Mitrofanis, 1997). The projections from RT to thalamic nuclei are highly topographically organized. Individual thalamic nuclei receive projections from a specific subset of spatially segregated reticular neurons (e.g., Jones, 1985, 2007; Kolmac and Mitrofanis, 1997; Pinault and Deschênes, 1998a; Pinault, 2004). Based on large numbers of juxtacellularly filled reticular neurons, Pinault and Deschênes (1998a) showed that the terminal fields of these neurons in thalamic nuclei are well-focused with a patchy distribution of boutons, and that RT–thalamic projections are organized largely in parallel with thalamo-RT projections with only a slight degree of divergence. For the relationship of the ventrobasal complex with RT, this divergence appears to lead to an intrathalamic pathway which links this first-order thalamic nucleus via RT with the higher order posterior thalamic nucleus (Crabtree *et al.*, 1998).

Whereas interconnections between different thalamic nuclei via the reticular nucleus might exist, the high degree of topography between RT and individual thalamic nuclei is remarkable. The result of this strict topography is that each individual, functionally distinct thalamic nucleus is represented in a restricted "sector" of RT (Gonzalo-Ruiz *et al.*, 1995; Jones, 1985, 2007; Hayama *et al.*, 1994; Kolmac and Mitrofanis, 1997; Crabtree, 1999; Stehberg *et al.*, 2001; Kimura *et al.*, 2007b, 2012). The relationships with the midline thalamic nuclei appear to be less strictly organized (Kolmac and Mitrofanis, 1997). Whereas projections from PV of the midline thalamus to RT have not been described, PV receives input from a group of cells located ventromedially in RT (Moga *et al.*, 1995; Vertes and Hoover, 2008; Li and Kirouac, 2012). Connections between RT, RE, and the hippocampus appear to be topographically organized. As discussed, RE is a major source of input to the hippocampus, and RE and the hippocampus project to the same rostral area of RT (Cavdar *et al.*, 2008). In addition, fibers from limbic and cognitive associated structures including the mPFC, mediodorsal nucleus, and anterior thalamic nuclei also appear to converge on the rostral RT (Cornwall *et al.*, 1990; Gonzalo-Ruiz *et al.*, 1995).

The main afferents to RT originate from the thalamus and the cortex. As mentioned, thalamic inputs to RT are collaterals of the thalamocortical axons, are strictly topographically organized, and rather faithfully reciprocate RT-thalamic projections (Jones, 1985, 2007; Mitrofanis and Guillery, 1993). Likewise, corticothalamic axons send collaterals to the RT sector associated with the thalamic nucleus to which they are interconnected. In this way, RT is organized such that distinct functional and modality-specific sectors can be parsed out, and these RT sectors receive congruent cortical and thalamic glutamatergic inputs (Kharazia and Weinberg, 1994; Eaton and Salt, 1996; Crabtree, 1999; Jones, 2006). There is, however, some overlap between modality specific sectors for some RT neurons. The firing properties of these

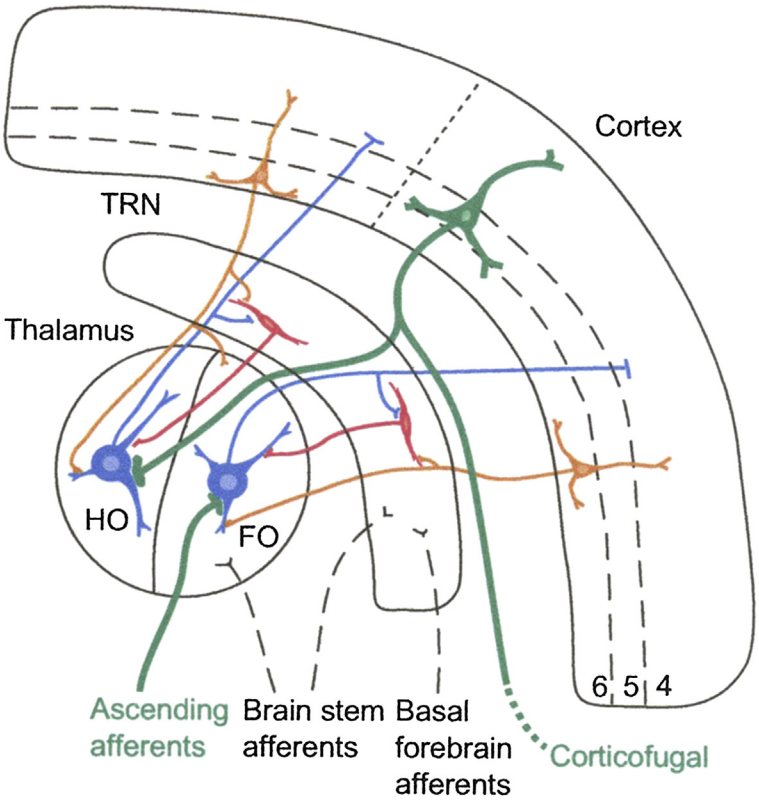

FIGURE 9 Schematic representation of the intricate relationships of the reticular nucleus (RT) of thalamus with the (dorsal) thalamus and specific layers of the cerebral cortex. The reticular nucleus (RT) (or TRN) receives collaterals from thalamocortical fibers originating in virtually all nuclei of the thalamus, while most of the corticothalamic fibers likewise issue collaterals to RT. However, as such collaterals are common for the corticothalamic fibers originating in layer 6, the "modulatory" corticothalamic projections, collaterals are absent from corticothalamic fibers arising from more superficial layers. This is correlated with a distinction in first-order and higher order thalamic nuclei and their cortical associations. So-called first-order (FO) thalamic nuclei receive their main "driving" afferents from ascending specific afferents, such as somatosensory or visual modalities, while so-called higher order (HO) thalamic nuclei receive their main driving afferents from layer 5 of the cerebral cortex. Thalamic afferents originating from layer 5 of the cortex and primary ascending fibers are morphologically very comparable, terminating as RL-type boutons, and thought to be drivers of the various thalamic nuclei (Sherman and Guillery, 2001). However, neither descending layer 5 axons nor ascending sensory afferents issue collaterals to the reticular thalamic nucleus. Apart from the dorsal thalamic and deep cerebral cortical layers, the reticular thalamic nucleus is targeted by several brainstem and basal forebrain inputs. *From Guillery, R.W., Feig, S.L., & Lozsadi, D.A. (1998). Paying attention to the thalamic reticular nucleus.* Trends in Neuroscience *21, 28–32.*

RT cells illustrate this crossmodal input, responding to sensory stimuli across two or more sensory modalities (Crabtree and Isaac, 2002; Yu *et al.*, 2011). Additionally, a recent study by Kimura and colleagues (Kimura *et al.*, 2007b) found a restricted population of RT neurons located in the auditory sector send projections to somatosensory thalamic nuclei including the ventral posterior and posterior nuclei, further establishing crossmodal connections.

The terminal fields of both cortical and thalamic afferents mostly form narrow disk-like patterns that are oriented perpendicular to the parent axons and conform to the shape and orientation of the dendrites of reticular neurons (Mitrofanis and Guillery, 1993). However, even though the topography of projections between the cortex and RT as well as between the thalamus and RT show such a strict point-to-point relationship, it is unclear how precise these relationships are at the microcircuit level (Pinault and Deschênes, 1998a; Guillery *et al.*, 1998; Sherman and Guillery, 2001, 2006). Thus, it is uncertain, for example, whether point-to-point relationships are present such that strict reciprocal relationships exist between individual thalamic and reticular neurons, whether cortical afferents project to reticular neurons that precisely target the same thalamic neurons as these corticothalamic fibers, or whether "adjacent" neurons in the thalamus are innervated by the reticular neurons. The actual organization of specific cortical–reticular–thalamic microcircuits may even differ across thalamic nuclei which may tip the balance between a precise inhibitory feedback, an inhibitory feed forward, or different forms of lateral inhibition in thalamic nuclei (Pinault and Deschênes, 1998b; Sherman and Guillery, 2001).

As discussed by Sherman and Guillery (2001), an important aspect of the innervation of RT may be that modulatory, but not driving, inputs mainly constitute thalamic or cortical projections to RT. For cortical inputs this would mean that corticothalamic fibers from layer 6, which terminate as type I fibers in the thalamus would send collaterals to RT, whereas corticothalamic fibers from layer 5, which are mainly corticofugal fibers descending to the brainstem or spinal cord would not project to RT (Fig. 9) (Deschênes *et al.*, 1994; Bourassa *et al.*, 1995). Likewise, ascending driving afferents, for example, those of the somatosensory system, would not collateralize to RT. Whether this distinction between type I and type II afferents in relation to the reticular nucleus can be regarded as a general rule remains to be established.

Afferents to RT also arise from the basal forebrain and brainstem, and include monoaminergic and cholinergic input. Immunohistochemical studies have found a significant dopaminergic innervation of the ventral RT which appears to originate from the substantia nigra-pars compacta (Anaya-Martinez *et al.*, 2006; García-Cabezas *et al.*, 2009; Cebrian and Prensa, 2010). Serotonergic input to RT primarily originates from the dorsal raphe nucleus and the supralemniscal nucleus (B9), while cholinergic

fibers arise from the basal forebrain and the pedunculopontine tegmental nucleus (Woolf *et al.*, 1986; Hallanger *et al.*, 1987; Vertes *et al.*, 2010; Rodriguez *et al.*, 2011). Other afferents include the substantia nigra-pars reticulata, zona incerta, and cerebellar nuclei (Cavdar *et al.*, 2002, 2006; Gulcebi *et al.*, 2012).

Functional Aspects

The prevailing interpretation of the functional role of RT is that it serves attentional mechanisms, as originally proposed in Crick's (1984) "searchlight hypothesis" (Guillery *et al.*, 1998; McAlonan and Brown, 2002). The above-described highly topographical arrangement of afferents and efferents to different sectors of RT suggests a specific functional role for RT for each thalamic nucleus. Lesions of RT produce impairments in attentional and priming functions but not sensorimotor deficits (Weese *et al.*, 1999). Additionally, increases in c-fos activity were detected in visual sectors of RT when rats attended to visual stimuli, but not in other sectors despite the presence of both visual and tactile stimuli (McAlonan *et al.*, 2000; Montero, 2000; Petrof and Brown, 2010). The RT importantly regulates the firing of thalamocortical projection neurons and, in this way, may influence the selection of the information that is transferred from the thalamus to the cortex.

The reticular nucleus also plays an important role as a pacemaker during synchronized firing of thalamocortical cells. Two different firing patterns exist in the thalamocortical system; that is, a "tonic" and a "burst mode" (Jahnsen and Llinás, 1984; McCormick and Fraser, 1990). The tonic mode is associated with vigilance and behavioral states. In the tonic mode of thalamocortical activity, information from ascending sensory pathways is transferred linearly through the thalamus to the cortex. Burst firing occurs during sleep, as well as during epileptic seizures (Fuentealba and Steriade, 2005). In the bursting mode, relay of information to the cortex is either prevented or nonlinearly transmitted. Thus, in the latter case, thalamocortical neurons may still respond during burst firing but the message is not relayed to the cortex in the same form as during tonic firing (Guido *et al.*, 1995; Guillery *et al.*, 1998). During burst firing, however, there is a higher signal-to-noise ratio, possibly providing a mechanism for the selection of specific, novel information to reach the cortex (Guido and Weynand, 1995; Guillery *et al.*, 1998).

The precise physiological mechanisms by which the RT exerts its gating role remain to be established. There might be a prominent contribution of descending corticothalamic fibers, at least for the visual system (Montero, 2000), that may bias the network to attending to a specific stimulus (Hartings *et al.*, 2000). Numerically, cortical inputs to RT dominate other inputs (Liu and Jones, 1999; Golshani *et al.*, 2001). Subcortical afferents, originating from the brainstem RF, the basal forebrain, or the thalamus also exert their influence on particular sectors of RT, although apparently less focused (Kolmac and Mitrofanis, 2001). Notwithstanding the specificity of connections and functions of RT, the nucleus might also act as a unit and generate general synchronized thalamocortical activity, in this way "closing" the thalamocortical gate as during sleep. In cats, sleep spindles, which occur during slow wave sleep, are generated and dependent on the bursting activity triggered by the RT (Paré *et al.*, 1987; Steriade *et al.*, 1987; Contreras *et al.*, 1996). The mechanisms by which the activity of RT neurons are synchronously entrained is presently unknown, but electrical synapses are thought to play a crucial role (Landisman *et al.*, 2002; Pinault, 2004; Fuentealba and Steriade, 2005; Nagaeva and Akhmadeev, 2006; Ferrarelli and Tononi, 2011).

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