Do the Anterior and Lateral Thalamic Nuclei Make Distinct Contributions to Spatial Representation and Memory?

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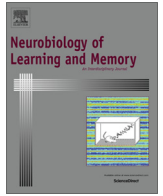
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Invited Review

Do the anterior and lateral thalamic nuclei make distinct contributions to spatial representation and memory?

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ABSTRACT

The anterior and lateral thalamus has long been considered to play an important role in spatial and mnemonic cognitive functions; however, it remains unclear whether each region makes a unique contribution to spatial information processing. We begin by reviewing evidence from anatomical studies and electrophysiological recordings which suggest that at least one of the functions of the anterior thalamus is to guide spatial orientation in relation to a global or distal spatial framework, while the lateral thalamus serves to guide behavior in relation to a local or proximal framework. We conclude by reviewing experimental work using targeted manipulations (lesion or neuronal silencing) of thalamic nuclei during spatial behavior and single-unit recordings from neuronal representations of space. Our summary of this literature suggests that although the evidence strongly supports a working model of spatial information processing involving the anterior thalamus, research regarding the role of the lateral thalamus is limited and requires further attention. We therefore identify a number of major gaps in this research and suggest avenues of future study that could potentially solidify our understanding of the relative roles of anterior and lateral thalamic regions in spatial representation and memory.

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1. Introduction

The thalamus has traditionally been described as a "relay" or "gateway" for highly processed sensory-motor information that is conveyed, in a feed-forward manner, to wide regions of the neocortex. The "limbic" or "association" region of the thalamus, however, has stepped into the spotlight as an area of interest in cognitive functions beyond a mere role in relaying sensory-motor information to cortical domains (Aggleton et al., 2010; Mizumori, Puryear, Gill, & Guazzelli, 2005; Roth et al., 2016; Sherman, 2016; Taube, 2007). The relationship between the limbic-association thalamus and cognitive functions is derived, in large part, from its topographical and reciprocal relationship with retrosplenial and parahippocampal limbic cortices, and parietal and frontal association cortices (summarized in Fig. 1). This anatomical linkage, along with behavioral assessments in subjects with damage to thalamic nuclei, supports the conclusion that this region occupies a key node in an extended hippocampal-limbic processing network involved in mnemonic functions.

Here, we summarize the evidence for a specific involvement of the limbic-association thalamus in spatial processing, which includes the use of a diverse set of stimulus sources and frames of reference to get from one place to another. For instance, it is well known that animals can learn to approach environmental locations using the fixed relationship between distal background cues and the goal location, or by simply learning to approach proximal stimuli directly associated with the spatial target, in a stimulus-response manner (O'Keefe & Nadel, 1978). Animals can also navigate independently of landmarks through a process of path integration, which involves tracking one's self-movement cues, such as optic flow, vestibular cues, proprioceptive cues, or efferent copies of movement commands, into a continuously updated representation of direction and distance in relation to a stable external reference point (McNaughton, Battaglia, Jensen, Moser, & Moser, 2006; Taube, 2007).

In the present review, we focus our attention on two key regions of the limbic-association thalamus, the anterior and lateral subregions, and summarize evidence suggesting that while the anterior thalamus is involved in establishing an organism's spatial orientation in relation to a global spatial framework based on background or distally located environmental landmarks and self-movement path integration mechanisms (e.g., vestibular, motor, proprioceptive), the lateral thalamic nuclei serve to establish and maintain spatial orientation and behavior in relation to visual and somatosensory cues that are proximally located to, or directly

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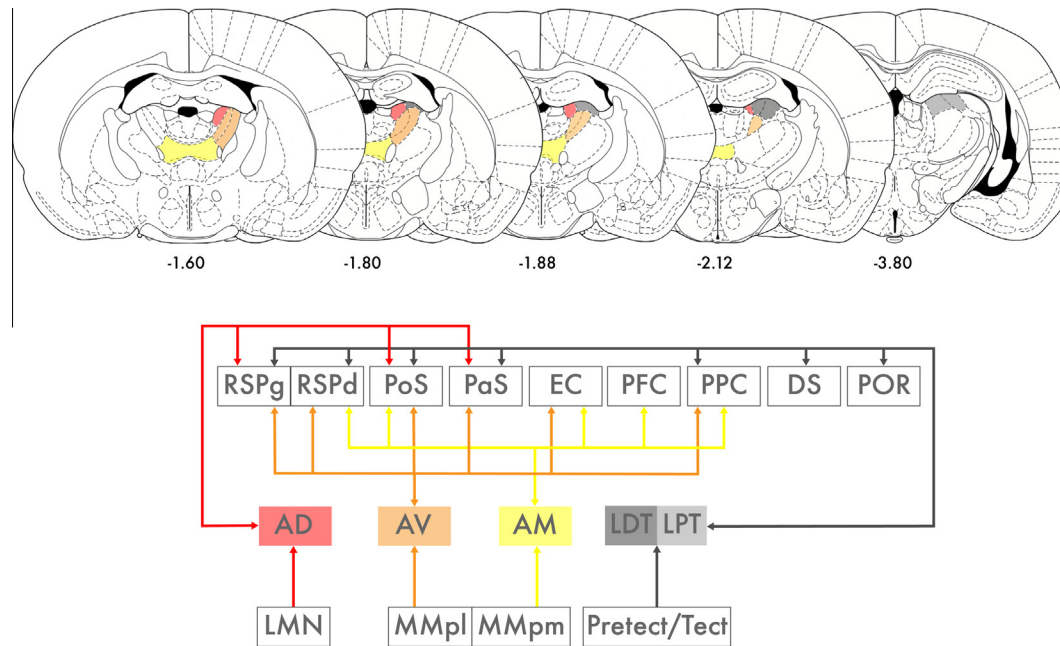E-mail address: bnjclark@unm.edu (B.J. Clark).

Fig. 1. *Top*, Panels from Paxinos and Watson (2009) showing the anterior-posterior extent of the anterior and lateral thalamus. Each color designates a specific subnucleus: anterodorsal (red), anteroventral (orange), anteromedial (yellow), laterodorsal (dark gray), and lateroposterior (light gray). Numbers below each panel indicate the anterior-posterior position of that section relative to bregma (in mm). *Bottom*, circuit diagram showing the primary subcortical-cortical connections of each nucleus. AD, anterodorsal thalamus; AV, anteroventral thalamus; AM, anteromedial thalamus; LDT, laterodorsal thalamus; LPT, lateroposterior thalamus RSPg, retrosplenial cortex-granular; RSPd, retrosplenial cortex-dysgranular; PoS, postsubiculum; PaS, parasubiculum; EC, entorhinal cortex, PFC, prefrontal cortex; POR, postrhinal cortex; PPC, posterior parietal cortex; DS, dorsal striatum. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

mark, a spatial target. Thus, it is hypothesized that anterior and lateral thalamic zones can be distinguished by the sensory information processed by each region, and the distal vs. proximal spatial frame of reference used in getting from one place to another. We first compare the subcortical-cortical connectivity of the anterior and lateral thalamus, and then discuss the experimental work supporting this working model. We also describe work that has used targeted manipulations of the thalamus, and conclude that, although the evidence from these studies strongly supports the linkage between the anterior thalamus and spatial processing, the lateral thalamus has not received similar attention. Thus, a secondary aim of this review is to identify the major gaps and unanswered questions in this body of research, which we hope will stimulate renewed interest and future research aimed at filling this void.

2. Anatomy and electrophysiology of the anterior-lateral thalamus

2.1. Subregions & connectivity

The anterior and lateral thalamus encompass a large territory of dorsal thalamic nuclei that can be subdivided, based on cytoarchitectural differences (Paxinos & Watson, 2009), into 5 subregions regions (Fig. 1, top), including three anterior subnuclei (anterodorsal, anteroventral, anteromedial) and two lateral subnuclei (laterodorsal and lateroposterior). Neuroanatomical studies have suggested that subcortical inputs to the thalamus differentiate anterior and lateral subregions (for review see Mizumori et al., 2005 and Jankowski et al., 2013; Fig. 1, bottom). Specifically, the anterior thalamus receives the bulk of its subcortical input from two distinct mammillary nuclei, with the anterodorsal thalamic nuclei receiving distinct projections from the lateral mammillary nuclei, whereas the anteromedial and anteroventral nuclei receive inputs from subzones of the medial mammillary nuclei

(pars medialis and pars lateralis, respectively). The lateral thalami receive inputs from tectal-pretectal pathways, such as the superior colliculus, lateral geniculate nucleus, reticular thalamus, and direct retinal inputs (Morin & Studholme, 2014; Thompson & Robertson, 1987). The superior colliculus rests within secondary visual pathways often associated with the production of movements that orient, or reflexively attend, a subject toward visual targets (Grieve, Acuna, & Cudiero, 2000; Milnar & Goodale, 1984; Reep & Corwin, 2009), but these pathways have also been linked to a high degree of multi-modal processing, especially from somatosensory cues, which in rodents stem from the vibrissae (Bezdudnaya & Keller, 2008; Cooper, Miya, & Mizumori, 1998; Robertson, Kaitz, & Robards, 1980; Weldon & Best, 1992; Wilber et al., 2015).

The anterior and lateral thalamus form largely overlapping thalamic-cortical loops with para- and postsubiculum, retrosplenial, and entorhinal cortex (Jankowski et al., 2013; Mizumori et al., 2005; Shires et al., 2013; Fig. 1, bottom). Nevertheless, one important distinction between the anterior and lateral thalamus is the large reciprocal projections between the anteromedial thalamus and prefrontal cortex, and between the lateral thalamus and dorsal striatum (Fig. 1, bottom). Lateral thalamo-striatal projections stem from both laterodorsal and lateroposterior regions, but the greatest density of projections have been observed in the lateroposterior thalamus (Cheatwood, Reep, & Corwin, 2003; Reep & Corwin, 2009). The lateroposterior thalamus, which is often characterized as a rodent homologue to the mammalian pulvinar, generally has a stronger reciprocal relationship with primary and secondary visual cortical regions (Nakamura et al., 2015; Roth et al., 2016). For instance, some recent work has indicated that the lateroposterior thalamus constitutes the strongest thalamic output to postrhinal and posterior parietal regions (Agster, Pereira, Saddoris, & Burwell, in press; Nakamura, Hioki, Furuta, & Kaneko, 2015; Olsen & Witter, in press; Pereira, Agster, & Burwell, in press), perhaps suggesting that this region has a greater role in guiding orientation in relation to visual-spatial targets.

2.2. Anterior-lateral thalamus and electrophysiology in behaving rodents

Several studies have investigated the characteristics of neural firing in the anterior and lateral thalamus, but the anterodorsal region has arguably received the most attention with respect to its role in spatial processing. This is due, in large part, to the discovery of neurons in this region that fire when an animal points its head in specific directions, called head directions cells (reviewed in Taube, 2007). Different head direction cells fire in different directions suggesting that this region tracks the moment-to-moment changes in an animal's heading and often draws comparisons to a neuron-like compass. An important feature of anterodorsal thalamic head direction cells is the fact that the direction in which they fire maximally can be controlled by environmental cues such that rotation of a salient room landmark can induce a corresponding shift in the preferred orientation of the cell (Yoder, Clark, & Taube, 2011). Control by landmarks appears to be predominantly guided by cues located in the distal background of the environment (Yoganarasimha, Yu, & Knierim, 2006; Zugaro, Berthoz, & Wiener, 2001). Further, the preferred direction of anterodorsal thalamic cells can be maintained in the absence of visual information and when entering novel environments, suggesting that self-movement cues (e.g., vestibular, motor, and proprioceptive stimuli) contribute to the stability of directional tuning (Goodridge, Dudchenko, Worboys, Golob, & Taube, 1998; Yoder et al., 2011). Thus, the anterodorsal thalamus has a pivotal position between self-motion and visual systems to provide a coherent percept of spatial orientation in an environment in relation to distal landmarks.

Head direction cells are not unique to the anterodorsal thalamus, and have also been reported in the anteroventral nuclei (Tsanov et al., 2011), anteromedial nuclei (Jankowski et al., 2015), and the laterodorsal thalamus (Mizumori and Williams, 1993). It is important to consider three differences in the neural activity between these regions. First, populations of head direction cells in the anteroventral thalamus are strongly modulated by theta activity (Tsanov et al., 2011), which express the same temporal resolution and frequency (7–10 Hz) as hippocampal theta. This oscillatory activity is possibly a consequence of its inputs from neurons in the medial mammillary nuclei, which have also been reported to oscillate at a similar theta frequency (Sharp & Turner-Williams, 2005). Secondly, the anteromedial thalamus contains neurons that have directional firing characteristics, but also contain subpopulations of neurons modulated by spatial location (Jankowski et al., 2015). These spatial cells have comparable location-specific firing characteristics as hippocampal place cells (Moser, Kropff, & Moser, 2008).

A final difference between subregions comes from the report by Mizumori and Williams (1993) indicating that neurons in the laterodorsal thalamus are unique in that they possibly display a greater dependency on visual stimuli and mnemonic processing. For instance, Mizumori and colleagues reported that laterodorsal thalamic neurons increase their directional firing across training trials, but only when training is conducted in a well-lit room. When testing was conducted in darkness (i.e., the room lights were turned off), directional modulation was maintained only for a short period of time suggesting that the orientation of these signals was dependent on visual cues. These observations are in contrast to anterior thalamic head direction cells, which typically form highly directional firing characteristics upon first exposure to an environment (Jankowski et al., 2015), and can be maintained for long distances in the absence of visual cues (Goodridge et al., 1998). In addition, anterodorsal thalamic head direction cells do not alter their firing rates or directional specificity with spatial learning (Dudchenko & Taube, 1997).

Although changes in directional tuning by laterodorsal cells during acquisition may reflect visual-mnemonic processing, it is important to note that non-visual cues can also play a role in processing lateral thalamus neural activity. As noted above, in tests conducted in pure darkness, laterodorsal cells typically lost their direction-specificity, but this occurred after a few minutes of testing. Additional control tests in darkness showed that if animals were restricted to a single maze arm, the directional preference could be maintained for longer periods of time compared to when the animal was restrained to the round central platform (Mizumori et al., 2005). These observations suggest that laterodorsal thalami are additionally influenced by non-visual, local maze cues, which is consistent with the observation that laterodorsal thalamic neurons fire in relation to somatosensory cues such as vibrissae stimulation (Bezdudnaya & Keller, 2008). In addition, a recent report indicated that subpopulations of directional cells in the laterodorsal thalamus fire along specific environmental routes and in specific forward or backward movement directions (Enkhjargal et al., 2014), and experiments using axonal calcium imaging indicate that the lateroposterior thalamus conveys movement related information to cortical regions, including locomotion speed, saccadic-related movements, and optic flow (Roth et al., 2016). Collectively, these observations parallel the diversity of neural firing in the primary input region of the lateral thalamus, the superior colliculus, which reportedly contains neurons that discharge in relation to a number of somatosensory-motor events, including egocentric body turns (e.g., turn left or turn right), and the direction of movement, e.g., toward the center of the maze vs. away from the center (Cooper et al., 1998). Interestingly, directionally modulated neurons have also been identified in the superior colliculus that appear to persist in the absence of distal landmarks (Cooper et al., 1998).

2.3. Summary, conclusions, and unanswered questions

The results described above suggest that the anterior and lateral thalamic nuclei can be distinguished on the basis of subcortical connectivity (Fig. 1, bottom), and electrophysiological firing characteristics. The anterior thalamus receives projections from the mammillary nuclei, which process visual-spatial and self-movement information (Taube, 2007; Yoder et al., 2011). The lateral thalamic nuclei in contrast receive inputs largely from pretectal-tectal pathways, in particular the superior colliculus, which contains neurons modulated by visual and somatosensory stimuli, independent of distal background cues (Cooper et al., 1998). Each anterior and lateral thalamic subregion contains directionally modulated neural populations that can be further discriminated on the basis of their firing characteristics—neurons in the lateral region fire in response to visual stimuli and proximal non-visual cues (possibly tactile cues), and cells in the anterior thalamus fire in relation to distal landmarks and self-movement cues.

A major step forward in further understanding the possible functional distinctions between thalamic nuclei will be to conduct experiments using high density recordings during precise behavioral and sensory manipulations. For example, further study is needed to understand the degree to which directional cells in the laterodorsal thalamus are controlled by visual cues vs. proximal maze-related or tactile cues. A question of additional importance is whether distal landmarks and self-movement cues preferentially control directional modulation in the anteroventral and anteromedial thalami as in the anterodorsal thalamus. The anatomical data suggest this that this might be the case as both anteroventral and anteromedial nuclei receive inputs from the medial mammillary regions, which reportedly contain cell populations that fire in response to the speed of linear and angular head movements (Sharp & Turner-Williams, 2005). However, the finding of theta modulation in both subregions and the fact that the anteromedial

zone has strong reciprocal connections with the prefrontal cortex (Fig. 1), suggests some specialization of functional roles in spatial learning (see Aggleton et al., 2010 for discussion).

In the sections below, we consider additional evidence for a functional dissociation between anterior and lateral thalamic regions from work using targeted manipulations (lesions or temporary neural inactivation). However, given the summary thus far we can establish some preliminary hypotheses regarding the role of each thalamic region in spatial memory and how disruption of these regions might impact resultant behavior. First, in agreement with previous assessments (Clark & Taube, 2012; Taube, 2007; Yoder, Clark, & Taube, 2011; Yoganarasimha et al., 2006), the anterior nuclei establish spatial orientation and directional trajectories in relation to a distal or global frame of reference, guided by self-movement cues and distal landmarks. In contrast, and drawing upon previous work on the function of secondary visual and tectal pathways, investigators have pointed to the possibility that the lateral thalamus has a role in directing attention toward visual-spatial targets (Grieve et al., 2000; Mlinar & Goodale, 1984; Mizumori et al., 2005; Reep & Corwin, 2009). The anatomical and electrophysiological work summarized above additionally points to a role for the lateral thalamus in processing local tactile or somatosensory information. We therefore suggest that one of the roles of the lateral thalamus serves to guide spatial orientation and attention in relation to a proximal frame of reference, which would involve the ability to self-localize and establish trajectories on the basis of local visual-tactile cues or to learn to approach cues directly associated, or closely associated, with spatial goals. Information regarding directional trajectories based on distal and proximal frames of reference may be integrated, and compared, with a common spatial framework within largely overlapping limbic-cortical output regions. Such an integration would allow mismatches between intended and actual trajectories to be detected and corrected during spatial behavior. The hypotheses above would therefore suggest distinct behavioral outcomes following discrete disruption of anterior and lateral thalamic function. Specifically, because the lateral thalamus has a pivotal position between secondary visual pathways, visual-cortical (postrhinal and parietal), and striatal targets (Cheatwood et al., 2003; Pereira et al., in press; Wilber et al., 2015; Fig. 1, bottom), this region may serve to form stimulus-response associations, or egocentric relationships (i.e., the goal is to the left or right of the stimulus) with proximal visual-tactile cues (Mitchell & Dalrymple-Alford, 2006; Mizumori et al., 2005). Impairments in stimulus-response learning and the use of proximal cues for orientation have been observed after lesions of the dorsal striatum (Kosaki, Poulter, Austen, & McGregor, 2015; Rice, Wallace, & Hamilton, 2015) and the parietal cortex (Save & Poucet, 2000), suggesting that damage to the lateral thalamus might produce similar impairments.

3. The role of anterior and lateral thalamic nuclei in spatial behavior

Studies investigating the role of anterior and lateral thalamic nuclei in spatial behavior can be organized into three general categories based on the type of spatial processing evaluated: allocentric navigation, egocentric-response navigation, and path integration. Briefly, allocentric navigation refers to the capacity to navigate on the basis of distinct environmental landmarks, which can include the spatial relationships between both proximal objects and distal landmarks that make up the space (O'Keefe & Nadel, 1978). Egocentric-response based navigation requires that animals navigate from one place to another using simple stimulus response associations either by learning a series of egocentric or self-referenced movements (e.g., turn right → goal), or learning to approach stimuli directly associated with a goal location in a simple stimulus-response manner. Fig. 2 provides a summary of the various studies investigating the impact of lesions or temporary inactivation of anterior and lateral thalamic nuclei with respect to these behavioral domains. We note that the research described in the sections below are restricted to studies that have utilized selective, fiber-sparing, lesions or temporary inactivation of thalamic nuclei, but we make note of some supporting studies in which non-fiber-sparing methods (electrolytic or ablation) were used.

3.1. Allocentric navigation

The prominent cortical-limbic connectivity of the anterior and lateral thalamic nuclei supports the hypothesis that lesions to any one of the subregions should produce spatial impairment. However, consistent deficits in allocentric navigation have only been observed when lesions include the anterodorsal thalamus. For instance, lesions restricted to the anteromedial thalamic nuclei appear to produce, at most, transient or temporary spatial deficits. Beracochea, Jaffard, Jarrard (1989) produced some of the first experimental evidence for this conclusion using the selective neurotoxic lesion approach and determined that large lesions of the anterior thalamus, which spared the anterodorsal thalamic nucleus, but failed to produce impairments in a spatial reference memory variant of the radial arm maze. Aggleton, Hunt, Nagle, and Neave (1996) also provided supporting evidence when testing anteromedial lesioned rats in a radial arm maze, but also demonstrated that anteromedial lesions can produce temporary deficits (in the initial test trials) during training in a spatial alternation task. It is important to note that Aggleton et al. (1996) have observed that large lesions, which include all three anterior thalamic nuclei, tend to produce greater impairments than smaller lesions confined to just the anterodorsal and anteroventral nuclei (see also Van Groen, Kadish, & Wyss, 2002b and Warburton, Baird, & Aggleton, 1997).

An important consideration is how anterior thalamic lesions might produce deficits in allocentric navigation. Consistent with observations that the orientation of anterodorsal thalamic head direction cells are preferentially controlled by distal background landmarks (Yoder, Clark, & Taube, 2011; Yoganarasimha et al., 2006; Zugaro et al., 2001), Dumont, Amin, and Aggleton (2014) recently reported that lesions of the anterior thalamus impair object-place paired associate acquisition, but only when animals were required to discriminate between identical object pairs on the basis of distal cues, rather than on the basis of the local proximal frame of reference, which included local odors and tactile cues. It is now known that animals can use distal cues to either navigate in the direction of reinforcement or to particular absolute places in the environment (Hamilton, Akers, Weisend, & Sutherland, 2007; Skinner et al., 2003). Stackman, Lora, and Williams (2012) evaluated the distinction between place vs. direction learning with respect to anterior thalamic function by training mice in a hidden platform procedure in the Morris water maze, and subsequently testing the animals in a probe test in which the pool had been linearly translated and leaving the platform in a position defined by its fixed relationship with the distal cues, which now was the opposite quadrant or absolute location. Navigation to the absolute location would indicate that rats used the distal cues to define a place in an environment, whereas navigation toward the relative platform location would suggest the use of distal cues to navigate in the direction of reinforcement. While control animals typically swam toward the relative location within the pool, animals with an inactivated anterodorsal thalamus showed an overwhelming preference for the absolute location. In a complementary study using a water T-maze, Peckford et al. (2014) confirmed that directional navigation was impaired after

TYPE	REFERENCE	MANIPULATION	AD	AV	AM	LDT	LPT	TASK	IMPAIRED
ALLOCENTRIC	Alcaraz et al. 2016	Lesion	●	●	●			T-Maze	Y
	Dumont et al. 2014a	Lesion	●	●	●			Item-Place (Distal)	Y
			●	●	●			Item-Place (Proximal)	N
	Dumont et al. 2014b	Lesion	●	●	●			MWM	Y
	Peckford et al. 2014	Lesion	●					Water T Maze	Y
	Ulrich et al. 2014	Lesion	●	●	●			T-Maze	Y
	Moreau et al. 2013	Lesion	●	●	●			MWM	Y
							●*		N
	Stackman et al. 2012	Inactivation	●					MWM	Y
	Aggleton et al. 2009	Lesion	●	●	●			SD	N
			●	●	●			MWM	Y
	Lopez et al. 2009	Lesion	●	●	●			MWM	Y
							●*		N
	Wolff et al. 2008	Lesion					●*	MWM (SRM)	N
			●	●	●			MWM (SRM)	Y
							●*	MWM (reversal)	N
			●	●	●			MWM (reversal)	Y
	Gibb et al. 2006	Lesion	●	●	●		●*	Odor-Place	Y
	Mitchell & Dalrymple-Alford 2006	Lesion	●	●	●		●*	RAM	N
								RAM	Y
	Mitchell & Dalrymple-Alford 2005	Lesion					●*	RAM	Y
			●	●	●			RAM	Y
	Mair et al. 2003	Lesion	●	●	●	●		RAM	Y
	Van Groen et al. 2002a	Lesion				●		MWM	Y
	Van Groen et al. 2002b	Lesion	●	●	●			MWM	Y
			●	●				MWM	Y
	Alexinsky, 2001	Lesion	●	●	●			RAM	Y
	Wilton et al. 2001	Lesion	●			●		MWM; Object-Place	Y
	Celerier et al. 2000	Lesion	●	●	●			SA	Y
	Warburton & Aggleton 1999a	Lesion	●	●	●			MWM-PST	Y
	Warburton et al. 1999b	Lesion	●	●	●			MWM; SA	Y
	Warburton et al. 1997	Lesion	●	●	●	●		SA	Y
			●	●	●			SA	Y
	Aggleton et al. 1996	Lesion	●	●	●			RAM	Y
			●	●				RAM	Y
					●			RAM	N
			●	●	●			SA	Y
			●	●				SA	Y
					●			SA	Y
	Aggleton et al. 1995	Lesion	●	●	●			SA	Y
	Mizumori et al. 1994	Inactivation				●		RAM	Y
	Berocohea et al. 1989	Lesion		●	●			RAM; SSDR	N
EGOCENTRIC	Moreau et al. 2013	Lesion	●	●	●		●*	MWM-Cued	N
	Wolff et al. 2008	Lesion	●	●	●		●*	MWM-RAM Hybrid	N
	Mitchell & Dalrymple-Alford 2006	Lesion					●*	Plus Maze	Y
			●	●	●			RAM	N
	Warburton et al. 1997	Lesion	●	●	●	●		EA	N
			●	●	●			EA	N
	Aggleton et al. 1996	Lesion	●	●	●			EA	N
			●	●				EA	N
					●			EA	N
PATH INTEGRATION	Peckford et al. 2014	Lesion	●					Food Carrying	Y
	Frohardt et al. 2006	Lesion	●					Food Carrying	Y

Fig. 2. Filled circles denote a manipulation of a particular subregion and lines that connect individual circles indicate a lesion or inactivation manipulation including all subregions connected by the line. (*) Denotes studies where lesions of the lateral thalamus only included the medial region and included additional damage to midline thalamic nuclei. AD, anterodorsal thalamus; AM, anteromedial thalamus; AV, anteroventral thalamus; EA, egocentric alternation; LDT, laterodorsal thalamus; LPT, lateroposterior thalamus; MWM, Morris water maze; MWM-Cued, cued variant of the Morris water maze; MWM-PST, pre-surgical training in the Morris water maze; N, no; RAM, radial-arm maze; Reversal, procedure in which the platform is moved to a new location in the Morris water maze; SD, structural discrimination; SA, spatial alternation; SRM, spatial reference memory; SSDR, serial spatial discrimination reversal task; Y, yes. (See above-mentioned references for further information.)

anterodorsal thalamic lesions. These findings collectively suggest that the anterodorsal thalamus is involved in processing information regarding the direction of movements, but the retrieval of the absolute location of the platform in relation to the distal cues was seemingly maintained after inactivation. It could therefore be argued that the anterodorsal thalamus might not be essential for the use of distal cues in navigation. Indeed, some studies have suggested that self-movement vestibular cues also contribute to directional navigation in the Morris water maze (Clark et al., 2015; Stackman et al., 2012), and the allocentric deficits described above therefore may reflect a general deficit in vestibular and self-movement cue processing. This general view can also be conceptualized in terms of predictive coding mechanisms (Roth et al., 2016; Sherman, 2016) such that the anterior thalamus may establish an expectation, or prediction, of the direction of reinforcement as well as the stable distal landmarks associated with the spatial trajectory. This expectation, based on a path integration based framework, may be compared with the distal landmarks that are associated and learned in relation to the goal direction, and the mismatch between the two stimulus sources may serve to correct errors in movements towards spatial targets. The notion that landmarks are processed and learned in relation to a stable spatial framework based on path integration (McNaughton et al., 2006) is supported by the observation that lesions of the vestibular system disrupts anterior thalamic head direction cell activity, despite repeated experience with familiar visual landmarks (Stackman & Taube, 1997).

With respect to the lateral thalamus, the evidence for a role in allocentric navigation has been limited to only a handful of studies, and for more than half of these, damage to the lateral thalamus largely encompassed only the rostral or medial regions of the lateroposterior thalamus, and also included extensive damage to other midline or anterior thalamic nuclei (see Fig. 2). Thus, the degree of overlap with other nuclei, and the limited lesion volume to the lateral thalamus, presents difficulties in drawing firm conclusions regarding the relationship with allocentric navigation. Regardless, two studies provide some clues. First, the earliest demonstration of lateral thalamic disruption comes from a study by Mizumori, Miya, and Ward (1994) in which rats were tested in a spatial reference memory variant of the radial arm maze before and after inactivation of the laterodorsal thalamus using tetracaine—a chemical that temporarily disables neurons from producing neural activity. As a consequence of inactivation, a significant increase in the number of errors were made by rats, and the errors returned to baseline levels in subsequent tests at a time point corresponding to the diffusion of the injected chemical. The observations made by Mizumori's work was later supported by Van Groen, Kadish, and Wyss (2002a) in which the authors tested animals with neurotoxic lesions of the laterodorsal thalamus in a standard hidden platform procedure in the Morris water task. In short, Van Groen reported that lesions produced acquisition and retention deficits (platform removal probe), but these deficits appeared to be mild in comparison to laterodorsal damage that also included the anterior thalamus (anterodorsal and anteroventral subregions). Collectively, the overall findings from lesion studies is that consistent allocentric spatial deficits are observed when damage at least includes the anterodorsal thalamus, but relatively milder impairments are observed after lesions of the anteromedial or laterodorsal thalamus.

3.2. Egocentric-response navigation

In contrast to the well-documented deficits in allocentric navigation after anterior-lateral thalamic lesions, there is presently no consistent evidence of comparable deficits in the expression of egocentric or a cued response-based memory (Fig. 2). It is important to make note of one study that reported that egocentric task acquisition was severely impaired after damage to the medial portions of the lateral thalamus (Mitchell & Dalrymple-Alford, 2006), which were largely concentrated in the lateroposterior thalamus, but did not produce damage to the laterodorsal thalamus. Although the medial portions of the lateroposterior thalamus have large connections with the dorsal striatum (Cheatwood et al., 2003), follow-up studies using similar medial lesions of the lateral thalamus, failed to observe impairments in an egocentric spatial memory task (Wolff, Gibb, Cassel, & Dalrymple-Alford, 2008), and failed to observe impairments in a cued-response task in which rats were required to learn to navigate toward a cued goal location (Moreau et al., 2013). This latter observation is particularly surprising given that lesions of the tectum and superior colliculus produce severe impairments in gerbils trained to orient to a proximal visual stimulus (Mlinar & Goodale, 1984). As noted in Fig. 2, the lesions in these studies were far from complete in terms of the lateral thalamus, which raises the question as to whether more extensive lesions that include all regions of the lateroposterior and the laterodorsal thalamus might produce impairments in egocentric or visual response learning. Indeed, the laterodorsal and lateroposterior group have reciprocal connections with the dorsal striatum, suggesting the possibility that spared connections with one of these regions and the striatum may have supported some residual functions after damage. Nonetheless, the collective observations clearly show that the anterior thalamus does not make a significant contribution to egocentric or response based navigation, but whether a similar conclusion can be made regarding the lateral thalamus requires further investigation.

3.3. Path integration

Given the identification of head direction cells in the anterior thalamus, which are dependent on intact self-movement cues especially from the vestibular system (Clark, Brown, & Taube, 2012; Clark & Taube, 2012; Stackman & Taube, 1997), it has been hypothesized that damage to the anterior thalamus might impair an animal's capacity to accurately navigate in environments devoid of landmarks or in complete darkness (McNaughton et al., 2006; Taube, 2007). This hypothesis has been experimentally tested in a study in which selective lesions of the anterior thalamus were produced in rats, and which were subsequently tested on a task requiring navigation based on path integration (Frohardt, Bassett, & Taube, 2006; Fig. 2). Briefly, the task involved rats searching an open-field environment for small, but solid, pieces of food (so they are not inclined to eat them where they find them) and carrying the food back to a home base or covered enclosure located along the edge of the open-field. The task can be performed while the animals have access to environmental cues, but can also be performed in complete darkness, or when the animals are blindfolded, thereby preventing the use of external environmental cues and encouraging the use of path integration (Whishaw et al., 2001). Using this experimental paradigm, Frohardt et al. (2006) tested animals with specific lesions of the anterodorsal thalamic nuclei and determined that lesioned animals, when blind-folded, were impaired at accurately carrying the food back to the home base. It is important to note however that the same animals were subsequently tested without blindfolds, and continued to display impairments in the same task. Thus, the results also support the conclusion that the behavioral impairments reflect a more general deficit in navigation rather than a specific impairment in path integration. In a recent study, Peckford et al. (2014) tested animals in a similar food-carrying paradigm, but without blindfolds, and demonstrated significant impairments in animals with neurotoxic damage to the anterodorsal thalamus. However, because the animals were not blindfold in the latter study, it is unclear whether

path integration based processing was required for accurate performance in the task.

3.4. Summary, conclusions, and unanswered questions

The results above support the general conclusion that the anterior thalamus has a role in allocentric navigation and path integration, but not in egocentric or cued-response navigation. Further, deficits after anterior thalamic lesions appear to be specifically related to an inability to produce directional trajectories based on self-movement cues or distal landmarks. Although deficits are most closely associated with damage to the anterodorsal nuclei, lesions that include all three anterior nuclei seem to produce greater deficits. However, it is important to note that selective neurotoxic lesions of the anteromedial and anteroventral nuclei reportedly have less consistent outcomes for spatial learning and memory, with studies describing mild impairments or a general absence of deficits.

A second conclusion relates to the issue of the limited number of studies providing evidence linking the lateral thalamus to spatial learning and memory. For instance, selective lesions/inactivation of the laterodorsal thalamus produce impairments in allocentric-based navigation, but perhaps milder impairments in lesioned animals. Whether these deficits can be linked to distal spatial processing or the use of local tactile-visual stimuli is not entirely clear from this work. Firm conclusions regarding the role of the lateral thalamus in egocentric navigation are not possible given the insufficient amount of lesion damage to the lateral nuclei, as well as additional damage to midline thalamic nuclei, observed in previous studies. The precise relationship between the lateral thalamus and spatial behavior therefore awaits further investigation with more targeted circuit manipulations and behavioral assessment.

4. The role of anterior and lateral thalamic nuclei in spatial representation

The hippocampus and parahippocampal cortex (postsubiculum, parasubiculum, medial entorhinal) contains neurons that fire as a function of an animal's location in an environment, but differ in their firing characteristics such that parahippocampal cortical neurons (grid cells) are active in multiple spatial locations arranged in a grid-like hexagonal pattern while hippocampal place cells fire in specific locations (Moser et al., 2008; O'Keefe & Nadel, 1978). Head direction cell activity has been observed in all regions of the parahippocampal cortex including those that receive output from the anterior and lateral thalamic nuclei (Taube, 2007). An additional class of neurons that fire along environmental boundaries, called border or boundary-vector cells, have also been identified in parahippocampal regions (Boccara et al., 2010; Lever, Burton, Jeewajee, O'Keefe, & Burgess, 2009; Solstad, Boccara, Kropff, Moser, & Moser, 2008). The sections above suggest a prominent role for limbic thalamic nuclei in spatial processing; thus, motivating the question of how these regions might contribute to the generation and maintenance of hippocampal representations of spatial

memory. Studies have addressed this question by either selectively damaging or inactivating thalamic nuclei, and subsequently measuring neural activity in the hippocampus or parahippocampal cortices. We summarize this work in Fig. 3.

4.1. Anterior-lateral thalamic nuclei and place cells

Previous experimental and theoretical work has proposed that place cells utilize signals derived from head direction cells to establish and maintain place cell orientation in an environment (McNaughton, Chen, & Markus, 1991; Yoganarasimha et al., 2006). This notion was investigated early on by Mizumori et al. (1994) who monitored hippocampal place cell activity in rats navigating a radial arm maze task before and after inactivation of the laterodorsal thalamus. Mizumori and colleagues determined that inactivation of the laterodorsal thalamus impaired hippocampal pyramidal cell activity such that some hippocampal neurons fired across a broader set of maze arms. In other inactivation sessions, cells maintained their location-specific firing, but demonstrated a significant change in firing rate (increases or decreases). Disruption of place cell activity was also observed by Calton et al. (2003) who recorded hippocampal place cells, but in animals with neurotoxic lesions of the anterodorsal thalamus. The authors determined that lesions of the anterodorsal thalamus failed to disrupt the within or between recording session stability of place cell activity, but produced noisier spatial firing (i.e., place cells had higher out of field firing rates), and surprisingly, increased the directionality of place fields. One interpretation of the latter observation is that lesions decreased spatial specificity based on distal and self-movement cues such that specific local spatial views, or body-centered cues, such as the external cues associated with a specific direction of movement, dominated neural activity as an animal passed through firing fields.

4.2. Anterior-lateral thalamic nuclei and head direction cells

Degraded place cell activity following anterior-lateral thalamic damage confirmed the hypothesis that head direction cell input from anterior-lateral thalamic nuclei may provide a mechanism by which the spatial specificity of hippocampal place cells are maintained. However, subsequent evidence strongly suggested that the influence of anterior and lateral thalamic input on hippocampal neural activity might be subserved by distinct and independent mechanisms. Notably, Golob, Wolk, and Taube (1998) showed that large neurotoxic lesions of the laterodorsal thalamus failed to disrupt head direction cell activity in the parahippocampal cortex (i.e., the postsubiculum). Interestingly, lesions of the laterodorsal thalamus failed to impair the stability of head direction cell activity in relation to a prominent distal landmark located along the outer edge of the recording chamber. That is, when the landmark was rotated by 90°, head direction cells would accurately shift their orientation in relation to the cue, even in animals with damage to the laterodorsal thalamus. Several studies have shown, however, that anterodorsal thalamic lesions (Goodridge & Taube,

TYPE	REFERENCE	MANIPULATION	AD	AV	AM	LDT	TASK	IMPAIRED
SPATIAL REPRESENTATION	Winter et al. 2015	Lesion/Inactivation	●	○			PHC Grid & HD	Y
	Calton et al. 2003	Lesion	●				HPC Place Cells	Y
	Golob et al. 1998	Lesion				●	PoS HD Cells	N
	Goodridge & Taube1997	Lesion	●				PoS HD Cells	Y
	Mizumori et al. 1994	Inactivation				●	HPC Place Cells	Y

Fig. 3. Grid, grid cell; HD, head direction cell; HPC, hippocampus; LDT, laterodorsal thalamus; PHC, parahippocampal cortex.

1997), or inactivation of the anterior thalamus (Winter, Clark, & Taube, 2015) completely abolish head direction cell activity throughout the parahippocampal cortex. Thus, while lesions to either the anterior thalamus or laterodorsal thalamus degrade place cell activity, only disruption of the anterior thalamus results in the complete loss of head direction cell activity in parahippocampal cortex.

4.3. Anterior-lateral thalamic nuclei and grid cells

The findings described above suggest that spatial impairments that follow anterior thalamic damage might be related to a disruption in head direction cell activity, and possibly related to degraded place cell activity. It is important to consider however the contribution of functional loss in other spatial representations in the hippocampal formation. The recent discovery of grid cells has given rise to a large number of computational models describing how they might be generated, many of which highlight the importance of directional heading in shaping and stabilizing grid cell activity (reviewed in Giocomo and Moser, 2011). Thus, most classes of models predict that disruption to head direction cell inputs, presumably conveyed by ascending thalamo-cortical projections, would completely abolish parahippocampal grid cell activity. In an effort to address this hypothesis, Winter et al. (2015) recorded grid cell activity in rats before and after lidocaine inactivation of the anterior thalamus, and in animals with lesions of the anterior thalamus. The results of this work clearly demonstrated that lesions/inactivation produced a complete loss of grid modulation by parahippocampal cortical cells; thus, supporting the possibility that a loss in grid cell activity may contribute to allocentric navigation and path integration impairments observed after anterior thalamic lesions.

4.4. Summary, conclusions, and unanswered questions

The findings above present two contrasting observations regarding the contributions of the anterior and lateral thalamus to hippocampal-parahippocampal spatial representation. First, laterodorsal lesions or inactivation result in large changes in hippocampal firing rates and spatial specificity, but the impact on place cell firing after anterior thalamic lesions are reportedly less severe, resulting in noisier and degraded, but largely intact, place field firing. Second, while laterodorsal thalamus lesions do not disrupt head direction cell activity in the parahippocampal cortex, anterior thalamic lesions/inactivation result in a complete loss of head direction and grid cell modulation. With respect to place cell processing, one key methodological difference that could explain these differences is the fact that testing in the Mizumori study involved navigation in the radial arm maze, which may require greater reliance on directional orientation to disambiguate the different arm locations. Some recent work by Grieves, Jenkins, Harland, Wood, Dudchenko (2016) supports this view in showing that place cells tend to express similar firing fields in environments that are arranged in parallel, i.e., in the same direction, but show unique firing fields in environments that are radially arranged, i.e., have different directional orientations (see also Fuhs, Vanrhoads, Casale, McNaughton, & Touretzky, 2005; Spiers, Hayman, Jovalekic, Marozzi, & Jeffery, 2015). Whether directional inputs from the anterior thalamus influence the establishment of unique place fields in identical, radially arranged, compartments is presently unclear, but would be consistent with the loss of head direction cell activity in major hippocampal input regions (Goodridge & Taube, 1997; Winter et al., 2015), and the reported loss of directional navigation after anterior thalamus inactivation (Stackman et al., 2012).

The precise mechanisms by which the lateral thalamus influences hippocampal place representations is unknown, but we can speculate that the lateral thalamus may have a greater role in maintaining spatial-specificity and directional orientation in relation to proximal stimuli. Local landmarks such as intra-maze objects and tactile cues can have an influence on place cell firing (Burke et al., 2011; Deshmukh & Knierim, 2013), and the linkage between local cues and place cell activity is thought to include a circuit involving perirhinal, postrhinal, and parietal cortical input, the latter of which have a strong reciprocal relationship with the lateral thalamus. The possibility that the lateral thalamus might have a role in local cue processing by hippocampal place cells would also be consistent with work showing that damage to the parietal cortex, which has a major reciprocal connection with the lateral thalamus, impairs place field orientation in relation to proximal cues, but not in relation to distal landmarks (Save, Paz-Villagran, Alexinsky, & Poucet, 2005).

A final consideration that has received limited attention is whether the anterior and lateral thalamus might have a role in spatial and contextual representations in postrhinal and parietal cortical targets (Olsen & Witter, in press; Pereira et al., in press; Wilber et al., 2015). For instance, the parietal cortex contains directionally modulated neural populations that fire in a distal spatial framework (Wilber, Clark, Forster, Tatsuno, McNaughton, 2014; Wilber et al., 2014), but also contains neural populations that fire in relation to egocentric body-turns and egocentric relationship with proximal visual cues (McNaughton et al., 1993). Whether information regarding the distal and proximal framework is provided to postsynaptic targets in the parietal cortex by anterior and lateral thalamic outflow, respectively, is unknown, but remains a major possibility given the strong connectivity between these three regions (Wilber et al., 2015). With respect to the postrhinal cortex, recent work has shown that neurons within this region respond to proximal stimuli and local contextual cues (Furtak, Ahmed, & Burwell, 2012). It has been recently suggested that the lateral thalamus, through its dense projections, likely plays a role in visual information processing by postrhinal neurons (Pereira et al., in press).

5. Conclusion

In the present review, we have summarized a large body of work directed toward understanding the functional organization of the limbic thalamus, and we have argued that the role of the anterior and lateral thalamic nuclei can be distinguished on the basis of the specific frame of reference and sensory information processed by each thalamic subregion. In short, we suggest that at least one of the functions of the anterior thalamic nuclei is to guide orientation using the allocentric relationships between path integration mechanisms and distant, background, environmental landmarks; whereas, the lateral thalamic nuclei guide spatial orientation and establishes trajectories on the basis of visual-somatosensory stimuli and proximal landmarks. The bulk of evidence supporting this distinction is provided by neuroanatomical and electrophysiological investigations, and to a lesser extent, studies using targeted manipulations of each subregion. We have therefore highlighted major gaps in this literature with respect to the assessment of behavioral outcomes following selective, and complete, disruption of the anterior and lateral thalamic subnuclei. For example, research aimed at discriminating between the anterior and lateral thalamic nuclei are greatly needed, especially the use of behavioral paradigms designed to explicitly separate distal and proximal sources of stimulus control, as well as egocentric, and path integration strategies (Kosaki et al., 2015; Save & Poucet, 2000; Stackman et al., 2012). Future studies that seek a

functional dissociation between thalamic subnuclei will benefit from advances in optogenetic and chemogenetic methods (Parker, Lalive, & Kreitzer, 2016; Smith, Bucci, Luikart, & Mahler, 2016), which would allow a precise assessment of hypotheses related to specific thalamo-cortical and thalamo-striatal pathways. Our general hope is that this review will assist in organizing further thinking regarding the functional role of the anterior and lateral thalamus, and to motivate future work directed toward determining the relationship between these subregions and spatial representation and memory.

Acknowledgments

References

Aggleton, J. P., Hunt, P. R., Nagle, S., & Neave, N. (1996). The effects of selective lesions within the anterior thalamic nuclei on spatial memory in the rat. *Behavioural Brain Research, 81*, 189–198.

Aggleton, J. P., O'Mara, S. M., Vann, S. D., Wright, N. F., Tsanov, M., & Erichsen, J. T. (2010). Hippocampal-anterior thalamic pathways for memory: Uncovering a network of direct and indirect actions. *European Journal of Neuroscience, 31*, 2292–2307.

Aggleton, J. P., Neave, N., Nagle, S., & Hunt, P. R. (1995). A comparison of the effects of anterior thalamic, mamillary body and fornix lesions on reinforced spatial alternation. *Behavioural Brain Research, 68*(1), 91–101.

Aggleton, J. P., Poirier, G. L., Aggleton, H. S., Vann, S. D., & Pearce, J. M. (2009). Lesions of the fornix and anterior thalamic nuclei dissociate different aspects of hippocampal-dependent spatial learning: implications for the neural basis of scene learning. *Behavioral Neuroscience, 123*(3), 504–519.

Agster, K. L., Pereira, I. T., Saddoris, M. P., Burwell, R. D. (in press). Subcortical connections of the perirhinal, postrhinal, and entorhinal cortices of the rat. II. Efferents. Hippocampus.

Alcaraz, F., Naneix, F., Desfosses, E., Marchand, A. R., Wolff, M., & Coutureau, E. (2016). Dissociable effects of anterior and mediodorsal thalamic lesions on spatial goal-directed behavior. *Brain Structure & Function, 221*, 79–89.

Alexinsky, T. (2001). Differential effect of thalamic and cortical lesions on memory systems in the rat. *Behavioural Brain Research, 122*, 175–191.

Beracochea, D. J., Jaffard, R., & Jarrard, L. E. (1989). Effects of anterior or dorsomedial thalamic ibotenic lesions on learning and memory in rats. *Behavioral and Neural Biology, 51*, 364–376.

Bezdudnaya, T., & Keller, A. (2008). Laterodorsal nucleus of the thalamus: A processor of somatosensory inputs. *Journal of Comparative Neurology, 507*, 1979–1989.

Boccara, C. N., Sargolini, F., Thoresen, V. H., Solstad, T., Witter, M. P., Moser, E. I., & Moser, M. B. (2010). Grid cells in pre- and parasubiculum. *Nature Neuroscience, 13*, 987–994.

Burke, S. N., Maurer, A. P., Nematollahi, S., Uprety, A. R., Wallace, J. L., & Barnes, C. A. (2011). The influence of objects on place field expression and size in distal hippocampal CA1. *Hippocampus, 21*, 783–801.

Calton, J. L., Stackman, R. W., Goodridge, J. P., Archey, W. B., Dudchenko, P. A., & Taube, J. S. (2003). Hippocampal place cell instability after lesions of the head direction cell network. *Journal of Neuroscience, 23*, 9719–9731.

Célérier, A., Ognard, R., Decorte, L., & Beracochea, D. (2000). Deficits of spatial and non-spatial memory and of auditory fear conditioning following anterior thalamic lesions in mice: Comparison with chronic alcohol consumption. *European Journal of Neuroscience, 12*, 2575–2584.

Cheatwood, J. L., Reep, R. L., & Corwin, J. V. (2003). The associative striatum: Cortical and thalamic projections to the dorsocentral striatum in rats. *Brain Research, 968*, 1–14.

Clark, B. J., Brown, J. E., & Taube, J. S. (2012). Head direction cell activity in the anterodorsal thalamus requires intact supragenual nuclei. *Journal of Neurophysiology, 108*, 2767–2784.

Clark, B. J., Hong, N. S., Bettenson, D. J., Woolford, J., Horwood, L., & McDonald, R. J. (2015). Maintained directional navigation across environments in the Morris water task is dependent on vestibular cues. *Journal of Experimental Psychology: Animal Learning and Cognition, 41*, 301–308.

Clark, B. J., & Taube, J. S. (2012). Vestibular and attractor network basis of the head direction cell signal in subcortical circuits. *Frontiers in Neural Circuits, 6*, 7. http://dx.doi.org/10.3389/fncir.2012.00007.

Cooper, B. G., Miya, D. Y., & Mizumori, S. J. (1998). Superior colliculus and active navigation: Role of visual and non-visual cues in controlling cellular representations of space. *Hippocampus, 8*, 340–372.

Deshmukh, S. S., & Knierim, J. J. (2013). Influence of local objects on hippocampal representations: Landmark vectors and memory. *Hippocampus, 23*, 253–267.

Dudchenko, P. A., & Taube, J. S. (1997). Correlation between head direction cell activity and spatial behavior on a radial arm maze. *Behavioral Neuroscience, 111*, 3–19.

Dumont, J. R., Amin, E., & Aggleton, J. P. (2014). Selective importance of the rat anterior thalamic nuclei for configural learning involving distal spatial cues. *European Journal of Neuroscience, 39*, 241–256.

Dumont, J. R., Wright, N. F., Pearce, J. M., & Aggleton, J. P. (2014). The impact of anterior thalamic lesions on active and passive spatial learning in stimulus controlled environments: Geometric cues and pattern arrangement. *Behavioral Neuroscience, 128*, 161–177.

Enkhjargal, N., Matsumoto, J., Chinzorig, C., Berthoz, A., Ono, T., & Nishijo, H. (2014). Rat thalamic neurons encode complex combinations of heading and movement direction and the trajectory route during translocation with sensory conflict. *Frontiers in Behavioral Neuroscience, 8*, 242.

Frohardt, R. J., Bassett, J. P., & Taube, J. S. (2006). Path integration and lesions within the head direction cell circuit: comparison between the roles of the anterodorsal thalamus and dorsal tegmental nucleus. *Behavioral Neuroscience, 120*, 135–149.

Fuhs, M. C., Vanrhoads, S. R., Casale, A. E., McNaughton, B., & Touretzky, D. S. (2005). Influence of path integration versus environmental orientation on place cell remapping between visually identical environments. *Journal of Neurophysiology, 94*, 2603–2616.

Furtak, S. C., Ahmed, O. J., & Burwell, R. D. (2012). Single neuron activity and theta modulation in postrhinal cortex during visual object discrimination. *Neuron, 76*, 976–988.

Gibb, S. J., Wolff, M., & Dalrymple-Alford, J. C. (2006). Odour-place paired-associate learning and limbic thalamus: Comparison of anterior, lateral and medial thalamic lesions. *Behavioural Brain Research, 172*, 155–168.

Giocomo, L. M., & Moser, E. I. (2011). Computational models of grid cells. *Neuron, 71*, 589–603.

Golob, E. J., Wolk, D. A., & Taube, J. S. (1998). Recordings of postsubiculum head direction cells following lesions of the laterodorsal thalamic nucleus. *Brain Research, 780*, 9–19.

Goodridge, J. P., Dudchenko, P. A., Worboys, K. A., Golob, E. J., & Taube, J. S. (1998). Cue control and head direction cells. *Behavioral Neuroscience, 112*, 749–761.

Goodridge, J. P., & Taube, J. S. (1997). Interaction between postsubiculum and anterior thalamus in the generation of head direction cell activity. *Journal of Neuroscience, 17*, 9315–9330.

Grieve, K. L., Acuna, C., & Cudiero, J. (2000). The primate pulvinar nuclei: Vision and action. *Trends in Neuroscience, 23*, 35–39.

Grieves, R. M., Jenkins, B. W., Harland, B. C., Wood, E. R., & Dudchenko, P. A. (2016). Place field repetition and spatial learning in a multicompartment environment. *Hippocampus, 26*, 118–134.

Hamilton, D. A., Akers, K. G., Weisend, M. P., & Sutherland, R. J. (2007). How do room and apparatus cues control navigation in the morris water task? Evidence for distinct contributions to a movement vector. *Journal of Experimental Psychology: Animal Behavior Processes, 33*, 100–114.

Jankowski, M. M., Passecker, J., Islam, M. N., Vann, S., Erichsen, J. T., Aggleton, J. P., & O'Mara, S. M. (2015). Evidence for spatially-responsive neurons in the rostral thalamus. *Frontiers in Behavioral Neuroscience, 9*, 256.

Jankowski, M. M., Ronnqvist, K. C., Tsanov, M., Vann, S. D., Wright, N. F., Erichsen, J. T., ... O'Mara, S. M. (2013). The anterior thalamus provides a subcortical circuit supporting memory and spatial navigation. *Frontiers in Systems Neuroscience, 7*, 45.

Kosaki, Y., Poulter, S. L., Austen, J. M., & McGregor, A. (2015). Dorsolateral striatal lesions impair navigation based on landmark-goal vectors but facilitate spatial learning based on a "cognitive map". *Learning & Memory, 22*, 179–191.

Lever, C., Burton, S., Jeewajee, A., O'Keefe, J., & Burgess, N. (2009). Boundary vector cells in the subiculum of the hippocampal formation. *Journal of Neuroscience, 29*, 9771–9777.

Lopez, J., Wolff, M., Lecourtier, L., Cosquer, B., Bontempi, B., Dalrymple-Alford, J., & Cassel, J. C. (2009). The intralaminar thalamic nuclei contribute to remote spatial memory. *Journal of Neuroscience, 29*, 3302–3306.

Mair, R. G., Burk, J. A., & Porter, M. C. (2003). Impairment of radial maze delayed nonmatching after lesions of anterior thalamus and parahippocampal cortex. *Behavioral Neuroscience, 117*, 596–605.

McNaughton, B. L., Battaglia, F. P., Jensen, O., Moser, E. I., & Moser, M. B. (2006). Path integration and the neural basis of the 'cognitive map'. *Nature Review Neuroscience, 7*, 663–678.

McNaughton, B. L., Chen, L. L., & Markus, E. J. (1991). Dead reckoning, landmark learning, and the sense of direction: A neurophysiological and computational hypothesis. *Journal of Cognitive Neuroscience, 3*, 192–202.

McNaughton, B. L., Mizumori, S. J., Barnes, C. A., Leonard, B., Marquis, M., & Green, E. (1993). Cortical representation of motion during unrestrained spatial navigation in the rat. *Cerebral Cortex, 4*, 27–39.

Mitchell, A. S., & Dalrymple-Alford, J. C. (2005). Dissociable memory effects after medial thalamus lesions in the rat. *European Journal of Neuroscience, 22*, 973–985.

Mitchell, A. S., & Dalrymple-Alford, J. C. (2006). Lateral and anterior thalamic lesions impair independent memory systems. *Learning & Memory, 13*, 388–396.

Mizumori, S. J., Miya, D. Y., & Ward, K. E. (1994). Reversible inactivation of the lateral dorsal thalamus disrupts hippocampal place representation and impairs spatial learning. *Brain Research, 644*, 168–174.

Mizumori, S. J. Y., Puryear, C. B., Gill, K. M., & Guazzelli, A. (2005). Head direction codes in hippocampal afferent and efferent systems: What functions do they serve? In S. I. Wiener & J. S. Taube (Eds.), *Head direction cells and the neural mechanisms underlying directional orientation* (pp. 203–220). MIT Press.

Mizumori, S. J., & Williams, J. D. (1993). Directionally selective mnemonic properties of neurons in the lateral dorsal nucleus of the thalamus of rats. *Journal of Neuroscience, 13*, 4015–4028.

Mlinar, E. J., & Goodale, M. A. (1984). Cortical and tectal control of visual orientation in the gerbil: evidence for parallel channels. *Experimental Brain Research, 55*(1), 33–48.

Moreau, P. H., Tsenkina, Y., Lecourtier, L., Lopez, J., Cosquer, B., Wolff, M., ... Cassel, J. C. (2013). Lesions of the anterior thalamic nuclei and intralaminar thalamic nuclei: Place and visual discrimination learning in the water maze. *Brain Structure and Function, 218*, 657–667.

Morin, L. P., & Studholme, K. M. (2014). Retinofugal projections in the mouse. *Journal of Comparative Neurology, 522*, 3733–3753.

Moser, E. I., Kropff, E., & Moser, M. B. (2008). Place cells, grid cells, and the brain's spatial representation system. *Annual Review in Neuroscience, 31*, 69–89.

Nakamura, H., Hioki, H., Furuta, T., & Kaneko, T. (2015). Different cortical projections from three subdivisions of the rat lateral posterior thalamic nucleus: A single-neuron tracing study with viral vectors. *European Journal of Neuroscience, 41*, 1294–1310.

O'Keefe, J., & Nadel, L. (1978). *The hippocampus as a cognitive map*. Oxford, UK: Oxford University Press.

Olsen, G. M., Witter, M. P. (in press). The posterior parietal cortex of the rat: architectural delineation and thalamic differentiation. Journal of Comparative Neurology.

Parker, P. R. L., Lalive, A. L., & Kreitzer, A. C. (2016). Pathway-specific remodeling of thalamostriatal synapses in Parkinsonian mice. *Neuron, 89*, 734–740.

Paxinos, G., & Watson, C. (2009). *The rat brain in stereotaxic coordinates* (6th ed.). San Diego, CA: Academic Press.

Peckford, G., Dwyer, J. A., Snow, A. C., Thorpe, C. M., Martin, G. M., & Skinner, D. M. (2014). The effects of lesions to the postsubiculum or the anterior dorsal nucleus of the thalamus on spatial learning in rats. *Behavioral Neuroscience, 128*, 654–665.

Pereira, I. T., Agster, K. L., Burwell, R. D. (in press). Subcortical connections of the perirhinal, postrhinal, and entorhinal cortices of the rat. I. Afferents. Hippocampus.

Reep, R. L., & Corwin, J. V. (2009). Posterior parietal cortex as part of a neural network for directed attention in rats. *Neurobiology of Learning and Memory, 9*, 104–113.

Rice, J. P., Wallace, D. G., & Hamilton, D. A. (2015). Lesions of the hippocampus or dorsolateral striatum disrupt distinct aspects of spatial navigation strategies based on proximal and distal information in a cued variant of the Morris water task. *Behavioural Brain Research, 289*, 105–117.

Robertson, R. T., Kaitz, S. S., & Robards, M. J. (1980). A subcortical pathway links sensory and limbic systems of the forebrain. *Neuroscience Letters, 17*, 161–165.

Roth, M. M., Dahmen, J. C., Muir, D. R., Imhof, F., Martini, F. J., & Hofer, S. B. (2016). Thalamic nuclei convey diverse contextual information to layer 1 of visual cortex. *Nature Neuroscience, 19*, 209–377.

Save, E., Paz-Villagran, V., Alexinsky, T., & Poucet, B. (2005). Functional interaction between the associative parietal cortex and hippocampal place cell firing in the rat. *European Journal of Neuroscience, 21*, 522–530.

Save, E., & Poucet, B. (2000). Involvement of the hippocampus and associative parietal cortex in the use of proximal and distal landmarks for navigation. *Behavioural Brain Research, 109*, 195–206.

Sharp, P. E., & Turner-Williams, S. (2005). Movement-related correlates of single-cell activity in the medial mammillary nucleus of the rat during a pellet-chasing task. *Journal of Neurophysiology, 94*, 1920–1927.

Sherman, M. S. (2016). Thalamus plays a central role in ongoing cortical functioning. *Nature Neuroscience, 16*, 533–541.

Shires, K. L., Hawthorne, J. P., Hope, A. M., Dudchenko, P. A., Wood, E. R., & Martin, S. J. (2013). Functional connectivity between the thalamus and postsubiculum: Analysis of evoked responses elicited by stimulation of the laterodorsal thalamic nucleus in anesthetized rats. *Hippocampus, 23*, 559–569.

Skinner, D. M., Etchegary, C. M., Ekert-Maret, E. C., Baker, C. J., Harley, C. W., Evans, J. H., & Martin, G. M. (2003). An analysis of response, direction, and place learning in an open field and T-Maze. *Journal of Experimental Psychology: Animal Behavior Processes, 29*, 3–13.

Smith, K. S., Bucci, D. J., Luikart, B. W., & Mahler, S. V. (2016). DREADDs: Use and application in behavioral neuroscience. *Behavioral Neuroscience, 130*(2), 137–155.

Solstad, T., Boccara, C. N., Kropff, E., Moser, M. B., & Moser, E. I. (2008). Representation of geometric borders in the entorhinal cortex. *Science, 322*, 1865–1868.

Spiers, H. J., Hayman, R. M., Jovalekic, A., Marozzi, E., & Jeffery, K. J. (2015). Place field repetition and purely local remapping in a multicompartment environment. *Cerebral Cortex, 25*, 10–25.

Stackman, R., Lora, J., & Williams, S. (2012). Directional responding of C57bl/6j mice in the Morris water maze is influenced by visual and vestibular cues and is dependent upon the anterior thalamic nuclei. *Journal of Neuroscience, 32*, 10211–10225.

Stackman, R. W., & Taube, J. S. (1997). Firing properties of head direction cells in rat anterior thalamic neurons: Dependence upon vestibular input. *Journal of Neuroscience, 17*, 4349–4358.

Taube, J. S. (2007). The head direction signal: Origins and sensory-motor integration. *Annual Review of Neuroscience, 30*, 181–207.

Thompson, S. M., & Robertson, R. T. (1987). Organization of subcortical pathways for sensory projections to the limbic cortex. II. Afferent projections to the thalamus lateral dorsal nucleus in the rat. *Journal of Comparative Neurology, 265*, 189–202.

Tsanov, M., Chah, E., Vann, S., Reilly, R., Erichsen, J., Aggleton, J., & O'mara, S. (2011). Theta-modulated head direction cells in the rat anterior thalamus. *Journal of Neuroscience, 31*, 9489–9502.

Ulrich, K., Aitken, P. N., Abraham, W. C., Dalrymple-Alford, J. C., & McNaughton, N. (2014). Effects of thalamic lesions on repeated relearning of a spatial working memory task. *Behavioural Brain Research, 261*, 56–59.

Van Groen, T., Kadish, I., & Wyss, J. M. (2002a). The role of the laterodorsal nucleus of the thalamus in spatial learning and memory in the rat. *Behavioural Brain Research, 136*, 329–337.

Van Groen, T., Kadish, I., & Wyss, J. M. (2002b). Role of the anterodorsal and anteroventral nuclei of the thalamus in spatial memory in the rat. *Behavioural Brain Research, 132*, 19–28.

Warburton, E. C., & Aggleton, J. P. (1999). Differential deficits in the Morris water maze following cytotoxic lesions of the anterior thalamus and fornix transection. *Behavioural Brain Research, 98*, 27–38.

Warburton, E. C., Baird, A. L., & Aggleton, J. P. (1997). Assessing the magnitude of the allocentric spatial deficit associated with complete loss of the anterior thalamic nuclei in rats. *Behavioural Brain Research, 87*, 223–232.

Warburton, E. C., Morgan, A., Baird, A. L., Muir, J. L., & Aggleton, J. P. (1999). Does pretraining spare the spatial deficit associated with anterior thalamic damage in rats? *Behavioural Neuroscience, 113*, 956–967.

Weldon, D. A., & Best, P. J. (1992). Changes in sensory responsivity in deep layer neurons of the superior colliculus of behaving rats. *Behavioural Brain Research, 47*, 97–101.

Whishaw, I. Q., Hines, D. J., & Wallace, D. G. (2001). Dead reckoning (path integration) requires the hippocampal formation: evidence from spontaneous exploration and spatial learning tasks in light (allothetic) and dark (idiothetic) tests. *Behavioural Brain Research, 127*, 49–69.

Wilber, A. A., Clark, B. J., Forster, T. C., Tatsuno, M., & McNaughton, B. L. (2014). Interaction of egocentric and world-centered reference frames in the rat posterior parietal cortex. *Journal of Neuroscience, 34*, 5431–5446.

Wilber, A. A., Clark, B. J., Demecha, A. J., Mesina, L., Vos, J. M., & McNaughton, B. L. (2015). Cortical connectivity maps reveal anatomically distinct areas in the parietal cortex of the rat. *Frontiers in Neural Circuits, 8*, 146.

Wilton, L. A., Baird, A. L., Muir, J. L., Honey, R. C., & Aggleton, J. P. (2001). Loss of the thalamic nuclei for "head direction" impairs performance on spatial memory tasks in rats. *Behavioral Neuroscience, 115*, 861–869.

Winter, S. S., Clark, B. J., & Taube, J. S. (2015). Disruption of the head direction cell network impairs the parahippocampal grid cell signal. *Science, 347*, 870–874.

Wolff, M., Gibb, S. J., Cassel, J. C., & Dalrymple-Alford, J. C. (2008). Anterior but not intralaminar thalamic nuclei support allocentric spatial memory. *Neurobiology of Learning and Memory, 90*, 71–80.

Yoder, R. M., Clark, B. J., Brown, J. E., Lamia, M. V., Valerio, S., Shinder, M. E., & Taube, J. S. (2011). Both visual and idiothetic cues contribute to head direction cell stability during navigation along complex routes. *Journal of Neurophysiology, 105*, 2989–3001.

Yoder, R. M., Clark, B. J., & Taube, J. S. (2011). Origins of landmark encoding in the brain. *Trends in Neurosciences, 34*, 561–571.

Yoganarasimha, D., Yu, X., & Knierim, J. J. (2006). Head direction cell representations maintain internal coherence during conflicting proximal and distal cue rotations: Comparison with hippocampal place cells. *Journal of Neuroscience, 26*, 622–631.

Zugaro, M. B., Berthoz, A., & Wiener, S. I. (2001). Background, but not foreground, spatial cues are taken as references for head direction responses by rat anterodorsal thalamus neurons. *The Journal of Neuroscience, 21*(RC154), 1–5.