Neuroscience and Biobehavioral Reviews 126 (2021) 544–559

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Lateral septum as a nexus for mood, motivation, and movement

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ARTICLE INFO

Keywords:
Reward
Motivation
Movement
Navigation
Anxiety
Planning
Place cells
Hippocampus
Septum

ABSTRACT

The lateral septum (LS) has been implicated in a wide variety of functions, including emotional, motivational, and spatial behavior, and the LS may regulate interactions between the hippocampus and other regions that mediate goal directed behavior. In this review, we suggest that the lateral septum incorporates movement into the evaluation of environmental context with respect to motivation, anxiety, and reward to output an 'integrated movement value signal'. Specifically, hippocampally-derived contextual information may be combined with reinforcement or motivational information in the LS to inform task-relevant decisions. We will discuss how movement is represented in the LS and the literature on the LS's involvement in mood and motivation. We will then connect these results to LS movement-related literature and hypotheses about the role of the lateral septum. We suggest that the LS may communicate a movement-scaled reward signal via changes in place-, movement-, and reward-related firing, and that the LS should be considered a fundamental node of affect and locomotor pathways in the brain.

1. Introduction

An initial theory of the septohippocampal system, which includes the hippocampus (HPC), lateral septum (LS), and medial septum (MS), conceptualized the system as nodes of emotion and affect processing (MacLean, 1949; Papez, 1937). As a result of the cognitive map hypothesis and the subsequent discovery of place cells (O'Keefe, 1976; O'Keefe and Dostrovsky, 1971; Tolman, 1948), the hippocampus is now conceived as having a primary role in navigation, as well as in spatial and episodic memory (Eichenbaum et al., 1999; Foster and Knierim, 2012; Hasselmo et al., 2002; Knierim, 2015; McNaughton et al., 2006).

While the hippocampus sends a massive projection to the LS, this projection and the LS have been relatively understudied compared to the connection between the HPC and the MS. However, the LS has been implicated in a wide variety of functions, including emotional, motivational, and spatial behavior (Table 1). These functions may involve interactions between the hippocampus and other regions that mediate goal-directed behavior (Jiang et al., 2018; Luo et al., 2011; Sweeney and Yang, 2016; Vega-Quiroga et al., 2018; Wirtshafter and Wilson, 2019, 2020; Wong et al., 2016). Specifically, hippocampally-derived contextual information may be combined with reinforcement or motivational information (Berridge, 2007; Berridge et al., 2009; Smith et al., 2011; Wyvell and Berridge, 2000) in the LS to inform task-relevant decisions (Wirtshafter and Wilson, 2019, 2020). The LS has additionally been studied in the regulation and control of mood and motivation (Anthony et al., 2014; Engin et al., 2016; Gray and McNaughton, 1983, 2003; Parfitt et al., 2017; Sheehan et al., 2004; Thomas et al., 1991; Yadin et al., 1993), with many contradictory results relating to the role of the LS in anxiety depending on type of task and exact experimental manipulation.

In this review, we posit that these contradictory results can be explained by redefining the LS as a structure that incorporates movement into the evaluation of environmental context with respect to motivation, anxiety, and reward, rather than as a specific regulator of anxiety or motivation. First, we will summarize the anatomical connections of the LS. Then, in Section 3, we will review the current theories of LS function. In Section 4, we will discuss the literature implicating the LS in the regulation of mood, including the correlates of anxiety and theta rhythm in the LS. In Section 5, we will discuss how movement is represented in the LS and how this representation may affect navigational strategies. In Section 6, we will review how space and context are represented in the LS, and the ways in which the LS may be important for matching context with behavior. In Section 7, we will discuss how the LS drives other limbic and dopaminergic brainstem targets to regulate

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https://doi.org/10.1016/j.neubiorev.2021.03.029
Received 21 September 2020; Received in revised form 18 February 2021; Accepted 26 March 2021
Available online 10 April 2021

Table 1

Table of representative LS studies. If a specific area of the LS was targeted, it is indicated. Main method(s) used in the study are indicated by the check boxes to the left of each citation, although we recognize there is some subjectivity involved in classification. Citations are listed in chronological order under each section to show the progression of research ideas and techniques.

STUDY TYPE

L P E G

- Lesion and inactivation (including electrolytic, chemical, selective et al.)
- Pharmacologic
- Electrophysiology/Stimulation
- Genetic/Optogenetic/DREADDs

Reactivity/Rage/Aggression/Anxiety/Fear

LS is anxiolytic

L	P	E	G		
■				Brady & Nauta, 1953	
■				Brady & Nauta, 1955	
■				Schnurr, 1972	*Rostral*
■				Albert & Richmond, 1976	
■	■			Grossman, 1977	
■		■		Albert, Brayley, & Milner, 1978	
■				Albert & Wong, 1978	*Ventral*
■				Gage, Olton, & Bolanowski, 1978	*Ventral*
■				Blanchard, Blanchard et al., 1979	*Ros/Ven*
■				D. S. Gray, Terlecki et al., 1981	*Rostral*
■				Clarke & File, 1982	
■				Melia, Sananes, & Davis, 1992	
■		■		Yadin, Thomas et al., 1993	
		■		Yadin & Thomas, 1996	
■				Vouimba, Garcia, & Jaffard, 1998	
■	■			Le Merrer, Cagniard, & Cazala, 2006	*Ventral*
	■			Lee & Gammie, 2009	
■	■			Singewald, Rjabokon et al., 2011	
		■		Guzman, Tronson et al., 2013	
	■			Lamontagne, Olmstead, & Menard, 2016	
		■		Wong, Wang et al., 2016	
		■		Parfitt, Nguyen et al., 2017	

LS is anxiogenic

L	P	E	G		
■				Myhrer, 1989	
■				Treit & Pesold, 1990	
■				Pesold & Treit, 1992	*Caudal*
■				Menard & Treit, 1996	
	■			Pesold & Treit, 1996	
	■			Degroot, Kashluba, & Treit, 2001	
	■			Trent & Menard, 2010	
			■	Anthony, Dee et al., 2014	
	■	■		Chee, Menard, & Dringenberg, 2014	
	■	■		Chee, Menard, & Dringenberg, 2015	
			■	Leroy, Park et al., 2018	

LS can be either anxiolytic or anxiogenic

L	P	E	G		
■				Sagvolden, 1976	
	■			Drugan, Skolnick et al., 1986	

Notable Reviews

J. A. Gray & McNaughton, 1983

E. Thomas, 1988

J. A. Gray & McNaughton, 2003

Conditioning/Cues/Discrimination/Context

L	P	E	G		
■				Ellen & Powell, 1962	
■				Kaada, Rasmussen, & Kveim, 1962	
■				Fox, Kimble, & Lickey, 1964	
■				Zucker, 1965	
	■			Berger & Thompson, 1977	
	■			Yadin & Thomas, 1981	
	■			E. Thomas, Yadin, & Strickland, 1991	
■	■			M'Harzi & Jarrard, 1992	
	■			Kita, Nishijo et al., 1995	
	■			Nishijo, Kita, Tamura, Eifuku et al., 1997	
	■			Nishijo, Kita, Tamura, Uwano et al., 1997	
■	■			Vouimba et al., 1998	
	■			Leutgeb & Mizumori, 2002	
■				Calandreau et al., 2007	
■				Calandreau et al., 2010	
■	■			Luo et al., 2011	*Dorsal*
■	■			Jiang et al., 2018	*Dorsal*
	■	■		McGlinchey & Aston-Jones, 2018	*Dorsal*
	■			Wirtshafter & Wilson, 2019	*Dorsal*

(*continued on next page*)

Table 1 (*continued*)

Self-Stimulation/Reward/Feeding

L	P	E	G		
	■			Olds & Milner, 1954	
	■			Sadowski & Dembinska, 1973	
	■			Terman & Terman, 1975	
■				Sotomayor et al., 2005	
■		■		Luo et al., 2011	*Dorsal*
■		■		Sartor & Aston-Jones, 2012	
		■		Harasta et al. 2015	

L	P	E	G		
	■			Sweeney & Yang, 2015	
	■			Sweeney & Yang, 2016	
■				Le Merrer, Gavello-Baudy, et al., 2007	
■	■			Jiang et al., 2018	*Dorsal*
	■	■		McGlinchey & Aston-Jones, 2018	*Dorsal*
	■			Wirtshafter & Wilson, 2020	*Dorsal*
■				Pantazis, & Aston-Jones 2020	

Hyperactivity/Exploration/Movement

L	P	E	G		
■				Dalland, 1970	
■				Kohler & Srebro, 1980	
■				Taghzouti, Simon, & Le Moal, 1986	
■				Myhrer, 1989	
	■			Zhou et al., 1999	

L	P	E	G		
■				Trent & Menard, 2010	
	■	■		Bender, Gorbati et al., 2015	
	■			Monaco et al., 2019	
	■			Wirtshafter & Wilson, 2019	*Dorsal*

Perseverance/Place/Space

LS in navigation behavior

L	P	E	G	
■				Dalland, 1970
■				J. B. Thomas, 1972
■				Dalland, 1974
■				Olton, Walker, & Gage, 1978
■				G. J. Thomas, 1979
■				G. J. Thomas & Brito, 1980
■				Rawlins & Olton, 1982
■	■			Fraser, Poucet et al., 1991
■				M'Harzi & Jarrard, 1992

Spatial correlates

L	P	E	G		
	■			Kita et al., 1995	
	■			Nishijo, Kita, Tamura, Uwano et al., 1997	
	■			Zhou et al., 1999	
	■			Bezzi, Samengo et al., 2002	
	■			Leutgeb & Mizumori, 2002	
	■			Takamura, Tamura et al., 2006	
	■			Tingley & Buzsaki, 2018	
	■			Monaco, De Guzman et al., 2019	
	■			Wirtshafter & Wilson, 2019	*Dorsal*
	■			Wirtshafter & Wilson, 2020	*Dorsal*

behavior. In Section 8 and the conclusion, we will propose our integrated theory of septal function. We suggest that the LS may communicate a movement-scaled reward signal via changes in place, movement, and reward-related firing, and that the LS should be considered a fundamental node of affect and locomotor pathways in the brain.

2. Anatomy

Broadly, the lateral septum is the primary non-cortical output of the hippocampus, which sends a projection to the LS from principal cells in all cornu ammonis (CA) subregions (Leroy et al., 2018; Risold and Swanson, 1997a, b). Although the LS is predominantly GABA-ergic (Risold and Swanson, 1997a), the ventral-most region may contain a small population of glutamatergic cells (Lin et al., 2003).

The LS has been traditionally divided into three main divisions (Berger et al., 1976; Berger and Thompson, 1978) which are distinct in terms of their major afferents and efferents. It is unclear how much functional distinction exists between the areas, as many studies on the LS examine the structure in its entirety and do not differentiate between subdivisions when describing findings. Perhaps the strongest functional distinctions can be made between the dorsal (LSd) and ventral (LSv) regions of the LS: the LS is elegantly organized in that progressively more ventral regions of the HPC innervate progressively more ventral, and larger, regions of the LS (n.b., individual neurons in the LS likely receive projections from multiple hippocampal pyramidal cells) (Risold and Swanson, 1997b; Swanson and Cowan, 1977).

This organization has functional implications for the LS, as dorsal and ventral HPC are believed to have broadly different functions. Compared to the ventral hippocampus, the dorsal hippocampus is more involved in spatial learning and memory, and contains a more stable and larger population of place fields. Dorsal hippocampus lesions are more disruptive to spatial learning than lesions to the ventral hippocampus (Hampson et al., 1999; Hock and Bunsey, 1998; Jung et al., 1994; Keinath et al., 2014; Royer et al., 2010). Conversely, the ventral hippocampus is more involved in emotional, social, and non-spatial processing: lesions of the ventral hippocampus are anxiolytic (Kjelstrup et al., 2002), and manipulation of the ventral hippocampus or its corresponding inputs and outputs can directly impact behaviors related to anxiety and fear such as defensive behaviors, predator approach, and behavioral inhibition (Felix-Ortiz et al., 2013; Gergues et al., 2020; Jimenez et al., 2018; Kheirbek et al., 2013; Padilla-Coreano et al., 2016; Parfitt et al., 2017; Yoshida et al., 2019; Zhang et al., 2014). Correspondingly, the LSv is more involved in regulation of 'emotional' behaviors, including anxiety regulation, kinship, and defensive/aggressive behaviors, than the LSd (Albert and Wong, 1978; Blanchard et al., 1979; Clemens et al., 2020; Le Merrer et al., 2006). Conversely, the LSd, (which receives projections from the dorsal HPC and sends projections to the VTA), is more involved in mediating associations with reinforcements such as cocaine (Jiang et al., 2018; Luo et al., 2011; Mahler and Aston-Jones, 2012; McGlinchey and Aston-Jones, 2018; Pantazis and Aston-Jones, 2020; Sartor and Aston-Jones, 2012). Although cells with spatially selective firing (place-like cells) are heavily concentrated in the caudodorsal LS (Wirtshafter and Wilson, 2020), they are found throughout the entirety of the LS (Leutgeb and Mizumori, 2002; Nishijo et al., 1997b; Takamura et al., 2006; Zhou et al., 1999). This wide distribution of place-like cells suggests spatial information may be used in all LS processing, for example to direct reinforcement-related behavior in LSd regions and affective behavior in LSv (Fig. 1).

In addition to dorsal/ventral differences, there are rostral/caudal differences in LS connections (Fig. 1), although the functional difference in these connections has been much less studied. While the entirety of the LS has connections with a variety of brainstem regions, the LSc is more heavily innervated by the brainstem than the rostral LS (LSr) (Risold and Swanson, 1997b). However, many of the brainstem regions that innervate the LSc send projections to hypothalamic regions that innervate the LSr (Risold and Swanson, 1997b). The LSr is noteworthy in that it has a large projection to the VTA (Jiang et al., 2018; Luo et al., 2011). These connections, both efferent and afferent, of LSc and LSr to the brainstem, as well as the bidirectional LS connections with classic cortical and basal ganglia circuits involved in locomotor behavior and orientation, may contribute to the integration of movement information entering the LS. Movement-related processing in the LS may then influence target regions involved in regulating behavior.

Like spatial information, movement-related inputs and outputs are spread throughout the LS and may be a primary component of LS function. Through multiple pathways, the LS is a synapse away from the mesencephalic locomotor region (MLR), which is involved in the initiation and control of movement, and contains cells which, similar to the LS, are modulated by speed (Garcia-Rill et al., 1983; Ryczko et al., 2017). The LS is additionally connected to many mesolimbic structures that represent both motivation and reinforcement (Berridge, 2007; Berridge et al., 2009; Smith et al., 2011; Wirtshafter and Stratford, 2010; Wyvell and Berridge, 2000), such as the VTA and striatum (Kremer et al., 2020; Lindvall, 1975; Luo et al., 2011; Risold and Swanson, 1997b; Swanson and Cowan, 1979; Vega-Quiroga et al., 2018), and the LS has firing correlates for reward anticipation as well as reward receipt (Wirtshafter and Wilson, 2019), which may represent both motivation and reinforcement, respectively.

More specifically, the LSr has reciprocal connections with the hypothalamus and suprammamillary nucleus, which are involved in arousal, the expression of voluntary movement, and defensive behaviors (Risold and Swanson, 1997b; Sinnamon, 1993; Swanson and Cowan, 1979). The hypothalamus has connections through the thalamus with the cingulate cortex (involved in orientation) the entorhinal cortex (involved in path integration) and the periaqueductional gray (involved in defensive behavior and motor circuit regulation) (Bush et al., 2015; Frank et al., 2000; Hasselmo et al., 2002; Koutsikou et al., 2015; Risold and Swanson, 1997b; Tovote et al., 2016; Whishaw et al., 2001). A number of studies have shown that LSr lesions promote defensive behaviors, which were not observed in studies with animals given LSc lesions (Blanchard et al., 1979; Gray et al., 1981; Schnurr, 1972). However, it is important to note that a number of other studies claim that lesions of LSr or the entirety of the LS cause behaviors that have been interpreted to be anxiolytic (Drugan et al., 1986; Menard and Treit, 1996; Pesold and Treit, 1992, 1996).

The LSc is reciprocally connected to the suprammamillary nucleus, and receives additional inputs from multiple brainstem regions, including the laterodorsal tegmental nucleus, the raphe, the VTA, and the locus ceruleus, all regions known to be involved in the modulation of behavioral states such as arousal (Groessl et al., 2018; Kremer et al., 2020; Lee and Dan, 2012; Risold and Swanson, 1997b). The vast majority of LSfcinnervation by the hippocampus is from subregion CA3 (Risold and Swanson, 1997b), suggesting a potential role of the LSc in pattern association-driven contextual behavior, functions attributed to CA3 (Ahn and Lee, 2014; Gilbert and Kesner, 2003; Kesner, 2013; Kesner et al., 2004). This function is supported by studies that show that the LSc connections with CA3 (afferent) and VTA (efferent) are specifically important for reward seeking and conditioned place preference (Jiang et al., 2018; Luo et al., 2011).

We propose the main inputs of the LS can be divided into structures providing place and contextual information (the dorsal hippocampus), structures providing movement-related information (likely brainstem regions), and a number of connections with affectual (e.g. amygdala and ventral HPC), motivational, and reinforcement areas (e.g. VTA, hypothalamus, nucleus accumbens) (Fig. 2). These inputs are somewhat anatomically organized (Fig. 1), with LSd having heavier involvement in spatial processing, the LSv more involved in emotional processing, the LSr having possible involvement in determination of cue, and the LSc in context and contextual reinforcement behavior, with motor and navigational signals spread throughout the entirety of the LS. We contend that the functions of the septohippocampal system in emotional and

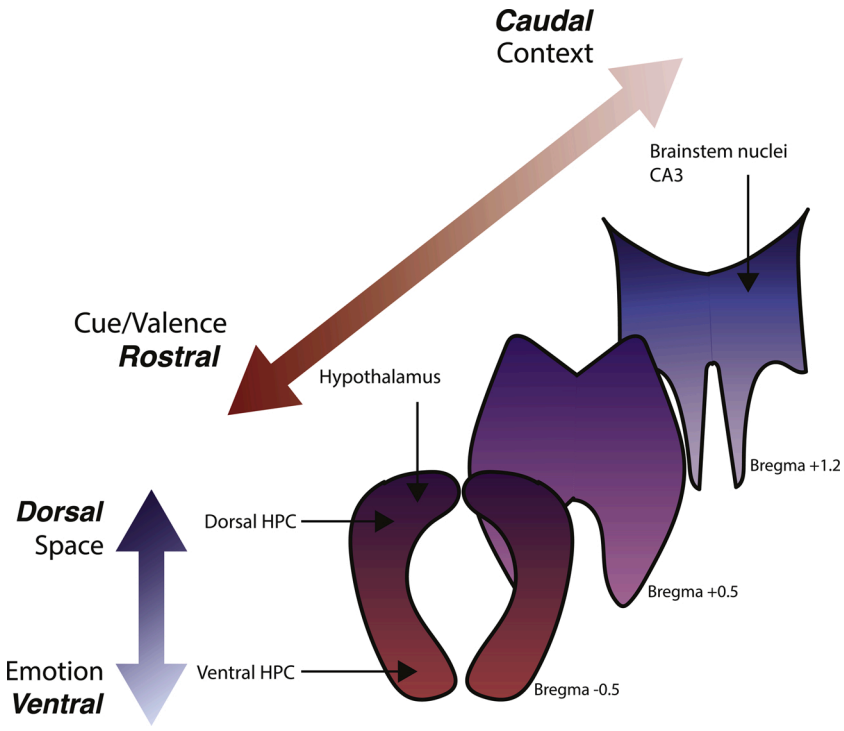

Fig. 1. LS inputs and functionality exists along dorsal/ventral and rostral/caudal gradients.
Diagrams of the LS at different rostral/caudal coordinates. The diagrams are labelled with the most anatomically distinct inputs for each region. The LSd receives input from dorsal hippocampus, with progressively more ventral regions of the LS receiving input from progressively more ventral regions of the hippocampus. This leads to a functional segregation with more spatial information located dorsally in the LS (although place-like cells have been observed throughout the LS), and more emotional/affect information located more ventrally. The LSr receives a large innervation from the hypothalamus and is thought to function more in the regulation of affect (possibly including anxiety), and may function in the perception of cue valence. The LSc's main hippocampal input is from the CA3, which has an important role in pattern separation and completion. The LSc also receives input from many brainstem nuclei, including the VTA. This connection has been shown to be important in reward seeking. Although many dopaminergic regions project to the LSc, spiking correlates of movement have been throughout the LS. (We additionally appreciate that the brainstem is important for functions beyond movement and reward seeking, but we are unaware of any studies showing these functions reflected in LS activity.).

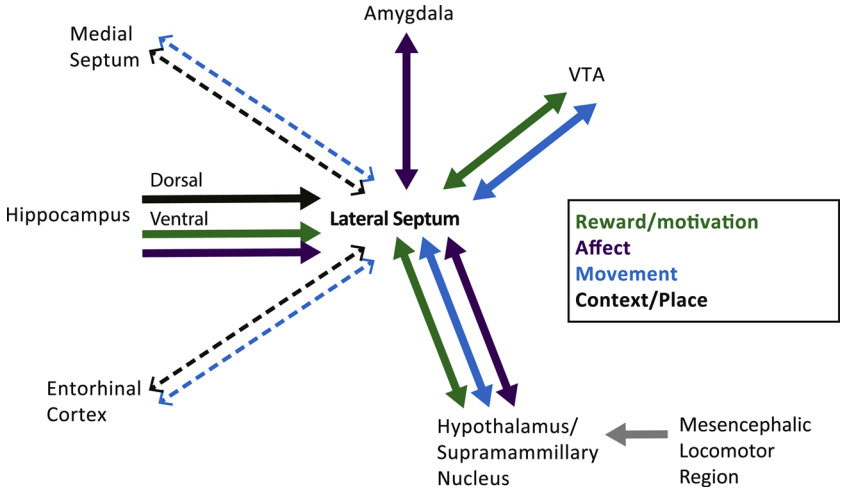

Fig. 2. The major inputs are functionally diverse and are important for different aspects of motivational behavior.
Partial connectivity diagram of major LS inputs. Arrows show if connection is input only or bidirectional. Arrow color signifies category of information that the structure provides the LS, although we appreciate the categories are not entirely distinct. Dotted lines signify debated projections. Grey arrow represents indirect LS connection. Spiking and LFP correlates of reward, affect, movement, and place can be found in the LS and are likely derived, at least in part, from the structures diagramed here.

valence processing are intertwined with and related to the system's function in movement and navigation. We will discuss how the hippocampal system represents place and movement, and how movement may be affected by emotional and cue processing in detail below.

3. current theories

Prominent contemporary theories of LS function primarily fall into two groups: those implicating the LS in emotional and affectual processing, mainly in regards to anxiety, and those implicating the LS in movement and/or spatial processing (Table 1). The idea of the LS having a prominent role in anxiety was advanced by J.A. Gray's seminal 1982 work, which proposed a model in which the septohippocampal system is a primary modulator of anxiety-related behaviors. In this theory, the septohippocampal system reflects anxiety caused by mismatches between actual sensory events and predicted events, and LS lesions are anxiolytic (Gray, 1982; Gray and McNaughton, 1983). However, multiple experiments have shown that LS lesions can additionally increase fear- and anxiety-related behaviors (Blanchard et al., 1979; Brady and Nauta, 1953, 1955; Wong et al., 2016). This led Thomas, in 1988, to propose that the LS is actually involved in the suppression of emotionally aversive states (Thomas, 1988). While functional anatomy of the LS, including connections with the amygdala and hypothalamus, suggest LS involvement in anxiety, and an extensive body of work has been completed in the past decades showing the LS's involvement in affective processing (Anthony et al., 2014; Chee et al., 2015; Degroot and Treit, 2004; Engin et al., 2016; Guzman et al., 2013; Lamontagne et al., 2016; Le Merrer et al., 2006; Lee and Gammie, 2009; Leroy et al., 2018; Melia et al., 1992; Menard and Treit, 1996; Parfitt et al., 2017; Pesold and Treit, 1992; Singewald et al., 2011; Treit and Pesold, 1990; Trent and Menard, 2010; Yadin and Thomas, 1996; Yadin et al., 1993) (for an excellent review see (Sheehan et al., 2004)), it remains unresolved how and in what way the LS modulates emotional states.

The most commonly studied potential neural correlate for anxiety in the LS is the theta rhythmic modulation of LS activity (Chee et al., 2014, 2015; Engin et al., 2016; Gray et al., 1977; Korotkova et al., 2018).

Although theta rhythm is complex in its presentations (Kramis et al., 1975; Vanderwolf et al., 1977), it is, broadly defined, a prominent 5−12 Hz oscillation often reflected in the local field potential and in the modulation of neural spiking in the hippocampus and some cortical and subcortical regions. Theta rhythm is present during a number of specific behavioral states, including locomotion, other voluntary movements, and rapid eye movement (REM) sleep (Jouvet, 1967; Kudrimoti et al., 1999; Louie and Wilson, 2001; Poe et al., 2000; Vanderwolf and Heron, 1964; Whishaw and Vanderwolf, 1973). Because theta is often elevated during periods of high anxiety, it is frequently used in conjunction with behavior to measure anxiety levels (Hsiao et al., 2013; Korotkova et al., 2018; Mikulovic et al., 2018; Pape et al., 2005; Sainsbury et al., 1987a, b; Whishaw, 1972).

The presence of theta in the LS is evidence for both the affectual theory of LS function and the idea that the LS plays an important role in movement and/or spatial processing. Multiple studies have shown a role for the LS in the regulation of theta and locomotion (Bender et al., 2015; Monaco et al., 2019; Tsanov, 2018; Wirtshafter and Wilson, 2019), but it is unclear whether lesions of the LS cause hyper- or hypo- activity, or if they even have an effect on general activity level (Albert and Richmond, 1976; Gage et al., 1978; Grossman, 1977; Kohler and Srebro, 1980; Myhrer, 1989; Pesold and Treit, 1992; Sagvolden, 1976; Taghzouti et al., 1986; Zucker, 1965). It has been proposed that the LS may control the regularity of locomotor speed, via effects on theta rhythm, rather than the speed of locomotion (Bender et al., 2015; Tsanov, 2018) (Fig. 3b). However, the LS interaction with locomotion is more complex than speed regulation, as animals with LS lesions can conditionally display highly regulated behaviors as well as behavioral perseverance (Dalland, 1974; Pesold and Treit, 1992; Singewald et al., 2011; Thomas, 1972).

In concert with movement processing, multiple studies have suggested that the LS links context with reward, an intuitive hypothesis given the LS's anatomical location between the hippocampus and multiple regions considered part of the classic reward system of the brain (Jiang et al., 2018; Le Merrer et al., 2007; Luo et al., 2011; Sotomayor et al., 2005; Vega-Quiroga et al., 2018; Wirtshafter and Wilson, 2020). However, these hypotheses and results fail to account for the LS's obvious effect on and responsiveness to movement and affect. We will attempt to reconcile these different hypotheses of LS function below.

4. LS role in mood

In relation to mood, the LS system has been primarily studied in the context of the regulation of anxiety, although additional studies have implicated the LS in regulating a variety of other affects and moods, including fear, rage, depression, and even sexual responsiveness. However, there is little consensus as to whether the LS positively or negatively regulates most of these states. For instance, a large body of lesion and pharmacologic studies have posited that LS-lesioned animals show lower levels of anxiety and LS stimulated animals show higher levels of anxiety, and thus that the LS is anxiogenic (Menard and Treit, 1996; Pesold and Treit, 1992; Trent and Menard, 2010). However, a similarly large body of work has contended that LS lesioned animals, or animals with GABA-antagonists injected into the LS, have higher levels of anxiety, and that the LS is thus required for anxiolysis (Degroot et al., 2001; Yadin et al., 1993) Table 1. As explained in this section, these seemingly contradictory views are reconcilable if one accepts the hypothesis that the LS is involved in evaluating changes in valence as the result of movement, and an LS-lesioned animal is apt to respond incorrectly to many situations requiring context-action pairing, including by showing situationally inappropriate locomotor and movement responses (such as licking during a lick suppression test or exhibiting aggression towards a previously unthreatening target).

We posit that many effects of LS disruption attributed to affective states are the result of disruptions in LS contextual interpretation of movement, which then drive inappropriate motor responses downstream. These responses may additionally explain the tendency for LS-lesioned animals to be hyperactive (Albert and Wong, 1978), and may explain the conflict in the literature over whether LS-lesioned animals are hyperaggressive or hyperdefensive (Albert and Wong, 1978; Gage et al., 1978; Grossman, 1977). We will use this section to discuss how LS disruption may explain contradicting results related to different affects.

4.1. The regulation of anxiety and theta rhythm by the LS

Theta modulation of activity has been associated with the processing and encoding of information (Foster and Knierim, 2012; Foster and Wilson, 2007; Hasselmo and Stern, 2014; O'Keefe and Recce, 1993; Siegle and Wilson, 2014; Tingley and Buzsaki, 2018), and changes in theta-rhythm frequency and amplitude have been associated with changes in anxiety and arousal. Because theta rhythm can be present in situations of anxiety or arousal, such as during fear conditioning or approach by a predator, there may be a link between hippocampal theta modulation and fear or anxiety modulation (Hsiao et al., 2013; Korotkova et al., 2018; Mikulovic et al., 2018; Pape et al., 2005; Sainsbury et al., 1987a, b; Whishaw, 1972) (Fig. 3b). Theta coherence, in which theta is synchronized between different brain regions (Fig. 3c) is believed to coordinate communication between brain regions (Hasselmo, 2005; Jones and Wilson, 2005; Siapas et al., 2005; van der Meer and Redish, 2011; Wirtshafter and Wilson, 2019), and disruptions in theta coherence between the hippocampus and associated areas have been implicated in anxiety (Adhikari et al., 2010, 2011; Jacinto et al., 2016; Lesting et al., 2013, 2011; Narayanan et al., 2007; Seidenbecher et al., 2003), although we could find no studies that examined HPC-LS coherence during anxiety.

One way in which it has been suggested to modulate anxiety is via manipulations of theta rhythm. It has been argued that all effective anxiolytic agents, including barbiturates, SSRIs, and benzodiazepines (but not antipsychotics or sedatives) cause a reduction in theta frequency (McNaughton and Coop, 1991; McNaughton et al., 2007; Wells et al., 2013). Curiously, many anxiolytic drugs work on different pharmacological ($GABA_A$, $5\text{-}HT1_A$, serotonin, etc.) and therefore anatomical targets, and their only commonality besides reduction of anxiety is dose-dependent reduction of theta frequency (McNaughton and Coop, 1991; McNaughton et al., 2007). In corollary, increased theta rhythm frequency during running, in serotonin receptor knockout mice, is correlated with higher levels of anxiety (Gordon et al., 2005).

If a reduction in theta frequency is a cause of anxiolysis, and increases in theta are correlated with higher levels of anxiety, we would expect to see that other perturbations that change theta frequency would additionally result in changes in anxiety levels. (The mechanism by which theta may modulate anxiety remains unclear, although it is hypothesized to potentially involve the nucleus incertus; see Korotkova et al., 2018 for a review.) While this has been consistently shown in the HPC and MS (Bannerman et al., 2004; Carpenter et al., 2017; Degroot et al., 2001; Lamprea et al., 2010; McEown and Treit, 2013; Menard and Treit, 1996; Pesold and Treit, 1992; Torras-Garcia et al., 2003; Zhang et al., 2017), perturbations of the lateral septum do not result in such a straightforward effect. Furthermore, in the LS, treatments have been found which dissociate changes in theta rhythm and anxiety, causing a decrease in anxiety but an increase in hippocampal theta frequency (Chee et al., 2014; Shin et al., 2009).

Because the mechanism by which theta may modulate anxiety remains unclear, it is additionally unclear why some anxiolytics would be theta-correlated and others not. It has been suggested that anxiety is functionally segregated within the LS, and that anxiety modulation in some areas of the LS is coupled with a reduction in theta frequency, while in other areas it is not (Degroot and Treit, 2004; Sheehan et al., 2004). It is possible that there is a dose-dependent effect with different pharmacological agents (Drugan et al., 1986), wherein some doses may affect theta rhythm while others do not. Finally, the results may be explained because it is possible that theta rhythm is confounded with processes or behaviors that often, but not always, coincide with anxiety,

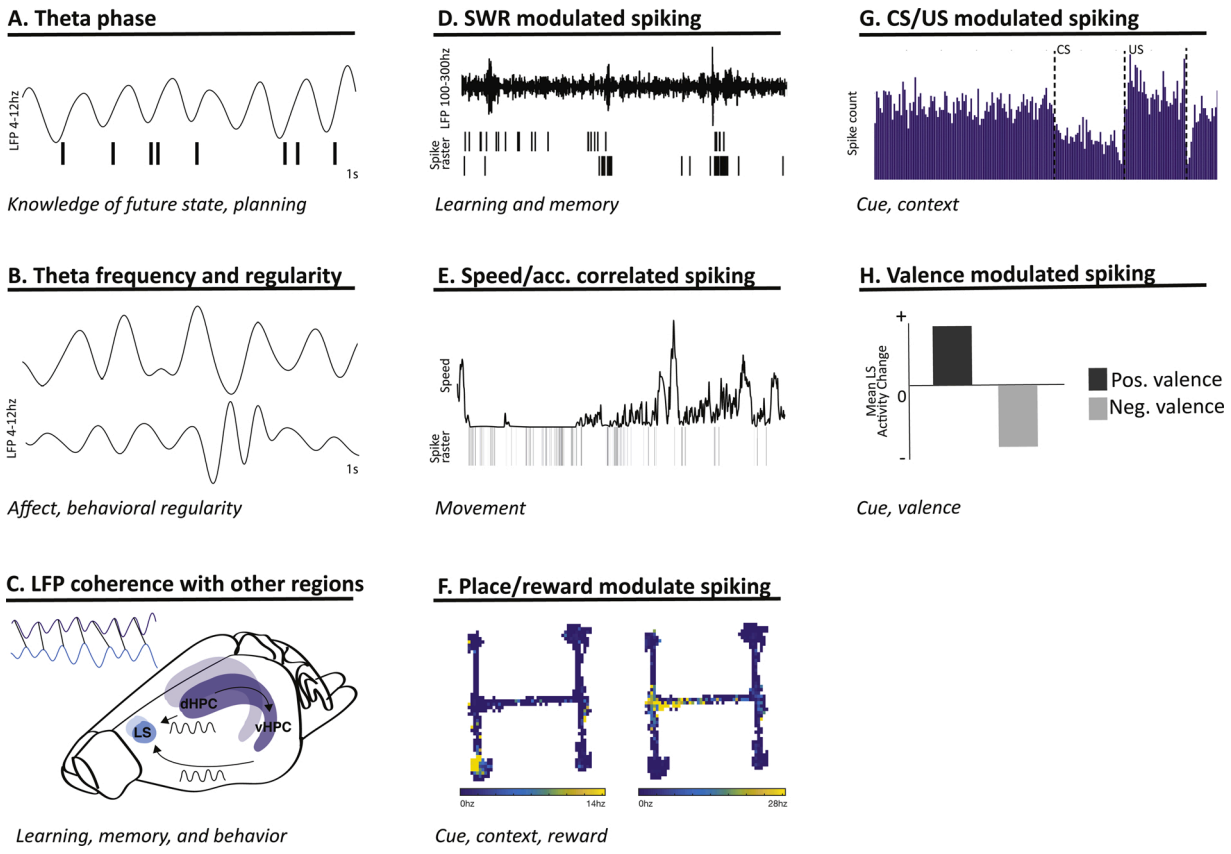

Fig. 3. Cellular and LFP correlates of information represented in the LS. The LS may represent different behavioral considerations through changes in LFP properties (left column) and firing rate (middle and right columns).

a. The LS is able to regulate theta phase coding, including preferred firing phase of LS cells, and cells exhibit phase precession (Monaco et al., 2019; Tingley and Buzsaki, 2018; Wirtshafter and Wilson, 2019). Phase information may be used to evaluate immediate information, such as reward gradients, and to plan future trajectories or movements (Foster and Knierim, 2012; Frank et al., 2000; Lisman and Redish, 2009; Olafsdottir et al., 2015; Pfeiffer and Foster, 2013; van der Meer and Redish, 2011), and may additionally be used to compute speed and acceleration correlates.

b. Changes in theta frequency have been correlated to changes in affect, although the connection between theta frequency and anxiety in the LS remains unclear (Chee et al., 2014, 2015; Engin et al., 2016; Korotkova et al., 2018). Regularity of theta rhythm in the LS has been shown to regulate regularity of locomotor activity (Bender et al., 2015; Tsanov, 2018). Multiple studies have shown a role for the LS in the regulation of theta and locomotion (Bender et al., 2015; Monaco et al., 2019; Tsanov, 2018; Wirtshafter and Wilson, 2019), but it is again unclear whether lesions of the LS cause hyper- or hypo- activity, or if they even have an effect on general activity level (Albert and Richmond, 1976; Gage et al., 1978; Grossman, 1977; Kohler and Srebro, 1980; Myhrer, 1989; Pesold and Treit, 1992; Sagvolden, 1976; Taghzouti et al., 1986; Zucker, 1965).

c. Theta rhythm coherence is believed to coordinate interactions between the HPC and extrahippocampal areas (Hasselmo, 2005; Jones and Wilson, 2005; Siapas et al., 2005; Wirtshafter and Wilson, 2019), and increased theta coherence between the HPC and LS has been observed during hippocampally-dependent tasks (Wirtshafter and Wilson, 2019). This coordination may extend to other areas down and upstream of the LS, such as the to the amygdala (Lesting et al., 2013; Seidenbecher et al., 2003).

c. It has been suggested that hippocampal replay, which occurs during sharp wave ripples (SWRs) in wake and sleep, is used to plan trajectories and in memory consolidation (Csicsvari et al., 2007; Foster and Wilson, 2006; Ji and Wilson, 2007; Louie and Wilson, 2001). Cells in the LS (Wirtshafter and Wilson, 2019) increase firing during SWRs at latency that would be expected based on a HPC to LS to VTA pathway (Gomperts et al., 2015; Wirtshafter and Wilson, 2019). The LS may therefore be transmitting spatial, motivational, and movement related signals to the VTA during SWRs, which may then be used in learning and memory.

d. Firing rate of LS cells is linearly correlated with the animal's speed and/or acceleration during movement (Wirtshafter and Wilson, 2019).

e. Place-like cells have been observed throughout the entirety of the LS (Bezzi et al., 2002; Kita et al., 1995; Leutgeb and Mizumori, 2002; Nishijo et al., 1997a; Takamura et al., 2006; Wirtshafter and Wilson, 2019, 2020; Zhou et al., 1999) and LS place fields are biased towards rewarded locations (Wirtshafter and Wilson, 2020).

f. Cells in the LS change firing rate to the CS and US in a variety of conditioning tasks (Berger and Thompson, 1977; Kita et al., 1995; Nishijo et al., 1997b; Thomas et al., 1991; Wirtshafter and Wilson, 2019; Yadin and Thomas, 1981), which may be integrated into cue and contextual representations for downstream decision making.

g. There is evidence that LS firing response may be valence dependent, with cells increasing firing to stimuli with positive valences and decreasing firing to negative valences (Yadin and Thomas, 1981).

such as respiratory rhythm (Tsanov et al., 2014).

If, in the LS, reductions in anxiety are not dependent on changes in theta rhythm, could these reductions be tied to a specific function of the LS as anxiolytic or anxiogenic? This, too, appears unclear. A number of studies contend that animals with LS-lesions show lower levels of anxiety and reduced fear behaviors and that, as a corollary, LS stimulated animals show higher levels of anxiety and increased fear behaviors (Anthony et al., 2014; Degroot et al., 2001). While these studies imply the LS is anxiogenic, in other studies, LS lesioned animals have higher levels of anxiety and perform more fear behaviors, and LS stimulation

causes a reduction in anxiety (Parfitt et al., 2017; Yadin et al., 1993). These studies would suggest the LS is anxiolytic. In support of this view, LS lesioned animals exhibit "septal rage," marked by increased aggressiveness, hyperactivity, and hyperdefensive behaviors (Albert et al., 1978; Albert and Richmond, 1976; Albert and Wong, 1978).

If the LS is, in and of itself, not anxiogenetic or anxiolytic, it may be modulating

anxiety indirectly in a way allowing for either anxiolytic or anxiogenic responses depending on the details of the experimental situation. As discussed, reductions in anxiety can be achieved with either an increase or decrease in hippocampal theta (Chee et al., 2014, 2015), suggesting that it is possible to decouple theta rhythm from anxiolysis. LS theta rhythm has been linked with a modulatory effect on locomotion (Bender et al., 2015). We suggest that the lateral septum is actually responsible for evaluating changes that occur during movement, which may result in differing anxiogenic or anxiolytic responses depending on context.

4.2. The LS and other "moods"

In a broad comparison of hippocampal and LS lesions, the biggest differences occur in comparisons of affective behavior (Gray and McNaughton, 1983). Animals with LS lesions or pharmacologic inactivations show many changes in affect and emotionality not seen in hippocampally lesioned animals (Gray and McNaughton, 1983; Lee and Gammie, 2009; Sheehan et al., 2004; Wong et al., 2016). Additionally, LS lesioned rats show changes in activity level and reactivity, not seen in HPC lesioned animals (Treit and Pesold, 1990).

Similar to LS research on anxiety, there are inconsistent or contradictory data linking the LS to a number of other affective states. For example, antidepressants and antipsychotics both increase LS c-Fos activity (Nomikos et al., 1997; Semba et al., 1996; Wan et al., 1995; Yanagida et al., 2016), but have opposing behavioral effects during forced swim (Molina-Hernandez et al., 2012; Weiner et al., 2003). Another seemingly contradictory result is that LS damage causes hypersexual behavior (Cavazos et al., 1997; Gorman and Cummings, 1992), suggesting that the destruction of the LS disinhibits sexual urges, but sexually arousing cues can also cause LS activation (Ferris et al., 2004; Pfaus and Heeb, 1997; Pfaus et al., 1993). There is additional debate as to whether rats with septal rage symptoms are displaying hyperdefensive or hyperaggressive behaviors (Albert et al., 1978; Albert and Richmond, 1976; Albert and Wong, 1978; Blanchard et al., 1979; Chee et al., 2015), and the conclusion may differ based on the exact type of perturbation performed (Clarke and File, 1982; Hakvoort Schwerdtfeger and Menard, 2008; Lamontagne et al., 2016; Leroy et al., 2018; Wong et al., 2016).

The extreme reactivity seen during septal rage fits with a broader common pattern of decreased behavioral inhibition and heightened activity and reactivity in LS lesioned animals (Ellen and Powell, 1962; Grossman, 1977). Consistent with these observations, animals with LS lesions performed before task training have trouble withholding behavioral responses on water lick suppression tests. This response is often attributed to lower levels of anxiety in these animals, despite that animals actually lick less if the lesions are performed after task acquisition (Fox et al., 1964; Kaada et al., 1962; Yadin et al., 1993). We posit that decreased inhibition and increased reactivity may not be related to anxiety levels at all, but rather linked to the LS's role in evaluating task-relevant changes in context that occur during movement, as discussed below. If the LS is not directly involved in anxiety modulation but instead in context and movement evaluation, perturbations of the LS may cause dysregulation of an animal's response, including exaggerated or subdued behaviors, depending on the exact context and perturbations. This interpretation would explain the discrepancies in results regarding whether the LS is anxiolytic or anxiogenic, as well as discrepancies in whether these animals are hyperdefensive vs. hyperaggresive and hyperactive vs. hypoactive.

5. LS role in locomotor movement & navigation

As we have previously reported, the lateral septum contains cells whose firing rates correlate with acceleration and/or speed (Fig. 3e), and these correlations are not driven by the hippocampus or hippocampal theta rhythm (Wirtshafter and Wilson, 2019). The LS does, however, have numerous direct connections (both efferent and afferent) with structures that display movement-correlated activity, including the lateral preoptic area, which may modulate locomotion (Sinnamon, 1993; Subramanian et al., 2018) and the hypothalamus and supramammillary nucleus, which may be involved in arousal and the expression of voluntary movement (Jones, 2003; Risold and Swanson, 1997b; Sinnamon, 1993). Additionally, the LS has indirect connections with the MLR (Risold and Swanson, 1997b) (Fig. 2), which is involved in the initiation and control of movement (Garcia-Rill et al., 1983; Noga et al., 2017; Ryczko et al., 2017). It has been demonstrated that MLR contains cells whose firing rate is modulated by velocity (Ryczko et al., 2017), much in the way LS cells are.

It has been proposed that the LS's modulation of theta may be used to control the regularity of running speed (Bender et al., 2015; Tsanov, 2018). However, given that animals can display well-modulated behavior with a damaged LS and given the strong association between theta and anxiety modulation, it is likely that the LS's role is more complicated that this suggestion. Rather, the LS speed and acceleration signal may be weighted or modified depending on the movement requirements of the task.

There are compelling functional reasons why speed and acceleration may be communicated to the LS separately from hippocampal input and theta rhythm. In the hippocampus, the phase at which a cell fires during theta can communicate information about the current, prospective, or retrospective spatial location. For instance, during theta precession, firing of individual HPC place cells begins on a particular phase of theta rhythm and progressively shifts forward as the animal moves through the place field, a process termed theta phase precession (Foster and Wilson, 2007; Mizuseki et al., 2012; O'Keefe and Recce, 1993). In addition, populations of hippocampal place cells can fire in theta sequences: ordered place cell sequences that occur during theta (Foster and Wilson, 2007; Wang et al., 2020). Theta sequences and phase precession are thought to contribute to prospective or future state decoding used in planning (Foster and Knierim, 2012; Frank et al., 2000; Olafsdottir et al., 2015; Pfeiffer and Foster, 2013). There is evidence that LS cells have firing phase preferences (Monaco et al., 2019; Tingley and Buzsaki, 2018; Wirtshafter and Wilson, 2019) and exhibit theta precession (Tingley and Buzsaki, 2018) (Fig. 3a), and thus may exhibit prospective coding. This coding may be used to integrate movement and value signals over a short period of time, such as to make an immediate cost-benefit analysis or evaluate reward gradients at choice points (Lisman and Redish, 2009; van der Meer and Redish, 2011). Using prospective coding to plan or evaluate movement is supported by the evidence that speed coding in the LS slightly precedes actual movement (Wirtshafter and Wilson, 2019). Additionally, because theta is believed to coordinate interactions between the HPC and extrahippocampal areas (Hasselmo, 2005; Jones and Wilson, 2005; Siapas et al., 2005; van der Meer and Redish, 2011; Wirtshafter and Wilson, 2019), theta phase coordination may be used to pass information about future state to the lateral septum (Fig. 3a,c,e).

5.1. Movement information in the LS contributes to navigational strategies

Although spatial information is present in the LS, different LS perturbations and different types of testing result in spatial deficits of

different magnitudes and types. Animals lesioned after acquiring an alternation task are able to maintain alternation levels only if the alternation is rewarded (Thomas, 1979). Lesions of the precomissural fornix, which is the pathway by which the HPC innervates the septum, cause similar deficits in alternation tasks, but the animals are largely able to recover during a rewarded task (Thomas, 1978). Because animals given LS lesions are able to recover back to pre-lesion levels of performance on rewarded tasks, animals may be switching task strategies to compensate for the deficits caused by the lesion.

Suggestively, LS-lesioned rats perform no worse than controls in a task that does not require route memory or path integration. In an elegant experiment performed by Rawlins and Olton rats were trained on an alternation task where the rat first ran down the arm of a T-maze, and then had to select the opposite arm to run down in order to get rewarded (Rawlins and Olton, 1982). As predicted from previous experiments, rats with LS lesions performed worse than controls but improved over time (although a minority reached criterion and it took them double the amount of time to learn as control rats). In a subsequent experiment, instead of rats being allowed to choose the first arm to run to, rats were placed in the initial arm. They then had to remember that arm location and select the opposite arm to be rewarded. Both control rats and lesioned rats were worse at this task than the task where animals were allowed to run to the initial arm. However, surprisingly, lesioned animals were no worse at this task than control animals (Rawlins and Olton, 1982). In other words, lesioned animals showed deficits on a task where they were able to use a strategy incorporating self-motion and route cues (egocentric navigation), but were comparable to controls when the only available strategy was to remember a specific location (allocentric navigation).

These deficits and the recovery seen in lesioned animals during spontaneous alternation suggest that lesioned animals are over-reliant on an allocentric strategy of navigation. Consistent with this idea, animals with LS lesions perseverate during alternation using "perseveration of places," such as perseveration based on intra- and extra-maze cues and scent trails. This suggests that external places are overweighed in animals with LS lesions (Dalland, 1970; Gray and McNaughton, 1983; Thomas, 1972). (This is in contrast to animals with hippocampal lesions, which may be over-reliant on path navigation and allocentric navigation strategies, and display a "perseveration of body turns" (Dalland, 1970; Gray and McNaughton, 1983; Lash, 1964)). This idea is borne out further based on the finding that animals with LS lesions perseverate based on contextual cues in an X-maze, rather than based on body turns or sensorimotor responses (Thomas, 1972).

The initial deficits in alternation seen after lesions, coupled with behavioral recovery, could be the animal switching from a primarily egocentric or path integration-based navigational strategy to a primarily relational, allocentric strategy. This switch from an egocentric strategy after LS lesions may be required in order to compensate for a loss of movement-related information after LS lesions, further supporting the importance of movement-related information in the LS.

6. LS role in space & context

6.1. The LS represents contextual associations during navigational and non-navigational tasks

Current theories of spatial representation in the LS are primarily in agreement that the LS is used to link context with rewarded or 'punished' outcomes (Jiang et al., 2018; Leutgeb and Mizumori, 2002; Luo et al., 2011; McGlinchey and Aston-Jones, 2018). However, the exact function of the LS in this pathway, and the reconciliation of these results with the idea that the LS has a modulatory role on movement, has been minimally investigated. We suggest that the hippocampus is used to make a representation of a context that can be then associated with a stimulus, and that this association can then be used in evaluation of the behavioral responses by a structure outside of the hippocampus, such as the LS. We will expand on this idea below.

Both the CA1 and CA3 regions of the hippocampus contain place cells that fire when the animal is in a specific location (Eichenbaum et al., 1999; Mizuseki et al., 2012; O'Keefe and Dostrovsky, 1971; O'Keefe and Nadel, 1978), and the firing of these place cells can be used to map an animal's location and trajectory (Davidson et al., 2009). In the HPC, these spatially modulated cells are additionally necessary for a variety of navigational tasks (Gray and McNaughton, 1983; Jarrard, 1993; McNaughton et al., 1989; Olton et al., 1978).

While cells with spatially-specific firing fields ('place-like cells') are found in the LS (Fig. 3f), the number of place fields reported in the LS varies in different studies, with results showing that between 15 % and 55 % of cells in the lateral septum have spatially selective firing (Bezzi et al., 2002; Kita et al., 1995; Leutgeb and Mizumori, 2002; Nishijo et al., 1997a; Takamura et al., 2006; Wirtshafter and Wilson, 2019; Zhou et al., 1999). (A single study found no place-like cells; we presume this result stems from a difference in sampling (Tingley and Buzsaki, 2018)). Analysis of other firing parameters, such as theta locking and responsiveness to sharp-wave ripples (SWRs), strongly suggested that these place-like cells were hippocampally derived (Wirtshafter and Wilson, 2019).

Given that the place-like cells in the LS are hippocampally derived, the hippocampus is likely providing task-dependent spatial information to the LS during non-navigational tasks. There is ample evidence that the hippocampus and LS both modulate firing rate for a variety of stimuli during a variety of conditioned tasks: For example, in associative conditioning tasks, HPC and LS units both change firing rates upon presentation of the conditioned stimulus during conditioning (Berger et al., 1976, 1983; Berger and Thompson, 1977, 1978; Wirtshafter and Wilson, 2019). It is hypothesized that the HPC is involved in providing contextual information to downstream structures such as the LS (Carreter-o-Guillen et al., 2015; Frohardt et al., 2000; Penick and Solomon, 1991).

The connection from the HPC to the LS, consisting of glutamateric projections arising in the CA fields, plays a prominent role in contextual fear conditioning. Pharmacologic manipulations of LS glutamate levels and electrical manipulations of glutamatergic fibers from the HPC to the LS change animals' response to conditioned freezing, with glutamate infusions and fimbria stimulation disrupting freezing during contextual conditioning (while glutamate infusions promote freezing during tone conditioning) (Calandreau et al., 2010; Vouimba et al., 1998). Opposite effects were seen with the infusion of glutamate agonists (Calandreau et al., 2010). This suggests that conditioning may be modulated by the connection between the HPC and LS and that the LS is necessary for contextual associations (Calandreau et al., 2007; Leutgeb and Mizumori, 2002; Luo et al., 2011).

The LS may contribute to contextual associations by over-representing task relevant contextual information. We recently reported that the fields of place-like LS cells are located more proximally to reward than hippocampal place cells (Wirtshafter and Wilson, 2020) (Fig. 3f). We suggested several circuit level mechanisms for this finding; most consistent with previous results was the idea that inputs from place cells coding for rewarded locations are prioritized over competing inputs, such as speed information from brainstem regions, while non-reward-related place cells are not prioritized (Wirtshafter and Wilson, 2019, 2020). This model would explain the smaller proportion of place-like cells in the LS compared to the HPC, as well as how the LS has more reward-related fields. Consistent with this model is the finding that LS non-place-like cells were several times more likely to contain movement-correlated firing than LS place-like cells (Monaco et al., 2019; Wirtshafter and Wilson, 2019).

This overrepresentation of reward locations in the LS may reflect the LS's emphasis of locations highly relevant for task performance and the

LS's ability to attach value to a cue. This idea has support in both non-spatial and spatial tasks: in non-spatial conditioning tasks, LS cells changed firing to the conditioned stimulus (Thomas et al., 1991; Wirtshafter and Wilson, 2019; Yadin and Thomas, 1981). Similarly, while recording from monkey LS during place-dependent and object-decimation go/no-go tasks, experimenters found place-differential LS neurons with contingency-differential responses (Kita et al., 1995; Nishijo et al., 1997b), with some LS cells responding only to correct place-object associations (Kita et al., 1995). Importantly, the place-differential responses in the LS could predict the animals' behavioral performance (Nishijo et al., 1997b).

However, focusing on the LS's role in contextual pairing, specifically of a stimulus and its valence, ignores the fact that LS-lesioned animals often present the 'correct' contextual response, but either display the behavior too frequently or display an exaggerated version of it (Sagvolden, 1976; Vouimba et al., 1998). This suggests that the LS may be fundamental in pairing the association with both the correct motor output and the correct timing or frequency of this motor output. The LS may accomplish this pairing by integrating incoming signals for reward, movement, future states, and context. This integration results in a firing rate signal in the LS which may reflect the value of potential movements. This value signal can be used to inform downstream responses. The failure of this integration may result in an inappropriate motor response, including the incorrect evaluation of movement-related responses to cue, as will be explained below.

6.2. *The lateral septum is important for matching context with behavior*

The septohippocampal system's role in contextual processing may indicate a broader role for the LS in motivational processes, including during exploration. We suggest that the LS is likely using contextual information to inform task-related goal directed behavior, and that many of the deficits seen in animals with LS lesions result from the inappropriate pairing of context and movement response.

Animals with non-specific septal lesions, including lesion that encompass the LS and MS, are unable to withhold responses on a variety of tasks, such as fixed interval conditioning, extinction trials, reversal learning, and go/no-go tasks (Ellen and Powell, 1962; Gray and McNaughton, 1983; Grossman, 1977). Animals given LS lesions before task acquisition are unable to normally suppress licking in a water lick suppression test (Fox et al., 1964; Kaada et al., 1962) and animals with LS lesions show increased reactivity to stimuli, whether the stimuli are neutral or negative (Gray and McNaughton, 1983), as well as profound hyperactivity, and inappropriate motor responses to a variety of tasks (Albert and Richmond, 1976; Albert and Wong, 1978; Gray and McNaughton, 1983). Animals with LS lesions show a decreased relative preference for novel objects, while, simultaneously, overall exploration was increased (Myhrer, 1989) and these examples of hyperactivity and hyperreactivity are unique to LS-lesioned animals (Albert et al., 1978; Gage et al., 1978; Gray and McNaughton, 1983).

The conflicts in whether animals with LS lesions show increased or decreased exploratory behavior do not support a simple interpretation that the LS decreases or increases fear, curiosity, drive, or arousal. Instead, LS may modulate movement control, perhaps through dopaminergic signaling originating in the brainstem (Taghzouti et al., 1986). Given that the LS firing correlates with movement, we suggest that many behavioral deficits and reactions seen with LS lesions are actually a failure of matching the appropriate movement-related response to context. When the septum is damaged and LS coding is disrupted, the animal may make incorrect contextual judgments and behavioral responses. In support of this idea, LS lesioned animals show major impairments when attempting cued navigation and other cued tasks (M'Harzi and Jarrard, 1992) and LS lesions inhibit acquisition of a cued response task during which the LS firing is modulated by a conditioned cue (Yadin and Thomas, 1981).

7. LS role in motivation & goal-directed behavior

Some of the first evidence that the septohippocampal system is involved in motivation and reward was obtained in self-stimulation experiments (Olds and Milner, 1954). In these experiments, which have been replicated in many conditions (Cazala et al., 1988; Terman and Terman, 1975) and species (Oshima and Katayama, 2010; Sadowski and Dembinska, 1973), it was discovered that animals can be trained to perform an operant task with a reward of stimulation to the LS. This effect is not dependent on the induction of theta (Ball and Gray, 1971), although it is interesting that rats tend to bar press for hypothalamic stimulation at particular periods in the theta cycle (Buno and Velluti, 1977). (While animals will also self-stimulate the hippocampal gyrus, it is at levels far below LS stimulation (Ursin et al., 1966)). The septum is additionally involved in the self-administration of addictive substances: The lateral septum, driven by the dorsal hippocampus and/or CA3, mediates context-induced reinstatement of cocaine and morphine seeking (Jiang et al., 2018; Luo et al., 2011; McGlinchey and Aston-Jones, 2018), and rats will self-administer morphine and cocaine into the LS (Cazala et al., 1998; Le Merrer et al., 2007).

The self-stimulation and self-administeration experiments suggest that a possible role for the LS is to evaluate an animal's interaction with rewarding stimuli. Reward- or reinforcement-related information is represented in the LS, through firing rate modulation, in multiple ways. For instance, place-like cell field locations in the LS tend to be highly concentrated around rewarded areas (Wirtshafter and Wilson, 2020). Additionally, cells in the LS can contingently code for reward-related locations and objects (Kita et al., 1995), and LS cells are responsive to both the CS and US during conditioning tasks (Thomas et al., 1991; Wirtshafter and Wilson, 2019; Yadin and Thomas, 1981). (It has been reported that this CS/US firing response is valence-dependent (Yadin and Thomas, 1981).) (Fig. 3g-h). While the source of these signals remains unclear, firing rate increases and decreases during conditioning are hippocampally associated (Wirtshafter and Wilson, 2019), and responses during approach conditioning are similar to responses seen in the nucleus accumbens (Nicola et al., 2004; Wan and Peoples, 2006; Wirtshafter and Wilson, 2019), which is directly innervated by the LS, and innervates the LS through the VTA (Luo et al., 2011; Risold and Swanson, 1997b).

Reward or valence information in the LS may then be integrated with other representations in the LS, such as speed or acceleration. These integrated representations may be used to regulate downstream behavioral response. This idea is supported by the fact that the LS, and to a lesser extent, the hippocampus, is involved in the acquisition and regulation of many ethologically natural reinforcements and behaviors, such as food intake (Jarrard, 1973; Sweeney et al., 2017; Sweeney and Yang, 2015, 2016), sexual behavior (Pfaus et al., 1993; Tsukahara et al., 2014), appetite (Sweeney et al., 2017; Tracy et al., 2001), and thirst (Carey and Procopio, 1974; de Arruda Camargo et al., 2010; Jarrard, 1973). Previous work has identified a pathway from the LS to VTA that regulates behaviors that require context-reward associations, such as cocaine seeking and conditioned place preference (Harasta et al., 2015; Jiang et al., 2018; Luo et al., 2011; Mahler and Aston-Jones, 2012; McGlinchey and Aston-Jones, 2018; Pantazis and Aston-Jones, 2020). The LS to hypothalamius circuit regulates food intake (Sweeney and Yang, 2015, 2016), and is additionally involved in conditioned place preference (Sartor and Aston-Jones, 2012). The hypothalamus and VTA may be receiving, from the LS, an 'integrated movement value signal', which incorporates cue and context (Wirtshafter and Wilson, 2019), to provide a cost and benefit analysis of potential actions and to influence goal-related firing.

Much of the LS's influence on downstream structures may occur by

modulating dopamine levels. It has been suggested that septal activity modulates dopaminergic systems through a GABAergic projection to the VTA, which terminates on GABAergic interneurons which, in turn, inhibit dopamine (DA) cells (Jiang et al., 2018; Luo et al., 2011). As a result of this "GABA-GABA" linkage, septal activation would be expected to disinhibit VTA DA cells. However, the LS's influence on the VTA is not that simple: LS stimulation can cause either an increase or decrease in firing in VTA DA neurons (Maeda and Mogenson, 1981), although it tends to cause an overall increase in VTA DA levels (Vega-Quiroga et al., 2018). The LS is potentially able to positively or negatively modulate the activity of VTA dopamine neurons by a variety of routes (Jiang et al., 2018; Le Merrer et al., 2007; Sotomayor et al., 2005; Swanson and Cowan, 1979; Vega-Quiroga et al., 2018). For example, VTA DA cell activity may be suppressed by direct GABAergic inputs from LS cells, whereas activation of LS projections terminating on inhibitory VTA interneurons may disinhibit DA cells (Jiang et al., 2018; Luo et al., 2011). The latter result might also be expected if LS projections to nucleus accumbens (NAc) suppress the activity of GABAergic NAc cells projecting to VTA DA neurons (Sotomayor-Zarate et al., 2010; Swanson and Cowan, 1979). It is possible that the relative strengths of these stimulatory and inhibitory effects might be influenced by the firing pattern of LS cells. Consistent with this idea, recent work has shown that DA neurons in the LS differentially respond to periods of movement/task engagement, versus non-engagement (Kremer et al., 2020). Because the LS contains DA receptors, and receives a large reciprocal DA input from the VTA (Risold and Swanson, 1997a, b), this circuit may involve a substantial amount of feedback.

The LS may be additionally influencing dopaminergic firing in the VTA and in other regions, such as the NAc, through other pathways. The NAc exhibits similar firing to the LS during conditioning tasks (the predominant response is cue inhibition in both regions (Nicola et al., 2004; Wan and Peoples, 2006)). The LS directly innervates the NAc and has a bidirectional connection to the VTA, which is bidirectionally connected to the NAc (Luo et al., 2011; Risold and Swanson, 1997b). However, DA antagonists injected directly into the NAc do not reduce NAc inhibition to cue (although VTA inactivation does), suggesting the crucial input for cue response is not, in fact, dopaminergic (du Hoffmann and Nicola, 2014; Yun et al., 2004). This leads us to suggest that a primary driver of NAc cue response may come directly from the lateral septum's GABAergic input into the NAc, which may be driven by output, either dopaminergic or GABAergic, from the VTA, combined with hippocampal output, which is modulated by cue and reward. The LS may, therefore, in this way, contribute to reward prediction and response during behavioral and conditioning tasks.

The connection from the HPC to the VTA and other dopaminergic structures through the LS may be used in the planning and execution of action. Both theta sequences, as previously discussed, and hippocampal replay, which occurs during SWRs in wake and sleep, may contribute to trajectory planning and memory consolidation (Csicsvari et al., 2007; Foster and Wilson, 2006; Ji and Wilson, 2007; Louie and Wilson, 2001). Theta-phase spiking correlates and theta-phase locking in the LS (Monaco et al., 2019; Tingley and Buzsaki, 2018; Wirtshafter and Wilson, 2019) may contribute to planning on a short-term time scale, such as at a decision point. Conversely, replay may be used for longer term planning and memory formation. Cells in both the LS (Wirtshafter and Wilson, 2019) and VTA (Gomperts et al., 2015; Martig and Mizumori, 2011; Redila et al., 2015; Roesch et al., 2007; Valdes et al., 2015), increase firing rate during SWRs (Fig. 3d). Dopaminergic VTA cells specifically reactivate during the replay of goal locations (Gomperts et al., 2015) (which may be the result of input from LS place-like cells that are preferentially concentrated around goal locations (Wirtshafter and Wilson, 2020)), and the timing of SWR firing increases in the LS and VTA relative to the HPC occur at about the latency that would be expected based on a HPC-LS-VTA pathway (Gomperts et al., 2015; Wirtshafter and Wilson, 2019). The LS may therefore be transmitting spatial, motivational, and movement- related signals to the VTA during SWRs, and be involved in planning and memory consolidation during periods of quiet wake and sleep.

8. Re-examining the septum: linking the LS to the selection of context-appropriate behavior

The view that the septohippocampal system is the center of spatial cognition is often presented as orthogonal to the idea that the system has an essential role in affective and motivational responses and learning, and vice versa (Table 1). However, an alternative possibility is that having coding for spatial and movement information in the same structures as motivational and mood information is functionally important. The presence of these overlapping populations may allow the septohippocampal system to evaluate value-weighted cues in conjunction with movement cost, or to integrate contextual information with movement information to evaluate the costs and benefits of context-specific behaviors.

The LS's anatomical position downstream from the HPC (providing information about context), and the brain stem (providing information about movement), may allow the LS to integrate context information with movement information to evaluate appropriate context-specific behaviors for use, downstream, in structures that modulate motivation, arousal, and the execution of plans. Therefore, animals with LS lesions are apt to respond incorrectly to many situations requiring context-action pairing, including by showing situationally inappropriate responses, such as an inappropriate locomotor or movement response. Consistent with this theory, animals with LS lesions have problems matching a motor response to an appropriate cue. Not only are they unable to complete cued navigational tasks, but they are unable to withhold responses on a variety of tasks, such as fixed interval conditioning, extinction trials, and go/no-go tasks (Grossman, 1977). Additionally, animals lesioned before task acquisition are unable to suppress licking in a water lick suppression test (Fox et al., 1964; Kaada et al., 1962) and show hyperactivity during fixed intervals (Ellen and Powell, 1962), both examples of an inability to modulate movement as required by the context and task.

The LS may accomplish this evaluation by translating movement, context, cues, and valence into firing rate changes in overlapping LS cell populations. Here, we theorize that a combination of these firing rate changes may serve as a value signal incorporating valence and effortful cost. This 'integrated movement value signal' would allow an animal to weigh the cost or consequence of context-dependent movement with respect to expected reward. If this hypothesis were true, we would expect the LS to contain contextual and/or place information, movement information, and reinforcement-related information, such as reward location and/or object valence. Each of these signals can be found in the LS (Fig. 3) and are integrated in such a way as to provide a potential value signal for downstream areas such as the VTA.

9. Conclusion

Given the convergence of mood, movement, and motivation information in the LS system, it is worth considering whether the LS is a central nexus in the brain for integrating these disparate inputs. In this review, we have discussed the ways in which the lateral septum is involved in processing and representing a number of behaviorally relevant factors, including cue, context, movement, and reward (Figs. 3 and 4). We suggest that many of the functions attributed to the LS, including the modulation of anxiety (Table 1), may instead be related to the LS's function integrating movement signals with different cues and contexts, and that septal damage therefore results in situationally inappropriate movement responses, which appear as heightened or

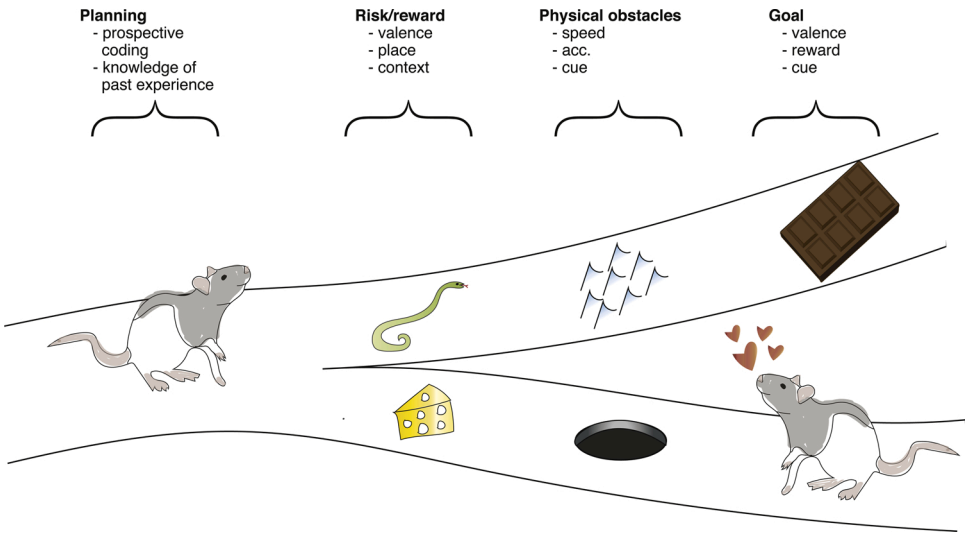

Fig. 4. Integration of task-relevant information in the LS may allow an animal to optimize performance in complex environments with multiple considerations. For instance, in a natural environment, an animal may have to balance risk and physical expenditure, such as passing a predator's den on a strenuous path, with reward, such as the chance to mate or get food. The different routes and places, and their associated obstacles ("cues") and times for traversal can all be represented as cellular correlates in the LS: movement- and place- related signaling would allow the animal to incorporate the speed and time it would take to traverse possible paths, and cue and valence firing could be used to attach relevance and value to possible obstacles along the path. In this example, the rat must choose between two paths, each with multiple rewards and dangers. As explained in Fig. 3, cellular correlates in the LS allow the animal to weigh evaluate the valence, context, reward, and location of each situation, as well as movement considerations (a selection of considerations is listed in the figure). The weighing of the costs and benefits of each context and movement may be integrated in the LS to provide guidance for downstream decisions.

lessened anxiety, aggression, or perseveration. The integration of these factors into a single firing-rate code in the LS may allow for downstream structures to weigh the costs and benefits of action and to optimize task performance across a conjunction of these factors, particularly in complex and ethologically relevant environments with multiple considerations (Fig. 4).

Author contributions

Writing – Original Draft, H.S.W.; Writing – Review & Editing, H.S.W., M.A.W.; Supervision, M.A.W.

Declaration of Competing Interest

The authors declare no competing interests.

Acknowledgements

H.S.W. was supported by the Department of Defense (DoD) through the National Defense Science & Engineering Graduate Fellowship (NDSEG) Program. Thank you to all readers who provided valuable feedback.

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