ROLE OF THE THALAMUS IN MOTIVATED BEHAVIOR

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ROLE OF THE THALAMUS IN MOTIVATED BEHAVIOR

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EDITORIAL
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Editorial: Role of the Thalamus in Motivated Behavior

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Editorial on the Research Topic

Role of the Thalamus in Motivated Behavior

Growing evidence shows that the thalamus, beyond serving as an information relaying center, has key roles in motivated behaviors (Martin-Fardon and Boutrel, 2012; James and Dayas, 2013; Kirouac, 2015; Millan et al., 2017; Huang et al., 2018; Choi et al., 2019; Otis et al., 2019; McNally, 2021). The aim of this Research Topic is to highlight the specific roles of distinct thalamic nuclei in a variety of motivated behaviors. Our collection of 10 articles includes four reviews, one mini-review, one perspective, one hypothesis-and-theory, and three original research papers. Among these, the majority focus on paraventricular thalamic nucleus (PVT, a midline thalamic nucleus), while others highlight rostral intralaminar thalamic nuclei (rILN), posterior intralaminar thalamic nuclei (also known as parafascicular thalamic nuclei, Pf), and mediodorsal thalamus (MD, another midline thalamic nucleus). Taken together, this collection provides evidence that thalamus integrates and processes information within the cortico-striatal-thalamo-cortical circuit to guide salience processing, adaptive controls, cognitive engagement, feeding and drug seeking.

The hypothesis-and-theory by Worden et al. proposes that thalamus functions as a central blackboard in cognition with an emphasis on three distinct thalamic nuclei: pulvinar, MD, and PVT. These nuclei, through their anatomical connections with cortical and other thalamic regions, entrain the cortico-cortical circuitry to take over routine tasks and therefore spare thalamus for engagement in novel tasks. Although empirical data directly corroborating these intriguing views are not yet available, a role of thalamus and its associated circuitry in cognitive and emotional processes is well-documented. The mini-review by Zhou et al. summarizes recent findings on thalamic circuits implicated in reward, pain processing, arousal, attention controls, and adaptive behavior. These thalamic activities (especially those associated with PVT) contribute to both normal (e.g., associative learning) and abnormal (e.g., drug addiction, posttraumatic stress disorder and schizophrenia) salience processing.

In our collection, five articles exclusively focus on PVT. The original research article by Quiñones-Laracuente et al. examined the time-dependent recruitment of pre-limbic (PL) prefrontal inputs onto PVT following auditory fear learning. The authors showed that PL to PVT projections are activated by conditioned stimuli (CS) 7 d, but not 2 h, following learning. In contrast, the PL-amygdala circuit is preferentially recruited 2 h following learning. In addition, unit recordings of Layer VI PL neurons, the origin of projections to PVT, exhibit increased cue-induced inhibition at later, but not earlier, time points. Together, these results suggest that PL signaling of simple fear associations shifts with time toward inhibitory modulation of PVT, which may underlie disinhibition of PVT neurons (via neurons in reticular nucleus of thalamus) and subsequently enhanced central amygdala output.

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The original research article by Matzeu and Martin-Fardon reported that posterior PVT injections of orexin-A peptide promotes reinstatement of extinguished cocaine seeking after intermediate (2–3 weeks), but not protracted (4–5 weeks), abstinence. Intermediate but not protracted abstinence is associated with an upregulation of orexin 2 receptor expression in PVT, while orexin cell numbers increase after both intermediate and protracted abstinence. This work extends previous work on the role of hypothalamic orexin (hypocretin) neurons in PVT in addiction-related behavior (Dayas et al., 2008; Mahler et al., 2014; Matzeu et al., 2016; Ubaldi et al., 2016; James et al., 2017; Matzeu and Martin-Fardon, 2020), and supports emerging evidence linking increased orexin signaling to addiction propensity (Thannickal et al., 2018; Fragale et al., 2019; James et al., 2019; Collier et al., 2020; Pantazis et al., 2020).

Munkhzaya et al. recorded PVT unit activities in rats performing a cue-licking task to determine the involvement of PVT in the predictive vs. incentive information of CS. Neural activity in PVT immediately after CS onset discriminates reward/non-reward association (predictive information) but not reward value (incentive information). In contrast, activity of PVT neurons that fire immediately before reward delivery is correlated with reward value but not predictive information. Together, these data capture the heterogeneity of PVT responses to discrete processes involved in cue-induced motivated behaviors.

PVT is also a regulator of stress (Beas et al., 2018; Dong et al., 2020). Rowson and Pliel provide a timely review on the sex-dependent effects of acute vs. chronic stress on PVT, and outline the implications of this dimorphism for motivated behaviors. Consistent with the idea of PVT as a complex integrator of varied physiological signals, Petrovich elegantly discusses the role of PVT in controling feeding behavior. Petrovich describes a framework whereby PVT integrates homeostatic and hedonic needs to feed with physiological and environmental stress signals, ultimately guiding the balance between food seeking and consumption.

Two reviews focus on ILN, recently implicated in goal-direct behaviors (Bradfield et al., 2013; Bradfield and Balleine, 2017; Li et al., 2018; Cover et al., 2019). Cover and Mathur reveal distinct anatomic, physiologic, and synaptic properties of rILN through comparison with other thalamic nuclei, such as thalamocortical relay nuclei and the Pf. Together with evidence implicating rILN in arousal, pain, executive function, and action control, the authors propose a unique role of rILN in task-dependent behavioral engagement, such as goal valuation based on interceptive and external factors, action learning, expression and reinforcement. Stayte et al. review the function of Pf and orbitofrontal cortex (OFC) in action selection. Further discussion of afferents of each structure leads to the hypothesis that Pf and OFC together contribute to internal state representation during action selection either through direct Pf to OFC projections or convergence of their respective inputs onto striatal cholinergic interneurons.

Finally, Mair et al. discuss the roles of medial prefrontal cortex (mPFC) and individual central thalamic nuclei (e.g., PVT, rILN, and MD) in delayed conditional discrimination tasks through lesion studies in rodents. The authors review electrophysiological findings in MD and mPFC during adaptive goal-directed behaviors, which suggest that MD affects both action and outcome-related neuronal responses in mPFC.

We appreciate these excellent contributions. These articles not only summarize the current findings on the role of individual thalamic nuclei mediating motivated behavior, but also raise intriguing questions about how thalamus exerts these effects. We hope that this issue gives impetus to ongoing work in the field to better characterize the role of thalamus in motivated behaviors and related disorders.

AUTHOR CONTRIBUTIONS

XL and MJ took the lead in writing this editorial. GM contributed to its finalization. All authors contributed to the article and approved the submitted version.

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Rat Paraventricular Neurons Encode Predictive and Incentive Information of Reward Cues

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The paraventricular nucleus of the thalamus (PVT) has been implicated in cue-induced motivated behaviors. Although reward-associated cues (conditioned stimuli, CSs) contain different types of information including predictive information of future reward delivery and incentive (motivational) value of the reward, it remains unknown whether PVT neurons represent predictive and incentive information of CSs. It is suggested that neural activity just after the onset of CSs (early activity) and that just before reward delivery (late activity) might more strongly represent predictive and incentive information, respectively. In this study, rats were trained to lick a tube, which was protruded close to their mouth just after a CS, to obtain a reward (sucrose or water) (cue-induced licking task). Auditory and visual CSs were used: each elemental cue (CS) predicted reward or non-reward outcome, while simultaneous presentation of the two elemental cues (configural cues) predicted the opposite reward outcome. We recorded PVT neurons in the cue-induced licking task, and report that half of the CS-responsive PVT neurons responded selectively to the CSs predicting reward outcome regardless of physical property of the cues (CS^+-selective). In addition, the early activity of the CS^+-selective neurons discriminated reward/non-reward association (predictive information) and was less sensitive to reward value and motivation reflected by lick latency (incentive information), while the late activity of the CS^+-selective neurons was correlated with reward value and motivation rather than reward/non-reward association. Early and late population activity of the CS^+-selective neurons also represented predictive and incentive information of the CSs, respectively. On the other hand, activity of more than half of the PVT neurons was correlated with individual licking during licking to acquire reward. Taken together, the results suggest that the PVT neurons engage in different neural processes involved in cue-induced motivated behaviors: CS encoding to determine reward availability and form motivation for reward-seeking behavior, and hedonic mouth movements during reward consumption.

Keywords: paraventricular nucleus of the thalamus, conditioned stimuli, predictive information, incentive information, seeking behavior

INTRODUCTION

The paraventricular nucleus of the thalamus (PVT) is one of the midline thalamic nuclei. The PVT receives inputs from the subcortical areas related to motivation and emotion including the hypothalamus, amygdala, hippocampus, dorsal raphe, etc. (Hsu and Price, 2009; Li and Kirouac, 2012) and also inputs from the frontal cortex related to higher cognition including the anterior cingulate, prelimbic, and infralimbic cortices (Li and Kirouac, 2012). The PVT, in turn, projects to output regions for motivated behaviors (e.g., the nucleus accumbens) and emotional expression (e.g., central nucleus of the amygdala) (Penzo et al., 2015; Do-Monte et al., 2017; Dong et al., 2017). These anatomical connections of the PVT suggest that the PVT might function as an interface among the converging inputs to modulate motivational action and emotional expression (e.g., Kelley et al., 2005; Haight and Flagel, 2014).

The PVT has been implicated in reward-seeking behaviors. Presentation of cues associated with rewards (palatable food, sucrose, cocaine, ethanol, etc.) increases *c-fos* or Fos expression in the PVT (Brown et al., 1992; Dayas et al., 2008; Igelstrom et al., 2010; Choi et al., 2010; Flagel et al., 2011; James et al., 2011), and modulated Ca^{2+}-fluorescent activity of PVT neurons (Choi et al., 2019; Otis et al., 2019). Lesion or inactivation of the PVT decreases reward-motivated behaviors including reward-anticipatory locomotion, locomotor sensitization to cocaine, conditioned place preference, cue- or cocaine-induced reinstatement of alcohol- or cocaine-seeking behavior, etc. (Nakahara et al., 2004; Hamlin et al., 2009; James et al., 2010; Marchant et al., 2010; Browning et al., 2014; Clark et al., 2017), while activation of the PVT neurons increases instrumental behaviors for sucrose (Labouèbe et al., 2016). These results suggest that the PVT might be involved in the transformation of information of reward-associated cues into reward-seeking motivation.

Behavioral studies suggest that reward-associated cues (conditioned stimuli, CSs) contain at least two types of information (Robinson and Berridge, 1993; Schultz, 2015); predictive information of future reward delivery and incentive (motivational) value of the reward. It has been suggested that neural activity during the initial onset of CSs (early activity) and that just before reward delivery (late activity) might more strongly represent predictive and incentive information, respectively (Fiorillo et al., 2008; Smith et al., 2011). Consistent with this idea, behavioral and neurophysiological studies reported that, when two CSs were serially presented before reward delivery, the first CS (i.e., temporally distant CS) conveyed the predictive value while the second CS (i.e., temporally proximal CS) conveyed the incentive value (Holland, 1977; Tindell et al., 2005; Meyer et al., 2014; Robinson et al., 2019). Furthermore, when a single CS was presented, the onset of CS conveyed the predictive value, while the subsequent CS period conveyed the incentive value (Ahrens et al., 2016).

Two previous neurophysiological studies reported differential neuronal responses during performance of a Pavlovian conditioning task or inhibitory responses to reward omission (Li et al., 2016; Do-Monte et al., 2017), consistent with a PVT role in motivated behaviors. However, it remains unknown how these two types of information are represented in the PVT. The present study investigated the neural representation of this information in the rat PVT by recording PVT neuronal activity in a cue-induced licking task (Oyoshi et al., 1996; Takenouchi et al., 1999; Toyomitsu et al., 2002; Matsuyama et al., 2011). The CSs consisted of both elemental (auditory or visual cues) and configural (simultaneous presentation of the auditory and visual cues) cues. In one case, each elemental CS predicted reward outcome by licking, but simultaneous presentation of those cues (configural stimulus) predicted no reward outcome. In the other case, each elemental CS predicted non-reward outcome, but simultaneous presentation of those elemental CSs (configural CS) predicted reward outcome. Here, we show that the activity of some CS-responsive PVT neurons represents predictive and incentive information of rewards regardless of stimulus sensory modality.

MATERIALS AND METHODS

Animals

Six male Wistar rats (270–330 g; Japan SLC, Inc., Hamamatsu, Japan), were used. The rats were individually housed with free access to water and laboratory chow, where temperature was controlled at 23 ± 1°C on a 12-h light–dark cycle. The rats were treated in accordance with the policies of the National Institutes of Health on the Care of Humans and Laboratory Animals and the guidelines for experimental animals at University of Toyama. The study was approved by the Ethical Committee for Animal Experiments at University of Toyama (Permit No.: A2014MED-37 and A2017MED-16).

Surgery

In accordance with our previous studies (Nishijo et al., 1998; Zou et al., 2017), the head restraint system of Nishijo and Norgren (1990, 1991, 1997) was used. After being anesthetized with an anesthetic mixture of midazolam (2 mg/kg, i.p.), medetomidine (0.15 mg/kg, i.p.), and butorphanol (2.5 mg/kg, i.p.), the acrylic dental cement was built up on the skull and small screws implanted into the skull and molded around the stainless-steel bars placed just above the skull. After the acrylic dental cement cured, these bars were removed, and an antibiotic was administered topically and systematically. These stainless-steel bars were later used as artificial earbars to painlessly hold the acrylic block on the skull in the stereotaxic instrument during a recording session (**Figure 1A**). Finally, a short 27-gage stainless tube, which was used as a reference pin during recording, was stereotaxically implanted in the acrylic dental cement near bregma. The coordinates of the reference pin were calibrated with reference to bregma.

After training in the cue-induced licking task (see section "Task Paradigms and Training"), a hole (diameter: 2.8–3.0 mm) was drilled through the dental cement and underlying skull (A, −1.20 to −3.6 mm from bregma; L, 0.3 mm left and right) for semi-chronic recording from the PVT under anesthesia. The dura

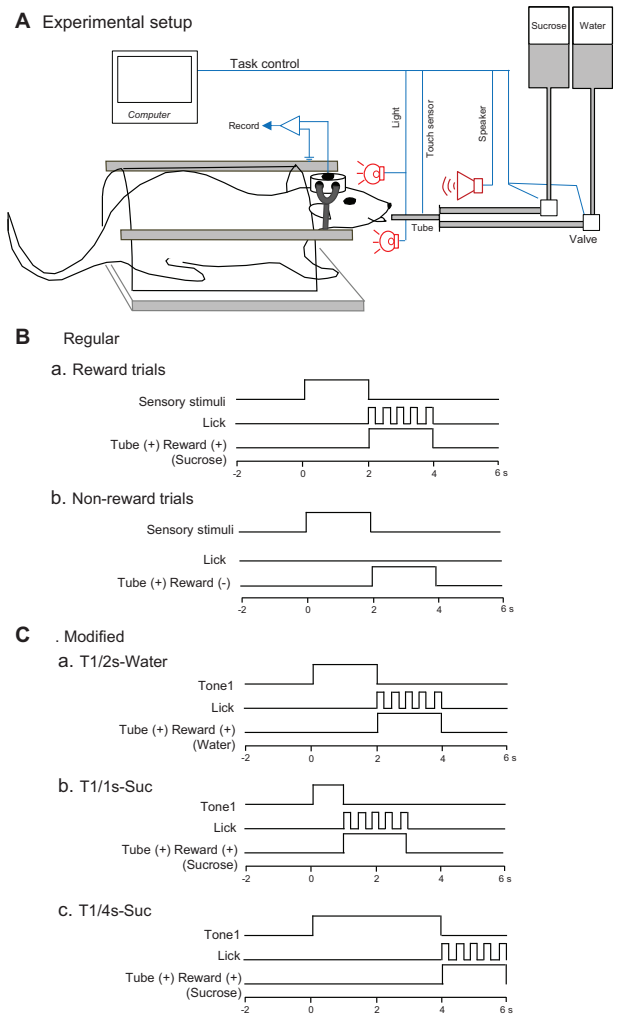

FIGURE 1 | Schema of the behavioral task. **(A)** Experimental set up. Heads of the rats were painlessly fixed in a stereotaxic instrument by artificial earbars. A tube was protruded close to its mouth after the conditioned stimuli (CSs). Licking was detected by a touch sensor signaling tongue contact on the tube. **(B)** Time chart of a regular cue-induced licking task in reward **(a)** or non-reward **(b)** trials. In the reward trials **(a)**, one of the CSs (tone, light, or configural stimuli) associated with reward (sucrose) was presented for 2 s before the tube was placed close to the rat's mouth. In the non-reward trials **(b)**, conditioned sensory stimulus and tube protrusion were similarly presented to the rat. In this situation, a reward solution was not delivered, and the rat usually did not lick the tube. **(C)** Time chart of a modified cue-induced licking task in water **(a)** and sucrose **(b,c)** trials. T1/2s-Water, 2-s Tone1 followed by water; T1/1s-Suc, 1-s Tone1 followed by sucrose; 4-s Tone1 followed by sucrose.

was removed, and a few drops of antibiotics were instilled into the hole. Then, the hole was sealed with a Teflon sheet and epoxy glue. After the rat recovered (5–7 days), it was retrained in the task before recording.

Task Paradigms and Training

Task paradigms and training were essentially similar to our previous studies (Oyoshi et al., 1996; Takenouchi et al., 1999; Toyomitsu et al., 2002; Matsuyama et al., 2011). Briefly, while the heads of the rats were painlessly fixed in a stereotaxic instrument, the rats were trained to lick a tube, which was protruded close to their mouths for 2 s after 2-s CSs, to obtain the 0.3-M sucrose solution or water (**Figure 1A**). The CSs consisted of auditory (2,860 or 530 Hz), visual (white light), and configural (simultaneous presentation of tone and light) stimuli (**Table 1**). Auditory CSs were present from a speaker 50 cm ahead of the rat, and visual CSs, from a white light in front of each eye. In reward trials of the regular cue-induced licking task, the rats licked the tube to obtain a reward (0.3 M sucrose solution or water; **Figure 1Ba**). A 2,860-Hz tone (Tone1), a white light in front of the right eye (Light1), or the simultaneous presentation of a 530-Hz tone and a white light in front of the left eye (Tone2 and Light2, respectively; Tone2 + Light2, configural CS) predicted reward outcome (the 0.3-M sucrose solution). In non-reward trials of the regular cue-induced licking task, Tone2, Light2, or simultaneous presentation of Tone1 and Light1 (Tone1 + Light1: configural CS) predicted no reward outcome (**Figure 1Bb**). In the modified cue-induced licking task, 2-s Tone1 was initially associated with water (**Figure 1Ca**). Then, 1 and 4-s Tone1 were associated with sucrose (**Figures 1Cb,c**).

The rats were initially trained with the CSs associated with and without reward in a block of 15–20 trials in each CS in the regular cue-licking task. Then, the rats were trained with the all CSs in the regular cue-induced licking task, where each CS was pseudo-randomly presented, until performance levels of the rats reached a 90–95% correct rate. Finally, the rats were trained in both regular and modified cue-induced licking tasks, as in the recording sessions (see section "Electrophysiological Recordings"). In this well-trained state, individual lick latencies to the 2-s CSs associated with sucrose were less than 300–500 ms in response to 2-s cues, consistent with previous studies (Oyoshi et al., 1996; Takenouchi et al., 1999; Toyomitsu et al., 2002; Matsuyama et al., 2011). The total number of trials per day in the training session was 200–250. A rat usually ingested 20–30 ml of liquids in the training and recording period. If the rat failed

TABLE 1 | List of conditioned stimuli (CSs) used in the regular and modified cue-induced tasks.

Regular cue-induced licking task	**Reward**
Elemental CSs (2 s)	
Auditory CSs	
Tone1 (2,860 Hz)	Sucrose
Tone2 (530 Hz)	No reward
Visual CSs	
Light1 (right)	Sucrose
Light2 (left)	No reward
Configural CSs (2 s)	
Tone1 + Light1	No reward
Tone2 + Light2	Sucrose
Modified cue-induced licking task	**Reward**
Tone1 (2 s)	Water
Tone1 (1 s)	Sucrose
Tone1 (4 s)	Sucrose

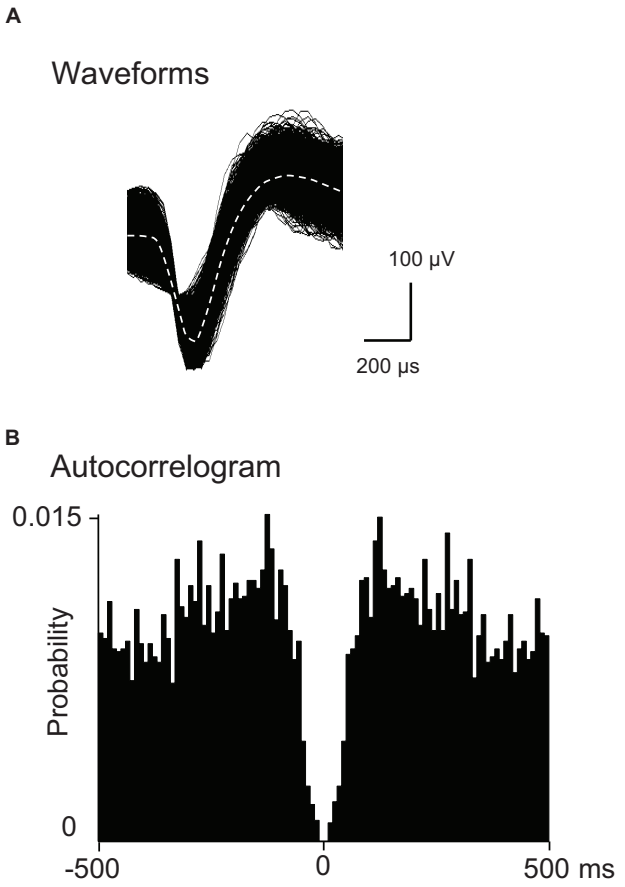

FIGURE 2 | Identification of PVT neurons. **(A)** An example of superimposed waveforms of PVT neuronal activity. **(B)** Autocorrelogram of the neuronal activity shown in **(A)** The ordinate indicates probability of spikes (bin counts were divided by the number of spikes in the spike train). Bin width = 1 ms.

to obtain 30 ml of the liquids during the task, the remainder was given to the rat in its home cage.

Electrophysiological Recordings

Each rat was tested every other day. After being placed in the stereotaxic instrument, a glass-insulated tungsten microelectrode (Z = 1.0–1.5 MΩ at 1 kHz) was stereotaxically inserted into the PVT at an angle of 10° with reference to the reference pin using a micromanipulator (SM-20, Narishige, Tokyo, Japan). The neuronal activities, CS triggers, and signals of the lick contacts on the tube were digitized and stored in a computer (MAP, Plexon Inc., Dallas, United States) system.

Spikes were isolated into single units with cluster analysis (Off-line sorter, Plexon Inc.). Then, an autocorrelogram of each unit identified by cluster analysis was analyzed: units with refractory periods≥2.0 ms in autocorrelograms were defined as single units. Furthermore, consistency of superimposed waveforms of the isolated units were inspected to confirm that the waveforms were those recorded from single units. Finally, the data were transferred to the NeuroExplorer program (Nex Technologies, Madison, AL, United States) for further analysis. Examples of superimposed waveforms of a PVT neuron are shown in **Figure 2A**. **Figure 2B** shows its autocorrelogram with the refractory period of 2 ms, suggesting that these spikes were recorded from a single unit.

When the PVT neurons had been isolated, they were initially tested with the regular cue-induced licking task (**Table 1**); each CS was pseudo-randomly presented with an inter-trial interval of 20–30 s, resulting in a total of 5–8 trials for each CS. Then, the neurons were sequentially tested with the modified cue-induced licking task with 8–10 trials for each condition with an inter-trial interval of 20–30 s; Tone1 (2 s) associated with water, Tone1 (1 s) associated with 0.3-M sucrose, and Tone1 (4 s) associated with 0.3-M sucrose. A previous study reported that when rats were trained to adapt to changes in reward association, the rats learned new associations within 2–3 trials (Toyomitsu et al., 2002). Therefore, in the modified cue-induced task, the data of the last five trials for each condition were analyzed and the data in the initial trials were discarded. In this modified task, water was introduced as less rewarding reinforcement compared with sucrose. Previous studies reported that manipulation, which modified motivational states, affected lick frequency (D'Aquila, 2010; Ostlund et al., 2013). Consistently, the mean lick number per trial was significantly lower in the reward trials with water than those with sucrose (Bonferroni test, $p < 0.0001$ after a one-way ANOVA) (**Supplementary Figure 1**). Furthermore, the 4-s CS (4-s Tone1) was tested after the 1-s CS to introduce "frustration effect" that promotes behavioral invigoration (see section "Discussion").

Experimental Design and Statistical Analyses

Data Analysis of Responses to CSs

Neuronal activity during the 2-s CS period was analyzed. The baseline firing rate was defined as the mean firing rate during the 500-ms "pre-CS" period. Significant neuronal responses (excitatory or inhibitory responses) to each CS were determined by a Wilcoxon signed rank test ($p < 0.05$) between the baseline firing rate and mean firing rate during the 2-s CS period. Response magnitude to the CS was defined as mean firing rates during the 2-s CS period minus the baseline firing rate. In each neuron, response magnitudes to all six CSs were compared by one-way ANOVAs ($p < 0.05$). PVT neurons with a significant main effect were defined as differential neurons. According to *post hoc* tests (Bonferroni test, $p < 0.05$), PVT neurons were defined as CS^+-selective neurons if their response magnitudes to all CSs associated with reward in the regular cue-induced licking task (Tone1, Light1, and Tone2 + Light2) were larger than those to all non-rewarding CSs (Tone2, Light2, and Tone1 + Light1).

To investigate temporal characteristics of the CS^+-related neurons, response magnitudes during the initial 500 ms after CS onset (early data set) and those during the last 500 ms of the CS (late data set) were separately analyzed. Response magnitudes in each data set were similarly defined: mean firing rates during the initial or last 500 ms of the CS period minus the baseline firing rate. These data were similarly analyzed by one-way ANOVAs

($p < 0.05$) with *post hoc* tests (Bonferroni test, $p < 0.05$). PVT neurons in the early data set were defined as early CS^+-selective neurons if their response magnitudes to all rewarding CSs associated with reward (Tone1, Light1, and Tone2 + Light2) were larger than those to all non-rewarding CSs (Tone2, Light2, and Tone1 + Light1) (Bonferroni test, $p < 0.05$ after a one-way ANOVA). Late CS^+-selective neurons were similarly defined based on the late data set.

Accumulating evidence suggests that neural population activity patterns represent stimulus relationships (e.g., Sereno and Lehky, 2011; Stokes et al., 2013; Chinzorig et al., 2020). Multidimensional scaling (MDS) has been widely used to decode neural population activity patterns into stimulus relationships. We hypothesized that population activity patterns of early and late CS^+-selective neurons differently represent CS relationships: population activity patterns of early CS^+-selective neurons might represent CS relationships based on predictive value while population activity patterns of late CS^+-selective neurons might represent CS relationships based on incentive value. To analyze CS relationships, response magnitudes of early and late CS^+-selective neurons were further analyzed by MDS. Each of these neurons was repeatedly (i.e., five times) tested with nine CSs (i.e., six and three CSs in the regular and modified cue-induced licking tasks, respectively), which yielded 45 stimulus arrays. Thus, the data matrices of neural activity in the 20 × 45 array derived from the 20 early CS^+-selective neurons and that derived from the 20 late CS^+-selective neurons were separately analyzed by MDS. In each data set, Euclidean distances (dissimilarities) between all possible pairs of CSs were calculated using the response magnitudes of each PVT neurons to the two CSs. The MDS program (PROXSCAL procedure, SPSS ver16; IBM Corporation, New York, NY, United States) positioned the CSs in a Euclidean stimulus space so that the spatial relationships among the CSs in the space represented the original relationships of the dissimilarities (Shepard, 1962). The clusters of the CSs were analyzed using the multiple discriminant analysis.

Data Analysis of Responses to Rewards

Single neuronal activity in response to rewards (unconditioned stimulus, US) (sucrose or water delivery for 2 s) was similarly analyzed. Significant neuronal responses (excitatory or inhibitory responses) to US after each rewarding CS were determined by a Wilcoxon signed rank test ($p < 0.05$) between the baseline firing rate and mean firing rate during the 2-s tube protrusion periods. The activity of US-responsive neurons was further analyzed to investigate neural correlation to individual licking. First, perievent histograms of neuronal spikes aligned with licking signals detected by the touch sensor (range = −80 ms to +80 ms; bin width = 20 ms) were computed using the data of the all reward trials. Then, the modulation index (MI; a normalized entropy measure; Tort et al., 2008) of the histogram was calculated, as follows:

$$\mathrm{H\ (entropy)} = -\sum_{j=1}^{N} p_j \log p_j$$

$$p_j = \frac{C_j}{C}$$

$$\mathrm{MI} = \frac{H_{max} - H}{H_{max}}$$

where N is the number of bins ($n = 8$), C is the total spike count in the histogram, C_j is the number of spike counts in the j^{th} bin, and H_{max} is the maximum possible entropy value (logN). Finally, the statistical significance of an MI value of a given US-responsive neuron was calculated by comparing it with a distribution of 200 surrogate MI values (Tort et al., 2008). The surrogate MI values were obtained by applying MI measure to trial shuffled data. The p-value was calculated assuming a normal distribution of the surrogate MI values. The neurons showing $p < 0.01$ and $C > 10$ were defined as neurons with significant lick correlation.

Histological Analysis

After the all recording sessions, small electrolytic lesions (20 μA for 20 s) were stereotaxically made around the recording sites under deep anesthesia (sodium pentobarbital 100 mg/kg, i.p.). Then, rats were transcardially perfused with saline and 10% buffered formalin. The brains of the rats were cut into 50-μm frontal sections, which were stained with cresyl violet. After all lesion sites being verified under a microscope, recording sites of neurons were stereotaxically plotted on the actual brain sections. Finally, these recording sites were transferred to corresponding locations on the corresponding sections of the rat brain atlas (Paxinos and Watson, 2017). In the present study, the rat PVT was divided into its anterior (AP −1.20 to −2.40) and posterior (AP −2.40 to −3.60) parts.

Initial results were presented as an abstract at a meeting (Munkhzaya et al., 2019) and summary of a doctoral thesis (Munkhzaya, 2019).

TABLE 2 | Categories and numbers of the rat PVT neurons.

Classification	*n*
Responses to CSs (CS-responsive)	100
Differential CS-responsive	85
CS^+-selective	43
Early CS^+-selective	20
Late CS^+-selective	20
Both early and late CS^+-selective	8
Other CS^+-selective	11
Other differential CS-responsive	42
Non-differential CS-responsive	**15**
Response to US (US-responsive)	133
Responsive only to US	59
Responsive to both CSs and US	74
Non-responsive	58
Total	217

RESULTS

Responses to the CSs

Of 217 PVT neurons, 100 (46.1%) showed excitatory responses to one or more CSs of the task (CS-responsive neurons). The five of these 100 neurons showed not only excitatory but also inhibitory responses, and were classified as other differential CS-responsive neurons (see below). **Table 2** shows summary of the response patterns of these 100 PVT neurons. Of the 100 CS-responsive neurons, 85 (39.2%, 85/217) responded differentially to the CSs with or without reward (differential CS-responsive neurons), and 15 (6.9%) responded non-differentially (non-differential CS-responsive neurons). Of the 85 differential CS-responsive neurons, 43 (19.8%, 43/217) responded stronger to any rewarding CS than any non-rewarding CS regardless of stimulus sensory modality (CS^+-selective neurons). **Figure 3A** shows the mean response magnitudes of the 43 CS^+-selective neurons to all CSs for 2 s in the regular cue-induced licking task. A statistical analysis indicated a significant main effect of cue type [$F(5, 252) = 33.6$, $p = 0.001$]. *Post hoc* tests indicated that these neurons significantly responded stronger to the rewarding CSs (Tone1, Light1, and Tone2 + Light2) than the non-rewarding CSs (Tone2, Light2, and Tone1 + Light1) (Bonferroni test, $p < 0.0001$; see **Supplementary Table 1** for individual comparisons). The remaining 42 (19.4%, 42/217) neurons differentially responded to various CSs (other differential CS-responsive neurons). These neurons responded differentially to specific CSs, but their response patterns did not match the criteria for CS^+-selective neurons. **Figure 3B** shows the mean response magnitudes of the 42 other differential CS-responsive neurons to all CSs for 2 s in the regular cue-induced licking task. A statistical analysis indicated a significant main effect of cue type [$F(5, 240) = 5.1$, $p = 0.0002$]. *Post hoc* tests indicated that these neurons significantly responded stronger to Light1 and Tone2 + Light2 than Tone2 (Bonferroni test, $p < 0.001$). **Figure 3C** shows the mean response magnitudes of the 15 non-differential CS-responsive neurons to all CSs for 2 s in the regular cue-induced licking task. A statistical analysis indicated no significant main effect of cue type [$F(5, 84) = 0.424$, $p = 0.831$].

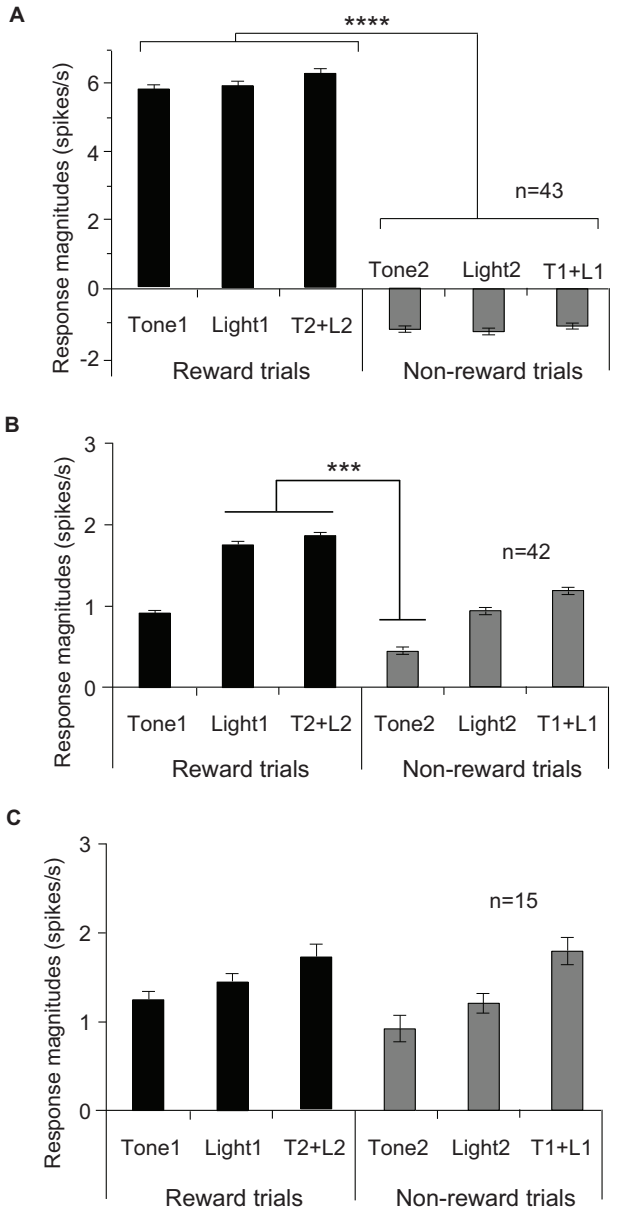

FIGURE 3 | Comparison of the mean response magnitudes (mean firing rates ± standard error of the mean, SEM) to the CSs in the three subcategories of the CS-responsive neurons. **(A)** CS^+-selective neurons ($n = 43$). Response magnitudes to the rewarding CSs are significantly greater than those to the non-rewarding CSs. **(B)** Other differential CS-responsive neurons ($n = 42$). **(C)** Non-differential CS-responsive neurons ($n = 15$). $^{****}p < 0.0001$; $^{***}p < 0.001$ (Bonferroni tests).

Responses of CS^+-selective neurons during the early and late 500 ms of the CSs were further analyzed. Of the 43 CS^+-selective neurons, 20 and 20 neurons showed early and late CS^+-selective responses, respectively. Of these 43 neurons, eight showed both early and late CS^+-selective responses (**Table 2** and **Supplementary Figure 2**). Furthermore, we analyzed neuronal activity during the middle part of the CSs (i.e., from 0.75 to 1.25 s after CS onset). However, the all 43 CS^+-selective neurons showed no CS^+-selective responses during the middle part of the CSs. In addition, we also analyzed neuronal activity during the early and late 500 ms of the CSs regardless of responses during the 2-s CS period, and found that another 11 neurons responded to some CSs during the early 500 ms of the CSs while another 7 neurons responded to some CSs during the late 500 ms of the CSs. However, all of these neurons showed non-differential responses to the CSs. **Figure 4** shows the activity of an early CS^+-selective neuron in the PVT. The neuron displayed excitatory responses to Tone1 (**Figure 4A**), Light1 (**Figure 4B**) and configural stimulus (Tone2 + Light2, **Figure 4F**) associated with sucrose solution in the regular cue-induced licking task. However, the neuron did not respond to Tone2 (**Figure 4D**), Light2 (**Figure 4E**), or configural stimulus (Tone1 + Light1, **Figure 4C**) predicting

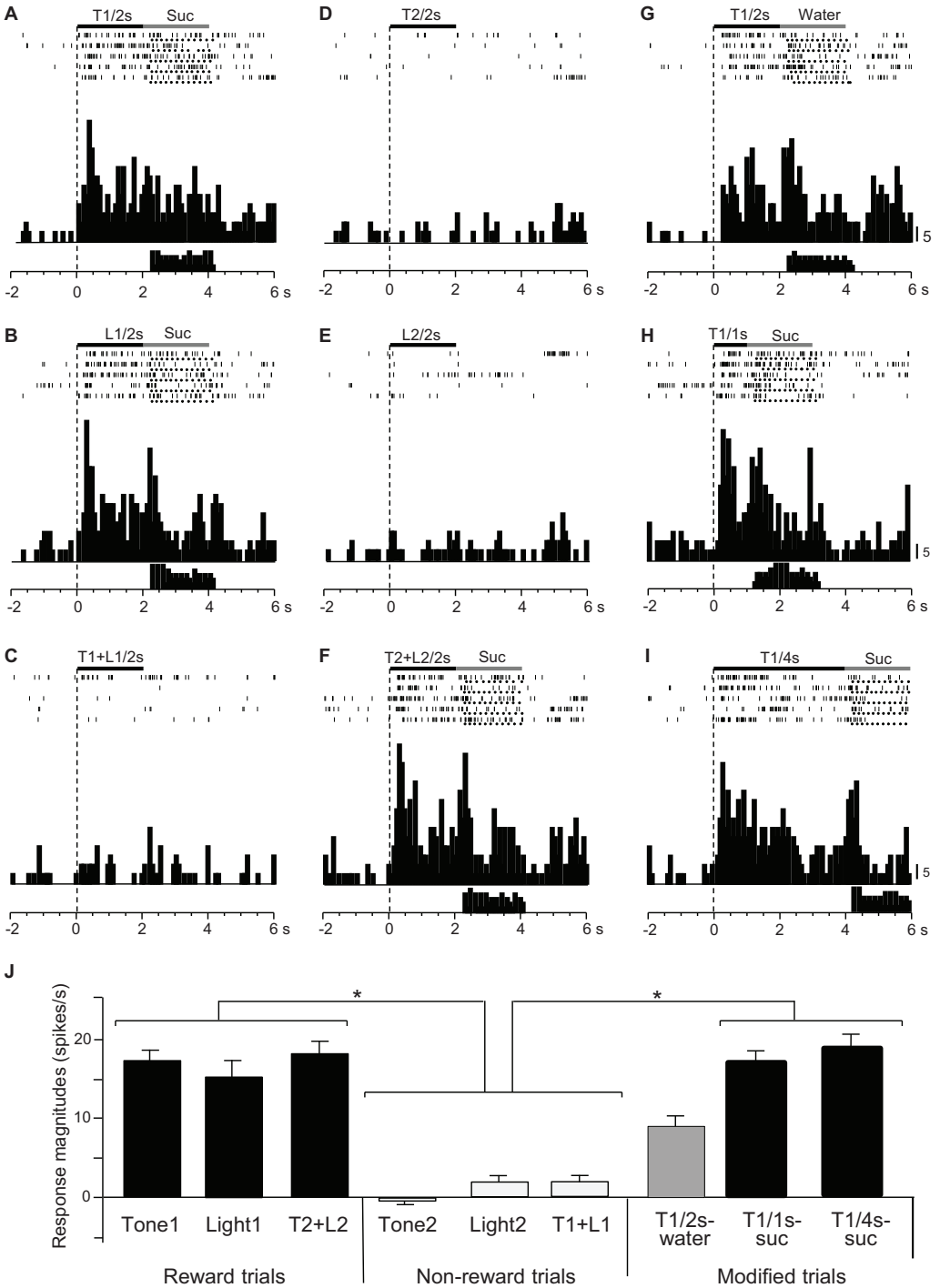

FIGURE 4 | Activity of an early CS^+-selective neuron that responds differently to CSs associated with reward and non-reward. **(A–F)** Responses to CSs in the regular cue-induced licking task. Raster displays and summed histograms indicate neuronal responses to Tone1 associated with the sucrose solution **(A)**, Light1 associated with the sucrose solution **(B)**, Tone1 + Light1 associated with non-reward **(C)**, Tone2 associated with non-reward **(D)**, Light2 associated with non-reward **(E)**, and Tone2 + Light2 associated with the sucrose solution **(F)**. **(G–I)** Responses to Tone1 associated with reward in the modified cue-induced licking task. Note that the neuron responded to the CSs associated with reward. Black and gray rectangles above the raster displays indicate CS duration and time of reward, respectively. Each dot below the raster line indicates one lick; each upper histogram shows summed neuronal responses; and each lower histogram shows summed licks. Abscissas indicate time; onset of CS at time 0; negative values represent the pre-trial control. Histogram bin width, 100 ms. Suc, 0.3 M sucrose solution. **(J)** Comparison of neuronal responses to the CSs (mean firing rate ± SEM). T1/2s, 2-s Tone1; L1/2s, 2-s Light1; T1 + L1/2s, 2-s Tone1 + Light1; T2/2s, 2-s Tone2; L2/2s, 2-s Light2; T2 + L2/2s, 2-s Tone2 + Light2; T1/1s, 1-s Tone1; T1/4s, 4-s Tone1; T1 + L1, Tone1 + Light1; T2 + L2, Tone2 + Light2; T1/2s-water, 2-s Tone1 associated with water; T1/1s-suc, 1-s Tone1 associated with sucrose; T1/4s-suc, 4-s Tone1 associated with sucrose. *$p < 0.05$ (Bonferroni test).

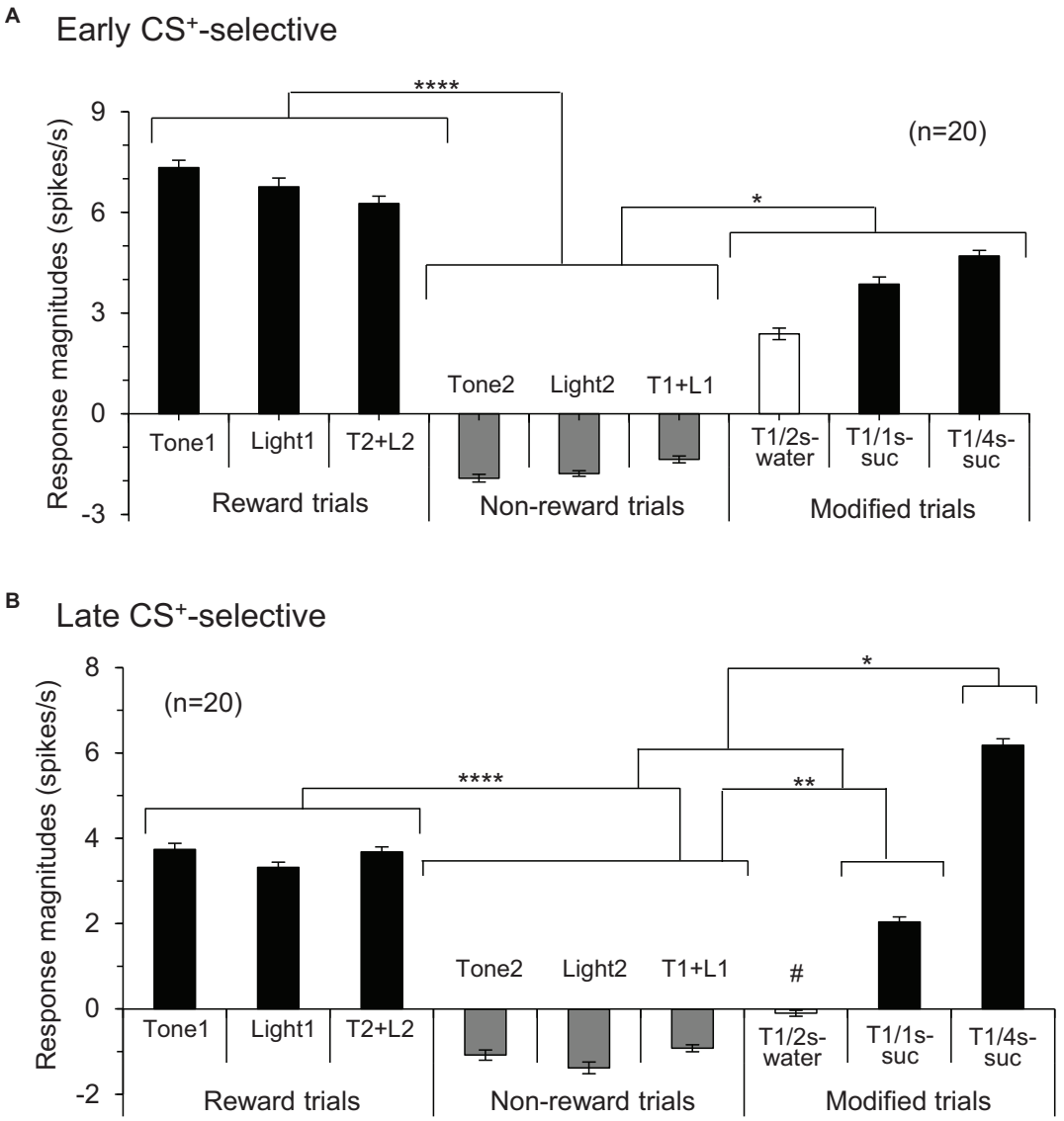

FIGURE 5 | Histograms of mean response magnitudes to CSs in the early **(A)** and late **(B)** CS^+-selective neurons (mean firing rates ± SEM). T1 + L1, Tone1 + Light1; T2 + L2, Tone2 + Light2; T1/2s-water, 2-s Tone1 associated with water; T1/1s-suc, 1-s Tone1 associated with sucrose; T1/4s-suc, 4-s Tone1 associated with sucrose. *, **, ****$p < 0.05$, 0.01, and 0.0001, respectively (Bonferroni test after one-way ANOVA). #, significant difference from Tone1, Light1, T2 + L2, and T1/4s-suc ($p < 0.001$).

non-reward. Furthermore, the neuron responded to Tone1 associated with rewards (water or sucrose) in the modified cue-induced licking task (**Figures 4G–I**). The mean response magnitudes during the early 500 ms of the CSs are indicated in **Figure 4J**. The statistical analysis indicated a significant main effect of cue type [one-way ANOVA: $F(8, 36) = 7.38$, $p = 0.001$]. *Post hoc* tests revealed that response magnitudes to all CSs associated with sucrose were greater than those associated with non-reward (Bonferroni test, $p < 0.05$; see **Supplementary Table 2** for individual comparisons). **Figure 5A** shows for the 20 early CS^+-selective neurons their mean response magnitudes to the early 500 ms of the CSs. A statistical analysis demonstrated a significant main effect of cue type [one-way ANOVA: $F(8, 171) = 22.5$, $p = 0.0001$]. *Post hoc* tests indicated that response magnitudes to all CSs associated with rewards were greater than those associated with non-reward (Bonferroni test, $p < 0.05$; see **Supplementary Table 3** for individual comparisons).

Figure 6 shows the activity of a late CS^+-selective neuron in the PVT. The neuron displayed CS^+-selective responses similar to those of the early CS^+-selective neurons; excitatory responses to Tone1 (**Figure 6A**), Light1 (**Figure 6B**), and configural stimulus (Tone2 + Light2, **Figure 6F**) associated with sucrose solution in the regular cue-induced licking task, and those to Tone1 associated with reward (sucrose) in the modified task (**Figures 6H,I**). The mean response magnitudes during the late

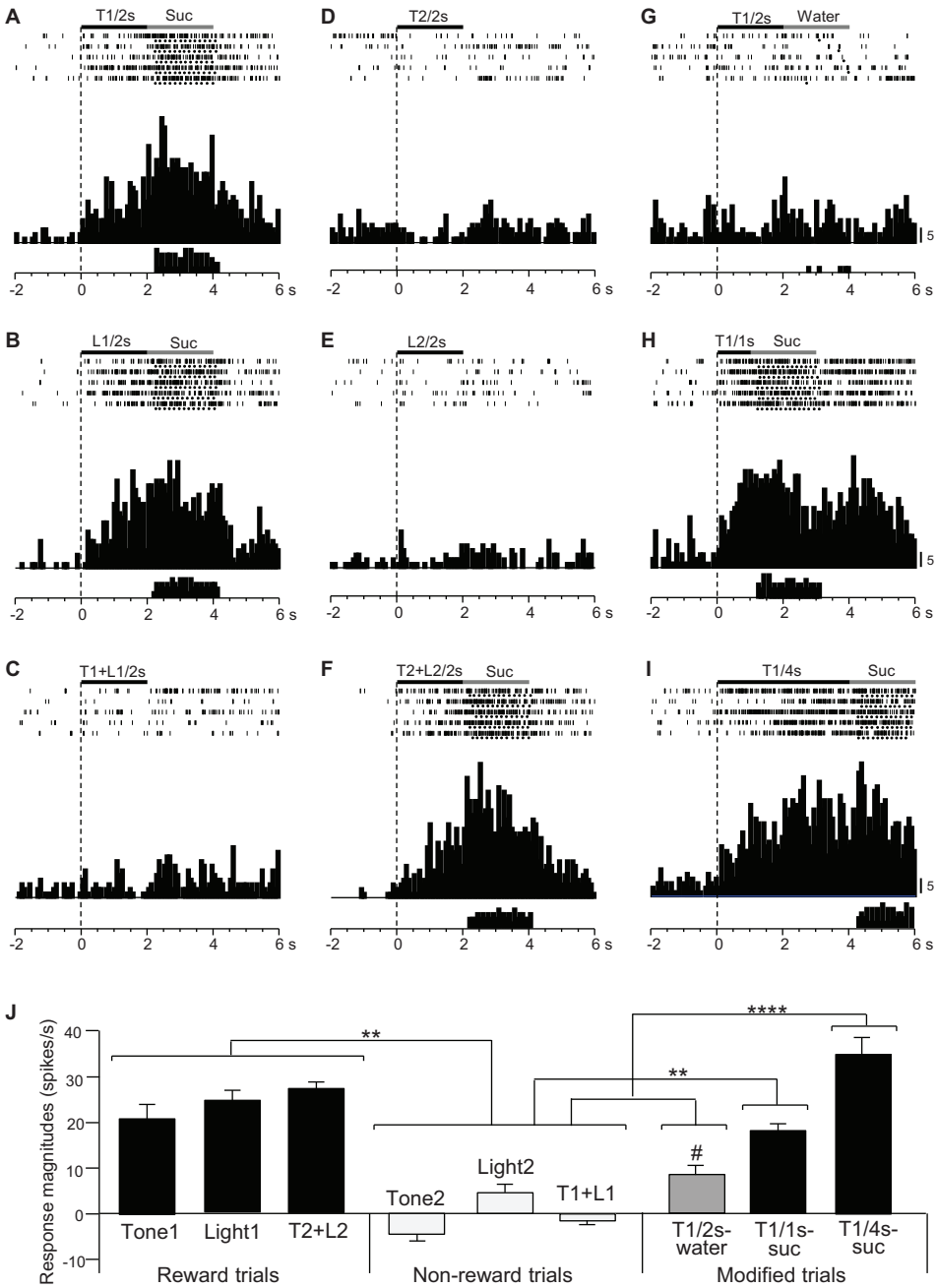

FIGURE 6 | Activity of a late CS^+-selective neuron that responded differently to CSs associated with reward and non-reward. **(A–F)** Responses to CSs in the regular cue-induced licking task. Raster displays and summed histograms indicate neuronal responses to Tone1 associated with the sucrose solution **(A)**, Light1 associated with the sucrose solution **(B)**, Tone1 + Light1 associated with non-reward **(C)**, Tone2 associated with non-reward **(D)**, Light2 associated with non-reward **(E)**, and Tone2 + Light2 associated with the sucrose solution **(F)**. **(G–I)** Responses to Tone1 associated with reward in the modified cue-induced task. Note that the neuron responded to the CSs associated with reward. **(J)** Comparison of neuronal responses to the CSs (mean firing rate ± SEM). T1/2s, 2-s Tone1; L1/2s, 2-s Light1; T1 + L1/2s, 2-s Tone1 + Light1; T2/2s, 2-s Tone2; L2/2s, 2-s Light2; T2 + L2/2s, 2-s Tone2 + Light2; T1/1s, 1-s Tone1; T1/4s, 4-s Tone1; T1 + L1, Tone1 + Light1; T2 + L2, Tone2 + Light2; T1/2s-water, 2-s Tone1 associated with water; T1/1s-suc, 1-s Tone1 associated with sucrose; T1/4s-suc, 4-s Tone1 associated with sucrose. **, ****$p < 0.01$ and 0.0001, respectively (Bonferroni test). #, significant difference from Tone1, Light1, and T2 + L2 ($p < 0.05$). Other descriptions as in **Figure 4**.

500 ms of the CSs are shown in **Figure 6J**. A statistical analysis indicated a significant main effect of cue type [one-way ANOVA: $F(8, 36) = 21.32$, $p = 0.0001$]. *Post hoc* tests indicated that response magnitudes to all CSs associated with sucrose were greater than those associated with non-reward (Bonferroni test, $p < 0.05$; see **Supplementary Table 4** for individual comparisons)

and that the response magnitude to Tone1 (4 s) associated with sucrose (T1/4 s-suc) was greater than that to Tone1 (2 s) associated with water (T1/2 s-water) (Bonferroni test, $p < 0.05$). **Figure 5B** shows the mean response magnitudes of the 20 late rewarding CS^+-selective neurons to the late 500 ms of the CSs. A statistical analysis revealed a significant main effect of cue type [one-way ANOVA: $F(8, 171) = 24.62$, $p = 0.001$]. *Post hoc* tests indicated that the response magnitudes to all CSs associated with sucrose were greater than those associated with non-reward (Bonferroni test, $p < 0.05$; see **Supplementary Table 5** for individual comparisons). Furthermore, the response magnitudes to Tone1 (4 s) associated with sucrose (T1/4 s-suc) were larger than those to 2 and 1-s CSs associated with sucrose (Bonferroni test, $p < 0.05$) as well as those to Tone1 (2 s) associated with water (T1/2 s-water) (Bonferroni test, $p < 0.0001$) (see **Supplementary Table 5** for individual comparisons). In addition, response magnitudes to 4- and 2-s CSs associated with sucrose were larger than those to Tone1 (2 s) associated water (T1/2 s-water) (Bonferroni test, $p < 0.0001$). Thus, response magnitudes to CSs associated with rewards tended to be larger in the following order; 4-s CS associated with sucrose >2 and 1-s CSs associated with sucrose >2-s CS associated with water.

Relationships to Lick Latencies

The above results suggest that the activity of late CS^+-selective neurons might correlate with motivation (lick latency) to reward. Latency has been reported to reflect impulsive drive to promote behaviors (Bari and Robbins, 2013; Berditchevskaia et al., 2016). **Figure 7A** presents the mean lick latencies after the CS offset during the recording of the late CS^+-selective neurons. A statistical analysis indicated a significant difference among the rewarding CSs [one-way ANOVA: $F(15, 131) = 12.4$, $p = 0.0001$]. The *post hoc* comparison revealed that mean latencies for water after Tone1 (2 s) (T1/2 s-water) were longer than those for sucrose after 2 and 4-s CSs (Bonferroni test, $p < 0.01$; see **Supplementary Table 6** for individual comparisons) and that the mean latencies for sucrose after Tone1 (1 s) (T1/1 s-suc) were longer than those for sucrose after Tone1 (4 s) (T1/4 s-suc) (Bonferroni test, $p < 0.0001$). Then, we analyzed the relationships between the mean lick latencies shown in **Figure 7A** and the mean late responses shown in **Figure 5B**. A simple linear regression analysis indicated a significant negative correlation between the mean response magnitudes during the last 500 ms of the rewarding CSs (**Figure 5B**) and lick latencies (**Figure 7A**) [$F(1, 5) = 18.585$, $p = 0.0125$]. Thus, stronger neuronal responses were followed by shorter licking latencies. However, the same analysis of the early CS^+-selective neurons indicated no such significant correlation between the mean response magnitudes and lick latencies [$F(1, 5) = 1.7974$, $p = 0.2511$].

We also analyzed this correlation in individual neurons. **Figure 7B** shows an example of a late CS^+-selective neuron showing a negative correlation between the response magnitudes during the late 500 ms of the rewarding CSs and the mean lick latencies after the rewarding CSs. A simple linear regression analysis indicated a significant negative correlation between response magnitudes and lick latencies [$F(1, 5) = 42.515$, $p = 0.003$]. Of the 20 late CS^+-selective neurons, 9 (9/20, 45%) showed similar significant negative correlations between neuronal response magnitudes and lick latencies (simple linear regression, $p < 0.05$; see **Supplementary Table 7** for *F*- and *p*-values of individual neurons). By contrast, only one early CS^+-selective neuron (1/20, 5%) showed a similar significant negative correlation (simple linear regression, $F(1, 5) = 11.8346$, $p = 0.0263$; see **Supplementary Table 7** for *F*- and *p*-values of individual neurons). **Figure 7C** shows an example of an early CS^+-selective neuron with no correlation between the response magnitudes during the late 500 ms of the rewarding CSs and the mean lick latencies after the rewarding CSs. A simple linear regression analysis indicated no significant correlation between response magnitudes and lick latencies [$F(1, 5) = 0.0097$, $p = 0.926$]. The ratios of the neurons with negative correlation were significantly higher in the group with the late CS^+-selective neurons compared to that with the early CS^+-selective neurons (Fisher's exact test, $p = 0.0319$) (**Figure 7D**). These results indicate that the late CS^+-selective neurons are more important to guide seeking behaviors after the rewarding CSs.

Temporal Representation of the CSs

To investigate the temporal representation of CSs, response magnitudes to CSs in the early and late CS^+-selective neurons were analyzed using an MDS analysis. First, the data sets of the firing rates of the 20 early CS^+-selective neurons during the early 500 ms of the CS were subjected to an MDS analysis (**Figure 8A**). The r^2 and stress values indicated that the stimuli were well represented in a two-dimensional space (r^2 value = 0.94, stress value = 0.159). The MDS data suggest that there are three groups of CSs: CSs associated with sucrose, those with water, and those with non-reward. The multiple discriminant analysis indicated a significant separation among these three groups (Wilks' lambda = 0.104, $p < 0.0001$).

Second, the representation of the CSs by late CS^+-selective neuronal activity during the last 500 ms of the CS was also analyzed (**Figure 8B**). The r^2 and stress values indicated that the stimuli were well represented in a two-dimensional space (r^2 value = 0.95, stress values = 0.169). The MDS data suggest that there are five groups of CSs: CSs associated with non-rewards, 2-s CSs associated with water, 1-s CSs associated with sucrose, 2-s CSs associated with sucrose, and 4-s CSs associated with sucrose. The multiple discriminant analysis indicated a significant separation among the five groups (Wilks' lambda = 0.006, $p < 0.0001$). It is noted that locations of CSs associated with water in the MDS space were different between the two MDS spaces derived from early and late CS^+-selective neuronal activity. CSs associated with water were located nearer the CSs associated with non-reward in the MDS space derived from late CS^+-selective neuronal activity compared with that derived from early CS^+-selective neuronal activity; the mean distance between CSs associated with water and non-reward was significantly

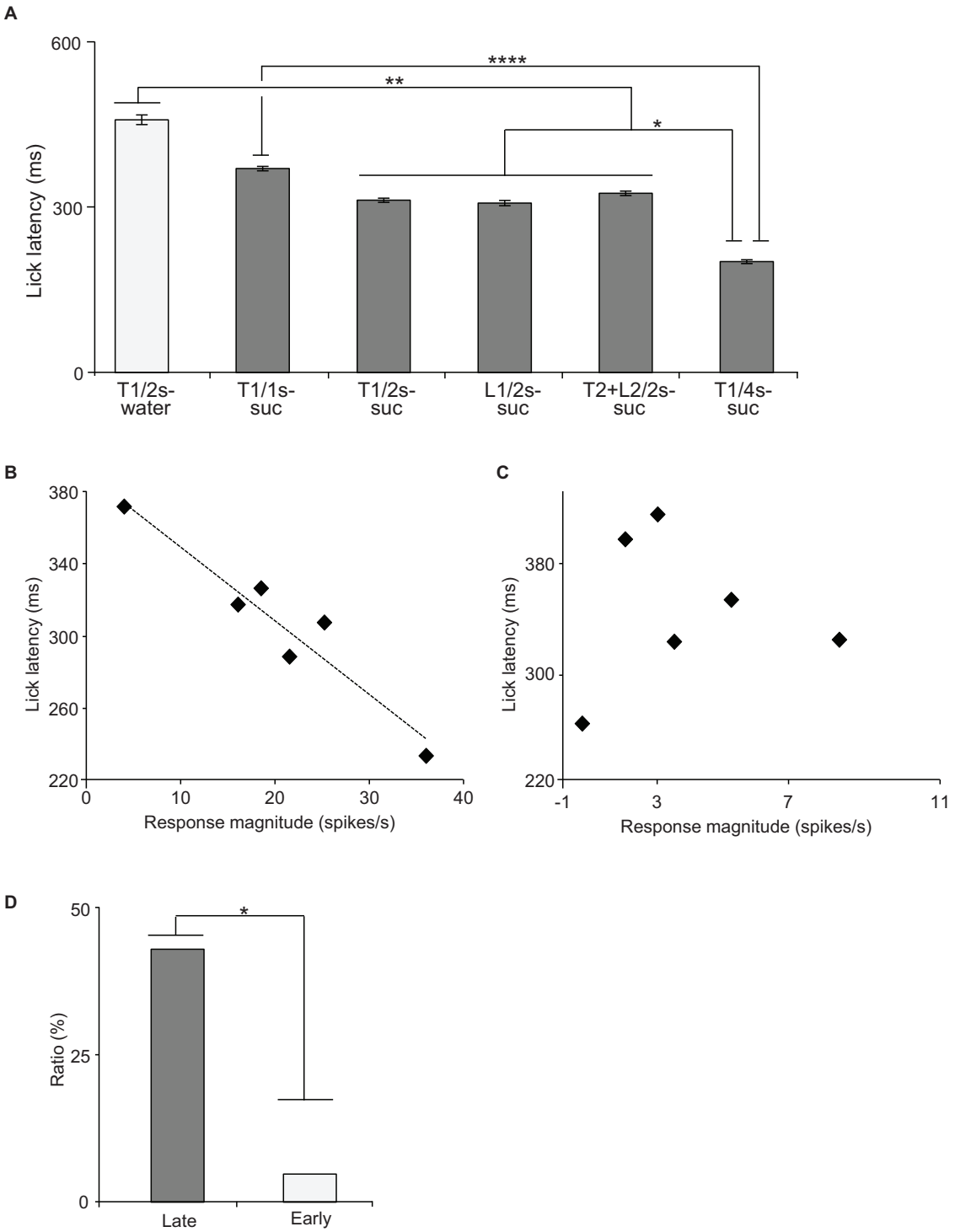

FIGURE 7 | Relationships between mean lick latencies and mean response magnitudes to the CSs associated with reward in the early and late CS^+-selective neurons. **(A)** Mean lick latencies after offset of the CSs associated with reward during recording of the late CS^+-selective neurons (n = 20). **(B)** An example of a late CS^+-selective neuron showing a significant negative correlation between mean lick latencies and mean response magnitudes to the rewarding CSs (p = 0.003, simple linear regression). **(C)** An example of an early CS^+-selective neuron showing no significant correlation between mean lick latencies and mean response magnitudes to the rewarding CSs (p = 0.926, simple linear regression). **(D)** Comparison of the ratio of neurons with significant negative correlation between late and early CS^+-selective neurons. T1/2s-water, 2-s Tone1 associated with water; T1/1s-suc, 1-s Tone1 associated with sucrose; T1/2s-suc, 2-s Tone1 associated with sucrose; L1/2s-suc, 2-s Light1 associated with sucrose; T2 + L2/2s-suc, 2-s Tone2 + Light2 associated with sucrose; T1/4s-suc, 4-s Tone1 associated with sucrose. *, **, ****p < 0.05, 0.01, and 0.0001, respectively.

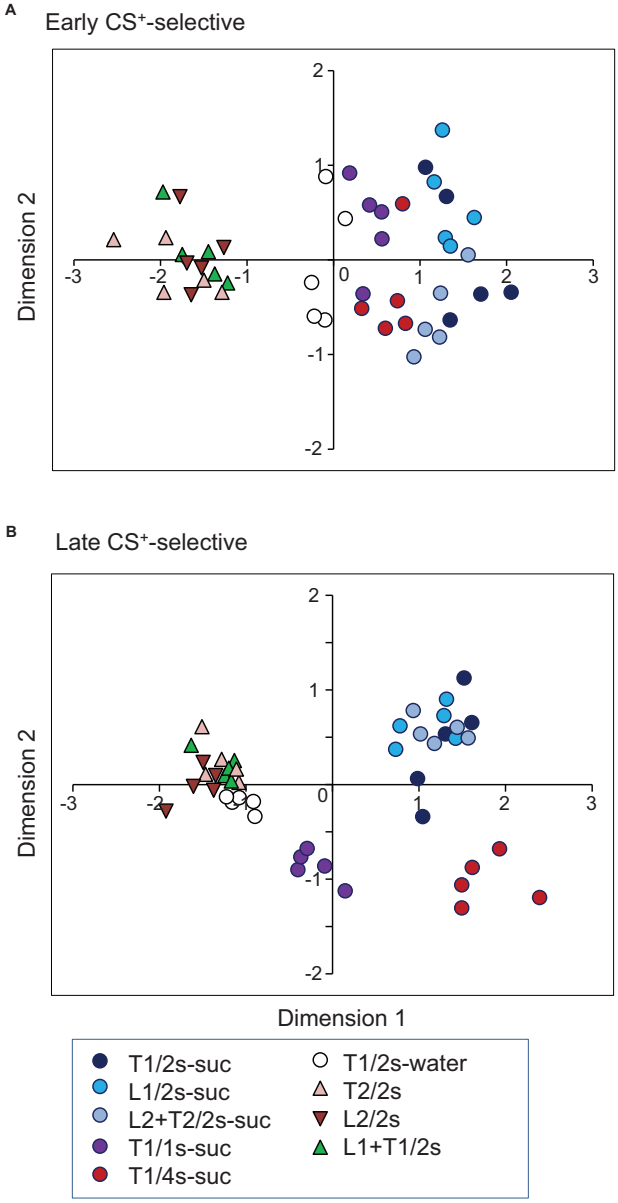

FIGURE 8 | Distributions of the nine CSs in two-dimensional space resulting from multidimensional scaling (MDS) of the activities of the 20 early CS^+-selective neurons **(A)** and the 20 late CS^+-selective neurons **(B)**. In **(A)** three clusters were recognized (multiple discriminant analysis, $p < 0.0001$ for all analyses), while five clusters were recognized in **(B)** (multiple discriminant analysis, $p < 0.0001$). T1/2s-suc, 2-s Tone1 associated with sucrose; L1/2s-suc, 2-s Light1 associated with sucrose; L2 + T2/2s-suc, 2-s Light2 + Tone2 associated with sucrose; T1/1s-suc, 1-s Tone1 associated with sucrose; T1/4s-suc, 4-s Tone1 associated with sucrose; T1/2s-water, 2-s Tone1 associated with water; T2/2s, 2-s Tone2 associated with non-reward; L2/2s, 2-s Light2 associated with non-reward; L1 + T1/2s, 2-s Light1 + Tone1 associated with non-reward.

smaller in the MDS space derived from late CS^+-selective neuronal activity (**Figure 8B**) than that derived from early CS^+-selective neuronal activity (**Figure 8A**) [t-test, $t(75) = -21.4942$, $p < 0.0001$].

Response to USs

A total of 133 neurons (61.3%, 133/217) showed excitatory responses to USs (US-responsive neurons), and did not show inhibitory responses (**Table 2**). Of the 133 US-responsive neurons, 59 responded only to USs, and 74 responded to both USs and CSs (**Table 2**). On the other hand, 11 early CS^+-selective and 18 late CS^+-selective neurons showed responses to USs. The ratios of US-responsive neurons were significantly greater in the late CS^+-selective neurons (90.0%, 18/20) than the early CS^+-selective neurons (55.0%, 11/20) (Fisher's exact test, $p < 0.05$).

The 38 of the 133 US-responsive neurons showed a significant correlation to individual lickings. **Figure 9** presents three examples of these correlations; US-responsive neurons showed activity increases before tongue contact on the tube (**Figure 9A**), around tongue contact (**Figure 9B**), and after tongue contact (**Figure 9C**).

Locations of the PVT Neurons

The distributions of CS- and US-responsive neurons are shown in **Figures 10A–F**, respectively. The late CS^+-selective neurons (open squares and filled triangles with open squares) were located more densely in the anterior part of the PVT, while early CS^+-selective neurons (open triangles and filled triangles with open squares) were located more evenly throughout the PVT. The ratio of the late CS^+-selective neurons to the CS^+-selective neurons was significantly higher in the anterior part than in the posterior part of the PVT (Fisher's exact test, $p = 0.0001$), while there was no significant difference between these ratios for the early CS^+-selective neurons (Fisher's exact test, $p = 0.227$) (**Figure 11**). The US-responsive neurons with and without lick correlation (filled and open circles) were also located evenly throughout the PVT. There was no significant difference in the ratio of US-responsive neurons with lick correlation to all US-responsive neurons between the anterior and posterior parts of the PVT (Fisher's exact test, $p = 0.0858$).

DISCUSSION

Response Characteristics of the CS^+-Selective PVT Neurons

The present results indicate that more than 50% of the differential CS-responsive neurons (i.e., CS^+-selective PVT neurons, 52.9%) responded selectively to the CSs associated with reward. These differential responses to the CSs were independent of physical properties of the CSs. The CS^+-selective PVT neurons responded selectively to the elemental CSs associated with reward regardless of physical properties of the CSs. Furthermore, these neurons also responded selectively to the configural CSs (i.e., simultaneous presentation of the auditory and visual CSs) associated with reward. It is noted that the reward predictability of the CSs in compound (i.e., configural CSs) was opposite to that of the elemental CSs presented alone, although the exact same sensory modalities were involved. These findings indicate that selective neuronal responses to the CSs are attributed to the reward predictability of the CSs rather than to the physical

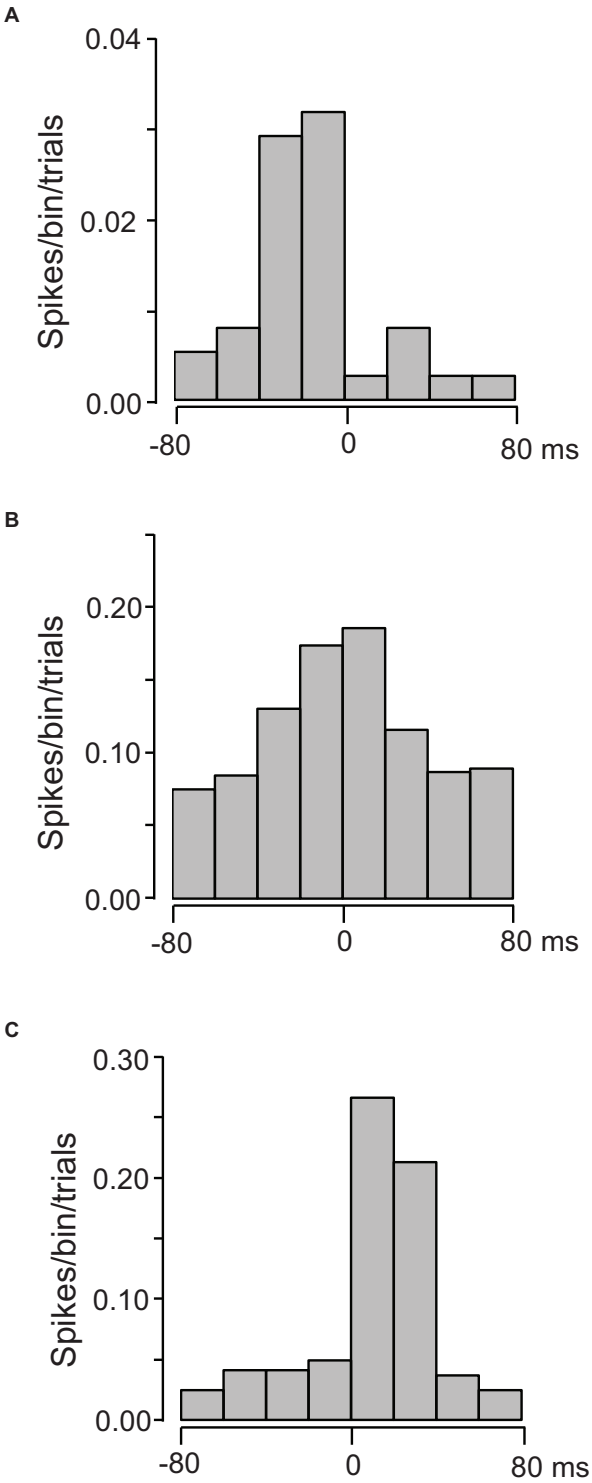

FIGURE 9 | Three examples of cross-correlograms between the activity of US-responsive neurons and individual licking. **(A)** A US-responsive neuron with a peak before lick contact on the tube (MI = 0.21175, $p < 0.0001$). **(B)** A US-responsive neuron with a peak around lick contact on the tube (MI = 0.023186, $p < 0.0001$). **(C)** A US-responsive neuron with a peak after lick contact on the tube (MI = 0.021035, $p < 0.0001$). Zero on time scale indicates tongue contact with the tube. Bin width = 20 ms.

properties of the CSs. These results suggest strongly that the CS^+-selective neurons are involved in the detection of cues associated with reward, consistent with a role of the PVT in cue-induced motivated behaviors (see section "Introduction"). Consistent with the present results, a presentation of cues associated with rewards (palatable food, sucrose, cocaine, ethanol, etc.) increases *c-fos* or Fos expression in the PVT (see section "Introduction"). The PVT receives afferent projections from the prefrontal cortex, amygdala, and septum (Hsu and Price, 2009; Li and Kirouac, 2012), where similar CS^+-selective neurons have been reported (Takenouchi et al., 1999; Toyomitsu et al., 2002; Matsuyama et al., 2011). Furthermore, optogenetic manipulation of responses in prefrontal neurons projecting to the PVT suppresses conditioned reward-seeking or retrieval of conditioned cues (Do-Monte et al., 2015; Otis et al., 2017). These findings suggest that the PVT integrates information of conditioned cues from these PVT-projecting areas.

Previous studies suggest that CSs have both predictive and incentive properties (Robinson and Berridge, 1993; Robinson and Flagel, 2009; Robinson et al., 2019). The predictive property of CSs indicates the availability of rewards in the near future, while the incentive property reflects incentive motivation or salience to evoke seeking behaviors (see section "Introduction"). Especially, incentive property enhances ongoing instrumental actions (Haight and Flagel, 2014). In our study, the late CS^+-selective neurons showed larger mean response magnitudes during the late 500 ms of the CS in the following order; 4-s CS associated with sucrose >2 and 1-s CSs associated with sucrose >CS associated with water. These differences in response magnitudes were negatively correlated with lick latencies. Analyses of the individual late CS^+-selective neurons also indicated that 45% of the late CS^+-selective neurons showed similar negative correlations. It is noted that the 4-s CS (Tone1) followed by sucrose was tested after 1-s CS followed by sucrose in the modified task. Introduction of the 4-s CS after the 1-s CS means reward omission at the time point 1 s after the CS onset. Previous studies reported that "frustration effect" is observed after trials with reward omission: a specific anticipated reward becomes more attractive after it has been omitted (Amsel and Roussel, 1952; Stout et al., 2003; Freidin and Mustaca, 2004). These findings suggest that behavioral and neurophysiological changes in response to the 4-s CS are attributed to frustration effect. Consistent with this idea, a previous study reported that uncertain association of reward with CSs enhanced attraction to a temporally proximal CS that conveyed incentive value (Robinson et al., 2019). Furthermore, late responses might also reflect motor preparation process that might reduce lick latencies. Human behavioral and EEG studies reported that reward affects this process (Mir et al., 2011; Schevernels et al., 2014), which might be mediated through the basal ganglia including the ventral striatum (Pasquereau et al., 2007; Galaro et al., 2019). The PVT might affect lick latency through its projections to the nucleus accumbens (see below). By contrast, the early CS^+-selective neurons showed no significant differences in mean response magnitudes during the initial 500 ms of the CS among the rewarding CSs, although response magnitudes to the CSs associated with rewards

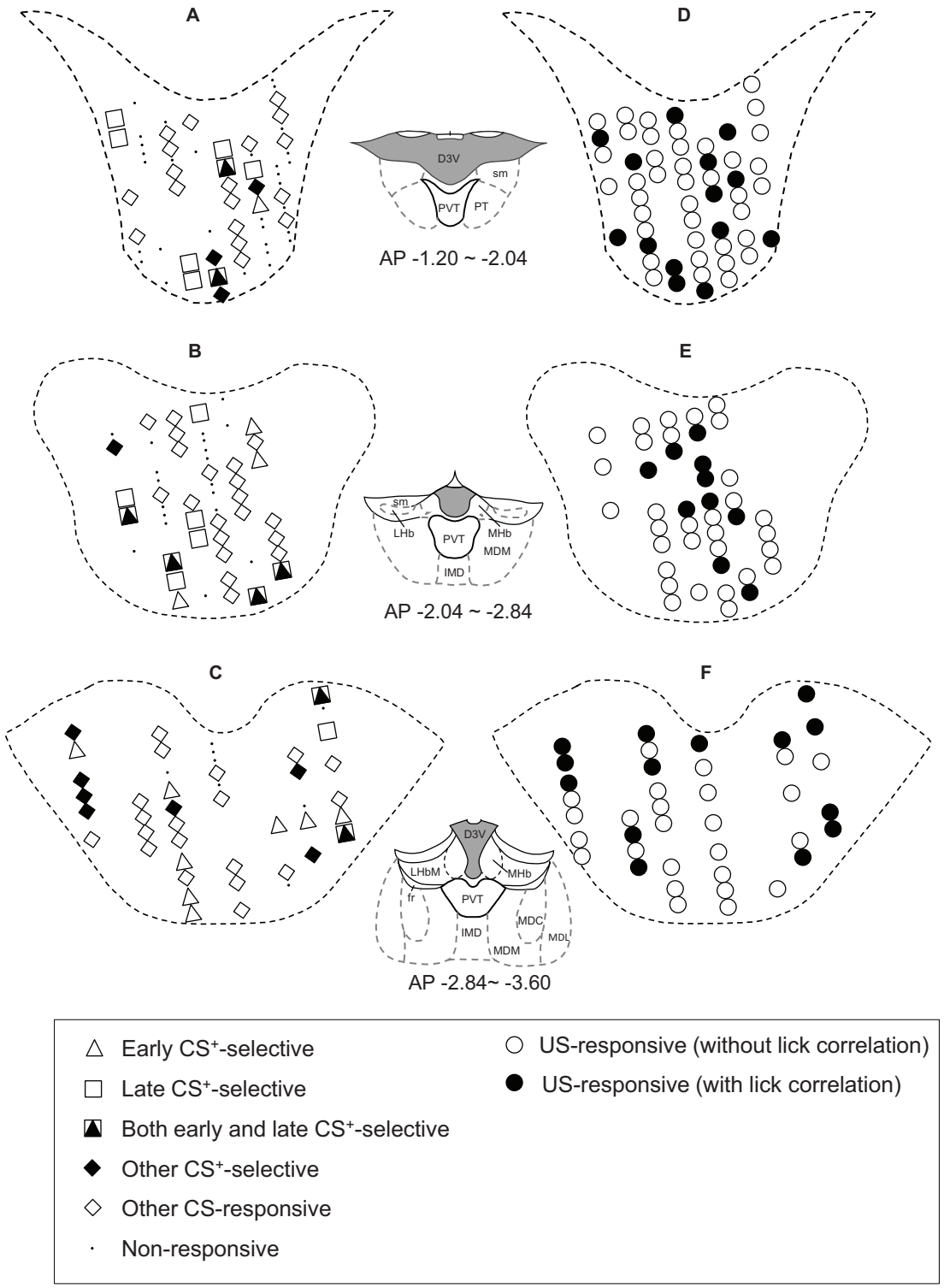

FIGURE 10 | Recording sites of the PVT neurons. **(A–C)** Distributions of CS-responsive neurons. **(D–F)** Distributions of US-responsive neurons. PVT neurons are plotted on coronal sections. AP (anterior-posterior) number in each section indicates the distance (mm) posterior from the bregma. Other CS-responsive, other differential CS-responsive neurons plus non-differential CS-responsive neurons in **Table 2**. D3V, dorsal 3rd ventricle; LHb, lateral habenular nucleus; sm, stria medullaris; PVT, paraventricular nucleus of the thalamus; PT, paratenial thalamic nucleus; MHb, medial habenular nucleus; MDM, mediodorsal nucleus of the thalamus, medial part; IMD, intermediodorsal nucleus of the thalamus; fr, fasciculus retroflexus; MDL, mediodorsal nucleus of the thalamus, lateral part; MDC, mediodorsal nucleus of the thalamus, central part.

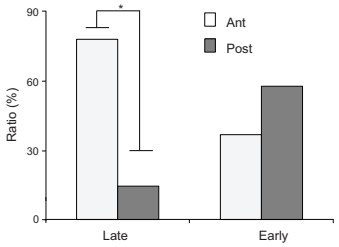

FIGURE 11 | Ratios of early and late CS^+-selective neurons in the anterior and posterior parts of the PVT. Late, late CS^+-selective neurons; Early, early CS^+-selective neurons; Ant, anterior part of the PVT; Post, posterior part of the PVT. $^*p < 0.05$.

were greater than those to CSs associated with non-reward. Furthermore, there was no significant correlation between the mean response magnitudes of the early CS^+-selective neurons and mean lick latencies. Analyses of the individual neurons indicated that only 5% of the early CS^+-selective neurons showed similar negative correlations. These results suggest that the activity of early CS^+-selective neurons reflects reward/non-reward contingency of CSs, while activity of late CS^+-selective neurons reflects the motivational significance of CSs. The MDS analyses support the above results. The MDS analysis of the early CS^+-selective neurons indicated three clusters of the CSs: CSs associated with non-reward, water, and sucrose. The MDS analysis of the late CS^+-selective neurons revealed five clusters of the CSs: CSs associated with non-reward, CS associated with water, 1-s CSs associated with sucrose, 2-s CSs associated with sucrose, and 4-s CS associated with sucrose, which were correlated to lick latencies. It is noted that the presentation of the CS associated with water resulted in longer latencies and that the same CSs associated with water were located nearer the CSs associated with non-reward in the MDS space based on the late CS^+-selective neuronal activity. Taken together, these results suggest that the activity of early CS^+-selective neurons reflects the predictive property of CSs, while activity of late CS^+-selective neurons reflects the incentive property of CSs.

In the present study, the late CS^+-selective neurons were more densely located in the anterior part of the PVT. Neuroanatomical studies reported that the anterior and posterior parts of the PVT have different anatomical connections; the posterior part of the PVT has stronger connections with areas related to stress and fear expression such as the amygdala (Vertes and Hoover, 2008; Li and Kirouac, 2008, 2012). Furthermore, optogenetic, genetic, or pharmacological manipulations of the anterior part of the PVT affect reward-seeking behaviors (Choi et al., 2012; Barson et al., 2015, 2017; Do-Monte et al., 2017), while *c-fos* expression increases in the anterior part of the PVT when motivation for food is increased by various behavioral and pharmacological manipulations (Warne et al., 2007; Choi et al., 2010; Mitra et al., 2011). In addition, optogenetic activation of projections from the anterior part of the PVT to the nucleus accumbens increased motivation for feeding in a stressful condition (Cheng et al., 2018), and cocaine treatment increased firing rates of neurons in the anterior part of the PVT (Yeoh et al., 2014). These findings suggest that the anterior part of the PVT controls motivated behaviors, which might be subserved partly by late CS^+-selective neurons. However, it should be noted that this difference between the anterior and posterior parts of the PVT is rather quantitative in the present study since some late CS^+-selective neurons were also located in the posterior part of the PVT, consistent with a previous study showing that genetic and anatomical characteristics of the PVT gradually changed from its anterior to posterior parts (Gao et al., 2020).

Neural Mechanisms of Reward-Seeking Behaviors

The PVT is one of the important areas in the meso-cortico-limbic circuits involved in reward "wanting" and hedonic "liking" (Richard et al., 2013). The PVT receives cue information from the prefrontal cortex, amygdala, and septum and sends projections to the nucleus accumbens (see section "Introduction"). Projection fibers from the PVT to the nucleus accumbens are glutamatergic/aspartatergic (Christie et al., 1987; Frassoni et al., 1997), and stimulation of the PVT increases dopamine release in the nucleus accumbens (Jones et al., 1989; Pinto et al., 2003; Parsons et al., 2007). It is reported that presentation of CSs associated with reward increases glutamate release, as well as dopamine release in the nucleus accumbens (Roitman et al., 2004; Batten et al., 2018), that increases in dopamine levels in the nucleus accumbens, are associated with the occurrence of operant action in response to CSs associated with reward (Roitman et al., 2004; Ko and Wanat, 2016), and that depletion of dopamine in the nucleus accumbens delays the latency of operant responses after the onset of CSs (Cole and Robbins, 1989). Furthermore, a recent study reported that dopaminergic projections to the nucleus accumbens core and shell were involved in reward association for instrumental responses and motivation for the responses, respectively (Heymann et al., 2020). Taken together, these findings suggest that the PVT, especially the late CS+-selective neurons, might enhance reward-seeking behaviors, as indicated by lick latency, through dopamine levels in the nucleus accumbens.

Unconditioned stimulus-responsive neurons with and without lick correlation were located in both the anterior and posterior parts of the PVT. Neurons with lick correlation have been reported in the PVT although their rostro-caudal presence has not been described yet (Li et al., 2016). The PVT receives projections from the superior colliculus (Krout et al., 2001), which is involved in oral sensory information processing and control of rhythmic tongue and oral movements (Auroy et al., 1991; Moore et al., 2014). In turn, the PVT sends projections to the nucleus accumbens (Vertes and Hoover, 2008; Li and Kirouac, 2008), which is involved in hedonic rhythmic mouth and tongue movements during ingestion of a sweet reward (Richard et al., 2013). There are two types of mouth movements in rodents (Grill and Norgren, 1978; Steiner et al., 2001): sweet solutions induce rhythmic tongue movements and mouth

expressions of "liking," while bitter solutions induce "disgust" gapes. Rhythmic licking movements during ingestion of sucrose and water in the present study might correspond to "liking" expression of mouth movements. Consistent with this idea, the mean number of licking was increased during ingestion of sucrose compared to water. These findings suggest that US-responsive neurons with lick correlation might be involved in hedonic reaction in response to palatable food through its connection to the nucleus accumbens.

In conclusion, the present results suggest that the anterior and posterior parts of the PVT are organized heterogeneously and that the PVT neurons engage in different neural processes involved in a cue-induced motivated behavior: CS encoding to determine reward availability and form motivation for reward-seeking behavior, and hedonic mouth movements during reward consumption. However, it should be noted that there were no direct measures of incentive values of the CSs in the present study, since it is difficult to test animals with various behavioral tests (such as approach, conditioned reinforcement, and Pavlovian-instrumental transfer) while single PVT neuronal activity was simultaneously recorded from head-fixed animals. Instead, we measured lick latency of the animals, which has been reported to reflect impulsive drive of animals (Bari and Robbins, 2013; Berditchevskaia et al., 2016). Further studies using psychostimulants such as amphetamine, which increased neuronal responses to temporally proximal cues (Tindell et al., 2005), would be interesting to observe changes in firing rates of late CS^+-selective neurons.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by Ethical Committee for Animal Experiments at University of Toyama.

AUTHOR CONTRIBUTIONS

HNJ designed the experiment. UM and CC performed the experiment. UM, CC, and HNJ analyzed the data and wrote the manuscript. UM, CC, JM, HNM, TO, and HNJ revised the manuscript. All authors discussed the results and approved the final manuscript.

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This study was performed as a doctoral thesis in University of Toyama, and a part of the results is available in abstract form from the university website (Munkhzaya, 2019).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnbeh.2020.565002/full#supplementary-material

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MINI REVIEW
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The Contribution of Thalamic Nuclei in Salience Processing

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The brain continuously receives diverse information about the external environment and changes in the homeostatic state. The attribution of salience determines which stimuli capture attention and, therefore, plays an essential role in regulating emotions and guiding behaviors. Although the thalamus is included in the salience network, the neural mechanism of how the thalamus contributes to salience processing remains elusive. In this mini-review, we will focus on recent advances in understanding the specific roles of distinct thalamic nuclei in salience processing. We will summarize the functional connections between thalamus nuclei and other key nodes in the salience network. We will highlight the convergence of neural circuits involved in reward and pain processing, arousal, and attention control in thalamic structures. We will discuss how thalamic activities represent salience information in associative learning and how thalamic neurons modulate adaptive behaviors. Lastly, we will review recent studies which investigate the contribution of thalamic dysfunction to aberrant salience processing in neuropsychiatric disorders, such as drug addiction, posttraumatic stress disorder (PTSD), and schizophrenia. Based on emerging evidence from both human and rodent research, we propose that the thalamus, different from previous studies that as an information relay, has a broader role in coordinating the cognitive process and regulating emotions.

Keywords: salience, motivated behaviors, thalamus, paraventricular thalamus, mediodorsal thalamus

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INTRODUCTION

Complex sensory inputs about the external world and constant update of the internal state are fed into our neural system at every moment. The ability to capture the most relevant information from the noisy background is critical to both learning and survival. The saliency of a stimulus is not only determined by its physical properties but also influenced by different behavioral context and motivational states (Puglisi-Allegra and Ventura, 2012). Therefore, salience processing requires the cooperation of sensory, emotion, and attention systems throughout the brain (Uddin, 2015; Peters et al., 2016).

A variety of neuroimaging studies have revealed the cortical nodes of the salience network, the dorsal anterior cingulate cortex (dACC), and anterior insula (AI) (Downar et al., 2000, 2001;

Seeley et al., 2007). Subcortical structures including the thalamus, the striatum, and the midbrain dopamine nuclei, which cooperate with the cortical nodes in cognitive control, also contribute to salience processing (Menon, 2011; Yeo et al., 2011; Wolff and Vann, 2019). Thalamic nuclei have reciprocal connections with the cerebral cortex and subcortical structures, participating in the regulation of arousal, emotion, and cognitive attention control (Schmahmann, 2003; Wolff and Vann, 2019). In the current mini-review, we will discuss the potential mechanism how the thalamus contributes to salience processing. Functional connectivity profiles of thalamic nuclei could throw light on how the thalamus might coordinate cortical and subcortical activities. Recordings of thalamic activities during adaptive behaviors provide critical evidence on how thalamic neurons encode salience and hence contribute to associative learning. We will also review recent evidence showing that dysfunction of thalamic nuclei is implicated in neural pathologies.

CONNECTIVITY PROFILES OF THALAMIC NUCLEI

Early ideas about thalamic anatomy and function were derived from classic studies of the LGN (lateral genicular nucleus) (Hubel and Wiesel, 1962). LGN neurons receive topographic input from the retina and exhibit highly topographic projections and specific laminar patterns of terminations in the primary visual cortex. Therefore, it was widely believed that the thalamus is responsible for precise "bottom-up" transmission of input to primary cortical targets. In fact, this traditional view merely represents the anatomy and function of a restricted group of thalamic nuclei; other thalamic nuclei show distinct projection patterns, which are also categorized as non-specific thalamic nuclei (Kamikawa et al., 1967; Van der Werf et al., 2002; Vertes et al., 2015). For example, axon collaterals of neurons in the paraventricular thalamus (PVT) extend to the prefrontal cortex (PFC), nucleus accumbens (NAc), bed nucleus of the stria terminalis (BNST), and central amygdala (CeA), allowing simultaneous activation of distant brain regions (Bubser and Deutch, 1998; Dong et al., 2017; Millan et al., 2017). Non-specific thalamic nuclei, such as the midline and intralaminar thalamus, which do not receive direct input from ascending tracts but have diffuse projections to limbic cortical areas, hypothalamus and striatum (Kuramoto et al., 2015, 2017), will be the main focus of the current review.

Thalamocortical projections exhibit interesting anatomical features, which support the role of the thalamus in orchestrating cortical activities and regulating cognitive functions. For example, single neurons in the mediodorsal thalamus (MD) send axons to multiple prefrontal areas and form patchy axon arbors. This organization allows MD neurons to recruit a specific set of cortical neurons in distant cortical regions, compatible with the role of the MD in coordinating task-relevant cortical representations. In addition, thalamic axon arborizations are found not only in the relay layer (layer4) but also in the superficial layers of the cerebrocortex (Avendano et al., 1990; Rubio-Garrido et al., 2009), which are essential for information transmission and cortical computation. Another key feature of the thalamocortical pathway is the robust feedforward inhibition mediated by cortical inhibitory neurons (Cruikshank et al., 2007, 2010; Bagnall et al., 2011). A recent study reported that two thalamic nuclei target distinct types of cortical interneurons in the PFC and thus have differential influence on dendritic and somatic activity (Anastasiades et al., 2020). These properties are well equipped for temporal precise and pathway-specific regulation of cortical output. Besides reciprocal connections with the cerebral cortex, the thalamus receives extensive input from the brainstem and hypothalamus, obtaining information about general arousal and interoceptive states (Sherman, 2007; Kumar et al., 2017). The thalamus also projects to the striatum and amygdala, supporting its role in orientating motivation and regulating emotion.

Altogether, the thalamus is in position to detect and orientate neural resources toward behavioral relevant stimuli. This view is further evidenced by myriad functional imaging studies (Robinson and Petersen, 1992; Peters et al., 2016). On top of that, emerging circuitry studies investigating thalamic control of awareness and cognitive process have brought to light the mechanism how the thalamus contributes to salience control (Floresco and Grace, 2003; Halassa et al., 2014; Rikhye et al., 2018). In the subsequent sections, we will highlight recent advances in understanding the role of thalamic pathways in arousal and attention control, pain and reward, and emotion regulation.

Thalamic Pathways Regulating Arousal State

Salience processing is often associated with amplification of certain sensory inputs and enhanced functional connectivity, whereas arousal also requires enhanced brain excitability and connectivity, but at a more general scale (Massimini et al., 2005; Nakajima and Halassa, 2017). Therefore, salience attribution could be conceptualized as dynamic control of specific arousal states of task-related neural circuits (Sakai, 2008). We will review evidence that thalamic circuitry participates in arousal regulation, aiming to give some clues on how the thalamus might contribute to salience processing.

Midline thalamic nuclei receiving hypothalamic and brainstem inputs connect with widespread cortical areas (Herkenham, 1979; Kuramoto et al., 2015). Hence, midline thalamic nuclei are well positioned anatomically to summate subcortical arousal information and modulate forebrain activity strongly and diffusely (Matyas et al., 2018; Ren et al., 2018). The PVT receives input from the brainstem arousal nuclei, such as the locus coeruleus and reticular formation (Krout et al., 2002; Li and Kirouac, 2012). Moreover, it is reciprocally connected with the suprachiasmatic nucleus (Alamilla et al., 2015; Yuan et al., 2018), which is the primary circadian pacemaker in the brain. Moreover, the PVT is also densely innervated by orexinergic fibers (Matzeu et al., 2014), the activation of which depolarizes postsynaptic PVT neurons (Ishibashi et al., 2005). Compelling evidence has demonstrated a key role of the orexin/hypocretin system in arousal and maintenance of the awaking state (de Lecea, 2012). Activation of the PVT effectively promotes wakefulness under the regulation of hypocretin neurons in the

lateral hypothalamus (Ren et al., 2018). Moreover, different PVT output pathways might be in charge of arousal regulation in various homeostatic states (Hua et al., 2018; Meffre et al., 2019). However, a recent study found a subpopulation of PVT neurons that are negatively modulated by wakefulness and arousal (Gao et al., 2020). This discrepancy might rise from the difference in anatomical location that previous studies focused on the posterior part of the PVT, whereas the recent one investigated a genetically defined subgroup of neurons which populates in the anterior part. Future studies examining the afferents of distinct PVT subregions and subpopulations will help clarify the role of the PVT in arousal.

The majority of thalamic neurons are glutamatergic; however, neurons in the reticular thalamus (TRN) are primarily GABAergic and exert inhibitory control over thalamic nuclei (Halassa and Acsady, 2016). Spontaneous firing of midline thalamic neurons in mice is phase-advanced to global cortical up states (Gent et al., 2018). Whereas enhanced spiking during sleep is found in TRN subnetworks that project to sensory-related thalamic circuits (Halassa et al., 2014; Chen et al., 2015b), attention decreases TRN responses to visual stimuli (McAlonan et al., 2008). The TRN regulates thalamocortical activities and has a causal role in generating sleep spindles (Bazhenov et al., 2000; Cueni et al., 2008; Halassa et al., 2011). Optogenetic manipulations of TRN activities bidirectionally modulate arousal states (Lewis et al., 2015; Herrera et al., 2016). Recent studies have revealed that cholinergic and noradrenergic inputs to the TRN participate in regulating sleep and arousal (Ni et al., 2016; Zhang et al., 2019).

Pain- and Reward-Related Thalamic Pathways

Neurocircuits regulating pain and reward have been considered as part of the system orientating attention toward various salient stimuli (Roland, 1992; Uddin, 2015; Kummer et al., 2020). Thalamic neurons receiving inputs from the spinal cord, the midbrain, and the hypothalamus (Yen and Lu, 2013; Kirouac, 2015) are activated by noxious and appetitive stimuli (Casey and Morrow, 1983; Kim et al., 2003). The medial and intralaminar thalamic nuclei are the major source of pain-associated information to the limbic cortex (Livneh et al., 2017; Meda et al., 2019; Liang et al., 2020a).

Inactivation of the dorsal thalamic nuclei has been shown to suppress pain and pain related aversion (Jurik et al., 2015; Cheng et al., 2017; Zhou et al., 2019). In addition, the ratio between excitation and feedforward inhibition of thalamic input to the cortex is important for the regulation of affective pain (Jurik et al., 2015; Meda et al., 2019). Activation of the PVT-CeA pathway induces mechanical allodynia (Liang et al., 2020b), reflecting a potential role of the PVT in pain-associated salience attribution. The PVT is also engaged in reward-seeking behaviors (James et al., 2011a; Browning et al., 2014; Choudhary et al., 2018). The PVT shows increased neuronal activation in response to reward and reward-associated cues (Igelstrom et al., 2010; James et al., 2011a; Yeoh et al., 2014; Munkhzaya et al., 2020). Suppression of PVT activities could attenuate reward-motivated behaviors (Hamlin et al., 2009; Ong et al., 2017) (but see Stratford and Wirtshafter, 2013; Zhang and van den Pol, 2017). A growing body of evidence suggests that the PVT plays a role in integrating complex homeostatic signals and informing adaptive behaviors during motivational conflicts (Ferrario et al., 2016; Choi and McNally, 2017; Meffre et al., 2019). Using *in vivo* single-unit recording, Zhu et al. showed that posterior PVT neurons could be activated by both rewarding and aversive stimulus and the cues predicting those outcomes, indicating that the pPVT encodes stimulus salience irrespective of valance (Zhu et al., 2018). By alterations of the behavioral context and modulation of homeostatic states, they further demonstrated that the PVT provides dynamic representation of salience and thus contribute to associative learning.

Thalamic Circuitry in the Regulation of Attention

By definition, salience describes the ability of a stimulus or an event to capture attention. On the other hand, salience attribution is strongly influenced by top-down attention control and emotional states. Thalamic nuclei, such as the anterior thalamic nuclei (ATN) and the MD, contribute to attention control primarily via their connections with limbic structures (Parnaudeau et al., 2013; Wright et al., 2015; Wolff and Vann, 2019). The ATN is densely connected with both the hippocampus and the frontal lobe and thus is believed to play a role in memory-guided attention (Leszczynski and Staudigl, 2016). Using deep brain stimulation (DBS) in human subjects, studies suggest that the ATN is involved in emotion–attention interaction (Hartikainen et al., 2014; Sun et al., 2015).

Accumulating evidence from human and animal studies have indicated that disruption of the MD impairs cognitive processes (Block et al., 2007; Nakajima and Halassa, 2017; Parnaudeau et al., 2018; Pergola et al., 2018). Anatomically, the MD receives modulatory input from the midbrain and brainstem and forms a reciprocal connection with the frontal cortex (Russchen et al., 1987; Mitchell, 2015; Collins et al., 2018). Single MD neurons receive convergence of small cortical inputs and project to multiple cortices across multiple layers (Rubio-Garrido et al., 2009; Kuramoto et al., 2017; Georgescu et al., 2020). Schmitt et al. (2017) proposed that the MD sustains rule representations in the PFC. Interestingly, enhancing MD excitability improved rule specificity and behavioral performance, in contrast to the reduction of rule information induced by enhancing PFC excitability. These results imply that the MD input exerts the effect by regulating the functional micro-circuitry in the PFC instead of non-selectively boosting the excitability of pyramidal neurons.

Dynamic control of salience is also reflected in the process of cognitive switching, which is important for action selection and behavioral flexibility. Thalamic nuclei are involved in cognitive switching primarily through connections with the striatum and PFC (Phillips et al., 2016). The centromedian (CM) and parafascicular nucleus (PF) are the major thalamic input to the dorsal striatum (DS) (Ilyas et al., 2019). Primate studies have suggested that the CM and PF provide the striatum with

information about salience (Matsumoto et al., 2001; Minamimoto and Kimura, 2002; Yamanaka et al., 2018). Studies in rodents extend these findings by showing that disruption of CM/PF-DS pathway increased the perseverative responses and aggravated the interference between new and old learning (Bradfield et al., 2013; Bradfield and Balleine, 2017; Saund et al., 2017; Kato et al., 2018). The MD also contributes to behavioral flexibility and probably exerts its role through feedforward inhibition (Kuroda et al., 2004; Rotaru et al., 2005; Block et al., 2007; Delevich et al., 2015). In addition, a recent study suggested that MD-mediated suppression preserves unused cortical traces for future use (Rikhye et al., 2018). Subnetworks in the TRN exert inhibitory control over spatially discrete thalamic targets, suppressing distracting inputs (Pinault and Deschenes, 1998; Zikopoulos and Barbas, 2012; Halassa et al., 2014; Wimmer et al., 2015). Although the PFC does not directly project to the TRN, the PFC could regulate modality specific TRN subnetworks via the globus pallidus (GP) (Nakajima et al., 2019). In addition, the TRN is innervated by amygdalar input, providing a mechanism for emotion-driven attention shift (Zikopoulos and Barbas, 2012).

Thalamic Circuitry in the Regulation of Emotion

Without adequate assignment of salience, stimuli that typically trigger mood and emotions can no longer attract one's interest to act and react. Thus, it is not surprising that aberrant functional connectivity in the salience network is frequently observed in depressed patients (Pannekoek et al., 2014; Yuen et al., 2014; Rzepa and McCabe, 2016). Functional MRI studies have reported decreased functional connectivity between the dACC and the MD in the depressed patients (Wang et al., 2012). Moreover, improved MD-PFC connectivity has been associated with effective depression treatments (Salomons et al., 2014; Leaver et al., 2016). Consistently, synaptic strength of the MD-PFC pathway is reduced in a rodent model of depression, while activation of this pathway is sufficient to reduce depression-like behavior (Miller et al., 2017). Interestingly, a recent study found that the visual thalamus could affect the midbrain monoaminergic centers via the lateral habenula (Huang et al., 2019). In addition, this pathway might mediate the antidepressive effect of light therapy.

Thalamic nuclei modulate both innate fear and conditioned fear responses (Li et al., 2004; Penzo et al., 2015; Salay et al., 2018). Fear extinction is a process involving progressive suppression of the salience of fear-associative cue or context. Manipulations of thalamic activities have been shown to bidirectionally modulate fear extinction (Padilla-Coreano et al., 2012; Matyas et al., 2014; Paydar et al., 2014; Do-Monte et al., 2015; Lee et al., 2019; Ramanathan and Maren, 2019). Thalamic neurons exhibit two firing modes, tonic and burst, which could modulate behaviors in opposite directions (Sherman, 2001). Using tetrode recording in free-moving mice, Lee et al. (2011) showed that the tonic firing frequency of MD neurons positively correlates with the extent of fear extinction. In addition, enhancing tonic firing of MD neurons facilitated fear extinction, whereas burst-evoking stimulation suppressed extinction, indicating that distinct firing modes of MD neurons might bidirectionally modulate salience of fear-associated cue (Lee et al., 2011; Georgescu et al., 2020).

On the other hand, augmented observational fear responses have been demonstrated in socially related conspecifics (Jeon et al., 2010). Social transmission of fear is associated with a significant increase of activity in the PVT, MD, and ACC (Chang and Debiec, 2016; Zheng et al., 2020). Since the PVT and MD have been reported to regulate social related behaviors (Zhou et al., 2017; Watarai et al., 2020; Yamamuro et al., 2020), they might participate in social salience modulation of fear response.

THALAMIC DYSFUNCTION AND NEUROPSYCHIATRIC DISORDERS

Given the essential role of the thalamus in salience processing, it is perhaps not surprising that altered connectivity patterns and responses of thalamic nuclei have been poised to contribute to the aberrant salience attribution in neuropsychiatric disorders. Below, we will describe the engagement of thalamic dysfunction in three distinct mental disorders, in which dysregulation of salience processing is often observed.

Drug Addiction Disorder

Drugs of abuse profoundly modulate neural response toward previous neutral stimuli which become associated with drugs. The development of incentive salience of drug-paired context or cues is an essential component of drug addiction (Koob and Volkow, 2016). As discussed above, the PVT is anatomically well positioned to coordinate drug-related behaviors (Browning et al., 2014; Zhou and Zhu, 2019). PVT neurons express orexin, opioid, and dopaminergic receptors and receive multiple neuromodulatory inputs (Mansour et al., 1986; Clark et al., 2017). PVT neuronal activity and plasticity in PVT-related pathways are modulated by drug-related behaviors (Deutch et al., 1998; Kolaj et al., 2014; Yeoh et al., 2014; Chen et al., 2015a; Zhu et al., 2016). Consistent with the idea that PVT neurons encode stimulus salience, a recent study showed that manipulations of the PVT-CeA pathway could bidirectionally modulate morphine-conditioned place preference, suggesting that the PVT-CeA pathway associates incentive salience of the drug with paired environment (Keyes et al., 2020). However, manipulations of the PVT pathways could result in diverse outcomes in literature (**Table 1**). Further investigation of the heterogeneity in anatomical location, connectivity profile, activity pattern, and genetic markers of the PVT neurons might help to resolve this ambiguity (Millan et al., 2017; McGinty and Otis, 2020).

The phenomenon that drug-seeking behaviors progressively increase after abstinence is termed incubation of craving (Lu et al., 2004; Pickens et al., 2011). In addition to the contribution of the mesolimbic dopaminergic signal (Caprioli et al., 2017; Rossi et al., 2020), glutamate has been shown to participate in incubation of craving (Li et al., 2015; Shin et al., 2016).

TABLE 1 | Effect of PVT manipulations on drug related behaviors.

Position/pathway	Manipulation	Effect (↑ - ↓)	Drug	Species	References
aPVT	Baclofen and muscimol	↓ Expression of CPP	Cocaine	Rat	Browning et al., 2014
aPVT	Orexins	↑ Drug consumption	Ethanol	Rat	Barson et al., 2015
	Ox2R antagonist	↓ Drug consumption			
aPVT	NTS	- Drug consumption in lower drinkers	Ethanol	Rat	Pandey et al., 2019
PVT	Electrolytic lesion	↓ Locomotor activity and sensitization	Cocaine	Rat	Young and Deutch, 1998
PVT	Excitotoxic lesion	- Acquisition of drug seeking	Ethanol	Rat	Hamlin et al., 2009
		↓ Context-induced reinstatement			
PVT	TTX or CART	↓ Drug-primed reinstatement	Cocaine	Rat	James et al., 2010
PVT	Orxr1 antagonist	- Cue induced reinstatement	Cocaine	Rat	James et al., 2011b
PVT	Baclofen and muscimol	Cue-induced drug-seeking in goal-trackers↓; in sign-trackers -	Cocaine	Rat	Kuhn et al., 2018
pPVT	OX2R antagonist	↓ Naloxone-precipitated CPA	Morphine	Rat	Li et al., 2011
	OX1R antagonist	- Naloxone-precipitated CPA			
pPVT	Orexins/OX1R or OX2R antagonist	- Drug consumption	Ethanol	Rat	Barson et al., 2015
pPVT	Orexin A	↑ Cocaine reinstatement	Cocaine	Rat	Matzeu et al., 2016
	OX2R antagonist	↓ Orexin primed reinstatement			
	OX1R antagonist	- Orexin primed cocaine seeking			
pPVT	Overexpression of D2Rs	↓ Locomotor sensitization	Cocaine	Mouse	Clark et al., 2017
pPVT	Orexin A	↑ Drug	Cocaine	Rat	Matzeu et al., 2018
	Dynorphin	- reinstatement			
	Orexin A and Dyanorphin	↓ Orexin-induced drug reinstatement			
pPVT	NTS	↓ Drug consumption in higher drinkers	Ethanol	Rat	Pandey et al., 2019
	NTS antagonist	↑ Drug consumption			
PVT→ NAc	Tetanus toxin	↓ Self-administration	Cocaine	Rat	Neumann et al., 2016
		- Incubation of craving after prolonged withdrawal			
pPVT→ NAc	Chemogenetic or optogenetic inhibition/optogenentic LTD	↓ Naloxone-precipitated withdrawal symptoms ↓ CPA	Morphine	Mouse	Zhu et al., 2016
PrL→ PVT	Chemogenetic inhibition	↓ Context or cue induced drug reinstatement	Cocaine	Rat	Giannotti et al., 2018
pPVT→ NAc	Chemogenetic/optogenetic inhibition	↓ Retrieval of CPP; - Acquisition of CPP	Morphine	Mouse	Keyes et al., 2020
pPVT→ CeA	Chemogenetic inhibition	↓ Acquisition of CPP; - Retrieval of CPP			
	Optogenentic activation	↑ CPP at suboptimal dose			
pPVT	Baclofen and muscimol	-	Heroin	Rat	Chisholm et al., 2020a
	Chemogenetic activation	↓			
PrL→ pPVT	Chemogenetic activation or inhibition	- Food restriction-induced augmentation of drug seeking			
pPVT→ NAc core	Chemogenetic activation	-			Chisholm et al., 2020b
pPVT→ NAc shell	Chemogenetic activation	↓			

Incubated methamphetamine (Meth) seeking selectively activated glutamatergic input from anterior intralaminar nuclei of the thalamus (AIT) to dorsomedial striatum (DMS) (Li et al., 2018). Furthermore, inactivation of the AIT-DMS pathway attenuated incubated Meth craving while leaving non-incubated Meth seeking intact. These results suggest a critical role of the AIT in the regulation of incentive salience and drug relapse.

Posttraumatic Stress Disorder

Posttraumatic stress disorder (PTSD) is a long-lasting and recurring mental disorder triggered by traumatic experience. Trauma recollection is associated with enhanced connectivity in the salience network, while salience connectivity is reduced following effective treatment in PTSD patients (Abdallah et al., 2019a,b). PTSD subjects showed significantly less activation of the thalamus (Lanius et al., 2001; Suarez-Jimenez et al., 2020). In a case report, new onset of PTSD occurred after thalamic infarct in a Korean War veteran (Duggal, 2002). In addition, an fMRI study showed that a larger magnitude of spontaneous activity in the thalamus is associated with lower reexperiencing symptoms in PTSD (Yan et al., 2013). Studies in rodent animals further analyzed the requirement of thalamic function during different time points of fear retrieval. For example, the PVT is gradually recruited during fear retrieval (Padilla-Coreano et al., 2012).

Suppression of the PVT-CeA pathway disrupts fear retrieval at late but not early time points, suggesting the induction of long-term plasticity in this pathway (Do-Monte et al., 2015; Penzo et al., 2015).

Psychotherapeutic strategies for treating PTSD often involve reassignment of salience and modulation of attentional processes (Badura-Brack et al., 2015). For example, eye movement desensitization and reprocessing (EMDR) is a treatment using alternating bilateral sensory stimulation (ABS) to interfere with fear memory recall (Novo Navarro et al., 2018). The mechanism underlying the therapeutic effect of visual ABS can be inferred from the study by Baek et al. They found that ABS could drive activity in the superior colliculus (SC)-MD pathway which induces sustained BLA inhibition during fear extinction (Baek et al., 2019). Their results argue that MD mediates the competition between visual–attentional process and emotional activity and serves as a key target of treatment for PTSD.

Schizophrenia

Schizophrenia is a mental disorder involving a range of problems in cognition, emotion, and behaviors. One influential theory about schizophrenia is that positive symptoms including hallucination and illusion could be attributed to aberrant assignment of salience to a certain experience or internal representation (Kapur, 2003; van Os and Kapur, 2009; Kim et al., 2018).

Abnormalities in structure and function of the thalamus have been associated with schizophrenia (Byne et al., 2009). According to genome-wide association studies, thalamic neurons express several schizophrenia-relevant genes (Watis et al., 2008; Pergola et al., 2015; Takahashi et al., 2015; Krol et al., 2018). A reduced volume of the thalamus has been found in schizophrenia patients (Volz et al., 2000; Konick and Friedman, 2001). A decreased number of parvalbumin (PV) neurons in the thalamus have been reported in human postmortem schizophrenia brains and rodent models (Danos et al., 1998; Steullet et al., 2018). Studies indicate that thalamocortical connections are compromised in schizophrenia (Sharp et al., 2001; Woodward et al., 2012; Avram et al., 2018; Delevich et al., 2020), which might cause disturbances in sensory gating and top-down control (Anticevic et al., 2014).

FUTURE DIRECTIONS

As discussed above, thalamic neurons could encode salient features of stimuli, contributing to cognitive process and emotional regulation. However, it remains unknown how the information of salience is integrated from distinct pathways in single thalamic neurons. Also, it is worth further investigating the role of the neuromodulatory system on salience control in the thalamus. Stress induces perturbations in the structure and function of the brain, which present a major risk factor for many neuropsychiatric disorders. Future studies describing the molecular and circuitry adaptations in acute and chronic stress, would help us to analyze the contribution of the thalamus to salience allocation under pathological conditions.

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Cocaine-Seeking Behavior Induced by Orexin A Administration in the Posterior Paraventricular Nucleus of the Thalamus Is Not Long-Lasting: Neuroadaptation of the Orexin System During Cocaine Abstinence

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Hypothalamic orexin (Orx) projections to the paraventricular nucleus of the thalamus (PVT) have received growing interest because of their role in drug-seeking behavior. Using an established model of cocaine dependence (i.e., long access [LgA] to cocaine), we previously showed that OrxA injections in the posterior PVT (pPVT) reinstated extinguished cocaine-seeking behavior in rats after an intermediate period of abstinence (2–3 weeks). Considering the long-lasting nature of drug-seeking behavior, the present study examined whether the priming effect of intra-pPVT OrxA administration was preserved after a period of protracted abstinence (4–5 weeks) in rats that self-administered cocaine under LgA conditions. Furthermore, to better understand whether a history of cocaine dependence affects the Orx system—particularly the hypothalamic Orx↔pPVT connection—the number of Orx-expressing cells in the lateral hypothalamus (LH), dorsomedial hypothalamus (DMH), and perifornical area (PFA) and number of orexin receptor 1 (OrxR1)- and OrxR2-expressing cells in the pPVT were quantified. Orexin A administration in the pPVT induced cocaine-seeking behavior after intermediate abstinence, as reported previously. At protracted abstinence, however, the priming effect of OrxA was absent. A higher number of cells that expressed Orx was observed in the LH/DMH/PFA at both intermediate and protracted abstinence. In the pPVT, the number of OrxR2-expressing cells was significantly higher only at intermediate abstinence, with no changes in the number of OrxR1-expressing cells. These data build on our previous findings that the hypothalamic Orx↔pPVT connection is strongly recruited shortly after cocaine abstinence and demonstrate that the priming effect of OrxA is not long lasting. Furthermore, these findings suggest that throughout abstinence, the Orx↔pPVT connection undergoes neuroadaptive changes, reflected by alterations of the number of OrxR2-expressing cells in the pPVT.

Keywords: orexin, cocaine, pPVT, abstinence, OrxRs

INTRODUCTION

The paraventricular nucleus of the thalamus (PVT) plays a major role in regulating arousal, attention, awareness states, food consumption, and energy balance (Bentivoglio et al., 1991; Groenewegen and Berendse, 1994; Van der Werf et al., 2002; Colavito et al., 2015; Kirouac, 2015). The PVT has been consistently shown to be activated during periods of arousal and stressful conditions (Peng et al., 1995; Bhatnagar and Dallman, 1998; Novak and Nunez, 1998; Bubser and Deutch, 1999; Novak et al., 2000; Otake et al., 2002). The PVT has attracted interest because of its connections with limbic and cortical structures that are part of the neurocircuitry that mediates drug-seeking behavior (Everitt et al., 2001; McFarland and Kalivas, 2001; Ito et al., 2002; Kalivas and Volkow, 2005; Belin and Everitt, 2008; Steketee and Kalivas, 2011). The PVT is selectively recruited during cocaine-seeking behavior that is induced by the presentation of cocaine-predictive stimuli (Matzeu et al., 2017), and its integrity is necessary for behavior that is motivated by the presentation of cocaine-predictive environmental stimuli (Matzeu et al., 2015). Some of the pivotal components of the neurocircuitry of addiction (Koob and Volkow, 2010) receive projections from the PVT (Kirouac, 2015), highlighting the potential importance of this thalamic nucleus in the regulation of compulsive drug seeking that characterizes addiction. The expression of orexin (Orx), also known as hypocretin, is restricted to a small group of neurons in the hypothalamus: lateral hypothalamus (LH), dorsomedial hypothalamus (DMH), and perifornical area (PFA; de Lecea et al., 1998; Peyron et al., 1998; Sakurai et al., 1998). Although Orx-containing neurons represent a relatively small proportion of cells, their projections are widely distributed throughout the brain (Peyron et al., 1998), thus explaining how they can play diverse roles in physiological functions, including energy homeostasis, arousal, sleep/wake cycles (Sutcliffe and de Lecea, 2000; Mieda and Yanagisawa, 2002; de Lecea, 2012), and reward function (e.g., drug-seeking behavior; Harris et al., 2005; Dayas et al., 2008; Martin-Fardon et al., 2010, 2016; Jupp et al., 2011; Sakurai and Mieda, 2011). Orexin neurons project to structures that control behavior that is motivated by drugs of abuse, such as septal nuclei, the central nucleus of the amygdala, the ventral tegmental area, the medial prefrontal cortex, the nucleus accumbens shell, and the PVT, especially its posterior part (pPVT; Peyron et al., 1998; Baldo et al., 2003; Kirouac et al., 2005; Hsu and Price, 2009). Importantly, OrxA in the pPVT has been directly implicated in cocaine-seeking behavior (Matzeu et al., 2016). A microinjection of OrxA in the pPVT reinstated (primed) extinguished cocaine-seeking behavior in animals that had a history of extended access to cocaine, an established animal model of cocaine dependence (Matzeu et al., 2016). Remaining unknown, however, are whether the priming effect of OrxA is long lasting and whether a history of cocaine dependence affects the Orx system, particularly the hypothalamic Orx↔pPVT connection.

Therefore, because of the remarkable long-lasting resistance to the extinction of cocaine-seeking behavior (Martin-Fardon et al., 2016) and strong recruitment of the Orx system (Martin-Fardon et al., 2016) and PVT (Matzeu et al., 2017) during cocaine-seeking behavior, the aim of the present study was to test the ability of microinjections of OrxA directly in the pPVT to reinstate extinguished cocaine-seeking behavior at 2–3 weeks of abstinence (i.e., intermediate abstinence) or 4–5 weeks of abstinence (protracted abstinence). These two time points were chosen based on previous reports from our group that contrasted long-term persistence of the motivating effects of cocaine-related stimuli vs. rapid extinction of the motivational effects of stimuli that were conditioned to a highly palatable food reward (Martin-Fardon and Weiss, 2017; Martin-Fardon et al., 2018). These time points correspond to the first and fourth cocaine-related stimulus presentations. Within the same time period after the last cocaine exposure, cocaine-related stimuli still induced the strong recovery of responding, whereas the presentation of highly palatable food reward-related stimuli did not (Martin-Fardon and Weiss, 2017; Martin-Fardon et al., 2018).

Behavioral specialization is observed among hypothalamic subregions, with the LH playing a role in the promotion (reinstatement) of drug seeking (e.g., Marchant et al., 2009) and the DMH/PFA playing a major role in the inhibition of this behavior (Marchant et al., 2012). A functional difference between the two subtypes of Orx receptors, OrxR1 and OrxR2, has been suggested (Aston-Jones et al., 2010). OrxR1 signaling is mainly involved in reward function, and OrxR2 signaling is mainly involved in arousal states. Consequently, to further understand whether a history of cocaine dependence affects the Orx system, which could explain the reinstating effect of OrxA when injected in the pPVT, a secondary aim of the present study was to quantify the number of Orx-expressing cells in three subregions of the hypothalamus (LH, DMH, and PFA) that produce Orx and the number of OrxR1- and OrxR2-positive cells in the pPVT at intermediate and protracted abstinence.

MATERIALS AND METHODS

Rats

Forty-three male Wistar rats (Charles River, Wilmington, MA, United States), weighing 200–225 g upon arrival in the laboratory, were housed two per cage in a temperature- and humidity-controlled vivarium on a reverse 12/12 h light/dark cycle with *ad libitum* access to food and water. The experiments were conducted during the dark phase. All of the procedures were conducted in strict adherence to the National Institutes of Health *Guide for the Care and Use of Laboratory Animals* and approved by the Institutional Animal Care and Use Committee of The Scripps Research Institute.

Self-Administration and Extinction Training

Figure 1 Rats that were designated for cocaine self-administration were surgically prepared with jugular catheters 7–10 days before beginning cocaine self-administration training in 6 h/day (i.e., long-access [LgA]) sessions. Each session was initiated by the extension of two retractable levers into the operant conditioning chambers (29 cm × 24 cm × 19.5 cm; Med Associates, St. Albans, VT, United States). Responses at the active

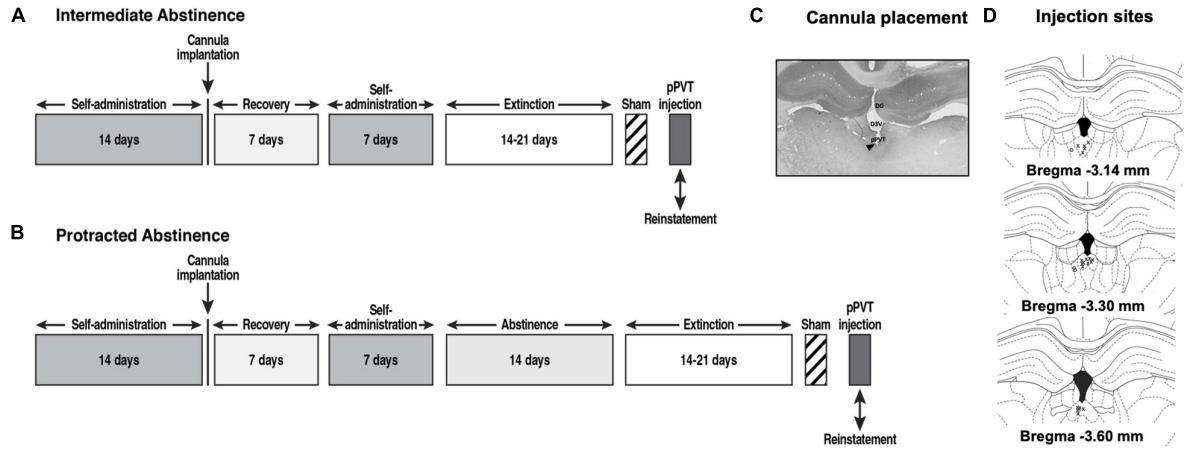

FIGURE 1 | Behavioral procedure at **(A)** intermediate abstinence and **(B)** protracted abstinence. **(C)** Representative photomicrograph of the cannula placement. The black triangle indicates the injection site. DG, dentate gyrus; D3V, dorsal third ventricle. **(D)** Schematic distribution of injection site tracks in the pPVT (*x*, rats with correct cannula placements; o, rats with cannula misplacements).

lever were reinforced on a fixed-ratio 1 (FR1) schedule by an intravenous (IV) infusion of cocaine (National Institute on Drug Abuse, Bethesda, MD, United States; 0.25 mg/0.1 ml/infusion) that was dissolved in 0.9% sodium chloride (Hospira, Lake Forest, IL, United States) and infused over 4 s. Each reinforced response was followed by a 20-s timeout (TO20) period that was signaled by the illumination of a cue light above the active lever. Responses at the inactive lever were recorded but had no scheduled consequences.

Cannulation

Fourteen days after beginning self-administration training, the rats that were designated for the reinstatement of cocaine seeking were implanted with a guide cannula (23-gage, 15 mm, Plastics One, Roanoke, VA, United States) that was aimed at the pPVT (anterior/posterior, −3.3 mm; medial/lateral, ±2.72 mm from bregma; dorsal/ventral, −2.96 mm from dura, 25° angle; Paxinos and Watson, 1997) and positioned 3.5 mm above the target injection point. After 7 days of recovery, the animals resumed self-administration training for an additional 7 days.

Extinction

The rats were divided into two subgroups with similar cocaine intake during self-administration training and tested at intermediate or protracted abstinence.

Intermediate Abstinence

Immediately following the completion of 21 daily self-administration sessions, the rats that were to be tested following intermediate abstinence underwent extinction training for 14–21 days (until the extinction criterion of ≤10 responses over three consecutive sessions was reached; Matzeu et al., 2016).

Protracted Abstinence

After the completion of 21 daily self-administration sessions, the rats that were to be tested following protracted abstinence were left undisturbed (with the exception of daily handling) in the vivarium for 14 days and then underwent extinction training for 14–21 days (until the extinction criterion of ≤10 responses over three consecutive sessions was reached), similar to intermediate abstinence rats. All of the extinction sessions lasted 2 h and began with extension of the levers into the operant chambers, with the same schedule of self-administration but without reward (cocaine) delivery.

Intra-PVT Microinjections

Figure 1 Following the last day of extinction training, the rats that were designated for intra-pPVT OrxA prime-induced reinstatement received a sham injection (Sham) for habituation to the microinjection procedure. Twenty-four hours later, they received an intra-pPVT microinjection of 0.5 μg OrxA (Matzeu et al., 2016; American Peptide, Sunnyvale, CA, United States) in 0.9% sodium chloride (Hospira, Lake Forest, IL, United States) or vehicle (i.e., 0.9% sodium chloride; Matzeu et al., 2016). The microinjections in the pPVT were performed using a microinfusion pump (Harvard 22 Syringe Pump, Holliston, MA, United States) and injectors that extended 3.5 mm beyond the guide cannula. The injections were performed at a flow rate of 0.5 μl/min over 1 min. The injectors were left in place for an additional minute to allow diffusion away from the injector tip. Following the injections, the rats were returned to their home cages for 2 min and then placed in the operant chambers under extinction conditions for 2 h. After the test, the rats were euthanized by CO_2 inhalation, and their brains were collected and snap frozen. The brains were sectioned coronally (40 μm) on a cryostat at −20°C, and injection tracks were verified (**Figures 1C,D**). Only rats with cannula placements that were located in the appropriate brain region were included in the data analysis.

Immunohistochemistry

In parallel with the behavioral experiments, a separate subgroup of rats was designated for histology. Following the last day of

extinction training (corresponding to the time at which the OrxA-induced reinstatement tests should have occurred) the rats ($n = 5$ for intermediate abstinence, $n = 5$ for protracted abstinence) were deeply anesthetized and transcardially perfused with cold 4% paraformaldehyde in 0.1 mM sodium tetraborate, pH 9.5. Brains were removed, postfixed in 4% paraformaldehyde overnight, and stored in 30% (w/v) sucrose, 0.1% (w/v) sodium azide, and potassium phosphate-buffered saline (KPBS) solution. The brains were sectioned coronally (40 μm) on a cryostat at −20°C and collected in a one-in-six series of adjacent sections. One section was then processed for OrxA immunodetection in the LH, DMH, and PFA, and the other two sections were processed for OrxR1 or OrxR2 detection in the pPVT. Briefly, coronal sections were blocked for 90 min using 5% normal donkey serum, 0.1% bovine serum albumin (BSA), and 0.3% Triton-X in PBS, followed by incubation for 48 h at room temperature with anti-OrxA antibody (1:15000, goat, Santa Cruz Biotechnology, Dallas, TX, United States), anti-OrxR1 (1:500, rabbit, Alamone Labs, Jerusalem, Israel), or anti-OrxR2 (1:500, rabbit, Alamone Labs, Jerusalem, Israel). The tissue sections were then incubated with ImmPress reagent with secondary antibodies for 90 min (anti-goat or anti-rabbit IgG, Vector Laboratories, Burlingame, CA, United States). OrxA, OrxR1, and OrxR2 immunostaining was visualized using DAB (Vectors Laboratories, Burlingame, CA, United States). Controls for antibody specificity were performed for all of the experiments by omitting the primary antibodies. This procedure was repeated for the secondary antibodies. OrxA-positive (Orx^+) cells were counted within sections that incorporated the LH, DMH, and PFA (typical range: −2.40 and −3.48 from bregma). $OrxR1^+$ and $OrxR2^+$ cells were counted within sections that included the pPVT (typical range: −2.80 and −3.80 from bregma). As a control for basal Orx, OrxR1, and OrxR2 expression for all groups, brains from two age-matched naive groups of rats that were handled daily for 5 min but were not exposed to the behavioral chambers ($n = 5$ for intermediate abstinence, $n = 5$ for protracted abstinence) were also processed for immunohistochemistry. The brain tissues were then processed as above for the other animals. Although investigating how OrxA-pPVT prime-induced reinstatement causes additional changes in the Orx/OrxRs system could be of interest, the rationale for processing the tissue for immunocytochemistry was to evaluate the state of the Orx/OrxR system at the time when the rats were tested with a microinjection of OrxA in the pPVT (i.e., 24 h after the last extinction session).

Statistical Analysis

The acquisition of cocaine self-administration was analyzed using two-way repeated-measures analysis of variance (ANOVA), with time (sessions) and lever (active vs. inactive) as factors. Reinstatement was analyzed using three-way ANOVA, with treatment (reinstatement conditions: extinction vs. sham vs. vehicle vs. OrxA), abstinence (intermediate vs. protracted), and lever (active vs. inactive) as factors. The number of Orx^+, $OrxR1^+$, and $OrxR2^+$ cells was analyzed separately using two-way ANOVAs, with abstinence (intermediate vs. protracted) and group (naive vs. cocaine) as factors. Significant main effects or interactions were followed by the Tukey *post hoc* test. Pearson's *r* correlation coefficients were calculated to establish linear dependence between the number of cocaine infusions that were earned during the last self-administration session and the number of Orx^+, $OrxR1^+$, and $OrxR2^+$ cells. All of the results are expressed as mean ± SEM. Values of $p < 0.05$ were considered statistically significant. The statistical analysis was performed using GraphPad Prism 8 software.

RESULTS

Three rats were lost because of cannula misplacement, thus reducing the number of animals to 40 (intermediate abstinence: OrxA-induced reinstatement, $n = 10$ LgA; immunohistochemistry, $n = 5$ naive and $n = 5$ LgA; protracted abstinence: OrxA-induced reinstatement, $n = 10$ LgA; immunohistochemistry, $n = 5$ naive and $n = 5$ LgA).

Cocaine Self-Administration Training and Extinction

Throughout the 21 days of self-administration training (6 h/day), the rats ($n = 30$) acquired cocaine self-administration (two-way ANOVA: session, $F_{20,1160} = 29.45$, $p < 0.001$; lever, $F_{1,58} = 393.8$, $p < 0.001$; session × lever interaction, $F_{20,1160} = 57.31$, $p < 0.001$; **Figure 2A**). The Tukey *post hoc* test confirmed that the rats increased their cocaine intake starting at session 4 vs. session 1 ($p < 0.001$) and vs. the inactive lever ($p < 0.001$). At the end of extinction training, the rats reached a comparable 3-day average (±SEM) number of responses between intermediate abstinence (7.0 ± 0.9 responses) and protracted abstinence (9.4 ± 1.1 responses; unpaired *t*-test, $t_{18} = 1.625$, $p > 0.05$). No differences were found in the number of sessions that were required to reach the extinction criterion between the two groups (intermediate abstinence: 18.0 ± 3 days, protracted abstinence: 19.0 ± 2 days; unpaired *t*-test, $t_{18} = 0.6200$, $p > 0.05$).

Comparison of OrxA Priming Effects at Intermediate Abstinence vs. Protracted Abstinence

The injection of OrxA in the pPVT reinstated (primed) cocaine-seeking behavior at intermediate abstinence. At protracted abstinence, the priming effect of intra-pPVT OrxA was lost (**Figure 2B**). Indeed, at intermediate abstinence, rats that were injected with OrxA exhibited a significant increase in the number of responses at the active lever compared with extinction, compared with the sham injection, compared with the vehicle injection, and compared with the number of responses at the inactive lever ($p < 0.001$; Tukey *post hoc* test following three-way ANOVA: treatment, $F_{3,104} = 24.30$, $p < 0.001$; abstinence, $F_{1,104} = 74.51$, $p < 0.001$; lever, $F_{1,104} = 7.112$, $p < 0.01$; treatment × abstinence interaction, $F_{3,104} = 12.66$, $p < 0.001$; treatment × lever interaction, $F_{3,104} = 8.98$, $p < 0.001$; abstinence × lever interaction, $F_{1,104} = 0.277$, $p > 0.05$; treatment × abstinence × lever interaction, $F_{3,104} = 8.541$,

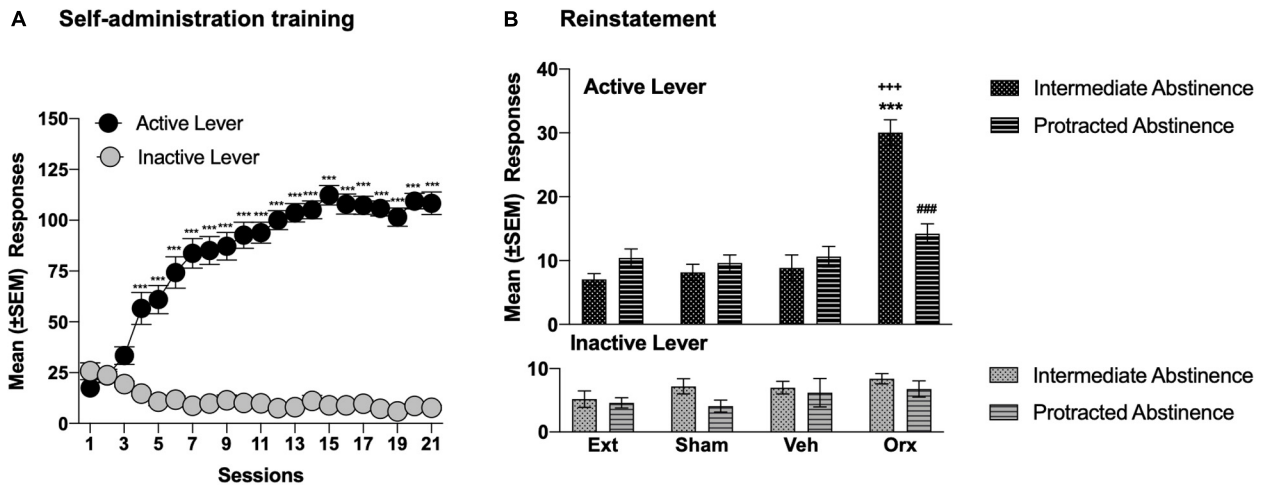

FIGURE 2 | OrxA in the pPVT reinstated cocaine-seeking behavior at intermediate abstinence but not protracted abstinence. **(A)** Time course of cocaine self-administration over 21 days of training. ***$p < 0.001$, vs. first session and vs. inactive lever (Tukey *post hoc* test). $n = 30$. **(B)** An injection of OrxA (0.5 μg) in the pPVT induced cocaine-seeking behavior at intermediate abstinence but not protracted abstinence. ***$p < 0.001$, vs. extinction, sham, and vehicle; $^{+++}p < 0.001$, vs. inactive lever; $^{###}p < 0.001$, vs. OrxA at intermediate abstinence (Tukey *post hoc* test). $n = 5$–10. Ext, extinction; Sham, sham injection; Veh, vehicle; Orx, orexin A. The data are expressed as mean ± SEM.

$p < 0.001$; **Figure 2B**). Responses at the inactive lever remained low and unaffected.

Number of Orx$^+$ Cells in the LH, DMH, and PFA: Intermediate Abstinence vs. Protracted Abstinence

Cocaine rats had a higher number of Orx$^+$ cells compared with naive rats, with no differences between intermediate abstinence and protracted abstinence in the LH ($p < 0.05$; Tukey *post hoc* test following two-way ANOVA; abstinence [intermediate abstinence, protracted abstinence], $F_{1,16} = 0.07$, $p > 0.05$; group [naive, cocaine], $F_{1,16} = 23.96$, $p < 0.001$; abstinence × group interaction, $F_{1,16} = 0.83$, $p > 0.05$; **Figures 3A–C**), DMH ($p < 0.05$; Tukey *post hoc* test following two-way ANOVA; abstinence [intermediate abstinence, protracted abstinence], $F_{1,16} = 0.03$, $p > 0.05$; group [naive, cocaine], $F_{1,16} = 20.14$, $p < 0.001$; abstinence × group interaction, $F_{1,16} = 0.35$, $p > 0.05$; **Figures 3D–F**), and PFA ($p < 0.01$; Tukey *post hoc* test following two-way ANOVA; abstinence [intermediate abstinence, protracted abstinence], $F_{1,16} = 0.50$, $p > 0.05$; group [naive, cocaine], $F_{1,16} = 50.55$, $p < 0.001$; abstinence × group interaction, $F_{1,16} = 1.62$, $p > 0.05$; **Figures 3G–I**). Correlation analysis did not reveal any significant relationship between the number of infusions that were earned during the last cocaine self-administration session and the number of Orx$^+$ cells in the LH, DMH, and PFA (**Table 1**).

Number of OrxR1$^+$ and OrxR2$^+$ Cells in the pPVT: Intermediate Abstinence vs. Protracted Abstinence

No differences in the number of pPVT OrxR1$^+$ cells were observed at intermediate abstinence or protracted abstinence compared with naive (two-way ANOVA; abstinence [intermediate abstinence, protracted abstinence], $F_{1,16} = 0.63$, $p > 0.05$; group [naive, cocaine], $F_{1,16} = 1.06$, $p > 0.05$; abstinence × group interaction, $F_{1,16} = 1.15$, $p > 0.05$; **Figures 4A–C**). The number of pPVT OrxR2$^+$ cells was significantly higher at intermediate abstinence compared with naive and protracted abstinence, but no differences were detected at protracted abstinence compared with naive ($p < 0.001$; Tukey *post hoc* test following two-way ANOVA; abstinence [intermediate abstinence, protracted abstinence], $F_{1,16} = 12.76$, $p < 0.05$; group [naive, cocaine], $F_{1,16} = 44.40$, $p < 0.001$; abstinence × group interaction, $F_{1,16} = 15.72$, $p < 0.01$; **Figures 4D–F**). Correlation analysis did not reveal any significant relationship between the number of infusions that were earned during the last cocaine self-administration session and the number of OrxR1$^+$ or OrxR2$^+$cells in the pPVT (**Table 1**).

DISCUSSION

Because of the remarkable resistance to extinction and long-term persistence of cocaine-seeking behavior (Martin-Fardon et al., 2016), the ability of microinjections of OrxA directly in the pPVT to reinstate extinguished cocaine-seeking behavior at 2–3 weeks (i.e., intermediate abstinence) or 4–5 weeks (protracted abstinence) of abstinence was evaluated. In parallel, to further understand whether a history of cocaine dependence affects the Orx system and thus explain the reinstating effect of OrxA when injected in the pPVT at intermediate abstinence vs. protracted abstinence, we analyzed the number of Orx$^+$ cells in the LH, DMH, and PFA and the number of OrxR1$^+$ and OrxR2$^+$ cells in the pPVT. We found a temporal change in OrxA's priming effects,

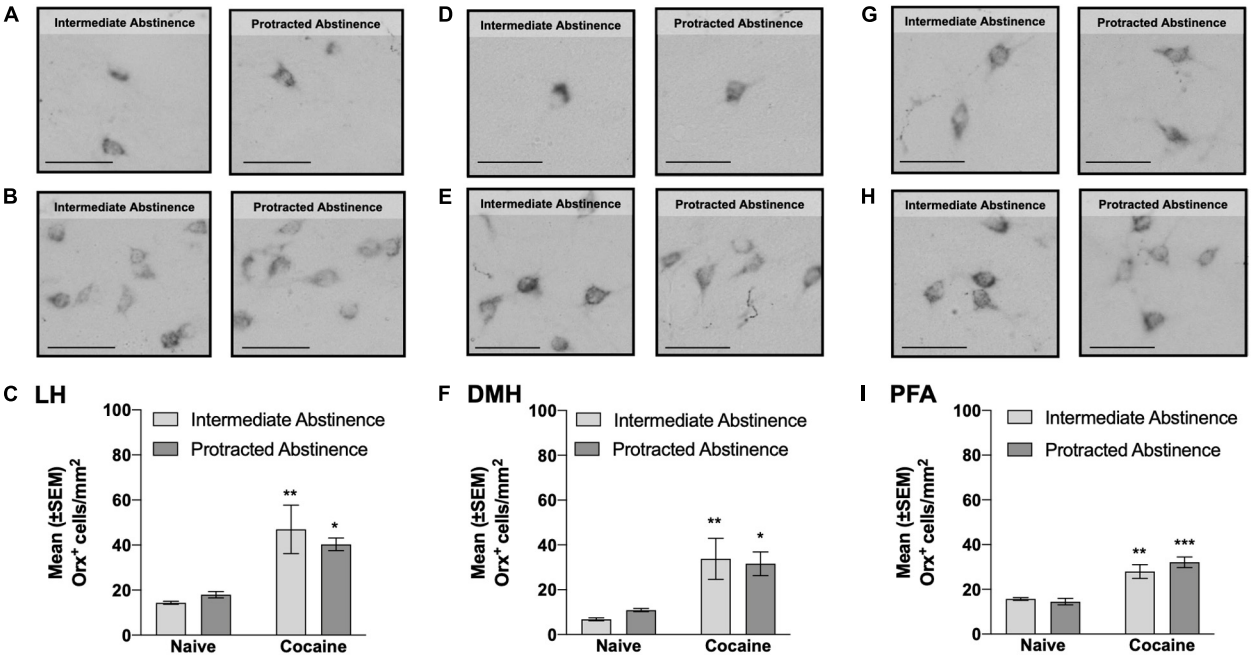

FIGURE 3 | Number of Orx$^+$ cells in the lateral hypothalamus (LH), dorsomedial hypothalamus (DMH), and perifornical area (PFA) measured at intermediate abstinence and protracted abstinence. **(A,B,D,E,G,H)** Typical photomicrographs of Orx immunostaining in naive rats **(A,D,G)** at the equivalent intermediate abstinence time point (left panels) and protracted abstinence time point (right panels) and in rats that self-administered cocaine LgA **(B,E,H)** at intermediate abstinence (left panels) and protracted abstinence (right panels). **(C,F,I)** A significantly higher number of Orx$^+$ cells was observed in cocaine LgA rats vs. naive rats in the LH, DMH, and PFA at both intermediate abstinence and protracted abstinence. $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, vs. naive (Tukey *post hoc* test). Scale bars = 50 μm. The data are expressed as mean ± SEM.

concomitant with temporal alterations of the number of OrxR2-expressing cells in the pPVT. Strong reinstatement was observed at intermediate abstinence, as reported previously (Matzeu et al., 2016), but no priming effects were detected at protracted abstinence. A higher number of Orx$^+$ cells was observed in the LH/DMH/PFA at both intermediate and protracted abstinence. In the pPVT, the number of OrxR2$^+$ cells was significantly higher at intermediate abstinence but not at protracted abstinence, with no changes in the number of OrxR1$^+$ cells. These data indicate that shortly after cocaine abstinence, the hypothalamic Orx↔pPVT connection is strongly recruited. As the duration of abstinence is extended, this connection undergoes further neuroadaptive changes.

TABLE 1 | Correlational analysis between the number of infusions earned during the last self-cocaine administration session and the number of Orx$^+$, OrxR1$^+$, and OrxR2$^+$ cells.

		Intermediate abstinence	Protracted abstinence
Structure	**Marker**	***Correlation; significance***	***Correlation; significance***
LH	Orx$^+$	$r = 0.20$; $p > 0.05$	$r = 0.26$; $p > 0.05$
DMH		$r = 0.62$; $p > 0.05$	$r = 0.62$; $p > 0.05$
PFA		$r = 0.49$; $p > 0.05$	$r = 0.47$; $p > 0.05$
pPVT	OrxR1$^+$	$r = 0.12$; $p > 0.05$	$r = 0.24$; $p > 0.05$
pPVT	OrxR2$^+$	$r = 0.81$; $p > 0.05$	$r = 0.84$; $p > 0.05$

Consistent with previous studies (Matzeu et al., 2016, 2018), OrxA injections in the pPVT induced cocaine-seeking behavior at intermediate abstinence, supporting the importance of Orx projections to the PVT in the modulation of cocaine-seeking behavior, at least during the early stage of cocaine abstinence. A possible behavioral confound following the OrxA injection in the pPVT could be the close position of the pPVT to the third ventricle and thus the possibility that OrxA diffused to the ventricles and exerted non-specific actions at other brain regions beyond the pPVT. However, the accuracy of the injections (depicted in **Figure 1**), the lack of behavioral effects at protracted abstinence, and our earlier studies that used a similar approach (Matzeu et al., 2015, 2016, 2018; Matzeu and Martin-Fardon, 2020) strongly dispute this possibility. One may argue that microinjection of OrxA in the pPVT reinstated cocaine-seeking behavior at intermediate abstinence simply because of non-specific locomotor activation. However, the observation that responses at the inactive lever remained negligible and unaffected following the intra-pPVT OrxA injection (**Figure 2B**) suggests that the behavior was indeed specific (i.e., directed to the active lever) and not attributable to a general non-specific increase in locomotion. A tentative explanation for OrxA's priming effects that were observed at intermediate abstinence may involve the mediation of arousal by the Orx system (Sakurai et al., 2010). In fact, the expectation of food reward was shown to activate neurons that contain OrxRs in the PVT (Choi et al., 2010). Most neurons in the PVT are sensitive to OrxA and OrxB, and

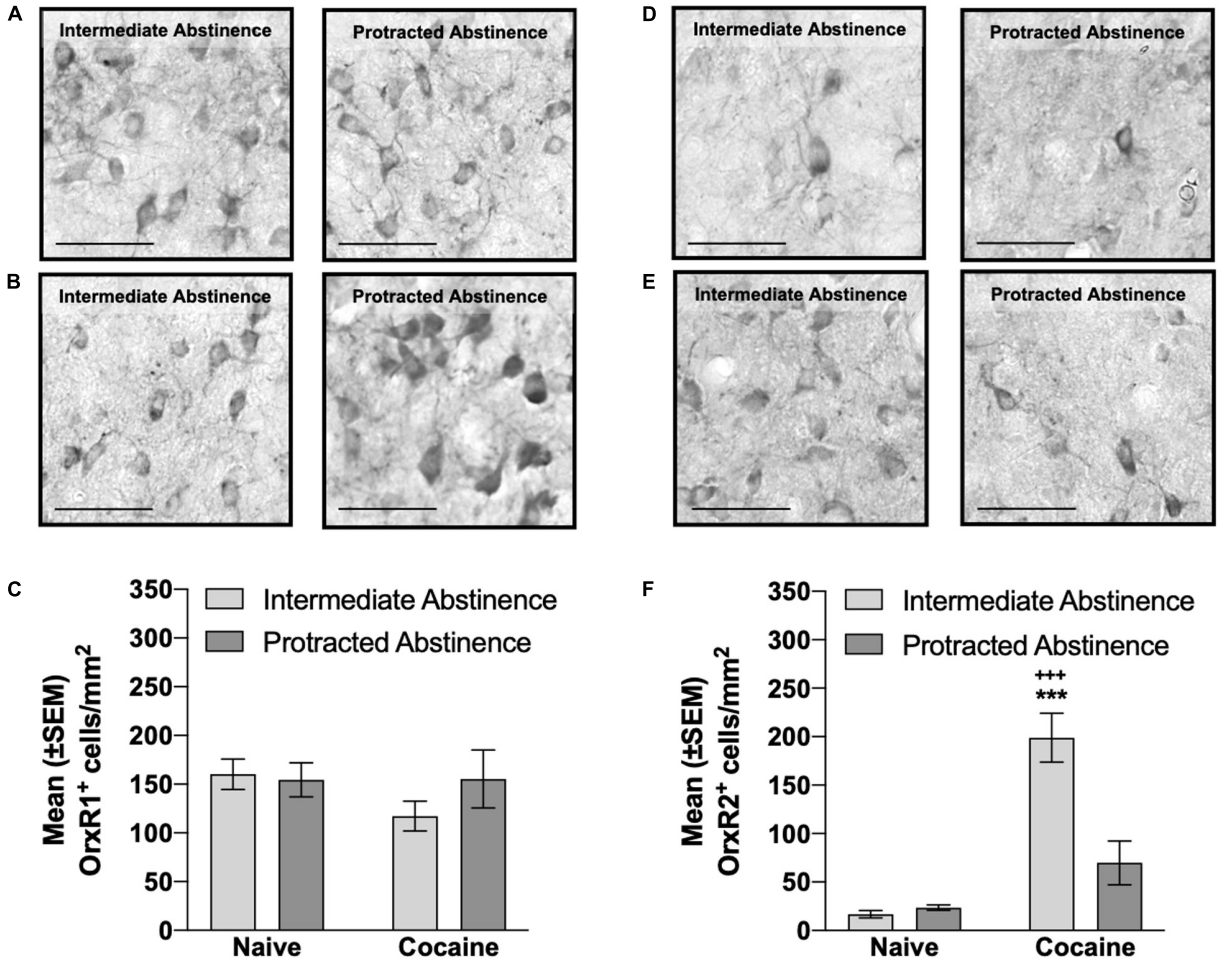

FIGURE 4 | Number of OrxR1$^+$ and OrxR2$^+$ cells in the pPVT measured at intermediate abstinence and protracted abstinence. **(A,B)** Typical photomicrographs of OrxR1 immunostaining in naive rats **(A)** at the equivalent intermediate abstinence time point (left panel) and protracted abstinence time point (right panel) and in rats that self-administered cocaine with LgA **(B)** at intermediate abstinence (left panel) and protracted abstinence (right panel). **(C)** Rats that self-administered cocaine with LgA exhibited a similar number of OrxR1$^+$ cells in the pPVT. **(D,E)** Typical photomicrographs of OrxR2 immunostaining in naive rats **(D)** at the equivalent intermediate abstinence time point (left panel) and protracted abstinence time point (right panel) and in rats that self-administered cocaine with LgA **(E)** at intermediate abstinence (left panel) and protracted abstinence (right panel). **(F)** Rats that self-administered cocaine with LgA had a significantly higher number of OrxR2$^+$ cells in the pPVT at intermediate abstinence compared with rats that were exposed to cocaine at protracted abstinence and compared with naive rats. $^{+++}p < 0.001$, vs. cocaine protracted abstinence; $^{***}p < 0.001$, vs. naive (Tukey *post hoc* test). Scale bar = 50 μm. The data are expressed as mean ± SEM.

the prefrontal cortex is an important target of Orx-activated PVT neurons (Ishibashi et al., 2005; Huang et al., 2006). The present results suggest that Orx inputs to the PVT might facilitate cortical activation that is linked to general arousal (Sato-Suzuki et al., 2002), which could explain the reinstatement of cocaine-seeking behavior. Moreover, OrxA administration in the PVT significantly increased dopamine levels in the nucleus accumbens (Choi et al., 2012), suggesting that the PVT is a key relay for Orx's effects on the mesolimbic dopamine system and reward-seeking behavior.

Another mechanism by which Orx induces cocaine-seeking behavior could be related to the role of the PVT in mediating anxiety- and stress-like responses, which are known to precipitate drug-seeking behavior. The PVT sends projections to the dorsolateral bed nucleus of the stria terminalis and central nucleus of the amygdala. These structures contain neurons that densely express both dynorphin and corticotropin-releasing factor (CRF; Li and Kirouac, 2008). The peptides dynorphin and CRF are implicated in the expression of negative emotional states and stress responses (Davis, 1998; Heinrichs and Koob, 2004; Shirayama and Chaki, 2006; Davis et al., 2010). Both OrxA and OrxB injections in the PVT produced anxiety-like behavior in rats in the open field (Li et al., 2010a) and elevated plus maze (Li et al., 2010b), suggesting that Orx may act as a stressor and thus precipitate drug-seeking behavior. Moreover, knowing that Orx regulates the hypothalamic-pituitary-adrenal (HPA) axis (for review, see James et al., 2017) and that Orx levels in cerebrospinal fluid increase in patients with panic/anxiety disorder (Johnson et al., 2010, 2012), one possibility could be that Orx injections in the pPVT might activate the HPA axis and consequently

increase corticosterone levels. However, to our knowledge, there is no evidence of a direct connection from the PVT to the paraventricular nucleus of the hypothalamus (e.g., Otake et al., 2002). Therefore, the hypothesis that microinjections of OrxA in the pPVT induce cocaine-seeking behavior through activation of the HPA axis requires further investigation. Surprisingly, however, the priming effect of OrxA was absent following a longer abstinence period (protracted abstinence). The reason for this temporal change in OrxA's priming effect is unclear but may be attributable to differential neuroadaptive changes (e.g., pPVT OrxR2 expression), revealed by immunohistochemistry, that occurred as the duration of abstinence increased.

Although no correlation was found between the number Orx^+ cells and the number of infusions that were earned during the last cocaine self-administration session, the persistent increase in the number of Orx^+ cells during abstinence suggested that cocaine compromised the Orx system even after an extended cocaine-free period. This observation is consistent with earlier findings that described maladaptive recruitment of the Orx system by chronic cocaine. A recent study showed that intermittent access to cocaine (i.e., another animal model that induces an addiction-like state) results in a higher number of Orx-expressing neurons in the LH, and this increase persists for up to 150 days of abstinence (James et al., 2019). The same authors also observed greater Orx neuron activity in response to a cocaine-associated cue and greater efficacy of the OrxR1 antagonist SB334867 in reducing cocaine-seeking behavior (James et al., 2019). Rats with higher motivation for cocaine had a higher number of Orx cells in the LH, and knocking down these Orx cells reduced the motivation for cocaine (Pantazis et al., 2020), suggesting that the number of LH Orx cells may be a marker of addiction susceptibility. Orexin mRNA expression increased in the LH following chronic alcohol exposure (Lawrence et al., 2006), during withdrawal from cocaine (Zhou et al., 2008), in postmortem tissue from heroin addicts, and in mice that were exposed to chronic morphine (Thannickal et al., 2018). Glutamatergic inputs to Orx neurons increased following chronic cocaine exposure (Yeoh et al., 2012, 2019), further supporting our present findings of persistent changes in the Orx system following exposure to drugs of abuse.

The overall increase in the number Orx^+ cells in the LH/DMH/PFA was somewhat unexpected when considering the reported functional dichotomy between hypothalamic subregions, in which Orx neurons in the LH participate in the regulation of reward processes, and Orx neurons in the DMH and PFA mediate responses to stressful events (Harris et al., 2005; Harris and Aston-Jones, 2006; Plaza-Zabala et al., 2010). The LH plays a central role in promoting and reinstating drug seeking, and the DMH/PFA plays a major role in inhibiting this behavior (Marchant et al., 2009, 2010, 2012). Corroborating these findings, concurrent intracranial self-stimulation of the DMH and LH decreased the reinforcing actions of self-stimulation of the LH (Porrino et al., 1983). Furthermore, administration of the inhibitory peptide cocaine- and amphetamine-regulated transcript in the DMH/PFA prevented the expression of extinction in a rat model of alcoholic beer seeking (Marchant et al., 2010). Considering evidence that the DMH/PFA regulates extinction and decreases LH activity (Porrino et al., 1983), activation of the DMH/PFA under physiological conditions may initiate the expression of extinction by inhibiting the LH (Porrino et al., 1983; Millan et al., 2011). Neuroplasticity that occurs during LgA cocaine self-administration and subsequent abstinence may prevent negative feedback from DMH/PFA neurons, such that LH neurons are no longer inhibited, reflected by a general upregulation of Orx in the LH/DMH/PFA. In agreement with this interpretation is a recent study that reported that intermittent access to fentanyl was associated with an increase in the number of Orx^+ cells in the LH/DMH/PFA, suggesting the general overall adaptation of Orx-producing cells to drugs in general (Fragale et al., 2020). The exact mechanisms and adaptations that can explain such findings are unclear and will need to be studied further.

Neurons in the PVT express OrxR2 mRNA (Trivedi et al., 1998; Marcus et al., 2001), which is consistent with electrophysiological studies that reported that Orx depolarized and excited PVT neurons via OrxR2 (Ishibashi et al., 2005). The increase in OrxR2 levels at intermediate abstinence may reflect an elevation of OrxR2-mediated orexinergic transmission in the pPVT, which might be responsible for the ability of OrxA administration in the pPVT to induce cocaine-seeking behavior at intermediate abstinence only. PVT neurons are mostly glutamatergic (Hur and Zaborszky, 2005; Huang et al., 2006; Barroso-Chinea et al., 2007; Kolaj et al., 2014; Gupta et al., 2018). Thus, one possibility could be that a microinjection of OrxA in the pPVT increased glutamate release, which was previously shown by cellular recordings of pPVT slice preparations (Matzeu et al., 2018). Therefore, the activation of OrxR2 in the pPVT by a microinjection of OrxA might have increased glutamate release from pPVT neurons, which in turn may have been responsible for reinstating cocaine-seeking behavior at intermediate abstinence. This possibility requires further testing. As abstinence progresses, the persistent increase in OrxR2-mediated Orx transmission in the pPVT might induce a negative feedback mechanism that causes a reduction of OrxR2-expressing cells in the pPVT and consequently blocks the ability of OrxA to induce cocaine-seeking behavior at protracted abstinence. A persistent increase in the levels of OrxR2 but not OrxR1 has been reported following chronic injections of cocaine in the nucleus accumbens, but no changes were observed in the prefrontal cortex, ventral tegmental area, hypothalamus, or dorsal striatum (Zhang et al., 2007), suggesting that only specific receptor subtypes (e.g., OrxR2) within specific brain regions (e.g., the nucleus accumbens and pPVT) undergo neuroadaptations following chronic cocaine. This plasticity of the Orx/OrxR2 system may underlie relapse vulnerability after the cessation of drug use. This hypothesis is supported by previous findings from our group that showed that OrxR2 in the pPVT mediates the reinstating effect of OrxA in rats with a history of cocaine dependence at intermediate abstinence (Matzeu et al., 2016). The absence of a correlation between the number $OrxR2^+$ cells and the number of infusions that were earned during the last cocaine self-administration session indicates that further studies are needed to define the precise mechanism by which such neuroadaptations occur during cocaine dependence and prolonged periods of abstinence.

In summary, the present study found that the discrete administration of OrxA in the pPVT elicited a priming effect that reinstated cocaine-seeking behavior in dependent animals at 2–3 weeks (intermediate abstinence) but not 4–5 weeks (protracted abstinence) of abstinence. The increase in Orx-expressing cells in the LH/DMH/PFA, together with the increase in OrxR2-expressing cells in the pPVT only at intermediate abstinence paralleled OrxA's priming effect, suggesting that the hypothalamic Orx↔pPVT connection is strongly recruited shortly after cocaine abstinence. As the duration of abstinence increases, this connection undergoes further neuroadaptive changes. Remaining unknown are whether OrxA's priming effect could be different at earlier abstinence (e.g., 24 h) vs. longer periods of abstinence (e.g., 6 months) and whether the Orx↔pPVT connection is differentially altered. Such findings may reveal valuable targets to mitigate the vulnerability to relapse that is associated with cocaine dependence that could be different as abstinence progresses.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by all procedures were conducted in strict adherence to the National Institutes of Health Guide for the Care and Use of Laboratory Animals and approved by the Institutional Animal Care and Use Committee of The Scripps Research Institute.

AUTHOR CONTRIBUTIONS

AM and RM-F participated in the study concept and design. AM performed the experiments, undertook the statistical analysis, interpreted the findings, and drafted the manuscript. Both authors critically reviewed the content and approved the final version for publication.

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REVIEW
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Influences of Stress and Sex on the Paraventricular Thalamus: Implications for Motivated Behavior

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The paraventricular nucleus of the thalamus (PVT) is a critical neural hub for the regulation of a variety of motivated behaviors, integrating stress and reward information from environmental stimuli to guide discrete behaviors *via* several limbic projections. Neurons in the PVT are activated by acute and chronic stressors, however several roles of the PVT in behavior modulation emerge only following repeated stress exposure, pointing to a role for hypothalamic pituitary adrenal (HPA) axis modulation of PVT function. Further, there may be a reciprocal relationship between the PVT and HPA axis in which chronic stress-induced recruitment of the PVT elicits an additional role for the PVT to regulate motivated behavior by modulating HPA physiology and thus the neuroendocrine response to stress itself. This complex interaction may make the PVT and its role in influencing motivated behavior particularly susceptible to chronic stress-induced plasticity in the PVT, especially in females who display increased susceptibility to stress-induced maladaptive behaviors associated with neuropsychiatric diseases. Though literature is describing the sex-specific effects of acute and chronic stress exposure on HPA axis activation and motivated behaviors, the impact of sex on the role of the PVT in modulating the behavioral and neuroendocrine response to stress is less well established. Here, we review what is currently known regarding the acute and chronic stress-induced activation and behavioral role of the PVT in male and female rodents. We further explore stress hormone and neuropeptide signaling mechanisms by which the HPA axis and PVT interact and discuss the implications for sex-dependent effects of chronic stress on the PVT's role in motivated behaviors.

Keywords: sex differences, paraventricular thalamus, stress, motivated behavior, HPA axis

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INTRODUCTION

The paraventricular nucleus of the thalamus (PVT) is the most dorsal midline thalamic nucleus that extends across the anterior-posterior axis of the brain (Kirouac, 2015). The PVT sends projections to several brain regions involved in arousal, the stress response, and motivated behavior including the nucleus accumbens (NAc; Neumann et al., 2016; Zhu et al., 2016; Beas et al., 2018; Cheng et al., 2018), bed nucleus of the stria terminalis (BNST; Hua et al., 2018), central nucleus of the amygdala (CeA; Do-Monte et al., 2015; Penzo et al., 2015; Chen and Bi, 2019; Keyes et al., 2020), basolateral amygdala (BLA; Amir et al., 2019), and the prelimbic and infralimbic cortex (Gao et al., 2020). The PVT regulates both positively and negatively valenced

motivated behaviors through its various limbic outputs, including natural reward and drug-seeking (Neumann et al., 2016; Zhu et al., 2016; Cheng et al., 2018), feeding (Cheng et al., 2018), approach-avoidance (Zhu et al., 2016; Cheng et al., 2018), and fear conditioning (Penzo et al., 2015), and these are potentially susceptible to the impact of stress. Also, there are distinct subpopulations of projection neurons and effects of acute and chronic stress across the anterior-posterior axis of the PVT (Bhatnagar and Dallman, 1998; Ver Hoeve et al., 2013; Gao et al., 2020), however, few studies have examined the relationship between these features (Beas et al., 2018; Gao et al., 2020).

The PVT is also activated by exposure to salient and stressful stimuli that activate the hypothalamic-pituitary-adrenal (HPA) axis and may be involved in integrating past experiences with present stimuli to guide adaptive behavior (Bhatnagar and Dallman, 1998; Bhatnagar et al., 2003; Choi and McNally, 2017; Beas et al., 2018; Zhu et al., 2018; Gao et al., 2020). As such, the PVT becomes activated upon each exposure to an acute stressor (Radley and Sawchenko, 2015), but it can develop a more robust role in behavior modulation across repeated stressor exposures (Bhatnagar et al., 2003). Therefore, this recruited role of the PVT indicates that the PVT is a site of plasticity in chronic stress-induced behavioral changes. This view is supported by converging evidence that stress hormones and neuropeptides, including glucocorticoids released directly as a result of activation of the HPA axis, contribute to stress-induced PVT plasticity.

Intriguingly, there is evidence that one stress-recruited role of the PVT in behavioral control is in modulating the HPA axis's response to acute stress, thus affecting the way that the HPA axis can regulate PVT function in turn (Bhatnagar and Dallman, 1998; Bhatnagar et al., 2002). However, whether there is a reciprocal modulatory relationship between the PVT and HPA axis that emerges as a consequence of repeated stress is not yet fully clear. Understanding precisely how the PVT and HPA axis bidirectionally interact is important to understanding how the PVT can guide motivated behavior following stress exposure. Furthermore, given the well-established role of sex differences in HPA axis activity and responsivity to stress, the PVT's role in regulating motivated behavior may be particularly susceptible to the sex-specific effects of stress. In this review, we discuss the literature detailing the interactions of sex, stress, and the HPA axis on the PVT and implications for its role in motivated behavior. This review will provide a framework for future studies to better clarify these complex interactions, providing essential information with implications for understanding sex differences in stress-related neuropsychiatric diseases.

ACUTE STRESS EFFECTS ON THE PVT, HPA AXIS, AND BEHAVIOR

Acute Stress and PVT Regulation of Motivated Behavior

While the roles of the PVT in motivated behaviors have been extensively reviewed elsewhere (Millan et al., 2017), the impact of and interaction between sex and stress on these roles is less well-examined. The PVT responds to both positively and negatively valenced salient stimuli and directly integrates information to modulate a variety of behaviors *via* limbic projections (Choi and McNally, 2017; Beas et al., 2018; Zhu et al., 2018; Gao et al., 2020). Some of the roles of the PVT are specifically toward signaling arousal (Gao et al., 2020) and salience (Zhu et al., 2018) that guide behavioral responses including fear (Do-Monte et al., 2015; Penzo et al., 2015), approach-avoidance (Zhu et al., 2016; Cheng et al., 2018), and drug-seeking behavior (Neumann et al., 2016; Zhu et al., 2016), all of which are sensitive to acute stress. Chemogenetic and optogenetic manipulation studies demonstrate that discrete anatomical outputs of the PVT are involved in these different behaviors. The projection from the PVT to the lateral division of the CeA is involved in fear conditioning (Penzo et al., 2015), and arousal is gated by populations of PVT neurons that project to the infralimbic cortex (Gao et al., 2020) and BNST (Hua et al., 2018). The PVT-NAc circuit has been implicated in drug-use behaviors like cocaine self-administration (Neumann et al., 2016) and aversion (including morphine withdrawal-induced aversion; Zhu et al., 2016), as well as feeding behavior in a novel environment (Cheng et al., 2018). Disrupting NAc-projecting PVT neurons reduces the acquisition of cocaine self-administration, indicating a role of the PVT-NAc circuit in early drug-seeking (Neumann et al., 2016).

The PVT participates in integrating multiple types of information to modulate behavior, including during motivational conflict, and the context and experimental conditions can impact the role of the PVT (Choi and McNally, 2017; Cheng et al., 2018; Choi et al., 2019). Under stressful conditions (food restriction) and in an anxiogenic context (novel environment), but not in the home cage, optogenetic activation of the anterior PVT (aPVT)-NAc circuit increases food consumption, indicating that this circuit promotes feeding during an approach-avoidance conflict (Cheng et al., 2018). BNST-projecting calretinin neurons in the PVT are activated by starvation to suppress sleep and promote arousal (Hua et al., 2018), and data from our group show that BNST-projecting PVT glutamate neurons are sufficient to reduce avoidance behavior in an anxiogenic context (elevated plus maze), an effect that may be due to feedforward inhibition of stress-responsive corticotropin-releasing factor (CRF) neurons in the BNST (Levine et al., 2020). Associative learning of salient stimuli rely on the PVT (Zhu et al., 2018), and the PVT is involved in balancing approach or avoidance behavior during situations of conflicting motivation following conditioning (Choi and McNally, 2017; Choi et al., 2019), discussed in "Chronic Stress and PVT Regulation of Motivated Behavior" section.

An additional layer of complexity in the role of the PVT in directing motivated behavior is that the PVT has functionally distinct populations of neurons across the anterior-posterior axis of the PVT. These different populations may be related to their differing circuit organization. For example, CeA projections regulating fear responses are primarily located in the posterior PVT (pPVT; Penzo et al., 2015). A population of D2 dopamine receptor (*Drd2*)-negative neurons, primarily located in the aPVT, project to the infralimbic region of the medial prefrontal cortex

and signal arousal (Gao et al., 2020). Conversely, *Drd2*-positive neurons primarily in the pPVT, project to the prelimbic region of the medial prefrontal cortex and the NAc and are responsive to stimulus valence (Beas et al., 2018; Gao et al., 2020). Due to the topographical and circuit organization of the PVT's role in behavior that is rapidly emerging in the literature, the impact of various stressors on the PVT's behavioral roles may also vary. Further, the PVT's ability to integrate prior experiences with the current context set it up to be a hub for stress memories critical for guiding motivated behaviors. Subsequent sections will discuss what is currently known regarding the activation of the aPVT and pPVT by acute and chronic stressors and their involvement in guiding appropriate behavioral responses. Also, females generally exhibit increased HPA reactivity to an acute stressor compared to males (Weinstock et al., 1998; Bangasser and Valentino, 2014). Given the many known sex differences in the effects of acute and chronic stressors on the brain and behavior but the relative dearth of research examining the female PVT, we will also consider that there may be critical sex differences in the PVT's role in motivated behavior and effects of stress on PVT physiology and function.

The Impact of Acute Stress on PVT Activation

The PVT is robustly activated upon exposure to acute stressors and salient stimuli (Zhu et al., 2018; Gao et al., 2020), and PVT activity is sensitive to stress exposure across different stress modalities. Exposure to acute stressors induces increased mRNA expression of the immediate early gene *Fos* or its protein product c-Fos in the PVT of rats, including loud noise (Burow et al., 2005), ether (Emmert and Herman, 1999), cold (Baffi and Palkovits, 2000), open field (Emmert and Herman, 1999), foot shock (Bubser and Deutch, 1999; Brown and Shepard, 2013), forced swim (Cullinan et al., 1995), social defeat (Lkhagvasuren et al., 2014), and physical restraint (Chastrette et al., 1991). Further, distinct stressors can elicit common increases in PVT c-Fos expression, suggesting that the PVT may serve a role of responding to and integrating salient stressors regardless of the specific modality. For example, Baisley et al. (2011) found that both predator (ferret) odor and foot-shock induced similar levels of PVT c-Fos expression. Other physiological stressors like systemically administered drugs of abuse, including cocaine and amphetamine, elicit robust, dose-dependent c-Fos expression in the PVT (Deutch et al., 1998). Food deprivation also increases *Fos* gene expression in both the aPVT and pPVT in obese but not lean Zucker rats (Timofeeva and Richard, 2001), suggesting that the PVT is sensitive to the level of perceived or real stress based on an animal's prior experience. Collectively, these data suggest that the PVT is poised to respond to many salient stimuli upon first exposure regardless of their valence, and they provide converging evidence for the PVT's role in motivated behavior across valence domains.

It is important to note that the majority of the work examining acute stress and the PVT has used either male Wistar (Lkhagvasuren et al., 2014; Careaga et al., 2019) or Sprague–Dawley rats (Chastrette et al., 1991; Bubser and Deutch, 1999; Emmert and Herman, 1999; Burow et al., 2005; Brown and Shepard, 2013). However, recent studies show that the PVT also is impacted similarly by acute stress in mice (Beas et al., 2018). While acute stress activation of the PVT has been less well-examined in mice, exposure to a single prolonged stress paradigm (a model of PTSD), consisting of exposures to restraint, swim, predator bedding, and diethyl ether in a single session, increased c-Fos expression in the PVT in C57BL/6 male mice (Azevedo et al., 2020). Differences in strain also have the potential to impact the effect of stressors on the PVT. One study found that acute restraint stress elicited higher PVT c-Fos in BALB/c mice, a more stress-sensitive strain, than C57BL/6 mice (O'Mahony et al., 2010).

And, mouse studies have shown that distinct populations of neurons across the anterior-posterior axis of the PVT may be differentially activated by stressful stimuli. Foot shock stress activates a population of pPVT neurons that project to the NAc (Beas et al., 2018). Multiple aversive stimuli, including foot shock and tail suspension, increase activity in a population of *Drd2*-positive neurons densely expressed in the pPVT, as measured by fiber photometry monitoring of calcium activity. In contrast, these same *Drd2* neurons are inhibited by positively-valenced stimuli such as social interaction and exposure to a thermoneutral zone, suggesting they are specifically activated by negatively-valenced stressful stimuli. *Drd2*-negative neurons that are primarily located in the aPVT, on the other hand, are inhibited by both positively and negatively-valenced stimuli (Gao et al., 2020), indicating their activity is suppressed by salient stimuli regardless of valence. These data are intriguing, as they suggest differential functions and valence sensitivity of the aPVT and pPVT. Data from male rats, however, have shown that exposure to various acute stressors (loud noise, restraint, or foot shock) increases *Fos* mRNA or c-Fos protein expression in both the anterior (Burow et al., 2005) and posterior (Brown and Shepard, 2013; Radley and Sawchenko, 2015) regions of the PVT when specifically examined. Whether differences across studies are due to organizational differences in function between species and strains, methods for monitoring activity, cell-type specificity, and/or other factors is currently unknown.

Sex Differences in Acute Stress Activation of the PVT

Few studies have examined the impact of acute stress exposure on the PVT and behavior in females, and more work is needed to better understand potential sex differences in the PVT in the acute response to stress. Similarly to males, acute stress exposure increases c-Fos expression in the PVT of females in response to both shaker stress (C57BL/6 mice; Mantella et al., 2004) and immobilization stress (Wistar rats; Ueyama et al., 2006), though direct comparison of c-Fos levels in the PVT in males and females across different stressors has not been performed. Following exposure to an acute stressor, an elevated HPA corticosterone response in females compared to males (Weinstock et al., 1998; Bangasser and Valentino, 2014) could be associated with increased activation of the PVT and differences in PVT-modulated behaviors, though this is not yet established in the existing literature. Following multiple stressor exposures,

differences in male and female PVT activation could cause differential plasticity within the PVT and have implications for subsequent behavioral or physiological regulatory activities of the PVT, discussed in "Chronic Stress Effects on the PVT, HPA Axis, and Behavior" section.

Ovarian hormones may further impact acute stress activation of the PVT in females and may differ across the anterior-posterior axis of the PVT, which may be important given that the aPVT and pPVT have been shown to sometimes regulate different motivated behaviors or different aspects of the same motivated behaviors (Ueyama et al., 2006; Do-Monte et al., 2017; Beas et al., 2018; Gao et al., 2020). In a study comparing stress-induced activation of the PVT between ovariectomized (OVX) rats with and without chronic estrogen (estradiol, E2) pellet replacement, acute immobilization stress increased c-Fos expression in the aPVT of OVX but not OVX + E2 rats; in contrast, it increased c-Fos expression in the mid-PVT in OVX + E2 but not OVX rats. Notably, c-Fos expression was unchanged in the pPVT in both groups (Ueyama et al., 2006), contrary to a previously observed immobilization stress-induced c-Fos activation of the pPVT in male rats (Chastrette et al., 1991). The impact of acute stress across the anterior-posterior axis in the PVT is unclear in intact cycling females because this study did not include a sham OVX control group, but these data highlight the ability of E2 to influence stress-induced activation of the PVT in an anatomically distinct manner (Ueyama et al., 2006).

As there are so few studies that include females, it is difficult to compare how the impact of stress on the PVT may differ from males. Drawing conclusions from the few studies including females is especially complicated as species, strain, and type of stressor may differentially impact the acute stress response in males and females. While males may universally exhibit increased PVT activation in response to acute stressor exposure, females may be prone to exhibit differential responses depending on the type of stressor or across the anterior-posterior axis of the PVT. Furthermore, there is evidence from Ueyama et al. (2006) that estrogen has a modulating role on the PVT response to stress (Ueyama et al., 2006), a topic that should be the focus of more extensive future study. Different PVT responses to acute stress in males and females can have implications for plasticity in the PVT following exposure to chronic stressors and impact subsequent stress responsivity in both motivated behaviors and HPA physiology.

CHRONIC STRESS EFFECTS ON THE PVT, HPA AXIS, AND BEHAVIOR

Chronic Stress and PVT Regulation of Motivated Behavior

While some motivated behaviors are regulated by the PVT in animals that were not previously exposed to chronic stress ("Acute Stress and PVT Regulation of Motivated Behavior" section), and acute stressors activate the PVT ("The Impact of Acute Stress on PVT Activation" and "Sex Differences in Acute Stress Activation of the PVT" sections), other behavioral roles of the PVT become engaged only following exposure to chronic stressors or repeated experiences (Bhatnagar et al., 2003; Penzo et al., 2015; Zhu et al., 2016; Keyes et al., 2020). The role of the PVT in using past experiences to guide appropriate behavioral responses is illustrated by a study showing that inactivation of the anterior and posterior PVT disrupts appropriate behavior during situations of motivational conflict following a conditioning paradigm in which a conditioned stimulus was paired with first an aversive stimulus and then paired with reward (or vice versa; Choi et al., 2019).

Because the PVT is activated by stressors across modalities and valence ("The Impact of Acute Stress on PVT Activation" section), it may be altered by chronic stress exposure across stress modalities, with implications for regulating different motivated behaviors. For example, creating an association between morphine reward and context over repeated training days in a conditioned place preference paradigm requires the PVT projection to the CeA, while the maintenance of this drug reward association, aversion during withdrawal, and morphine-primed relapse following extinction are dependent on the PVT-NAc pathway (Zhu et al., 2016; Keyes et al., 2020). These data demonstrate the role of the PVT-NAc circuit in drug-related behaviors, particularly following the formation of a drug memory (but see also "Acute Stress and PVT Regulation of Motivated Behavior" section for discussion regarding the PVT-NAc pathway participation in the acquisition of cocaine-seeking behavior). Negatively-valenced learning and memory also involve the PVT in both forming fear memory and in the expression of a fear response. Inactivation of PVT neurons that project to the CeA during either fear conditioning (Penzo et al., 2015) or retrieval (Do-Monte et al., 2015; Penzo et al., 2015) reduces freezing during a retrieval test, and activation of this pathway increases expression of conditioned fear without altering avoidance behavior in novel anxiogenic contexts (Chen and Bi, 2019). These findings suggest that repeated exposure to a stressful or aversive stimulus, such as shock, may be important for the recruitment of the PVT-CeA projection in controlling stable behavioral responses to the stimulus.

These roles for PVT outputs in motivated behavior are likely related to their anatomical location within the PVT. Several studies have shown that the pPVT may be particularly involved in controlling responses to conditioned fear. In male Sprague–Dawley rats trained in a cued fear conditioning paradigm to expect foot shock following the presentation of a tone, pPVT lesions reduce fear expression-freezing following tone presentation (Li et al., 2014). Activating dopamine β-hydroxylase (*Dbh*)-positive locus coeruleus terminals in the pPVT before fear conditioning increases freezing in a retrieval test 24 h later (Beas et al., 2018), suggesting that biogenic amines provide important salience information to the pPVT to promote the consolidation of conditioned fear.

The evidence from the fear literature shows that some chronic stressors can change the way the PVT is engaged by an acute stressor and modulate behavioral responses to it. However, the specific role of the PVT is sensitive to chronic/repeated stress modality, and this too may be specific for varying PVT circuits/subpopulations. In some cases, chronic stress may recruit the PVT to become a modulatory brake on stress reactivity or

anxiety-like behavior expression, though the available evidence is limited. For example, pPVT lesions cause increased anxiety-like defensive burying time and height in rats previously exposed to chronic restraint stress compared to non-stressed rats, while either the lesion or chronic stress alone did not impact these behaviors (Bhatnagar et al., 2003). Thus, in many instances, the modulatory role of the PVT in motivated behavior emerges only following repeated exposure to stress-related behavioral stimuli in which integration of these prior experiences is key to appropriate behavioral expression. This recruited engagement of the PVT in behavioral regulation of the stress response could be driven by stress-induced plasticity in the activation or function of the PVT *via* direct HPA-dependent or independent mechanisms, and it may result in an altered role of the PVT in regulating the HPA axis. Whether these lasting effects of chronic stress exposure are HPA-axis dependent or independent is not clear, but bidirectional interaction between the PVT and HPA axis has the potential to impact both behavior and physiology.

The Impact of Chronic Stress on PVT and HPA Axis Activation

Chronic stress exposure modifies the HPA axis response to an acute stressor, typically measured by blood concentrations of pituitary and adrenal stress hormones. The manner of the alteration depends on the consistency of modality across the chronic and acute stressors. The HPA axis response is typically habituated to an acute stressor that is homotypic to (the same modality as) the chronic paradigm but facilitated when it is heterotypic (novel or a different modality than the chronic stressor), detailed in **Table 1** (Bhatnagar and Dallman, 1998; Bhatnagar et al., 2002; Gray et al., 2014; Radley and Sawchenko, 2015). For example, rats exposed to chronic cold stress (Bhatnagar and Dallman, 1998) or chronic variable stress (Radley and Sawchenko, 2015) followed by acute heterotypic restraint stress, exhibit pronounced ACTH and corticosterone responses. Conversely, rats exposed to chronic restraint exhibit blunted ACTH and corticosterone responses to acute homotypic restraint stress (Gray et al., 2014). It is notable, however, that these effects of chronic stress on HPA adaptations are not universal and may be influenced by the type, severity, and pattern of stressors, as well as the specific neuroendocrine endpoint, being assessed (ACTH or CORT; Grissom and Bhatnagar, 2009; Belda et al., 2015).

Intriguingly, there is evidence that the PVT plays a vital role in this altered HPA axis response, and studies measuring PVT activation and function during acute stress exposure after a history of chronic stress or in rodents with programmed behavioral trait backgrounds provides insight into the relationship between stress, the PVT, and the HPA axis. As discussed in "Acute Stress Effects on the PVT, HPA Axis, and Behavior" section, acute stress activates the PVT, and even after multiple exposures to the same stressor, c-Fos is typically still induced in the PVT (Radley and Sawchenko, 2015). This occurs after chronic restraint (Radley and Sawchenko, 2015) and chronic intermittent hypoxia (Sica et al., 2000; **Table 1**). There is additional evidence for the roles of the PVT in chronic stress responses from studies that do not specifically measure responses to an acute stressor. Chronic social isolation increases PVT c-Fos (Stanisavljevic et al., 2019), and exposure to a flooded cage increases aPVT activation after chronic exposure, an effect that is reversed after a period of normal housing (Akazawa et al., 2010), suggesting these changes in PVT activation may recover with sufficient time without stress exposure.

However, the level of PVT activation elicited by an acute stressor is often inversely related to the displayed stress reactivity. Male rats bred for high trait anxiety exhibit lower c-Fos expression in the PVT in response to acute exposure to a novel open field compared to rats bred to exhibit low anxiety (Salome et al., 2004). Similarly, following fear conditioning, male rats that exhibit less freezing after context re-exposure 15 days later have higher PVT c-Fos than high-freezers and controls that did not go through training after the second re-exposure to the fear conditioning context (Careaga et al., 2019). Together, these studies suggest that stress-evoked activation of the PVT may suppress the behavioral response to the stressor, discussed in "Chronic Stress and PVT Regulation of Motivated Behavior" section, possibly *via* modulation of the HPA axis.

PVT Influence on the Neuroendocrine Response to Stress

The inverse relationship between PVT activation and stress reactivity hints at a role for the PVT in suppressing HPA axis activation in response to acute stressors, and interestingly, this modulatory role of the PVT emerges only following chronic stress. Lesion studies show that the PVT has inhibitory activity on the HPA axis whether the acute stressor is homotypic or heterotypic to the chronic stress paradigm. **Table 2** details the impact of lesion studies across heterotypic and homotypic stress paradigms. For example, early work characterizing the impact of chronic stress on PVT activation by a heterotypic acute stressor in male rats showed that acute restraint stress elicited a greater HPA axis response in rats with a history of chronic cold stress exposure compared to those without a stress history (Bhatnagar and Dallman, 1998); a follow-up experiment showed that lesioning the pPVT further increased the HPA axis ACTH response to the heterotypic stressor in rats exposed to chronic stress but not in stress-naïve controls (Bhatnagar and Dallman, 1998). These data suggest that acute stressor-induced activation of the PVT serves to suppress the acute HPA axis response only after a history of chronic stress, such that removing this PVT brake disinhibits the HPA axis, leading to an even more robust stress response than that facilitated by heterotypic stress exposure.

The PVT serves the same inhibitory function on HPA axis activation during homotypic chronic stress paradigms, evidenced by one study showing that lesioning the pPVT attenuates HPA axis habituation in a homotypic restraint stress paradigm (Bhatnagar et al., 2002). Together, these lesion studies show that the pPVT has an inhibitory influence on the HPA response to both heterotypic (Bhatnagar and Dallman, 1998) and homotypic (Bhatnagar et al., 2002) stressors, regardless of the chronic stress paradigm, but only in rats with previous exposure to chronic stress. Other groups also find support for the involvement of the aPVT in habituation to homotypic stress. One

TABLE 1 | The impact of heterotypic and homotypic stress paradigms on the PVT and HPA axis.

Sex	Species/ strain	Age/weight	Chronic stressor	Acute stressor	PVT response vs. no chronic stress	PVT response vs. no acute stress/baseline	HPA response vs. no chronic stress (post-stress timing)	HPA response vs. no acute stress/baseline (post-stress timing)	Citation
Heterotypic stress									
Male	Rat Sprague–Dawley	200–225 g	Cold	Restraint	aPVT: – c-Fos mPVT: – c-Fos pPVT: ↑ c-Fos (60 min)	-	↑ ACTH (15 min) ↑ CORT (30 min)	-	Bhatnagar and Dallman (1998)
Male	Rat Sprague–Dawley albino	275–325 g	Chronic variable stress	Restraint	Total: ↓ c-Fos aPVT: ↓ c-Fos pPVT: – c-Fos	Total: ↑ c-Fos aPVT: ↑ c-Fos pPVT: ↑ c-Fos	↑ ACTH (30 min) ↑ CORT (30, 60, 90 min)	↑ ACTH (30, 60 min) ↑ CORT (30, 60, 90 min)	Radley and Sawchenko (2015)
Male	Rat Sprague–Dawley	190–205 g	Defeat	Restraint	-	-	↑ACTH (15 min) ↑CORT (30 min)	-	Bhatnagar and Vining (2003)
Female	Rat Sprague–Dawley	PND 69–71	Defeat	Restraint	PVT: –c-Fos	-	↓ ACTH (baseline)	-	Ver Hoeve et al. (2013)
Male	Mouse C57BL/6N	Adult	CORT (4 weeks, drinking water)	Forced Swim	PVT: ↓ c-Fos	-	-	-	Kinlein et al. (2019)
Homotypic/chronic stress									
Male	Rat Sprague–Dawley	200–225 g	Restraint	Restraint	-	-	↓ ACTH (15 min) ↓ CORT (15, 30 min)	-	Bhatnagar et al. (2002)
Male	Rat Sprague–Dawley albino	275–325 g	Restraint	Restraint	Total: ↓ c-Fos aPVT: ↓ c-Fos pPVT: – c-Fos	Total: ↑ c-Fos aPVT: ↑ c-Fos pPVT: ↑ c-Fos	– ACTH – CORT	– ACTH ↑ CORT (30, 60 min)	Radley and Sawchenko (2015)
Male	Rat Sprague–Dawley	54–55 days	Restraint	Restraint	pPVT: ↓ c-Fos vs. acute stress	-	↓ ACTH (AUC, 0–90 min) ↓ CORT (AUC, 0–90 min)	-	Gray et al. (2014)
Male	Rat Sprague–Dawley	70 days	Restraint	Restraint	-	pPVT: – c-Fos	-	-	Lui et al. (2012)
Male	Rat Sprague–Dawley	85 days	Restraint	Restraint	-	-	↓ CORT (30, 60 min) ↓ CORT (AUC/min, 0–60 min)	-	Bhatnagar et al. (2005)

(Continued)

TABLE 1 | Continued

Sex	Species/ strain	Age/weight	Chronic stressor	Acute stressor	PVT response vs. no chronic stress	PVT response vs. no acute stress/baseline	HPA response vs. no chronic stress (post-stress timing)	HPA response vs. no acute stress/baseline (post-stress timing)	Citation
Female	Rat Sprague–Dawley	105 days	Restraint	Restraint	-	-	↑ CORT (60 min) – CORT (AUC/min, 0–60 min)	-	Bhatnagar et al. (2005)
Male	Rat Sprague–Dawley	220–250 g	Restraint + GR and MR antagonists in the PVT	Restraint	-	-	↑ ACTH (AUC 0–60 min, vs. vehicle + chronic stress)	-	Jaferi and Bhatnagar (2006)
Male	Rat Sprague–Dawley	200–250 g	Intermittent hypoxia	Hypoxia	-	PVT: ↑ c-Fos	-	-	Sica et al. (2000)
Male	Rat Wistar	2.5 months	Continuous Social Isolation	-	pPVT: ↑ c-Fos	-	-	-	Stanisavljevic et al. (2019)
Male	Rat Sprague–Dawley	6–7 weeks 230–270 g	Continuous Flooded Cage	-	aPVT: ↑ c-Fos	-	-	-	Akazawa et al. (2010)

group showed a partial attenuation of habituation to homotypic restraint stress with an aPVT lesion (Fernandes et al., 2002). These studies suggest that the PVT is recruited after chronic stress to suppress HPA axis activation and potentially influence motivated behavior.

PVT Activation by Heterotypic and Homotypic Stressors

The evidence from lesion studies showing a role of the PVT in mediating the HPA axis effects of chronic stress is supported by studies assessing c-Fos activation in the PVT in response to homotypic and heterotypic acute stressors following chronic stress, detailed in **Table 1**. Whether an acute stressor is homotypic or heterotypic to the chronic stress paradigm, PVT c-Fos is usually induced by the acute stressor, but the level of this activation can differ from that evoked in no-chronic stress controls and may depend on subregion within the PVT (Bhatnagar and Dallman, 1998; Radley and Sawchenko, 2015). Radley and Sawchenko (2015) showed that in a heterotypic stress paradigm, the total PVT, driven by the aPVT, displayed decreased c-Fos expression in response to an acute restraint stressor in rats with a history of chronic variable stress compared to rats without. Others have reported that c-Fos expression in the pPVT (but not aPVT) was instead increased in chronically stressed rats following an acute heterotypic stressor (Bhatnagar and Dallman, 1998). However, the same study showed that a pPVT lesion exacerbated the HPA axis facilitation, so increased recruitment, in this case, may reflect a homeostatic upregulation of pPVT control of the HPA axis serving to buffer hyperexcitation.

Overall, the limited evidence available reinforces the implication that PVT activation suppresses acute stress responsivity. This simplistic interpretation suggests that in the case of homotypic stress, PVT activation would be higher in response to an acute stressor in subjects with a history of chronic stress compared to those without. However, many studies find that acute stress activation of the PVT is reduced compared to those without chronic stress in homotypic stress paradigms as it is in heterotypic paradigms. For example, in the same study, Radley and Sawchenko (2015) observed a similar reduction in c-Fos expression in the aPVT and total PVT in response to an acute homotypic restraint stressor following chronic restraint as they did in their similar, but heterotypic, paradigm discussed above (Radley and Sawchenko, 2015). Other groups report a similar decrease in c-Fos expression but in the pPVT (Gray et al., 2014), or they report no increase from baseline at all (Lui et al., 2012), while Radley and Sawchenko (2015), find the pPVT c-Fos expression no different from no-chronic stress control rats in the homotypic stress paradigm (Radley and Sawchenko, 2015).

Specific findings shed light on the intricacies of the relationship between the PVT and HPA axis that are defined by functionally distinct segments of the PVT. Early studies indicated that the pPVT but not the aPVT may be primarily involved in mediating the effects of chronic stress (Bhatnagar and Dallman, 1998; Bhatnagar et al., 2002), and many have focused on the posterior region of the PVT (Bhatnagar and Dallman, 1998; Bhatnagar et al., 2000, 2002, 2003; Bhatnagar and Vining,

TABLE 2 | The impact of PVT lesions on the HPA axis and behavior in chronic stress paradigms.

Sex	Species/strain	Age/weight (g)	Chronic stressor	Acute stressor	Lesion	HPA axis response (post-stress timing, comparison group)	Behavior change (comparison group)	Citation
Male	Sprague–Dawley rat	225–300	Restraint	Restraint	aPVT	Partial attenuation of CORT habituation (30 min vs. acute only)	-	Fernandes et al. (2002)
Male	Sprague–Dawley rat	200–225	Restraint	Restraint	pPVT	Attenuation of ACTH (15 min) and CORT (15, 30 min) habituation (Day 8 vs. Day 1)	-	Bhatnagar et al., 2002
Male	Sprague–Dawley rat	200–220	Restraint	Restraint	pPVT	↓ CORT (30 min, dexamethasone vs. vehicle)	-	Jaferi et al. (2003)
Male	Sprague–Dawley rat	200–225	Cold	Restraint	pPVT	↑ ACTH (30 min vs. sham lesion)	-	Bhatnagar and Dallman (1998)
Male	Sprague–Dawley rat	200–225	Restraint	-	pPVT	-	↑ defensive burying height and duration (vs. no stress + lesion)	Bhatnagar et al. (2003)

2003; Jaferi et al., 2003; Jaferi and Bhatnagar, 2006). Lesion studies have shown that pPVT lesions increase HPA output in chronically stressed rats in both homotypic and heterotypic stress paradigms, however, these studies did not examine the effects of aPVT lesions because their initial experiments uncovered no effects of chronic stress on c-Fos expression in the aPVT (Bhatnagar and Dallman, 1998; Bhatnagar et al., 2002). And as discussed above, Radley and Sawchenko (2015) found that the aPVT (but not pPVT) showed reduced c-Fos activation in response to an acute stressor in both homotypic and heterotypic stress paradigms compared to chronic stress-naïve controls. Together, these studies suggest that the PVT, across its anterior-posterior axis, can be impacted by chronic exposure to stress, but that anatomically distinct populations may be impacted differently by chronic stress and in turn, alter HPA responsivity or motivated behavior differently through distinct PVT circuitry.

While the reduced c-Fos expression in the PVT in homotypic stress paradigms is seemingly in conflict with a hypothesis that PVT activation is inversely related to HPA axis activation in response to acute stress exposure, it reinforces the evidence from the literature suggesting that the PVT is responsive to acute stressors across modalities. And as such, its roles in motivated behaviors may be sensitive to stressors across modalities and timeframes. Further, the variability in findings from these studies speaks to the complexity of the PVT's organization and function, and they suggest that targeted analysis of specific subpopulations (including those defined by topographical location, molecular class, or circuit organization) may provide insight clarifying the results of studies measuring overall c-Fos activation patterns in the PVT.

Circuit-Specific Tuning of the PVT

One particularly interesting contrast is that while both the HPA axis and PVT have altered responses to and roles in acute stress responsivity following exposure to chronic stress, the HPA axis response depends on whether the acute stressor is the same (homotypic, habituation) or a different modality (heterotypic, facilitation) than the chronic stressor, while the PVT's role does not (always inhibitory). These studies suggest that the PVT alone does not control the HPA axis response but that chronic stress engages it to somehow interact with the broader stress control circuity in the brain at the level of the paraventricular nucleus of the thalamus, where the activation of corticotropin-releasing factor (CRF) neurons initiates the HPA axis. However, the PVT has been described to be a hub of stress memory with the ability to directly integrate information about past and current stressors and contexts and control adaptive behavior (Bhatnagar and Dallman, 1998; Hsu et al., 2014). A recent study shows that the PVT is particularly important for appropriate action selection when there is a motivational conflict between cues that previously predicted appetitive (sucrose availability) and aversive (foot shock) stimuli (Choi et al., 2019). This suggests that the PVT is not a simple brake on HPA axis activation but that its role in guiding motivated behavior and stress responses is highly tuned to the past and present circumstances and the type of stimuli and stressors presented. Thus, while the general PVT neuron

population may show similar responses to both homotypic and heterotypic stress, specific subpopulations of neurons within the PVT might be sensitive to differences in these stressors.

One potential mechanism through which the PVT may influence HPA axis activity differentially in homotypic and heterotypic stress paradigms is through its glutamatergic (vGlut2-positive) projection to the BNST (Myers et al., 2014), a key limbic target of the PVT primarily consisting of GABAergic projection and interneurons. BNST GABA neurons project to the parvocellular region of the paraventricular nucleus of the hypothalamus (PVN) and can directly inhibit CRF neurons (Dong et al., 2001; Bienkowski and Rinaman, 2011; Crestani et al., 2013; Colmers and Bains, 2018; Song et al., 2020). Therefore, the PVT may be able to provide indirect inhibitory control on the HPA axis *via* the BNST. One study found that in response to an acute novel restraint stressor, rats previously exposed to chronic variable stress (CVS) exhibited lower c-Fos activation in BNST-projecting PVT (PVT-BNST) neurons and PVN-projecting BNST (BNST-PVN) neurons, as well as a potentiated HPA axis response (ACTH and corticosterone), compared to chronic stress-naïve rats (Radley and Sawchenko, 2015). These results suggest that decreased glutamatergic drive from the PVT onto BNST-PVN GABAergic neurons may provide a circuit mechanism for disinhibition of the HPA axis response to heterotypic stress, leading to facilitation of acute stress responsivity. Further, this study found that PVT-BNST neurons did not have decreased c-Fos expression in response to an acute restraint stressor in a homotypic paradigm (even though the total PVT did show decreased c-Fos expression in both paradigms); as such, the intact PVT-BNST-PVN inhibitory brake on the HPA axis may be sufficient to suppress the physiological response to the acute stressor. The differential response in BNST-projectors to heterotypic and homotypic stressors may be one mechanism through which the PVT discriminates between heterotypic and homotypic stress in tuning HPA axis activity.

This study suggests that specific PVT neuron activity becomes an important inhibitor of the HPA axis response to acute stress following chronic stress (Radley and Sawchenko, 2015). Further, this study implicates the BNST, known to inhibit paraventricular hypothalamus CRF neurons that initiate the HPA axis stress response *via* GABAergic projections, as a key target of the PVT neurons modulated by chronic stress. As such, chronic stress may not only recruit the PVT to modulate motivated behavior but also to indirectly inhibit acute stress responsivity *via* the BNST. During homotypic stress, the continued activation of the BNST projection population, as part of a broader network modulating HPA axis function, may be sufficient to support HPA axis habituation. In contrast, reduced activation during heterotypic acute stress may permit HPA axis sensitization through disinhibition *via* the BNST intermediate GABAergic synapse. Altogether, these findings implicate the PVT as a site of chronic stress-induced plasticity across stress exposures that ultimately recruits the PVT to become a modulatory brake on stress responsivity that is sensitive to stress modality, with implications for its role in motivated behavior. However, further characterization of the role of the PVT in modulating motivated behaviors through HPA axis regulation, as well as the potential reciprocal relationship between the effects of chronic stress on the PVT and HPA axis, is necessary.

Hormone and Neuropeptide Modulation of PVT Function

Overall, following chronic stress, the PVT is activated similarly by an acute stressor regardless of whether it is the same as previously experienced (homotypic) or novel (heterotypic) stressors. The evidence that the PVT is responsive to stressors across modalities, both acutely and following chronic stress, suggests that stress hormones released in response to HPA axis activation broadly across modalities act within the PVT to shape its function. However, the specific subpopulations of PVT neurons, such as those that project to the BNST, are somehow able to tune their responses to homotypic vs. heterotypic stressors after chronic stress, perhaps a learned function that allows for discrimination between and integration of past and new experiences, different threat levels, and other features to guide adaptive behavioral output. The ability of the PVT to respond to yet discriminate between stressors across time may be achieved by either differential stress hormone responses or recruitment of different endogenous hormone and neuropeptide signaling systems across various stressors and chronological presentations. Here we discuss the literature regarding the effects of stress hormones and neuropeptides on the function of the PVT.

Stress Hormones

Stress hormones including glucocorticoids such as corticosterone/cortisol (rodents/primates, CORT) and mineralocorticoids such as aldosterone may participate in the HPA axis habituation to chronic stress *via* their effects on the PVT. One study found that 4 weeks of chronic CORT administration through drinking water blunts activation of the PVT in response to a subsequent acute stressor (Kinlein et al., 2019), similar to what occurs during habituation to a homotypic stressor (Gray et al., 2014; Radley and Sawchenko, 2015). In line with this, stress-induced adaptations in the PVT that modulate future HPA axis activity are mediated through the glucocorticoid receptors (GR) and mineralocorticoid receptors (MR) in the PVT. Inhibition of GR and MR in the pPVT before each exposure to a chronic stressor prevents HPA axis ACTH habituation to a subsequent acute homotypic restraint stress (Jaferi and Bhatnagar, 2006), suggesting that stress hormone signaling directly in the pPVT is necessary for appropriate HPA axis habituation.

Interestingly, chronic homotypic stress may also elicit a role of the PVT in tuning HPA axis negative feedback. Following chronic homotypic stress, lesioning the pPVT disrupts the ability of the synthetic glucocorticoid dexamethasone to mimic CORT when exogenously administered and provide appropriate negative feedback onto the HPA axis 30 min after the start of acute restraint stress (Jaferi et al., 2003), while this lesion does not impact normal dexamethasone suppression in rats without a history of chronic stress. This may reflect a recruited role of the PVT in the suppression of the HPA axis but only following chronic stress exposure, in line with the inhibitory role of the

PVT only following chronic stress observed in earlier lesion studies (Bhatnagar and Dallman, 1998; Bhatnagar et al., 2002).

Together, these data suggest that repeated activation of the HPA axis may lead to chronic stress hormone-induced plasticity in the PVT, causing the structure to be selectively recruited after chronic stress exposure to play new or altered roles in stress responsivity. Repeated exposure to CORT may be one explanation for why the PVT has a similar c-Fos response to both heterotypic and homotypic acute stressors, as CORT is released in response to stressors across modality and paradigm. However, the impact of this repeated exposure to CORT may differ among different PVT circuits, allowing tuning of the HPA axis and discrimination between stress modalities. Further, these findings are particularly intriguing because they suggest that the recruited ability of the PVT to tune HPA axis activation (and thus stress hormone release) in response to acute stress is a direct product of repeated exposure to those same hormones, implicating a reciprocal relationship between the PVT and HPA axis in stress.

Neuropeptides

Another mechanism through which the PVT can be impacted by chronic stress exposure is through interactions with endogenous neuropeptides. Neuropeptide Y (NPY), αMSH, serotonin, vasopressin, and CRF are all found in PVT (Freedman and Cassell, 1994; Forcelli et al., 2007), and hypothalamic neuropeptidergic neurons, including those that express NPY, cocaine, and amphetamine-regulated transcript (CART), and orexin, project to the PVT (Lee et al., 2015). The role of the orexin/hypocretin system in the PVT has been the most widely studied and extensively reviewed (Martin-Fardon and Boutrel, 2012; Matzeu et al., 2014), while the involvement of other neuropeptides' signaling and PVT subpopulations have been understudied to date. The literature suggests that orexin/hypocretin in the PVT is involved in modulating behavioral responses in anxiogenic contexts (Li et al., 2010). Specifically, stimulation of hypothalamic orexin neurons in male rats reduces time spent in a social interaction zone and increases c-Fos expression and orexin 1 receptor internalization in the PVT (Heydendael et al., 2014), suggesting that orexin signaling plays a pro-stress role in guiding motivated behavior *via* its actions the PVT. This is supported by direct evidence that site-directed administration of a dual orexin receptor antagonist to the PVT reduces latency to enter a social interaction zone (Dong et al., 2015), and intra-PVT administration of the endogenous ligands for orexin receptors, orexin A and orexin B, each increase avoidance of the open arms of the elevated plus-maze (Li et al., 2010).

There is also a role for the actions of orexin in the PVT in balancing the behavioral response to natural and drug rewards (Matzeu et al., 2014, 2018). For example, intra-pPVT orexin-A delivery reinstates self-administration of cocaine or sweetened condensed milk following the conditioning and extinction of this behavior (Matzeu et al., 2018). However, simultaneous dynorphin A administration to activate endogenous kappa opioid receptors blocks cocaine but not sweetened condensed milk reinstatement, indicating a complex interaction between orexin and dynorphin signaling in the pPVT in the regulation of drug-related appetitive motivated behavior that is dependent on prior repeated exposures and learned associations between drug rewards and the cues that predict them (Matzeu et al., 2018). On top of its role in motivated behavior, PVT orexin signaling may be a key component of the PVT's recruited role in modulating acute HPA axis stress responses. For example, administration of an orexin receptor antagonist during each of four daily forced swim stressors in the pPVT attenuates the facilitation of the HPA axis response to acute heterotypic restraint stress on the fifth day (Heydendael et al., 2011).

There is limited evidence about the role of other neuropeptide systems in the PVT, suggesting that there may be many more signaling mechanisms for stress-induced changes in the PVT and its role in motivated behavior and acute stress responsivity. Acute stress increases nociception/orphanin FQ mRNA in the PVT (Zambello et al., 2008), but it is unknown whether this undergoes plasticity with chronic stress or has an impact on behavior. Whether and how other neuropeptides from the hypothalamus and other distal and intra-PVT neurons modulate PVT function acutely and after chronic stress exposure remains to be examined. And, as previously discussed, current studies almost exclusively use male rats. Further study of the impact of these neuropeptidergic systems in the PVT in females is especially important as sex differences have been found in the consequences of chronic stress and exercise on orexin neurons in the hypothalamus (James et al., 2014) and after chronic stress alone on hypocretin (orexin)-1 receptor gene expression in the prefrontal cortex (Lu et al., 2017). There are still many remaining questions about the role of neuropeptides in the PVT on HPA axis activity and motivated behavior, including whether neuropeptides interact with stress hormones in the PVT's recruited role in heterotypic and homotypic stress responses. But together, these studies suggest that neuropeptides could influence the tuning of HPA axis activity through the PVT. These neuropeptides may be recruited by different stressors depending on the stress modality, severity, or pattern, allowing the PVT to tune its function to discriminate among different stress modalities and behavioral paradigms, potentially impacting different motivated behaviors.

Sex Differences in Chronic Stress Effects on the PVT and HPA Axis

The majority of studies examining the role of chronic stress on PVT and HPA axis activation occur in male Sprague–Dawley rats (Bhatnagar and Dallman, 1998; Sica et al., 2000; Bhatnagar et al., 2002, 2003; Bhatnagar and Vining, 2003; Lui et al., 2012; Gray et al., 2014). It is therefore unclear how these findings of the effects of homotypic and heterotypic stress paradigms on the PVT and HPA axis can be extended to females, as well as to other species and strains. Here we summarize what is known about the chronic stress impact on the PVT and HPA axis in females and how they compare to findings in males.

Chronic Stress in Adulthood

Sex differences in the HPA axis response to acute and chronic stress have been well established in the literature and reviewed by others (Goel et al., 2011; Bangasser and Valentino, 2014;

Green and McCormick, 2016), but the role of the PVT in the sex-specific consequences of stress is less clear. Male rats exposed to chronic defeat and then heterotypic restraint exhibit facilitation of their HPA response to the acute restraint compared to non-stressed controls (Bhatnagar and Vining, 2003). However, adult female rats exposed to a similar paradigm do not exhibit differences in the CORT response following exposure to an acute restraint stressor compared to those without a history of chronic stress, though they do have blunted ACTH at baseline (Ver Hoeve et al., 2013). These studies suggest that chronic stress has a sex-dependent effect on future HPA activity that may be related to more robust stress-induced adaptations in the PVT of males than females, at least for heterotypic stress. Furthermore, one group shows that exposure to a homotypic restraint paradigm results in more robust habituation of the HPA axis response in males than in females (Bhatnagar et al., 2005), suggesting that females may not as readily adapt to repeated stress exposure; however, sex differences in HPA axis habituation across studies do not always show this exact pattern, as previously reviewed (Heck and Handa, 2019).

Activation of the PVT in chronic stress paradigms may also differ between males and females. The c-Fos expression is increased in the PVT of female mice following exposure to an acute stressor (Mantella et al., 2004), as has been shown in males. However, while male rats with a history of chronic stress exposure subsequently exposed to a heterotypic stressor (chronic cold exposure followed by acute restraint) exhibit increased PVT c-Fos expression compared to controls that were not chronically stressed (Bhatnagar and Dallman, 1998), female rats exposed to a heterotypic stressor (social defeat followed by restraint) do not exhibit different acute stress-induced PVT activation compared to non-stressed control rats (Ver Hoeve et al., 2013). Whether this difference is due to a sex difference or due to the use of a chronic defeat paradigm is unclear, but males in a different study exposed to a chronic variable stress paradigm exhibit reduced c-Fos expression in the anterior and whole PVT following novel stressor exposure compared to stress-naïve controls (Radley and Sawchenko, 2015). These data suggest that plasticity within the PVT following chronic stress exposure may differ in males and females. As the PVT is involved in both regulating motivated behavior and the HPA axis, differences in PVT plasticity could manifest in sex-specific vulnerability to chronic stress-induced disruptions in motivated behavior, perhaps more robustly in males.

Chronic Stress During Development

Research from developmental stress models suggests that stress affects the activation of the PVT from an early age and that the female PVT may be more sensitive to developmental stress than the male PVT, though the evidence is limited. pPVT activity is observed in newborn rat pups (Gibbs et al., 1990), suggesting a developmental role of pPVT activity that could be disrupted with early life stress exposure. One study examining early life conditions found that female rats raised in large litters with reduced access to food and maternal care compared to those raised in smaller litters exhibited higher anxiety-like behavior in adulthood and reduced PVT activation in response to acute stress, suggesting a heterotypic-like stress effect on the female PVT (Spencer and Tilbrook, 2009). On the other hand, males in this same study did not exhibit differences in acute stress-induced PVT activation (Spencer and Tilbrook, 2009), suggesting that females are more susceptible to early life stress. Another study showed that adolescent male Sprague–Dawley rats exposed to chronic stress followed by a heterotypic or homotypic stressor show similar pPVT c-Fos expression in response to the acute stressors as a cohort of males that underwent the same paradigm in adulthood (Lui et al., 2012). These data suggest that the effects of chronic stress on the male PVT and its response to acute stressors are fairly stable across development, while female responses are more sensitive to the developmental stage.

In addition to sex- and age-dependent effects of chronic stress, the reversibility of these effects may also diverge in males and females. When male and female rats were exposed to early life stress, males given a running wheel in late adolescence expressed a more robust PVT c-Fos activation in response to an acute restraint stressor than controls and those exposed to early life stress alone; in contrast, females exhibited a less robust c-Fos response than the other groups, showing that chronic early life stress can cause sex-dependent PVT plasticity (James et al., 2014). These male rats also exhibited a behavioral recovery of early life stress effects when given a running wheel, while females did not, providing a link between differential PVT activity and the impact of stress on behavior and suggesting that the reversal of developmental stress effects on the PVT is more achievable in males than females (James et al., 2014). This inability of PVT plasticity to recover hints at a potential mechanism for females' increased susceptibility to stress-induced neuropsychiatric disease phenotypes in humans.

Future studies are necessary to further dissect the role of the PVT in the intricate, sex-specific HPA axis-PVT relationship during heterotypic and homotypic stress. Though data about the impact of chronic stress on the activity of PVT in females is limited, these studies suggest that PVT adaptations to chronic stress may differ in males and females, particularly in their response to novel acute stressors, and depend on the developmental stage. Bhatnagar and colleagues propose that the potentiated HPA and PVT response in males exposed to chronic stress and a heterotypic stressor allows an organism to integrate previous information to adequately respond to a novel threat (Bhatnagar and Dallman, 1998; Hsu et al., 2014); it is, therefore, possible that this adaptation is disrupted or is mechanistically different in females and has potential implications on the future stress response. Differential adaptations following chronic stress in the PVT in males and females that alter the activity of the HPA axis can have sex-specific consequences on motivated behaviors through both PVT and HPA axis-driven mechanisms.

CONCLUSIONS

The PVT is an important regulator of motivated behavior, and additional regulatory roles of the PVT emerge only after exposure to repeated behaviors or stimuli; this is particularly pronounced following repeated exposure to stress. PVT activity is both responsive to acute and chronic stress and has the

ability, particularly following chronic stress exposure, to regulate the HPA axis response to acute stress. Furthermore, distinct neuronal populations within the PVT have independent roles in guiding future motivated behavior and the neuroendocrine stress response and may be impacted differently by chronic stress. Due to the complexity of the PVT's organization and its impact on motivated behavior, the potential consequences of stress on the PVT's role in behavioral control are equally complex. Recent studies using fiber photometry have shown stress-responsive activity of PVT neurons in discrete circuitry, and optogenetic and chemogenetic studies have shown the complexity of the PVT's role in motivated behavior through modulation of distinct behaviors through projections to different target regions. However, the impact of chronic stress in these distinct circuits and the potential impact on behavior is still understudied. Increased specificity with a future study focusing on the impact of heterotypic and homotypic stress paradigms in distinct PVT circuitry will provide more precise insight into the impact of stress on the PVT's role in motivated behaviors. Furthermore, an improved understanding of the impact of stress hormones and neuropeptides within these circuits in heterotypic and homotypic stress paradigms is important because signaling mechanisms are involved in aberrant behavioral responses to novel or acute stimuli following exposure to stress are relevant for understanding stress-related neuropsychiatric disease. Future research on the PVT's role in heterotypic and homotypic stress paradigms will have a greater impact on understanding mechanisms of neuropsychiatric disease than studying these interacting components independently. This may be particularly important in females, who have increased susceptibility to stress-related neuropsychiatric diseases, and a more complete understanding of sex differences in the impact of heterotypic and homotypic stress on the PVT and its role in motivated behaviors is necessary.

AUTHOR CONTRIBUTIONS

SAR and KEP wrote and edited the manuscript. All authors contributed to the article and approved the submitted version.

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The Thalamus as a Blackboard for Perception and Planning

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It has been suggested that the thalamus acts as a blackboard, on which the computations of different cortical modules are composed, coordinated, and integrated. This article asks what blackboard role the thalamus might play, and whether that role is consistent with the neuroanatomy of the thalamus. It does so in a context of Bayesian belief updating, expressed as a Free Energy Principle. We suggest that the thalamus-as-a-blackboard offers important questions for research in spatial cognition. Several prominent features of the thalamus—including its lack of olfactory relay function, its lack of internal excitatory connections, its regular and conserved shape, its inhibitory interneurons, triadic synapses, and diffuse cortical connectivity—are consistent with a blackboard role. Different thalamic nuclei may play different blackboard roles: (1) the Pulvinar, through its reciprocal connections to posterior cortical regions, coordinates perceptual inference about "what is where" from multi-sense-data. (2) The Mediodorsal (MD) nucleus, through its connections to the prefrontal cortex, and the other thalamic nuclei linked to the motor cortex, uses the same generative model for planning and learning novel spatial movements. (3) The paraventricular nucleus may compute risk-reward trade-offs. We also propose that as any new movement is practiced a few times, cortico-thalamocortical (CTC) links entrain the corresponding cortico-cortical links, through a process akin to supervised learning. Subsequently, the movement becomes a fast unconscious habit, not requiring the MD nucleus or other thalamic nuclei, and bypassing the thalamic bottleneck.

Keywords: thalamus, blackboard architecture, Bayesian cognition, spatial steering, supervised learning, pulvinar, MD nucleus, paraventricular nucleus

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INTRODUCTION

The thalamus occupies a central position in the brain. Because of its volume and extensive cortical connections (Sherman and Guillery, 2006) it has significant metabolic costs. Compared to its cost and central position, many theories of thalamic function have an unsatisfactory aspect; if the thalamus is merely a relay for sense data, or merely an enforcer of cortical

rhythms, or a controller of arousal, why devote all that expensive brain real estate to such simple functions, which could perhaps be done more locally in cortex or brainstem? These thalamic functions do not seem to license the significant cost of the thalamus.

These are not the only theories of thalamic function. It has been proposed (Baars, 1988; Mumford, 1991; O'Reilly et al., 2017, 2020; Dehghani and Wimmer, 2018) that the thalamus acts as a blackboard or global workspace in the brain. Blackboard functions appear sufficiently important to justify having the thalamus; but what exactly do they mean? What does a blackboard do? Is the neuroanatomy and neurophysiology of the thalamus consistent with a blackboard function?

This article addresses those questions, relating the blackboard proposals to Bayesian inference in the brain, as entailed by the Free Energy Principle (Friston, 2003). In this article, we will use spatial cognition, planning of movements, and risk-reward trade-off decisions as three examples to illustrate the role of the thalamus as a central blackboard, central in terms of its physical location and role in information processing. This will be evinced through its highly specific anatomical structure and underlying connectivity as a blackboard system. In this role, the thalamus can be regarded as instantiating a generative model of objects in a three-dimensional peripersonal space.

This article explores two key ideas:

- **The thalamus is a blackboard for cognition**, particularly for 3-D spatial cognition, movement planning; and risk-reward trade-offs.
- **The thalamus entrains the cortex**, so that routine movement tasks and possibly also risk-reward decisions are taken over by cortico-cortical links, releasing thalamic resources for more context-sensitive processing.

In a formal approach to planning and decision making, planning can be realized through probabilistic inference, expressed as minimization of free energy (Attias, 2003; Baker et al., 2009; Botvinick and Toussaint, 2012; Mirza et al., 2016; Kaplan and Friston, 2018). In this formulation, the agent builds a (minimum free energy) internal model of the world (including its 3D spatial structure). This is usually referred to as a generative model. Then the agent represents its beliefs about the future, present, and the past as joint probability distributions over states, actions, and consequent outcomes in the future (Kaplan and Friston, 2018).

The other side of the coin, learning to infer, habituates this implicit inference enabling fast and automatic recognition of the most likely cause of sensations—and the aptest behavioral responses (Friston, 2003). In Machine Learning, this process has also been referred to as "amortization" (Gershman and Goodman, 2014). In what follows, we explore the potential roles played by the thalamus within these frameworks, specifically through its modulatory role in the attentional selection and subsequent "voting" in cortico-cortical entrainment.

These proposals articulate a central and vital role for the thalamus and agree with many experimental findings. Spatial cognition and the control of movement are cardinal functions of animal brains; but spatial cognition is hard, involving precise geometry and the fusion of multi-modal sense data, which require a scarce central resource—the thalamus—also implying a need to delegate routine tasks to cortex quickly and efficiently, by configuring cortico-cortical pathways.

THEORIES OF THALAMIC FUNCTION

For many years, the prevailing characterization of the function of the thalamus has been that it acts as a relay. This idea was derived originally from consideration of primary thalamic nuclei such as the LGN, which evidently relay information from sense organs to the cortex (Jones, 2007). The idea has been extended to higher-order thalamic nuclei such as the Pulvinar and the MD nucleus—suggesting that those nuclei relay information between cortical regions and subcortical regions.

In recent years, evidence from thalamic neurophysiology and its engagement by diverse cognitive tasks have brought the "relay" interpretation into question (Sherman, 2007), especially for higher-order thalamic nuclei. There are two main reasons for this. First, studies of thalamocortical neuroanatomy speak of an increasingly complex picture (e.g., Halassa and Sherman, 2019), of the thalamus connected to diverse cortical regions, which have a wide range of different functions, *via* different types of circuit "motif" including driving and modulatory connections, both focal and diffuse, convergent and divergent (Shipp, 2003; Sherman and Guillery, 2006; Barron et al., 2015; Homman-Ludiye et al., 2020). The most remarkable aspect of thalamic neuroanatomy—that the thalamic nuclei are close yet have no lateral connections to one another (Sherman and Guillery, 2006)—remains unexplained. Similarly, the unique anatomy of the TRN (Pinault and Deschênes, 1998) has yet to be accounted for.

Second, studies suggest thalamic involvement in a very wide range of cognitive functions, including perception, attention (Saalman and Kastner, 2014; Wimmer et al., 2015; Schmitt et al., 2017), memory (Dumont and Aggleton, 2013; Warburton, 2018), task engagement (Marton et al., 2018), learning, motor control (Ouhaz et al., 2018), and executive decision-making (Do Monte et al., 2015). Put simply, the accumulating evidence about the role, importance, and connectivity of the thalamus has outrun the "thalamus as a relay" picture. The notion that cognitive processing is restricted to the cortex—with the thalamus acting as a kind of message boy—appears to be untenable. To quote Sherman (2017): "The conventional, textbook view of thalamocortical interactions needs a drastic makeover." In short, higher-order thalamic nuclei may not merely pass information among cortical regions. We need to ask what those nuclei do to—or with—this information, as it traverses the thalamocortical loops.

In the light of the above, it seems unlikely that there will ever be an exclusive theory of thalamic function, that the thalamus does "this and only this." Several proposals are now gaining traction that may not be mutually exclusive. Some examples include: passing efference copies of motor controls to cortical regions, to help to anticipate their effects (Sherman, 2016); controlling information/cost trade-offs (Dehghani and Wimmer, 2018); updating mental representations (Wolff and Vann, 2019);

playing a role in solving the binding problem (Treisman, 1998), entraining oscillations between disparate cortical areas to coordinate processing (Malekmohammadi et al., 2015); deep predictive learning (O'Reilly et al., 2017). The thalamus has also been proposed to integrate predictions from across disparate cortical areas, and subsequently compute the accuracy of those predictions (Grossberg and Versace, 2008; Bennett, 2020; George et al., 2020). The thalamus has further been suggested to operate as an attentional gate or searchlight (Crick and Koch, 1998).

The proposals in this article—for the role of higher-order thalamic nuclei—are not offered as exclusive proposals; rather, as a formal account of the computational anatomy of higher-order thalamic functions that complement or contextualize existing proposals. In what follows, we elaborate the relay picture of the thalamus in three important respects. First, following Mumford (1991), we propose that the thalamus acts as a blackboard, allowing different specialist cortical regions to cooperate in solving cognitive problems. Second, following the Bayesian brain hypothesis (Knill and Pouget, 2004; Doya, 2007; Rao, 2010)—and its expression *via* the Free Energy Principle (Friston, 2003)—we propose that in its blackboard role, the thalamus brings about a particular result—the aggregation, or summing, of the free energy contributions from diverse cortical regions, as they join in dynamic coalitions for active perceptual inference and planning. Third, we propose that the scarce bottleneck of thalamic processing is engaged particularly in novel tasks; and that thalamocortical circuits then train cortico-cortical links to take over those tasks as they become amortized and habitual. We hope that this thalamic blackboard picture may serve as an indicative framework to bring together the many interpretations of thalamic function which are now emerging. First, we describe—from first principles—what a blackboard is.

BLACKBOARD ARCHITECTURES AND CORTICAL MODULES

The concept of a blackboard (Nii, 1986; Llinas and Anthony, 1993) has emerged over the past decades from computer science and artificial intelligence. A blackboard is a central store of information that can be addressed selectively (that is, written and read) by a set of independent computing processes, enabling them to solve problems cooperatively. In essence, one computing process may post partial information or hypotheses to a part of the blackboard, and other processes may retrieve that information selectively, enabling them all to work together to reach a solution.

The blackboard is an analogy to a group of human experts working cooperatively on a problem. Each expert may write an idea on any part of the blackboard. All the other experts can see what has been written and may contribute their own ideas. In this way, the group can collaborate to accomplish more than any single expert on their own.

In artificial intelligence, the computing processes may be accomplished by small independent expert systems, each one with limited knowledge. This was proposed by Erman et al. (1980) as an approach to sensor fusion. In scientific or commercial computing, the blackboard may be a computer database, such as a Relational Database (Date, 1976), and the computing processes may be independent computer applications with different users. In cognitive neuroscience, the computing processes may be different (i.e., functionally segregated) cortical regions, and the blackboard may be the thalamus which they all connect to (Zeki and Shipp, 1988). In the first instance, this proposal is consistent with the very widespread connectivity of the thalamus.

At any moment, to control its own movements, an animal needs to understand the locations and movements of things around it, inferred from its sensory data. The mammalian cortex has many cortical modules concerned with different kinds of sensory data, and with ways of analyzing sense-data, such as:

- Edge detection.
- Motion detection.
- Stereopsis.
- Sound location.
- Locations of touch and movement sensations.
- Shape from shading.
- Shape from motion.
- Linking data from two or more sense modalities.
- Recognition of learned shapes or movements.
- Knowledge of hierarchical structures, such as bodies and body parts.

We will consider these analytic attributes as cortical **knowledge sources** that are functionally segregated in different regions in the cortex (for instance, in visual or somatosensory maps) (Zeki and Shipp, 1988; Tononi et al., 1994; Friston and Buzsaki, 2016). It appears that many different types of knowledge source, and many different instances of some types, operate in parallel to maintain an internal model of an animal's surroundings at any moment (Crick and Koch, 1998; Thomson and Bannister, 2003; Zikopoulos and Barbas, 2007; Saalmann and Kastner, 2009; Cruikshank et al., 2012; Lewis et al., 2015).

When it comes to recognizing an object with multiple features and its respective location, separate representations are encoding "what" and "where" in the visual hierarchy (Ungerleider and Haxby, 1994). From the perspective of Bayesian belief updating under the free-energy principle, these cortical knowledge sources can be seen as sets of marginal probability distributions (Friston et al., 2017a; Parr et al., 2020) that inherit from a factorization of probabilistic beliefs about the causes of sensation. For example, knowing what something is conditionally independent of where something is. In terms of Bayesian belief updating in the brain, the implicit factorization of probabilities implies the additivity of free energy gradients[1] from different knowledge sources during multisensory integration. In this article, the role of the thalamus is taken to be the integration of free energy gradients from rapidly formed dynamic coalitions of knowledge sources. The modularity in question subsequently calls upon a gating mechanism that establishes the different types of interactions

[1] In predictive coding schemes that implement free energy minimisation, the free energy gradients can be regarded as precision weighted prediction errors. More generally, these gradients reflect the discrepancy between some posterior and prior probabilistic beliefs, encoded in neuronal activity.

among these factorized representations. The ensuing proposal is then that the thalamus acts as a blackboard, though which inference based on different cortical knowledge sources are integrated into a Bayesian or posterior belief distribution over the causes of sensations. We will first focus on this integrative role—and then turn to the question: why are these Bayesian beliefs necessary for sentient behavior.

For any blackboard application—sensor fusion, computer databases, or sense data integration—there are some core requirements for the blackboard. First, the blackboard must be able to store information, if only for short periods, so that different knowledge sources can read and write information to the blackboard asynchronously. The reading and writing, in this context, corresponds to belief updating that could be mediated by variational message passing, belief propagation, or predictive coding; depending upon the nature of the generative model—and the particular way in which free energy gradients induce neuronal dynamics (Rao and Ballard, 1999; Bogacz, 2017; Friston et al., 2017b).

The suggestion that the thalamus, acting as a blackboard, needs to store information for short periods, is found in other formulations, such as Dumont and Aggleton (2013) and Warburton (2018), which implies that thalamic nuclei are also involved in longer-term memory. The complex roles of the thalamus imply that any thalamic nucleus may contribute to several functions; so short-term and long-term storage are not in conflict.

Second, the blackboard cannot just hold an unstructured heap of facts or hypotheses. Each knowledge source must be able to address its inferences selectively to some part of the blackboard. These inferences must be segregated on the blackboard, and knowledge sources must be able to selectively retrieve information from the blackboard. In short, the dynamic connectivity of the thalamus and thalamocortical connections must embody the generative model's delicate causal architecture that is learned or distilled from the world.

These core requirements are implicit in the blackboard metaphor. A physical blackboard holds information as chalk marks, and these chalk marks are distributed across the plane of the blackboard so that different experts can read or write selectively to different parts of the blackboard. These requirements will be called the **addressing** requirements.

A blackboard architecture accommodates—simply and compellingly—the computational architectures required for Bayesian belief updating. In Bayesian inference, the posterior probability of some hypothesis (for instance, the probability that there is an object at some location in space) is proportional to its prior probability, multiplied by the likelihood that the hypothesis would have caused the current sensations. In variational treatments of Bayesian belief updating—of the sort implied by the free-energy principle—the posterior or conditional probability can be factorized to represent contributions from different knowledge sources, explaining conditionally independent aspects of sense data (e.g., *what* something is and *where* something is). This implies that the log probability of the hypothesis corresponds to the sum of log probabilities from different knowledge sources (modulo a constant for all hypotheses). Based on a physical analogy, this negative log probability can be expressed as Free-Energy, and the task of a brain in finding the most likely hypothesis is to minimize its free-energy or to minimize surprise inherent in sensory input. This minimization can be cast as a gradient flow on free energy, furnishing a straightforward description of neuronal dynamics (Friston et al., 2017a). Just as the log probabilities add, so do free-energy gradients.

This approach to cognition has a strong theoretical basis, because it can be shown, under very general conditions (Worden, 1995), that Bayesian cognition affords the greatest the fitness—and so is the target towards which the evolution of brains converges. Furthermore, the Bayesian brain can explain many different aspects of cognition (Knill and Pouget, 2004; Doya, 2007; Seth, 2015; Omidvarnia et al., 2017).

The ensuing Bayesian approach can be applied to a central problem in animal cognition, which impacts an animal's survival at every moment of the day—the problem of inferring the locations of objects in peripersonal space from multi-modal sense data. The animal needs to know these locations at every moment to control its physical movement, from locomotion through to visual saccades. The application of Bayesian mechanics to the location of objects leads straightforwardly to a requirement for a blackboard architecture—where different knowledge sources are assimilated to furnish conditional probabilities for the spatial locations of objects.

The combination of blackboard architecture and Bayesian inference leads to a specific kind of blackboard—a **probability aggregator** (Worden, 2020b), where probabilities are factorized distributions encoding specialized representations, so logs of probabilities (and their gradients) are to be added, as in the Free Energy Principle (Friston, 2003; Parr et al., 2020). In the aggregator architecture, different hypotheses about the spatial locations of objects are segregated by location. For example, for any given hypothesis—that there is an object X at location Y—different knowledge sources estimate conditional probabilities for the hypothesis (based on different types of sense data) and post them to the blackboard. The blackboard aggregates (i.e., sums) the log contributions from the different knowledge sources. By Bayes' theorem, this summation (when combined with a prior log probability) estimates the overall log probability of the location hypothesis, from the contributions of all the knowledge sources, aggregating information from different modalities and marginal representations. Maximizing the posterior or conditional log probability (i.e., minimizing the free energy) produces the most probable identity and location for each object, in the light of all the sensory evidence at hand.

To illustrate this principle: vision gives the animal a two-dimensional projection of its surroundings, encoded as 2-D locations of neurons in some retinotopically mapped visual cortex. To elaborate a three-dimensional model, as needed to control movement, various knowledge sources are applied (Leibo et al., 2015), such as:

1. Stereopsis.
2. Shape from shading.
3. Shape from motion.

According to varying circumstances, different knowledge sources may provide the most decisive depth information at different times, and they may confirm one another, or they may compete, inferring different depths. All this is encapsulated in a Bayesian estimate of depth from the different knowledge sources[2]. One way in which this could be computed is to sum the log probabilities of different depth hypotheses as an aggregate on a blackboard and to determine the most probable depth from the maximum of the sum—where the sum of the gradients in any variable is zero.

As a second illustration, consider the (multisensory) problem of integrating visual information and proprioceptive information, as is needed for instance in hand-eye coordination, or in paw-eye coordination for primates (Ernst and Banks, 2002). Proprioception gives information about the position of a limb, possibly through inferring joint angles; and vision gives conditionally independent information about the location of the same limb. At different times, one or the other knowledge source may dominate; but at all times, the best (fittest, most accurate) way to combine the two estimates—to estimate the location of the limb—is by Bayesian estimation. This can be done through the blackboard aggregation of log probabilities from the two knowledge sources. We will now unpack the implicit gating mechanisms in terms of attention and the pulvinar.

ROLES OF THALAMIC NUCLEI

The role of the thalamus in cognition can be characterized by considering the roles of higher-order nuclei of the thalamus, including the pulvinar, the Mediodorsal (MD) nucleus, and the paraventricular thalamus (PVT). An interpretation of their roles is consistent with recent findings on the role of the MD nucleus in learning and memory for complex spatial configurations, and the PVT for balancing danger and reward.

The Pulvinar

The pulvinar links mainly to posterior cortical regions involved in sense data processing, such as the visual cortex. This is consistent with a role for the pulvinar in mainly sensory processing: specifically, in building and maintaining a 3-D spatial model of "what is where" in the animal's immediate surroundings, based on multi-modal sense data (see Rudrauf et al., 2017). This generative model of space underwrites Bayesian inference and learning—fitting to all sense data (except olfaction), using the blackboard/aggregator architecture.

In building a 3D generative model of the animal's surroundings, attention to the most informative and precise inputs is important. Diverse evidence points to the pulvinar playing a role of this kind:

- There is a double dissociation effect in processing visual information whereby deactivating the lateral pulvinar suppresses V1 responses to visual stimuli, whereas superficial visual layers with overlapping receptive fields become more responsive as an effect of pulvinar activation (Purushothaman et al., 2012).
- The presence of presynaptic acetylcholine receptors in thalamocortical pathways (Lavine et al., 1997), known to modulate the gain of evoked responses in visual perception.
- Lesions to the pulvinar result in focal attention deficits (Snow et al., 2009).
- Neural activity in the pulvinar that is associated with task-relevant stimuli but not with distractors can be decoded, implying a filtering process (Strumpf et al., 2012; Saalman and Kastner, 2014) discuss how the Pulvinar regulates the flow of information between visual areas (Warburton, 2018), reviews the role of thalamic nuclei in object recognition tasks.

These examples and others (Shipp, 2004; Kanai et al., 2015) speak to a form of attentional selection mediated by the neuromodulatory effects of the type afforded by the pulvinar. The pulvinar is in the position to selectively enable pre-synaptic gain sensitivity to particular types of information. Note that the pulvinar is itself selecting the inputs that it aggregates. In other words, the pulvinar is, effectively, predicting the precision or weights that should be afforded the various knowledge sources: it is effectively selecting the kinds of knowledge sources that influence belief updating in a base optimal fashion.

In the Bayesian inference thought to be performed by animals or humans, the difficult problem is finding the optimal balance between the different types of sensory evidence and their implicit conditional probability distributions in relation to the different types of priors. That is, weighing the prior beliefs according to the sensory evidence sampled by the agent. This balance is mediated by the relative precisions (i.e., negative entropies) of the particular belief distributions in question. Deploying and mixing information is just as important to the agent as the information itself. The best candidate in maintaining this balance—by enabling specific representations (i.e., cortical knowledge sources)—is the pulvinar, inferring, and mediating visual attentional set.

The Mediodorsal Nucleus

The MD nucleus is strongly linked to the prefrontal cortex, whose role relates to executive planning for actions. For non-human primates, this planning is largely the planning of complex spatial movements, asking questions such as "Can I reach that piece of fruit?" "Can I jump to that branch?" and "Is it strong enough to bear my weight?" There have been extensive investigations of the role of the MD nucleus in executive decision making, learning, and spatial cognition (Aggleton and Nelson, 2015; Mitchell, 2015; Parnaudeau et al., 2015; Ouhaz et al., 2018; Parnaudeau et al., 2018; Wolff and Vann, 2019), leading to a complex picture of many related roles for the MD nucleus. Here, we particularly address the need for spatial control of movement in tasks where MD-related deficits have been observed (Mitchell, 2015).

Movement-planning decisions depend on the 3-D configuration of objects in space, as represented in the

[2]Technically, the weight afforded different sources is determined by the precision or confidence placed in the corresponding marginal beliefs- or, when combining sense-data the precision of the likelihood of those data relative to the precision of prior beliefs about the causes of those data.

pulvinar—but now require internal simulation of the planned movement—"If I jump, how far will I go?" and on memories of recent similar movements—"The last time I tried this. . .." These "what if" questions must be played out (possibly by imagining the movement at a declarative level) against the background of what is where now. That is the nature of planning. Then, when a satisfactory plan has been found, it must be carried out and monitored—another task requiring an accurate moment-to-moment model of what is where in three dimensions.

When we refer to "spatial cognition" or "spatial processing" in the context of the Pulvinar or the MD nucleus, we are referring specifically to a three-dimensional spatial model of the locations of objects immediately around the animal, as perceived and used to plan and control muscular movements, rather than to a two-dimensional navigational space. The latter space is linked to the hippocampus, to place cells and head direction cells, and the thalamic nuclei linked to the hippocampus, such as the anterior dorsal nucleus (Taube, 1995), and the ventral midline nuclei (Jung et al., 2019).

One might propose that the MD nucleus of the thalamus (and possibly other thalamic nuclei) uses a shared generative model of peripersonal space, as orchestrated in the pulvinar, to plan, to test in imagination, and then to execute, novel or complex movements, with the PFC.

This interpretation of the role of the MD nucleus is consistent with:

1. Its position in the thalamus, where it has access to the 3-D spatial model of current reality.
2. Its extensive cortical connections, particularly to the PFC with its executive role in planning.
3. Experimental findings on learning and memory for complex spatial configurations, in the presence of lesions to MD nucleus or PFC.
4. Its reciprocal connections with the supplementary motor area known for its contributions to movement control (Cunnington et al., 1996; Chen et al., 2010).
5. Recent theoretical formulations (Parr and Friston, 2018) suggesting that during inference, ascending messages from the MD nucleus to the motor cortex represent the free energy expected under each potential outcome, given the set of actions being considered.

Before comparison with the experimental findings, we outline the proposed mode of functioning of the MD nucleus in the setting:

- The PFC makes an executive decision that a certain goal needs to be achieved (e.g., grasping a piece of fruit, jumping across a stream). The goal requires a coordinated sequence of physical movements.
- If the goal or the circumstances are novel, it is necessary to plan and simulate the movements in three dimensions before carrying them out: failure in simulated 3-D space is cheaper than real failure.
- The MD nucleus acts as a blackboard for this simulation, using the model of objects in space computed from sense data in the pulvinar blackboard.
- The MD nucleus orchestrates cortical motion-control knowledge sources, which entertain possible movements.
- Planning may involve recalling memories of recent similar movements, for comparison.
- The action trajectory with the minimum expected free energy is selected.
- If PFC evaluates the likely level of success to be sufficient, the sequence is carried out—with pulvinar and MD nuclei acting as blackboards for the monitoring of the outcome: see "planning as inference" (Attias, 2003; Baker et al., 2009; Botvinick and Toussaint, 2012; Maisto et al., 2015; Kaplan and Friston, 2018).
- For novel sequences, cortical activity is coordinated through cortico-thalamocortical (CTC) driver pathways.
- If some sequence is repeated successfully, CTC driver activity produces plastic changes in the corresponding direct cortico-cortical pathways, *via* experience-dependent learning.
- After several successful repetitions, any movement sequence becomes "compiled" into direct cortico-cortical pathways, which are faster than the CTC path, and bypass the thalamic planning bottleneck.
- So successful planned movement sequences become habitual and unconscious, as the thalamus entrains cortex. This is learning to "infer" (Gershman and Niv, 2010; Series and Seitz, 2013).

This process is similar to the distinction in AI between "deep" or "causal" knowledge (such as explicit spatial modeling of movements), and "compiled" rules which are cheaper and faster to apply, once they have been compiled. In a similar vein, machine learning considers this habitation in terms of "amortization" (Rice and Barone, 2000; Zhang et al., 2018); namely, deferring the computational cost of planning by resorting to a hardwired habit (in the right context). The role of the thalamus is to do itself out of a job—to do the expensive central "bottleneck" work of explicit modeling of movements in space only when it is necessary, for novel challenges, consequently entraining direct cortico-cortical pathways to take over the job—which they can do in parallel, faster and without conscious involvement.

The process of thalamus training cortex is illustrated in **Figure 1**.

We note that this suggestion, that the MD Nucleus trains the cortex in new movements, is not intended to be an exclusive account of what the MD nucleus does. As was noted in "Theories of Thalamic Function" section of the article, thalamic nuclei are involved in so many types of cognitive function that any one account of their function is bound to be incomplete. Different accounts, such as those cited in "Theories of Thalamic Function" section, can coexist.

Given the many studies of the role of the MD nucleus in learning and task performance, the evidence may sometimes seem contradictory. However, the overall picture seems to be that the MD nucleus is more involved in "rapid trial-by-trial associative learning and decision-making" (Mitchell, 2015) than in habitual tasks.

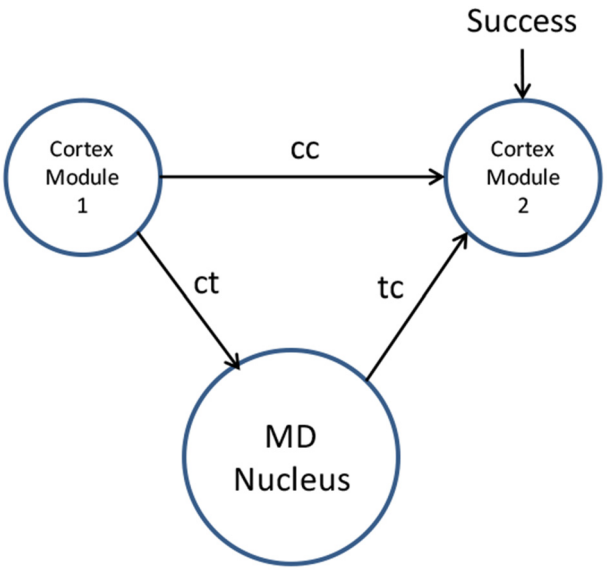

FIGURE 1 | Mediodorsal (MD) nucleus training cortex by associative learning (i.e., "this is what I see myself doing in this situation"). Novel movements are coordinated by the MD nucleus relay driver neurons through corticothalamic paths (ct) followed by thalamocortical paths (tc). Repeated movements lead to synaptic changes facilitating a direct cortico-cortical path (cc) to cortex module 2. These cortico-cortical paths then manage the habitual movement without thalamic involvement.

Heuristically, this process can also be understood by analogy to a SatNav (satellite navigation system). The first time any route is needed, the SatNav does an expensive spatial computation—comparing different routes for cost, time, and traffic, and so on. But if a route is selected and traveled, the spoken instructions are recorded—and the next time that route is needed, it is only necessary to replay the recording, with appropriate timings. Cortico-cortical links act as the recorder, and complex spatial computation is no longer needed. Only much more circumscribed planning (inference) is required—the cortex has learned to infer.

The notion that skilled habitual behavior is learned active inference could be compared with experimental results for spatial tasks with MD and PFC lesions. Potential neuroscience experiments best fitted to test this notion would use some task requiring the planning of spatial movements, in the following sequences:

a. Test novel—test habitual.
b. MD lesion—test novel—test habitual.
c. Test novel—MD Lesion—test habitual.
d. PFC lesion—test novel—test habitual.
e. Test novel—PFC Lesion—test habitual.

Here "test novel" tests the performance of the task when it is still new, and requires explicit planning of movements in space; while "test habitual" tests the same task when it has become familiar and routine. The key contrast is between sequences (b) and (c); (b) should show a greater impairment than (c), because in (c), the MD nucleus is no longer needed for habitual movements; while (d) and (e) should be more similar to each other than (b) and (c), because PFC lesions should affect novel and habitual movements comparably.

Several recent experiments have been sufficiently close to this design to shed light on the nature of spatial planning (Gaffan and Parker, 2000; Mitchell and Gaffan, 2008; Mitchell and Chakraborty, 2013). Those experiments lend support to the interpretation that the MD nucleus, by training the cortex, delegates the work and so does itself out of a job. In essence, these experiments suggest that lesions to the MD nucleus before training disrupt learning and performance; but lesions after training do not disrupt the performance of learned discrimination. These results are reviewed by Mitchell (2015) who writes: "*Recent evidence from monkey models of cognition shows that the magnocellular subdivision of the mediodorsal thalamus (MDmc) is more critical for learning new information than for retention of previously acquired information. Further, consistent evidence in animal models shows the mediodorsal thalamus (MD) contributes to adaptive decision-making.*"

To more fully test the hypothesis that the MD nucleus is used to plan movements, and subsequently, MD entraining cortex in the planned movements, similar experiments could be done on non-human primates with MD functioning temporarily inhibited, for instance using optogenetic suppression (Rikye et al., 2018), using a task with explicit planning of movements; for instance, requiring monkeys to move an object to a goal around various obstacles or traps. A two-dimensional version of this test could be configured with a computer screen and a mouse-guided ball, as shown in **Figure 2** below.

Experiments using these sorts of tasks could explore not only the role of the MD nucleus but also the number of examples needed to train the cortex and make a task habitual (as measured by reduced task completion times).

The Paraventricular Nucleus

A key aspect of animal behavior, with a strong influence on survival, is making decisions that balance danger against

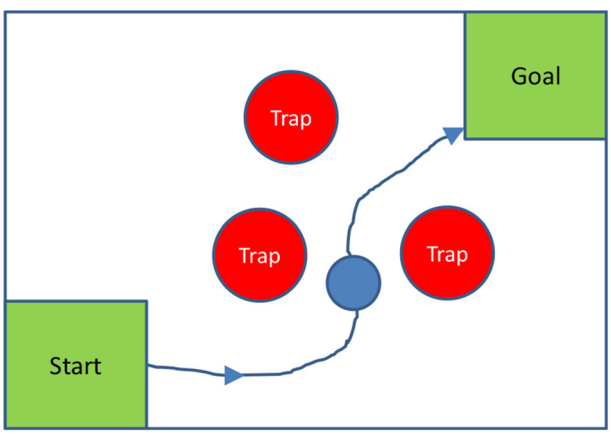

FIGURE 2 | Two-dimensional spatial planning task: a monkey is required to guide a ball to a goal, by moving a mouse, without touching any trap. In the diagram, traps are stationary; but they could also move, to make the planning task harder.

reward—for instance, knowing whether to feed or flee, explore or exploit (Cohen et al., 2007; Humphries and Prescott, 2010; Humphries et al., 2012; Friston and Buzsaki, 2016; Konig and Buffalo, 2016). In rodents, the thalamic paraventricular nucleus is known to be involved in these kinds of decisions (Choi and McNally, 2017; Choi et al., 2019).

In a free-energy formulation of a risk-reward trade-off, there needs to be some common currency in which both risk and reward are represented, to ensure a seamless trade-off. The common currency is a logarithm of the probability of survival; diverse risks, such as predation, reduce this logarithm, and rewards such as food increase it. In any situation, there is a diverse set of risks, and the probabilities of death from the different risks can usually be multiplied (factorization); therefore the (expected) free energies can be added.

This calculation is therefore suitable for an aggregator architecture, adding together the free energies from a dynamic coalition of knowledge sources, much as we propose the pulvinar sums free energies in spatial perception and movement planning. Crucially, for the risk-reward trade-off, as there are many potential risks, and a few of them are significant at any time, free energies from a dynamic coalition of knowledge sources need to be summed—so hard-wired cortico-cortical connections are less suitable to do the sum, and a central blackboard/aggregator is a more suitable architecture. This is consistent with the known role of the paraventricular nucleus in these trade-offs, and a blackboard role for the thalamus.

Based on the result for motion control (cited in "The Mediodorsal Nucleus" section) that the thalamus is no longer involved when a motion becomes habitual (e.g., Mitchell, 2015), and our interpretation that the thalamus "trains" cortico-cortical circuits to perform habitual movements, we might venture a similar prediction for risk-reward behavior. While Choi et al. (2019) have shown that temporary suppression of the paraventricular nucleus by chemogenetics disrupts risk-reward trade-offs when they are novel, we would predict that when some trade-off becomes routine, suppression of paraventricular thalamus, in a similar manner to that investigated by Choi et al. (2019) would no longer disrupt it. Testing this prediction would depend on some risk becoming routine.

HOW IS THE BLACKBOARD ADDRESSED?

The examples of depth perception and multi-sensory integration illustrate how hypotheses from different knowledge sources need to be combined to support Bayesian inference in scene construction (Hassabis and Maguire, 2007; Mirza et al., 2016). Stereopsis, shape from motion (Murray et al., 2003), and shape from shading can each operate across a large part of the visual field. Further, the varying spatial location has been shown to impact perceptions of the same object (Finlayson et al., 2020) and therefore to impact which relevant cortical knowledge sources would be dynamically engaged. There can be many instances of each type of knowledge source operating in parallel, at different parts of the visual field. How are their probabilities to be aggregated? Which instance of shape from motion should be aggregated with which instance of stereopsis?

There is one possible answer to these questions. Two knowledge source instances can only be aggregated (i.e., their log probabilities should be added) if they refer to the same latent causes—that is, to a thing at the same inferred location. Therefore, hypotheses on the blackboard need to be segregated by location—to instantiate the prior belief that two things cannot occupy the same location in space. For features in the animal's immediate surroundings (including its own limbs), segregation by hypothesis implies segregation by location. This question, of the appropriate combination of information from different cortical knowledge sources, has also been cast as the binding problem—how to bind together the activities of different cortical modules (Treisman and Gelade, 1980; Tononi et al., 1994; Treisman, 1998; Fingelkurts et al., 2010; Feldman, 2013). The current analysis suggests that a possible solution to the binding problem is binding by inferred location[3], through the blackboard.

There is a further important requirement for Bayesian inference about objects in space. There is an important prior probability that in an allocentric frame of reference, most of the things surrounding the animal do not move. This prior is so universal that it can be represented and used in animal brains, for two related purposes: first, if something is known with high confidence to be static, the animal does not need to keep checking its location. Second, something which moves deserves attention. This would involve mandating attention appropriately: anteriorly to the PFC and motor cortex *via* the MD thalamus and posteriorly *via* the pulvinar (Feldman and Friston, 2010; Brown et al., 2011; Vossel et al., 2015; Parr and Friston, 2017; Mirza et al., 2019) but will not be explored further in this article.

So far, we have discussed the requirement for segregation of information in the blackboard at Marr's (Marr, 1982) level 2, of algorithms and data structures. The question arises: how can segregation by location be implemented at Marr's level 3 of neural implementation? We shall approach neural levels in three steps. Among many possible neural implementations, it is worth picking out two extremes, namely, "focal" and "distributed" representations.

In a **focal** neural implementation, one location in real space may be represented by the firing of a few neurons at a specific location in the brain. This is the kind of representation used in the V1 visual cortex and used in somatosensory maps in the brain. The focal representation of the V1 cortex is replicated in the thalamic LGN, which connects to V1 by topographically organized relay neurons. In secondary thalamic nuclei such as the MD nucleus and the pulvinar, the situation is less clear. While there are two concentric visual maps in the pulvinar, their relation to cortical maps is a much more "blurred" (i.e., distributed) relationship (Shipp, 2003).

In a **distributed** representation of space, one point in space is represented not by the enhanced firing of neurons clustered at some location in the brain, but by a pattern of firing across many neurons. One can illustrate a distributed representation in

[3]This means that if two stimuli have the same or overlapping inferred locations on the blackboard, they are bound together—so that even when there are very many stimuli, the sets of stimuli which are bound together are small sets.

a single dimension, by the example of a Fourier representation. If there is a set of neurons arranged along a single dimension in the brain (called x), then a pattern of firing rates R ∼ [1 + cos (kx)] across those neurons can represent an object at location k. If there are many neurons arranged along the dimension x, then their firing rates can simultaneously represent the locations k, k′, and so on of many objects, by superposition of the different cos (kx) patterns of firing rates.

Such a Fourier-like representation is capable of high capacity and high spatial precision (as is required to segregate information on the blackboard); if many neurons (or synapses) with different internal position x are involved in representing one wave-like cos (kx) pattern, then k can be determined to high precision. One output neuron can have its input synapses spatially distributed as cos (kx), and so be preferentially sensitive to 1 value of k, with high selectivity.

The Fourier representation generalizes to three dimensions, provided that neurons and synapses are extended in three dimensions (as they are in the thalamus), and not in a 2-D sheet, as in cortex. That is, a represented position **k** can be a three-vector; then the distribution of firing rates can be [1 + cos(**k.x**)], a wave-like distribution in the volume of the thalamus, representing positions with high precision in three dimensions. Because the output neurons can be selective in **k**, the same set of neurons can, by superposition of firing rates, represent the positions of many objects (different **k** values) simultaneously.

The Fourier representation of position information is only given as one example of a distributed representation, but it seems to be a powerful and instructive example. It shows how, in a three-dimensional volume of the thalamus, a distributed neural representation could give three-dimensional spatial segregation of information with high precision and high capacity—which is one requirement for a blackboard role. It is notable that each thalamus, unlike many parts of the brain, has an approximately spherical shape, with comparable extension in all three dimensions, so enabling it to store positions with high precision in three dimensions, using a distributed representation. This regular shape of the thalamus is preserved across many species (Jones, 2007).

SPATIAL STEERING OF SENSE DATA

Small regions or modules of the cortex can be classified along a spectrum between two extremes:

1. Regions dedicated to a particular patch of incoming sense-data, such as parts of the V1 visual cortex, or of somatosensory cortex; these regions are typically parts of sensory maps, and perform some homogeneous function across the map, such as edge detection.
2. Regions dedicated to a particular function, such as face recognition or word recognition, may use sensory data from many different sources and locations.

There are regions of cortex between the two ends of the spectrum—for instance in higher visual areas concerned with inferring shapes and form (Zeki and Shipp, 1988; Lueck et al., 1989). This characterization of the cortex—by such a spectrum—may be a simplification, but it serves to define a lower limit to the diversity of cortical regions to which the thalamus is connected.

We focus on the second end of the spectrum, noting that a face recognition module needs to learn and recognize faces across a large part of the visual field. We also note an insight from building artificial neural nets. It is possible to build a working neural net for face recognition; but to make it learn faces in the shortest possible time, all the faces must be properly aligned on some input grid of the net (Denker et al., 1987). Variable alignment leads to much slower learning. The requirement for spatial alignment extends to hierarchical multi-layer "deep" nets (LeCun et al., 2015). If there is a "nose recognition module" serving the face recognition module, the output of the nose recognition module needs to be properly aligned as an input to the face recognition module. That is, the nose needs to be at the center of the face.

This leads to a requirement for **spatial steering** of sense-data between cortical modules. In some models of hierarchical pattern recognition (Olshausen et al., 1993, 1995; Lee and Mumford, 2003), spatial steering is accomplished by direct cortico-cortical connections. The spatial steering needs to be rather precise. Consider recognizing a face 10 m away, and the need to align the recognized nose properly on the face. Absolute displacements from the animal, rather than relative displacements within an object need to be aligned (Worden, 2020b). If precise alignment is done by the selection of alternative cortico-cortical fiber bundles, it may require prohibitive numbers of bundles, most of which are idle most of the time. In machine learning and some treatments of spatial attention, this steering is cast as attentional orientation or selection; e.g., see Humphreys et al. (2009).

Since a thalamic blackboard needs to segregate information by spatial location, there is an alternative way to do the spatial steering of sense-data needed for hierarchical pattern recognition. If the "nose recognizer" posts its results to an inferred location (an address in the blackboard), and the face recognizer reads (as it must) from the same location, the combination of reading and writing has **steered** the sense-data spatially between these two cortical modules. Segregation of information on the blackboard, together with selective writing and reading, implies steering of sense-data. Spatial steering of sense-data is one of the core functions of the thalamus as a blackboard.

This leads to a more powerful concept of the thalamic "gating" of information. Gating is often conceived as the thalamus simply switching neural paths on and off; a kind of simple on-off filtering, or tuning up and down of arousal. But it can also be seen as a precise spatial routing of sense data and neuronal message passing between cortical modules. This is a much more demanding requirement than simple gating. It is a requirement for signal processing rather than for computation. If the thalamus does spatial steering of sensory information, how might it do it? Distributed representations—in particular, Fourier representations—are again instructive.

An analogy from engineering—to illustrate this—is a **steerable phased antenna array** used, for instance, in satellite communications. For steering in one dimension, this is a regular

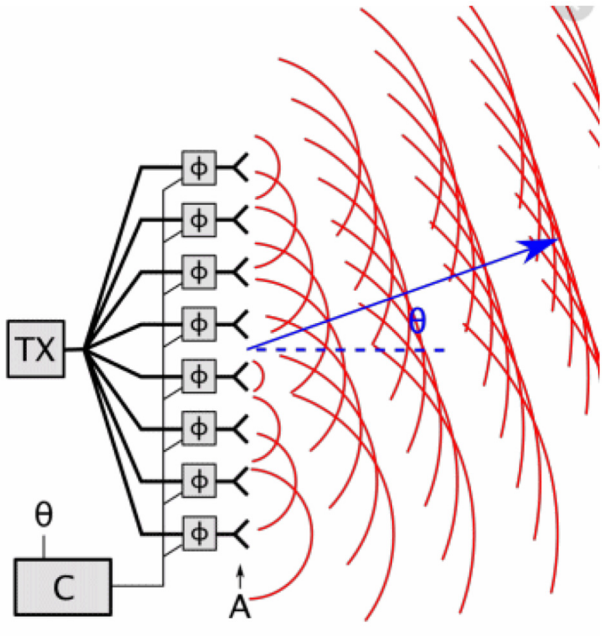

FIGURE 3 | The use of a phased array antenna, where the relative phase of the signals emitted by neighboring antennae controls the direction of the signal emitted.

linear array of small antennae, all transmitting at the same frequency (and therefore at the same wavelength). If the antennae are all in phase, then the radiated signal has a strong peak at 900 from the line of the array, where they all interfere constructively. However, if there is a phase lag between each antenna and the next one, the peak of constructive interference is moved away from 900. By controlling the relative phases of the antennae, the output signal can be spatially steered in different directions. This is illustrated in **Figure 3**.

This illustrates how a time lag between each antenna and the next one, which is less than one cycle of their oscillations, means that the wavefronts are all in phase at some angle θ to the vertical, where θ is determined by the time lag.

The steerable array principle could be applied in the thalamus, as follows:

- The phase of the neural signals is the phase of firing relative to some prominent thalamocortical rhythm, for instance, an alpha rhythm at 10 Hz, with a 100 ms cycle time.
- The relative phase of different neurons or synapses is controlled by introducing time lags in the range of 0–100 ms.
- Locations are represented in a Fourier representation, with three-dimensional wave vectors **k**.
- Each thalamic relay neuron has a wave-like spatial distribution of input synapses cos (**k.x**) over some region of positions **x** in the thalamus.
- The represented position **k** is tuned by varying the time lags on input synapses in the 0–100 ms range, in a way dependent on the position of the synapse in the brain.

With the Active Inference framework in mind, this type of attentional modulation would be mediated by nonlinear synaptic mechanisms of the sort reviewed above—and implicated in the deployment of precision. The basic idea is that to compute the posterior estimate of spatial location, the log-prior and log-likelihood would each be multiplied by their respective precisions (represented in the thalamus) then summed together. In this case, information *per se* is not affected since the logs themselves, which are provided by the cortex, are not being modified. However, the message passing is affected—messages being switched on or off—depending upon the afforded precisions.

This is only a high-level sketch of how the thalamus could steer sense data, and many details remain to be resolved. However, even based on this high-level sketch we can start to compare the requisite computational architecture with thalamic neuroanatomy.

THALAMIC NEURO-ANATOMY FOR STEERING AND AGGREGATION

The previous sections have examined the hypothesis of the thalamus as blackboard at Marr's (1982) Level 2, of algorithms and data structures. How does this description map onto thalamic neuro-anatomy, at Marr's Level 3? The hypothesis can be related to several prominent features of thalamic neuroanatomy and physiology, including:

- Quasi-independent thalamic relay cells.
- Thalamo-cortical rhythms.
- Diffuse cortical connectivity of higher-order thalamic nuclei.
- Inhibitory interneurons.
- The regular three-dimensional shape of the thalamus.
- Driver and modulator pathways.
- Triadic synapses.

The following discussion applies mainly to higher-order thalamic nuclei such as the MD nucleus and the Pulvinar, rather than first-order nuclei such as LGN (which appears to have only a minor spatial steering function). Higher-order nuclei occupy most of the volume of the thalamus. In contrast to neurons in the cortex, thalamic relay neurons have no local excitatory connections. Is this distinctive feature consistent with a blackboard role?

In what follows, we use the term "relay neuron" purely to describe a type of neuron which is prominent in all thalamic nuclei (except the TRN)—without implying that the function of any nucleus is only a "relay" function.

A lack of local recurrent excitatory connections implies that it is not possible to sustain some pattern of neural firing by local positive feedback. This limits the ability of the thalamus to complex computations or to carry out one blackboard function—short-term memory for example—using only local connections within the thalamus. However, hypotheses can be sustained over unlimited periods by positive feedback between the thalamus and cortex, for instance in a 10 Hz alpha rhythm. This cycle can not only sustain short-term memory; it can also

support a near-Bayesian optimal fit of hypotheses and sense data, as described in Worden (2020b). The lack of local excitatory connections in the thalamus does not rule out a blackboard role. It is known (O'Reilly et al., 2020) that a 10 Hz alpha rhythm is specifically associated with layer 5 neurons in the cortex and to the pulvinar.

Relay neurons in thalamic nuclei can support segregation by location in a distributed representation, as described in the previous section. For a distributed representation to give good separation in all three spatial dimensions, the neurons must be extended in all three dimensions—as is done by the approximately regular three-dimensional shape of the thalamus. In a distributed representation, segregation is not by relay neurons, but by patterns of firing across many relay neurons. In this connection, there may be a role for inhibitory interneurons.

In many signal processing applications, the linearity of transducers is required. This kind of fidelity in the message passing may be important in the thalamus for two reasons:

1. As an example of a distributed representation, the Fourier representation depends on linearity, in the following sense: if a point at position **k** is represented by a firing pattern [1 + cos (**k.x**)], a non-linear transform of this pattern (a harmonic distortion) would lead to higher harmonics like cos (2 **k.x**) and so on—producing spurious represented objects at positions 2 **k**, 3 **k** and so on. The linearity of the transducers will minimize the occurrence of such spurious "ghost" traces.
2. The overall probability of a hypothesis, evaluated from all relevant knowledge sources, is the one with maximum model evidence with weighted factors summed over all sources, with different sums for different distributions across the distributed representation. For the hypothesis with maximum model evidence to be found, the summation needs to be as close to linear as possible.

Seen as a transducer or amplifier, a neuron is not typically expected to be highly linear. A relay neuron on its own is expected to introduce non-linear distortion. However, inhibitory interneurons, which are a prominent feature of the thalamus, may play a role here.

Again, if we recourse to engineering analogies, the design of an **operational amplifier** uses negative feedback (through resistors) to convert a high-gain, non-linear amplifier into a lower-gain, but highly linear amplifier. In the same way, local negative feedback by inhibitory interneurons could convert the non-linear high amplification of a relay neuron into a more linear amplification—which is better suited to carry a factorized representation and to sum log-likelihoods for Bayesian maximum marginal likelihood estimation.

Next, consider the spatial steering function of the blackboard. To serve any signal steering function, the blackboard/thalamus must have two distinct types of inputs. These are the signal being steered (i.e., information *per se*) and the instructions about where and how to steer it. A prominent feature of thalamic neuroanatomy is the distinction between driver and modulator pathways (Sherman and Guillery, 2006). This two-way distinction could be linked to the distinction between signal and steering instructions, and could even be the same distinction.

Next consider the mechanism for spatial steering, using a distributed neural representation, and neural firing phased relative to a thalamocortical "carrier" frequency (e.g., at 10 Hz). As in a phased antenna array, signal steering can be accomplished by introducing a controllable phase shift within the 100 ms cycle. To tune a given relay neuron to be sensitive to a region in inferred location **k**, different phase shifts would need to be applied to different input synapses of the neuron, depending on their location in the thalamus. In this way, thalamocortical connections to a given cortical module could all be sensitive to a small region around some position $\mathbf{k_0}$, with the center $\mathbf{k_0}$ of the region of attention being tuneable within the thalamus.

A distinctive feature of the thalamus is the presence of triadic synapses in glomeruli (Sherman and Guillery, 2006, 2011), where three or more neural inputs converge in one synaptic structure. This contrasts with the more usual dyadic input-output relation between two neurons and supports the convergence of two or more neural inputs—such as a sensory signal and its steering control.

Triadic synapses could have the function of introducing a controllable time delay (a phase shift), in the region 0–100 ms, to give spatial steering of a distributed neural representation. As an alternative to controllable delays, the use of sigma-pi neurons for signal steering is discussed in (Worden, 2020b). Triadic synapses could play a sigma-pi role in the thalamus.

These proposals for steering mechanisms are most relevant to secondary thalamic nuclei such as the pulvinar, rather than to primary nuclei such as LGN, which seem to support a more map-like relay function. The secondary nuclei are amongst the largest in the thalamus and have diffuse cortical connections, consistent with spatial steering to diverse cortical knowledge sources.

While the pulvinar is largely concerned with orchestrating sense-data from the posterior cortex, including vision, the other large secondary thalamic nucleus, the MD nucleus, is more closely linked with higher-level decision-making functions in the prefrontal cortex (Mitchell et al., 2014; Mitchell, 2015; Dehghani and Wimmer, 2018). The MD nucleus may be involved in motor and proprioceptive inference (Friston et al., 2015, 2016), where 3-D movement creates new possibilities and new options to compare. For non-human primates, decision-making is largely deciding about physical movement in space and time. The control of motion, like the perception of objects in local space from sense data, is intimately linked with the representation of three-dimensional space. So it is reasonable to expect that the MD nucleus, like the pulvinar, is concerned with the spatial segregation and spatial steering of information—both sense-data and motor commands.

It appears that in many ways, the neuroanatomy and physiology of the thalamus may be consistent with a blackboard/aggregator function, including spatial segregation and steering of sense data and processed sense data. The match appears to be good, and it can lead to suggestions for further experimentation and modeling, providing informed predictions

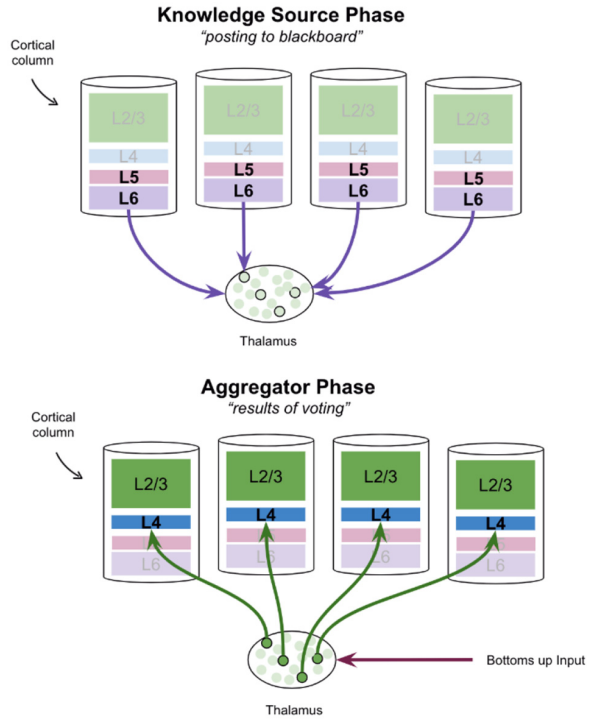

FIGURE 4 | A proposal for how the thalamus may aggregate votes from cortical knowledge sources, and then post results back to those knowledge sources, in two successive phases. Note that in the frontal cortex there is no layer 4, but instead, thalamic relay neurons synapse directly onto pyramidal cells in L2/3.

for detailed tests and models of a thalamic blackboard/spatial steering function.

In the context of the interactions between the thalamus and the cortex, several additional observations are consistent with the idea that the thalamus operates as a blackboard whereby hypotheses from cortical knowledge sources are aggregated, exchanging information in an aggregator cycle (Worden, 2020b) between the thalamus and cortex:

- Cortex and thalamus oscillate on the same alpha cycle (Lörincz et al., 2009; Hughes et al., 2011).
- Cortical columns appear to oscillate between superficial layers "on" while deep layers "off" (Lörincz et al., 2015; Pluta et al., 2015; Naka and Adesnik, 2016).
- Layer 6 corticothalamic neurons provide modulatory input to thalamic relay neurons that project to the same column (Reichova and Sherman, 2004; Thomson, 2010; Sherman, 2017).
- Relay neurons only burst if they get this modulatory input (Jahnsen and Llinás, 1984; Hughes et al., 1999; Sherman, 2001; Guillery and Sherman, 2002).

The alpha cycle may be a mechanism by which cortical knowledge sources communicate with the thalamic blackboard. It has been proposed that entire thalamocortical networks oscillate between a "knowledge source phase" and an "aggregator phase" (Worden, 2020b). In this interpretation, the deep layers of cortical columns, specifically layer 6, post hypotheses to the thalamic blackboard on the "knowledge source phase." Once these hypotheses are integrated, the results of this process are posted back to cortical columns during the "aggregator phase." This is shown in **Figure 4**. Hypotheses that are *consistent* with bottoms-up input will be reinforced as only relay neurons with both modulatory and driving input will burst fire (Jahnsen and Llinás, 1984; Hughes et al., 1999; Sherman, 2001; Guillery and Sherman, 2002). This proposal of thalamus function has remarkable consistencies with various theories of cortical columns which have attributed a "voting" process to the modulatory input from layer 6 corticothalamic neurons to thalamic relay neurons (Grossberg and Versace, 2008; Bennett, 2020).

If knowledge sources post "what is where" to the thalamic blackboard, then this suggests that a given knowledge source either: (a) contains representations of different locations in space (e.g., a nose detector that can detect noses in multiple locations in space) or (b) a given feature (e.g., "nose") is duplicated across multiple knowledge sources, each with separate spatial receptive fields (e.g., multiple nose detectors, for detecting noses in different locations in the visual field). Interestingly, recent theories of cortical columns corroborate both ideas whereby a given column contains spatial representations, and features are duplicated across columns. Specifically, Hawkins' "Thousand Brains Theory" of intelligence (Hawkins et al., 2019) proposes that each cortical column generates a complete model of the world. He suggests that each column builds a complete 3D map of objects/features across a broad receptive field, as opposed to only representing a specific feature at a specific location. Hawkins goes on to propose that "grid-like" cells within each cortical column represent a location in space, which he suggests exists in layer 6. The thalamic blackboard proposal can be interpreted as an application of Hawkins' theory, whereby these redundant and overlapping models of the world can be integrated and disambiguated with each other through oscillatory phases with the thalamus.

This is an unsettled topic in which proposals are still fluid. In contrast to Hawkins' proposals, we note the suggestion in Worden (2020b) that cortical knowledge sources need only store and manipulate small **relative** displacements between features of an object, reducing their need for high spatial precision.

Cortical columns or modules have also been interpreted as simply *factors* of the Bayesian beliefs held by a system (Parr et al., 2020). It is commonly assumed that posterior beliefs are independent of each other, and hence factorizable, this is known as the "mean-field approximation" that renders Bayesian inference tractable in the form of variational Bayes or approximate Bayesian inference. This kind of inference could plausibly be implemented in the brain, as described above (Parr et al., 2020).

THALAMIC NEURO-ANATOMY TO ENABLE CORTICAL LEARNING

In this section, we discuss how thalamocortical neuroanatomy might support the second key function of the thalamus proposed

in this article—which is to train direct cortico-cortical pathways, to do itself out of a job.

As shown in computational models of variational inference, computing the posterior requires a separate optimization for each data point to compute the best fit variational posterior (Kim et al., 2018). In other words, an inference can be computationally expensive and slow as it scales linearly with the amount of data. A computational technique called "amortized inference" dramatically improves the speed of inference by instead training a neural network to learn the mapping between observations and variational parameters (Gershman and Goodman, 2014; Marino et al., 2018). In other words, *learning* to infer. This process "amortizes" (or distributes) the computational cost of inference over many observations, as opposed to redoing this optimization each time. Through this lens, thalamocortical networks can be thought of as training corticocortical networks to infer on their own.

To describe this process, we consider the involvement of the MD nucleus in a typical movement planning task, which is to reach out and grasp a piece of fruit. In considering this task, it is worth recalling the analogy of the recording SatNav—which for the first use of a route, does complex spatial planning; and for later uses, simply replays the recording.

Note that any movement planning task has a natural hierarchical structure—where the hierarchy is a (time*limb) hierarchy. To grasp a piece of fruit, the task has four stages:

1. **Arm move**: Move the arm so that the hand is in the right place.
2. **Hand grasp**: Pick the fruit.
3. **Hand to mouth**: Move the fruit to the mouth.
4. **Eat fruit**: Chew.

Each step must be started approximately when the previous step has been completed—so the steps form a natural hierarchy (of depth 1) in time. A more realistic deeper hierarchy could involve sub-steps within steps, and parallel movements for within a step different body parts, such as fingers. The full movement involves the arm, hand, fingers, and mouth—so will involve several distinct regions of the cortex (suppose that cortical modules A, B, C, D carry out steps 1, 2, 3, 4 of the sequence). This is consistent with the extensive thalamocortical connections of the MD nucleus.

The hierarchical structure breaks the task down into steps that may be learned at different times. In this case, both the "hand grasp" and "eat fruit" steps would have been learned previously (i.e., recorded by cortical modules B and D), and the new learning task is just to replay B and D when needed, to "string them together" with novel arm movements from modules A and C. A hierarchical breakdown of the learning task is usually essential to narrow down the space of learnable patterns, to make learning feasible from small numbers of learning examples.

The first time that the novel arm movement (1) is made, cortical module A records it. On completion of (1), the previously learned grasping movement (2) is re-played by a cortical module B. This replay sequence is initially coordinated through cortico-thalamo-cortical (CTC) pathways. Each time the sequence is replayed successfully, there are plastic changes in the direct cortico-cortical links so that they can soon take over the job—it becomes habitual—and the CTC pathways are no longer needed. The movement becomes a top-down sequential cascade of cortical modules, each one replaying its learned sequence of movements (possibly by triggering sub-movements) and then triggering the next cortical module (Haruno et al., 2003; George and Hawkins, 2009; Maisto et al., 2015; Rikhye et al., 2019).

RELATIONS TO EXISTING WORK

There is a huge body of experimental work on thalamic neuroanatomy and neurophysiology to which this article is indebted, and which has not been fully referenced. For work before 2007, we have relied on the definitive books by Sherman and Guillery (2006) and Jones (2007) and references therein.

Since the ideas of this article about spatial segregation and steering of sense data are mainly applicable to higher-order thalamic nuclei such as the MD nucleus and the pulvinar, we have focused on articles directly relevant to them, including Shipp (2003), Sherman and Guillery (2013), Mitchell et al. (2014), Mitchell (2015), and Usrey and Sherman (2019). Similarly, work on thalamocortical connectivity (Behrens et al., 2003) has been used for insights into the connectivity of higher-order thalamic nuclei such as the pulvinar.

Beyond that, this article has been influenced by works that abstract general architectural or computational principles about the thalamus, such as Sherman (2016), Nakajima and Halassa (2017), and Halassa and Sherman (2019). The thalamic circuit motifs explored by (Halassa and Sherman, 2019) are particularly relevant—for instance, motifs involving triadic synapses, or other motifs that can be mapped onto the thalamus-as-blackboard concept in ways that remain to be explored.

The blackboard notion has been investigated by several authors, notably Baars (1988), Mumford (1991), O'Reilly et al. (2017, 2020), and Dehghani and Wimmer (2018). This article links these ideas to Bayesian inference, notably the Free Energy Principle of Friston (2003).

The computational model of O'Reilly et al. (2017, 2020) is relevant to this article, since it shares several important features, yet has key differences. Like the model of this article, their model hinges on the pulvinar in a blackboard role, and on a cortico-pulvinar alpha rhythm. However, the two models use these ingredients for different purposes. The main difference is that the model of O'Reilly and colleagues is largely a model of learning. Learning is typically a process that takes place over longer timescales (days or weeks); whereas this article also addresses a more basic, pre-learning question: how does the thalamus contribute to immediate spatial cognition on sub-second timescales?

While O'Reilly and colleagues interpret the 10 Hz cortico-pulvinar alpha rhythm as supporting a predictive learning process, predicting over the next fraction of a second, but driving synaptic changes which take place over days or weeks, in this article the same 10 Hz rhythm defines a phase for spatial steering of processed sense-data. Steering sense-data is a pre-learning process, operating at time scales of tens to 150 ms, and it provides the input data for cortical knowledge sources such as shape from shading, stereopsis, or shape from motion, which need

involve no learning. Spatial steering is required for perceiving the 3-D shapes of irregular rocks or terrain or plants, simply for locomotion, before any question arises of learning how to classify objects by their shapes—as in the O'Reilly model. Therefore the two models both depend on cortico-pulvinar alpha rhythms but propose different interpretations of what those rhythms do. These proposals may even co-exist. This may pave the way for productive experimental studies.

Although this article has concentrated on spatial cognition as the main example to exhibit the type of orchestration, gating, and steering implied by thalamic architecture, another key theme is that of balancing prior preferences (rewards as encoded by the agent) and exploratory drive. In the context of decision-making, planning as inference, and learning to infer, the thalamus can be seen as a purveyor of precision. More specifically, the MD nucleus would have the vitally important role of assigning appropriate precisions to simulated future consequences of particular behaviors and evaluating these according to the agent's prior preferences. This hypothesis is in line with research in neuroanatomical connectivity between the PFC and the MD (Funahashi, 2013), and its putative consequences in both working memory and how it is used by thalamic nuclei. A basic idea formulated using the Active inference framework would be that there is a comparison in natural units (nats) between the log probability of information gain given a particular prior preference and the log prior preference itself, thus allowing the agent to decide whether to explore or exploit (Parr and Friston, 2018; Da Costa et al., 2020). This aspect of goal-directed behavior, and the role MD nucleus plays in reward evaluation as well as in the explore-exploit trade-off—remains to be explored. There are links to the role of the paraventricular thalamus in the risk-reward trade-off, discussed in this article.

Part of the territory of this article has been explored in more computational detail, with less emphasis on thalamic neuro-anatomy and with greater emphasis on the scaling, speed, and precision achievable by a blackboard/aggregator architecture, in (Worden, 2020b). Some key results in that article, relevant to this article, are:

1. In terms of required cortical connectivity and its energy costs, the hub-and-spoke architecture of a blackboard is much more efficient than a fully distributed cortico-cortical architecture.
2. The required spatial steering of hypotheses (for instance, in hierarchical pattern recognition) must be steering in absolute positions relative to the animal—not just relative positions within an object. This places a high requirement on the precisions underlying signal steering.
3. Spatial steering involves the accurate computation of spatial displacements; this is 3-vector subtraction, and it can be done with high precision and fast in a distributed Fourier representation.
4. The spatial steering function and its implied neuromodulation is more efficiently done in the central blackboard/aggregator, than separately in each cortical knowledge source. The latter approach would require massive replication of the steering functionality.

This article has said little about the issue of object constancy in an allocentric frame of reference, and how an aggregator architecture might exploit that important prior probability. The lack of local recurrent excitatory connections in the thalamus, preventing local persistence by positive feedback, seems to underline that problem. Worden (2020a) investigates a radical solution—that as well as neural synaptic connectivity, there is a physical wave excitation in the thalamus, which serves as a short-term memory for spatial information in a Fourier-like representation. The considerations of this article, about the neural implementation of the aggregator function, apply whether or not that more radical suggestion of a wave excitation in the thalamus is correct.

Finally, the preservation of the thalamic architecture across mammalian species, and many others (Sherman and Guillery, 2006; Jones, 2007) seems to point to an early evolutionary origin and a universal functional role. It is worth noting that a requirement for precise spatial steering of sense-data has existed since the first compound eyes evolved, with up to 10,000 receptors, in the Cambrian period (Parker, 2003). There would be little point for a Cambrian animal to have a high-resolution vision if its brain cannot precisely steer the signal to specialized processors. Precise spatial steering and Bayesian likelihood aggregation have been strong requirements on brains, and those requirements have been met by animal brains, for more than 500 million years.

CONCLUSION

This article has described a promising alignment between two different approaches in the study of the brain:

1. Bayesian inference, as formalized in the Free Energy Principle, as a framework to understand active inference and scene construction as the aggregation of multiple knowledge sources.
2. The distinctive neuro-anatomy and neuro-physiology of the thalamus, whose functional anatomy is ideally suited to instantiate this aggregation.

This article speaks on an important issue: because of functional segregation in the brain, there must be an underlying architecture and computational mechanism to bring together different types of information from dynamic coalitions of knowledge sources, which have to be weighted according to their precisions—in light of (approximate) Bayesian inference. We propose that this is what the thalamus is there for. The implicit modularity of cortical representations calls upon a factorization (i.e., a mean-field approximation) that is inherent in any form of (approximate) Bayesian inference.

Active Bayesian inference and the Free Energy Principle are now firmly established as an apt explanation for many aspects of cognition. There is little doubt that they should apply to one core requirement on animal brains, which is to understand the forms and locations of objects around the animal from moment to moment, based on multi-sense-data.

For this, active inference entails a set of hypotheses about "what is where" around the animal; and various attributes (e.g., "what" and "where") are processed by a wide range of cortical modules. The thalamus is well placed to unite these, acting as a blackboard/aggregator for hypotheses about spatial forms and positions of things in peripersonal space.

The requisite neuronal message passing and belief updating align well with many distinctive features of thalamic neuroanatomy and physiology, including:

- Quasi-independent thalamic relay cells.
- Thalamo-cortical rhythms.
- Diffuse cortical connectivity of higher-order thalamic nuclei.
- Inhibitory interneurons in the thalamus.
- The regular three-dimensional shape of the thalamus, preserved across many species.
- Olfaction bypasses the thalamus, as it does little to constrain spatial locations. Driver and modulator pathways. Triadic synapses.

Each of these features of the thalamus is consistent with a generative model that plays the role of a spatial aggregator. The alignment between the thalamus and the blackboard/aggregator model is promising at this stage. Much remains to be done to test it and validate it. If the alignment has validity, then further testing of it will involve a twin-track program:

1. Theoretical and computational investigations of the Blackboard model—to explore its viability, neural architecture requirements, scaling, and performance.
2. An empirical investigation of thalamic neuroanatomy and physiology, testing whether it is compatible with Bayesian belief updating of the sort described above.

If this is done, no doubt many of the specific proposals in this article will prove to be wrong, or need modification; but the pursuit and cross-fertilization of these twin tracks will be a productive way to increase our understanding of the thalamus (Donoho et al., 2005).

The most important proposal in this article is to suggest that the passive idea of "the thalamus as a relay" is no longer sufficient. The "relay" notion often emerges as a straightforward interpretation of experiments, but it fails to address the complexities of neuronal representation and processing not yet revealed by those experiments. As an expression of what the thalamus does, it is too weak. We should supplement the passive "relay" notion with more active notions, such as thalamic **steering** *via* precisions entailed by processed sense-data between cortical modules, and the aggregation of Bayesian beliefs—recognizing that precise spatial steering is difficult, essential, and worth doing centrally.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

RW contributed ideas concerning the blackboard architecture, aggregation, steering, and thalamus training cortex. MB contributed concerning cortical knowledge sources, the alpha cycle, and amortization. VN contributed concerning the free energy principle and active inference. All authors contributed to the article and approved the submitted version.

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Parafascicular Thalamic and Orbitofrontal Cortical Inputs to Striatum Represent States for Goal-Directed Action Selection

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Several lines of evidence accrued over the last 5–10 years have converged to suggest that the parafascicular nucleus of the thalamus and the lateral orbitofrontal cortex each represent or contribute to internal state/context representations that guide action selection in partially observable task situations. In rodents, inactivations of each structure have been found to selectively impair performance in paradigms testing goal-directed action selection, but only when that action selection relies on state representations. Electrophysiological evidence has suggested that each structure achieves this function *via* inputs onto cholinergic interneurons (CINs) in the dorsomedial striatum. Here, we briefly review these studies, then point to anatomical evidence regarding the afferents of each structure and what they suggest about the specific features that each contribute to internal state representations. Finally, we speculate as to whether this role might be achieved interdependently through direct PF→OFC projections, or through the convergence of independent direct orbitofrontal cortex (OFC) and parafascicular nucleus of the thalamus (PF) inputs onto striatal targets.

Keywords: state, context, goal-directed action, orbitofrontal cortex, parafascicular thalamic nucleus, cholinergic interneurons, striatum

INTRODUCTION

To select the optimal action in many given situations, it has been posited that organisms must mentally represent that situation (or "internal context," "latent cause," or "state;" Gershman et al., 2010; Gershman and Niv, 2012) by integrating features of their internal environment with those of the external environment. To draw upon an example we have given previously (Bradfield and Hart, 2020), if you visit a particular restaurant often, upon visiting you might combine external information about the sights/sounds/smells of the restaurant itself with internal knowledge that it is Saturday and therefore pasta is the daily special, before making an order for pasta. This integrated "state" representation has been claimed to rely on both the parafascicular nucleus of the thalamus (PF) and the orbitofrontal cortex (OFC), particularly when it requires unobservable features to be inferred from memory. How exactly each structure might achieve this function, however, has yet to be considered.

The first suggestion that the PF of the rat might provide information about internal state and/or context to "higher centers" was made in Deschênes et al. (1996) based on the unique morphology of the PF's glutamatergic projection neurons, the specific topographical arrangement of their outputs to basal ganglia and cerebral cortex, and the rich variety of excitatory and inhibitory afferents PF receives. These features, the authors argued, meant that PF was well-placed to integrate multiple and varied synaptic inputs, and combine them in a way that addressed specific pools of neurons as one might expect of a region combining multiple elements into a unified contextual representation. Twenty-four years later, there have now been several studies employing various techniques, manipulations, and behavioral assays, that have converged to suggest that PF does indeed provide some kind of internal state or context representation (Brown et al., 2010; Bradfield et al., 2013a; Aoki et al., 2015; Bradfield and Balleine, 2017). This information is suspected to influence action selection *via* PF inputs onto cholinergic interneurons (CINs) in the dorsomedial striatum, which is thought to modulate local spiny projection neurons (SPNs), which then co-ordinate to select actions following the currently inferred internal state (Bradfield et al., 2013a; Matamales et al., 2016; Apicella, 2017). Although it is beyond the scope of the current review, recent evidence suggests that how SPNs perform this action selection function is *via* outputs to the substantia nigra reticulata (SNr), through both the direct and indirect pathways. Most recently, it has been suggested that although the direct pathway is always involved in goal-directed action selection, the indirect pathway outputs become particularly important for action selection when unobservable information must be inferred (e.g., during a reversal, Peak et al., 2020).

This role for PF appears to parallel that of the lateral OFC in many ways, at least in rodents (Wilson et al., 2014; Parkes et al., 2018; Bradfield and Hart, 2020). Moreover, the modulation of action selection according to the internal state by dorsomedial CINs has also separately been shown to rely on inputs from lateral OFC (Stalnaker et al., 2016). In this review article, we will explore how the PF and OFC might function independently and/or possibly interdependently to form cohesive representations of the internal state.

Inactivating the Parafascicular Thalamic Nucleus or Lateral Orbitofrontal Cortex Impairs Goal-Directed Action Selection That Relies on State Representations

Because we and others have extensively reviewed the studies of behavioral consequences of PF and lateral OFC inactivations for goal-directed action elsewhere (Bradfield et al., 2013b; Wilson et al., 2014; Sharpe et al., 2019; Bradfield and Hart, 2020), for present purposes we shall do so only briefly, to reveal their commonalities. More specifically, we have limited our review to studies that employed tasks in which animals could make a goal-directed choice between two or more options that have been studied with regards to both PF and lateral OFC. It is worth noting, however, that numerous other studies (e.g., Brown et al., 2010; Baltz et al., 2018; Malvaez et al., 2019; Zhou et al., 2019) indicate a role for either OFC or PF separately in representing states with regards to other psychological phenomena such as incentive learning and maze learning. It will be of some interest to future studies to employ such tasks in the examination of the alternate structure (i.e., if OFC was studied previously, to study PF using the same task) to determine whether OFC and PF function also appear consistent across those tasks.

The first common finding involving goal-directed choice is that lesions of both PF and lateral OFC have been found to leave instrumental outcome devaluation—the primary behavioral assay used in the laboratory to assess goal-directed action—intact (Ostlund and Balleine, 2007; Balleine et al., 2011; Bradfield et al., 2013a; Bradfield and Balleine, 2017; but see Gremel and Costa, 2013). This suggests that goal-directed action *per se* does not depend on the integrity of either PF or OFC. For the procedure employed in each of these studies, rats were trained to press two levers for two food outcomes (e.g., left-lever pellets, right lever-sucrose, or the opposite arrangement, counterbalanced). Animals were then tested for their ability to flexibly alter their responding in a goal-directed manner when one of the outcomes was reduced in value as a result of it being fed to satiety (i.e., sensory-specific satiety, Balleine and Dickinson, 1992) and animals were subsequently allowed to choose which lever to press. All groups in all of these studies, regardless of whether they had received excitotoxic or sham lesions of PF or lateral OFC, selectively responded on the lever on the test that had previously earned the still-valued outcome. This intact performance suggested that all animals were able to elicit actions motivated by both: (a) the current value of the outcome; and (b) the contingency between action and outcome, and thus fulfilled the two goal-directed action criteria (Balleine and Dickinson, 1998).

Despite this result, there is evidence that another measure of goal-directed action, contingency degradation, is impaired by PF lesions in rats (Bradfield et al., 2013a), as well as by the selective knockdown of brain-derived neurotrophic factor (BDNF) used to reduce activity-dependent neuroplasticity in the lateral OFC of mice (Zimmermann et al., 2017). For contingency degradation, rats are typically once again trained to press the left and the right lever for a pellet and a sucrose outcome, respectively (counterbalanced). After several days of training, one of these outcomes also begins to be delivered freely, in the absence of lever press. This is done in a manner such that the probability of receiving a pellet (if pellets are the degraded outcome) is equivalent regardless of whether the animal presses the pellet lever or not. This serves to degrade the contingency between that specific lever and its outcome, which is evidenced when the animal reduces its pressing on the pellet lever but continues to press the sucrose lever.

As reviewed previously (Bradfield and Hart, 2020), successful contingency degradation performance requires animals to reduce interference between competing contingencies in a manner that outcome devaluation does not. Specifically, whereas outcome devaluation requires only that the animal learn only two excitatory lever press-outcome associations (e.g., left lever-pellets, right lever sucrose, represented in the left panel of **Figure 1**), contingency degradation requires the animal to first

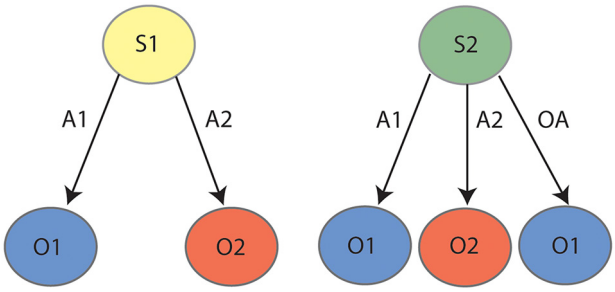

FIGURE 1 | State-space representation for contingency degradation: during the initial phase (left panel) the animal learns that action 1 (A1) earns outcome 1 (O1) and action 2 (A2) earns outcome 2 (O2). During degradation (right panel), the animal learns that in addition to A1–O1 and A2–O2, taking any "other action" (OA, anything other than pressing the levers, e.g., sitting, sniffing, exploring, et cetera) also earns O1, which serves to degrade the contingency between A1 and O1. It is posited that the animal partitions the initial learning contingencies (A1–O1, A2–O2) and the degradation contingencies (A1–O1, A2–O2, OA–O1) into two states, state 1 (S1) and state 2 (S2), respectively.

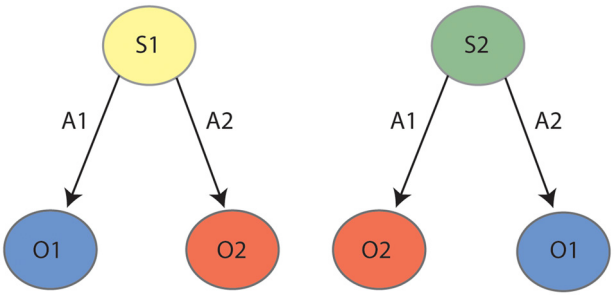

FIGURE 2 | State-space representation for outcome reversal: during the initial phase (left panel) the animal learns that action 1 (A1) earns outcome 1 (O1) and action 2 (A2) earns outcome 2 (O2). During reversal (right panel), the animal learns the reverse contingencies: A1–O2 and A2–O1. It is posited that the animal partitions the initial learning contingencies (A1–O1, A2–O2) and the reversed contingencies (A1–O2, A2–O1) into two states, state 1 (S1) and state 2 (S2), respectively.

learn these same associations, but then to also learn a "no lever press-pellet" association that competes with the left lever-pellet association. We (Bradfield et al., 2013a,b) and others (Schoenbaum et al., 2013) have speculated that in instances such as these, the animal does not unlearn the initial contingency, but rather retains it alongside the new (no lever press-pellet) contingency, and uses internal context/state information to infer whether pressing the pellet lever or abstaining from pressing it is the optimal action to earn a pellet. That is, as shown in **Figure 1** and in a manner reminiscent of Yael Niv's latent cause theory (Gershman et al., 2010; Gershman and Niv, 2012); if the animal infers the initial lever press acquisition state/latent cause [state 1 (S1)] it will press the lever to earn a pellet, but if it infers the degradation state/latent cause [state 2 (S2)] it will withhold lever pressing to earn a pellet. Thus, the fact that PF inactivation and lateral OFC inactivation/BDNF knockdown impairs contingency degradation but not outcome devaluation is consistent with a role for each in representing states, because only degradation requires the partitioning of competing contingencies into separate states.

A final behavioral assay that is impaired by inactivations of both PF and lateral OFC is reversal learning. As reviewed previously (Manning et al., 2020), the regulation of reversal learning by lateral OFC has been demonstrated across many varied paradigms, but for current purposes, we will describe the only such paradigm that unambiguously recruits goal-directed actions. In this procedure, rats were once again trained to press two levers for two unique outcomes, but these contingencies were later reversed. That is, if the left lever initially earned pellets it was reversed to earn sucrose, and if the right lever initially earned sucrose it was reversed to earn pellets. Animals were again subject to an outcome devaluation test as previously described, and intact animals uniformly responded on the lever that earned the valued outcome following the reversed contingencies. Animals that had experienced PF lesions (Bradfield et al., 2013a) or chemogenetic inactivation of the lateral OFC (Parkes et al., 2018), on the other hand, responded on both levers equally, suggesting that the initially-learned lever press contingencies were interfering with the performance of the reversed contingencies. As shown in **Figure 2**, it has been posited that animals partition the two sets of contingencies into two internal state representations: State 1 (initial) and State 2 (reversal). Animals that cannot partition the states in this manner would be expected to respond as per both sets of contingencies and press the levers equally, as was observed for animals with PF or lateral OFC inactivation. We have further explicitly demonstrated that intact animals do concurrently retain both the initial and the reversed contingencies in this paradigm (Bradfield and Balleine, 2017), indicating that they must use internal state information to determine with which set of contingencies to act in accordance.

Parafascicular and Orbitofrontal Cortical Efferents Onto Striatal Cholinergic Interneurons

The behavioral studies reviewed above reveal some striking parallels between the function of the PF and of the lateral OFC in tasks for which goal-directed choices rely on mental representations of states. Additional evidence from electrophysiological, immunohistochemical, and behavioral studies have further demonstrated that this function of PF/OFC inputs manifests *via* inputs onto striatum, particularly (but not exclusively) the cholinergic interneurons (CINs), which are purported to use this information to modulate the local SPNs for accurate action selection (Bradfield et al., 2013b; Stalnaker et al., 2016; Bradfield and Balleine, 2017).

With regards to PF, we (Bradfield et al., 2013a) found that asymmetric lesions of PF and posterior dorsomedial striatum produce identical behavioral results to bilateral PF lesions: leaving outcome devaluation intact but impairing contingency degradation and outcome reversal learning. Interestingly, asymmetric lesions of the PF and *anterior* dorsomedial striatum did not affect behavior in any of our tasks, suggesting that this

particular function is specific to the PF→posterior dorsomedial striatal pathway. Further, we demonstrated that lesioning the PF selectively reduced both the action potential frequency, as well as the phosphorylation of ribosomal protein S6 (indicative of reduced CIN activity) of CINs in the dorsomedial striatum, whereas it appeared to *increase* SPN activity in the same region, as evidenced by a significant increase in the number of phospho-Thr202-Tyr204-ERK1/2 (pERK1/2)-labeled SPNs. Thus, although PF does project directly onto SPNs as well as CINs, this particular pattern of responding is most consistent with SPN reactivity being modulated indirectly throughout this task, *via* the loss of CIN modulation as a result of PF lesion, because the direct loss of glutamatergic PF inputs onto SPNs should have manifested as a decrease rather than an increase in SPN activity. Matamales et al. (2016) later directly implicated CINs in dorsomedial striatum in state inference when they demonstrated that the selective toxigenic ablation of CINs in this region also replicated the behavior observed after bilateral PF lesions, leaving outcome devaluation intact but impairing outcome reversal.

With regards to the lateral OFC, Stalnaker et al. (2016) first recorded directly from putative dorsomedial striatal CINs in rats whilst they performed a task in which different outcomes (vanilla or chocolate milk) were earned in different amounts (one or three drops) by different responses (left or right), depending on which "block" was currently active (e.g., in block 1, a left response may have earned three drops of vanilla milk and a right response earned one drop of chocolate milk, et cetera). Switches between blocks occurred in the absence of any change in external stimuli such that rats needed to infer the block change when responses earned different outcomes. Optimal choices following block transition would be more likely if animals were able to infer a new state, rather than overwriting their prior learning about each action-outcome pairing. They found that the activity of CINs was selective to particular blocks and that if this activity appeared to miscode a block, the animal made poorer choices. Moreover, the SPNs recorded in the same study were significantly worse than the CINs at decoding block identity. Finally, when the lateral OFC was lesioned in one hemisphere, CINs in the ipsilateral dorsomedial striatum reduced block decoding to chance level (and interestingly, enhanced decoding of single events). Together, these results suggest that in intact animals, CINs infer some kind of state representation that enables the animal to identify the currently active block, allowing them to make accurate choices accordingly, and they further suggest that this function is dependent on inputs from lateral OFC.

Together, these studies suggest that dorsomedial striatal CINs infer state representations that are used to guide action selection, and that this role for striatal CINs depends on inputs from PF and lateral OFC. It is worth noting, however, that this work is not definitive and almost certainly presents an oversimplified characterization of the mechanisms that underlie the psychological phenomenon of state representation. Indeed, there are complexities both within the striatum (e.g., other neurons/interneuron types), as well as PF and lateral OFC circuitry with other brain regions, that are not captured here that are likely to also contribute to state representation and its influence over action selection.

Anatomical Evidence for Lateral Orbitofrontal Cortical and/or Parafascicular Representations of Internal State

Caveats aside, it is clear from the studies outlined above that PF, OFC, and dorsomedial striatal CINs work in concert with each other (and possibly with other neuronal types/brain regions) to achieve accurate state representation and subsequent goal-directed action selection. What is not clear is how the PF and lateral OFC might coordinate to achieve this function. For instance, do PF and lateral OFC contribute similar or unique information to the state representation? Do they achieve this independently, interdependently, or both? Although it is not possible to answer these questions with any certainty as there have not been any direct studies of how PF-OFC circuitry might relate to internal state representation, here we will provide our speculative view based on the anatomical connections of each structure. Although the characterization of this circuitry presented here has been simplified for ease of communication (see **Figure 3**), it is worth noting that both OFC (Reep et al., 1996; Hoover and Vertes, 2011) and PF (Mandelbaum et al., 2019) display heterogeneity that is often topographical with regards to their projection patterns which likely underlie different functions. Thus, the state representation function might only rely on the very specific projections that were the focus of the studies above i.e., lateral OFC→centrodorsomedial striatum (Stalnaker et al., 2016; PF→posterior dorsomedial striatum Bradfield et al., 2013a; Bradfield and Balleine, 2017). Nevertheless, there is some suggestion that state representation as it could relate to non-goal-directed, stimulus-dependent responding could rely on adjacent but non-identical neuronal ensembles/pathways (e.g., PF (anterior dorsomedial striatum, dorsolateral CINs; Brown et al., 2010; Aoki et al., 2015, 2018).

As has been noted elsewhere (Schuck et al., 2018; Bradfield and Hart, 2020), the OFC is anatomically well-placed to represent internal state because it receives sensory inputs of multiple modalities, including from olfactory, gustatory, visual, and somatic/sensory cortices. It also receives inputs from regions involved in learning and memory such as the hippocampus, and emotion such as the amygdala. The lateral OFC is thus well-placed to integrate information about an organism's current circumstances from multiple sensory inputs with learned information from memory about which actions may have historically resulted in optimal outcomes in the current environment, as well as emotional information about the organism's current desires. This is precisely the type of information that is necessary to infer internal states for accurate action selection in partially observable task situations.

As mentioned previously, the PF has also been noted for being anatomically well-placed to receive and integrate several disparate inputs in the way one might expect of a structure encoding internal state or context information (Deschênes et al., 1996). Similar to lateral OFC, the rat PF receives some sensory

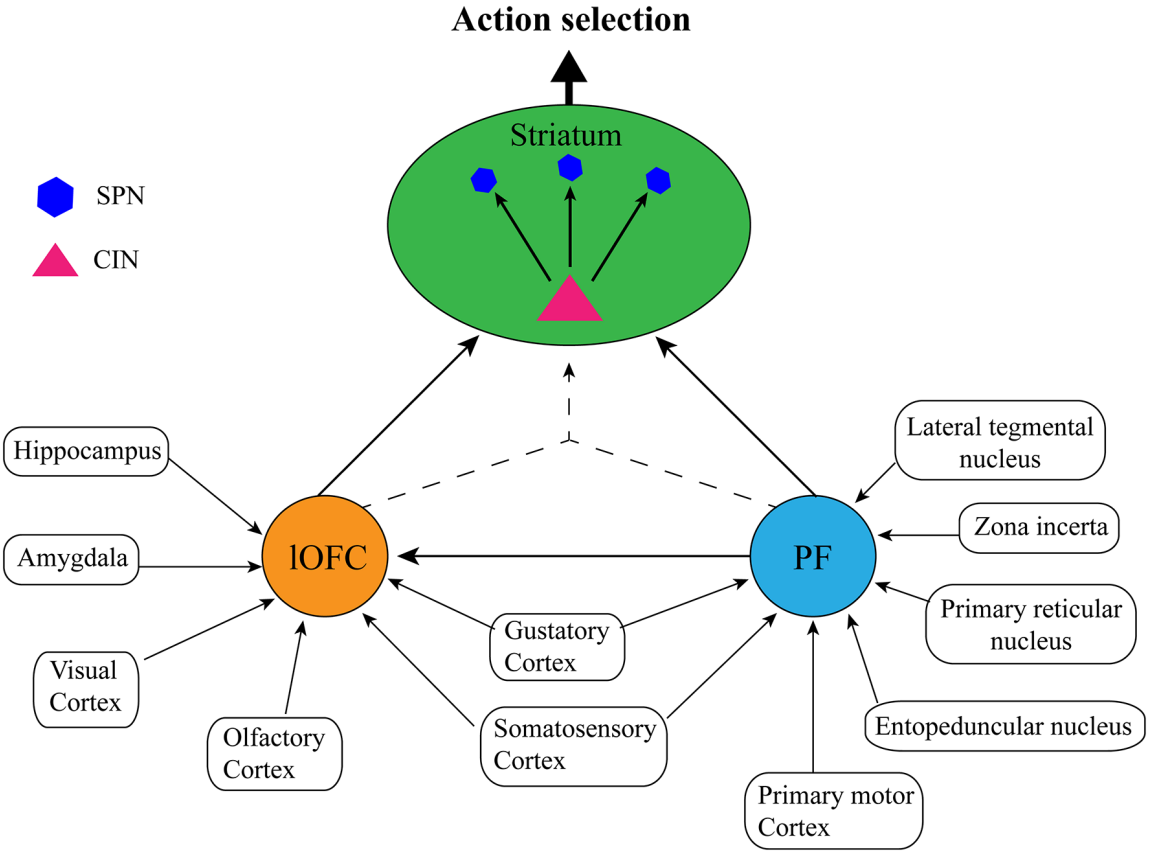

FIGURE 3 | Proposed simplified circuit of internal state representations: The lateral orbitofrontal cortex (lOFC) receives afferents conveying sensory information from visual, olfactory, gustatory, and somatosensory cortices, spatial and memory information from the hippocampus, and emotional information from the amygdala, the parafascicular nucleus of the thalamus (PF) receives sensory inputs from the gustatory cortex and somatosensory cortex, as well as action planning and execution, arousal/attentional information from the lateral tegmental nucleus, zona incerta, primary reticular nucleus, entopeduncular nucleus, and the primary motor cortex. Each structure performs independent integration of these inputs, and then either communicates directly *via* PF→lateral OFC→striatal cholinergic interneurons (CINs), or by converging lateral OFC→striatal CINs/PF→striatal CINs projections to form a cohesive, single internal state representation. Striatal CINs then modulate the striatal projection neurons (SPNs) to influence action selection according to the internal state.

inputs that could allow it to identify current circumstances, such as inputs from the gustatory cortex and inputs from the primary somatosensory cortex (Cornwall and Phillipson, 1988). In contrast to lateral OFC, however, PF does not receive any direct inputs (that we know of) from visual, auditory, or olfactory cortices, hippocampus, or amygdala. In further contrast to the lateral OFC, all other primary sources of inputs to PF appear to play some role in motor function or arousal/attention. Specifically, major inputs to PF include those from the primary motor cortex, primary reticular nucleus, entopeduncular nucleus, zona incerta, and laterodorsal tegmental nucleus (Cornwall and Phillipson, 1988), each of which plays some role in planning and executing movements, and/or mediating attention and arousal. Although we will not address it further here, the mediation of attention, in particular, has also been persuasively argued to be central to PF's contextual regulation of dorsomedial striatal CINs (see Apicella, 2017).

Overall, therefore, it would appear that the afferents of the lateral OFC and PF are relatively distinct, despite the apparent similarity of these structures concerning their cognitive/behavioral function regarding goal-directed choices. In our view, the information regarding motor responses that are conveyed to PF could be the missing puzzle piece that, in addition to the sensory, emotional, and memory-based inputs received by lateral OFC, is necessary for the formation of a single, cohesive state representation. This can be illustrated using the example of the goal-directed reversal learning procedure outlined above. As mentioned, we (Bradfield and Balleine, 2017) have previously demonstrated that animals who have undergone reversal learning simultaneously retain both sets of competing contingencies, for example, State 1: left lever-pellets, right lever sucrose; State 2: left lever-sucrose, right lever pellets (see **Figure 2**). To effectively form and distinguish between these state representations in the absence of any change in context or stimuli, it seems that motor information about which action is being/has been performed would be crucial to link it with which outcome is ultimately earned. For example, if on one day after placement in the operant chamber the animal presses the left

lever and earns pellets, for example, it might infer state 1, whereas on another day it might press the left lever and earn sucrose, thus inferring state 2. Such motor information about which lever is pressed appears to be readily available *via* multiple inputs to the PF but is not available to lateral OFC.

If our assertion here is correct, it assumes that the lateral OFC and PF both integrate disparate information which is then further integrated to form a single, internal state representation to influence action selection. How this could work in a practical sense is illustrated by the following example: when the animal is initially placed into the operant chamber, any state inference that it makes initially would be based on the integration of their current sensory inputs (telling them they are in the operant chamber) combined with their memory of what happened in the operant chamber the day before (e.g., yesterday State 1 was active so infer State 1 will be active again today). Based on the afferents outlined above, this initial inference is most likely to rely on lateral OFC. However, it is only when the left lever is actually pressed and pellets are delivered to the food receptacle that the animal can confirm that State 1 and not State 2 is currently active, and this inference more likely relies on PF that receives feedback about the motor action performed. In a broader sense, we, therefore, suggest that whereas the lateral OFC might form integrated representations about the sights and smells of the environment with memories about what contingencies were previously active here and what outcome(s) is currently desirable, whereas the PF might form and infer integrated representations of current sensory circumstances with motor response-outcome information. One straightforward way in which to test whether this is the case would be to demonstrate that performance in a task that does not require prior motor response-outcome history for state representation formation does not rely on PF. An example of such a task would be sensory preconditioning, which involves the learning of "value-free" stimulus-stimulus associations and has been shown to relate to neuronal activity in the lateral OFC (Sadacca et al., 2018), consistent with lateral OFC forming state representations based on memories, emotions, and external information in the absence of motor history information.

If the OFC and PF do function in the manner described here, one final question is whether they each form their own, unique but partial state representations which individually influence striatal CINs, or whether they contribute unique information to a single state representation which either influences CINs or is formed by the striatal CINs themselves. What is clear from the inactivation studies outlined above, and suggested by the afferents of each structure, is that both the PF and lateral OFC do form some kind of integrated representation rather than just representing individual elements of state representation. If either structure did the latter (e.g., impaired motor learning generally) we would expect their inactivation to produce broader behavioral deficits in learning and performance, not the specific deficits that were only observed once contingencies were altered.

There is a direct projection from PF to lateral OFC (Reep et al., 1996; Hoover and Vertes, 2011) suggesting a potential anatomical basis for these structures to communicate to form a cohesive representation of the internal state. This is not a particularly dense pathway, however, and there is no evidence of any reciprocal projections from OFC→PF, suggesting that any communication between them must be unidirectional. Thus, if a cohesive state representation were formed *via* this pathway alone, then the PF could only influence striatum indirectly *via* lateral OFC→striatal outputs. Given the density of the direct pathway from PF→dorsomedial striatum, this seems unlikely. An alternate possibility is that OFC inputs containing a unique sensory/emotion/memory representation, and PF inputs containing a unique sensory/motor representation, converge on the same striatal CINs, which then combine postsynaptically to form a cohesive state representation. This possibility is more consistent with our prior notion that internal state information is formed postsynaptically by CINs (Bradfield et al., 2013a). A final possibility is that both of these things occur: the PF projects to both OFC and striatal CINs and OFC also projects to striatal CINs, to achieve accurate goal-directed selection according to the currently inferred state.

Conclusion and Potential Implications

In summary, behavioral evidence from local inactivation studies suggests that there are certain parallels between the function of the lateral OFC and PF with regards to the modulation of goal-directed actions involving choice. Specifically, the patterns of results yielded from these studies are suggestive of each structure forming some kind of internal state representation that is then used to guide goal-directed actions (although this role for lateral OFC may also extend to "model-free" habitual actions: see Wilson et al., 2014). Here, we have briefly reviewed these parallels, before discussing anatomical evidence that may be suggestive of how the OFC and PF could complement each other in achieving this function. As these observations are purely speculative at this stage, it will be of interest to determine whether they are borne out by future studies.

If correct, and translatable between species, this function of PF/OFC/CINs could be of great importance. There is already some suggestion that these functions do translate, based on several lines of evidence suggesting that OFC (Fellows, 2003; Valentin et al., 2007; Balleine and O'Doherty, 2010; Wallis, 2012), PF (Bell et al., 2018a), and striatal CINs (Bell et al., 2018b, 2019) play similar roles in regulating behavioral flexibility in humans to that which has been identified in rodents. In the vastly more rich and complex world that is inhabited by people relative to laboratory rodents, one could imagine that the ability to infer internal states accurately to exercise the appropriate action to each situation could be central to effective functioning. Every time one drives a different car, for example, they would have to infer the slight differences in how hard to press the accelerator or brakes, or whether they are driving manual or automatic and thus need to change gears, all whilst paying attention to the road. If this ability is lost, as it potentially is in Parkinson's disease patients who experience not only a loss of dopaminergic inputs to striatum but also a loss of thalamic inputs to striatal CINs (Smith et al., 2014, 2016), it could deeply impair the ability of individuals to flexibly switch between actions as each situation

dictates. This is potentially the neurobiological mechanism that underlies "cognitive rigidity" that is typical of individuals with Parkinson's disease dementia (Kehagia et al., 2010; Smith et al., 2016).

Despite some functional similarities across species, however, there is some anatomical evidence to suggest that the nature of PF projections to striatum and cortex does differ somewhat between rodents and primates. Specifically, it has been noted that, in rats, it is the same PF neurons that project directly to the striatum that also project to cortical regions (Deschênes et al., 1996), but this was found not to be the case in primates, where striatal-projecting neurons and cortical-projection neurons in PF appear to be separate (Parent and Parent, 2005). Thus, although there is evidence of some parallels across species with regards to the function of the PF and OFC inputs onto CINs within the striatum, there are also likely differences in how this manifests across species. Again, future studies are necessary to determine how much anatomical, functional, and cytoarchitectural homology there is between these structures and circuits in rodents, primates, and humans, and how applicable these findings could be to individuals with various conditions affecting them such as Parkinson's disease dementia.

AUTHOR CONTRIBUTIONS

LB completed the first draft. AD, SS, and BV contributed to and edited this draft. SS and LB created the figures. All authors contributed to the article and approved the submitted version.

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REVIEW
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Central Thalamic-Medial Prefrontal Control of Adaptive Responding in the Rat: Many Players in the Chamber

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The medial prefrontal cortex (mPFC) has robust afferent and efferent connections with multiple nuclei clustered in the central thalamus. These nuclei are elements in large-scale networks linking mPFC with the hippocampus, basal ganglia, amygdala, other cortical areas, and visceral and arousal systems in the brainstem that give rise to adaptive goal-directed behavior. Lesions of the mediodorsal nucleus (MD), the main source of thalamic input to middle layers of PFC, have limited effects on delayed conditional discriminations, like DMTP and DNMTP, that depend on mPFC. Recent evidence suggests that MD sustains and amplifies neuronal responses in mPFC that represent salient task-related information and is important for detecting and encoding contingencies between actions and their consequences. Lesions of rostral intralaminar (rIL) and ventromedial (VM) nuclei produce delay-independent impairments of egocentric DMTP and DNMTP that resemble effects of mPFC lesions on response speed and accuracy: results consistent with projections of rIL to striatum and VM to motor cortices. The ventral midline and anterior thalamic nuclei affect allocentric spatial cognition and memory consistent with their connections to mPFC and hippocampus. The dorsal midline nuclei spare DMTP and DNMTP. They have been implicated in behavioral-state control and response to salient stimuli in associative learning. mPFC functions are served during DNMTP by discrete populations of neurons with responses related to motor preparation, movements, lever press responses, reinforcement anticipation, reinforcement delivery, and memory delay. Population analyses show that different responses are timed so that they effectively tile the temporal interval from when DNMTP trials are initiated until the end. Event-related responses of MD neurons during DNMTP are predominantly related to movement and reinforcement, information important for DNMTP choice. These responses closely mirror the activity of mPFC neurons with similar responses. Pharmacological inactivation of MD and adjacent rIL affects the expression of diverse action- and outcome-related responses of mPFC neurons. Lesions of MD before training are associated with a shift away from movement-related responses in mPFC important for DNMTP choice. These results suggest that MD has short-term effects on the expression of event-related activity in mPFC and long-term effects that tune mPFC neurons to respond to task-specific information.

Keywords: central thalamus, prefrontal cortex, reward guided, mediodorsal nucleus of thalamus, intralaminar nuclei of the thalamus, anterior cingulate (ACC), conditional discrimination, midline thalamic nuclei

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INTRODUCTION

To survive in a dynamic environment organisms must be able to adapt efficiently to changes in conditions, responding in ways that optimize favorable consequences. Behavioral ecologists have demonstrated that foraging animals select among food patches of different quality in a way that maximizes food intake while reducing energy costs (Stephens and Krebs, 1986). Animals often have to simultaneously evaluate other negative and positive factors such as predation risk and mating opportunities (Nonacs, 2001), making seemingly simple decisions more complicated. Rats utilize complex strategies to optimize food acquisition, weighing information about the size and location of food items, exposure, deprivation, circadian time, risk of predation, and possible theft by conspecifics (Whishaw and Dringenberg, 1991; Whishaw et al., 1992). Wood mice in the wild exploit information about food access, experience with the food source, and predation risk in making foraging decisions (Navarro-Castilla et al., 2018; Hernández et al., 2019). Many species learn to exploit heterospecific alarm calls to evade potential predators and thus increase their foraging efficiency (Magrath et al., 2015). Eastern gray squirrels shift energy towards vigilance and away from foraging following exposure to red-tailed hawk calls and use subsequent bird chatter as a cue to safety (Lilly et al., 2019). Evolution has equipped organisms with neural mechanisms that allow them to choose a course of action likely to produce favorable consequences based on current goals, past experiences, updated information about action-outcome contingencies, and sensory evidence. This requires the ability to integrate allocentric information about the external world with egocentric information about the organization and execution of actions, internal state conditions, the anticipation of likely outcomes, and assessment of the actual consequences of behavior.

Medial prefrontal cortex (mPFC) plays a critical role in adaptive goal-directed behavior (Miller and Cohen, 2001; Dalley et al., 2004; Chudasama, 2011; Kesner and Churchwell, 2011; Balleine, 2019). mPFC has robust afferent and efferent connections with multiple thalamic nuclei that are clustered in the central thalamus and are hence referred to as central thalamic nuclei (**Figure 1**). Central thalamic nuclei are elements in large-scale networks connecting mPFC with the hippocampus, basal ganglia, amygdala, other areas of the neocortex, and visceral and arousal systems in the brainstem that give rise to adaptive goal-directed behavior. They include the paraventricular (PV), paratenial (PT), reuniens (Re), and rhomboid (Rh) midline nuclei; the central medial (CM), central lateral (CL), and paracentral (PC) rostral intralaminar nuclei; the anterior medial (AM) and interanteromedial (IAM) anterior nuclei; and the mediodorsal (MD) and ventromedial (VM) nuclei (Groenewegen, 1988; Sesack et al., 1989; Berendse and Groenewegen, 1991; Ray and Price, 1992; Vertes, 2002, 2004; Hoover and Vertes, 2007). Although early studies focused on MD, the main source of thalamic input to middle layers of mPFC, it is now clear that MD has limited effects on mPFC function and that other central thalamic nuclei contribute importantly to the effects of mPFC on goal-directed behavior (Dalley et al., 2004; Balleine and O'Doherty, 2010; Chudasama, 2011; Euston et al., 2012; Mitchell et al., 2014; Mair et al., 2015; Marton et al., 2018; Parnaudeau et al., 2018; O'Mara and Aggleton, 2019; Wolff and Vann, 2019; McGinty and Otis, 2020).

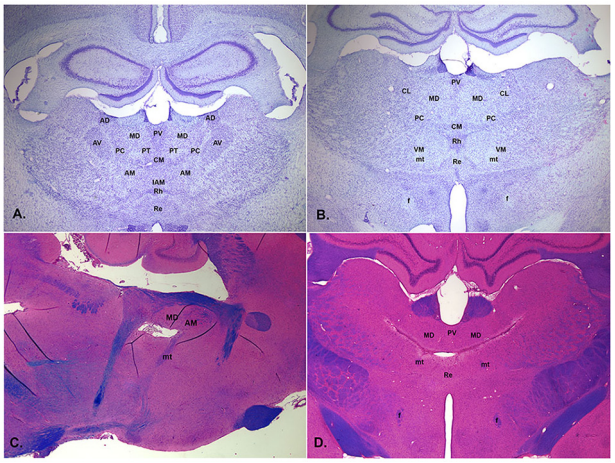

FIGURE 1 | Low magnification photomicrographs of central thalamus showing normal appearance of coronal sections stained with thionin approximately 2.3 mm **(A)** and 2.8 mm **(B)** posterior to bregma and thalamic lesions from the post-thiamine deficiency (PTD) model of the Wernicke-Korsakoff syndrome (WKS) stained with luxol blue, hematoxylin, and eosin in the sagittal section about 0.9 mm off midline (**C**, tissue from Mair et al., 1988) and in the coronal section about 3.2 mm posterior to bregma (**D**, tissue from Mair et al., 1991). PTD treatment produces bilaterally symmetric lesions centered on the mediodorsal (MD) and intralaminar nuclei that tend to spare the anterior nuclei. It is associated with behavioral impairments consistent with the performance of WKS patients on comparative neuropsychological tasks (Mair, 1994). Labeled structures include the MD, centrolateral (CL), paracentral (PC), central medial (CM), reuniens (Re), rhomboid (Rh), ventromedial (VM), anterodorsal (AD), anteromedial (AM), anteroventral (AV), interanteromedial (IAM), and paratenial (PT) nuclei and the fornix (f) and mammillothalamic tract (mt).

Vertes et al. (2015) classified a group of nuclei along the thalamic midline as limbic based on prominent afferent and efferent connections with limbic-related structures and evidence that they serve limbic-related functions, including affective behaviors, reward-guided responding, response-related working memory, and behavioral flexibility. These nuclei include PV, PT, Re, Rh, and CM nuclei and the medial division of MD. PC, CL, and more lateral divisions of MD are reciprocally connected to more dorsal motor-related areas in anterior cingulate and agranular medial areas of mPFC (Groenewegen, 1988; Berendse and Groenewegen, 1991; Ray and Price, 1992; Vertes, 2002; Hoover and Vertes, 2007). Recent evidence indicates that thalamocortical neurons in MD are strongly excited by the driver and modulatory input from PFC and indirectly influence reciprocally-connected neurons in PFC by enhancing cortical connectivity and regulating neuronal activity (Barbas et al., 1991; Xiao et al., 2009; Schmitt et al., 2017; Collins et al., 2018). The projections of the rostral intralaminar nuclei have thalamocortical and thalamostriatal projections to areas that are interconnected by corticostriatal projections: connections that appear organized to control interactions between mPFC and the

basal ganglia and thus selection of goals, actions, and associative stimuli (Berendse and Groenewegen, 1990; Groenewegen and Berendse, 1994; Grillner et al., 2005; Mannella et al., 2016). The intralaminar and midline nuclei receive prominent subcortical inputs from periaqueductal gray, parabrachial nuclei, superior colliculus, hypothalamus, and brainstem nuclei (Krout and Loewy, 2000a,b; Krout et al., 2001, 2002; Bayer et al., 2002). These provide signals related to visceral, nociceptive, orienting, and arousal functions consistent with a role for these nuclei in behavioral state control of mPFC function (Kinomura et al., 1996; Schiff and Purpura, 2002; Mair and Hembrook, 2008).

The ventromedial nucleus (VM) has dense reciprocal connections with the agranular medial cortex and adjacent motor and cingulate areas. Afferent inputs to VM include branches of axons that also innervate MD and GABAergic projections from the basal ganglia. Thalamocortical neurons in VM have dense widespread projections to layer 1 in agranular medial and adjacent motor and cingulate cortices and less dense projections in parietal and occipital cortices that appear organized to control integrative motor responses (Vertes, 2002; Hoover and Vertes, 2007; Kuramoto et al., 2017; Collins et al., 2018; Sierveritz et al., 2019). The anterior thalamic nuclei receive inputs from the subicular complex of the hippocampal formation and are reciprocally connected to the retrosplenial cortex, an important hub for spatial cognition. The IAM and AM nuclei are also reciprocally connected to anterior cingulate and prelimbic areas of mPFC (Vertes, 2002; Hoover and Vertes, 2007). Lesions of the anterior thalamic nuclei affect allocentric spatial learning tasks (Aggleton and Nelson, 2015; O'Mara and Aggleton, 2019).

Anatomical analyses indicate that rodent mPFC is homologous to primate anterior cingulate and premotor cortices and lacks an area homologous to primate dlPFC (Preuss, 1995; Uylings et al., 2003; Vogt et al., 2013; Schaeffer et al., 2020). Here we focus on interactions between mPFC and thalamus in rodents to avoid the complexity of factoring in the influence of primate dlPFC on thalamocortical interactions. In this article, we review the two convergent approaches that have been used to elucidate the role of thalamo-prefrontal pathways in generating adaptive responses. The first is to lesion or manipulate the activity of these pathways and study the effects on behavioral measures of adaptive responding. Here we use behavioral measures to examine the influence of different thalamic nuclei on functions supported by mPFC. The second is to record the activity of mPFC and central thalamic neurons in awake, behaving animals to understand what information is represented and how cortical and thalamic neurons interact during adaptive goal-directed behavior. Here, we emphasize recordings comparing mPFC with MD, given the lack of data to support comparisons with other central thalamic nuclei. We focus on spatial delayed conditional discriminations: tasks that have received considerable attention in both behavioral and electrophysiological recording studies. These tasks incorporate important features of adaptive goal-directed responding: flexible reward-guided choice, where different responses are reinforced on different trials; conditional discrimination, where a preceding stimulus indicates which response alternative will be reinforced; working memory, where information must be represented briefly in memory; spatial navigation, where behavioral events are distributed topographically; and motor planning, where organisms must organize and execute a series of actions to obtain reinforcement. Lesion studies in rats have provided evidence that pathways connecting mPFC with the striatum, pallidum, and thalamus are critical for spatial delayed conditional discrimination (Dunnett, 1990; Reading and Dunnett, 1991; Kesner et al., 1996; Mair et al., 1998, 2002; Floresco et al., 1999; Burk and Mair, 2001a; Porter et al., 2001; Bailey and Mair, 2005; Zhang et al., 2005; Sloan et al., 2006).

BEHAVIORAL STUDIES OF mPFC FUNCTION

Early studies of delayed response deficits in monkeys (Jacobsen, 1936) led investigators to focus on the role of the prefrontal cortex in working memory: the ability to hold information online and guide behavior with these internal representations (Goldman-Rakic and Selemon, 1997; Fuster, 2001). Subsequent studies identified the principal sulcus of monkey dlPFC as a critical site for visuospatial working memory (Goldman and Rosvold, 1970; Goldman et al., 1971) and ventral lateral PFC for non-spatial working memory (Goldman-Rakic, 1996; Meyer et al., 2011). Early lesion studies in the rat associated mPFC with impairments of spatial reversal, delayed response, and delayed alternation and orbitofrontal PFC with increased perseveration and responding during extinction: findings consistent with effects of dlPFC and orbitofrontal cortex lesions in non-human primates (Divac, 1971; Kolb et al., 1974; Larsen and Divac, 1978). These results led to the view that portions of rodent mPFC are homologous to primate dlPFC. Anatomical studies have challenged that view by demonstrating homology between rodent mPFC and primate anterior cingulate and premotor cortices, but not dlPFC, based on relative location, cytoarchitecture, receptor binding studies, and anatomical and functional connectivity (Preuss, 1995; Vogt et al., 2013; Schaeffer et al., 2020).

Effects of mPFC Lesions on Spatial Delayed Conditional Discrimination

Working memory is important for adaptive responding: allowing organisms to hold and manipulate information online while monitoring fluctuations in the environment (Miller et al., 2018; Cavanaugh et al., 2020). Early lesion studies indicated that mPFC lesions in the rat have a selective effect on working memory, impairing delayed conditional discriminations based on response-related egocentric information while sparing maze tasks that require an allocentric solution (Becker et al., 1980; Kolb et al., 1983; Kesner et al., 1996; de Bruin et al., 2001). Porter and Mair (1997) tested this distinction by comparing the effects of PFC lesions on a series of tasks trained in automated 8 arm radial mazes, beginning with an allocentric 8 arm task trained in a lighted room with many visible cues and changing in stages to end with two choice egocentric DNMTP (**Figure 2**). Neither mPFC nor complete PFC lesions affected the allocentric tasks, including two choice DNMTP where three arms were selected at random for each trial from the eight arms of the maze (i.e., no predictable configuration between the arms) both with

and without visible external cues (**Figures 2A,B**). Both mPFC and complete PFC lesions produced stable impairment only at the last stage of training where the same three arms were used on every trial in a T-configuration such that choice responses were defined by the egocentric direction of turning (left vs. right) from the stem of the T and the room was darkened and mazes covered to eliminate external allocentric visual cues (**Figure 2C**). Porter et al. (2000) confirmed these findings by comparing the effects of mPFC and hippocampal lesions on the allocentric and egocentric versions of 2-choice radial maze DNMTP. Both hippocampal and mPFC lesions produced delay-independent impairment for rats trained pre-surgically and tested post-surgically with the egocentric version (**Figure 2D**) while hippocampal lesions produced delay-dependent impairment and mPFC lesions spared the allocentric version (**Figure 2E**). To test possible explanations for deficits, tasks were switched after initial post-surgical testing. Interestingly, rats trained initially with the allocentric version of DNMTP were protected from effects of mPFC, but not hippocampal, lesions when switched to the egocentric version (**Figures 2D,F**).

These findings have several important implications. First, since egocentric and allocentric versions of radial maze DNMTP used the same deprivation procedures and water reinforcement it is unlikely that the egocentric impairment is related to reinforcement mechanisms or to the ability to utilize reinforcement-related information flexibly to select different response alternatives on different trials. Second, the ability of mPFC lesioned rats to perform the egocentric version following extensive allocentric training (**Figure 2F**) indicates that the deficits observed for egocentric DNMTP (**Figures 2C,D**) cannot be ascribed to the repetition of the same response alternatives on every trial. This rules out interference effects or difficulty of temporal discrimination produced by frequent repetition of response alternatives. One possibility consistent with these results is that rats were biased by pre-and post-surgical allocentric training to rely on allocentric cues or an internalized spatial map of the maze when subsequently switched to egocentric DNMTP (see Porter et al., 2000 for a discussion of this possibility).

Third, the spared ability of rats with mPFC or complete PFC lesions to perform allocentric DNMTP shows that the effects of mPFC lesions on egocentric DNMTP deficits cannot be ascribed to a generalized impairment of working memory. mPFC lesions in these studies involved agranular medial, anterior cingulate, and prelimbic cortices while the complete PFC lesions additionally damaged agranular insular and ventral orbital areas (cortical areas based on Öngür and Price, 2000; Heidbreder and Groenewegen, 2003). These results are consistent with reports that similar mPFC lesions impair egocentric while sparing allocentric spatial memory in other tasks (Kolb et al., 1983; Harrison and Mair, 1996; Kesner et al., 1996; de Bruin et al., 2001) and, further, spare other measures of working memory, including olfactory continuous non-matching-to-sample (Koger and Mair, 1994) and visual object memory (Kesner et al., 1996; Ennaceur et al., 1997). Ragozzino et al. (1998, 2002), report that more ventral mPFC lesions involving IL and MO areas affect working memory for allocentric spatial and visual object information. These findings are consistent with the view that different regions of PFC support different domains of working memory (Goldman-Rakic, 2005; Kesner and Churchwell, 2011). More recent evidence has shown that different modalities of working memory are mediated by other areas of the association cortex (Miller et al., 2018; Xu, 2018; Buchsbaum and D'Esposito, 2019; Cavanaugh et al., 2020) indicating that working memory may represent a property of cortex that extends beyond PFC.

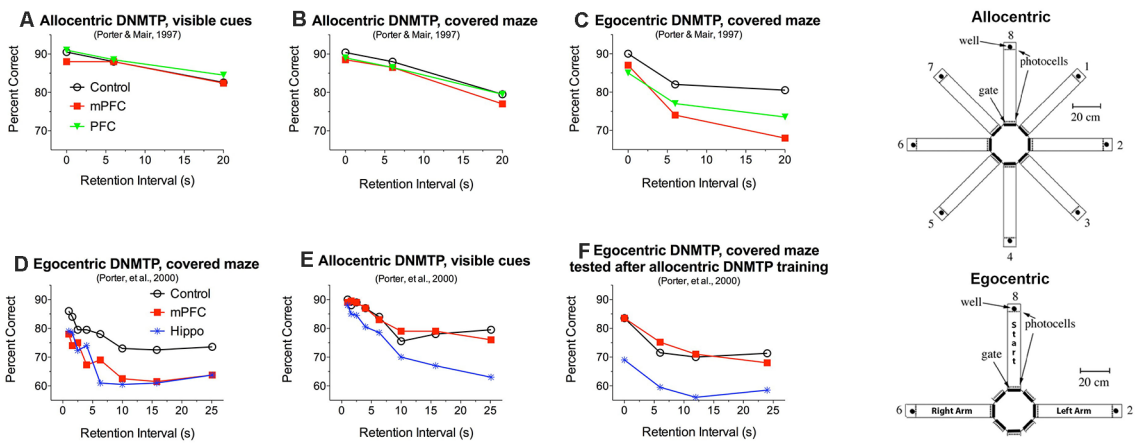

FIGURE 2 | Effects of medial prefrontal (mPFC), complete prefrontal (PFC), and hippocampal (Hippo) lesions on allocentric and egocentric versions of 2-choice DNMTP trained in eight arm radial mazes. Samples and choices in egocentric DNMTP were between the same two arms on every trial, located to the left and right of the holding arm. Arms for allocentric DNMTP were selected at random on every trial from the eight alternatives so that their configurations were unpredictable. For egocentric DNMTP external cues were minimized by covering mazes and training in the dark, while allocentric DNMTP was trained in uncovered mazes with lights on and many visible external cues. mPFC and PFC lesions impaired egocentric **(C,D)** and spared allocentric DNMTP **(A,B,E)** while hippocampal lesions impaired both tasks **(D,E)**. Rats that received extensive allocentric training (30 presurgical and 20 postsurgical sessions) were protected when subsequently switched to egocentric DNMTP **(F)**. Data are replotted from studies cited.

The delay-independent effects of mPFC lesions on DMTP and DNMTP (**Figures 2**, **4H**) are consistent with evidence that PFC lesions affect the ability to use conditional or other learned rules to select between choice alternatives independent of demands on working memory (Petrides, 1985; Winocur and Eskes, 1998; Sharpe and Killcross, 2015; Germann and Petrides, 2020). Stevens and Mair (1998) tested this idea with an auditory match-to-position (AMTP) task in which the discriminative stimulus was turned off at different times before (mnemonic) or after (non-mnemonic) the choice response. While all groups performed better for non-mnemonic conditions where stimuli were present at the time of choice, mPFC and central thalamic lesions produced comparable deficits for mnemonic and non-mnemonic choice. These results demonstrate an impairment in a trial-to-trial selection based on a learned conditional rule where the discriminative stimulus is present at the time of choice. They do not rule out a role for working memory in monitoring actions and outcomes or utilizing learned information about the conditional rule in nonmnemonic AMTP trials. Analyses of DMTP (Mair et al., 1998) and DNMTP (Harrison and Mair, 1996; Porter et al., 2000) in operant chambers that allow precise measurement of response time (RT) data have revealed significant increases in choice RT for mPFC lesions (**Figure 5D**). Other analyses in these studies showed that matching for RT did not affect deficits in response accuracy. Thus mPFC lesions appear to have two distinct effects on egocentric spatial delayed conditional discriminations: delay-independent impairment of response accuracy and slower RTs for choice responses.

Effects of mPFC Lesions on Instrumental Behavior

mPFC lesions that produce DMTP (Mair et al., 1998) or DNMTP (Harrison and Mair, 1996; Porter et al., 2000) impairments have been found to spare discrimination learning when tested subsequently for serial reversal learning where choices involved the same levers, in the same apparatus, with the same reinforcement used for the DMTP or DNMTP tasks. This suggests that mPFC lesions that affect delayed conditional discrimination spare rule-based discrimination learning where the same response alternative is associated with reinforcement on every trial. Other evidence suggests that mPFC lesions can affect rule-based responding when stimuli are difficult to discriminate (Bussey et al., 1997) or under conditions that make it difficult to detect and attend to information relevant to action selection (Birrell and Brown, 2000; Dalley et al., 2004; Chudasama, 2011; Fisher et al., 2020; Bubb et al., 2021). For instance, mPFC lesions increase RT and decrease accuracy for responding to brief luminance cues in the 5-choice serial reaction time task (Muir et al., 1996; Chudasama et al., 2003). Interestingly, more posterior (Muir et al., 1996) or ventral (Chudasama et al., 2003) mPFC lesions were found to increase premature responding in this task, indicative of impaired inhibitory control.

Similar results have been observed for a visual-spatial reaction time (VSRT) designed around the octagonal hub used for radial DNMTP tasks (**Figure 3**). In VSRT trials, rats entered the hub from the observation arm (see **Figure 3**), triggering a brief luminance cue that indicated the correct response port where a nose poke was reinforced with water. In DNMTP rats entered a similar hub from the holding arm where they were presented with open gates for two arms. They received water reinforcement for responding to the arm not reinforced on the preceding sample trial (**Figure 2**; see above). mPFC lesions increased RT and impaired accuracy of VSRT and produced egocentric radial maze DNMTP impairment consistent with earlier results shown in **Figure 2** (Bailey and Mair, 2004). Lesions of adjacent M1 and M2 motor cortex also affected VSRT accuracy and RT but spared egocentric DNMTP. Thus, mPFC lesions affected the trial-to-trial selection of spatially defined response alternatives following learned conditional rules in VSRT and egocentric DNMTP, while M1M2 lesions affected sensory-, but not a memory-guided choice. The effects of M1M2 lesions on VSRT are consistent with evidence linking motor and premotor cortices with control of intentional movements guided by external stimuli (Brown et al., 1991; Muir et al., 1996; Georgopoulos and Carpenter, 2015).

It has been argued that mPFC is important for evaluating actions and outcomes along multiple dimensions (Skvortsova et al., 2014). The anterior cingulate area of mPFC has been implicated in discriminating the utility of different reward options in effort-based decision-making (Walton et al., 2006; Hart et al., 2020). Consistent with this view the prelimbic area of mPFC has been implicated in the ability to detect action-outcome contingencies (Balleine and O'Doherty, 2010; Balleine, 2019). Balleine and Dickinson (1998) first showed that prelimbic lesions make instrumental responding insensitive to outcome devaluation. Subsequent work found that these effects only occur with lesions made before initial training (Ostlund and Balleine, 2005; Hart and Balleine, 2016). Thus, the prelimbic cortex appears to be critical for encoding action-outcome associations but is not the location where they are stored (Balleine, 2019). More recently, Alcaraz et al. (2018) used chemogenetic methods to dissect the contributions of thalamocortical and corticothalamic projections to dorsal mPFC on encoding action-outcome encoding. They report that thalamocortical projections are important for both outcome- and contingency-devaluation, while corticothalamic projections are important for outcome-, but not contingency-devaluation.

Fuster (2001) argued that PFC is organized to remember, plan, and execute actions: integrating perceptions and actions in time to support goal-directed behavior. Consistent with this mPFC lesions affect recency discriminations used to assess temporal order memory in the rat (Kesner and Churchwell, 2011). Other evidence indicates that prefrontal and premotor cortices interact with striatum to support action sequence learning in humans and non-human primates (Kennerley et al., 2004; Poldrack et al., 2005; Di Russo et al., 2017). Bailey and Mair (2006, 2007) showed comparable effects of frontal cortical and striatal lesions in rats trained to perform a series of nose poke responses in an action sequence learning task. For unlesioned controls repetition learning increases RT to initiate learned sequences, reflecting motor planning, and decreased RT for subsequent responses in the sequence, reflecting the benefits of habitual learning. Lesions involving agranular medial and anterior cingulate areas of mPFC increased RT to initiate learned

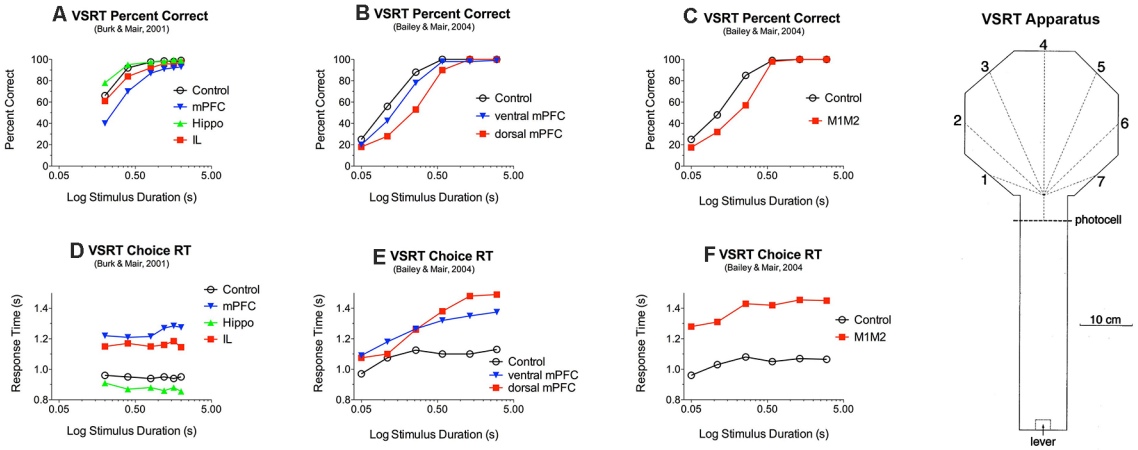

FIGURE 3 | Effects of medial prefrontal (mPFC) and motor (M1M2) cortex and rostral intralaminar (IL) thalamic lesions on reaction time (RT) and accuracy of responding to luminance cues in the visuospatial reaction time (VSRT) task. VSRT trials were initiated by a lever press at the end of the arm. A brief luminance cue was then triggered to indicate the S+ response port when the rat crossed the photocell just before entering the octagonal hub. Water reinforcement was delivered in the S+ port if the rat entered it first within a 3.0 s limited hold. PFC and M1M2 lesions had duration-dependent effects on response accuracy **(A,B,C)** and increased RT for **(D,E,F)**. IL thalamic lesions increased RT **(D)** but did not have a significant effect on choice accuracy **(A)**. Data are replotted from studies cited.

sequences, suggesting a role for these areas in motor preparation, while sparing the decrease in RT for later nose pokes in learned sequences, providing evidence of spared habitual repetition learning. Parallel effects were observed for lesions in related areas of the striatum (Bailey and Mair, 2006).

Adaptive goal-directed behavior depends on multiple functions supported by mPFC. There is strong evidence for the role of mPFC in working memory, although it seems unlikely that this extends across all domains of information or that it is sensitive to the length of the memory delay. Beyond remembering stimulus information, working memory is important for monitoring actions and outcomes across time (see Dalley et al., 2004), holding stimulus information online to control attention, and maintaining goal-related information during motor planning. mPFC is important for flexible responding where trial-to-trial response selection is based on a learned conditional rule. mPFC has also been implicated in several attentive processes that allow animals to respond efficiently to task-relevant information. A case could also be made for a fundamental role of mPFC in detecting and encoding relationships between actions and their consequences and thus the capacity for adaptive goal-directed responding. Such impairment could potentially account for the profound effects of mPFC lesions on conditional responding, particularly for tasks that require flexible selection of different responses on different trials. Finally, mPFC is also thought to play an important role in organizing and executing temporal sequences of actions.

BEHAVIORAL STUDIES OF CENTRAL THALAMIC FUNCTION

mPFC interacts with multiple central thalamic nuclei to control neural networks that give rise to adaptive goal-directed behavior (Mitchell et al., 2014; Mair et al., 2015; Halassa and Sherman, 2019; Fresno et al., 2019). To what extent do individual nuclei contribute to mPFC control of intentional responding? Early studies focused on MD, in part because of prominent connections with PFC and its implication in early studies of amnesia (Victor et al., 1971; Isseroff et al., 1982; von Cramon et al., 1985; Zola-Morgan and Squire, 1985). Several lines of research broadened this focus to include contributions of other central thalamic nuclei: anatomical evidence that multiple central thalamic nuclei have afferent and efferent connections with PFC and PFC-related pathways (Groenewegen, 1988; Sesack et al., 1989; Berendse and Groenewegen, 1991; Ray and Price, 1992; Vertes, 2004; Hoover and Vertes, 2007); clinical studies associating thalamic amnesia with damage to other parts of central thalamus (Carlesimo et al., 2011; Van der Werf et al., 2003); findings from the post-thiamine deficiency (PTD) model of the Wernicke-Korsakoff syndrome that intralaminar lesions produce cognitive impairment in this model (**Figures 1C,D**; Mair, 1994; Mair et al., 2015); and evidence that the hippocampal-anterior thalamic axis plays a critical role in episodic memory (Aggleton and Brown, 2006). A complete review of this literature is beyond the scope of this article. Here we will focus on response-related measures of learning and memory that depend on mPFC in the rat.

Effects of Intralaminar, Mediodorsal, and Ventromedial Nuclei on Spatial Delayed Conditional Discrimination

Large central thalamic lesions involving intralaminar nuclei and adjacent areas of MD produce delay-independent impairment comparable to mPFC lesions, affecting both the speed and accuracy of DMTP and DNMTP choice (Mair and Lacourse, 1992; Burk and Mair, 1998). Similar deficits were observed

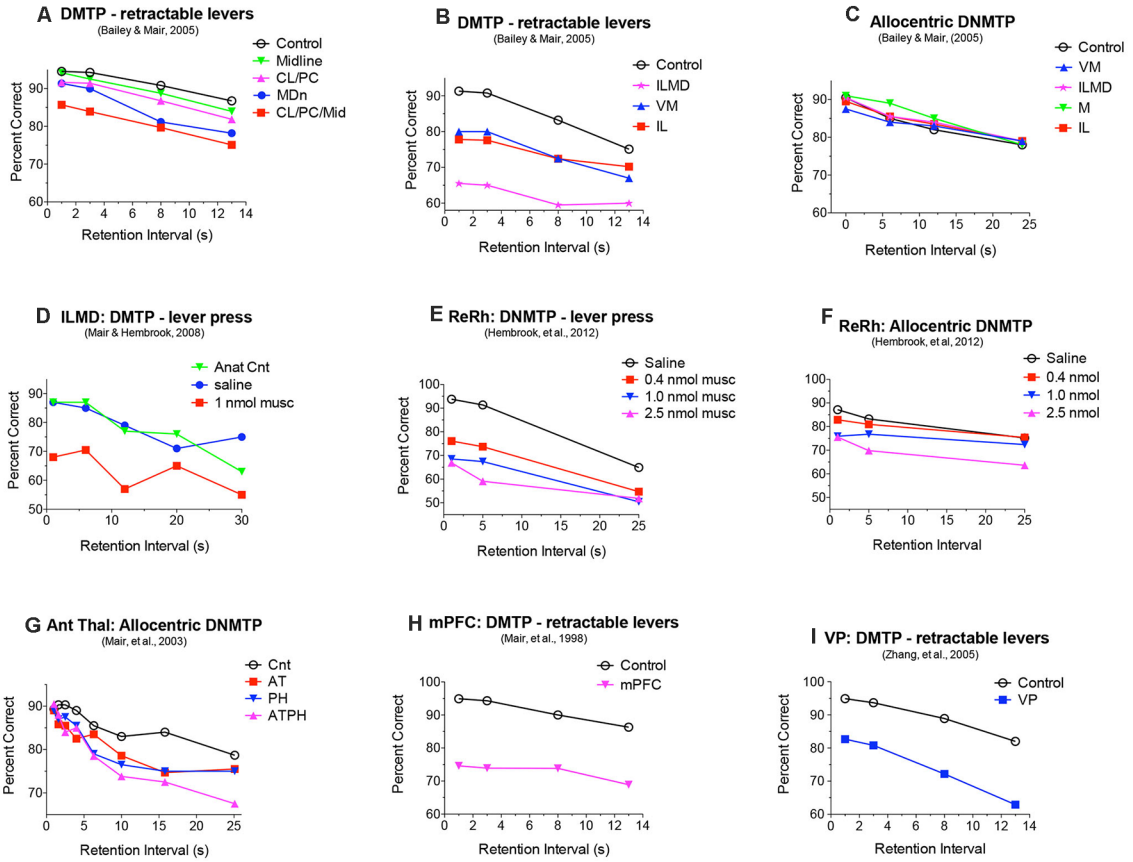

FIGURE 4 | Effects of central thalamic lesions on delayed matching (DMTP) and non-matching (DNMTP) to position accuracy. Lesions of the mediodorsal nucleus (MD) produced delay-dependent **(A)** and lesions of rostral intralaminar (IL), ventromedial (VM), and IL and MD combined (ILMD) produced delay-independent impairment **(B)** of egocentric DMTP trained with retractable levers, an impairment also observed with reversible inactivation of IL and MD **(D)**. IL, ILMD, and VM lesions did not have significant effects on allocentric radial maze DNMTP **(C)**. Reversible inactivation of reuniens (Re) and rhomboid (Rh) nuclei in the ventral midline thalamus produced delay-independent impairment of DNMTP trained with retractable levers at all muscimol doses tested **(E)** and allocentric radial maze DNMTP only at the highest dose tested **(F)**. Anterior thalamic (AT) lesions produced delay-dependent impairment of allocentric radial maze DNMTP comparable to the effects of parahippocampal cortex (PH) lesions **(G)**. Combined AT and PH lesions produced a larger deficit, comparable to the effects of hippocampal lesions **Figure 2E** on this task. Lesions of the medial prefrontal cortex (mPFC) and ventral pallidum (VP) produce delay-independent impairment of DMTP **(H,I)** comparable to the effects of IL, ILMD, and VM lesions **(B)**. Data are replotted from studies cited.

for the PTD model (Mair et al., 1991; Robinson and Mair, 1992) where MD and intralaminar nuclei are consistent sites of thalamic pathology (**Figure 1**). Reversible inactivation of these nuclei with microinjected drugs can produce comparable impairment of accuracy without affecting response speed (**Figure 4D**; Porter et al., 2001; Mair and Hembrook, 2008). To control for the effects of response accuracy, and thus the frequency of reinforcement, on deficits produced by thalamic lesions a staircase method was used to define the memory delay producing 75% accuracy for PTD (Robinson and Mair, 1992) and radiofrequency thalamic lesions (Mair and Lacourse, 1992). This method was successful in matching lesion and control groups for response accuracy (and thus reinforcement density) while demonstrating significant impairment in the length of retention interval producing 75% accuracy for both PTD (6.1 vs. 14.6 s for controls) and radiofrequency lesions (7.4 vs. 17.8 s).

Discrete lesions targeting specific nuclei have more specific effects. Bailey and Mair (2005) compared the effects on DMTP of lesions targeting MD, intralaminar, midline, and ventromedial (VM) nuclei that were carefully positioned to avoid damaging anterior thalamic nuclei. Lesions restricted to lateral intralaminar (CL, PC) or dorsal midline nuclei did not significantly affect performance alone, but combined in the larger CL/PC/Mid lesion produced a delay independent impairment (**Figure 4A**) that did not affect response time (RT; **Figure 5A**). Lesions restricted to MD resulted in delay-dependent deficits that did not affect RT. Burk and Mair (1998) found a non-significant trend towards impairment and no effect on RT for MD lesions with a similar DMTP task in which sample response requirements were manipulated. Other studies examining the effects of MD on spatial memory tasks have produced mixed results for rats and monkeys (Mitchell and Chakraborty, 2013). Young et al. (1996) found a delay-dependent

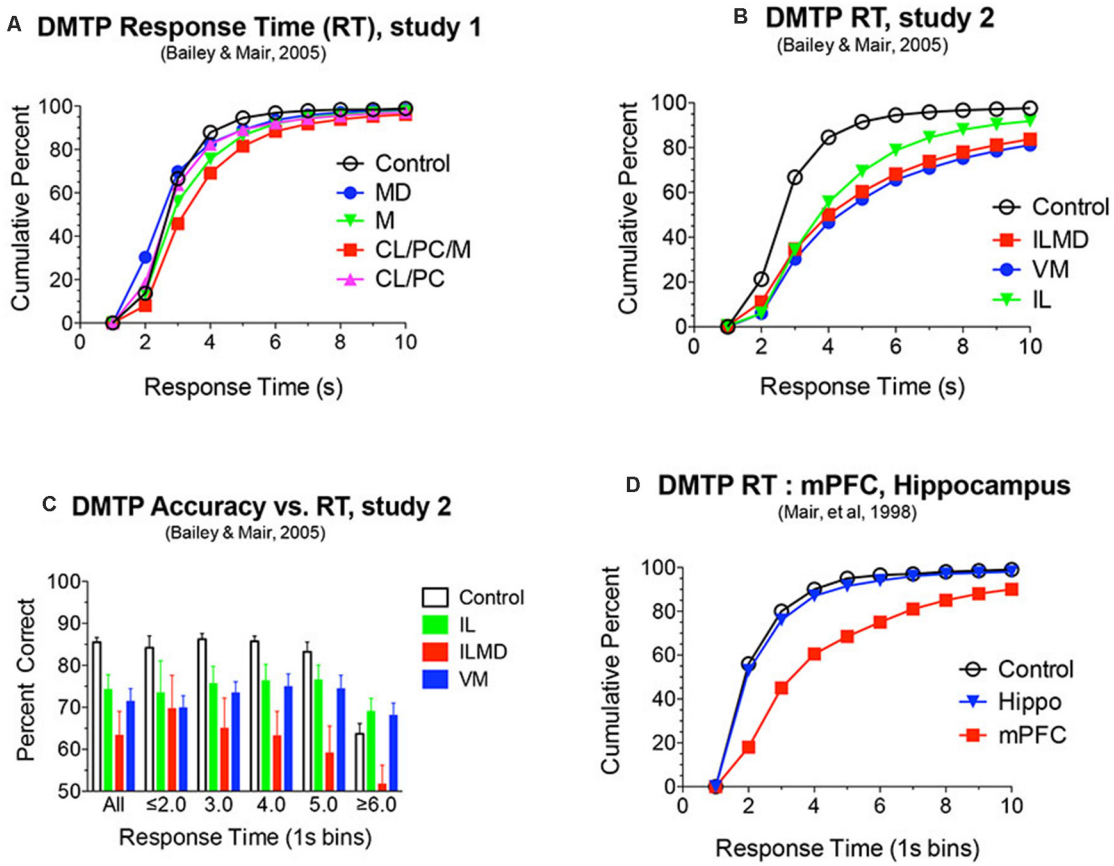

FIGURE 5 | (A,B,D) Response time (RT) analyses of DMTP choice plotted as cumulative functions. RT was measured from the lever press marking the end of the memory delay to the choice press (see **Figure 6**). RT was increased significantly by rostral intralaminar (IL), ventromedial (VM), and large lesions damaging IL and the mediodorsal (MD) nuclei (ILMD; **B**). These same lesions produced delay independent impairments of DMTP (**Figure 4B**). To test whether the increase in RT could account for the decrease in DMTP accuracy, separate analyses were conducted for responses divided into discrete RT bins. Restricting responses to 1 s time bins did not affect significant deficits produced by each of the lesions for RT bins with sufficient numbers of responses to support these analyses **(C)**. mPFC, but not hippocampal, lesions were associated with a similar increase in DMTP RT **(D)** and accuracy **Figure 4H**. Data are replotted from studies cited.

impairment for MD lesions in a fine-grained analysis of temporal decay in an operant DNMTP task where rats were trained to stability at a series of delays and rate of decay inferred from an asymptotic performance at each delay. By contrast, Hunt and Aggleton (1998) found significant effects of MD lesions on errors to criterion learning DMTP trained in a T-maze but not for temporal decay of this task once learned. Clearly, MD lesions do not produce DMTP or DNMTP deficits comparable to the more substantial, delay-independent effects of mPFC lesions which affect accuracy and RT for these tasks (**Figures 2**, **4**, **5**).

Bailey and Mair (2005) found that complete intralaminar lesions involving CL, PC, and CM produced delay independent deficits for DMTP accuracy (**Figure 4B**) and RT (**Figure 5B**) comparable to effects of mPFC lesions. VM lesions also produced delay independent deficits with a more substantial increase in RT. Large ILMD lesions, involving midline, MD, and intralaminar nuclei caused delay independent impairment about twice as severe as intralaminar (or VM) lesions (**Figure 4B**) and increased RT comparable to VM lesions (**Figure 5B**). To test whether deficits in DMTP or DNMTP accuracy are secondary to effects of thalamic lesions on response speed, separate analyses of response accuracy were conducted with restricted RT windows (Mair and Lacourse, 1992; Burk and Mair, 1998, 1999; Bailey and Mair, 2005). The results of these analyses have consistently shown effects of thalamic lesions on DMTP and DNMTP accuracy persist with RT restrictions except for long RTs where group differences are limited by floor effects (**Figure 5C**). Intralaminar lesions have broad effects on adaptive responding that can affect functions spared by mPFC lesions. These include olfactory continuous non-matching to sample (Koger and Mair, 1994; Zhang et al., 1998) and serial reversal learning (Mair et al., 1991; Harrison and Mair, 1996; Burk and Mair, 1998).

Bolkan et al. (2017) used optogenetic methods to demonstrate a delay-dependent effect of MD inhibition in mice for T-maze DNMTP. Interestingly they found evidence for a directional interaction where thalamocortical projections of MD support

sustained firing in mPFC during the memory delay and cortico-thalamic projections the subsequent choice response. Other recent studies have shown that persistent cortical activity depends on thalamocortical loops involving MD and mPFC for attentional control (Schmitt et al., 2017) and VM for preparatory activity in the motor cortex (Guo et al., 2017). Collins et al. (2018) used optogenetics to dissect cortico-thalamocortical networks involving MD and VM. They report that MD and VM are excited by reciprocally-connected neurons providing layer 5 "driver" and layer 6 "modulatory" afferents from mPFC, that appear organized to activate and maintain persistent firing in thalamocortical neurons. Collins et al. also found that thalamocortical projections of MD strongly activate layer 2/3 cortico-cortical neurons while VM provides subthreshold excitation across layers in mPFC. The predominant thalamocortical and corticothalamic connections between VM and dorsal agranular medial areas of mPFC (Vertes, 2002; Hoover and Vertes, 2007) seem consistent with the implication of VM supporting preparatory responses in the motor cortex (Guo et al., 2017). Taken together these results suggest that cortico-thalamocortical circuits support the temporary maintenance of information in mPFC important for adaptive responding that extends well beyond the traditional view of working memory as a temporary buffer for sensory or episodic information.

Effects of Midline and Anterior Nuclei on Spatial Delayed Conditional Discrimination

Intralaminar lesions that extend into anterior areas of the thalamus produce delay independent impairment of allocentric radial maze DNMTP (Mair et al., 1998), a task spared by intralaminar lesions that do not affect anterior thalamus (Bailey and Mair, 2005; see above). The anterior thalamic nuclei are important nodes in hippocampal-related pathways that support allocentric spatial learning and memory (Aggleton and Nelson, 2015; O'Mara and Aggleton, 2019). Multiple reports indicate that anterior thalamic lesions affect allocentric DNMTP and other measures of spatial memory spared by mPFC, intralaminar, and MD lesions (Warburton et al., 1997; Mair et al., 2003; Wolff et al., 2008). Mitchell and Dalrymple-Alford (2006) compared effects of anterior thalamic lesions with lateral thalamic lesions involving intralaminar and MD and found evidence of a double-dissociation consistent with these findings: anterior thalamic lesions affected the post-surgical acquisition of an allocentric spatial memory task trained in a radial maze and spared performance of a pre-surgically trained egocentric memory task, while lateral lesions of MD and the intralaminar nuclei had opposite effects. Alcaraz et al. (2016) reported an analogous double dissociation in which lesions damaging MD and intralaminar nuclei affected a spatial outcome-devaluation task while sparing an allocentric spatial memory task, while anterior nucleus lesions had the opposite effects. The severe effects of anterior thalamic lesions on spatial function have been attributed to different functions mediated by individual anterior thalamic nuclei as well as "covert effects" of anterior thalamic lesions on distributed hippocampal-related networks (Aggleton and Nelson, 2015). While AM and IAM are reciprocally connected to mPFC, these connections are not critical for egocentric function spared by anterior thalamic lesions and insufficient to disrupt allocentric function spared by mPFC lesions.

The reuniens (Re) and rhomboid (Rh) nuclei in the ventral midline thalamus are important sources of thalamic input to the hippocampus and mPFC that appear organized to modulate mPFC—hippocampal interactions (Vertes et al., 2006). Early evidence showed that these nuclei are important for spatial memory tasks that depend on both mPFC and hippocampus. Lesions damaging Re and Rh affect radial maze measures of spatial memory while sparing visually-guided choice in VSRT and action sequence learning (Hembrook and Mair, 2011). Localized inactivation of Re and Rh with low doses of muscimol (0.4 or 1.0 nmol) affects operant DNMTP, a task sensitive to the effects of both mPFC and hippocampal lesions, while sparing allocentric radial maze DNMTP, a task sensitive to the effects of hippocampal but not mPFC lesions (Hembrook et al., 2012). Subsequent studies have confirmed an important role for Re and Rh in aspects of spatial memory and cognitive control that requires the coordinated activity of the hippocampus and mPFC (Dolleman-van der Weel et al., 2019; Mathiasen et al., 2020). Both the anterior thalamic and ventral midline Re and Rh are organized to support interactions between mPFC and hippocampus. Anterior thalamic nuclei, with strong retrosplenial, cingulate, and mammillary body connections, appear specialized to support allocentric hippocampal function. Re and Rh, with their extensive connections with the hippocampus and mPFC, appear specialized to support interactions between them (Dolleman-van der Weel et al., 2019; Mathiasen et al., 2020).

Effects of Thalamic Lesions on Instrumental Behavior

Intralaminar lesions increase RT without affecting the accuracy of conditional responses to brief luminance cues in the VSRT task, while mPFC lesions increase RT and decrease accuracy (see above), and hippocampal lesions had no significant effect on RT or accuracy (Burk and Mair, 2001b). Other reports indicate that both MD (Chudasama and Muir, 2001) and Re (Prasad et al., 2013) lesions increase premature responding without affecting responses to luminance cues in the 5 choice task. This suggests a role for MD and Re on inhibitory control, but not sensory attention. The effects of intralaminar lesions on VSRT RT are consistent with evidence that intralaminar, but not MD, lesions affect choice RT for DMTP and DNMTP tasks (**Figures 5A,B**; see above). The effect of MD lesions on premature responding is consistent with the effects of lesions damaging the prelimbic area of mPFC.

Lesion studies have also demonstrated parallel effects of MD and prelimbic cortex lesions on action-outcome learning. Thus, MD lesions were found to abolish the effects of outcome devaluation (Corbit and Balleine, 2003). Like prelimbic lesions, MD lesions affect outcome devaluation only when made before initial training (Ostlund and Balleine, 2008). Thus, both prelimbic and MD appear to be essential for the acquisition, but

not the expression, of goal-directed behavior. The importance of connections between the prelimbic cortex and MD for action-outcome learning was confirmed by a crossed lesion study, where lesions damaging MD in one hemisphere, PL in the other, and contralateral projections of MD in the corpus callosum affected comparable to bilateral MD or prelimbic lesions on outcome devaluation (Bradfield et al., 2013). Recently, Alcaraz et al. (2018) used chemogenetic methods to provide evidence that thalamocortical projections from lateral MD to dorsal mPFC affect both outcomes- and contingency-devaluation, while corticothalamic pathways between these areas affect the outcome- but not contingency-devaluation.

Dorsal midline lesions damaging the PV and PT nuclei have not been associated with significant effects on egocentric DNMTP (Mair and Lacourse, 1992) or DMTP tasks (Bailey and Mair, 2005; **Figures 4A**, **5A**). They have extensive limbic-related connections with systems that are important for instrumental behavior, including inputs from visceral-, arousal-, and emotion-related areas in the brainstem, hypothalamus, and limbic forebrain and projections to prelimbic and infralimbic areas of mPFC, agranular insular and entorhinal cortices, subiculum, nucleus accumbens, and striatum, and the extended amygdala (Krout and Loewy, 2000a,b; Krout et al., 2001, 2002; Bayer et al., 2002; Vertes and Hoover, 2008; Kirouac, 2015). PV and PT thus appear organized to integrate information related to the behavioral state to influence brain systems that support adaptive goal-directed behavior. Functional analyses have focused more on PV than PT. These have provided evidence that PV affects reward-seeking behavior (McGinty and Otis, 2020), control of wakefulness (Ren et al., 2018), the salience of stimuli related to reward, aversion, novelty, and surprise in associative learning (Zhu et al., 2018), and conditioned and unconditioned emotional behavior (Barson et al., 2020). Lesion studies have shown that PV affects the attribution of incentive salience to reward cues in sign tracking (Haight et al., 2015).

Adaptive goal-directed responding requires organisms to plan and execute actions based on current and remembered information about the external environment, internal state conditions, and action-outcome contingencies. Central thalamic nuclei link mPFC with multiple neural networks that support these functions. No individual nucleus has proven critical for mPFC function in general. Nevertheless, lesions of specific nuclei can account for some effects of mPFC lesions, showing the importance of thalamocortical and cortico-thalamic pathways in these functions. For instance, intralaminar and VM lesions produce delay-independent impairments comparable to mPFC, affecting RT and accuracy of egocentric DMTP and DNMTP. Lesion studies have also shown that some nuclei that are reciprocally connected with mPFC can affect functions spared by mPFC lesions. For instance, anterior thalamic lesions affect measures of allocentric DNMTP spared by mPFC lesions. This suggests that mPFC can influence functions of thalamic circuits without being a critical node in the circuit, presumably through top-down control. To elucidate functional interactions between the thalamus and cortex it is important to move beyond behavioral analyses and examine the information represented by neurons in these pathways during adaptive goal-directed behavior and how this is influenced by cortico-thalamic and thalamocortical projections.

WHAT INFORMATION IS REPRESENTED BY mPFC NEURONS DURING ADAPTIVE GOAL-DIRECTED BEHAVIOR?

Lesion studies have revealed important roles for mPFC and adjacent motor cortices in reward-guided learning and decision-making and provided evidence that different subregions of mPFC support specific aspects of reward-guided responding. Lesions of more dorsal areas affect memory for motor responses, response selection, and reward-guided choice while more ventral lesions of PL and IL affect allocentric and visual memory and supervisory attentional control (Dalley et al., 2004; Chudasama, 2011; Kesner and Churchwell, 2011). To what extent do mPFC neurons represent information related to functions affected by mPFC lesions? Are there abrupt transitions in the response properties of mPFC neurons that correspond with behavioral functions ascribed to dorsal and ventral subregions?

Single unit recordings in awake, behaving rats have revealed mPFC neurons with responses related to movement, actions, preparation to respond, anticipation and delivery of rewards, errors, working memory delay, and spatial location during different tasks (Jung et al., 1998; Pratt and Mizumori, 2001; Chang et al., 2002; Baeg et al., 2003; Hok et al., 2005; Euston and McNaughton, 2006; Cowen and McNaughton, 2007; Totah et al., 2009, 2013; de Saint Blanquat et al., 2010; Euston et al., 2012; Horst and Laubach, 2012; Hyman et al., 2012, 2013; Powell and Redish, 2014; Insel and Barnes, 2015). We developed the dynamic DNMTP (dDNMTP) task to examine neuronal responses related to each of these functions in a single task incorporating features known to be sensitive to mPFC lesions (**Figure 6**). dDNMTP is trained in open octagonal arenas with retractable levers and spouts for water reinforcement on four walls 90° apart (N, E, S, W). Trials consist of a series of four lever presses. The sample phase begins with a base lever (randomly selected for each trial) extending for the start. This retracts when pressed and the sample lever extends (90° to the left or right randomly selected). This retracts when pressed and water reinforcement is delivered from the spout immediately above. After a memory delay (randomly selected for each trial) the base lever extends again for the delay response. This retracts when pressed and the levers 90° to the left and right extend for the choice response. When the lever not extended for the sample is pressed reinforcement is delivered (∗) and the levers retracted. The dDNMTP choice is egocentrically defined like DMTP and DNMTP tasks affected by mPFC lesions. The open arena provides sufficient space to characterize the movement-related neuronal activity and visible cues to examine allocentric spatial coding. By starting trials at randomly selected locations, responses related to the spatial location can be distinguished from behavioral events which shift in location for trials beginning at different base levers.

Of 1,335 isolated neurons recorded with moveable tetrode arrays, 458 (34.3%) exhibited criterion event-related activity of which 445 (33.3%) exhibited temporal patterns of activity related

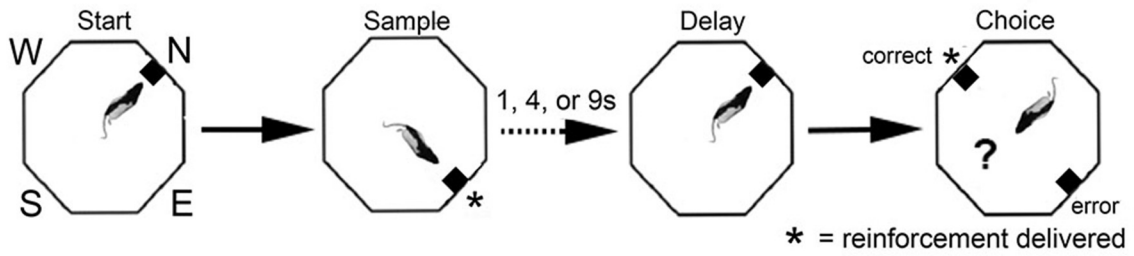

FIGURE 6 | Schematic drawing of dynamic DNMTP (dDNMTP) task. Training occurred in open octagonal chambers, equipped with levers on four walls, 90° apart, with a drinking spout above each lever to deliver reinforcement. Trials began with a randomly selected lever (N, E, S, or W) extending for the start response. The sample and correct choice levers were 90° to the left or right of the start lever, which also served as the delay lever (extending at the end of the memory delay to initiate the choice response). The length of the retention interval and the direction of the sample lever (L vs. R) were randomly selected for each trial. Reinforcement was given following the sample press and when the non-matching to sample lever was pressed during the choice phase. See text for details.

to actions or outcomes that were characterized as normalized population peri-event time histograms (PETH; **Figures 7**, **8**). These included preparation to respond, movement between levers, lever-press responses, reinforcement anticipation, reinforcement delivery, errors, and memory delays. Action-related responses (**Figure 7**) included 129 that fired during periods of movement, 58 that fired during lever press responses, and 44 that fired during preparation before the start response. Movement-related responses included neurons that fired during all periods of movement between levers (M1; $n = 97$) and others that were directionally specific and fired during movements from the base to the sample and from the base to the choice levers (M2; $n = 32$). Lever press-related responses included neurons firing during all four lever presses (LPE; $n = 28$) and others that fired only during base lever presses (BLP; $n = 30$).

Outcome related responses ($N = 191$) included reinforcement anticipation (RA; $n = 50$) that fired beginning 0.7 s before predictable times of reward and persisted for an average of 2.7 s throughout reward delivery; reinforcement excitation (RE, $n = 63$) that fired within 0.2 s after reward delivery and remained elevated for an average of 3.0 s; error responses (E; $n = 4$) that fired within 0.2 s of when the expected reward was not delivered; delay (D) responses ($n = 58$) that started firing within 0.4 s of when sample rewards were delivered and continued until the delay lever press; and post-reinforcement (PR) responses ($n = 16$) that began after reward delivery ended when rats disengaged from drinking spouts where rewards were delivered.

Spatial mapping of neuronal activity during dDNMTP revealed areas of activation consistent with event-related analyses, thus neurons firing during lever presses or reinforcement have higher activity in locations of response levers, and reward spouts and movement-related responses are associated with elevated activity on pathways between levers. Some neurons fire in all possible locations where associated events occur while others are spatially-restricted, firing in a subset of possible locations. **Figure 9** (from Onos et al., 2016) shows examples of spatially-restricted responses. Spatial heat maps and event-related rasters and PETHs are shown for three neurons with delay related responses **(A,G; B,H**; and **F,L)** along with single examples for base lever press **(C,I)**, reinforcement excitation **(D,J)**, and reinforcement anticipation **(E,J)**. Although the data were insufficient for vector or decoding analyses (Georgopoulos and Carpenter, 2015; Yin et al., 2018) these results are consistent with a population code representing information about actions and their location in allocentric space.

Histological analyses show substantial overlap between the distributions of all response types in mPFC. Statistical analyses revealed biases between dorsal and ventral mPFC, with dorsal areas having more neurons with motor-related responses, including movement between all levers (M1), lever presses (both LPE and BLP), and preparatory responses (**Figure 10**). Ventral areas had relatively high concentrations of neurons firing during movement towards rewards (M2), delay periods following reinforcement, reinforcement anticipation (RA), and post-reinforcement (PR). There was a relatively even distribution of neurons firing during reinforcement delivery (RE) consisting of about 15% of event-related responses in dorsal and ventral compartments (Francoeur and Mair, 2018). Thus, while there are differences in the broad distributions of different response types between dorsal and ventral mPFC, there was no evidence of an abrupt transition in the types of information represented in different regions of mPFC.

Each of the response types observed in rodent mPFC during dDNMTP represents task-specific aspects of goal-directed behavior that are consistent with mPFC functions identified by behavioral analyses of lesion effects. PFC relies on working memory to temporarily maintain information not available to the senses to support adaptive goal-directed responding. This is thought to be represented by persistent neuronal firing during delay intervals (Fuster and Alexander, 1971; Fuster, 2001; Goldman-Rakic, 2005) although evidence has been presented that working memory may also be implemented by sequential neuronal activation (Rajan et al., 2016). Working memory for cognitive information is associated with delay-related activity in primate dlPFC (Fuster and Alexander, 1971; Fuster, 2001; Goldman-Rakic, 2005). Enel et al. (2020) have recently presented evidence that delay-related activity in monkey anterior cingulate cortex, the likely homolog of rodent mPFC (Preuss, 1995; Vogt et al., 2013; Schaeffer et al., 2020), represents information about reward value. This is consistent with the

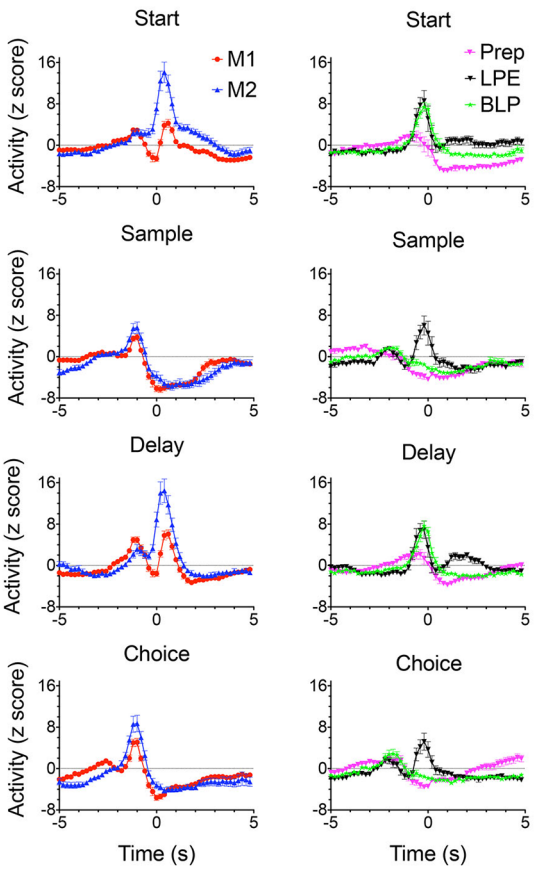

FIGURE 7 | Normalized population PETHs based on all examples observed of action-related responses. Movement 1 (M1) fired during movements toward each lever in the sequence (*N* = 97). Movement 2 (M2) fired during movements toward the sample and choice levers and were directionally specific (*N* = 32). Lever press excitation (LPE) fired during each of the 4 lever presses in the sequence (*N* = 28). Base lever press (BLP) fired during start and delay lever presses (*N* = 30). Preparatory (Prep) exhibited activity that ramped up to a peak just before the start and (to a lesser extent) the delayed responses (*N* = 44). Activity is aligned with each of the lever presses and plotted for 5 s before until 5 s after the aligned event. Error bars represent the standard error of the mean. Data are replotted from Francoeur and Mair (2018).

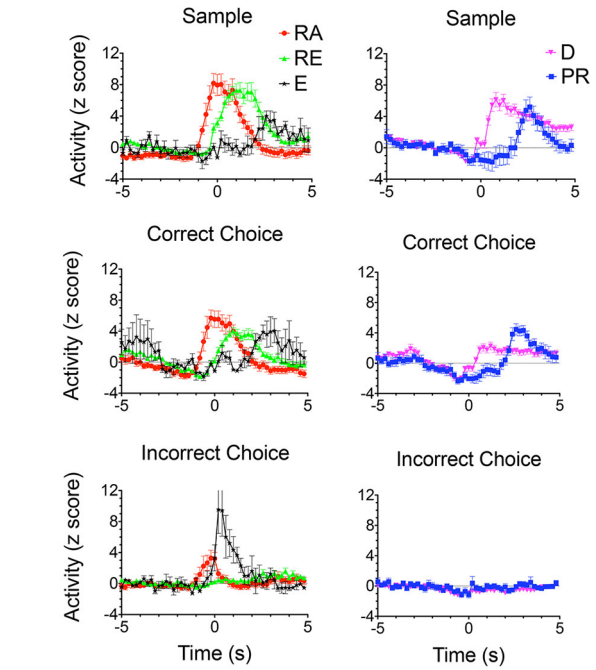

FIGURE 8 | Normalized population PETHs based on all examples observed of outcome-related responses. Each of these responses differentiated reinforced sample and correct choice responses from unreinforced incorrect choices. Reinforcement anticipation (RA) responses began 0.6–0.8 s before sample and choice responses and lasted until 1.6 s after reinforcement began or 0.2 s after errors when reinforcement was not delivered (*N* = 50). Reinforcement excitation (RE) began when reinforcement was delivered and lasted an average of 2.7 s (*N* = 63). Error (E) responses lasted for an average of 1.6 s after incorrect responses when expected reinforcement was not delivered (*N* = 4). Delay-related responses exhibited increased activity lasting across the memory delay, on average from 0.4 to 5.0 s after sample reinforcement and 0.2–1.6 s following correct choice reinforcement (*N* = 58). Some delay-related had spatially-restricted firing patterns (**Figures 9A,B,F**) and thus potentially carried information about the location of sample reinforcement across the delay interval sufficient to support a correct DNMTP choice. Post-reinforcement responses lasted on average from 2.3 to 3.6 s after reinforcement began, a time when rats tended to disengage after consuming reinforcement from the drinking spout (*N* = 16). Activity is aligned with each of the lever presses and plotted for 5 s before and after the aligned event. Error bars represent the standard error of the mean. Data are replotted from Francoeur and Mair (2018).

finding of delay period activity related to reinforcement delivery in mPFC during the dDNMTP task (**Figure 8**). At least three other response types represent information not immediately available to the senses presumably held in working memory. These include preparatory responses before the start response, reinforcement anticipation before sample and choice responses, and post-reinforcement responses.

The preponderance of neurons with responses related to actions and outcomes is consistent with evidence implicating mPFC in action-outcome contingency: clearly, mPFC neurons represent information required for this function. Similarly, the concentration of neurons with preparatory responses in dorsal mPFC for dDNMTP (**Figure 7**) and other tasks (Jung et al., 1998; Chang et al., 2002; Totah et al., 2009, 2013) is in keeping with evidence that lesions here selectively affect the initiation of learned action sequences (Bailey and Mair, 2007). The importance of mPFC for organizing temporal sequences of behavior is supported by normalized population PETHs (**Figures 7**, **8**) that reveal a cascade of tightly coupled neuronal responses that effectively tile the temporal interval between initial preparation to when rats disengage from reinforcement following choice responses. Finally, recording studies have consistently shown large populations of neurons tuned to respond to task-relevant information. Here 445/1,335 isolated neurons exhibited one of ten discrete response types related specifically to the arbitrary actions and outcomes of dDNMTP (**Figures 7**, **8**). Similar numbers are reported for the proportion of mPFC neurons exhibiting task-specific event-related activity for different behavioral tasks (Jung et al., 1998; Pratt and Mizumori,

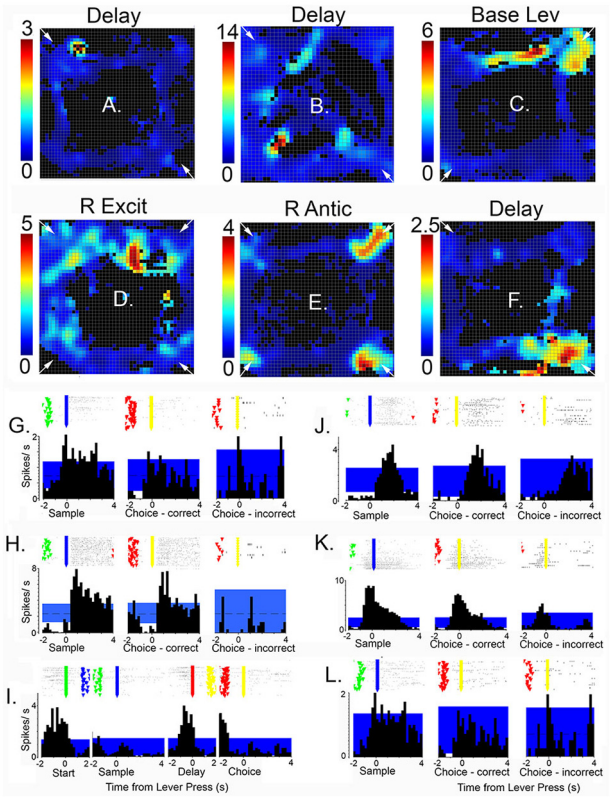

FIGURE 9 | Heat maps, raster plots, and peri event time histograms (PETHs) of neurons exhibiting spatially-restricted event-related responses. Results are shown for six neurons, three with delay-related responses **(A,G,B,H,F,L)**, along with examples of base lever press **(C,I)**, reinforcement excitation **(D,J)**, and reinforcement anticipation **(E,K)**. Heat maps are oriented with levers/drinking spouts in each corner. Calibration bars to the left indicate activity in spikes/s. Rasters show activity in trial 1 at the bottom and trial 60 at the top with event markers for lever presses (green, blue, red, and yellow for the start, sample, delay, and choice lever presses, respectively). Time scales and aligned events are matched for PETHs and overlying raster plots. The blue band marks the 99% confidence interval for PETHs. This figure is reproduced from Onos et al. (2016).

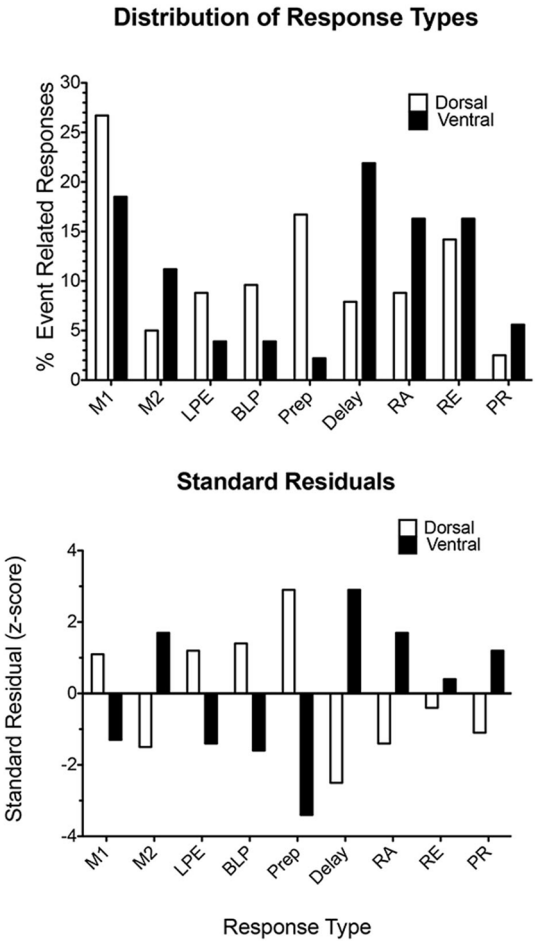

FIGURE 10 | Distribution of response types observed in dorsal and ventral areas of mPFC. The upper plot compares the percent of responses in each compartment exhibiting each of the most common response types observed during dDNMTP. The lower plot shows standard residuals indicating the contributions of each response type to the significant chi-square comparing the distribution of different response types in dorsal and ventral mPFC. Abbreviations are the same as for **Figure 11**. Figure is reproduced from Francoeur and Mair (2018).

2001; Chang et al., 2002; Baeg et al., 2003; Hok et al., 2005; Euston and McNaughton, 2006; Cowen and McNaughton, 2007; Totah et al., 2009, 2013; de Saint Blanquat et al., 2010; Euston et al., 2012; Horst and Laubach, 2012; Hyman et al., 2012, 2013; Powell and Redish, 2014; Insel and Barnes, 2015). These tuning properties of mPFC neurons seem consistent with evidence that mPFC lesions affect the ability of rats to detect and discriminate information relevant to adaptive action selection (Birrell and Brown, 2000; Dalley et al., 2004; Chudasama, 2011; Fisher et al., 2020; Bubb et al., 2021).

Electrophysiological analyses of neuronal activity in awake, behaving animals support the homology of rodent mPFC with primate anterior cingulate and premotor cortices. Premotor neurons in monkeys have been shown to encode movement-related information in extrinsic coordinates related to actions rather than muscle-like activity (Kakei et al., 2001, 2003), with imprecise coding of directional or spatial information in single neurons that presumably rely on population coding to achieve precision (Georgopoulos and Carpenter, 2015; Yin et al., 2018). Motor responses are preceded by preparatory activity related to motor planning (Shenoy et al., 2013; Murakami and Mainen, 2015). Other reports have described neuronal responses that precede expected reinforcement or mark the delivery or absence of expected reinforcement in monkey motor, premotor, and anterior cingulate cortices (Roesch and Olson, 2003; Amiez et al., 2006; Matsumoto et al., 2007; Marsh et al., 2015) as well as human medial PFC (Domenech et al., 2020). Recently, Enel et al. (2020) reported that delay-related activity in monkey anterior cingulate represents information about the expected value of action outcomes. This homology is also consistent with recent results from resting-state fMRI analyses that rodent mPFC has stronger connections with motor areas of cortex than the more broadly distributed

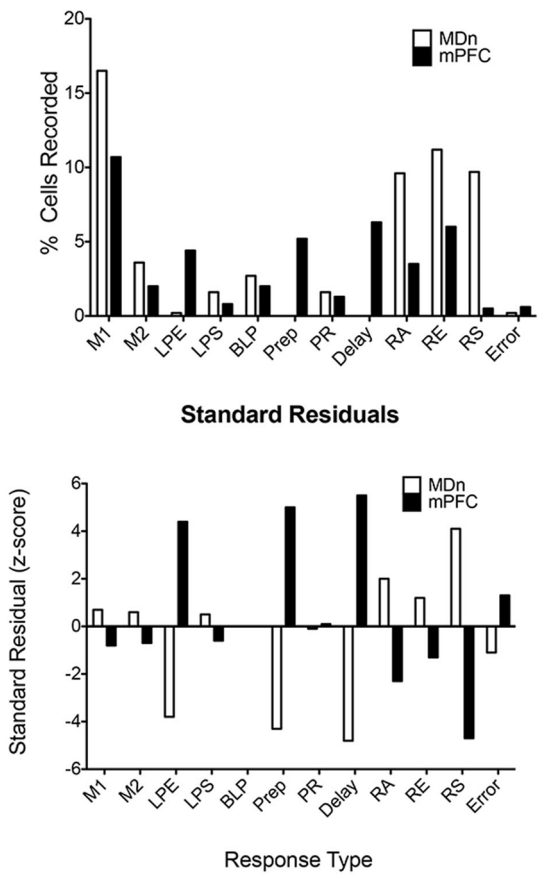

FIGURE 11 | Distribution of response types observed in the mediodorsal thalamic nucleus (MDn) and mPFC during the dDNMTP task. Standard residuals indicate the contributions of each response type to the significant chi-square comparing the distribution of different response types in MDn and mPFC. Results are shown for movement 1 (M1) and 2 (M2), lever press excitation (LPE) and suppression (LPS), base lever press (BLP), preparation (Prep), post-reinforcement (PR), error (E), and reinforcement anticipation (RA), excitation (RE), and suppression (RS). The figure is reproduced from Miller et al. (2017).

connections of primate mPFC: an organization in the rat more closely related to premotor than dlPFC areas of primates (Schaeffer et al., 2020).

HOW DO CENTRAL THALAMIC NUCLEI INFLUENCE EVENT-RELATED RESPONSES OF mPFC NEURONS?

Cortical projections excite the thalamus through driver and modulatory projections from layers 5 and 6 of mPFC. Thalamic projections activate excitatory cortico-cortical neurons and inhibitory interneurons to enhance cortical connectivity and thus regulate the activity of mPFC neurons (Cruikshank et al., 2012; Rovó et al., 2012; Bolkan et al., 2017; Schmitt et al., 2017; Collins et al., 2018; Huo et al., 2020; Lee et al., 2020). To what extent do central thalamic neurons exhibit patterns of behavioral event-related activity comparable to mPFC? How does the activity of central thalamic nuclei affect action- and outcome-related responses of mPFC neurons?

Early studies revealed similar patterns of elevated firing during memory delays for neurons in MD and dlPFC in monkeys performing delayed response tasks: activity hypothesized to represent information held on-line in working memory (Fuster and Alexander, 1971; Tanibuchi and Goldman-Rakic, 2003; Watanabe and Funahashi, 2004a,b). Delay-related activity in primate MD differs from dlPFC in representing information about motor responses rather than sensory cues. Population vector analyses indicate that MD responses shift from sensory- to motor-related responses during the delay interval, suggesting a role for MD in constructing prospective memory information in dlPFC (Watanabe and Funahashi, 2012). Neurons in adjacent areas of oculomotor thalamus, including the rostral intralaminar nuclei, exhibit visual- and motor saccade-related responses during memory-guided saccade or anti-saccade tasks that resemble responses in reciprocally-connected areas of frontal eye fields in several important ways (Wyder et al., 2003; Tanibuchi and Goldman-Rakic, 2005; Tanaka and Kunimatsu, 2011). Neurons in the oculomotor thalamus differ from frontal eye fields in exhibiting responses more strongly related to movement information and in their sensitivity to differences in cognitive or behavioral demands (Costello et al., 2016). Studies of primate MD and oculomotor thalamus have focused primarily on sensory- and motor-related responses observed in dlPFC and frontal eye fields and not on reward-related responses observed in reciprocally-connected areas of mPFC (Amiez et al., 2006; Matsumoto et al., 2007; Enel et al., 2020).

The limited evidence available for the rat, suggests that MD neurons represent task-relevant sensory, motor, and reinforcement information (Oyoshi et al., 1996; Han et al., 2013; Courtiol and Wilson, 2016). Miller et al. (2017) compared neuronal responses in MD directly with earlier results for mPFC for rats performing the dDNMTP task. Of 1179 isolated neurons in nine rats, 254 (22%) exhibited criterion event-related responses, 237 (20.1%) with temporal patterns that matched response types in mPFC (**Figures 7**, **8**). The percentage of corresponding responses is consistent with the strong excitatory projections of mPFC to MD. There were disparities in the relative number of different response types (**Figure 11**): MD had more responses related to movement (45% vs. 29% for mPFC) and reinforcement (51% vs. 27%), relatively few related to lever press actions (2.1% vs. 14.9%), and no responses spanning the memory delay (vs. 12.7% for PFC) or during preparation before the start response (vs. 9.6% for mPFC). The lack of preparatory activity in MD may reflect the role of VM as a thalamic hub for circuits supporting motor preparation (Guo et al., 2017). Choice in dDNMTP is defined by movements towards levers (**Figure 6**). Choice responses in dDNMTP are associated with increased frequency of movement-related responses and decreased frequency of lever press responses (Francoeur and Mair, 2020). Thus, the preponderance of MD responses related to movement and reward in dDNMTP is

indicative of a role in the reward-guided choice. These results are consistent with evidence from studies of monkeys that MD contains numerous neurons that represent information about forthcoming movements during choice responses in ocular delayed response tasks (Watanabe and Funahashi, 2012). The large proportion of MD neurons with reward-related responses during dDNMTP is in keeping with the prominence of reward-related responses in mPFC (**Figures 8**, **9**) and convergent inputs to MD from reward-related areas in the orbitofrontal cortex, ventral pallidum, and amygdala. The lack of delay-related responses in MD is surprising given the prominence of these responses in primate MD during delayed response tasks. This may reflect distinct properties of primate dlPFC (Watanabe and Funahashi, 2012), that lack a homolog in the rodent brain.

Analyses of normalized population histograms reveal close correspondence in temporal patterns of activity in MD and mPFC. **Figure 12** shows normalized PETHs for the two response types observed most frequently in both MD and mPFC during dDNMTP: movement between all lever presses (M1) and reinforcement excitation (RE). The close timing of these responses seems consistent with the strong excitatory projections from mPFC to MD and the reciprocal thalamocortical projections from MD to mPFC. Reinforcement suppression responses stand out as the one conspicuous MD response type that does not have a corresponding population in mPFC (**Figure 11**). Ventral pallidum (VP) contains neurons that fire in response to rewards and their predictive stimuli (Ahrens et al., 2016; Ottenheimer et al., 2018; Richard et al., 2018) and provides a robust inhibitory projection to MD that could potentially contribute to these responses (Root et al., 2015). We have recently recorded neuronal activity of VP neurons in rats performing the dDNMTP task and found that 117/177 (68%) of neurons with criterion event-related responses exhibit elevated firing when the reward is delivered, consistent with the timing of reinforcement suppression responses in MD (Krell, 2020).

Francoeur et al. (2019) examined the effects of central thalamic inactivation on mPFC by injecting muscimol at sites (affecting MD and IL) and doses previously found to produce delay independent impairment for DMTP (**Figure 4D**; Mair and Hembrook, 2008) and sensory-guided choice for VSRT (Newman and Mair, 2007) when applied bilaterally. To avoid disrupting behavior, which is necessary to characterize dDNMTP event-related responses, we inhibited the central thalamus unilaterally and recorded the activity of mPFC neurons in the ipsilateral mPFC. The effects of thalamic inhibition were examined by comparing the activity of single neurons across three sessions, 1 day apart: baseline (no injection), thalamic inhibition (unilateral muscimol injection), and recovery (no injection). Central thalamic inhibition increased the average firing rate for some mPFC neurons and reduced it for others while broadly suppressing event-related responses for actions and outcomes. **Figure 13** (from Francoeur et al., 2019) shows results for an mPFC neuron with a reinforcement anticipation response that exhibited increased activity with thalamic inhibition. **Figures 13A–C** show waveforms recorded at each microwire electrode for all action potentials in each 60 m recording session, with the 3D cluster plots, and inter-spike interval (ISI) histograms recorded. These confirm the identity of the neuron recorded across the 3 days and show the decrease in ISI as activity increased during day 2 inactivation for this neuron. Panels D to L in **Figure 13** show raster plots and normalized PETHs on day 1 **(D,G,J)**, day 2 **(E,H,K)**, and day 3 **(F,I,L)** aligned with reinforced sample **(D,E,F)** and correct choice **(G,H,I)** and unreinforced incorrect choice **(J,K,L)**. Event-related responses observed on day 1 largely disappeared with thalamic inhibition on day 2 and recovered substantially on day 3. Averaged across all neurons studied, day 2 thalamic inhibition reduced normalized activity during critical response windows to 46.9% of the day 1 response and this recovered to an average of 79.5% during day 3 recovery. Mixed model ANOVAs revealed significant effects of inactivation on day 2 and significant recovery on day 3 based on normalized activity during critical response windows. These effects did not interact with response type, the effect of thalamic inhibition on average firing rate (increased, decreased, or unchanged), location of neuron in dorsal vs. ventral mPFC, or muscimol dose. These results show that dDNMTP event-related responses are reduced nonspecifically in mPFC with behaviorally-significant inactivation of MD and IL.

Optogenetic studies have provided evidence that MD amplifies and sustains behaviorally-relevant information in PFC (Bolkan et al., 2017; Schmitt et al., 2017; Parnaudeau et al., 2018). These results suggest that MD may help tune mPFC neurons to respond to task-relevant information during adaptive goal-directed behavior. To test this possibility, we compared the effects of unilateral MD lesions made before and after initial dDNMTP training. Neuronal responses were then compared in ipsilateral (experimental) and contralateral (control) mPFC (Francoeur, 2019). The unilateral lesions did not have significant effects on behavioral performance. MD lesions made before training were associated with decreased activity of all mPFC neurons in the lesioned hemisphere and a shift in the predicted direction for event-related responses: namely more lever-press-related and fewer movement-related responses in the lesioned hemisphere. MD lesions made after initial training affected the activity of neurons with criterion event-related responses, but not neurons with uncorrelated activity. Lesions made after initial training did not affect the distribution of response types in mPFC in the lesioned vs. unlesioned hemisphere.

The available results suggest that the central thalamus has important short-term and long-term effects on mPFC function during adaptive goal-directed behavior. In the short term, MD amplifies and sustains neuronal responses in mPFC representing task-relevant information (Bolkan et al., 2017; Schmitt et al., 2017; Parnaudeau et al., 2018). Consistent with this, MD lesions produce delay-dependent impairment of response-related DMTP and DNMTP and other tasks that require flexible responses when action-outcome contingencies change. MD lesions made after initial dDNMTP training affect the activity of mPFC neurons with criterion event-related

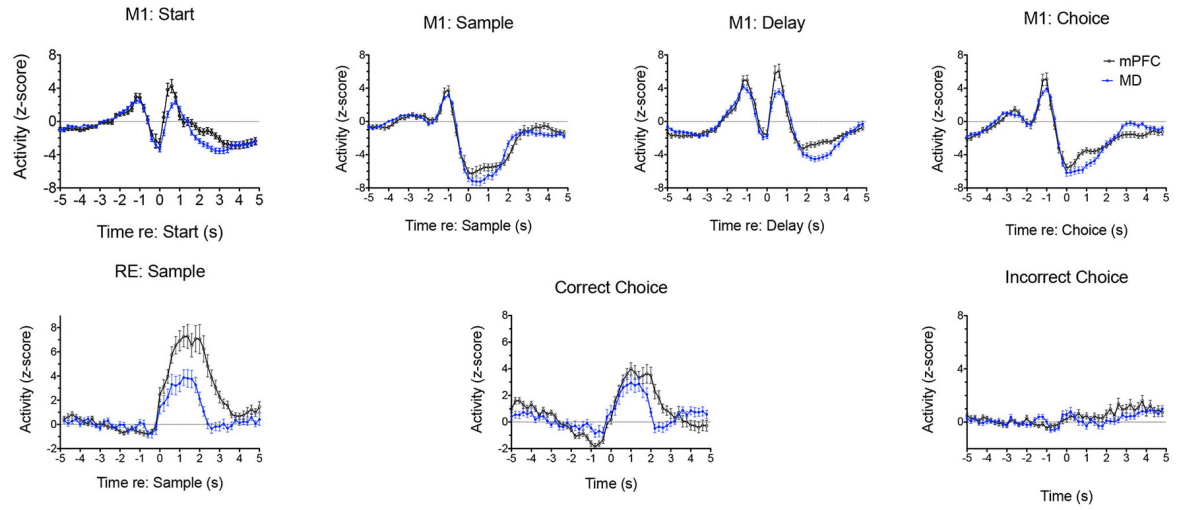

FIGURE 12 | Normalized population PETHs comparing the two most common responses in mediodorsal thalamus (MD) and medial prefrontal cortex (mPFC). Movement 1 (M1) responses aligned with the start, sample, delay, and choice lever presses are based on all samples observed in MD (n = 91) and mPFC (n = 97). Reinforcement excitation (RE) responses aligned with reinforced sample and correct choice and unreinforced incorrect choice responses are based on all examples observed in MD (n = 47) and mPFC (n = 63). Error bars represent the standard error of the mean. Data are replotted from Miller et al. (2017).

responses, an effect that could potentially contribute to these behavioral deficits. MD lesions made before initial dDNMTP are associated with fewer movement-related and more lever press-related responses in mPFC of the lesioned than the unlesioned hemisphere. This provides evidence of a longer-term impact of MD on mPFC function and suggests that one function of MD is to tune mPFC neurons to respond to task-specific information important for adaptive responding. This finding seems consistent with evidence that MD lesions made before (but not after) initial training affects the sensitivity of rats to outcome-devaluation, a hallmark of goal-directed action (Balleine, 2019).

Adjacent IL nuclei have more widespread projections than MD, targeting layer 1 of mPFC and related areas of the cerebral cortex and providing the main thalamic input to the striatum. Lesions or inactivation of the IL nuclei, which inevitably affect juxtaposed areas of MD, produce delay independent impairments of DNMTP and DMPT, increase RT for sensory-guided responding in the VSRT task, and can interfere with habitual, rule-based learning. Inactivation of IL and MD has variable effects on mPFC activity, increasing firing of some neurons and reducing firing of others, and has broad effects on the expression of diverse dDNMTP-related responses in mPFC. These results are consistent with the hypothesis that these nuclei regulate information transmission in cortico-cortical and cortico-basal ganglia circuits that give rise to goal-directed behavior (Saalmann, 2014; Perrin and Venance, 2019).

CONCLUSIONS

1. Medial prefrontal cortex (mPFC) supports multiple functions required for adaptive goal-directed behavior: working memory, flexible trial-by-trial response selection, attending to task-relevant information, encoding relationships between actions and their consequences, and organizing and executing action sequences. mPFC lesions produce delay-independent impairments of egocentric (response-related) DMTP and DNMTP tasks that affect RT and accuracy of responding. They spare comparable allocentric tasks.
2. During the dDNMTP task, mPFC functions are served by discrete populations of neurons with responses related to preparation to respond, movements between levers, lever press responses, reinforcement anticipation, delivery of or lack of expected reinforcement, and memory delay following reinforcement. Population analyses show that these different response types effectively tile the temporal interval from when dDNMTP trials are initiated until they end.
3. No individual thalamic nucleus can fully account for the broad effects of mPFC lesions on adaptive goal-directed behavior. Lesions of specific nuclei have distinct effects on behavior consistent with their anatomical connections.

   (a) MD has very limited effects on egocentric DMTP or DNMTP tasks that depend on mPFC. While some reports find no significant effect of MD lesions on these tasks, others have described delay-dependent deficits that spare RT or impaired acquisition that disappears with training. The reports of delay-dependent deficits are consistent with evidence that MD sustains and amplifies neuronal responses that represent behaviorally-relevant information in mPFC. Impairments in the acquisition are consistent with evidence that MD interacts with PFC to detect and encode action-outcome contingencies that are the basis of goal-directed learning.

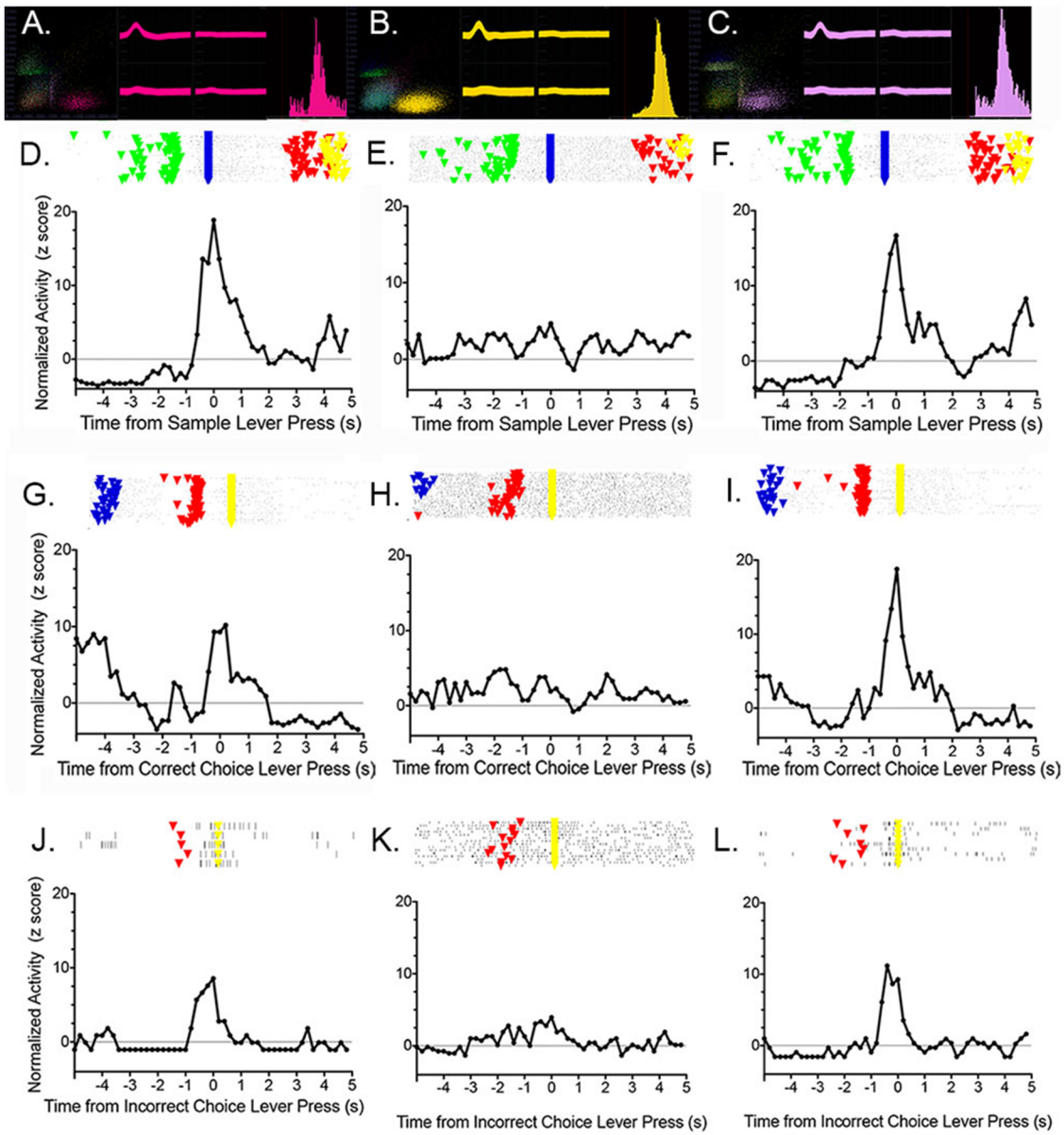

FIGURE 13 | Effects of unilateral thalamic inactivation by 1.0 nmol muscimol near the junction of the paracentral and mediodorsal nuclei on a reinforcement anticipation (RA) response in ipsilateral mPFC. Results are shown for pre-inactivation day 1 **(A,D,G,J)**, inactivation day 2 **(B,E,H,K)**, and post-inactivation day 3 **(C,F,I,L)**. 3D cluster plots, waveforms at each tetrode wire, and the interspike interval histograms **(A,B,C)** confirm the identity of the neuron held across 3 days and show the increase in activity observed during thalamic inactivation. Rasters and normalized PETHs aligned with sample **(D,E,F)**, correct choice **(G,H,I)**, and incorrect choice **(J,K,L)** reveal typical RA responses on days 1 and 3 that disappear during day 2 thalamic inactivation. Figure reproduced from Francoeur et al. (2019).

(b) Rostral intralaminar and VM nuclei affect speed and accuracy of responding based on learned conditional rules, effects consistent with their prominent connections with striatum and motor cortices, respectively. Like mPFC lesions rostral intralaminar and VM lesions produce delay-independent impairments affecting response speed and accuracy for egocentric DMTP and DNMTP tasks while sparing allocentric DNMTP.

(c) Anterior thalamic and ventral midline Re and Rh nuclei affect allocentric spatial function, consistent with their prominent connections with the hippocampal system. Anterior thalamic lesions spare egocentric DMTP and DNMTP tasks affected by mPFC lesions. ReRh lesions affect tasks that depend on both mPFC and hippocampus.

(d) Dorsal midline nuclei integrate inputs from visceral-, arousal-, and emotion-related areas of the brain and

influence cortical and subcortical circuits related to mPFC function. They are important for behavioral-state control of adaptive responding and response to salient stimuli in associative learning. Dorsal midline lesions spare DMTP and DNMTP tasks that depend on mPFC.

4. During the dDNMTP task, most MD neurons with criterion event-related responses (237/254) exhibit temporal patterns of firing that closely match response types in mPFC. A preponderance of these are movement and reinforcement-related responses critical for dDNMTP choice. MD lesions made before initial training selectively decrease the number of movement-related responses in mPFC.
5. Drug inactivation of MD and adjacent intralaminar nuclei broadly suppresses the expression of event-related activity in mPFC during the dDNMTP task. Optogenetic studies suggest that MD amplifies and sustains behaviorally-relevant information in the PFC, a process that might help tune mPFC neurons to respond to task-relevant information during goal-directed behavior or suppress the expression of event-related activity during more prolonged drug inactivation.

AUTHOR CONTRIBUTIONS

RM was primarily responsible for writing the article. MF and BG contributed to writing and discussion of the manuscript. All authors contributed to the article and approved the submitted version.

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Rostral Intralaminar Thalamus Engagement in Cognition and Behavior

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The thalamic rostral intralaminar nuclei (rILN) are a contiguous band of neurons that include the central medial, paracentral, and central lateral nuclei. The rILN differ from both thalamic relay nuclei, such as the lateral geniculate nucleus, and caudal intralaminar nuclei, such as the parafascicular nucleus, in afferent and efferent connectivity as well as physiological and synaptic properties. rILN activity is associated with a range of neural functions and behaviors, including arousal, pain, executive function, and action control. Here, we review this evidence supporting a role for the rILN in integrating arousal, executive and motor feedback information. In light of rILN projections out to the striatum, amygdala, and sensory as well as executive cortices, we propose that such a function enables the rILN to modulate cognitive and motor resources to meet task-dependent behavioral engagement demands.

Keywords: thalamostriatal, basal ganglia, consciousness, cognitive control, attention, thalamocortical, memory

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INTRODUCTION

The mammalian thalamus can be parcellated into ∼60 nuclei defined by cytoarchitecture and connectivity properties (Jones, 2007). Examination of afferent and efferent connections reveals several organizational themes among the nuclei. The first, and perhaps most studied, grouping is the first-order sensory relay nuclei. These regions receive inputs from peripheral sensory systems and faithfully transmit information to the corresponding primary sensory cortical region through direct glutamatergic synapses. The lateral geniculate nucleus of the thalamus, for example, relays visual information from the retina to the primary visual cortex.

A second class of thalamic nuclei are referred to as higher-order association nuclei. These relay nuclei are noted for being innervated by a primary sensory cortical area and, in turn, project to the corresponding secondary sensory cortical region. For example, a primary target of the visual cortex is the thalamic pulvinar nucleus which, in turn, serially innervates higher order visual cortical areas to facilitate spatial attention through synchronization of visual cortical areas (Saalmann et al., 2012). Other proposals for the function of such cortico-thalamo-cortical (or trans-thalamic) pathways suggest roles in entraining otherwise isolated cortical regions, providing efference copies to subcortical systems, or serving as a coincidence detector for parallel cortico-cortical signaling (Sherman, 2016). Another example of higher-order association nuclei in the thalamus is the reticular nucleus. Enveloping the lateral boundary of the thalamus, this GABAergic cellular group receives axon collaterals from passing thalamo-cortical and cortico-thalamic projections and innervates nearly all thalamic nuclei. These circuits enable feedforward and feedback inhibitory circuits to modulate thalamocortical signaling, as well as exert lateral inhibition across otherwise disconnected thalamic nuclei with limited inhibitory microcircuitry (Crabtree, 2018).

The final group of thalamic nuclei are located on the midline or nestled within the internal medullary lamina. This grouping is referred to as the "non-specific" thalamus for the long-held, but since, challenged view that these nuclei globally activate the cortex (Groenewegen and Berendse, 1994). Along the midline are the paraventricular, intermediodorsal, paratenial, reuniens, rhomboid, and in primates, subfascicular nuclei (Jones, 2007). More caudally, the medullary lamina splits and contains the parafascicular nucleus (Pf), and more laterally, the centré median nucleus (referred to here as CeM). The boundary distinguishing these two nuclei is undetectable in rodents and other smaller mammals; thus, the posterior intralaminar nuclei are referred to solely as the Pf in these species with the consideration that the lateral component of this nucleus is homologous to the CeM (Jones, 2007). Located anteriorly within the lamina are the rostral intralaminar nuclei (rILN): the central lateral (CL), paracentral (PC), and central medial (CM) nuclei. In the rodent, these three nuclei are parceled from a continuous band of neurons spanning from the midline, curving around the ventrolateral boundary of the mediodorsal nucleus and terminating ventral to the hippocampal dentate gyrus and lateral to the lateral habenula (**Figure 1**) (Franklin and Paxinos, 2008). Delineating the boundaries of the PC is difficult, which is usually defined by the more flattened appearance of cells compared to the adjacent medially-located CM and dorsally-positioned CL. This general structure of the rILN is preserved in the cat but disrupted and discontinuous in the primate (Jones, 2007).

In the following sections we review rILN anatomical connectivity, examine how these connections confer roles for these nuclei within specific functional domains, and assess potential involvement of the rILN in multi-system disease states. Finally, we present a conceptual framework describing how these thalamic nuclei contribute to a wide array of behavioral functions. Our review primarily draws from studies conducted in rodents. However, we note findings derived from other species where appropriate.

rILN ANATOMICAL CONNECTIVITY

Like the relay thalamic nuclei, the intralaminar nuclei are primarily composed of glutamatergic projection neurons. A notable difference from thalamic relay nuclei, however, is the breadth of afferents that arise from sensory, motor, and limbic modalities to innervate the rILN (**Figure 2**). The rILN (and Pf) are predominately innervated by subcortical areas. Major excitatory afferents to the rILN include the superior colliculus, hypothalamic supramammillary nucleus, reticular formation, parabrachial nucleus, and deep cerebellar nuclei, as well as several first- and higher- order thalamic nuclei (Krout and Loewy, 2000; Krout et al., 2001, 2002). Whereas both the rILN and the Pf receive input from the cortex, the rILN are notably innervated by a wider range of cortical regions including cingulate, retrosplenial, parietal, insula, prefrontal, somatosensory, supplementary motor, auditory, and visual cortices (Van der Werf et al., 2002; Prasad et al., 2020). In contrast, only the frontal and parietal cortices innervate the Pf (Cornwall and Phillipson, 1988).

Inhibitory inputs to the rILN arise from the substantia nigra pars reticulata, habenula, zona incerta, thalamic reticular nucleus, and the external segment of the globus pallidus (Carter and Fibiger, 1978; Van der Werf et al., 2002; Rizzi and Tan, 2019). The rILN are also innervated by a range of modulatory inputs including the periaqueductal gray, cholinergic pontine and tegmental nuclei, noradrenergic locus coeruleus, and serotonergic raphe nuclei (Van der Werf et al., 2002; Huerta-Ocampo et al., 2020). Accordingly, the rILN are enriched in metabotropic receptors as compared to the thalamic relay neurons (Phillips et al., 2019). Together, this compilation of anatomically, neurochemically, and functionally diverse efferents endows the rILN as distinct thalamic integrators of inputs from many cortical and subcortical cerebral centers.

Examination of rILN efferents reveals a pattern of projections distinct from that of both thalamocortical relay neurons and the Pf. Whereas, the thalamic relay nuclei generally target cortical regions related to a specific sensory or functional modality and the Pf weakly projects to a restricted number of cortical areas, the rILN defy cortical functional boundaries and innervate widely. Neural circuit-specific investigation reveals subtle differences in innervation patterns between the rILN nuclei that are most apparent when comparing the CL and CM (**Figure 2**). Collectively, these nuclei send excitatory projections to cingulate, agranular insula, lateral orbital, parietal, retrosplenial, entorhinal, frontal eye field, gustatory, visceral, auditory, visual, motor, and somatosensory cortices (Yanagihara et al., 1987; Berendse and Groenewegen, 1991; Van der Werf et al., 2002).

The intralaminar nuclei also differ from the thalamic relay nuclei in their innervation of subcortical regions. In particular, these nuclei densely innervate the striatum. All three nuclei of the rILN project to the entirety of the striatal complex (Van der Werf et al., 2002). These projections are loosely topographically organized with the laterally-positioned CL most densely innervating the dorsolateral striatum and the medially-located CM targeting the dorsomedial striatum. Although the nucleus accumbens receives denser input from adjacent midline paraventricular and intermediodorsal nuclei, both the CM and PC innervate this ventral region as well (Van der Werf et al., 2002). The caudally-lying Pf, in comparison, innervates the striatum more densely (Mandelbaum et al., 2019). Whereas projections generally span the majority of the striatum, the Pf more strongly innervates the dorsolateral striatum and nucleus accumbens (Sadikot et al., 1992; Van der Werf et al., 2002).

How does rILN anatomical connectivity compare to that of the other non-specific thalamic nuclei? The rhomboid and reuniens nuclei are notably reciprocally connected with the medial prefrontal cortex and hippocampus, suggesting roles in higher-order cognitive processes (Cassel et al., 2013). The paraventricular, paratenial, and intermediodorsal nuclei are innervated by a range of brainstem structures and primarily project to the ventral striatum, medial prefrontal cortex, and amygdala; connectivity that is proposed to contribute to viscerosensory awareness and motivation (Van der Werf et al., 2002; Millan et al., 2017). In comparison, the rILN appear to be

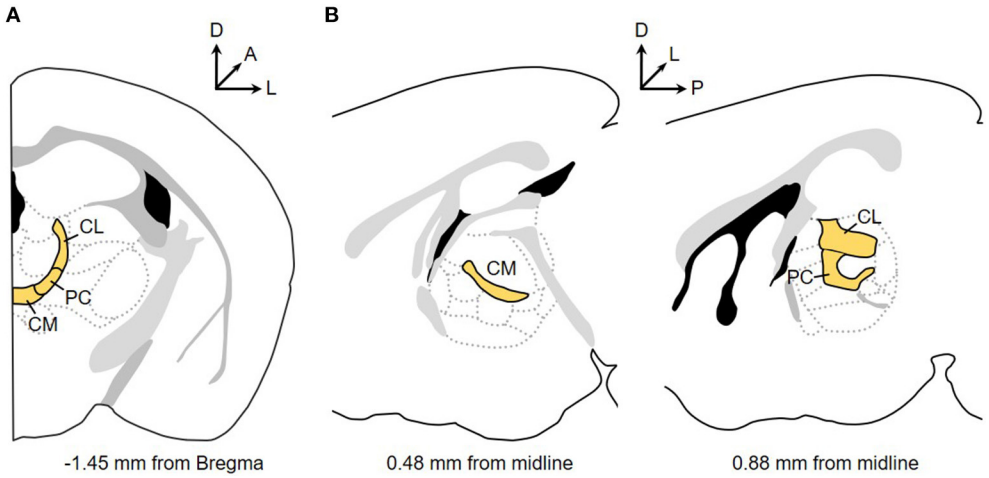

FIGURE 1 | The mouse rostral intralaminar nuclei (rILN). Coronal **(A)** and sagittal **(B)** perspectives of the central lateral (CL), paracentral (PC), and central medial (CM) nuclei. Arrows indicate orientation of dorsal (D), lateral (L), anterior (A), and posterior (P) planes.

innervated by a wider range of cortical and brainstem regions in addition to uniquely projecting to the cingulate cortex and dorsal striatum.

rILN afferent and efferent connectivity reveal additional anatomical patterns that may inform function. First, examination of thalamocortical and thalamostriatal projections shows that the rILN innervate striatal areas that are also targeted by cortical regions that the rILN also directly innervate and/or receive cortico-thalamic projections (Hunnicutt et al., 2016). For example, CM projections to the striatum converge with prelimbic and medial orbital corticostriatal projections; CM projections also directly terminate in prelimbic and medial orbital cortices (Hunnicutt et al., 2016). These connectivity patterns may serve to synchronize or entrain thalamic and cortical components of functional systems (e.g., motor, limbic, or sensory) to guide basal ganglia output activity. Second, the rILN are innervated by the basal ganglia output nucleus, the substantia nigra pars reticulata, and are also innervated by nuclei that receive inputs from the substantia nigra pars reticulata, including the superior colliculus, pedunculopontine nucleus, and reticular formation. Through rILN innervation of the striatum, these thalamic nuclei may complete subcortical- basal ganglia re-entrant loops. Whereas cortico-striatopallidal-thalamocortical loops (Alexander et al., 1986; Aoki et al., 2019; Lee et al., 2020) are proposed to facilitate action-outcome learning (Redgrave et al., 2011), consideration for subcortical- basal ganglia loops has been largely overlooked until relatively recently (McHaffie et al., 2005). Functional validation of such loops may uniquely implicate the rILN in a range of basal ganglia -mediated behaviors.

rILN projections exhibit notable differences in cortical synaptic targets, as compared to the thalamic relay nuclei. First-order thalamic relay axons terminate in middle cortical layers whereas higher-order nuclei innervate superficial layers (Jones, 2001). In contrast, rILN projections terminate in superficial (I), middle (III), and deep (V) cortical layers (Van der Werf et al., 2002; Unzai et al., 2017). Whereas, the functional significance of this innervation pattern is unknown, this arrangement may enable robust and coordinated activation of targeted cortical columns. In agreement, high frequency rILN stimulation induces c-fos expression spanning cortical layers II though VI (Shirvalkar et al., 2006).

In the striatum, comparison of rILN and Pf afferent synaptic morphology reveals striking differences between the two thalamic projections. rILN terminals form axo-spinous synapses on striatal medium spiny neurons (MSNs) (Raju et al., 2006) that induce large facilitative AMPA receptor -mediated responses (Ellender et al., 2013). Pf axons, in contrast, synapse on MSN dendritic shafts and induce relatively weaker NMDA receptor -mediated responses characteristic of a more modulatory influence on MSN signaling (Lacey et al., 2007; Ellender et al., 2013). Moreover, rILN axons sparsely arborize in the striatum. Their long axon collaterals contact many MSNs through *en passant* boutons, whereas Pf neurons form dense clusters of terminals to focally converge on fewer neurons (Deschênes et al., 1995). Together, these properties may enable the rILN to effectively drive MSN output signaling across larger volumes of the striatum. Of note, these studies exclusively examined neurons within the CL nucleus. It remains to be determined whether the PC and CM share similar synaptic properties in their striatal terminations.

PHYSIOLOGICAL FEATURES OF THE rILN

The extensive connectivity of the rILN with brainstem, basal ganglia, and cortical regions distinguishes these nuclei from the primarily unimodal thalamic relay nuclei. Further distinguishing the rILN are unique physiological features. In awake monkeys, cats, and mice, rILN neurons exhibit tonic single-spike firing at 6–8 Hz (Glenn and Steriade, 1982; Gent et al., 2018; Redinbaugh et al., 2020). Sensory events evoke transient burst firing and the majority of rILN neurons exhibit changes in firing rate

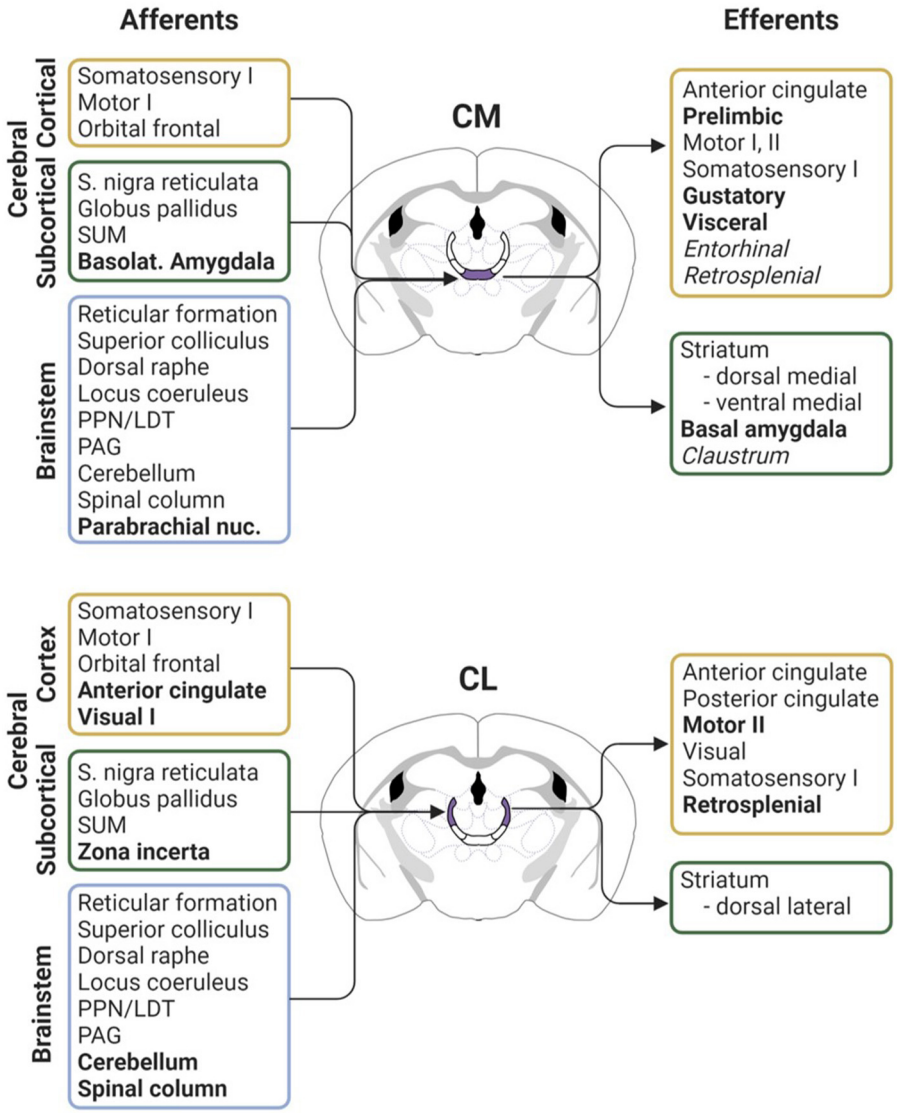

FIGURE 2 | Comparative anatomical connectivity of the rodent CM and CL intralaminar nuclei. Afferent inputs (left) and efferent outputs (right) for the CM (top; purple) and CL (bottom; purple) nuclei. Bolded text indicates notably denser or exclusive projections as compared between the two thalamic nuclei. Italicized text denotes sparse projection innervation. Figure created with BioRender.com. Connectivity derived from: Krettek and Price (1977), Wise and Jones (1977), Carter and Fibiger (1978), Beckstead (1979), Wang et al. (1999), Ichinohe et al. (2000), Krout and Loewy (2000), Barthó et al. (2002), Krout et al. (2002), Van der Werf et al. (2002), Vertes et al. (2012), Rizzi and Tan (2019), Huerta-Ocampo et al. (2020), and Prasad et al. (2020). LDT, laterodorsal tegmental nucleus; PAG, periaqueductal gray; PPN, pedunculopontine nucleus; SUM, supramammillary nucleus; I, primary cortex; II, secondary cortex.

correlating to eye position or saccadic activity (Schlag and Schlag-Rey, 1984; Schlag-Rey and Schlag, 1984; Wyder et al., 2003). In relation to oculomotor saccades, some cells exhibit pause-rebound firing with pauses in firing occurring during or following saccadic activity; other rILN neurons burst fire prior to or during saccadic activity and are typically selective for a saccade direction in cats (Schlag-Rey and Schlag, 1984). In primates, rILN neurons frequently increase firing during delay periods in sensory-cued reaction time tasks (Wyder et al., 2003; Schiff et al., 2013).

rILN firing activity is governed by sleep-wake states. During non-REM sleep or under anesthesia, tonic firing diminishes as rILN neurons predominately fire in short infrequent bursts (3–6 spikes at 300–600 Hz with inter-burst intervals of 3–10 Hz) that correspond with cortical slow wave activity at relatively hyperpolarized membrane potentials (Glenn and Steriade, 1982; Lacey et al., 2007; Redinbaugh et al., 2020). Depolarizing low-threshold calcium spikes facilitate the brief action potential bursts, which are notably less prevalent in Pf neurons (Brunton and Charpak, 1998; Lacey et al., 2007). rILN burst firing is phase-advanced to the onset of slow wave sleep up-states. Mimicking these firing bursts through optogenetic rILN activation enhances slow wave activity suggesting a causal role for the rILN in driving

cortical synchrony during sleep (Gent et al., 2018). rILN activity during REM sleep is generally similar to that of wake states in regard to both tonic and burst firing rates (Glenn and Steriade, 1982).

A distinct population of neurons was identified in the cat dorsal CL characterized by larger cell bodies and significantly faster sleep-associated firing frequencies of 800–1,000 Hz spike bursts. Moreover, this bursting activity is largely preserved in REM sleep and awake states (Steriade et al., 1993). These faster firing rates notably correlate with optimal CL stimulation frequencies to induce wakefulness in primates (Redinbaugh et al., 2020) and rats (Liu et al., 2015), suggesting that the rILN causally facilitate awareness through activation of cortical or subcortical targets.

FUNCTIONAL ATTRIBUTES OF THE rILN

Given their extensive anatomical connectivity, it is not surprising that the rILN are associated with a wide range of behavioral functions. Broadly, these nuclei are implicated in consciousness, sensory and pain processing, executive function, and action control. We review the anatomical and behavioral evidence for each of these functions below.

Consciousness and Arousal

Heavily innervated by the reticular formation, the rILN were historically considered to serve as a continuation of the ascending reticular activating system (ARAS): the series of brainstem-located nuclei responsible for regulating sleep-wake states. rILN neuronal activity shifts from tonic to burst firing in the transition from sleep to wake states (Glenn and Steriade, 1982). Correspondingly, electrical stimulation of the feline rILN induces a so-called "recruiting response" of slow wave activity that spans much of the cortex (Morison and Dempsey, 1941). Although similar responses may also be evoked through stimulation of various higher-order thalamic neurons, the rILN endure as a target in clinical applications. While rILN damage is associated with cognitive impairment and disorders of consciousness (Schiff, 2008), deep brain stimulation targeting this region demonstrates therapeutic efficacy in patients in chronic minimally conscious states (Schiff et al., 2007; Giacino et al., 2012). In examination of the mechanisms mediating consciousness, rILN activation that accompanies sleep to wake transitions increases cortical deep layer firing rates in the lateral intraparietal area and modulates synchrony between this region and the frontal eye field in primates (Redinbaugh et al., 2020). rILN activation similarly induces rapid wakefulness in sleeping mice and enhances global cortical synchrony through local activation of the cingulate cortex that propagates to posterior cortices through a dorsal thalamic relay (Gent et al., 2018). Thus, these nuclei may promote arousal through coordinated cortical activation.

Abnormal regulation of arousal by the rILN may underlie other pathological conditions. Individuals with temporal lobe epilepsy, the most common form of epilepsy, exhibit increased connectivity between the rILN and ARAS brain structures and the occipital lobe (González et al., 2019). Chemogenetic suppression of the rILN blocks seizure activity in a rodent model of epilepsy (Wicker and Forcelli, 2016) and deep brain stimulation targeting adjacent thalamic structures reduces seizure frequency in patients (Li and Cook, 2018). Together, these findings suggest that the rILN participate in seizure propagation through abnormal connectivity with cortical and arousal-regulating brain regions.

Cognition

Learning

The high connectivity of the rILN with brain structures comprising the limbic system enables these nuclei to influence cognitive processes (Yanagihara et al., 1987; Vertes et al., 2015). Assessments of rILN contributions to learning reveal conflicting results. For example, rodents with rILN lesions show intact learning ability in finding a hidden platform over multiple trials in the Morris water maze in one study (Lopez et al., 2009), but exhibited significant impairments in another (Mair et al., 1998) despite similar experimental parameters. Manipulations specifically inhibiting the rILN to striatum pathway demonstrate intact ability to learn a two-lever appetitive operant task, but pronounced impairments in reversal learning (Kato et al., 2018). Future interrogation of specific rILN projection circuits are likely to determine unique contributions to specific types of sensory and motor learning.

Memory

Matching-to-sample or position tasks assess sensory discrimination with versions that implement a delay prior to the response period to test working memory. Lesioning the rILN produces impairments on delayed spatial or olfactory discrimination tests indicating a deficit in working memory, but not sensory discrimination (Mair et al., 1998; Zhang et al., 1998). Moreover, electrical rILN stimulation improves performance when delivered during the delay or response period of the delayed matching-to-position task, further implicating the rILN in working memory and retrieval processes (Mair and Hembrook, 2008). rILN-lesioned rats successfully complete radial arm mazes in the presence of spatial cues but show significant deficits when forced to use an egocentric navigation strategy (Mair et al., 1998; Mitchell and Dalrymple-Alford, 2006). Together, these experiments demonstrate a consistent role for the rILN in working memory. This functional process is likely mediated through rILN projections to the cortex, as selective elimination of the rILN thalamostriatal pathway does not impair spatial working memory (Kato et al., 2018).

The rILN contribute to other memory processes. High frequency rILN stimulation enhances object recognition memory following a 2-hour delay between first object interaction and re-testing for recognition of that object and induces transcription of zif268, an immediate early gene upregulated during long-term potentiation, in the anterior cingulate cortex and hippocampal dentate gyrus (Shirvalkar et al., 2006). In an assessment of spatial long-term memory function, rILN-lesioned rats successfully recall the location of a hidden platform in the visual-cued Morris water maze 5 days, but not 25 days, following acquisition (Lopez

et al., 2009). Whether this deficit in remote spatial memory is due to impaired memory formation or retrieval remains unclear.

The rILN are also susceptible to pathology in cognitive disorders marked by memory impairment. Alpha-synuclein deposits form in the rILN in individuals with Parkinson's disease or Lewy Body Dementia (Brooks and Halliday, 2009). The functional consequence of this pathology is unclear, but may contribute to cognitive impairment observed in Parkinsonian patients. In a beta-amyloid model of Alzheimer's disease, rILN stimulation rescues both spatial memory deficits and dendritic regression in the prefrontal cortex and hippocampus (Tsai et al., 2020). Given that the rILN innervate brain regions mediating saccade initiation (frontal eye fields) as well as working memory and attention (prefrontal cortex and posterior parietal cortex), these thalamic nuclei may govern multiple functions supporting cognition.

Sensory-Related Attention

The involvement of the rILN in arousal naturally extends to attentional processes. Abnormal rILN connectivity with ARAS-regulating brainstem structures correlates with deficits in visuospatial attention in humans (González et al., 2019). Visual or somatosensory -cued transitions from relaxed to attention-demanding states correspond to increased (non-specific) intralaminar nuclei activity (Kinomura et al., 1996). Moreover, rILN firing during a sensory-cued reaction time task correlates to performance. Incorrect responses during this task correspond to smaller increases or less sustained shifts in rILN firing during the cue-response delay, suggesting a role for these nuclei in attentional effort (Schiff et al., 2013). Unilateral rILN lesions in cats commonly result in contralateral visual neglect (Orem et al., 1973) and bilateral lesions in rats produce deficits in spatial orientation (Jeljeli et al., 2000). Correspondingly, non-specific intralaminar nuclei stimulation in cats induces eye movement and improves perception during visual orientation (Hunsperger and Roman, 1976).

The rILN receive glutamatergic input from the intermediate and deep layers of the superior colliculus (Krout et al., 2001). This pathway provides a source for multimodal sensory information to the rILN (Stein and Meredith, 1993). Accordingly, rILN responses are not limited to visual stimuli. These nuclei also fire in response to auditory tones and touch (Grunwerg and Krauthamer, 1992; Sanford et al., 1992). Given the presence of dedicated thalamocortical relay circuits for processing specific sensory modalities, it is unlikely that the rILN directly contribute to sensory perception. Rather, these thalamic nuclei are hypothesized to facilitate attentional engagement of sensory events (Groenewegen and Berendse, 1994; Schiff et al., 2013). One function for such a role is to prepare for motor responding. Indeed, rILN firing associated with self-initiated and visually-cued eye movements commences prior to the movement (Schlag-Rey and Schlag, 1984). rILN neurons rarely encode sensory cues without also exhibiting saccade-related activity (Wyder et al., 2003), suggesting that this region may participate in the transformation of sensory signals into motor commands (Wyder et al., 2004). Alternatively, saccade-related rILN activity may serve to facilitate visuospatial awareness by priming cortical areas for processing new information that follows execution of the saccade (Purpura and Schiff, 1997).

Pain

In addition to sensory-evoked activity, rILN neurons fire in response to a range of noxious stimuli with large receptive fields (Zhang and Zhao, 2010; Deng et al., 2020). Connectivity with both brainstem and limbic structures positions this thalamic region to participate in pain processing. Several afferents are proposed to relay pain information to the rILN including the glutamatergic ventrolateral periaqueductal gray (Deng et al., 2020) and ipsilateral spinoparabrachial pathway (Deng et al., 2020). Additionally, the rILN are directly innervated by the spinal cord (Wang et al., 1999) and the trigeminal nerve (Sato et al., 2020). Chemically inhibiting the rILN alleviates behavioral responses to mechanical allodynia (Sun et al., 2020) and local activation of 5-HT1A/7 receptors reduces response to tail shock (Harte et al., 2005).

The rILN are hypothesized to mediate the emotional and motivational aspects of pain (Sewards and Sewards, 2002) and may potentially do so through reciprocal connectivity with the basolateral and central amygdala (Krettek and Price, 1977; Vertes et al., 2012; Deng et al., 2020; Sun et al., 2020). Moreover, μ-opioid receptors are highly expressed in the rILN (Mansour et al., 1994). Receptor activation hyperpolarizes rILN neurons and shifts activity from tonic to constrained burst firing (Brunton and Charpak, 1998), providing a pharmacological target for modulating the pain response. Lastly, morphine administration induces greater c-fos expression in the male rat rILN as compared to females (D'Souza et al., 1999). Although the behavioral significance of this finding requires further study, it may implicate the rILN in mediating sex differences observed in endogenous and μ-opioid activated analgesia in humans (Wiesenfeld-Hallin, 2005).

CLINICAL CORRELATES OF RILN FUNCTION

The extensive anatomical connectivity and involvement of the rILN in a range of behaviors suggest that these nuclei may participate in disorders spanning multiple functional systems. Schizophrenia presents a constellation of symptoms encompassing sensory, motor, and cognitive dysfunction (Delevoye-Turrell et al., 2007; Hartmann et al., 2015; Morris et al., 2018; Wilquin et al., 2018; Culbreth et al., 2020). Whereas, hyperactive striatal dopamine signaling may contribute to pathology (Abi-Dargham et al., 2009; Sekiguchi et al., 2019), evidence also exists for non-specific thalamic hypofunction. Schizophrenic patients exhibit thalamic structural alterations with reduced volume and glutamate receptor expression, in addition to altered thalamic connectivity with cortex and striatum (Watis et al., 2008; Steullet, 2019). Thalamic hypoactivity is observed in patients who perform poorly on oculomotor tasks requiring cognitive control (Camchong et al., 2006). These cognitive deficits are presumed to be mediated

by reduced mediodorsal thalamus to PFC signaling based on neuroimaging methods (Huang et al., 2019). Given that the rILN lie immediately adjacent to this nucleus and project to the PFC, the rILN may also participate in schizophrenia pathology. In support of rILN hypofunction in schizophrenia, elimination of NMDA receptors from the intralaminar nuclei induces deficits in working memory, spatial memory, and attention in mice (Yasuda et al., 2017), which are cognitive deficits characteristic of schizophrenia (Mohamed et al., 1999). These animals also exhibit altered sleep patterns and reduced cortical oscillatory activity; symptoms that are also present in schizophrenia (Chan et al., 2017). The induction of this phenotype by loss of rILN NMDA receptors suggests that loss of excitatory drive onto the rILN may contribute to some of the negative symptoms and cognitive deficits observed in schizophrenia.

The rILN are innervated by motor centers including the reticular formation and cortical supplementary motor area and, in turn, project to both the primary motor cortex and striatum. High frequency rILN stimulation produces general increases in locomotion (Shirvalkar et al., 2006). Conversely, lesions result in delayed initiation of goal-directed actions (Burk and Mair, 2001) and impaired motor coordination (Jeljeli et al., 2000). Chemogenetic suppression of rILN signaling causes decreases in spontaneous locomotion (Cover et al., 2019) and optogenetic inhibition produces motor cessation (Giber et al., 2015). rILN innervation of the striatum is specifically implicated in a range of action-related functions. The rILN relay excitatory signaling arising from the cerebellar dentate nucleus to the striatum (Chen et al., 2014) and contribute to motor coordination (Sakayori et al., 2019). Eliminating thalamostriatal glutamate release impairs motor coordination, further emphasizing the influence of this projection on action expression (Melief et al., 2018). Virally lesioning striatal-projecting rILN neurons degrades behavioral flexibility and switching between learned actions (Kato et al., 2018). Together, these findings emphasize a multifaceted role for the rILN in action execution. Therefore, these nuclei may contribute to disease states characterized by generalized disordered actions, such as Attention Deficit Hyperactivity Disorder (Jones et al., 2020).

Recent studies report that the rILN evoke dopamine release in the striatum through a di-synaptic circuit involving striatal cholinergic interneurons. Specifically, activation of rILN terminals synapsing on striatal cholinergic interneurons results in local striatal dopamine release (Cover et al., 2019). This is enabled by downstream striatal cholinergic interneuron innervation of nigrostriatal dopamine terminals (Cachope et al., 2012; Threlfell et al., 2012). Optogenetic activation of striatal rILN terminals is behaviorally reinforcing in a dopamine D1 receptor -dependent manner, demonstrating that this local dopamine release mechanism is functionally significant (Cover et al., 2019). Taken together, these findings stand to implicate the rILN in a range of action and cognitive-related behaviors associated with striatal dopamine signaling. Substance abuse, for example, is marked by pathological execution of maladaptive and harmful actions. In an animal model of methamphetamine self-administration, rILN-mediated incubation of drug craving is dependent on striatal D1-receptor signaling (Li et al., 2018). Moreover, increased midline and intralaminar thalamic activity is associated with cue-evoked craving and physiological arousal in alcohol drinkers (Wang et al., 2019). Understanding how drugs of abuse influence rILN signaling may thus reveal novel therapeutic targets for addiction treatment.

DISCUSSION

In vivo recordings demonstrate that the rILN are driven by ARAS activity. Accordingly, rILN firing activity and rILN-induced cortical activation are strongly modulated by sleep and wake arousal states. However, the rILN are not a simple continuation of ARAS; rILN reciprocal connectivity with cortical regions and the basal ganglia elevates this thalamic center to a higher-order integration center. This is supported by the behavioral evidence that rILN activation globally enhances consciousness, memory function, and perceptual decision-making. Conversely, negatively modulating rILN activity broadly impairs motor function, sensory perception, and cognitive ability (**Figure 3B**). Together, these findings suggest that rILN function, spanning from minimal activity (e.g., unconsciousness) to maximal activity (i.e., optimized task engagement), provides a continuum of effective behavioral responses required of a particular task. Thus, we propose that t the rILN facilitate degrees of behavioral engagement, which we define as the application of cognitive, affective, and motor faculties required to achieve a goal (**Figure 3A**).

An essential component to our model of rILN function is the integration of sensory, motor, cognitive, and ARAS inputs. We propose that this culmination of afferents enables the rILN to drive behavioral engagement in a manner sensitive to changing task demands. For example, heightened rILN activity correlates to successful performance on tasks that prompt transition from low to high arousal states or require prolonged attentional engagement (Kinomura et al., 1996; Schiff et al., 2013). Thus, the rILN may be tuning behavioral engagement to optimize reward acquisition.

Through their innervation by cognitive cortical regions and re-entrant basal ganglia circuits, the rILN may exert a gain control function for cognitive and action engagement commensurate with task or goal relevance (e.g., driven by salience, internal state, and reward value). In this way, the rILN may appear to participate in attentional allocation. Traditional models describe attention as a causal filter for enhancing relevant sensory information (Broadbent, 1958). However, an alternative perspective describes attention as the consequence of competition for state representation driven by inputs conveying sensory information, prior knowledge, and internal state to the basal ganglia (Krauzlis et al., 2014). Under this framework, the rILN stand to contribute to attentional processes by relaying to the striatum an ARAS-driven signal integrating salient sensory cues and cortically-based outcome judgements. The rILN-to-striatum projection, for instance, could inform basal ganglia decision-making

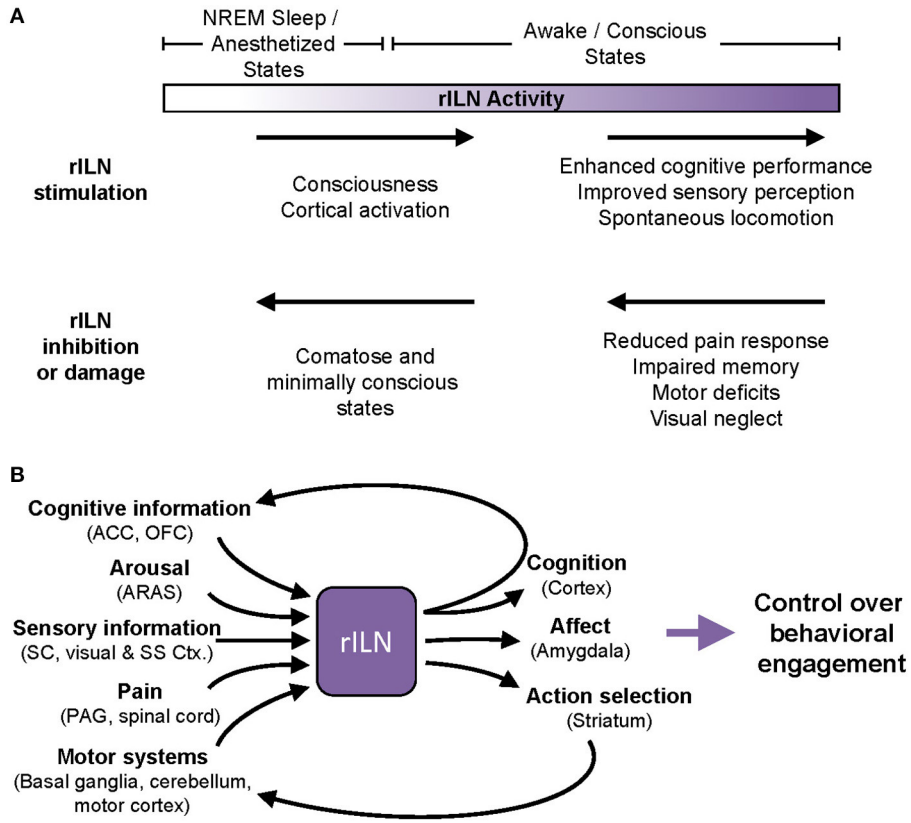

FIGURE 3 | A proposal for modulation of cognitive and behavioral engagement by the rILN. **(A)** Clinical and experimental evidence demonstrate that rILN activity modulates behavioral processes. Minimal rILN activity (left) occurs during sleep or under anesthesia, whereas heightened rILN function (right) is associated with consciousness and optimal attentional states. Within this spectrum of activity, modulations to rILN function induce bi-directional changes in sensory perception, executive function, and motor control. **(B)** The rILN are anatomically positioned to regulate behavioral engagement. The rILN receive information related to cognitive control and decision-making, arousal, sensory information, pain, and motor function (left). Integrating these diverse signals, the rILN may drive task-relevant gains in cognitive and action control through excitation of efferent processes including cognitive networks, affective responses, and action execution (right). ACC, anterior cingulate cortex; ARAS, ascending reticular arousal system; Ctx, cortex; NREM, non-REM; OFC, orbitofrontal cortex; SC, superior colliculus; SS, somatosensory.

and, consequently, attention. Through this context-dependent enhancement of attention, or rather, influence on basal-ganglia decision-making, the rILN may facilitate the optimal engagement of cognitive resources and selection of actions to achieve reward acquisition. This action selection notion is supported by findings that rILN to striatum circuit activation elicits striatal dopamine release (Cover et al., 2019) and supports action reinforcement (Cover et al., 2019; Johnson et al., 2020). Investigation of how rILN activity and manipulations of these nuclei modulate both cortical and basal ganglia output signaling stands to inform how the rILN enhance task-dependent behavioral engagement.

This conceptual framework leads to the following testable predictions:

- Interoception: rILN activity increases with enhanced goal valuation due to interoceptive factors (e.g., unlocking a door to access a food reward in the face of hunger).
- Pain: rILN activity increases with enhanced goal valuation due to pain (e.g., unlocking a door required to escape fire).
- Social cognition: rILN activity increases with enhanced goal valuation due to complex external factors (e.g., unlocking a door to avoid an argumentative individual).
- Action expression: The rILN are engaged for both goal-directed and habitual action strategies as long as the internal or external factors driving reward acquisition are of sufficient incentive salience.
- Action learning and reinforcement: As an animal learns that a particular action leads to reward, rILN activity increases lead to further engagement in that behavior.
- Attention: Measures of executive and selective attention paid to goal-relevant cues will positively scale with increasing reward value and rILN activity.
- Conscious awareness: Increasing rILN activity correlates with decreases in attention paid to goal-irrelevant cues.
- Cognitive control: rILN inhibition evokes more pronounced deficits in tasks that require greater attentional effort or

cognitive load as compared to easier versions that can be successfully completed with less engagement.

Our conceptual framework suggests that global enhancement of function is achieved through the *coordinated* activation of rILN efferents. Therefore, the results of manipulations to select rILN projections may occlude functional contributions mediated through multiple efferent targets. For example, selectively activating rILN cortical or striatal projections during sensorimotor learning may individually produce negligible or modest enhancements in performance. Activating all rILN projection neurons, however, may significantly improve learning through simultaneous excitation of striatal and cortical targets.

We predict that rILN activity manipulations may manifest in a variety of ways depending on the task. For instance, rILN activity may closely correlate with performance measures such as reaction time or accuracy, indicating fine-tuned sensitivity to behavioral outcome. Determining how the rILN activates for a particular task, in a rILN output pathway -specific manner, is poised to provide clarity for the extant data that indicates rILN signaling correlates with a range of behaviors, from saccades to reversal learning. Testing the predictions proposed here stands to elucidate the extent and limits of rILN involvement in behaviors spanning functional modality, skill-level, and attentional demand.

CONCLUSION

Inspection of rILN anatomical connectivity and behavioral contributions reveals the distinct involvement of the rILN in an extensive number of functional systems. We herein propose that the rILN support a gain modulation function for adjustable engagement in goal-relevant tasks. Dysfunction in this system then would, unsurprisingly, implicate rILN pathology in a range of disorders. Future study of this system presents challenges, however. Neuroimaging resolution constraints limit investigation of the rILN in humans. *In vivo* recordings or manipulations in animals generally favor targeting of the more accessible CL nucleus. However, the robust behavioral findings from the limited interrogations of the rILN should encourage future investigation, which would benefit from rILN output-specific functional interrogation particularly centering on the understudied CM.

The high degree of integration that the rILN exhibit with many neural systems positions this area to be relevant to affective, cognitive, and action-related neuropathologies. Supporting the functional hypothesis for rILN in behavioral engagement described herein, pathological rILN activation would facilitate an overly-engaged behavioral state with a particular reward or goal, such as is the case with methamphetamine craving (Li et al., 2018). Conversely, pathological suppression of rILN activity would be predicted to give rise to cognitive and behavioral states mirroring the negative symptoms of schizophrenia (e.g., poor cognitive performance and social disengagement). Specifically targeting the rILN for therapeutic benefit may, therefore, present a range of novel therapeutic opportunities.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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The Function of Paraventricular Thalamic Circuitry in Adaptive Control of Feeding Behavior

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The paraventricular nucleus of the thalamus (PVT) is a complex area that is uniquely embedded across the core feeding, reward, arousal, and stress circuits. The PVT role in the control of feeding behavior is discussed here within a framework of adaptive behavioral guidance based on the body's energy state and competing drives. The survival of an organism depends on bodily energy resources and promotion of feeding over other behaviors is adaptive except when in danger or sated. The PVT is structurally set up to respond to homeostatic and hedonic needs to feed, and to integrate those signals with physiological and environmental stress, as well as anticipatory needs and other cognitive inputs. It can regulate both food foraging (seeking) and consumption and may balance their expression. The PVT is proposed to accomplish these functions through a network of connections with the brainstem, hypothalamic, striatal, and cortical areas. The connectivity of the PVT further indicates that it could broadcast the information about energy use/gain and behavioral choice to impact cognitive processes—learning, memory, and decision-making—through connections with the medial and lateral prefrontal cortical areas, the hippocampal formation, and the amygdala. The PVT is structurally complex and recent evidence for specific PVT pathways in different aspects of feeding behavior will be discussed.

Keywords: arousal, energy homeostasis, feeding, interoception, stress, taste, viscerosensory

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INTRODUCTION

The paraventricular nucleus of the thalamus (PVT) is a complex, multimodal area that is uniquely embedded across the core feeding, reward, arousal, and stress circuits (Hsu et al., 2014; Colavito et al., 2015; Millan et al., 2017). Its structural position and connectivity enables it to direct feeding behavior in response to physiological, cognitive, hedonic, and environmental signals and perturbations (Millan et al., 2017; Petrovich, 2018a). The PVT can regulate both food foraging (seeking) and consumption and may balance their expression. These regulations occur under the prominent influence of bodily internal (interoceptive) signals. Here, it is conceptualized that the PVT core function is to ensure animal's survival—promoting behaviors that avoid starvation and danger, and balancing foraging against threats and other competing behaviors. Together with guiding behavioral expression, the PVT is set up to broadcast the information about the behavioral choice and energy gain/loss, and accordingly impact cognitive processes—learning, memory, and decision-making. It could accomplish this within a complex and widespread network of connections with brainstem, hypothalamic, striatal, and cortical areas, including the ventral

subiculum and CA1 within the hippocampal formation (Thompson and Swanson, 2003; Cenquizca and Swanson, 2006; Kirouac, 2015; Vertes et al., 2015). Determining the function of specific PVT pathways has been the focus of recent investigations and will be discussed here in the context of feeding behavior.

PVT IN ADAPTIVE BEHAVIORAL CONTROL: PRIORITIZING FEEDING OVER OTHER BEHAVIORS, EXCEPT WHEN IN DANGER

Hunger and stress are primary survival threats and the PVT guides behavioral choice in response to each and when they compete. Because energy is essential for survival, feeding is prioritized over other behaviors, except when an animal is in danger or when there is a sufficient surplus of energy. Adaptive control of feeding behavior, therefore, involves balancing hunger versus other competing drives and resolving their priorities. Indeed, the PVT is critical for appropriate behavioral selection in conflict settings when an animal needs to choose between competing behaviors: food seeking versus threat avoidance (Choi and McNally, 2017) or when an ambiguous cue signals both (Choi et al., 2019).

A unique feature of the PVT is that it is well positioned to integrate the information about animal's energy state and external prospects for gaining or depleting energy. In addition to energy, hunger and satiety signals, including dense innervation by orexigenic and anorexigenic neuropeptides, the PVT contains neurons that are sensitive to glucose and receives information about the bodily glucose state (Labouèbe et al., 2016; Beas et al., 2020). The PVT can also receive information about pending energy expenditures, such as approaching danger, stress, or changes in wakefulness/arousal states. It receives stress and arousal information from the brainstem and hypothalamus and it is interconnected with the medial (prelimbic and infralimbic) and lateral (insular) prefrontal cortical areas, the hippocampal formation, and the amygdala (Kirouac, 2015). Thus, the PVT is well positioned to detect when energy totals change or are expected to change, and guide behavioral outcome accordingly, along with recruiting arousal, while simultaneously broadcasting that information via cognitive (cortical) systems (**Figure 1**).

THE PVT CIRCUITRIES FOR FOOD SEEKING AND CONSUMPTION

Depletion of energy and other homeostatic signals drive food seeking behaviors and consumption. Cues associated with food and feeding location, or memory of hedonic or aversive post-ingestive effects, can also drive these behaviors in the absence of hunger (Petrovich, 2018a). The connections of the PVT indicate that it could receive these multifaceted signals and in turn control both food seeking and consumption and may be balancing their expression. Distinct and potentially competing PVT circuitries appear to regulate these two behaviors. Food seeking involves planning, navigation, risk assessment, and learning and memory, and PVT's connections with the prefrontal cortex, hippocampal formation, and the amygdala would enable these computations (Kirouac, 2015). Thus the PVT is well positioned to bias food seeking over other behaviors, and to re-direct it to consumption when food is found, or avoidance when faced with danger.

Food Consumption: Homeostatic, Hedonic, and (No)Feeding Under Stress

Early evidence that the PVT is critical in the control of food consumption came from lesion and inactivation studies (Bhatnagar and Dallman, 1999; Stratford and Wirtshafter, 2013). These studies showed that shutting down PVT drives food consumption. The rodent PVT does not contain GABA neurons (Arcelli et al., 1997), however, GABAergic inputs from the zona incerta were shown to powerfully drive consumption, particularly of high-energy (high fat) food (Zhang and van den Pol, 2017). Fasting and ghrelin increased activity of that pathway, and repeated photostimulations caused weight gain, indicating a role in homeostatic regulation. Other substantial GABA inputs to the PVT include forebrain and brainstem areas that could provide multiple ways to stimulate feeding (Kelley et al., 2005; Petrovich, 2018a,b; Otis et al., 2019). Notably, hypothalamic AgRP neurons, which also express NPY and GABA, mediate rapid food consumption via GABA or NPY release (Krashes et al., 2013). In addition, the central nucleus of the amygdala (CEA) is well positioned to mediate cognitive, stress, and hedonic effects on feeding potentially together with the PVT (Petrovich, 2018a).

In addition to direct inputs, the CEA and PVT are interconnected via multiple relays (Kirouac, 2015; Vertes et al., 2015; Petrovich, 2018a). The CEA and PVT connections have been highlighted in regard to stress (Hsu et al., 2014) and the PVT-CEA pathway is critical for fear memory acquisition and retrieval (Do-Monte et al., 2015; Penzo et al., 2015). In the context of feeding behavior, the CEA is necessary for inhibition of feeding under fear (Petrovich et al., 2009; Reppucci and Petrovich, 2018), and its neurons that express protein kinase C-delta drive anorexic effects in response to diverse aversive events (Cai et al., 2014). Intriguingly, the CEA also has stimulatory effects and drives hedonic eating but via distinct neurons that express serotonin receptor 2a (Douglass et al., 2017) and prepronociceptin (Hardaway et al., 2019). Whether these different groups of neurons are interconnected with the PVT and how these connections are organized is an important question for future research. Indeed, the CEA-PVT system may be an important site of dysregulation that could cause unnecessary food avoidance, or excessive hedonic eating.

The CEA and PVT are well positioned to impact palatability and hedonic eating, as both are prominently involved in processing taste and visceral sensory information (Thompson and Swanson, 2003; Kirouac, 2015). Changes in taste perception intensity could underlie maladaptive overeating or under-eating, such as when palatable tastes are intensified to become irresistible or when they are diminished, due to anhedonia or stress, and nothing tastes good. Whether such malfunctions would occur with overactive or underactive CEA–PVT circuitry remains to be investigated. Another important question is whether that

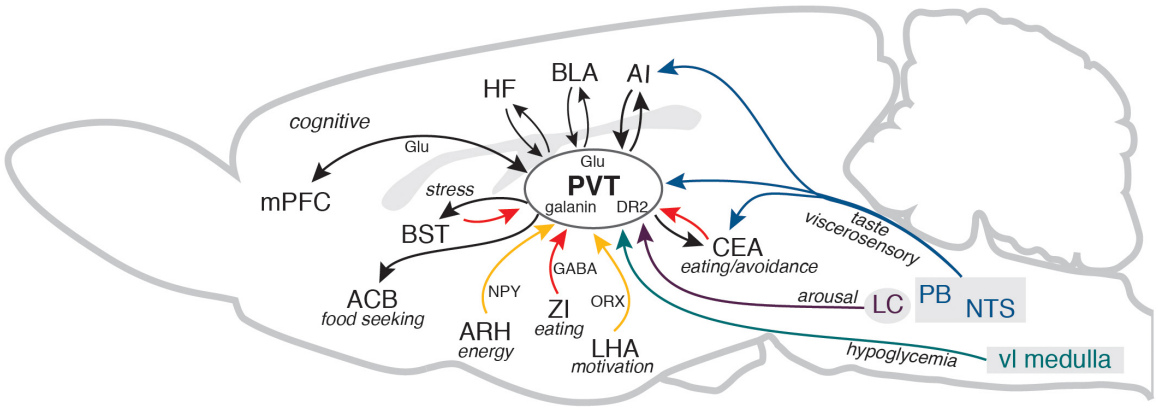

FIGURE 1 | The diagram illustrates several key PVT connections discussed in the manuscript in the context of adaptive control of feeding behavior. For clarity, some connections between the areas, other brains areas that participate in the circuitry, and different PVT neurons that contain specific peptides or receptors are not shown. Cortical and thalamic glutamatergic pathways (Glu) are shown in black and GABA pathways from the ZI, CEA, and BST are shown in red. AI, agranular insular cortex; ACB, nucleus accumbens; ARH, arcuate nucleus of the hypothalamus; BLA, basolateral area of the amygdala; BST, bed nuclei of the stria terminalis; CEA, central nucleus of the amygdala; DR2, dopamine receptor 2; HF, hippocampal formation (ventral CA1 and subiculum); LC, locus coeruleus; LHA, lateral hypothalamic area; mPFC, medial prefrontal cortex; NPY, neuropeptide Y; NTS, nucleus of the solitary tract; ORX, orexin/hypocretin; PB, parabrachial nucleus; PVT, paraventricular nucleus of the thalamus; vl medulla, ventrolateral medulla; ZI, zona incerta. The sagittal outline of the rat brain was adapted from Swanson (2018).

system functions differently in males and females, as there are sex differences in hedonic and eating disorders (Culbert et al., 2021; Quigley et al., 2021). Nevertheless, as discussed next, there is support for the role of the CEA and the thalamus (possibly including PVT) in a neural circuitry underlying individual differences in taste perception.

A recent study by Veldhuizen, Small and colleagues (Veldhuizen et al., 2020) showed that the CEA responses in humans were correlated with intensity ratings across multiple tastants and that these individual differences were also reflected in activation patterns in the thalamus. Their psychophysiological and dynamic causal modeling analyses suggested that inhibitory inputs from the amygdala to the thalamus act as a central gain mechanism that influences taste intensity perception. An intriguing possibility is that the PVT was among thalamic nuclei identified in that study. The activity patterns were concentrated in the mediodorsal and ventral posterior medial thalamic areas that span the PVT location. Thus, it is possible that the PVT contributed to the observed thalamic activity in that study, but was not specifically detected due to its size and limits of fMRI resolution. The PVT is interconnected with the CEA and insular cortex, and could be a missing link in the observed functional circuitry from the CEA to the insular cortex and to the ventral posterior medial thalamus, where the CEA impacted activity without direct connections (Veldhuizen et al., 2020).

PVT Circuitries Shutting Down Feeding When Sated or Under Stress

When sated or when faced with danger, it is adaptive to stop feeding and prioritize other behaviors. In accordance, activation of anorexigenic GLP-1 (glucagon-like peptide-1) receptors in the PVT decreased food intake and seeking behaviors (Ong et al., 2017). Given that inhibitory inputs to the PVT drive consumption, excitatory inputs or disinhibition of the PVT projecting neurons should shut down feeding. The ventromedial nucleus of the hypothalamus (VMH) is considered to inform the PVT during states of energy surplus, within its broader output to normalize homeostasis, and activation of glutamatergic inputs to the PVT from the VMH SF1 neurons (expressing steroidogenic factor 1) were shown to suppress food intake (Zhang et al., 2020). Interestingly, that manipulation did not impact metabolism, indicating that the VMH-PVT pathway may exclusively regulate the behavioral component of energy balance.

Danger shuts down feeding and stress-related signals should impact the PVT in the opposite direction from signals that drive feeding. Consistent with this notion, under stress, the locus coeruleus dopaminergic pathway has been shown to disinhibit the posterior PVT projecting neurons via a D2 receptor mechanism (Beas et al., 2018). In addition, as mentioned above the CEA GABAergic pathways to the PVT could be important in cessation of feeding under threat.

Food Seeking Behaviors: PVT Circuitries for Homeostatic and Cognitive Signals

In contrast to consumption, which has been typically elicited by inhibition of the PVT, excitation or inhibition of the PVT neurons and pathways have been shown to mediate food seeking [also see Cheng et al. (2018) for both food seeking and consumption after activation]. Similarly, drug reward seeking can be elicited by both activation and inhibition of the PVT and its pathways (Millan et al., 2017).

Activation of glucose responsive PVT neurons stimulated sucrose-seeking (Labouèbe et al., 2016) and Fos induction patterns indicate activation of PVT neurons during food anticipatory locomotion when hungry (Nakahara et al., 2004; Angeles-Castellanos et al., 2007), palatable food anticipation when sated (Mendoza et al., 2005), and renewal of cue-induced food seeking after extinction (Anderson and Petrovich, 2017,

2018). On the other hand, medial prefrontal cortex (mPFC) inputs to the PVT and PVT-nucleus accumbens (ACB) pathways are inhibited during conditioned sucrose seeking (Otis et al., 2017, 2019), and photoinhibition of the anterior PVT and its pathway to the ACB enhanced sucrose seeking (Do-Monte et al., 2017). Interestingly, that manipulation selectivity drove responding when sucrose reward was unexpectedly omitted, in accordance with a role of the PVT in balancing food seeking versus consumption based on food availability. In that regard, PVT lesions enhanced food cue driven sign-tracking (lever directed) over goal-tracking (food cup directed) behaviors (Haight et al., 2015), and blockade of ORX-R2 in the PVT of sign-tracking prone rats reduced their sign-directed behavior (Haight et al., 2020). In contrast, the blockade of ORX-R1 in the PVT of sign-tracking prone rats decreased sign- and increased goal-directed behaviors 24 h later (Haight et al., 2020), indicating potential memory consolidation effects, similar to prior findings after systemic ORX-R1 blockade (Keefer et al., 2016). Furthermore, anterior PVT neurons were recruited when ORX-R1 were blocked systemically, which inhibited cue-induced consumption (Cole et al., 2015).

In addition to cortical inputs, hypothalamic inputs to the PVT from the arcuate nucleus AgRP (NPY/GABA) neurons have been shown to drive food seeking behaviors (Livneh et al., 2017; Wang et al., 2021). The AgRP neurons are sensitive to energy balance signals and powerfully drive food consumption, via GABA or NPY release (Krashes et al., 2013). Notably, the AgRP-PVT pathway was shown to be important for food seeking and learning about food location but not for consumption (Wang et al., 2021). Interestingly, that pathway engaged AgRP and NPY, rather than GABA signaling, consistent with the notion that different substrates underlie food seeking and consumption.

In contrast to adaptive behaviors, activation of AgRP neurons in the absence of food induced stereotypic, repetitive, seemingly compulsive behaviors (increased grooming, marble burying) in mice (Dietrich et al., 2015). The data suggested that different AgRP circuitries drive these behaviors from those driving consumption but whether they involve inputs to the PVT is not known. Nevertheless, the effect was mediated by NPY Y5 receptors, which are present in the PVT area of the thalamus (Wolak et al., 2003). Systemic NPY administration is well known to strongly enhance food motivation and wheel running in an animal model of anorexia (Flood and Morley, 1991; Nergardh et al., 2007). Thus, it is plausible that the NPY–PVT pathway may drive excessive behaviors when food is absent during extreme states of hunger, perhaps similar to behaviors observed in anorexia nervosa.

How these different excitatory and inhibitory inputs are integrated within the PVT to control food seeking and whether they mediate the effects via the same output is unknown. Accumulating evidence indicates that the PVT outputs via the ACB mediate food seeking behaviors (Choi et al., 2012; Do-Monte et al., 2017; Ong et al., 2017; Cheng et al., 2018; Campus et al., 2019; Otis et al., 2019). The PVT is a complex structure and the connections of the rostral and caudal parts are distinct (Li and Kirouac, 2012). Recently, two distinct neuronal types within the PVT have been identified based on the presence of the dopamine D2 receptors (type 1) or Galanin (type 2) and other characteristics (Gao et al., 2020), These neurons are differently distributed across rostro-caudal extent of the PVT—type 1 neurons are more abundant caudally and type 2 rostrally but they have similar distribution in the middle of the PVT —and appear to function via parallel connections with the mPFC. Importantly, the type 2 neurons control arousal via the infralimbic cortex (Gao et al., 2020).

The anterior PVT has extensive connections with the prelimbic cortex and the ventral subiculum (Vertes, 2004; Li and Kirouac, 2012), while the posterior part of the PVT is more heavily interconnected with CEA and viscerosensory areas and has been implicated in stress (Hsu et al., 2014). The posterior PVT receives inputs from the ventrolateral medulla that drive hypoglycemia (glucoprivation)-induced food seeking via the ACB core (Beas et al., 2020). Interestingly, both anterior and poster PVT are needed to resolve motivational conflict when a cue signals reward and punishment (Choi et al., 2019). How reward and stress are integrated across the anterio-posterior PVT, and how they engage the type 1 and type 2 neurons, are important questions for future research.

HUNGER, AROUSAL, AND STRESS INTEGRATION WITHIN THE PVT: IT IS ALL ABOUT ENERGY

Energy metabolism is tightly coupled with feeding behavior, however, energy is required for all behaviors and cell functioning but how that information is integrated across the neural systems underlying non-feeding behaviors is not clear. Similar to hunger, stress engages arousal and energy resources. The PVT is uniquely positioned to integrate hunger, arousal, and stress and adaptively regulate behavioral choice.

In addition to guiding food seeking and consumption, the PVT is important in stress and arousal (Hsu et al., 2014; Colavito et al., 2015; Millan et al., 2017). Notably, the PVT is one of the densest outputs of the lateral hypothalamic neurons that express the neuropeptide orexin (ORX; also known as hypocretin), which is critical for wakefulness, arousal and motivation (Peyron et al., 1998; Petrovich, 2019). Furthermore, the PVT is under the strong influence of interoceptive signals. In addition to the internal signals related to energy balance, the PVT receives prominent viscerosensory information, including pain, in addition to taste (Thompson and Swanson, 2003; Kirouac, 2015; Millan et al., 2017). In turn, the PVT can communicate with cortical and striatal areas within an interconnected network to determine and produce the most adaptive behavioral output (Kirouac, 2015; Vertes et al., 2015). Through these connections, the PVT could impact behavioral, hedonic, and decision-making circuitries, as well as memory formation and recall (Petrovich, 2018a).

Stress and arousal can have a major impact on feeding behavior and energy metabolism (Hsu et al., 2014; Colavito et al., 2015). Stress can inhibit or induce eating, depending on the type of stressor and timing. Anticipatory stress inhibits eating (Petrovich et al., 2009; Petrovich, 2018a), while palatable food consumption is enhanced post stress (Adam

and Epel, 2007). Arousal is essential in behavioral control, from regulation of sleep/wakefulness, to reward motivated behaviors and production of excitement or induction of aversive fear and stress states. The PVT is crucial for wakefulness (Shao et al., 2019), and that circuitry was recently shown to include inputs from ORX neurons and outputs to the ACB (Ren et al., 2018).

Feeding associated anticipatory locomotion and hunger-associated arousal require the PVT (Nakahara et al., 2004; Hua et al., 2019). ORX neurons enhance arousal in response to fasting (Yamanaka et al., 2003) and support hedonic feeding and drug reward motivation via the PVT (Choi et al., 2010, 2012; Matzeu et al., 2014). Wakefulness due to hunger requires calretinin PVT neurons that project to the bed nuclei of the stria terminalis, and that pathway was proposed to mediate stress aspects of arousal during starvation (Hua et al., 2019).

Behavioral Prioritization Based on Internal State: Adding Feelings and Action to Taste

The PVT receives very prominent visceral sensory information, including nociception. That information can arrive directly from the brainstem (nucleus of the solitary tract, parabrachial nucleus) as well as from multiple interconnected areas—including the hypothalamus, amygdala, bed nuclei of the stria terminals, and insular cortex (Thompson and Swanson, 2003; Kirouac, 2015; Petrovich, 2018a). An important function of the PVT is to appropriately match the internal state of the body with behavioral and cognitive states, and dynamically adjust them to ensure animal's survival.

Because energy is essential for survival, hunger is an aversive state. Arousal is important for the intensity of affective states that accompany motivated behaviors. The visceral sensory (interoceptive) information has been historically associated with affect and emotion. More recently, the visceral processing neural network has been implicated in biasing many higher-order functions in humans, including the concept of self (Critchley and Harrison, 2013). Thus, in addition to guiding behavior, the PVT may be important for translating the meaning of internal states in terms of animals' perception, cognition, and affect, as well as an overall sense of well being.

COMPARISON TO PREVIOUSLY PROPOSED PVT FUNCTIONS

The PVT role in the adaptive control of feeding behavior that was put forward in this perspective relates to previously proposed functions for this brain area. The PVT has been hypothesized to play a critical role in wake control (Shao et al., 2019), and wakefulness and arousal are essential in the control of feeding behavior. At the minimum an animal needs to be awake in order to be able to forage and consume food, and vigor can enhance these behaviors. On the other hand, vigilance and arousal due to stress or approaching danger may shut down feeding. How the PVT integrates information about wakefulness and arousal with food foraging and consumption in an adaptive manner is an exciting area of future research.

Here, it was proposed that the PVT circuitry resolves competition between feeding and other survival behaviors, and guides switching between food seeking and consumption. The functional circuitry highlighted here was built upon the anatomical connections originally outlined by Kirouac in the context of behavioral control (Kirouac, 2015). The proposed adaptive control of feeding is related to the PVT function in resolving motivational conflicts (McGinty and Otis, 2020; McNally, 2021) and in gating which reward motivated behaviors are expressed (Haight and Flagel, 2014; Millan et al., 2017). The PVT was previously identified as critical to individual differences in Pavlovian conditioned responses (sign- vs. goal-tracking) and was postulated to underlie multiple forms of stimulus-reward learning (Haight and Flagel, 2014).

Similar to food seeking and consumption, the PVT is important for drug seeking and intake of at least some drugs (Matzeu et al., 2014; Millan et al., 2017). It is also important in drug addiction and relapse, as well as aversive states associated with drug withdrawal (Millan et al., 2017). It has been conceptualized that the PVT mediates appetitive motivation in feeding and drug addiction through its extensive connectional network (Millan et al., 2017). In agreement with the idea that common PVT substrates mediate natural and drug motivation, hunger and satiety signals have been shown to impact drug seeking and self-stimulation via the PVT (James et al., 2010; Choudhary et al., 2018; Chisholm et al., 2021). Similarly, an addiction mechanism that was suggested to involve impairments in response inhibition and PVT connectivity with the ventromedial prefrontal cortex (Huang et al., 2018) may also underlie maladaptive hedonic eating.

In addition to reward, the PVT mediates behavioral control in the context of stress (Hsu et al., 2014) and has been proposed to be a key part of the emotional processing network (Barson et al., 2020). Motivated behaviors are accompanied by affect and as discussed briefly in above section "Behavioral Prioritization Based on Internal State: Adding Feelings and Action to Taste" it is adaptive for hunger and satiety to be associated with negative and positive valence states, respectively. The PVT is well positioned to interpret interoceptive signals and affect in the context of feeding and other survival drives, and to integrate that information across behavioral and cognitive networks.

CONCLUDING REMARKS

This perspective presented a framework for the PVT function in the control of feeding behavior within the context of energy balance and survival mechanisms, and discussed recent progress in identifying distinct PVT functional circuitries (**Figure 1**). That progress has been significant but has also revealed many pressing questions: Which specific PVT subsystems (cells and circuits) control different components of feeding behavior (seeking vs. consumption)? Do common or different PVT substrates mediate homeostatic, hedonic, and cognitive feeding and how are those systems regulated under stress? Do PVT outputs function in parallel or do they overlapping and where? Are

there sex differences in the PVT circuits and their function? The conceptual framework presented here could provide a starting point in addressing these questions.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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frontiers in Behavioral Neuroscience

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Time-Dependent Recruitment of Prelimbic Prefrontal Circuits for Retrieval of Fear Memory

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The long-lasting nature of fear memories is essential for survival, but the neural circuitry for retrieval of these associations changes with the passage of time. We previously reported a time-dependent shift from prefrontal-amygdalar circuits to prefrontal-thalamic circuits for the retrieval of auditory fear conditioning. However, little is known about the time-dependent changes in the originating site, the prefrontal cortex. Here we monitored the responses of prelimbic (PL) prefrontal neurons to conditioned tones at early (2 h) vs. late (4 days) timepoints following training. Using c-Fos, we find that PL neurons projecting to the amygdala are activated early after learning, but not later, whereas PL neurons projecting to the paraventricular thalamus (PVT) show the opposite pattern. Using unit recording, we find that PL neurons in layer V (the origin of projections to amygdala) showed cue-induced excitation at earlier but not later timepoints, whereas PL neurons in Layer VI (the origin of projections to PVT) showed cue-induced inhibition at later, but not earlier, timepoints, along with an increase in spontaneous firing rate. Thus, soon after conditioning, there are conditioned excitatory responses in PL layer V which influence the amygdala. With the passage of time, however, retrieval of fear memories shifts to inhibitory responses in PL layer VI which influence the midline thalamus.

Keywords: PL, amygdala, PVT, fear retrieval, time differences

INTRODUCTION

Memories of threatening experiences can last a lifetime (LeDoux, 2000; Gale et al., 2004), but the location of such fear memories within the brain is thought to change over time (for reviews see: Frankland and Bontempi, 2005; Do Monte et al., 2016). The prelimbic cortex (PL) is necessary for the retrieval of auditory fear memories (Sierra-Mercado et al., 2011; Courtin et al., 2014), especially via its projections to the amygdala (Herry and Johansen, 2014). Control of retrieval of fear memories by PL initially involves direct projections to the basolateral amygdala (BLA, 6 h following conditioning), but later shifts to indirect activation of the central nucleus of the amygdala (CeM) via projections to the paraventricular thalamus (PVT) (7 days following conditioning) (Do-Monte et al., 2015; Penzo et al., 2015; Choi and McNally, 2017). While optogenetic techniques have confirmed the necessity of these shifting circuits (Do-Monte et al., 2015), little is known about the time-dependent changes in PL outputs.

Conditioned tones activate PL neurons at both early and late timepoints following conditioning, as indicated by the activity marker c-Fos, with activation at later times occurring in PL neurons

that project to PVT thalamus (Do-Monte et al., 2015). PL neurons that project to PVT are located in layer VI of PL (Vertes, 2002; Li and Kirouac, 2012), and c-Fos expression profiles have confirmed that conditioned activity in PL shifts from superficial to deep layers with the passage of time (DeNardo et al., 2019). However, there are several limitations with the use of c-Fos as an indicator of conditioned neuronal activity. c-Fos levels cannot differentiate between conditioning-induced changes in spontaneous activity vs. changes in cue-induced activity, and inhibitory responses are poorly detected by c-Fos (Chung, 2015). Whereas the majority of prior studies focused on excitatory tone responses in PL (Burgos-Robles et al., 2009; Sotres-Bayon et al., 2012), there is an emerging role of inhibitory responses of PL neurons in aversive conditioning (Courtin et al., 2014; Diehl et al., 2020).

In the present study, we combine retrograde tracers with c-Fos labeling to confirm the time-dependent shift in PL outputs from BLA to PVT. We then record from individual PL neurons at several post-conditioning timepoints, comparing the conditioned responses of neurons in layer V (putative BLA-projecting) to those in layer VI (putative PVT-projecting). By recording both tone responses and spontaneous activity, our goal was to characterize the effects of the passage of time more accurately on retrieval circuits.

RESULTS

PL Neurons Projecting to BLA Are Activated at Early Timepoints, Whereas PL Neurons Projecting to PVT Are Activated at Later Timepoints

We first used the activity marker c-Fos to indicate when PL neurons projecting to different targets were activated following conditioning. Within the same animal, we infused separate retrograde tracers into BLA (cholera toxin subunit b, CTB) and PVT (Fast Blue, FB), and co-labeled PL for c-Fos. One week after surgery, rats were fear conditioned to a 30 s tone with a co-terminating foot shock, and were given a retrieval test either 2 h or 7 days after conditioning (**Figure 1A**). Unconditioned control rats (no cond) were never exposed to foot shock, but were given tones during the retrieval test at either the 2 h or 7 days timepoint. One hour after the retrieval tests, all groups were sacrificed. Coronal slices of PL were immunostained against c-Fos and visualized with a florescent microscope (triple labeling).

As shown in **Figure 1B**, freezing responses to the tone were similar for early and late retrieval groups [55% for 2 h, 61% for 7 days, $t_{(12)} = -0.45$, $p = 0.66$]. Examples of tracer and c-Fos neuronal labeling can be seen in **Figure 1C**. Neurons projecting to BLA were located in layers II/III and layer V of PL (Vertes, 2004), whereas neurons projecting to PVT were largely limited to Layer VI, consistent with prior anatomical reports (Vertes, 2002; Arruda-Carvalho and Clem, 2014). The number of retrogradely labeled neurons observed in PL following tracer infusions into BLA or PVT did not differ statistically [BLA: 58 counts/cm^2 for no cond, 41 counts/cm^2 for cond $t_{(19)} = 1.45$, $p = 0.16$; PVT: 208 counts/cm^2 for no cond, 182 counts/cm^2 for cond $t_{(26)} = 0.86$, $p = 0.40$]. We quantified the proportion of layer distribution for PL-BLA neurons (52.3% in layer II/III, 47.7% in layer V, and 0.0% in layer VI) and PL-PVT neurons (0.0% in layer II/III, 9.4% in layer V, and 90.6% in layer VI). **Figure 1D** shows that early fear retrieval (2 h) significantly increased c-Fos expression in BLA-projecting neurons [3.0% no cond, 9.9% cond, $t_{(8)} = 3.84$ $p = 0.005$], but not in PVT-projecting neurons [2.8% no cond, 8.0% cond, $t_{(9)} = 1.74$ $p = 0.12$]. In contrast, late fear retrieval (7 days) significantly increased c-Fos expression in PVT-projecting neurons [2.8% no cond, 8.0% cond, $t_{(16)} = 2.27$ $p = 0.038$], but not in BLA-projecting neurons [5.6% no cond, 3.6% cond, $t_{(7)} = 0.48$ $p = 0.64$]. Thus, the passage of time shifted PL output from BLA targets to PVT targets.

PL Neurons in Layer V Show Excitatory Responses at Early Timepoints, Whereas Those in Layer VI Show Inhibitory Response at Later Timepoints

We next recorded from individual PL neurons using *in vivo* extracellular electrophysiology, during the following phases: pre-conditioning, early retrieval (2 h and 24 h after conditioning), and late retrieval (≥4 days after conditioning) (**Figure 2A**). We targeted layer V neurons vs. layer VI neurons to distinguish cells likely projecting to BLA vs. PVT (see tracer labeling in **Figure 1C**). Using fixed-array wire electrodes (NB Labs) or silicon probes (NeuroNexus), we recorded from a total of 483 PL neurons: 264 in layer V and 219 in layer VI.

As shown in **Figure 2A**, conditioned freezing levels were equivalent at all three post-conditioning timepoints [2 h: 66%, 24 h: 74%, ≥4 days: 77%, $F_{(1,27)} = 0.96$, $p = 0.39$]. Single neuron recordings were obtained from isolated waveforms recorded across layers V and VI of PL (**Figures 2B–D**). Representative examples of responses from single units recorded at different times and are shown in **Figures 2E,F**. Layer V neurons (putative BLA projecting) showed the expected conditioning-induced increases in tone responses early after conditioning (2 h, 24 h), but these were no longer present by 7 days. In contrast, neurons in Layer VI (putative PVT projecting) showed almost no conditioned excitation, but a pronounced conditioned inhibition at later timepoints. Layer VI neurons also exhibited an increase in the rate of spontaneous firing during the 7 days session.

The rest of the recording data were obtained from experiments in which the electrode was advanced 200–300 microns between timepoints, sampling different sets of PL neurons. The heatmaps of **Figure 3A** show the normalized tone responses (displayed as z-scores) of each neuron recorded from layers V and VI. For each 5 s time bin, the color red indicates significant excitation ($Z > 1.96$, $p < 0.05$, two-tailed) whereas blue indicates significant inhibition ($Z < -1.96$, $p < 0.05$, two-tailed). In layer V, excitatory tone responses were present at all timepoints but they were most prevalent during the 2 h timepoint. However, at ≥4 days, the percentage of excitatory responsive cells was lower than at pre-conditioning (16 vs. 23%, see ring insets in **Figure 3A**). In contrast, Layer VI neurons showed few excitatory tone responses prior to conditioning, which further decreased to negligible levels by ≥4 days. However, Layer VI neurons developed inhibitory

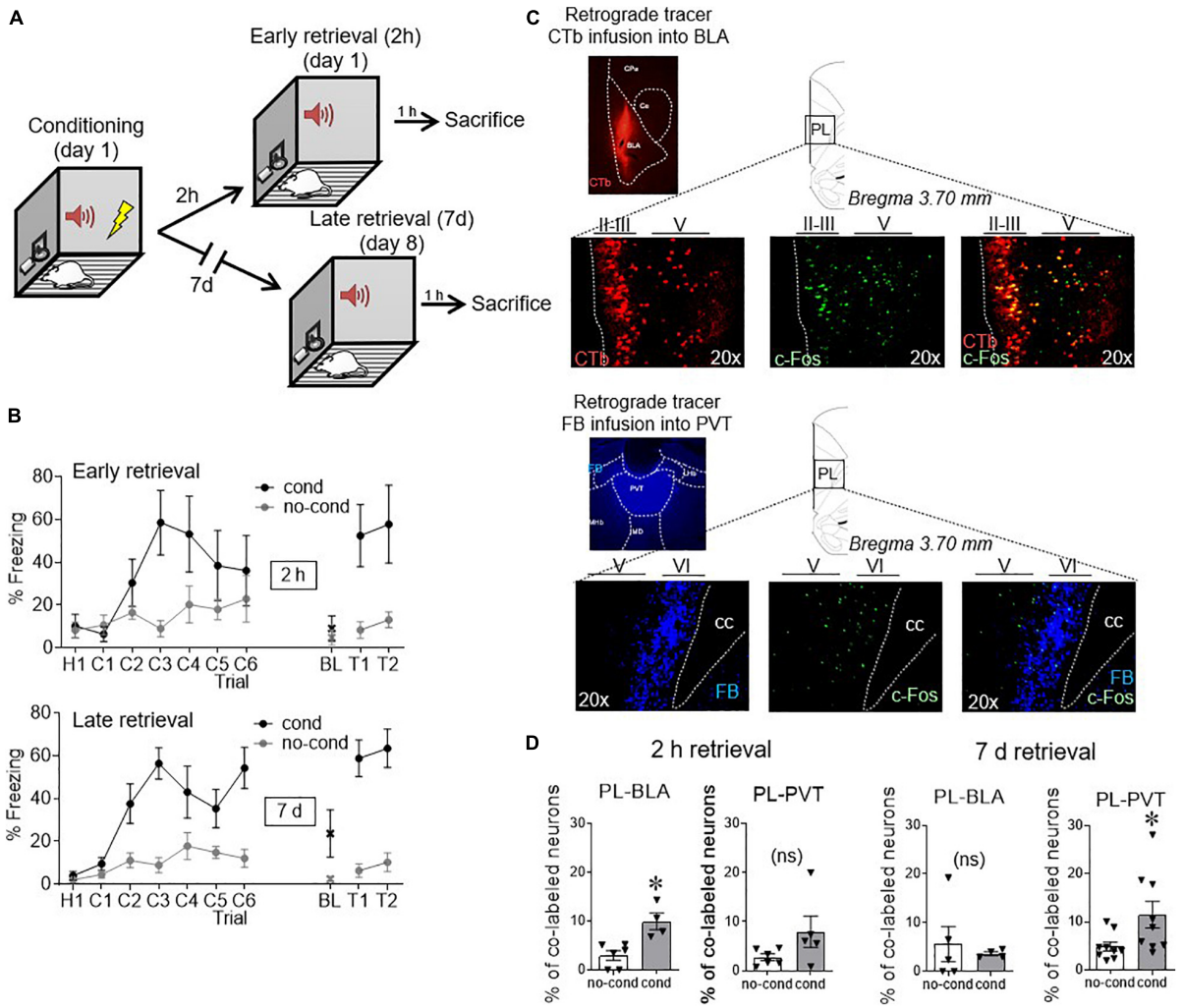


FIGURE 1 | Conditioned activity in PL neurons shifts with time, from BLA-projecting to PVT-projecting neurons. **(A)** After retrograde tracer infusions, rats received fear conditioned followed by retrieval tests either 2 h or 7 days later. **(B)** Freezing levels during conditioning and early retrieval **(top)** and late retrieval **(bottom)**. **(C)** Example micrographs of retrograde tracers infused into BLA and PVT and their respective staining in PL neurons, together with c-Fos staining (performed at 2 h in BLA and 7 days in PVT). **(D)** Group data of co-labeling of tracers with c-Fos in PL. PL-BLA neurons showed significant activation during the 2 h (but not 7 days) retrieval test, whereas PL-PVT neurons showed significant activation during the 7 days (but not 2 h) retrieval test. *$p < 0.05$. $n = 6$ rats per group. Error bars depict mean and SEM in this and subsequent figures. ns = not significant.

responses at all post-conditioning timepoints, with the largest percentage at 24 h (see ring inset). At ≥4 days, inhibitory responses in layer VI decreased somewhat but were still greater than pre-conditioning.

These patterns of time-dependent changes in tone responses are apparent in the group averages (**Figure 3B**). At each timepoint, recorded neurons were divided into two sets: those with z-scores greater than 0 (direction of excitation, red lines) and those with z-scores less than 0 (direction of inhibition, blue lines). The averaged tone responses for each set were plotted against the pre-conditioning average (gray lines). In layer V, the excitatory tone responses showed a trend toward an increase at 2 h [RM ANOVA, $F_{(1,69)} = 2.54$, $p = 0.11$] and 24 h [RM ANOVA, $F_{(1,61)} = 1.54$, $p = 0.22$], which reduced back to baseline at ≥4 days [RM ANOVA, $F_{(1,69)} = 0.26$, $p = 0.61$]. In layer V, inhibitory responses were no different from pre-conditioning levels. In layer VI, excitatory responses were no different from pre-conditioning levels in any timepoint. However, inhibitory responses were significantly larger than pre-conditioning at ≥4 days [RM ANOVA, $F_{(1,38)} = 31.7$, $p < 0.001$]. Taken together, these findings suggest a time-dependent shift in PL signaling of the tone-shock association: from Layer V excitatory responses to Layer VI inhibitory responses.

Neurons in Layer VI Increase Their Spontaneous Firing Rate at the Late Timepoint

Our observation that late retrieval of fear memory is associated only with inhibitory tone responses in Layer VI appears to

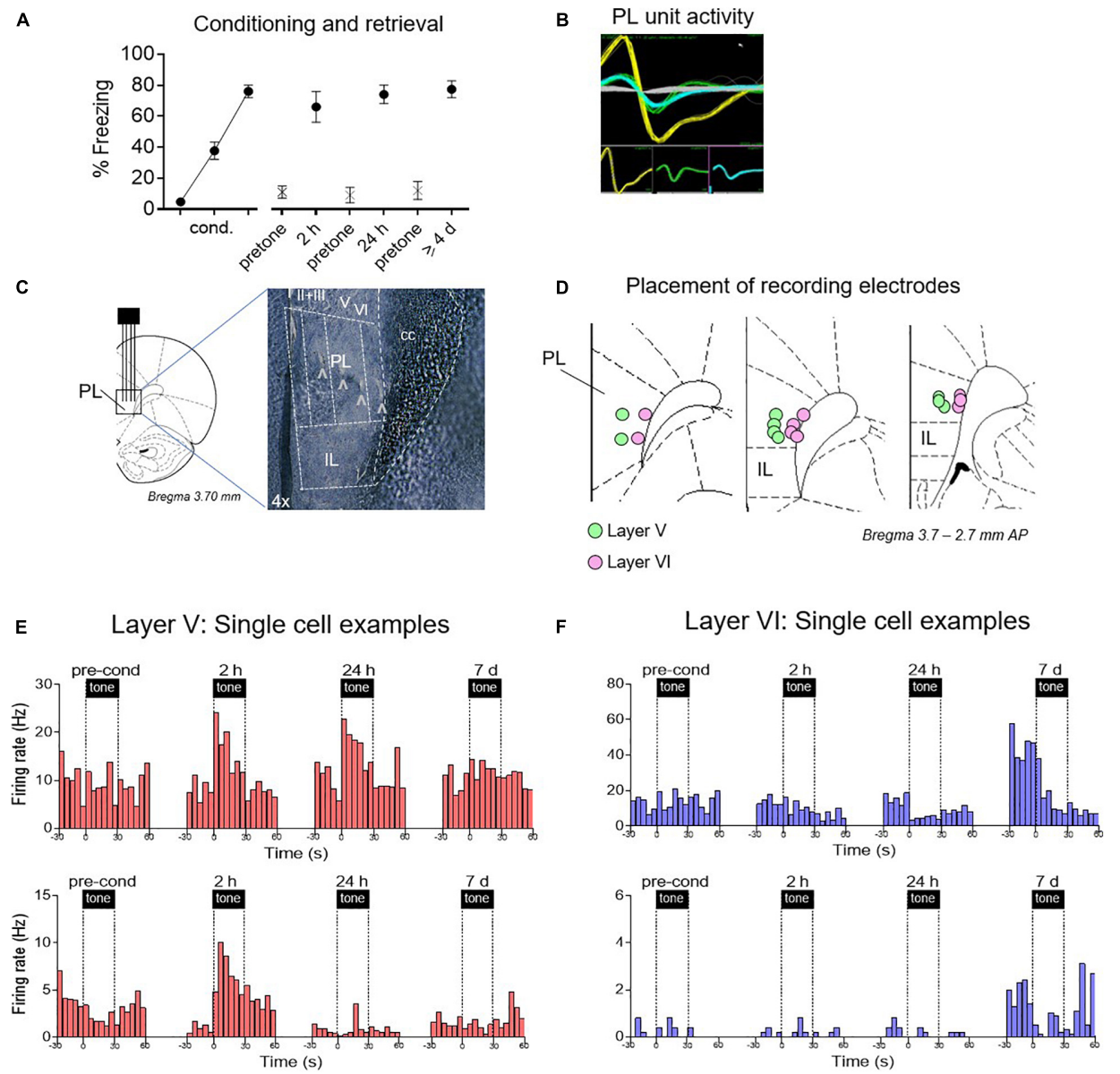
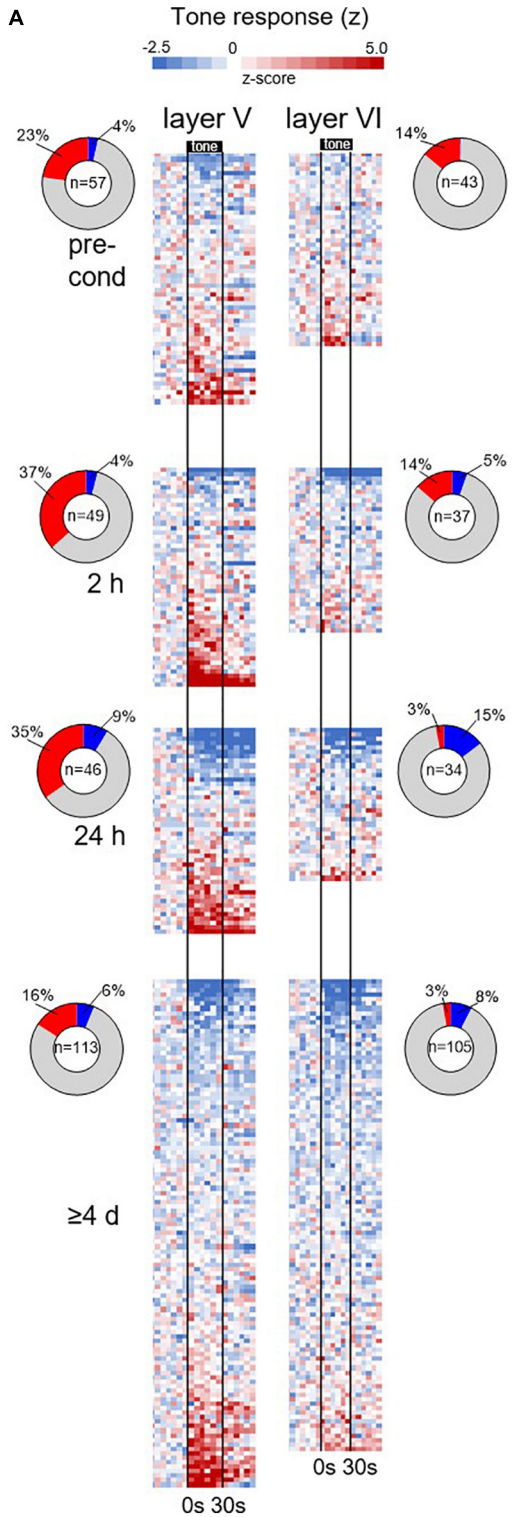
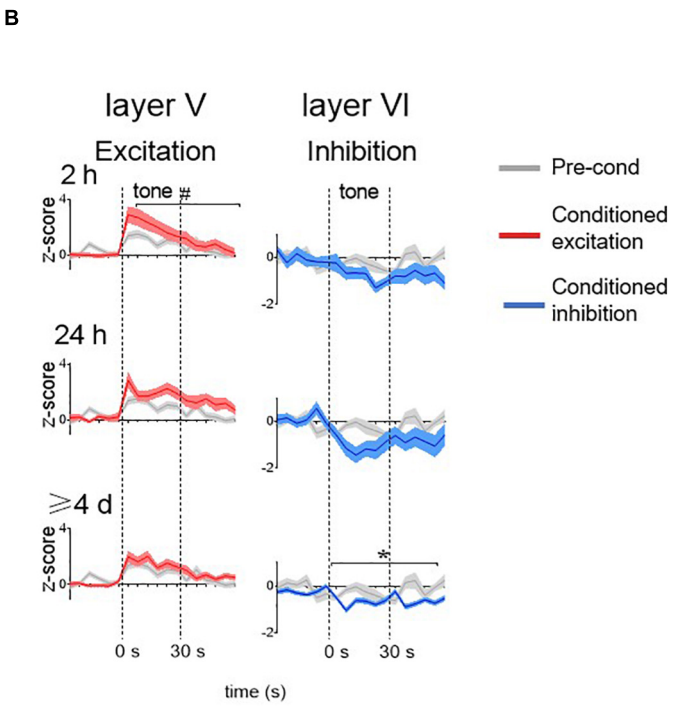


FIGURE 2 | Examples of time-dependent changes in conditioned responses of PL neurons. **(A)** Freezing across retrieval tests (blocks of two trials). After electrode implantation, PL neurons were recorded before conditioning, and 2 h, 24 h, and ≥4 days after conditioning. **(B)** Examples of discriminated unit waveforms. **(C,D)** Placement of silicon probe or wire array electrodes in either layer V or layer VI of PL. **(E)** Peri-stimulus time histograms (PSTHs) of representative PL neurons Layer V in red, showing significant excitatory responses. **(F)** PSTHs of representative PL neurons in Layer VI in blue, showing significant inhibitory responses.

conflict with the increase in c-Fos we observed in PL neurons projecting to PVT at the ≥4 days timepoint (**Figure 1D**). However, an increase in *Fos* expression could reflect an increase in spontaneous activity of these neurons. To assess this, we examined the rate of spontaneous firing (60 s prior to the first tone of the session) over time in both layers V and VI. As shown in **Figure 3C**, the firing rate of Layer V appeared constant across time, however, the firing rate of Layer VI neurons showed a significant increase from 24 h to ≥4 days (2.45–4.28 Hz, Kruskal–Wallis H test, $p = 0.017$). The increase in spontaneous rate in Layer VI is also apparent in the single cell examples shown in **Figure 2F**. In a separate control experiment, 1 rat was exposed to tones without shocks, and then tested with tones 4 days later. Under these conditions, there was no significant increase in the spontaneous firing rate of 88 PL neurons across time (baseline: 2.93 Hz; 2 h: 3.12 Hz; 24 h: 3.24 Hz; 7 days: 3.24 Hz, Kruskal–Wallis H test $p = 0.83$). Thus, the increase in c-Fos labeling we observed at late timepoints in PL neurons projecting to PVT (**Figure 1D**; Do-Monte et al., 2015) likely reflects a conditioned increase in spontaneous activity of these neurons at late timepoints.





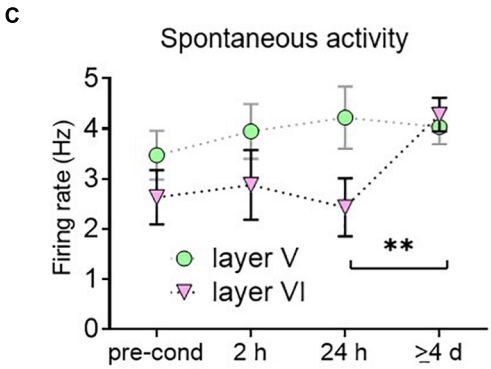


FIGURE 3 | Group data for time-dependent changes in conditioned responses of PL neurons. **(A)** Tone responses of all neurons recorded at each timepoint, based on color-coded depiction of z-scores normalized to pre-tone rate. Each row is a separate cell, and bins are 5 s. Cells are ordered based on the magnitude of the z score averaged across the tone. Vertical black lines indicate onset and offset of 30 s tone. Inset: ring depicts the percentage of neurons showing significant excitatory or inhibitory responses at each timepoint. Number in center indicates the number of cells recorded at that timepoint. **(B)** Averaged tone responsiveness of layer V and layer VI neurons, showing trends toward conditioned excitation ($z > 0$, red) or toward conditioned inhibition ($z < 0$, blue). **(C)** Group data of spontaneous firing rate of PL neurons in layer V and VI (calculated from 60 s period prior to onset of first tone). The spontaneous rate of layer VI neurons significantly increased at the ≥4 days timepoint. # $p = 0.11$; *$p < 0.05$; **$p < 0.01$.

DISCUSSION

Combining c-Fos expression with retrograde tracers, we showed that PL neurons projecting to BLA are activated by the tone conditioned stimulus at early, but not late, timepoints after fear conditioning, whereas PL neurons projecting to PVT showed the opposite pattern. Our unit recording supported the findings for BLA-projecting neurons, revealing excitatory conditioned tone responses in layer V neurons at early, but not late, timepoints. However, Layer VI neurons (the origin of PVT projections) showed inhibitory conditioned responses that increased with the passage of time. These neurons also showed increased spontaneous activity at the late timepoint. Taken together, these results suggest that prelimbic signaling of fear associations shifts with time, from tone-induced excitation to tone-induced inhibition, and that PL modulation of BLA converts to PL modulation of PVT.

Our study follows up on our prior optogenetic findings that PL neurons projecting to BLA were necessary for early (but not late) fear memory, whereas PL neurons projecting to PVT were necessary for late (but not early) fear memory (Do-Monte et al., 2015). However, several questions remained unanswered. In our previous work, the activity of PL neurons projecting to BLA was never assessed. Our present observation that these neurons show increased tone responses during early, but not late, retrieval agrees with the necessity of PL projections to BLA at the early timepoint. The lack of significant tone responses in BLA-projecting neurons at late timepoints supports a shift (rather than an addition) of fear circuits with the passage of time. Consistent with this, PL neurons projecting to PVT showed no conditioned response at the early timepoint, but developed a conditioned response with the passage of time.

We found that the conditioned responses of PL neurons in layer VI consisted of tone-induced inhibition, rather than tone-induced excitation. This was an unexpected finding given that most prior studies of auditory fear conditioning have demonstrated conditioned excitatory responses in PL neurons (Burgos-Robles et al., 2009; Chang et al., 2010; Courtin et al., 2014; Giustino et al., 2016) that are correlated with freezing (Herry et al., 2008; Dejean et al., 2016). This discrepancy may be due to the reliance on a relatively early post-conditioning timepoint in these studies (immediately, 2 h, or 24 h after conditioning). In agreement with this, we and others have observed increases in early gene expression at the early timepoint (Do-Monte et al., 2015; Pollack et al., 2018). Early fear signaling seems to fit a Hebbian model, in which tone-shock pairing leads to potentiation of auditory inputs (LeDoux et al., 1990; but see Grewe et al., 2017). However, with the passage of time, we observed that excitatory tone responses in PL neurons returned to baseline levels. Courtin et al. (2014) observed inhibitory conditioning responses in PL neurons, however, these cells expressed parvalbumin, suggesting they are inhibitory interneurons. The neurons we recorded are likely projection cells, because their average firing rates (mean: 3.6 Hz, range: 0.02–14.8 Hz) were below the cut-off of 15 Hz that has been previously shown to differentiate projection cells from interneurons in PL (Sotres-Bayon et al., 2012).

We propose a model (**Figure 4**) in which fear retrieval circuits shift with the passage of time, from excitatory responses in prelimbic-amygdalar projections, to inhibitory responses in prelimbic-thalamic projections. Inhibitory responses of prelimbic neurons might be driven by inputs from ventral hippocampus (Sotres-Bayon et al., 2012) which would in turn disinhibit PVT outputs to the amygdala, perhaps via the reticular nucleus (Pinault, 2004; Li and Kirouac, 2012).

The existence of conditioned inhibitory responses of PL neurons projecting to PVT appears to disagree with ours and others' findings of an increase in c-Fos expression during late retrieval, and that optogenetic silencing of this projection impaired late fear retrieval. However, in the present study, we also observed an increase in spontaneous activity during late timepoint in these neurons, which could account for the increase in c-Fos expression. Additionally, the optogenetic silencing in our previous study was initiated 10 s prior to tone onset, which would have reduced spontaneous activity. A conditioning-induced increase in spontaneous activity may facilitate late retrieval, perhaps by release of neurotrophic factors within the PVT (Penzo et al., 2015). However, it is also possible that the inhibitory responses we observed are simply a correlate of late retrieval, without having a causal role.

Some caveats need to be considered when interpreting our findings. For the c-Fos co-labeling results, we only found differences in conditioning vs. no conditioning for PL-BLA at 2 h and PL-PVT at 7 days. There is no significant interaction effect between PL-BLA and PL-PVT neuronal activity across time. In most of our recordings, different groups of neurons were sampled at different timepoints, leaving open the possibility that factors other than the passage of time were responsible for the differences we observed between recordings. Another caveat is that we did not record from identified neurons known to project to BLA vs. PVT, but instead used cortical layer location to suggest a likely target. Our recording findings resembled our c-Fos findings, which were based on confirmed targets, however, it will be necessary to use neuronal tagging methods (Burgos-Robles et al., 2017) to confirm differences in conditioned responses of specific PL subpopulations.

In humans, neuroimaging research has focused on retrieval tests that occur 24 h after fear conditioning, and show that dACC activity is positively correlated with fear responses (Milad et al., 2007; Morey et al., 2015; Fullana et al., 2016; Marin et al., 2016; Savage et al., 2020). Considering our findings, it would be interesting to study brain activity at later timepoints. Perhaps assessing human prefronto-thalamic activity days or weeks after conditioning would yield a better understanding of the retrieval of fear memories.

MATERIALS AND METHODS

Bar–Press Training

A total of 14 male Sprague–Dawley rats (Harlan Laboratories, Indianapolis, IN, United States) weighing 300–360 g were used in this study. Rats were restricted to 18 g/day of standard laboratory chow, followed by 10 days of training to press a bar for

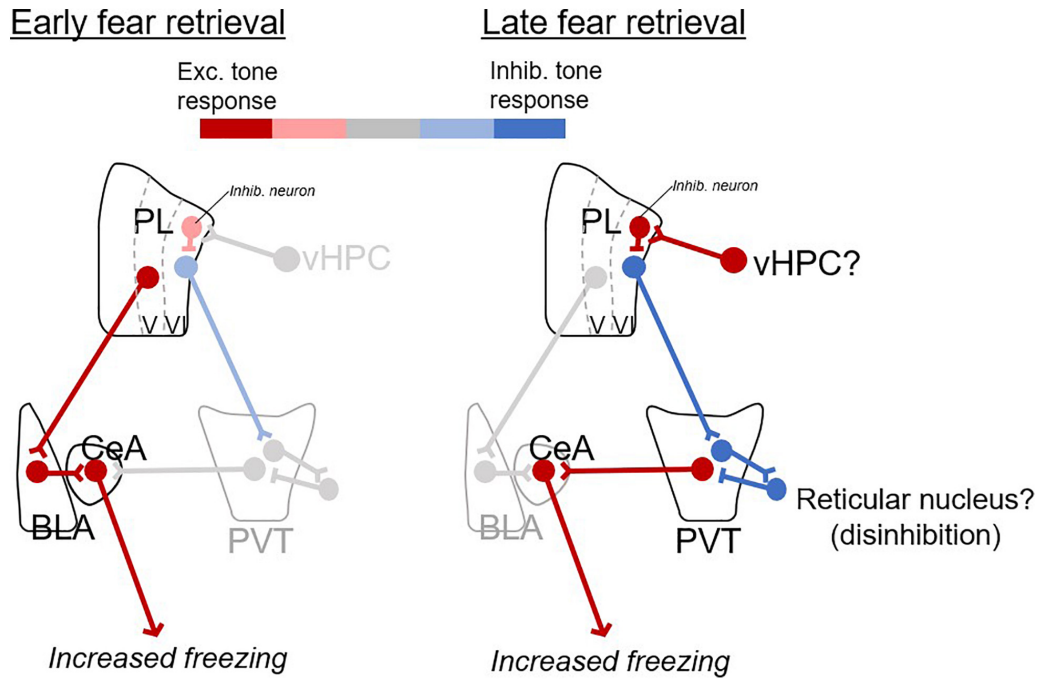


FIGURE 4 | Proposed model of prelimbic circuits for early and late fear retrieval. Changes in excitatory (red) and inhibitory (blue) responses with the passage of time. For early retrieval **(left)**, excitatory CS responses from PL to BLA excite CeA output to produce freezing. For late retrieval **(right)**, inhibitory CS responses from PL to PVT disinhibit PVT (via neurons in the reticular nucleus of thalamus), which excites CeA and produces freezing. The ventral hippocampus (vHPC) is suggested as a likely candidate for inducing inhibitory CS responses in PL neurons.

sucrose pellets on a variable interval schedule of reinforcement averaging 30 s (VI–30 s). Rats were trained until they reached a criterion of >10 presses/min. All procedures were approved by the Institutional Animal Care and Use Committee of the University of Puerto Rico School of Medicine, in compliance with National Institutes of Health's Guide for the Care and Use of Laboratory Animals (Eighth Edition).

Retrograde Tracer Surgery

Prior to fear conditioning, rats were anesthetized with isofluorane inhalant gas (5%) in an induction chamber and positioned in a stereotaxic frame. Isofluorane (1–2%) was delivered through a face mask for anesthesia maintenance. Rats were stereotaxically infused in the right hemisphere with retrograde tracers in BLA and PVT. Fast Blue (Sigma-Aldrich), was infused in PVT (0.1 μL; −2.8 mm AP; +1.8 mm ML; −5.2 mm DV, at a 70° from horizon angle placement) and cholera toxin B Alexa Fluor 594 (CTb, Thermo Fisher Scientific), another retrograde tracer, was infused in BLA (0.25 μL; −2.8 mm AP; ±4.8 mm ML; −8.85 mm DV). Tracers were infused at a rate of 0.01 μL/min for Fast Blue and 0.025 μL/min for CTb, and the injectors were left in place for 10 min to allow the tracers to diffuse. Following surgery, rats were allowed 1 week to recover prior to behavior experiments.

Fear Conditioning

We used the same parameters for auditory fear conditioning as in our previous studies (Burgos-Robles et al., 2007; Sierra-Mercado et al., 2011). Briefly, rats were conditioned with a pure tone (30 s, 4 kHz, 75 dB) co-terminating with a shock delivered through the floor grids (0.5 s, 0.5 mA). The inter–trial interval was variable, averaging 3 min. Rats were fear conditioned with one habituation tone (without shock), followed by six tone-shock pairings, over a period of 33 min. Fear retrieval tests consisted of two tone presentations, presented at three timepoints following conditioning: 2 h, 24 h, 4, or 7 days.

Immunohistochemistry for c-Fos

One hour after the end of the final behavioral test, rats were anesthetized with sodium pentobarbital (450 mg/Kg, i.p.) and then perfused transcardially with 250 ml of 0.9% saline followed by 500 ml of cold fresh 4% paraformaldehyde (PFA) in 0.1 M phosphate buffer (PBS) at pH 7.4. Brains were removed and fixed overnight in 4% PFA, and transferred to 30% sucrose in 0.1 M PBS for 48 h, for cryoprotection. Frozen sections were cut coronally (40 μm) with a cryostat (CM 1850; Leica) at different levels of the prefrontal cortex, paraventricular thalamus, and amygdala.

Sections were initially blocked in a solution of 2% normal goat serum (NGS, Vector Laboratories, United States) and 0.1% Tween (Tween-20, Sigma-Aldrich, United States) in 0.1 M PBS (pH 7.4) for 1 h. Afterward, sections were incubated overnight at room temperature with anti-c-Fos serum raised in rabbit (Ab-5, Oncogene Science, United States) at a concentration of 1:2,000. Sections were then incubated for 2 h at room temperature in a solution of fluorescent secondary-antibody Alexa Fluor 488 (1:500; Life Technologies). Sections were cover slipped with

anti-fading mounting media (Vector Laboratories) and examined under an epifluorescent microscope.

Single Unit Recordings From PL

Two types of electrodes were used to record from PL neurons: a 2 × 8 fixed wire array (NB Labs, TX, United States) (10 rats) and a silicon probe (two rats that where conditioned and one rat for naïve recordings). The array consisted of two columns, spaced 500 μm apart, with eight stainless steel wires each 50 μm diameter and insulated with Teflon. There was 50 μm of space between each wire. Extracellular waveforms that exceeded a voltage threshold were digitized at 40 kHz and stored on a computer (MAP box, Plexon Inc.). Waveforms were then sorted offline using three-dimensional plots of principal component and voltage vectors (Offline Sorter; Plexon Inc.) and clusters corresponding to individual neurons were tracked. The silicon probe had four shanks with eight contacts per shank (NeuroNexus, Buzsaki32 mounted on a dDrive). The shanks were spaced 200 μm apart. Eight contacts were etched into the edge of the tip of each shank. The distance between the first and last contact was 140 μm. The movable drive was lowered 150 μm after every recording session, in order to record from a different set of neurons at each timepoint. Continuous voltage measurements were sampled and digitized at 30 kHz (Intan Technologies, RHD 2000 system). Voltages were then automatically threshold and sorted using Klusta software[1].

Data Analysis

Rats' behavior was recorded with digital video cameras (Micro Video Products, Bobcaygeon, ON, Canada) and analyzed for freezing using ANY-Maze software 5.2 (Stoelting, United States). Alpha values were set at 0.05 throughout all statistical analysis.

c-Fos immuno-labeled neurons were automatically counted at 20X magnification with an Olympus microscope (Model BX51) equipped with a digital camera, a fluorescence halogen lamp, with multiple filter cubes. Micrographs were generated for prelimbic cortex (PL, +2.40 to +3.70 AP). The counts of c-Fos immuno-labeled neurons were averaged for the right hemisphere (infused side) in three different sections for each structure (Metamorph software version 6.1). The density of c-Fos labeling was calculated by dividing the number of c-Fos positive neurons by the total area of each region (counts/0.1 mm^2). The number of co-labeled neurons (c-Fos + retrograde tracer) was automatically counted and expressed as a percentage of the total number of tracer- labeled neurons. We applied an extreme studentized deviate analysis within each experimental group to detect potential outliers. We detected one outlier in the conditioned PL-BLA tagged neurons at 2 h and one outlier in the conditioned PL-BLA tagged neurons at 7 days. These outliers were removed from the dataset. Two tailed, unpaired Student's *t*-test was used to compare no-cond versus cond groups.

Timestamps of neural spiking and flags for the occurrence of tones and shocks were exported to NeuroExplorer (NEX Technologies) for peri-stimulus time histogram (PSTH) and spontaneous rates analysis. A total of 483 PL neurons were recorded (264 in layer V and 219 in layer VI). Neurons that exceeded 15 Hz during a spontaneous recording session were presumed to be putative interneurons as per previous studies from our laboratory using unsupervised cluster analysis (Sotres-Bayon et al., 2012). To detect significant tone-elicited changes in PL activity, we determined whether neurons changed their firing rate significantly during the first, or second, or third 5 s bin after tone onset. A z-score for each of these three bins was calculated relative to 12 pre-tone bins of equal duration. For the pie chart insets in **Figure 3A**, PL neurons were classified as showing excitatory or inhibitory tone responses if any of the initial three tone bins was greater than 1.65 z for excitation or less than −1.65 z for inhibition ($p < 0.05$, one tailed). Group data for tone-responses (group PSTHs) in **Figure 3B** were generated by averaging all tone responses that were net positive (conditioned excitation) and all tone responses that were net negative (conditioned inhibition). These were compared with pre-conditioning tone responses that were net positive or net negative, respectively, using repeated measures ANOVA. Spontaneous activity was collected for 2 min before tones were played. Spontaneous activity change through time was analyzed with a Kruskal–Wallis *H* test.

[1]http://klusta.readthedocs.io/en/latest/

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by the Institutional Animal Care and Use Committee of the University of Puerto Rico School of Medicine.

AUTHOR CONTRIBUTIONS

KQ-L and GQ: conceptualization, methodology, writing – original draft, and writing – review and editing. KQ-L, AV-M, and GQ: investigation. GQ: funding acquisition, resources, and supervision. All authors contributed to the article and approved the submitted version.

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