THE COGNITIVE THALAMUS

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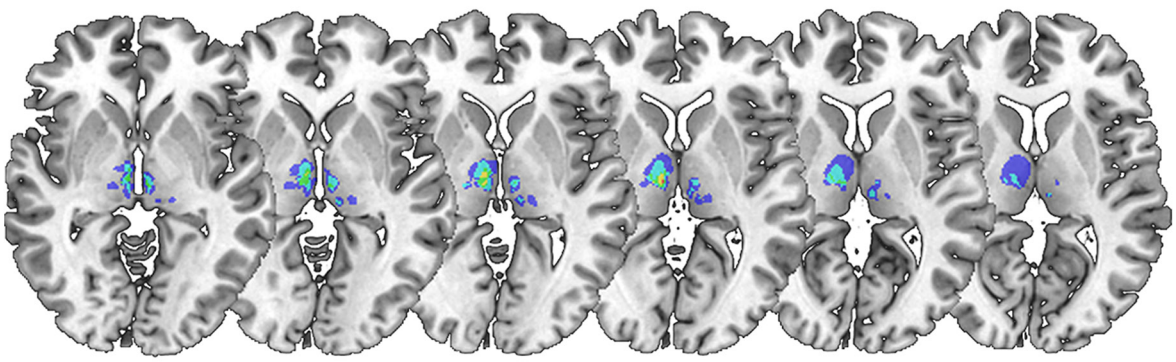

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THE COGNITIVE THALAMUS

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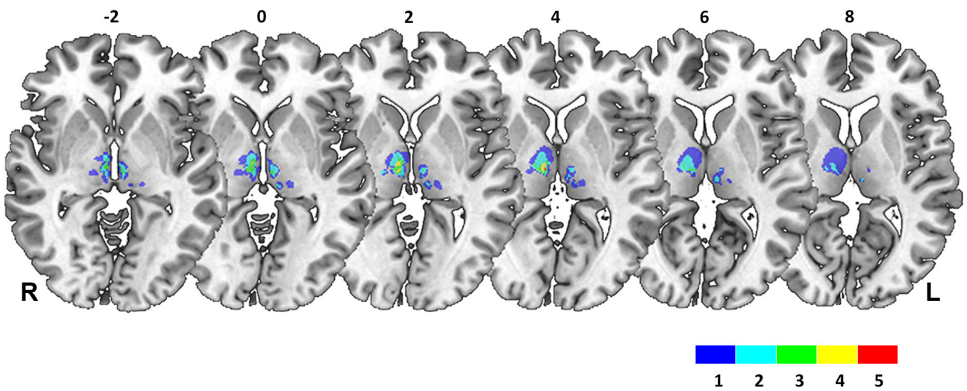

Overlay plot of thalamic lesions in patient sample. Lesion volumes of all 14 patients are plotted on axial sections of a MNI brain template with numbers denoting z-coordinates in MNI space. Different colors denote the number of overlapping lesions per voxel, ranging from 1 to a maximum of 5 individual lesion volumes. Image display follows radiological convention with right hemisphere (R) shown on left side of picture. L, Left; R, Right hemisphere. (Figure 1 (A) from Ostendorf et al., 2013, Front. Syst. Neurosci., doi: 10.3389/fnsys.2013.00010).

Cognitive processing is commonly conceptualized as being restricted to the cerebral cortex. Accordingly, electrophysiology, neuroimaging and lesion studies involving human and animal subjects have almost exclusively focused on defining roles for cerebral cortical areas in cognition. Roles for the thalamus in cognition have been largely ignored despite the fact that the extensive connectivity between the thalamus and cerebral cortex gives rise to a closely coupled thalamo-cortical system. However, in recent years, growing interest in the thalamus as much more than a passive sensory structure, as well as methodological advances such as high-resolution functional magnetic resonance imaging of the thalamus and improved electrode targeting to subregions of thalamic nuclei using electrical stimulation and diffusion tensor imaging, have fostered research into thalamic contributions to cognition.

Evidence suggests that behavioral context modulates processing in primary sensory, or first-order, thalamic nuclei (for example, the lateral geniculate and ventral posterior nuclei),

allowing attentional filtering of incoming sensory information at an early stage of brain processing. Behavioral context appears to more strongly influence higher-order thalamic nuclei (for example, the pulvinar and mediodorsal nucleus), which receive major input from the cortex rather than the sensory periphery. Such higher-order thalamic nuclei have been shown to regulate information transmission in frontal and higher-order sensory cortex according to cognitive demands.

This Research Topic aims to bring together neuroscientists who study different parts of the thalamus, particularly thalamic nuclei other than the primary sensory relays, and highlight the thalamic contributions to attention, memory, reward processing, decision-making, and language. By doing so, an emphasis is also placed on neural mechanisms common to many, if not all, of these cognitive operations, such as thalamo-cortical interactions and modulatory influences from sources in the brainstem and basal ganglia. The overall view that emerges is that the thalamus is a vital node in brain networks supporting cognition.

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Table of Contents

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EDITORIAL
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The cognitive thalamus

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Keywords: mediodorsal thalamus, anterior thalamus, intralaminar thalamus, thalamocortical interactions, pulvinar

The thalamus, once viewed as passively relaying sensory information to the cerebral cortex, is becoming increasingly acknowledged as actively regulating the information transmitted to cortical areas. There are a number of reasons for this change. First, evidence suggests that first-order thalamic areas, like the lateral geniculate nucleus, ventral division of the medial geniculate nucleus, and the ventral posterior nuclei, can modulate neural processing along the sensory pathways to the cortex according to behavioral context (O'Connor et al., 2002; McAlonan et al., 2008). Second, much of the thalamus receives relatively little input from the sensory periphery, instead receiving its major driving input from the cortex. This higher-order thalamus forms pathways between cortical areas, which can strongly influence cortical activity (Theyel et al., 2010; Purushothaman et al., 2012; Saalmann et al., 2012). Third, lesions to higher-order thalamic areas, such as the pulvinar and mediodorsal nucleus, can produce severe attention and memory deficits (Saalmann and Kastner, 2011; Baxter, 2013; Bradfield et al., 2013; Jankowski et al., 2013; Mitchell and Chakraborty, 2013), suggesting an important role for the thalamus in cognition.

In this Research Topic, we bring together neuroscientists who study different parts of the thalamus, particularly the higher-order thalamic nuclei, to highlight thalamic contributions to learning (Bradfield et al., 2013; Habib et al., 2013), memory processes (Baxter, 2013; Funahashi, 2013; Jankowski et al., 2013; Mitchell and Chakraborty, 2013; Saalmann, 2014), set-shifting (Bradfield et al., 2013; Minamimoto et al., 2014; Saalmann, 2014), language (Klostermann et al., 2013), as well as movement monitoring and control (Ostendorf et al., 2013; Prevosto and Sommer, 2013; Minamimoto et al., 2014). These studies incorporate a range of methods, from molecular to systems-level approaches, and connect rodent, non-human primate and human data, for a better understanding of human cognition.

The first three articles focus on movement monitoring and motor control. Based on lesion data from clinical subjects, Ostendorf et al. (2013) show that the central thalamus makes an important contribution to predicting the perceptual consequences of eye movements. Focusing on cerebellocortical pathways incorporating the central and ventral lateral thalamus, Prevosto and Sommer (2013) review evidence for thalamic modulation of movement processing based on cognitive requirements. Encompassing a number of thalamic nuclei, including the pulvinar, mediodorsal and ventral intermediate nuclei, Klostermann et al. (2013) discuss contributions of the thalamus and basal ganglia to language perception and production.

The Research Topic continues on the theme of behavioral flexibility. Minamimoto et al. (2014) show that that the macaque centromedian nucleus, in the intralaminar thalamus, plays a role in counteracting behavioral biases, which contributes to flexible behavior via interactions with the basal ganglia. Bradfield et al. (2013) review evidence from rodent studies that another intralaminar thalamic nucleus, the parafascicular thalamus, also contributes to behavioral flexibility, whereas the mediodorsal thalamic nucleus plays a key role in acquiring goal-directed behavior.

Next, the focus shifts to memory processes. Jankowski et al. (2013) review contributions of the anterior thalamus, and its interactions with the hippocampus and cortex, to memory processing and spatial navigation in rodents. This includes evidence for oscillatory activity at theta frequencies

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in the anterior thalamus. Habib et al. (2013) investigate memory processes in the auditory thalamus, showing differential molecular events underlying safety learning and fear conditioning.

Finally, there are four reviews highlighting different functions of the large mediodorsal thalamic nucleus and its interactions with the prefrontal cortex in primates. Mitchell and Chakraborty (2013) discuss the effects of lesions of the mediodorsal thalamus, supporting its role in memory and other cognitive processes. Baxter (2013) argues that the mediodorsal thalamus regulates plasticity within prefrontal cortex as well as the flexibility of prefrontal-dependent operations. Funahashi (2013) reviews contributions of the mediodorsal thalamus to spatial working memory, including how interaction between the thalamus and prefrontal cortex can enable sensory-to-motor transformations of maintained information. To conclude, Saalmann (2014) proposes that the mediodorsal thalamus regulates synchrony between neurons in prefrontal cortex and, consequently, their information exchange according to cognitive control demands.

This Research Topic highlights the key contributions of the thalamus to neural processing in cortico-cortical, hippocampo-cortical, cortico-striatal and cerebello-cortical pathways. Although the underlying mechanisms of thalamic influence on these pathways remain to be clarified, there is growing evidence that the thalamus plays a key role in dynamically routing information across the brain (Saalmann et al., 2012; Xu and Sudhof, 2013). Such a role may involve flexibly synchronizing ensembles of neurons, thereby configuring brain networks for the current behavioral context. Taken together, the articles in this Research Topic show that thalamic interactions with cortical and subcortical areas are integral to behavioral flexibility, memory processes and cognition in general.

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A role of the human thalamus in predicting the perceptual consequences of eye movements

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Internal monitoring of oculomotor commands may help to anticipate and keep track of changes in perceptual input imposed by our eye movements. Neurophysiological studies in non-human primates identified corollary discharge (CD) signals of oculomotor commands that are conveyed via thalamus to frontal cortices. We tested whether disruption of these monitoring pathways on the thalamic level impairs the perceptual matching of visual input before and after an eye movement in human subjects. Fourteen patients with focal thalamic stroke and 20 healthy control subjects performed a task requiring a perceptual judgment across eye movements. Subjects reported the apparent displacement of a target cue that jumped unpredictably in sync with a saccadic eye movement. In a critical condition of this task, six patients exhibited clearly asymmetric perceptual performance for rightward vs. leftward saccade direction. Furthermore, perceptual judgments in seven patients systematically depended on oculomotor targeting errors, with self-generated targeting errors erroneously attributed to external stimulus jumps. Voxel-based lesion-symptom mapping identified an area in right central thalamus as critical for the perceptual matching of visual space across eye movements. Our findings suggest that trans-thalamic CD transmission decisively contributes to a correct prediction of the perceptual consequences of oculomotor actions.

Keywords: efference copy, corollary discharge, visual stability, prediction, thalamus, human, lesion, sensorimotor

INTRODUCTION

Active perceptual exploration helps animals and humans to sample relevant aspects of the external world, but constantly changes sensory input. These self-generated changes in sensory input (so-called reafference) would severely impair coherent percepts when not properly distinguished from environmental changes. Forward models have been proposed as a candidate mechanism to anticipate the perceptual consequences of actions by an internal monitoring of corresponding motor commands (Wolpert and Miall, 1996). The existence of such internal monitoring signals had been proposed for a long time as an efficient means to disambiguate self-induced displacements of perceptual input from external changes in the outside world (Purkyně, 1825; Von Helmholtz, 1866). Important experimental support for internal monitoring processes was obtained by Von Holst and Mittelstaedt (1950) and Sperry (1950) who coined the hypothetical underlying signal "efference copy" or "corollary discharge" (CD), respectively.

Recently, single-unit recordings in non-human primates identified a CD pathway that conveys oculomotor monitoring information from brainstem structures to the frontal eye field (FEF) via central portions of the thalamus (Sommer and Wurtz, 2002). Additional experimental evidence suggests that information carried through this pathway bears direct functional relevance for visuomotor behavior: transient inactivation of this pathway on the thalamic level impaired oculomotor behavior in a task that required internal monitoring of saccade metrics (Sommer and Wurtz, 2002). Similar findings have been observed in patients with focal thalamic stroke (Gaymard et al., 1994; Bellebaum et al., 2005), suggesting that trans-thalamic CD is critical for accurate generation of rapid oculomotor sequences. These findings do however not directly address the question whether trans-thalamic CD signals are also involved in anticipating the perceptual changes imposed by saccades and whether CD signals may thus ultimately aid perceptual stability across eye movements.

Recently, we aimed to address this question in a single patient with a focal ischemic lesion of the right central thalamus (Ostendorf et al., 2010). The behavioral assessment of CD function in this patient seemed warranted because of the close anatomical overlap of his focal lesion with the homologous thalamic site in the monkey brain at which CD signals had been recorded (Sommer and Wurtz, 2002, 2004). We used a simple visuomotor task to assess a possible deficit in the perceptual matching of space across eye movements: subjects were instructed to report the apparent direction of an unpredictable target displacement that happened in temporal contingency with a saccadic eye movement to this target stimulus. Attenuation of motion perception during saccades (Burr et al., 1982) limits the usefulness of intrasaccadic motion cues to guide this perceptual decision. Hence, surprisingly large object displacements can escape conscious detection when they take place during saccadic eye movements, a phenomenon called saccadic suppression of displacement (SSD; Bridgeman et al., 1975). However, small modifications of the original task can lead to dramatic performance

improvements in healthy subjects (Deubel and Schneider, 1994; Deubel et al., 1996): a short blanking of the target reverses SSD to high perceptual sensitivity for displacement detection that can even exceed performance under steady fixation (Deubel et al., 1996). Thus, a faithful representation of target position is apparently retained across eye movements and can, at least under certain conditions, be combined with accurate and precise oculomotor monitoring information to effectively guide perceptual judgments.

Compared to age-matched control subjects, we observed a lateralized deficit for this task variant in the patient, manifesting as inaccurate matching of locations across eye movements (Ostendorf et al., 2010). He showed a systematic bias of perceptual reports toward apparent backward displacements that was consistent with an internal underestimation of eye movement amplitudes. Side and sign of this perceptual deficit were identical to additional impairments observed for the generation of rapid saccade sequences, pointing toward a common disruption of internal monitoring underlying both behavioral deficits. Moreover, the putative deficit in eye movement monitoring led to a systematic dependency of perceptual decisions on saccadic errors in the patient (Ostendorf et al., 2010). While normal subjects can reliably predict trial-to-trial variations in eye movement targeting and anticipate the associated perceptual mismatches (Collins et al., 2009), he systematically misattributed self-induced visual errors to external stimulus changes (Ostendorf et al., 2010). Taken together, behavioral deficits in this patient were consistent with an incomplete and noisy CD signal, leading to uncertain and hypometric estimates of executed eye movements.

Here, we aim to address specificity and generalizability (Robertson et al., 1993) of our previous findings by probing perceptual performance in a larger sample of 14 patients who sustained focal thalamic lesions from ischemic stroke in different portions of the thalamus. As in our case study (Ostendorf et al., 2010), we used the original intrasaccadic displacement task in which SSD is expected to appear (Bridgeman et al., 1975) and the task variant proposed by Deubel et al. (1996) in which high perceptual sensitivity in normal subjects has been demonstrated repeatedly (Deubel et al., 1996; Collins et al., 2009). We compared perceptual performance in the patient group with a sample of control subjects in these two task variants. We capitalized on intra-individual differences between task conditions and saccade directions (Bellebaum et al., 2005) to identify deficits in the trans-saccadic matching of visual space in individual patients. Beyond standard groupwise comparisons, the acquisition of high-resolution imaging data at the time of behavioral testing allowed us to perform voxel-based lesion-symptom mapping (Rorden and Karnath, 2004) in order to identify thalamic regions critical for task performance.

METHODS

SUBJECTS

Fourteen patients with focal lesions of the thalamus [mean age ± standard deviation (SD), 40.6 ± 9.1 years; five females] participated in this study. Patients were recruited from the Department of Neurology, Charité - Universitätsmedizin Berlin, Germany and were part of a patient cohort that had participated in a recent neuropsychological study (Liebermann et al., 2013). Twenty healthy subjects (38.8 ± 7.8 years; eight females) served as controls. Handedness was assessed by Edinburgh-Handedness-Inventory (Oldfield, 1971) with a laterality quotient of ≥40 and ≤40 denoting right and left-handedness, respectively. In the patient group, 13 subjects were right-handed, one left-handed and none ambidextrous (mean laterality quotient ± SD, 64.2 ± 36.2). 17 control subjects were right-handed, two left-handed, and one ambidextrous (mean laterality quotient ± SD, 68.3 ± 55.1). Average years of education (±SD) were 14.3 (±2.8) in patients and 16.1 (±2.3) in control subjects. No significant differences emerged for these demographic measures between patients and the control subjects. Control subjects had no history of neurological or psychiatric disorders and all but one were naive with respect to the purpose of the study. Informed consent was obtained from all subjects before participation in the study, which was approved by the local Ethics Committee (Charité - Universitätsmedizin Berlin, Campus Mitte, Germany). Apart from a slight right-sided hemiparesis accompanied by prickling paresthesia in one patient (P11), neurological examination was normal in all patients at the time of testing (see **Table 1** for initial symptoms of individual patients).

IMAGING AND LESION RECONSTRUCTION

Imaging and lesion reconstruction was identical to Liebermann et al. (2013). In brief, structural imaging was performed on a clinical whole-body scanner (Magnetom Vision, Siemens) at 1.5 T. For reconstruction of lesions, a three-dimensional dataset was acquired, using a magnetization prepared rapid acquisition gradient-echo imaging sequence (MPRAGE, isotropic resolution 1 mm). To screen for additional extra- and intrathalamic lesions at the time of testing, axial images of the whole brain and coronal images of the thalamic region were acquired using a T2-weighted turbo inversion recovery magnitude sequence (whole brain and thalamus, voxel-size 0.91 × 0.9 × 5 mm and 0.95 × 0.9 × 2 mm, respectively). High-resolution imaging revealed no further lesions except for single lacunar lesions in four patients [left cerebellum, lobule VI (patient P6) and lobule VIIIb (patient P3), right cerebellum, lobule VI (patient P5), and genu of corpus callosum (patient P8)]. In addition, the thalamic lesion of one patient extended slightly into the right hypothalamus (patient P13).

Individual brain scans were spatially normalized using MATLAB (The MathWorks, Natick, MA, USA) and the Statistical Parametric Mapping package (SPM5, Wellcome Department of Imaging Neuroscience, London, http://www.fil.ion.ucl.ac.uk/spm). Individual MRI data sets were normalized to a T1 Montreal Neurological Institute (MNI) template provided with SPM by using the unified segmentation and normalization function. This method has recently been demonstrated to provide reliable normalization of focally lesioned brains to template images (Crinion et al., 2007), although cost function masking might still be recommended for larger lesions (Andersen et al., 2010). For identification of affected thalamic nuclei in individual patients, lesions were co-registered to an atlas of the human thalamus (Morel, 2007). Coronal reconstructions from MRI data sets were evaluated against corresponding atlas plates. Relative

Table 1 | Demographic and lesion characteristics of patients.

Patient	Age	Sex	Years of education	IQ	TSL (months)	Lesion side	Lesion vol. (cm^3)	Initial symptoms
1	51	F	9	94	22	R	0.13	Left hemiparesis and hypesthesia
2	45	M	13	130	0.25	L	0.06	Right hyp-/paresthesia
3	40	M	18	n/a	12	L	0.07	Right hemiparesis, diplopia
4	45	M	18	118	1	L	0.03	Anomic aphasia, dizziness
5	36	M	13	124	29	B (R>L)	0.03	Diplopia, anomic aphasia
6	43	F	13	n/a	12	B (L>R)	0.36	Vigilance disturbance, aphasia
7	31	M	13	112	8	R	0.12	Left hemiparesis and paresthesia, headache
8	53	M	12	100	1	R	2.35	Left hemiparesis, ataxia, vigilance disturbance, dizziness
9	25	F	13	101	0.5	R	0.21	Headache, nausea
10	37	M	13	118	10	R	0.2	Left hemiparesis, amnesia
11	57	F	13	118	60	L	0.15	Right hemiparesis and paresthesia*
12	39	M	18	130	11	R	0.26	Diplopia, dysarthria, vertigo
13	32	F	18	124	2	L	0.2	Right hemiparesis, diplopia, vertigo
14	34	M	16	118	45	B (R>L)	1.13	Right hemiparesis, diplopia, dysarthria, loss of consciousness

Asterisk indicates persistent symptom (only patient P11).

Abbreviations: Lesion vol., lesion volume; TSL, time since lesion.

lesion extent for a given thalamic nucleus was rated in three increments (less than 1/3, between 1/3 and 2/3, more than 2/3 of nucleus volume affected, see **Figure 1B**). Lesion overlap and subtraction plots (Rorden and Karnath, 2004) were generated on a group level for further lesion-to-symptom mapping. For this analysis, lesions were manually traced in normalized three-dimensional space with MRIcron software (version as of December 2012, www.mccauslandcenter.sc.edu/mricro/mricron/index.html). Estimation of lesion volume and lesion overlap and subtraction analyses (Rorden and Karnath, 2004) were conducted with resulting volumes of interest (VOIs) in MRIcron. For further statistical analysis we used non-parametric voxel-based lesion-symptom mapping as implemented in NPM, which is part of the MRIcron software package. Only voxels that were lesioned in at least 2 patients were included in this analysis.

EXPERIMENTAL SET-UP AND TASK

The intrasaccadic displacement task was identical to Ostendorf et al. (2010). Stimuli were presented on a 22-in. CRT-monitor (screen resolution, 1024 × 768 pixels; refresh rate, 110 Hz) at a viewing distance of 50 cm. Subjects' heads were stabilized by a head- and chinrest. Eye movements were recorded with high-speed video-oculography (Sensomotoric Instruments; sampling rate, 500 Hz) of the right eye. Experiments were carried out in an otherwise darkened room. Subjects completed the experiments in multiple test sessions on different days. All stimuli were white (luminance, 56.5 Cd/m^2) and presented on a homogenous gray background (luminance, 13.1 Cd/m^2).

Trials started with presentation of a fixation cross (extent, 0.5°) at 6 or 8° left or right from screen center (see **Figure 2** for task schematic). After a variable foreperiod (1600–2400 ms), the fixation cross was switched off and a target cue (diameter, 0.5°) was presented at the other screen side at 6 or 8° eccentricity, respectively. Subjects were instructed to perform a saccadic eye movement toward this target, which was switched off during saccade execution and reappeared either directly (STEP condition) or after a temporal gap of 250 ms (BLANK condition) at an unpredictable position. Target displacement for a given trial was adapted by three independent, randomly interleaved staircases with a constant step size of 3° in the STEP task (BLANK task, 1.5°). Specifically, when the subject indicated a target displacement to the left for a given displacement level, the next displacement level for a given staircase would be shifted by 3° (BLANK task, 1.5°) to the right, i.e., staircases followed a one-up, one-down logic. Staircases started at a displacement level of 7° (GAP task, 3.5°) right- and leftward and 0° (no displacement) with respect to initial target position. Interleaved displacement levels for the three staircases enabled sampling the point of subjective target constancy with a resolution of 1° (BLANK task, 0.5°) while collecting a sufficient number of trials at higher confidence levels. In both conditions, subjects reported the apparent jump direction by pressing one of two manual response keys. Response registration was limited to maximally 5 s and the target was switched off when a key press was recorded or maximum response time had elapsed. The screen was then blanked for 1600 ms and a next trial started. Saccade direction was fixed within five to six blocks of 24 trials each.

DATA ANALYSIS

Eye movement data were low-pass filtered, visualized, and analyzed in Matlab by using the ILAB toolbox (Gitelman, 2002) and self-written routines. Saccade onset and offset were determined by a fixed velocity criterion (threshold, 30°/s). Start and end positions were determined as fixation periods preceding saccade onset and following saccade end. We ensured that intrasaccadic target displacements occurred during the first half of the saccadic eye movement [mean delay after saccade onset (±SD), 19 (±4) ms; see lower right panel in **Figure 2**]. Cumulative gaussians were

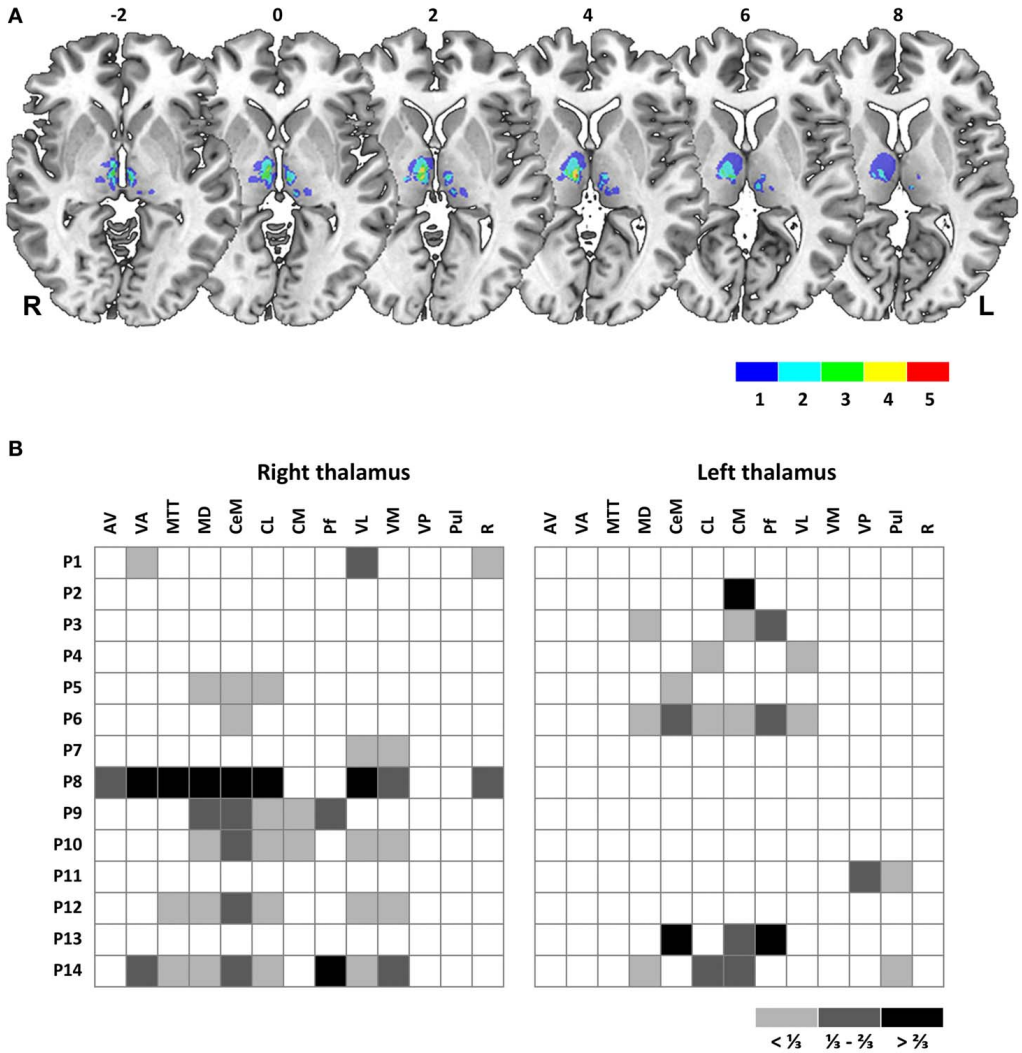

FIGURE 1 | (A) Overlay plot of thalamic lesions in patient sample. Lesion volumes of all 14 patients are plotted on axial sections of a MNI brain template with numbers denoting z-coordinates in MNI space. Different colors denote the number of overlapping lesions per voxel, ranging from 1 to a maximum of 5 individual lesion volumes. Image display follows radiological convention with right hemisphere (R) shown on left side of picture. L, Left; R, Right hemisphere. **(B)** Affected thalamic nuclei, as determined by co-registration of individual MRI to an established atlas of the human thalamus (Morel, 2007). Relative lesion extent for a given nucleus is displayed in three increments: White, not affected, light gray, less than 1/3 of total volume affected, dark gray, between 1/3 and 2/3 affected, black, more than 2/3 affected. Patients are labeled by ascending numbers. Abbreviations: AV, anteroventral nucleus; VA, ventral anterior nucleus; Mtt, mamillothalamic tract; MD, mediodorsal nucleus; CeM, central medial nucleus; CL, central lateral nucleus; CM, centromedian nucleus; Pf, parafascicular nucleus; VL, ventral lateral nucleus; VM, ventral medial nucleus; VP, ventral posterior nucleus; Pul, pulvinar; R, reticular nucleus.

fitted to the perceptual response data in Matlab by using psignifit, a toolbox that implements the maximum-likelihood method described by Wichmann and Hill (2001). From psychometric functions, we determined the point of subjective target stationarity (PSS) as a measure of bias in perceptual reports and the standard deviation of the fitted cumulative gaussian as a measure of just-noticeable difference (JND). For easier comparison of perceptual performance between conditions and subjects, we converted the psychometric function to percent correct (discarding trials with null displacement) and averaged resulting values for corresponding negative and positive displacement levels. We determined a perceptual threshold as the absolute displacement needed to achieve correct responses in 75% of trials (Ostendorf et al., 2010, 2012). Statistical analyses of oculomotor and perceptual response data were performed in SPSS, version 19.0 (IBM, Armonk, NY, USA). Tests on group differences between single measures of interest were performed by using *t*-tests and Mann–Whitney *U*-tests, respectively. Group differences were evaluated by repeated measures ANOVA with factors GROUP (control vs. patient group), CONDITION (BLANK vs. STEP), and SIDE (rightward vs. leftward saccades). Significance threshold was set at $P = 0.05$.

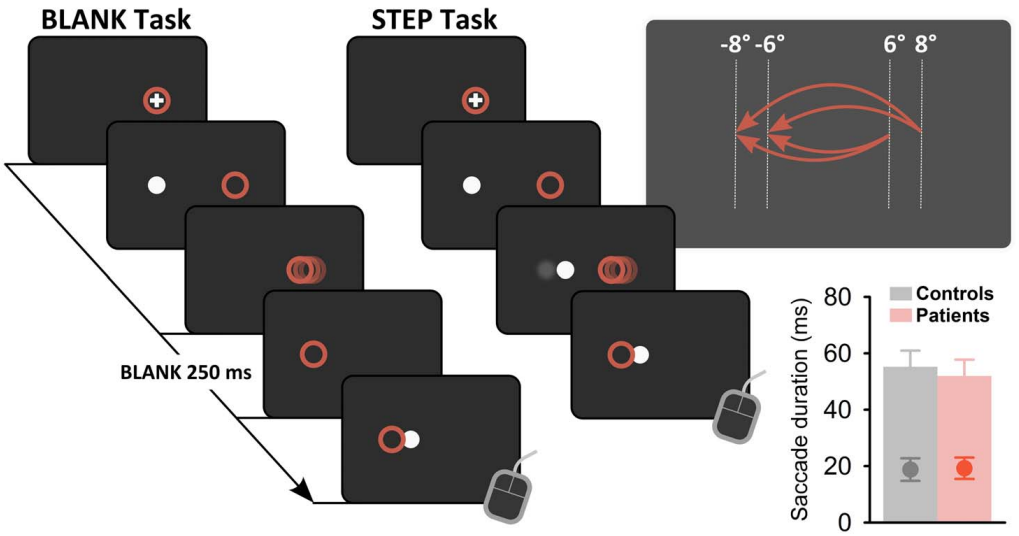

FIGURE 2 | Task schematic. In both task conditions, subjects fixated on a fixation cross, presented on right or left side of screen. After a variable foreperiod (1600–2400 ms), the fixation cross was extinguished and a target stimulus (white dot) presented on the other side of screen. Subjects performed a saccadic eye movement to this target (actual eye position, red circles). Saccade onset triggered a stimulus change: in the BLANK condition, the target was switched off and reappeared 250 ms later at a displaced position. In the STEP condition, saccade onset triggered a direct displacement of the target. In both conditions, subjects were instructed to indicate the apparent displacement direction by means of a button press at trial end. Upper panel on right side shows possible start and end positions of requested saccades for a block of leftward saccade direction, yielding stimulus amplitudes of −12, −14, and −16°, respectively. Lower panel on right side shows average saccade duration for control subjects (gray bar) and patients (red bar) with average trigger times for gaze contingent stimulus changes superimposed (gray and red circles, respectively). Error bars denote ±1 SD.

RESULTS

LESION CHARACTERISTICS

In our sample, 6 patients (43%) sustained a unilateral right, 5 patients (36%) a unilateral left and 3 patients (21%) a bilateral thalamic lesion. Time since lesion varied from 25–60 months (mean, 15.3 months), lesion volume ranged from 0.03–2.35 cm^3 (mean, 0.38 cm^3). Thalamic lesions predominantly involved the ventral, medial, and lateral parts of the thalamus (see **Figure 1A** for an overlap of individual lesion volumes). Most commonly affected nuclei were mediodorsal (MD, 9 patients, 64.3%) and ventral lateral (VL, 8 patients, 57.1%) as well as intralaminar nuclei: the central medial (CeM) and central lateral (CL) nuclei and the centromedian-parafascicular complex (CM-Pf) were affected in 8, 8, and 7 patients (57.1, 57.1, and 50%), respectively. By contrast, the anterior and posterior nuclei were largely spared. A display of affected nuclei for individual patients is given in **Figure 1B**. Further patients' characteristics are summarized in **Table 1** (with premorbid intelligence level estimated by the MWT-B, a German equivalent to the National Adult Reading Test).

OCULOMOTOR PERFORMANCE

Patients and control subjects did not differ in terms of basic oculomotor performance. The grand average of saccadic reaction times (SRT) was 202 ms and repeated-measures ANOVA revealed no significant effect of SIDE [$F_{(1,\ 32)} = 1.99$, $P = 0.17$], CONDITION [$F_{(1,\ 32)} = 1.18$, $P = 0.29$], or GROUP [$F_{(1,\ 32)} = 0.45$, $P = 0.51$] and no significant interaction between these factors (all $P \geq 0.08$). We assessed amplitude errors of first saccades as amplitude gain (saccade amplitude divided by stimulus amplitude). A repeated-measures ANOVA on saccade gain revealed a significant effect of SIDE [rightward vs. leftward saccade direction, $F_{(1,\ 32)} = 43.0$, $P < 10^{-6}$] with on average slightly more hypometric leftward saccades [average gain for leftward (rightward) saccades, 0.90 (0.94)]. This finding is readily explained by monocular recording of the right eye in our study (Collewijn et al., 1988). No effect of GROUP [controls vs. patients, $F_{(1,\ 32)} = 0.79$, $P = 0.38$] or CONDITION [BLANK vs. STEP, $F_{(1,\ 32)} = 1.57$, $P = 0.22$] and no interactions between factors were observed (all $P \geq 0.15$).

We also analyzed the systematic and variable error of saccade landing positions. Paralleling the analysis of amplitude gain, repeated-measures ANOVA revealed a significant effect of SIDE on systematic targeting errors [$F_{(1,\ 32)} = 41.8$, $P < 10^{-6}$] with leftward saccades falling systematically shorter of target position [mean targeting error for leftward (rightward) saccades, −1.59° (−0.87°)]. A marginally significant effect of CONDITION was observed [$F_{(1,\ 32)} = 3.9$, $P = 0.06$], but no effect of GROUP [$F_{(1,\ 32)} = 1.8$, $P = 0.19$] and no interactions between these factors (all $P \geq 0.09$) were noted. We assessed the variable error of saccade landing positions as standard deviation of targeting errors. For this measure, a repeated-measures ANOVA showed a significant effect of SIDE [$F_{(1,\ 32)} = 9.7$, $P = 0.004$] and GROUP [$F_{(1,\ 32)} = 5.2$, $P = 0.03$], with a slightly larger targeting scatter for leftward saccades [standard deviation of targeting error for leftward (rightward) saccades, 1.06° (0.93°)] and for the patient

group [patients (controls), 1.11° (0.88°)], respectively. No effect of CONDITION [$F_{(1, 32)} = 1.7$, $P = 0.21$] and no significant interactions between these factors (all $P \geq 0.49$) were observed.

PERCEPTUAL PERFORMANCE

Figure 3 plots exemplary results for one control subject (S8, **Figures 3A,B**) and one patient with a lesion in the right thalamus (P12, **Figures 3D,E**). Replicating previous findings (Deubel et al., 1996), psychometric functions in the control subject reveal improved performance for the BLANK compared to the STEP condition for both saccade directions with more accurate (i.e., less-biased PSS) and more precise performance (i.e., steeper slope of psychometric functions and corresponding lower JND). This is reflected in a strong improvement of detection threshold for the BLANK condition for both saccades direction [see **Figure 3C**; average threshold for BLANK (STEP), 0.3° (1.35°)]. The same pattern can be observed for rightward saccades in the patient, with threshold improving from 1.88° in the STEP condition to 0.84° in the BLANK condition. By contrast, no improvement is apparent for leftward saccades with almost identical thresholds in the STEP (1.34°) and BLANK (1.33°) task. Psychometric functions (**Figure 3D**) demonstrate that the lack of threshold improvement for leftward saccades was mainly caused by a larger forward bias of the psychometric function [PSS in the STEP (BLANK) condition, 0.98° (1.32°)].

Figure 4 plots group average thresholds for the STEP and BLANK condition. Inspection of the graphs suggests a robust effect of task condition with improved perceptual performance in the BLANK compared to the STEP condition (average improvement, 37 and 49% for patients and control subjects, respectively). For both patient and control group, this improvement in the BLANK condition is on average larger for leftward than rightward saccades (average improvement 51 vs. 37%, respectively). Repeated-measures ANOVA confirmed a main effect of CONDITION [BLANK vs. STEP condition, $F_{(1, 32)} = 65.3$, $P < 10^{-8}$], no effect of SIDE [rightward vs. leftward saccade direction, $F_{(1, 32)} = 1.5$, $P = 0.24$], but a significant interaction between CONDITION and SIDE [$F_{(1, 32)} = 7.1$, $P = 0.01$]. Furthermore, average thresholds in patients are higher compared to the control sample in all conditions [average thresholds in patients (controls), 1.5° (1.16°)]. A significant main effect of the between-subject factor GROUP [control subjects vs. patients,

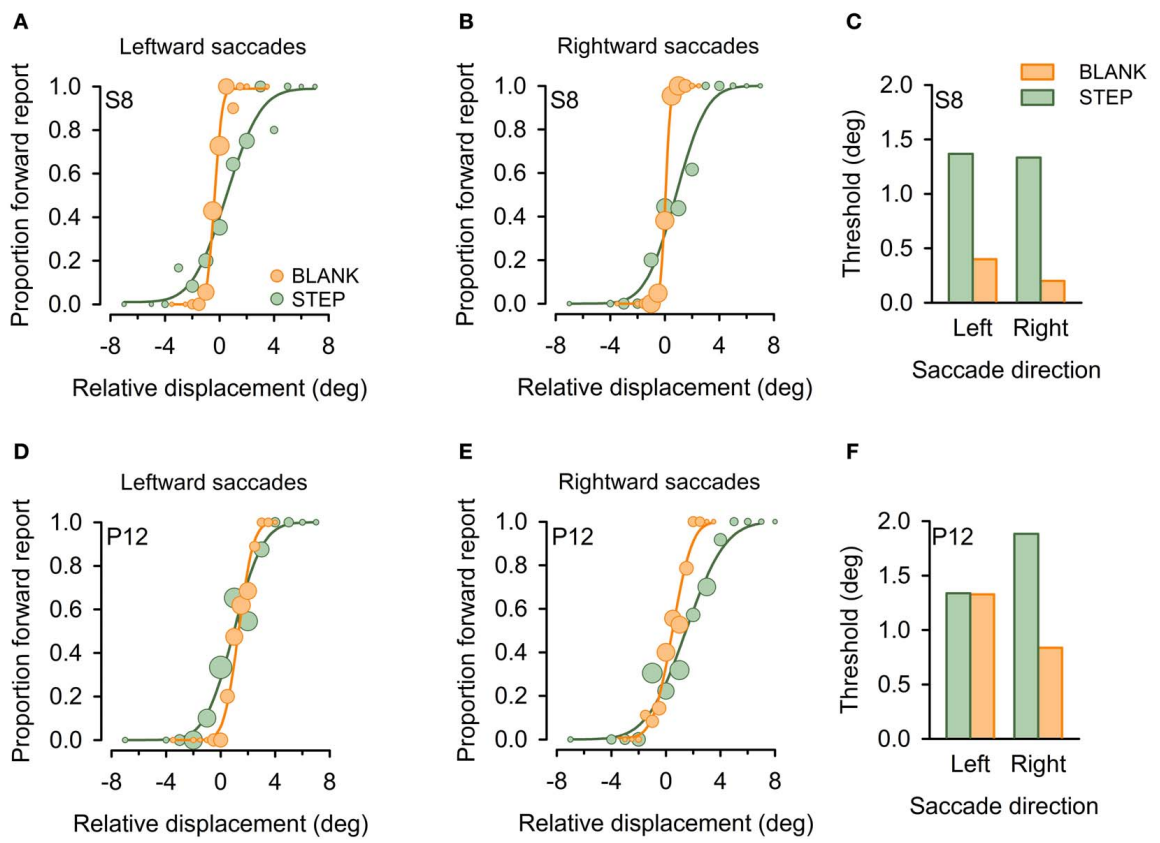

FIGURE 3 | Example psychometric functions in individual subjects. Data are shown for one healthy control subject (S8, **A–C**) and a patient with a focal lesion in the right central thalamus (P12, **D–F**) for the STEP condition (green) and the BLANK condition (orange). Circles denote proportion of trials in which subjects reported an apparent stimulus jump in saccade direction (forward), plotted against relative displacement level. Negative values refer to target displacements against saccade direction. Circle size represent the number of trials for a given target jump. Cumulative gaussians were fitted to perceptual response data separately for leftward **(A,D)** and rightward **(B,E)** saccades. (**C** and **F**) display resulting detection thresholds, calculated as absolute displacement needed to achieve 75% correct responses.

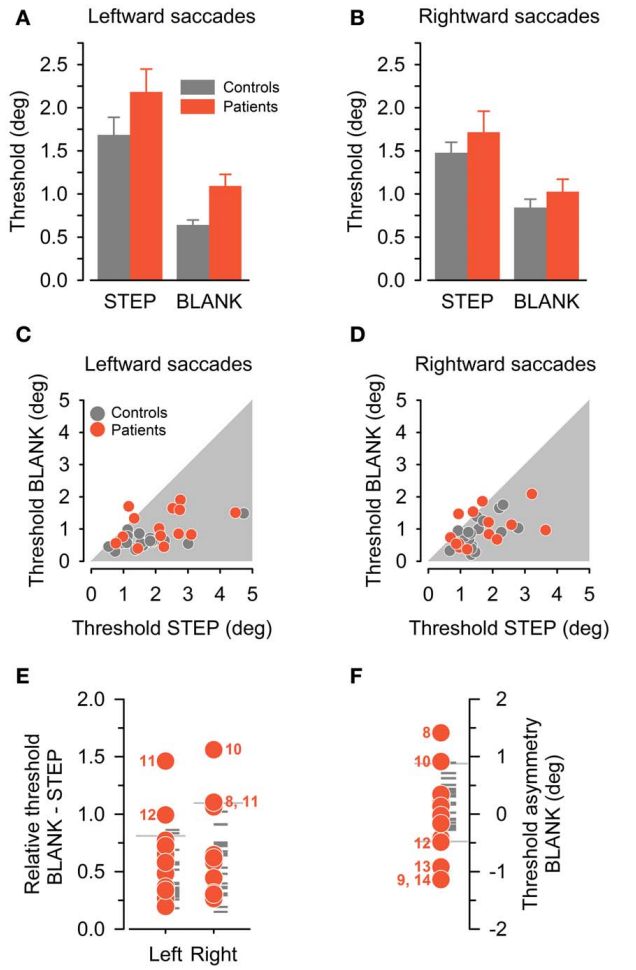

FIGURE 4 | Perceptual performance in control subjects (gray color) and patients (red color). (A,B) Group average detection thresholds (mean ± SEM) are plotted separately for leftward **(A)** and rightward **(B)** saccade direction and for the STEP and BLANK condition. **(C,D)** Individual detection thresholds in BLANK task, plotted against corresponding threshold in STEP task, separately for leftward **(C)** and rightward **(D)** saccade direction. **(E)** Detection thresholds in BLANK task relative to STEP task, separately for leftward and rightward saccades. Reference lines denote corresponding control subjects' mean plus 1.96 SD. **(F)** Asymmetry of detection threshold in BLANK task for rightward minus leftward saccade direction. Reference lines denote the ±1.96 SD-interval of control subjects' sample. In **(E)** and **(F)**, patients with relative thresholds beyond 1.96 standard deviation of the controls' mean are marked with their ID number.

$F_{(1,\ 32)} = 4.7, P = 0.04$] was confirmed statistically with no interaction of GROUP with CONDITION, SIDE, or CONDITION × SIDE (all $P \geq 0.24$).

Individual thresholds exhibited considerable variability in our comparatively large and heterogeneous sample of control subjects. This can be appreciated by inspection of **Figures 4C,D**, plotting individual thresholds in the BLANK condition against corresponding thresholds in the STEP condition. Most datapoints are located below unity line (i.e., within gray-shaded area), confirming on an individual level the perceptual benefit of the BLANK manipulation. By contrast, one patient apparently exhibited a paradoxical deterioration of thresholds in the BLANK condition for leftward saccades, three patients for rightward saccades.

INDIVIDUAL CASE ANALYSIS

For further analysis of individual perceptual performance in patients, we capitalized on individual threshold differences between the two task conditions (BLANK vs. STEP) and saccade directions in the BLANK task (rightward vs. leftward), similar to previous approaches in the literature (Bellebaum et al., 2005). In these analyses, we scored performance as deficient if a patient's threshold was found to be beyond ±1.96 SD of the control subjects' mean. **Figure 4E** plots perceptual thresholds in the BLANK condition relative to the corresponding threshold in the STEP condition (i.e., a relative threshold of unity indicates identical thresholds in BLANK compared to STEP task, a threshold below unity a proportional improvement). For all but one subject and saccade direction, relative thresholds of control subjects are indeed below unity, indicating a relative improvement in perceptual performance.

Compared to the control group, four of our patients exhibited impaired performance in this analysis, one for leftward, two for rightward saccade directions, and one for both saccade directions (abnormal thresholds are marked by corresponding patient ID number). This includes patient P10, previously reported as a case study (Ostendorf et al., 2010). For all but one of the five affected saccade directions, the missing BLANK effect was caused by a systematic forward shift of the psychometric function in the BLANK compared to the STEP condition (cf. psychometric function for leftward saccades in exemplary patient, **Figure 3D**). However, no obvious pattern emerged concerning lateralization of the behavioral deficit with respect to lesion side: three patients sustained right sided thalamic damage with behavioral deficits manifesting ipsilateral to lesion side in two patients (P8, 10) and contralateral to lesion side in one case (P12). One patient (P11) sustained a left-sided lesion and exhibited a bilateral behavioral deficit.

In a next analysis step, we compared individual performance in the BLANK task for rightward vs. leftward saccades. **Figure 4F** plots individual threshold asymmetry sores (calculated as a subtraction of leftward from rightward thresholds). Thresholds in the control group were found to be symmetrical on average, with slightly higher thresholds for rightward saccades [average threshold asymmetry in control group (±SD), 0.20° (±0.35°)]. Compared to the control group, six patients exhibited an abnormal threshold asymmetry, two with higher thresholds for rightward saccades and four with higher thresholds for leftward saccades (abnormal threshold asymmetries are marked by corresponding patient ID number).

Asymmetry of BLANK thresholds was primarily driven by systematic biases of the psychometric function: for three patients (P8, 10, 12), abnormal asymmetry was caused by a forward bias for one saccade direction, for the other three patients (P9, 13, 14), a backward bias for one saccade direction was the main factor driving the asymmetry. These differences in perceptual biases for rightward vs. leftward saccade direction could not simply be attributed to corresponding differences in targeting error of corresponding saccades (Pearson's correlation, $P = 0.21$).

No consistent association of lesion side and the behavioral deficit emerged: four patients sustained right-sided thalamic damage with higher thresholds manifesting ipsilateral to lesion side in two patients (P8, 10) and contralateral to lesion side in the other two (P9, 12). One patient with a left-sided lesion exhibited increased thresholds ipsilateral to lesion side (P13) and one patient with a bilateral, predominantly right-sided lesion exhibited increased thresholds for leftward saccades as well (P14).

As a final behavioral probe of internal monitoring, we analyzed a possible dependency of perceptual report on saccade targeting error: with only unreliable CD information available, the correct attribution of visual errors after saccade execution to either self-induced targeting errors or external stimulus jumps should be more difficult. Perceptual reports should increasingly become contaminated by oculomotor noise. Previous studies showed that normal subjects can indeed take their own trial-by-trial oculomotor imprecision into account for the perceptual matching of stimulus locations across eye movements (Collins et al., 2009; Ostendorf et al., 2010). For analysis, we binned perceptual data in the BLANK condition on an individual basis according to the oculomotor targeting error. As in Ostendorf et al. (2010), we used eight bins of equal sample size, separately for rightward and leftward saccades.

No significant correlation emerged between binned oculomotor targeting error and perceptual reports for all but one control subject and saccade direction (Pearson's correlation; see **Figures 5C,D**, plotting group averages of perceptual report bins against corresponding quantized targeting error). By contrast, significant correlations emerged for seven patients in this analysis (**Figures 5A,B**): one patient exhibited a significant correlation for leftward saccades, three patients for rightward saccades ad three patients for both saccade directions. This dependency of perceptual performance on targeting errors could not be explained by deficient oculomotor performance: no significant differences emerged when comparing systematic and variable targeting errors in affected vs. non-affected patients (for both BLANK and STEP condition and leftward and rightward saccades, all $P \geq 0.26$). Again, as with the two other behavioral measures reported above, no obvious pattern of lateralization emerged with respect to thalamic lesion side: of the seven patients performing deficiently, two patients with right-sided lesions exhibited the behavioral deficit for ipsilateral saccade direction (P8, 10), one patient with a right-sided lesion showed it for contralateral saccade direction with respect to lesion side (P9). One patient with a bilateral, predominantly right-sided lesion, showed a significant correlation for rightward saccades (P5). Two of the three patients exhibiting a

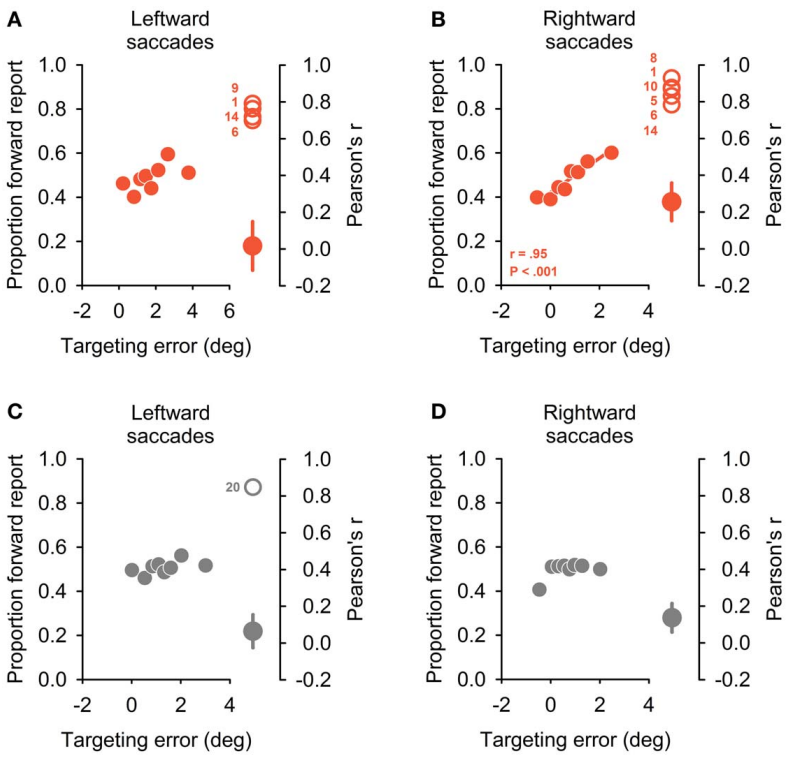

FIGURE 5 | Dependency of perceptual reports on oculomotor targeting errors. On left side of the four panels, the proportion of forward reports is plotted against relative oculomotor error for eight error bins of equal sample size. Positive targeting errors refer to hypometric primary saccades. Plots depict the group average for the patient group **(A,B)** and control sample **(C,D)**, separately for leftward **(A,C)** and rightward **(B,D)** saccade directions. A significant correlation emerged only for rightward saccades in patients **(B)** and the inset indicates correlation coefficient and corresponding *P*-value (Pearson correlation). Right side of the four panels depicts significant individual correlation coefficients (open circles) together with average coefficient for the rest of the patient group **(A,B)** or control subject sample **(C,D)**, respectively (filled circles, mean ± SEM). Significant correlations emerged in four patients and one control subject for leftward and in 6 patients and no control subject for rightward saccades.

behavioral deficit for both saccade directions sustained bilateral lesions (P6, 14); one had a right-sided lesion (P1).

LESION-SYMPTOM MAPPING

The observed differential deficits in the perceptual matching of visual space across eye movements could not simply be explained by lesion acuity. For none of the three behavioral measures did time since lesion significantly differ between impaired und unimpaired patients (all $P \geq 0.4$). Likewise, no significant association between the presence of extrathalamic lesions and behavioral deficits emerged for the three scores (Pearson's chi-square, $\chi^2 \leq 0.31, P \geq 0.58$).

Acquisition of high-resolution MR image datasets at the time of testing allowed for further investigation of a possible common lesion zone in patients performing deficiently in the perceptual matching of space across eye movement. To this end, we performed voxel-based lesion-symptom mapping in our patient sample, taking the three behavioral scores elaborated on above as dichotomous classifiers to rate patients as impaired versus unimpaired. **Figure 6** shows overlay plots of superimposed lesions of patients classified as impaired for a specific score minus those classified as unimpaired. Such an overlap-subtraction logic aims to reveal regions that are critical for task performance while controlling for the effect of commonly affected, but innocent bystander regions (Rorden and Karnath, 2004). Overlay lesion plots are shown separately for (1) abnormal thresholds in BLANK relative to STEP task (**Figure 6A**), (2) abnormal threshold asymmetry in BLANK task (**Figure 6B**), and (3) a dependency of perceptual reports on oculomotor targeting errors (**Figure 6C**).

For all three measures, overlay plots indicate a restricted portion of right central thalamus as region of maximum lesion overlap for impaired vs. unimpaired patients. For further illustration of the thalamic portion critical for task performance, we generated a statistical voxel-based lesion-symptom map, using non-parametric mapping (NPM) as implemented in MRIcron. This map was based on threshold asymmetry in the BLANK task (**Figure 4E**) as the behavioral measure of interest that yielded the highest degree of lesion overlap (**Figure 6B**). **Figures 7B,C** shows the resulting statistical map at a threshold of $P < 0.05$, uncorrected. Consistent with the three overlay images, this map identifies an area in right central thalamus as critical for the detection of intrasaccadic visual displacements. This area (cluster-size, 70 voxels) was centered at MNI-coordinates [8, −15, 4] and mostly encompasses lateral portions of MD nucleus, intralaminar nuclei, and medial parts of the ventrolateral nucleus. In principle, such an uncorrected map should be interpreted with caution, since it allows for the erroneous detection of false-positive findings. However, the individual lesion reconstruction with respect to an atlas of the human thalamus (see **Figure 1B**) allowed for a complementary analysis of affected nuclei in behaviorally impaired vs. unimpaired patients. This analysis confirmed a significant clustering of impaired performance with lesions of the right MD, CeM, and CL nuclei (Pearson's chi-square, all $\chi^2 \geq 4.7, P \leq 0.03$).

The map of statistical power shown in **Figure 7A** serves as reminder of a relevant limitation in our study population: lesion size in most patient cases was small and lesion topology biased toward medial and ventral portions of thalamus (see also lesion overlays, **Figure 1A**). This resulted in a limited coverage of both thalamic volumes where there was sufficient statistical power to detect a behavioral effect. Thus, while lesion-to-symptom mapping in our patient sample converges on a critical role of a restricted area of right central thalamus in predicting the visual consequences of saccadic eye movements, no firm conclusions can be drawn on a null contribution of left thalamus or more lateral, anterior, and posterior thalamic regions.

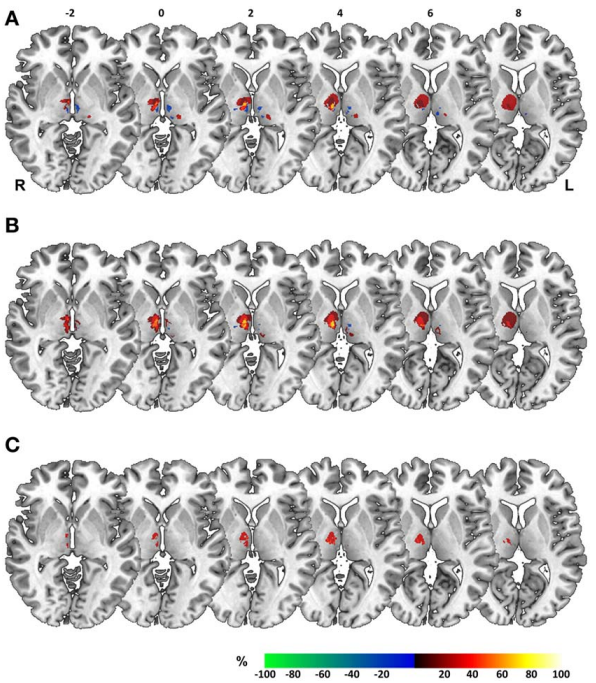

FIGURE 6 | Overlay lesion plots. Overlay plots of superimposed lesions of impaired minus unimpaired patients, shown on axial sections of a MNI brain template with numbers denoting z-coordinates in MNI space. Colors denote the percentage of overlapping lesions of patients performing deficiently for a specific perceptual measure after subtraction of unimpaired patients. Overlap-subtraction plots are thresholded at 15%, i.e., only regions lesioned more or less frequently in at least 15% of the impaired vs. unimpaired patients are shown in this plot. Behavioral measures for construction of overlay plots comprised **(A)** abnormal thresholds in BLANK relative to STEP task, **(B)** threshold asymmetry in the BLANK task for right- vs. leftward saccades. and **(C)** a systematic dependency of perceptual reports on oculomotor targeting errors. L, Left; R, Right hemisphere.

DISCUSSION

In the present study, we aimed to further elucidate the role of trans-thalamic CD pathways in the perceptual matching of visual input before and after an eye movement in human subjects. To this end, we used a visuomotor task requiring a perceptual judgment about the apparent direction of intrasaccadic stimulus displacements. We assessed performance in this task in a STEP and BLANK version, the latter allowing for high perceptual sensitivity in healthy subjects (Deubel et al., 1996). Accurate and precise perceptual decisions require matching of visual input before and after an eye movement and need to incorporate internal monitoring information of intervening eye movements, since

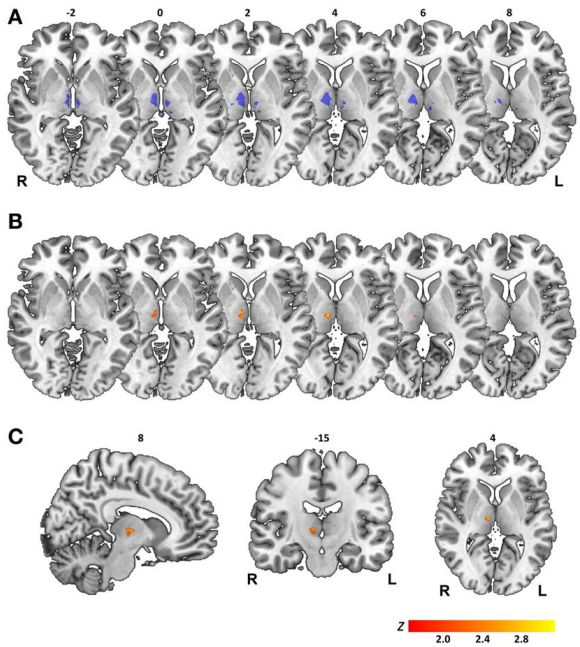

FIGURE 7 | Results of statistical voxelwise lesion-symptom mapping. **(A)** Map of statistical power. Color-coded in blue are voxels where there is sufficient power to detect statistical effects at a threshold of $P < 0.05$, uncorrected. Map is shown on axial sections of a MNI brain template with numbers denoting *z*-coordinates in MNI space. L, Left; R, Right hemisphere. **(B)** Statistical map generated for threshold asymmetry in BLANK task is shown on corresponding axial sections. **(C)** Statistical map shown on sagittal, coronal, and axial sections with numbers denoting [*x*, *y*, *z*] coordinates of MNI space. Color scale in **(B,C)** indicates Z-scores (Liebermeister test), thresholded at $P < 0.05$ uncorrected.

oculomotor targeting errors render a sole reliance on visual errors insufficient.

Detection thresholds varied considerably in our comparatively large and heterogeneous group of healthy control subjects. However, individual threshold differences between conditions and saccade directions emerged as a more consistent measure across subjects (Bellebaum et al., 2005). Replicating previous findings, we noted a strong and highly significant improvement of detection performance in the BLANK compared to the STEP task for both saccade directions in healthy individuals (Deubel et al., 1996). Performance differences between these task variants might be driven by a differential weighting of internal monitoring with respect to visual reafferent information: Transient disappearance of the target in the BLANK condition might signal a possible violation of positional constancy to the visuomotor system (Deubel and Schneider, 1994; Deubel et al., 1996). Perceptual decisions might then more strongly rely on CD-driven internal predictions of visual reafference (Hamker et al., 2011). Consistent with this idea, non-stationary behavior of other stimulus features [such as stimulus motion (Gysen et al., 2002) or form changes (Demeyer et al., 2010)] has been shown to increase displacement detection across eye movements in a similar manner.

In recent case study (Ostendorf et al., 2010), we reported on a patient with a focal thalamic lesion who exhibited a lateralized deficit in the BLANK condition with an increased perceptual threshold relative to saccades in the other hemifield and relative to the STEP condition. Building on this case report, we contrasted performance in fourteen patients with focal thalamic lesions in different parts of the thalamus. We observed a similar impairment in perceptual performance in seven patients of our sample, with one patient failing to demonstrate a BLANK benefit, three patients exhibiting a large asymmetry between saccade directions and three patients demonstrating impairments for both of these behavioral measures (with the latter group including the single case reported previously).

Increased perceptual threshold in the single case mainly arose from a forward shift of the psychometric function (Ostendorf et al., 2010), i.e., from a systematic bias of the patient to report a backward jump of the target. This perceptual bias would be consistent with an internal underestimation of saccade amplitudes, e.g., a hypometric CD of corresponding oculomotor actions used for the perceptual judgment. Sign of this systematic error was consistent with oculomotor error patterns in rapid saccade sequences observed in this (Ostendorf et al., 2010) and other patients (Bellebaum et al., 2005) and in non-human primates after transient inactivation of CD transmitting relay neurons in central thalamus (Sommer and Wurtz, 2002). It also conformed to systematic changes of perceptual decisions induced by transcranial magnetic stimulation (TMS) over the FEF as the putative cortical target area of this trans-thalamic CD pathway (Ostendorf et al., 2012). In the current study, increased detection thresholds were caused by a forward shift of psychometric functions in the majority of individual cases. However, behavioral impairments manifested as backward shift of the psychometric function in three cases. Similar findings were reported by Gaymard et al. (1994) in two patients with thalamic stroke and suggest that disturbances of trans-thalamic CD transmission might also give rise to an internal overestimation of actual ocular state after eye movements. Oculomotor CD will pass through the thalamus as population code (Sanger, 2003). Partial damage to the pool of CD-transmitting neurons might then serve as possible explanation for idiosyncratic biases emerging on a perceptual level, depending on average saccade vectors represented by deficient vs. intact relay neurons.

Additional analyses of control subjects' data demonstrated that perceptual performance in the BLANK task was largely independent from oculomotor noise with no correlation between perceptual report and corresponding saccade targeting error for all but one subject and saccade direction. This further corroborates previous findings that healthy individuals can take CD information of oculomotor actions into account for their perceptual judgments (Collins et al., 2009). This would be expected if the visuomotor system is able to generate accurate and precise predictions of the visual error after saccade execution on a trial-by-trial basis, presumably by utilizing oculomotor CD (Guthrie et al., 1983). Mismatches between the internal prediction and actual reafference could then correctly be attributed to external stimulus displacements. By contrast, seven patients in the present study exhibited a systematic dependency of perceptual reports on oculomotor targeting errors. Apparently, these patients were not able to disambiguate self-induced targeting errors from external stimulus changes and consequently misattributed oculomotor errors to external stimulus changes.

Behavioral findings in our actual patient sample confirm that thalamic damage can indeed compromise the perceptual matching of space across eye movements and clearly suggests generalizability of the basic pattern of behavioral impairment previously observed in a single patient (Ostendorf et al., 2010). Beyond the issue of generalizability, single-case studies cannot speak to the anatomical specificity of brain-behavior relationships (Robertson et al., 1993). In this regard, findings of the actual study may aid to refine the mapping of behavioral impairments to a specific lesion topology. With a sizable number of patients being behaviorally unimpaired, acquisition of high-resolution imaging allowed for a voxel-based lesion-symptom mapping. The additional reconstruction of individual lesions with respect to an established atlas of the human thalamus (Morel, 2007) served as a second approach in lesion classification.

Lesion-symptom mapping in our patients converged on a restricted portion of the right central thalamus as critical for the matching of visual space across saccades. Following the nomenclature proposed by Morel (2007), this thalamic region comprised lateral portions of the MD nucleus (including the parvocellular and paralamellar division), central parts of intralaminar nuclei (mainly comprising the CL nucleus) and medial parts of the VL (i.e., ventral lateral posterior, VLp) and ventral posterior lateral nucleus (VPL). This thalamic region conforms well to the thalamic projection zone of pathways ascending from superior colliculus (SC) to the FEF identified in rhesus monkeys (Benevento and Fallon, 1975; Harting et al., 1980). It also complies with the anatomical reconstruction of intra-thalamic sites at which putative CD and eye position signals have been recorded in non-human primates (Schlag-Rey and Schlag, 1984; Schlag and Schlag-Rey, 1984; Sommer and Wurtz, 2004; Tanaka, 2007).

The region of central thalamus identified in our analysis is also largely consistent with previous patient studies that used the execution of rapid saccade sequences (Bellebaum et al., 2005) or intervening eye movements during the delay of a memory-guided saccade task (Gaymard et al., 1994) as a proxy to infer on internal updating mechanisms. In one of these studies, inspection of lesion topology suggests a more lateral location compared to the common lesion zone in our study, but involvement of central thalamic regions was presumed to underlie the behavioral deficit (Gaymard et al., 1994). In the other study (Bellebaum et al., 2005), lesions of behaviorally impaired patients were determined to affect the VL nucleus in three cases and the MD nucleus in another two cases. In this context, it seems important to note that positive evidence for a critical role of the right central thalamus in our study should not be taken as evidence against a possible role of left thalamus or more anterior, posterior and lateral thalamic portions for the perceptual matching of visual space across eye movements. Limited coverage in our patient sample precludes further inferences on a group level for these thalamic regions. Indeed, two patients that exhibited impairments in one behavioral measure in our study sustained focal and selective lesions of either the VL or ventral posterior (VP) nucleus, respectively.

With experimental evidence merged across human lesion studies, the lateralization of behavioral deficits with respect to thalamic lesion side remains largely equivocal so far. Inferring from the general organization of the visuomotor system, behavioral deficits would be expected for contraversive saccades after unilateral lesions of trans-thalamic CD pathways. In keeping with this notion, transient inactivation of functionally identified thalamic relay neurons led to a behavioral impairment for contraversive saccades in non-human primates (Sommer and Wurtz, 2002). Studies in human subjects with focal lesions in the thalamus yielded heterogeneous results with behavioral deficits manifesting contralateral (Gaymard et al., 1994; Bellebaum et al., 2005) and/or ipsilateral (Gaymard et al., 1994; Bellebaum et al., 2005; Ostendorf et al., 2010) to lesion side. Similarly, patients in our study exhibited behavioral deficits for both ipsiversive and contraversive saccade direction without any obvious relation of lateralization to lesion topology. In addition, bilateral behavioral deficits were not consistently associated with bilateral structural pathology.

Recent neurophysiological findings may at least partially account for these findings by demonstrating that the recipient area in frontal cortex receives oculomotor CD from both superior colliculi and hence all saccade directions (Crapse and Sommer, 2009). Moreover, CD information for both saccade directions is already present on the thalamic level (Tanaka, 2007) and might cross from the contralateral SC at tectal or thalamic levels (Crapse and Sommer, 2009). These findings in non-human primates might help to explain heterogeneous findings in human lesion studies, as partial lesions of CD pathways at the thalamic level might impair CD for some, but not all saccade directions. At present however, the spatial distribution of thalamic CD relay neurons is unclear and it is questionable whether a putative "saccadotopy" of CD within central thalamus might be sufficiently widespread and consistent across subjects to be picked up with MR imaging approaches.

Despite clear experimental evidence for a deficit in the internal monitoring of eye movements in seven of our patients, the subjective impression of visual stability was preserved in all our patients. This suggests compensatory mechanisms that operate efficiently outside the controlled setting of the laboratory. One likely factor contributing to the maintenance of visual stability may be the phenomenon of SSD itself (Bridgeman et al., 1975): general dampening of displacement detection across eye movements will attenuate the disturbing effect of saccade targeting errors on subjective perceptual continuity. Furthermore, relative positions between objects in a visual scene could be used as CD-independent source for a matching of visual space across eye movements (Gibson, 1966; Deubel, 2004). Oculomotor CD transmitted via the healthy thalamus and eye position information transmitted through spatially segregated thalamic relays (Gaymard et al., 2001; Sommer, 2003) represent candidate signals that might suffice to maintain perceptual coherence under these circumstances.

In conclusion, our results suggest that the integrity of central thalamus is critical for accurately predicting the visual consequences of eye movements. Successful disambiguation of self-induced vs. external changes in sensory input is central to adaptive behavior for various species and modalities (Crapse and Sommer, 2008). A global deficit in this elementary monitoring function has been presumed to contribute to debilitating symptoms in neuropsychiatric diseases, such as hallucinations

and delusions of control (Feinberg, 1978; Fletcher and Frith, 2009). In this regard, findings in our study may serve as an exemplary instantiation of a circumscribed disturbance in such prediction mechanisms.

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Cognitive control of movement via the cerebellar-recipient thalamus

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The cognitive control of behavior was long considered to be centralized in cerebral cortex. More recently, subcortical structures such as cerebellum and basal ganglia have been implicated in cognitive functions as well. The fact that subcortico-cortical circuits for the control of movement involve the thalamus prompts the notion that activity in movement-related thalamus may also reflect elements of cognitive behavior. Yet this hypothesis has rarely been investigated. Using the pathways linking cerebellum to cerebral cortex via the thalamus as a template, we review evidence that the motor thalamus, together with movement-related central thalamus have the requisite connectivity and activity to mediate cognitive aspects of movement control.

Keywords: motor thalamus, central thalamus, thalamus, cognition, cerebellum, timing, executive control, language

INTRODUCTION

The majority of our knowledge of the primate thalamus at the systems level is based on the study of circuits for sensation (e.g., retinogeniculostriate pathway). Questions of how thalamic circuits contribute to movement and cognition are largely unanswered. The more complex the behavior, the more that motor and cognitive processes will need to interact with each other. Imagine, as a brief example, the actions and calculations that are intertwined as a driver merges into highway traffic. The degree to which motor and cognitive processes may co-occur is constrained by environmental factors (Knoblich and Flach, 2001; Pulvermüller and Fadiga, 2010; Filimon et al., 2013), but it is well accepted that motor and cognitive systems must be able to share information and run simultaneously (Cisek and Kalaska, 2010; Koziol et al., 2012). Here we review evidence for cognitive processes in movement-related thalamus, with special emphasis on cognitive functions that are particularly developed in primates, as opposed to more common functions such as associative learning that are found in all vertebrates, or even arthropods (Giurfa, 2013).

Motor thalamus is classically delineated according to cerebellar and basal ganglia projection zones. This review will primarily focus on the two juxtaposed thalamic regions that receive inputs from so-called motor and non-motor domains of the *dentate nucleus*, the output node of the lateral cerebellum. The first region corresponds to typical cerebellar territories of the motor thalamus (**Figure 1A**, left, and violet in **Figure 1B**), which are essentially found posteriorly to basal ganglia territories, in the ventral lateral complex (VL) of the thalamic nuclei (VLps and VLc subdivisions as well as nucleus X) and the oral division of the ventral posterolateral nucleus (VPLo). Those thalamic nuclei in turn project to cortical motor areas [primary motor cortex (M1), premotor cortex (PM) and the supplementary motor area (SMA)]. Additionally, projections from nucleus X and caudal regions of VLc also target the pre-SMA and frontal and parietal associative cortices (Wiesendanger and Wiesendanger, 1985a,b; Middleton and Strick, 2001; Morel et al., 2005; Prevosto et al., 2010). The second thalamic region considered in this review is composed of the central thalamus (**Figure 1A**, right, and green in **Figure 1B**). This region contains the rostral intralaminar complex [mainly the central lateral nucleus (CL) and, for cerebellar territories, to a lesser extent the paracentral nucleus (Pcn)] together with paralaminar regions of the mediodorsal nucleus (MD) and VL (Schlag-Rey and Schlag, 1989; Groenewegen and Berendse, 1994). The posterior intralaminar system (centre médian and parafascicular nuclei), heavily interconnected with basal ganglia, will not be discussed here. The central thalamus targets association cortices as well as motor cortices, with a gradient of projections (Rouiller et al., 1999; Morel et al., 2005; Prevosto et al., 2010). Most cortical regions that receive cerebellar inputs are recipients of thalamic inputs from these two contiguous thalamic regions, with different weights. As mentioned above, motor thalamus predominantly targets motor cortical regions. In contrast, central thalamus has widespread access to both associative and motor cortex.

CONTEXTUAL MODULATION OF ACTIVITY IN THALAMUS AND CEREBELLUM

The influence of cognitive functions on the neuronal activity of motor thalamus is far from established. It is well known, however, that only a subset of neurons in the motor thalamus is concerned solely with basic motor parameters. Many of the neurons contribute, instead, to more elaborate features of movement planning and execution. This functional distinction is in agreement with findings that both cerebellum and basal ganglia are implicated in higher level functions that expand and complement their role in movement (Middleton and Strick, 1994; Aglioti, 1997; Haber and Calzavara, 2009). Similarly, motor thalamus, as classically defined by its subcortical inputs, has long been known to project to cortical regions well beyond motor and PM (e.g., Kievit and Kuypers,

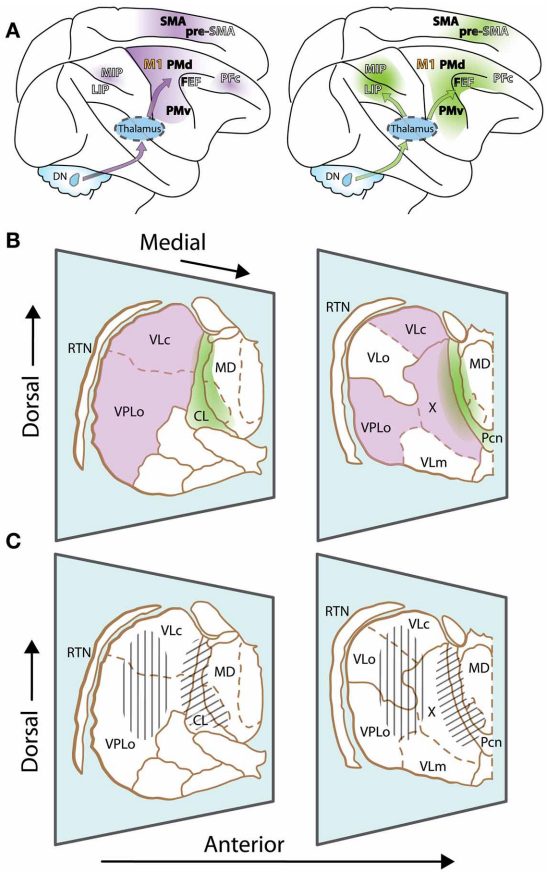

FIGURE 1 | The motor thalamus and ascending cerebellar inputs to cerebral cortex. (A) Lateral view of the rhesus monkey brain with hemispheres separated to expose mesial wall on top. Arrows schematically represent cerebello-cortical pathways relayed via cerebellar territories in lateral (left, violet) and central thalamus (right, green). Gradients of color on cortex indicate relative strength of inputs. Left: PFc, MIP are set apart, as inputs to such non-motor cortices are relayed via medial and dorsal regions of the classic motor thalamus, topographically distinct from regions relaying inputs to motor cortices. Names of cortical areas are color-coded as follows: Primary motor cortex, orange; non-primary motor fields, black; association cortices, white (non-exhaustive presentation). FEF and Pre-SMA have dual color-coding, as they receive inputs from "non-motor" cerebellar domains, but display some non-primary motor features as well. **(B)** Two representative sections of the thalamus of *Macaca mulatta*, viewed from a lateral anterior perspective (thalamic nuclei delineated according to (Olszewski, 1952)). Only relevant nuclei are labeled. Reticular thalamic nucleus (RTN) is not part of the motor thalamus but mediates cortical inhibitory control of thalamic activity. Cerebellar domains in lateral and central thalamus are presented in violet and green, respectively. The diffuse borders of central thalamus encompass the rostral intralaminar group (central lateral nucleus, CL, and the paracentral nucleus, Pcn) and paralaminar regions of the VL complex and MD. **(C)** Same sections as **(B)**, but illustrating effector-related *functional*, as opposed to *hodological*, compartments. Hatching shows the rough somatotopic locations of regions related to arm (vertical) and eye (diagonal) movements. Other abbreviations: DN, dentate nucleus; MIP, medial intraparietal area; LIP, lateral intraparietal area; M1, primary motor cortex; PMd, dorsal premotor cortex; PMv, ventral premotor cortex; FEF, frontal eye fields; PFc, prefrontal cortex; SMA, supplementary motor area; pre-SMA, pre-supplementary motor area; VLo, ventrolateral nucleus pars oralis; VPLo, ventroposterolateral nucleus pars oralis; MD, mediodorsal nucleus; VLc, ventrolateral nucleus pars caudalis, X, nucleus X of the thalamus.

1977). Conversely, top down cortical control that mediates cognitive signals from the prefrontal cortex (Brunia, 1999) may also influence movement-related activity in motor thalamus. This latter control is thought to be an important factor in volitional and selective gating of ascending inputs (Nadeau, 2008). As will be discussed below, volitional and context-dependent modulation of activity are hallmarks of cognitive influence on movement-related processing in the thalamus.

A classic demonstration that motor-related activity in thalamus is not always tightly associated with specific movement parameters came from oculomotor research (Schlag and Schlag-Rey, 1984; Schlag-Rey and Schlag, 1984). In their seminal papers, Schlag-Rey and Schlag introduced a bold proposal, namely the central controller hypothesis, which proposed that eye-movement related activity in the central thalamus specifies the timing of particular actions. The activity modulations in central thalamic regions are highly sensitive to context, and their specific sets of projections have been shown to mediate aspects of cognitive processing such as working memory (van der Werf et al., 2002). Indeed, if the context in which a movement is made influences neuronal activity during motor preparation and execution, this information must be stored and effectively accessed; in other words, working memory properties are needed (for more details on primate working memory circuits, see Constantinidis and Procyk, 2004).

Similar findings of contextually modulated activity, as well as selective modulation of preparatory activity for volitional movements, have been observed in the cerebellar dentate nucleus (Grimm and Rushmer, 1974; Mushiake and Strick, 1993; Ashmore and Sommer, 2013; Prevosto et al., 2013), the source of cerebello-thalamic projections from the lateral cerebellum. These results support the concept that some cerebello-thalamo-cortical pathways may be involved in higher order aspects of motor control and behavior. This suggestion raises two related issues. First, considering the potential involvement of cerebello-cortical circuits in cognitive functions that underlie complex behavior (Diamond, 2000; Koziol et al., 2012), what evidence exists that thalamus mediates the relevant activities? Then, for those activities that motor thalamus conveys, does the thalamus have an active, participatory role, or does it primarily act as a relay?

CEREBELLO-THALAMO-CORTICAL CIRCUITS HAVE THE REQUISITE CONNECTIVITY FOR COGNITIVE INVOLVEMENT

Although it gradually emerged that motor regions of the thalamus project to a wide array of cortical targets outside agranular (motor) cortex (Kievit and Kuypers, 1977; Wiesendanger and Wiesendanger, 1985b; Schmahmann and Pandya, 1990; Shook et al., 1991), relating those pathways to their subcortical sources has proven difficult. Indeed, beyond the confusion arising from diverse nomenclatures (Percheron et al., 1996), a structural definition of the motor thalamus has always been complicated by the fact that ascending axonal arborizations cover regions that straddle multiple cytoarchitectonically-defined nuclei (Kalil, 1981; Percheron et al., 1996; Mason et al., 2000). Conversely, thalamocortical projections originate from longitudinal regions that cross over nuclei borders (Kievit and Kuypers, 1977; Percheron et

al., 1996). Therefore, the input-output arrangement of thalamic pathways is one of tremendous complexity.

Only with the advent of transneuronal tracers has it been possible to map with precision the reciprocal, polysynaptic pathways between cerebellar output nuclei and associative regions outside of the motor cortices (Lynch et al., 1994; Clower et al., 2001; Kelly and Strick, 2003; Ramnani, 2006; Strick et al., 2009; Hashimoto et al., 2010; Prevosto et al., 2010; Lu et al., 2012) (**Figure 1A**). It appears that the majority of cortical areas, notably prefrontal, medial frontal, and posterior parietal regions providing inputs to the cerebellum (via the pontine nuclei), in turn receive cerebello-thalamo-cortical inputs (Strick et al., 2009; Ramnani, 2012). Curiously, a number of cortical regions thought to be crucial for cognition, such as the rostral temporal lobe and the ventrolateral prefrontal cortex, do not participate in these closed loops. This fact suggests a commonality between cortical areas that communicate with the cerebellum: it appears that they all contribute to the planning, control, or monitoring of movement.

The diversity of lateral cerebellar output channels, however, raises the question of their organization. Formerly, the loops that traverse lateral cerebellum through VL (**Figures 1A,B**) (Asanuma et al., 1983; Stein and Glickstein, 1992) were seen primarily as pathways for posterior parietal areas to gain access to PM (Thach, 1987; Stein and Glickstein, 1992), in agreement with known VL contributions to movement planning (Strick, 1976). However, the modern understanding that cerebro-cerebellar connections are largely reciprocal, and consequently target a variety of cortical areas outside the motor cortices, forces a re-evaluation of the ways in which lateral cerebellum, and its thalamic targets, may contribute to behavior. As explained above, lateral cerebellar ascending projections may be divided largely into two streams, one relayed via motor thalamus, the other via central thalamus. It is tempting to attribute the origin of each stream to motor and non-motor domains of the dentate nucleus respectively, with corresponding motor and cognitive functions. However, while cerebellar output channels are essentially segregated from each other, many cortical areas receive inputs from both central and more lateral thalamic regions (**Figures 1A,B**), making it difficult to separate both streams. In the two following sections, we will attempt to illuminate how the two thalamic regions differ in their contributions to the cognitive control of movement.

COGNITIVE-RELATED INPUTS TO CENTRAL THALAMUS

It is notable that identified cerebellar projections to central thalamic regions (formerly "non-specific" thalamus; Sasaki et al., 1979; Kalil, 1981; Asanuma et al., 1983; Sultan et al., 2012) were first considered to be potential output pathways for cerebellar cognitive signals (Leiner et al., 1986). This hypothesis assumed that inputs relayed through the central thalamus would constitute a separate, "non-specific" pathway that would exert a general influence through widespread thalamocortical projections. This view is compatible with the fact that central thalamus targets not only association cortices but also PM, SMA, and pre-SMA with considerable divergence (**Figure 1A**; Morel et al., 2005). This projection system, however, has been shown to be much more specific than previously conceived (van der Werf et al., 2002) and can influence selective regions, in addition to having a general impact on cortical activation levels. Specific influences carried via central thalamus, such as the modulation of preparatory activity mentioned above, would likely have different temporal dynamics than motor-related signal carried by the motor thalamus. Functional distinction between central and motor thalamus is less obvious at the transition zone in medial and dorsal parts of VL. Indeed, the fact that cerebellar inputs to prefrontal cortex seem to be relayed via caudal VLc and nucleus X (Middleton and Strick, 2001) argue for an involvement of motor thalamic regions in higher-level functions (see below). Accordingly, it has been proposed that cerebellar-recipient neurons of the caudal regions of central thalamus may be considered part of a functional continuum with more lateral "motor" cerebellar territories (Percheron et al., 1996). It has also been suggested that the mediodorsal (MD) thalamic nucleus, the main source of thalamic inputs to prefrontal cortex (Giguere and Goldman-Rakic, 1988; Ray and Price, 1993), may convey cerebellar signals (Sasaki et al., 1979; Tian and Lynch, 1997). If so, cerebellar inputs to MD would be expected to be found alongside motor signals from the superior colliculus (SC), which are relayed by the lateral MD to the frontal eye fields (FEF) (Sommer, 2003). Paralaminar regions of MD, however, are dominantly innervated by basal ganglia inputs, and cerebellar projections there are limited (Stanton, 1980; Kalil, 1981; Percheron et al., 1996; Mason et al., 2000; Erickson et al., 2004). It is thus likely that the majority of ascending cerebellar projections to frontal associative cortex is transmitted either via central thalamus or more lateral cerebellar territories (formerly "classical" motor thalamus).

Eye-movement related circuits show the limitations in distinguishing these pathways purely based on connectivity. The oculomotor thalamus largely overlaps with central thalamus (Schlag-Rey and Schlag, 1989; Tanaka and Kunimatsu, 2011) (**Figures 1B,C**, right) and targets both the lateral intraparietal area (LIP) and the FEF (Kievit and Kuypers, 1977; Huerta et al., 1986; Prevosto et al., 2010) (**Figure 1A**), two prominent nodes in the cortical circuits for the selection and control of eye movement. Both of these cortical regions receive inputs from the same caudal dentate region (Lynch et al., 1994; Prevosto et al., 2010). However, in comparison to LIP, dentate inputs to FEF may also be relayed via more lateral (paralaminar) thalamic regions (Okuda, 1994).

How this functional ensemble may contribute to higher level function is starting to be understood. For instance, central thalamus is known to contribute to working memory via its action on forebrain arousal (Mair et al., 2011). This action has often been related to the ascending reticular activation system, which notably provides intralaminar nuclei with profuse cholinergic inputs (Groenewegen and Berendse, 1994). Central thalamus, however, has the requisite connectivity to mediate subcortical influence on selective cortical circuits. Recent results showing that intact cerebello-thalamo-cerebral pathways are crucial for the normal functioning of working memory (Law et al., 2011) are compatible with this view.

Recent data implicate the lateral cerebellum in verbal working memory, but also point out contributions to spatial processing, timing, and executive functions (Leiner et al., 1989, 1993; Chen and Desmond, 2005; Strick et al., 2009; Schmahmann, 2010; Bellebaum et al., 2012; Ramnani, 2012; Stoodley, 2012). The exact

involvement of central thalamus in these functions is not yet clear, although there is evidence that it contributes to timing, in addition to working memory. Saccade-related neurons in central thalamus have been shown to display early activity that is particularly associated with the timing of self-initiated eye movements (Tanaka, 2007a; Tanaka and Kunimatsu, 2011). Complementary saccade-related activity patterns have been found in central thalamus that could signal the timing for acquisition and processing of reafferent information following saccades (Schlag-Rey and Schlag, 1984). Although neuronal activity related to self-initiated eye movements has been observed in basal ganglia, the thalamic neurons related to the timing of proactive movements were found predominantly in cerebellar territory (Tanaka, 2007a), in agreement with the putative involvement of the dentate nucleus in the initiation of volitional movements (Shibasaki et al., 1986; Ashmore and Sommer, 2013) (**Figure 2**). Thus, central thalamus appears well suited to transmit anticipatory activity related to volitional, self-timed movements from the lateral cerebellum to connected cortical areas (Maimon and Assad, 2006; Fried et al., 2011).

COGNITIVE-RELATED INPUTS TO VL/VPLo THALAMUS

While encouraging, the above conclusions were based largely on oculomotor studies. An important issue is the extent to which those findings generalize to skeletomotor movements, which are associated with thalamic activity in the VL and VPLo nuclei (**Figures 1B,C**, left).

Recordings in the cerebellar dentate nucleus (a dominant contributor to VL, see above) have described a population of neurons with long-lead activity (Grimm and Rushmer, 1974; Strick, 1983). Correspondingly, among arm-movement VL units, most cerebellar-recipient neurons increase their discharge before movement initiation, sometimes before the first change in electromyographic potential (Strick, 1976; Anderson and Turner, 1991). While the cerebellum is known for its role in the timing of movement (Salman, 2002), the involvement of cerebellar-recipient motor thalamus in the timing of volitional arm-movement is less clear. Notably, arm-movement neurons in cerebellar-recipient thalamus are commonly found to be more responsive to visually cued movement than to spontaneous or memory-based movement (van Donkelaar et al., 1999). Similar contextual modulation has been described in neurons from the "motor" domain of the dentate that target ventral premotor cortex (Mushiake and Strick, 1993) as well as in the medial intraparietal area (Colby and Duhamel, 1996), a region of the posterior parietal cortex that receives dentate inputs via motor thalamus (Prevosto et al., 2010). However, comparable effects have been described across effectors and brain structures, as exemplified by greater response to visually-guided than to spontaneous arm movements (van Donkelaar et al., 1999, 2000) and saccades (Mano et al., 1996) in thalamus and cerebellum, respectively. Thus, context dependency of neuronal activity may reflect a widespread influence found across functional divisions of the thalamus. Notably, a growing body of imaging and clinical studies (Ide and Li, 2011; Peterburs et al., 2011; van der Salm et al., 2013) indicate that cerebellar territories of the motor thalamus provide a critical contribution to executive control functions of the frontal lobe. This contribution could rely on motor thalamic inputs to non-primary motor regions and (less densely) to associative cortical regions, or central thalamic inputs to the same regions, or both (**Figure 1A**).

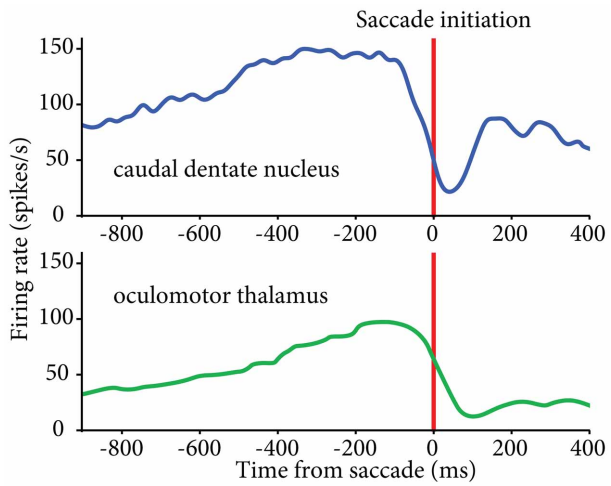

FIGURE 2 | Similar patterns of activity found in caudal dentate nucleus (top) and oculomotor thalamus (bottom) for self-initiated eye movements. Activity aligned to the initiation of self-timed saccades. Oculomotor thalamus data reproduced from Tanaka (2007a); dentate nucleus data from our lab (see Ashmore and Sommer, 2013).

More speculative is the potential role of motor thalamus in coordinating cognitive and motor aspects of language production. Results from stimulation studies found that language deficits can be induced at the same thalamic location as motor effects related to language production (Johnson and Ojemann, 2000). This intriguing finding is in agreement with the demonstration that ventral premotor cortex contains neurons specifically activated during vocalization (Coudé et al., 2011), in a region that receives dense projections from cerebellar-recipient thalamus (Matelli et al., 1989). This ventral premotor region is considered homologous to the motor portion of Broca's area in humans (Binkofski and Buccino, 2004) and is part of a dual cerebello-cortical system supporting verbal working memory (Chen and Desmond, 2005).

THE THALAMUS AS A SITE FOR MOTOR/COGNITIVE INTERACTIONS

If the motor and central thalamic neurons are involved in higher-order functions, the question remains whether their activities are driven mainly by their ascending inputs (i.e., whether thalamic neurons are just relays), or if these inputs, coupled with descending cortical modulation, results in thalamus-specific information processing.

Evidence from the well-characterized circuit from the SC to FEF via MD thalamus mentioned above (Sommer and Wurtz, 2004a,b) offers a template for a relay function: SC-receiving MD relay neurons essentially behave as a high-pass filtered version of SC inputs (Sommer and Wurtz, 2004a). This is fitting with the role of this circuit as a corollary-discharge pathway, i.e., carrying copies of a motor command.

Cerebellar-receiving thalamic neurons, which are not necessarily part of a corollary-discharge pathway, may behave differently.

It is known that the activity of motor thalamic neurons is shaped by cortical inputs (Guillery, 1995). This is evidenced, for example, by the high baseline firing rate of pallidal-recipient thalamic neurons, which likely results from a dual modulatory cortical control, one direct and excitatory, the other indirect and inhibitory (Selemon and Goldman-Rakic, 1988; Anderson and Turner, 1991; Guillery, 1995; Band and van Boxtel, 1999). Similarly, the activity of eye position thalamic neurons reflects properties of both brainstem inputs (separate horizontal/vertical channels; delays compatible with ascending inputs) and cortical inputs (hysteresis; long lead activity) (Schlag and Schlag-Rey, 1984; Tanaka, 2007b), in agreement with the view of intralaminar nuclei as a site of convergence of subcortical and cortical inputs (Kemp and Powell, 1971). It is thus conceivable that cortical inputs modulate cerebellar-recipient neurons' activity at least as strongly as their primary drive.

Another type of thalamic-specific interaction potentially occurs through converging ascending inputs from multiple subcortical sources. Demonstrated convergence patterns of this type, such as between dentate and interpositus nucleus projections (Shinoda et al., 1985), or cerebellar and basal ganglia projections (Sakai et al., 2002), have been studied only within pathways contributing to motor cortical areas, and are essentially inconclusive for the question of motor-cognitive interaction in the thalamus. However, the thalamus also has been shown to convey cerebellar inputs to striatum that derive from both motor and non-motor regions of the dentate nucleus (Kemp and Powell, 1971; Hoshi et al., 2005). Interestingly, the central thalamus seems to be the main relay for this pathway (Ichinohe et al., 2000; Hoshi et al., 2005). It is conceivable that, reciprocally, basal ganglia inputs to cerebellar thalamic regions contribute to both motor and non-motor circuits.

The two preceding types of interactions (subcortico-cortical and subcortico-subcortical) point to a dominant role of central thalamus in mediating cognitive aspects of movement control. Another aspect of thalamic connectivity suggest a third way by which both motor a central thalamic regions could actively contribute to cognitive control of movement. There is evidence that single thalamic regions provide inputs to functionally separate cortical areas, such as motor and associative cortices (Wannier et al., 1992). This divergence seems to represent a final sorting of signals that arise from selective regions of the dentate nucleus. Data from separate studies suggest that dentate regions where output channels overlap could target distributed cerebral cortical regions. Such is the case for caudal dentate projections to the FEF and LIP (Lynch et al., 1994; Prevosto et al., 2010), for dentate projections to the anterior intraparietal area, PMv, and M1 (Clower et al., 2005), and possibly for ventral dentate to the medial intraparietal area and the pre-SMA (Wiesendanger and Wiesendanger, 1985a; Akkal et al., 2007; Prevosto et al., 2010). While this organization does not validate a specific role for the thalamus in motor-cognitive interaction, it indicates that there may be a unique and overlooked role of motor thalamus in conveying such signals to separate regions. How those dentate projections interact in the thalamus with top-down cortical control and ascending inputs from other subcortical regions is not known, although it can be construed that this arrangement would likely contribute to behavioral flexibility.

CONCLUSIONS

Concordant results from a variety of studies indicate that movement-related thalamus takes part in circuits for higher-level control of behavior. A prior, parsimonious viewpoint was that distinct subcortico-thalamo-cortical pathways were likely to mediate separate functions (e.g., Sommer, 2003). Recent findings seem to paint a more nuanced picture.

First, each pathway consists of sub-streams, both in the thalamus and in the subcortical networks leading to it. These sub-streams may play differing roles in movement, or perhaps have differing contributions according to behavioral context. Accordingly, cerebellar-receiving thalamic neurons are possibly involved in both straightforward visuomotor control and higher level modulations of that control, such as the initiation of self-timed movements (**Figure 2**). The degree to which these conclusions hold across effectors, however, is still unclear. Second, the discovery of reciprocal, disynaptic connections between the cerebellum and the basal ganglia (Bostan and Strick, 2010) imply direct communications between these two principal pathways to cerebral cortex. The fact the central thalamus is posited as the main relay for cerebellar inputs to striatum underlines its relevance for high-level behavior in association with "core" motor thalamus.

Hence the overall conclusion from clinical, physiological, and anatomical studies is that the thalamus appears suited to relay, or perhaps even to mediate, the influence of cognitive processes on motor processes. Because in mammals, and particularly in primates, most behaviors comprise a cognitive component, it is not surprising to find prevalent cognitive modulation of motor circuits. The surprise comes perhaps from the fact that circuits beyond the cerebral cortex, including nuclei of the motor and central thalamus, seem to be so critical for cognitive-motor interactions.

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Functional roles of the thalamus for language capacities

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Early biological concepts of language were predominantly corticocentric, but over the last decades biolinguistic research, equipped with new technical possibilities, has drastically changed this view. To date, connectionist models, conceiving linguistic skills as corticobasal network activities, dominate our understanding of the neural basis of language. However, beyond the notion of an involvement of the thalamus and, in most cases also, the basal ganglia (BG) in linguistic operations, specific functions of the respective depth structures mostly remain rather controversial. In this review, some of these issues shall be discussed, particularly the functional configuration of basal network components and the language specificity of subcortical supporting activity. Arguments will be provided for a primarily cortico-thalamic language network. In this view, the thalamus does not engage in proper linguistic operations, but rather acts as a central monitor for language-specific cortical activities, supported by the BG in both perceptual and productive language execution.

Keywords: thalamus, language, corrtex, selective engagement, basal ganglia

INTRODUCTION

Over the last decades, functional imaging and neurophysiological techniques have allowed for an increasingly detailed allocation of mental functions to cortical structures and processes, whereas subcortical functions in cognitive processing still remain somewhat elusive. This discrepancy might, amongst others, be due to the fact that a precise assessment of processes in tiny and remote depth structures is comparably difficult with the prevailing research tools, such as magnetic resonance imaging (MRI) or electroencephalography (EEG). Thus, methodological properties could to a certain extent reinforce classical cortico-centric concepts of cognitive and, particularly, language capacities, based on the fundamental findings of Broca and Wernicke in the nineteenth century (Broca, 1861; Wernicke, 1874).

It is not a new claim, however, that a structural requisite of complex behavioral functions is the evolution of specific two-way thalamo-cortical operational units (Sanides, 1970). Concerning this view, corroborating information appears to come in from clinical observations in the many patients who, alongside with thalamic lesions, develop cognitive dysfunctions. Respective deficits can affect a wide range of behaviors, related to perceptual, attentional, mnemonic, executive or, specifically, linguistic capacities (e.g., Dejerine and Roussy, 1906; Bogousslavsky et al., 1988; Van Der Werf et al., 2000; Fimm et al., 2001; Liebermann et al., 2013), but naturally this notion leaves many questions open. For example, do thalamic structures take part in the proper programming of behaviors? Or do they rather 'just' relay information between cortical regions involved in the generation of given mental actions? Are relay functions stable or flexible, and how should flexibility be implemented? Finally, can 'thalamic functions' be generalized, or are they specific for any given task or process?

These questions shall be shortly discussed against the background of concepts of thalamo-cortical working models, ideas on thalamic functions in cognition and respective clinical data in the particular field of human language.

BASIC PRINCIPLES OF THALAMO-CORTICAL INTERACTION

Growing insight into principles of cortico-thalamic communication let the label 'cortical function' for the designation of higher-order processes appear out-dated. The basic idea underlying this term was that, once primary, e.g., sensory, information has reached its cortical projection area via thalamic relay nuclei, the finishing of respective processing would comprise a chain of exclusively cortical processes. This view, however, seems in contradiction to more recent descriptions of cortico-thalamic signaling (e.g., Murphy et al., 1999; Sherman and Guillery, 2011). In modern concepts, the thalamus consists of first-order nuclei which relay mainly sensory inputs to their cortical projection areas, and, to a larger extent, of higher-order nuclei which propagate information from one cortical area to another and also receive messages from their projection sites. In so doing, a number of compositional and cellular properties entail that thalamic nuclei *ab initio* act on the messages to and from cortical areas (Guillery and Sherman, 2002).

Even in first-order nuclei, such as the lateral geniculate, only a minority of synaptic connections comes from the retina; the vast majority of contacts is made with modulatory cells, e.g., local interneurons or layer VI and, in case of higher order thalamic nuclei, also layer V corticofugal neurons (Van Horn et al., 2000; Lam and Sherman, 2010). With respect to layer V output, it appears further interesting that, while having another target projection, e.g., on spinal or brain stem motor neurons, the connection with the thalamic neuron derives from an axonal branch. Thus, higher-order nuclei seem to be informed about output

signals (transformed into behavior) by efference copy which, in turn, acts on the information sent back from the thalamus to the subsequent cortical projection (cf. Von Holst and Mittelstaedt, 1950; Sherman, 2005).

Besides the description of this connectivity, meticulous research has demonstrated that thalamic relay neurons modulate informational transfer by working in specific discharge modes (cf. Jahnsen and Llinas, 1984; Steriade et al., 1998; Steriade, 2000). Under the condition of relatively depolarized membrane potentials prevailing in awake state, cells convey synaptic input in a tonic 'spiking mode', supposed to be the basis of relatively precise, i.e., 'linear' transmission of presynaptic to postsynaptic action potentials in a fairly wide frequency range (McCormick and Feeser, 1990). This functional state can, at least regarding first-order thalamic nuclei, be conceived as a prerequisite for providing the organism with exact information about its physical environment, but also about internal or even mental states. Further, with relatively hyperpolarized membrane potentials thalamic relay neurons may discharge so called low-threshold calcium spikes, triggering bursts of action potentials. During sleep, this bursting mode, which only occasionally occurs in the awake state, becomes rhythmic and entrains larger assemblies of neighboring neurons. This propensity is only interrupted by relatively strong stimuli, so that it disconnects the organism from real world information (McCormick and Feeser, 1990). While awake, for reasons of membrane and synaptic physiology, bursting of relay neurons is usually followed by tonic spiking. In this case, the initial burst discharged from the thalamus has been proposed to act as a 'wake-up call' to get the cortex engaged in the processing of the subsequently conveyed information (Guido and Weyand, 1995; Sherman, 2001; Swadlow and Gusev, 2001; Swadlow et al., 2005). The control of these states is not fully understood, but certainly the reticular nucleus, surrounding the thalamus as a thin cell sheet of GABA-ergic inhibitory neurons comes into play here. The reticular neurons are both driven by branches from ascending relay neurons and related corticofugal output from layer VI, and hyperpolarise the driving thalamo-cortical cells via back-projections. Thus, the control of the discharge mode and thalamocortical transmission, appears to be organized in a dynamic balance of bottom-up and top–down factors (Yingling and Skinner, 1977; Crick, 1984; Guillery et al., 1998; Lam and Sherman, 2010).

Altogether, the properties of thalamic relay together with reticular neurons seem to serve a flexible spatiotemporal gating of information on the way to and between cortical areas. Distinct discharge modes allow for recruiting downstream targets or disrupting them from further informational flow. This and their widespread connections appear to enable thalamic nuclei to monitor and adapt the network constellations needed for ongoing behaviors, a function rather emerging from an intricate two-way exchange with cortical information than from processing between hierarchically organized brain structures.

MODELS OF THALAMIC INVOLVEMENT IN LINGUISTIC CAPACITIES

Various models on the roles of subcortical structures in language processing have been formulated, mostly including the thalamus and the basal ganglia (BG). Closest to the described principles of thalamo-cortical communication is the 'Selective Engagement Model' (Crosson, 1985). In this concept, thalamic nuclei, e.g., the centromedian parafascicular complex, monitor the activity state of distributed cortical areas and control their functional connectivity via connections passing through the inferior thalamic peduncle. In case of linguistic information, this primarily refers to frontal and temporo-parietal cortices between which, for example, phonemic, lexical and semantic information is exchanged during language perception and production. In a number of further models, cortico-thalamic language processing is complemented by the BG. These views build upon cortico-striato-thalamo-cortical network properties (Alexander et al., 1986, 1987) the most important of which shall therefore be summarized. In short, the striatum receives excitatory input from almost all cortical regions (Alexander et al., 1986; Mink, 1996; Delong and Wichmann, 2007). Back projection to cortical areas is organized in parallel and interconnected circuitries encompassing limbic, associative and motor loops reaching the BG 'output nuclei', namely the internal pallidum (GPi) and the reticular part of the substantia nigra (SNpr) which send inhibiting GABAergic efferences to the thalamus (Alexander et al., 1986; Delong and Wichmann, 2007; Schroll et al., 2012). The 'output nuclei' receive convergent signal projections via the 'direct pathway' as well as via the 'indirect pathway' which encompasses the external pallidum (GPe) and the downstream subthalamic nucleus (STN) (Alexander et al., 1986; Mink, 1996). Concurrently the STN receives 'hyperdirect' input from cortical regions (Nambu, 2004; Lambert et al., 2012) which is thought to lead to a procrastination of the BG response (Frank, 2006).

Neurotransmission is mainly GABA-ergic, with the exception of glutamatergic STN output (Wilson, 2004; Delong and Wichmann, 2007). BG activity states are modulated by dopaminergic drive from the pars compacta of the substantia nigra (SNpc) to the striatum (Bamford et al., 2004). For distinct striatal receptor profiles this unfolds complex, partially opposed effects on the direct and indirect route. Finally, the BG output nuclei convey signals to anterior and ventrolateral portions of the thalamus and its intralaminar nuclei and from there back to the cortex (Delong and Wichmann, 2007; Obeso et al., 2008). This assembly of parallel routes with distinct effects on signal propagation, spread and speed is thought to enable the organism with essential functions, such as the selection, temporal filtering and sequencing of competing information (Temel et al., 2005; Tinaz et al., 2006). Further, the mentioned properties have been related to the formation and alignment of behaviors on the basis of habitual rules (Barnes et al., 2005).

In the specific context of language processing, the "Response-Release Semantic Feedback Model" claims thalamic and BG functions in language production (Crosson, 1985, 1992; cf. Murdoch, 2001; Murdoch and Whelan, 2009). As in the Selective Engagement Model, thalamic nuclei are posited to control the interaction between fronto-opercular and temporo-cortical cortices for the integration of lexico-syntactic with semantic information. The resulting signal is further passed on to the BG which are thought to coordinate the release of the provided language plan into speech.

A further dichotomy between thalamic and BG functions in language processing has been suggested in the "Declarative/Procedural Model." This concept is basically in parallel to claims raised with respect to mnemonic operations (Mishkin et al., 1997; Eichenbaum, 2006). It has been argued that the BG as an apparatus for habit formation and application provide the requirements to apply grammatical rules to linguistic raw data. The supply with respective information, in turn, involves temporo-thalamic networks for transforming arbitrary 'world knowledge' into lexical input signals (Ullman, 2001, 2004; Wahl et al., 2008).

Borrowed from the classical model of cortico-striato-thalamo-cortical motor processing (Alexander et al., 1987), the 'Lexical Selection Model' views the BG as a machinery to align word-related input to ongoing language plans. This is mainly conceived as a process in which an excess supply of lexical alternatives has to be monitored for unsuited candidate words to be inhibited from further processing. Only the remaining information will be signaled to the thalamus which then initiates fronto-cortical word release (Wallesch and Papagno, 1988; cf. Mink, 1996; Norris and McQueen, 2008).

Finally, it should be mentioned that most linguistic models do not focus on the link between specific operations and brain structures, but rather on the processes themselves. Nonetheless some of these concepts are of interest in this context. In the 'Motor Theory of Speech Perception' (Liberman et al., 1967; Liberman and Mattingly, 1985) it is presumed that auditory language information is instantaneously 'motorically reconstructed' as an internal imagery of the heard as own speech. Somewhat similarly, the 'Embodied Cognition Theory' posits that, e.g., lexical entries are not stored as arbitrary, amodal information, but are tightly linked to sensorimotor processes thought to be necessary for the simulation of word meaning. In line with such 'horizontal language representation', it has, for example, been demonstrated that the perception of action words goes along with activations of brain areas involved in the execution of the implied content. Although this refers to the cortical regions (Hauk et al., 2004; Pulvermuller et al., 2005), an additional involvement of basal motor structures could be reasonably assumed for motor imagery and seems supported by respective experiments in patients with BG disease (Tremblay et al., 2008). Future research, particularly in the field of Deep Brain Stimulation (DBS) specifically and reversibly impacting on defined BG structures, might shed light on this open issue, still difficult to access by nowadays research tools.

CLINICAL FINDINGS

Although, from a clinical perspective, there is little doubt that 'thalamic aphasia' exists (Benson and Ardila, 1996; Neau and Bogousslavsky, 1996; Demonet, 1997; Nadeau and Crosson, 1997; Kuljic-Obradovic, 2003; Schmahmann, 2003; De Witte et al., 2011) it is not easy to relate defined language disorders to particular lesions within the thalamus. This is due to a number of reasons. Deficits have often been described in thalamic infarction, but owing to a relatively complex and sometimes variant vascular supply (Van Der Werf et al., 2000; Schmahmann, 2003; Carrera et al., 2004; Carrera and Bogousslavsky, 2006; Hermann et al., 2008; De Witte et al., 2011; Nolte et al., 2011; Hebb and Ojemann, 2012) aphasic syndromes (i) have been observed with different locations of damage, (ii) comprise heterogeneous linguistic deficits, (iii) mostly do not occur in isolation, but go along with other neuropsychological deficits, (iii) and are often accompanied by further extra-thalamic lesions. Further, it has been stated that, in terms of topography, information processed in thalamic areas is propagated in a very divergent and intermingled manner. Hence, the allocation of specific symptoms to particular nuclei is genuinely more difficult at this level than it is for cortical regions with their relatively precise functional description (Bruyn, 1989).

Since language deficits have also frequently been described following other subcortical damage, e.g., BG lesions (Damasio et al., 1982; Perani et al., 1987; Weiller et al., 1990; Hillis et al., 2001; Russmann et al., 2003; Hillis et al., 2004; Han et al., 2005; Choi et al., 2007; Pellizzaro Venti et al., 2012), there have been attempts to differentiate the aphasia types occurring in thalamic vs. striato-capsular and paraventricular white matter infarction (Kuljic-Obradovic, 2003). The authors found that, contrasting these lesion types, thalamic aphasics were characterized by relatively high impairments of comprehension, word finding difficulties and by different types of paraphasias. In other reviews and in-depth studies the scope of language symptoms following thalamic lesions mainly of the dominant hemisphere was relatively wide, the most prominent features being reduced spontaneous speech up to mutism, dysnomia, paraphasias up to jargon and impaired comprehension (Jonas, 1982; Van Der Werf et al., 2000; Schmahmann, 2003; Carrera and Bogousslavsky, 2006; Hermann et al., 2008; De Witte et al., 2011). Many patients had preserved non-propositional speech, i.e., language repetition remained relatively intact. Another striking feature was the preservation of the speech syntax in this cohort. From this it was concluded that a 'transcortical aphasia' type was more likely to occur in left thalamic damage than in other brain lesions apart from that of the dominant supplementary motor region (SMR) (Jonas, 1981, 1982). In this regard, thalamic nuclei and the SMR were proposed to form a functional unit in language processing (cf. also Penfield and Roberts, 1959). Further, it should be mentioned that in cases with extended lesions confined to the thalamus, e.g., by primary hemorrhage, permanent global aphasia has been observed (Kumar et al., 1996).

More specific assumptions about the thalamic structures relevant for language processing were formulated by Nadeau and Crosson (Nadeau and Crosson, 1997). Arguments were mainly derived from observations in patients with infarctions of the tuberothalamic and paramedian arteries in which aphasia appears to be more common than after occlusion of the other two thalamic main blood suppliers, the thalamogeniculate and posterolateral choroideal arteries. Particularly tuberothalamic infarction of dependent anterior thalamic structures leads to word finding difficulties, low performance in phonemic and semantic verbal fluency tasks, paraphasia with relatively spared language comprehension. Further, amnesic syndromes may occur and hypomotivational states with apathy, low arousal, and dysexecutive features, in particular, perseverative behavior appear to be common. Although paramedian infarction leads to even more

prominent neuropsychiatric sequels (Carrera and Bogousslavsky, 2006), e.g., vigilance fluctuations and confusional states, it can provoke a similar syndrome of transcortical aphasia, comprising reduced word production, phonemic and semantic paraphasia, misnomia and perseverations with largely preserved language comprehension (Molnar, 1959; Davous et al., 1984; Tuszynski and Petito, 1988; Clarke et al., 1994; Van Der Werf et al., 2000; Schmahmann, 2003; Hermann et al., 2008; De Witte et al., 2011). The link between both types of thalamic infarctions was seen in an affection of a network, linking widespread frontal cortex regions with the intralaminar centromedian complex (supplied by the paramedian artery) via the inferior thalamic peduncle, dependent on tuberothalamic supply (cf. Yingling and Skinner, 1977).

Aphasia following infarction of the inferolateral or posterior thalamus, caused by an occlusion of thalamogeniculate or posterolateral choroideal arteries, seems less frequent (Carrera et al., 2004), although it has also been argued that, e.g., the pulvinar had rich collateral perfusion so that respective symptoms might often be compensated (Lhermitte, 1984; Nadeau and Crosson, 1997).

Another line of evidence for thalamic language functions comes from data which were collected in the context of thalamotomy for the treatment of movement disorders (Ojemann and Ward, 1971; Ojemann, 1975, 1976, 1983a,b; cf. Hebb and Ojemann, 2012). In contrast to today, in the nineteen sixties and seventies different target points and trajectories were chosen for this procedure so that cognitive performance could be assessed under test stimulations at different regions of the thalamus. Concerning language, it was found that object anomia and lexical memory disorders followed from current injection in the dorsal lateral thalamus and pulvinar (Fedio and Van Buren, 1975), whereas repetitive (mis)naming was observed under stimulation of the anterior portions of the ventrolateral thalamus and phonemic and syllabic repetitions occurred in intermediate locations. Although from a current perspective, the anatomical precision of these data is not completely clear, they appear to indicate functions of dorsal and, in particular, pulvinar thalamic regions in lexical processing. In this regard, it should be further mentioned that decline in verbal fluency tasks has also been observed in patients with thalamic DBS of the ventral intermediate nucleus (VIM) for the treatment of tremor (Troster et al., 1999).

In contrast to the large corpus of evidence that suggests a direct involvement of the left thalamus in language functions, the role of the BG appears more obscure. Clinically, language dysfunctions after BG (capsular/striatal) infarction show high variability and even though aphasia occurs frequently (Weiller et al., 1990; Kumral et al., 1999; Han et al., 2005; Jung et al., 2005; Choi et al., 2007; Pellizzaro Venti et al., 2012) infarction of the BG can also go along with unimpaired language (Nadeau and Crosson, 1997; Kuljic-Obradovic, 2003). Aphasic symptoms are usually distinct from those in 'thalamic aphasia.' They have been characterized by widely preserved comprehension, repetition and naming but more strongly affected fluency (Kuljic-Obradovic, 2003). Especially infarction of the caudate nucleus have been associated with perseveration and paraphasia (Kreisler et al., 2000). Causing mechanisms have been discussed controversially, encompassing assumptions about a specific language function of the proper BG (Damasio et al., 1982) and their projections to cortical areas (Perani et al., 1987; Russmann et al., 2003), or alternatively, lesions of white matter fiber pathways (Damasio et al., 1982; Nadeau and Crosson, 1997; Kuljic-Obradovic, 2003), thalamic dysfunction resulting from BG lesions (Pellizzaro Venti et al., 2012), concomitant cortical compression (e.g., of the perisylvian fissure) and cortical hypoperfusion after BG infarction leading to aphasia (Nadeau and Crosson, 1997; Hillis et al., 2001, 2004; Han et al., 2005; Choi et al., 2007).

Apart from aphasic disorders, which thus to many authors do not appear to be a direct cause from BG lesions, stuttering speech is observed after BG lesions (Tani and Sakai, 2011) and can be associated with impaired timing and coordination of language output most likely occasioned directly within the BG (Alm, 2004).

EXPERIMENTAL FINDINGS

At this point, only a small selection of experimental findings on thalamic involvement in linguistic processes shall be given to indicate the heterogeneity of respective data. In a number of functional imaging studies thalamic participation in language tasks has been shown. For example, concerning fundamental functions of language recognition, left thalamic activation has been found during the differentiation of distinct speech sounds, alongside with activity in the planum temporale, the superior temporal and Heschl's gyri of the dominant hemisphere (Alain et al., 2005). Even the thalamic first-order auditory nucleus, the medial geniculate body, has been shown to be active during the recognition of speech sounds involving cortical feedback loops, a function presumed to be relevant for communication (Von Kriegstein et al., 2008) and which was found impaired in dyslexic persons (Diaz et al., 2012). Further, joint thalamic and frontotemporal involvement has been reported during lexico-semantic operations and object recall (Assaf et al., 2006). Similar functions were allocated to dorsomedial (Van Der Werf et al., 2003) and pulvinar (Nadeau and Crosson, 1997; Kraut et al., 2003a) regions of the thalamus. For the chronometrical sequence of activations during respective tasks, it has been proposed that the dorsomedial thalamus and pre-supplementary motor areas engage in the concept formation of perceived signals, whereas subsequent pulvinar activity reflects downstream processes for the semantic alignment of this with the ongoing input (Kraut et al., 2002, 2003a; Slotnick et al., 2002). The communication with and binding of cortical areas involved in this is thought to be mediated by the pulvinar induction of a common gamma rhythm in, e.g., temporo-parietal regions (Slotnick et al., 2002).

Evidence for cortico-thalamic language processing has also been provided by a study with simultaneous depth and scalp recordings in the context of DBS for the treatment of movement disorders (Wahl et al., 2008). In derivations from DBS electrodes in the ventrolateral thalamus, nearby generated language-related potentials (LRP) were identified during syntactic phrase analysis, interspersed between left frontal and temporo-cortical LRPs. During semantic phrase analysis both cortical and thalamic LRPs appeared as a sustained LRP with indistinguishable dynamics at either level. Of note, during recordings from the relatively close STN no such LRP were seen. Thus, whereas thalamo-cortical networks are involved in complex syntactic and semantic phrase

analysis, we did not find evidence that the same held true of the classical cortico-striato-thalamo-cortical circuitry which STN forms part of.

On the other hand, BG contributions to linguistic tasks have indeed been demonstrated. Particularly, the caudate has been found to be involved in a number of linguistic tasks, e.g., concerning word matching operations (Mummery et al., 1998), language selection in bilinguality (Crinion et al., 2006; Friederici, 2006) and lexico-morphological processing (Fiebach et al., 2004) and was supposed to support syntactic operations (Kotz et al., 2009).

On a more general level, a number of studies have assigned rule-based, i.e., grammatical functions of language processing to the BG, as opposed to knowledge-driven, lexical processes. This has been inferred from experimental findings in particular BG disease or under functional manipulation of structures such as the STN by DBS. For example, patients with Chorea Huntington have been reported to display particular difficulties in the analysis of passive instead of active sentence structures which has been interpreted as a striatal deficit of parsing increased grammatical complexity. Further, patients with Parkinson's disease (PD) were found to show increased difficulties in building regular past tense verb forms when their DBS of the STN was switched on vs. switched off (Ullman et al., 1997; Teichmann et al., 2008). In contrast to this, no difference between either stimulation state was obtained for irregular verbs, depending on lexical knowledge instead of rule-based operations exerted on the given verb (Phillips et al., 2012). Thus, a concept for these findings may be that malfunction of the BG leads to deficits in applying combinatorial rules to linguistic messages, compatible with proposed superordinate BG functions, such as the sequencing or time-critical selection of input signals in general (Temel et al., 2005; Tinaz et al., 2006). Another interesting aspect of the above mentioned study was that active vs. inactive DBS of the STN led to enhanced naming of 'manipulated' (indicative of a motor connotation) instead of 'non-manipulated' (as indicative of absent motor connotations) objects, in parallel with an ameliorated motor condition of PD patients. This appears to tie in with views as formulated in the Embodied Cognition Theory according to which the use and understanding of lexical symbols depends on an internal imagery of their physically experienced implications (see above). In terms of brain structures, such concepts are of interest since they do not imply a strict distinction between sensorimotor and cognitive processes, but rather conceive them as dependent aspects of holistic behavior.

Whichever specific BG structures may be involved in a particular language task, we consider the thalamus - an agglomerate of, admittedly, very distinct nuclear clusters - to contribute to virtually all cognitive demands. This point of view is based on much of the said above, but also on a number of own studies on subcortical processing beyond language. In the aforementioned DBS setting, we addressed functions as diverse as selective attention, response preparedness, cognitive control or the consciousness of perception (Klostermann et al., 2006; Marzinzik et al., 2008; Nikulin et al., 2008; Wahl et al., 2008; Klostermann et al., 2009). We regularly identified neurophysiological correlates of a thalamic involvement, always accompanied by cortically generated event-related potentials (ERP). In the given context, two findings deserve special mention: first, based on chronometrical ERP analysis, thalamic as well as cortical regions could 'lead' or 'initiate' a given cognitive process (Klostermann et al., 2006); second, in complex ERP sequences the number of components was identical at cortical and thalamic levels, compatible with primary to higher-order event processing in joint subsequent thalamo-cortical steps (Klostermann et al., 2009).

A CONCLUDING VIEW

Coming back to the initial questions of if and how the thalamus contributes to language capacities, we would like to propose (fully aware of the personal angle of this concept) that this is the case in essentially the same way in which it holds true for most non-linguistic cognitive operations. We consider the most relevant thalamic functions to be the control and adaptation of corticocortical connectivity and bandwidth for informational exchange. These functions appear to be built mainly on three properties of thalamocortical neurons: first, their local and remote feed-forward and feed-back connections with almost any cortical region as a prerequisite for establishing flexible network constellations; second, their ability to convey information in distinct discharge modes for regulating the likelihood with which messages are passed on from one cortical region to another, and third, a sequential circuitry of thalamocortical information allowing for the adaptation of final messages in an iterative process involving various downstream relay nuclei.

In this view of transthalamic network orchestration, corticothalamic signals have two functions. They notify thalamic neurons that a specific area has become active, so that functionally related regions can be engaged, for example, the superior temporal gyrus upon fronto-opercular input during word perception. In turn, thalamic neurons will receive the output message from the activated downstream cortex, and so forth. Having said this, it remains open how this iterative process should be adapted to the ongoing demands, particularly in the context of rapidly changing cognitive operations, as required for language processing. In this regard, it is of note that, although thalamic facilitation or disruption of signal propagation has mainly been related to long-acting vigilance conditions, changes of respective neuronal 'state functions' certainly also act at shorter intervals in support of ongoing changes of cognitive demands. In terms of language, this can, for example, be conceived as the selection and sequencing of words into phrase structures, emerging from poorly structured phonemic, lexical or syntactic information. On a neuroanatomical level, related functions have been ascribed to the BG, conceived as an apparatus for the coding of overlearned procedures. In this capacity (in line with a number of study results and some clinical observations in subcortical aphasics), the information necessary for the timing of transthalamic cortical engagement could be provided.

Altogether, we favor a concept in which spatially distributed cortical language operations are flexibly (dis-)engaged and (de-)coupled by various thalamic neuronal assemblies, including anterior, intralaminar, dorsomedial nuclei as well as pulvinar

subregions of the dominant hemisphere. Further, we consider likely that the timing of transthalamic network constellations is supported by BG computations for the composition of cortically provided information. In this view, human language is not a hierarchically organized cognitive function, but the compound output of interdependent subcortical and cortical systems, specialised in network activation, linguistic programming and temporal process alignment.

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Neural signal for counteracting pre-action bias in the centromedian thalamic nucleus

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Most of our daily actions are selected and executed involuntarily under familiar situations by the guidance of internal drives, such as motivation. The behavioral tendency or biasing towards one over others reflects the action-selection process in advance of action execution (i.e., pre-action bias). Facing unexpected situations, however, pre-action bias should be withdrawn and replaced by an alternative that is suitable for the situation (i.e., counteracting bias). To understand the neural mechanism for the counteracting process, we studied the neural activity of the thalamic centromedian (CM) nucleus in monkeys performing GO-NOGO task with asymmetrical or symmetrical reward conditions. The monkeys reacted to GO signal faster in large-reward condition, indicating behavioral bias toward large reward. In contrast, they responded slowly in small-reward condition, suggesting a conflict between internal drive and external demand. We found that neurons in the CM nucleus exhibited phasic burst discharges after GO and NOGO instructions especially when they were associated with small reward. The small-reward preference was positively correlated with the strength of behavioral bias toward large reward. The small-reward preference disappeared when only NOGO action was requested. The timing of activation predicted the timing of action opposed to bias. These results suggest that CM signals the discrepancy between internal pre-action bias and external demand, and mediates the counteracting process—resetting behavioral bias and leading to execution of opposing action.

Keywords: reward, thalamus, basal ganglia, attention, monkey, action-selection

INTRODUCTION

In our daily life, most actions are selected and executed involuntarily, but they are appropriately incited by motivational, habitual or innate drive. For example, when actions are followed by different values of rewards, the highest one among the alternatives tends to be chosen frequently (Thorndike, 1898; Herrnstein, 1961), and to be executed quickly and accurately (Schultz et al., 1992; Watanabe et al., 2001; Minamimoto et al., 2005). Such a behavioral manifestation, the tendency or bias towards one over others (i.e., behavioral bias), reflects the consequence of action-selection or the decision-making process in advance of action execution. However, when we face unexpected situations (e.g., the highest option is unavailable), the pre-action bias is no more valid or even an obstacle, so that it should be withdrawn and replaced by an alternative that is suitable for the situation. This counteracting process is crucial to warranting our behavioral flexibility under unexpected situations, while pre-action bias allows us to execute actions efficiently without special effort. The two processes, internal-driven pre-action bias and external-driven counteracting to it, are considered to work in a complementary fashion.

Accumulating evidence suggests that the cortico-basal ganglia network, and especially the striatum, is a critical node for generating behavioral bias with respect to its role in action-selection or decision-making (Samejima et al., 2005; Hikosaka et al., 2006; Graybiel, 2008; Lau and Glimcher, 2008). In contrast, the neural basis for the counteracting process remains to be fully identified. A potential circuit is the thalamic centromedian-parafascicular (CM-PF) complex and its reciprocal connections with the cortico-basal ganglia system (Kimura et al., 2004; Minamimoto et al., 2009). Previously, we demonstrated that a subset of CM neurons of behaving monkeys responds to salient sensory stimuli (Matsumoto et al., 2001; Minamimoto and Kimura, 2002) and that it responds preferentially after instruction of actions associated with small reward while the behavioral bias toward large-reward action is manifested (Minamimoto et al., 2005). In addition, electrical stimulation of the CM nucleus mimics the counteracting process—slowing reaction to the larger-reward option (Minamimoto et al., 2005). These results suggested that CM plays important roles in detecting unexpected events and counteracting motivationally driven behavioral bias (Kimura et al., 2004; Minamimoto et al., 2009).

To understand the exact role of CM in the counteracting process, however, neural activity of CM needs to be better characterized in relation to behavioral bias in various situations. Here,

we studied single-neuron activity in the thalamic CM nucleus while the monkey performed behavioral tasks with the following conditions: a GO-NOGO task in which two types of actions were associated with either large or small reward or were equally rewarded, and NOGO task in which only NOGO action was requested but with large or small reward instructed by visual signal. We found that CM neuron discharges after instruction for small-reward action signaled the discrepancy between the strength of pre-action bias and external demand to perform opposing action, the timing of which predicted the timing of opposing action. These results provide a better understanding of the role of CM in sensory-driven counteracting to internal pre-action bias.

MATERIALS AND METHODS

The present study was performed on the data that was partly published in a brief report (Minamimoto et al., 2005).

EXPERIMENTAL ANIMALS

We used two male Japanese monkeys (*Macaca fuscata*): monkey SJ (5.8–7.5 kg) and monkey MA (6.7–8.0 kg). All surgical and experimental procedures were approved by the Animal Care and Use Committee of Kyoto Prefectural University of Medicine and were in accordance with the National Institutes of Health *Guide for the Care and Use of Laboratory Animals*. The monkeys had limited access to water for 4–5 days per week, but they received food and water *ad libitum* on weekends.

BEHAVIORAL TASK

Monkeys sat in a primate chair in a sound-attenuated and electrically shielded room. They faced a panel in which a rectangular hold button and two instruction buttons were embedded. In the GO-NOGO task, when the monkeys pressed the hold button for 200–600 ms with their hand contralateral to the thalamus recording, one of two instruction buttons was illuminated yellow as a cue stimulus (**Figure 1A**). After an additional 1.2–2.2 s holding period, its color turned to either green or red, instructing GO or NOGO action, respectively. With the GO instruction, the monkeys had to release the hold button and press the illuminated target button within 3 s. With the NOGO instruction, the monkeys had to continue pressing the hold button for another 700–800 ms. In biased blocks, combinations of either a large water reward (0.3 ml, +R) after the successful GO trials and small water reward (0.1 ml, −R) after the successful NOGO trials or *vice versa* were run in single blocks of 40–120 correct trials (**Figure 1B**). In the even-reward block, successful trials were equally rewarded to both GO and NOGO trials (0.2 ml, **Figure 1C**). The occurrence of GO and NOGO trials was not predictable (average probability was 0.5). In NOGO task (**Figure 1D**), only NOGO actions were requested, but the reward, either a large (0.3 ml, +R) or small water reward (0.1 ml, −R), was given for successful trials. The reward size was indicated by colored instruction. A low (300 Hz) or high (1 kHz) tone was sounded after a correct behavioral reaction, which was followed by a large or small reward, respectively. For both GO-NOGO and NOGO tasks, when the monkey made an error, including failure to keep holding the button down and performing incorrect action, all LEDs flashed and the trial was aborted and the same trial condition was repeated. Through 1 month of training, the monkeys achieved performing the behavioral task at a high correct performance rate (>90%).

SURGERY

Surgery was performed under sterile conditions with the monkey under deep sodium pentobarbital anesthesia. Anesthesia was induced with ketamine hydrochloride (10 mg/kg, i.m.) and sodium pentobarbital (Nembutal; 27.5 mg/kg, i.p.), and supplemental Nembutal (6 mg/kg, i.m., for 2 h) was given as needed. Four head-restraining bolts and two recording chambers were implanted under stereotaxic guidance on the skulls of each monkey. The chamber for recording neuronal activity in the thalamus was positioned vertically over the thalamus. The center of the chamber was positioned midline and adjusted according to Horsley–Clark stereotaxic coordinates (anterior 12–13 mm). The other chamber was not used in this study.

ELECTROPHYSIOLOGICAL RECORDINGS AND DATA COLLECTION

We recorded the activity from single neurons that were located primarily in the CM nucleus as well as surrounding thalamic nuclei, such as parafascicular nucleus (PF) and dorsolateral PF (PFdl). Action potentials from single neurons were recorded using tungsten microelectrodes (2–5 MΩ at 1 kHz, FHC, Bowdoinham, ME) that were inserted through the implanted recording chamber and advanced by means of an oil-drive micromanipulator (MO-95; Narishige, Tokyo, Japan). The action potentials were amplified, filtered (50 Hz to 3 kHz) and isolated by spike sorter with a template-matching algorithm (multi-spike detector; Alpha Omega Technologies, Nazareth, Israel). Onset times of the action potentials were recorded on a laboratory computer (9821XV13; NEC, Tokyo, Japan) together with the onset and offset times of stimuli and the behavioral events such as pressing and releasing the button. In this study, we selectively studied the activity of long-latency-facilitation (LLF) type of neurons, which show burst discharges after unexpectedly presented auditory and/or visual stimuli of long latency (visual, 250–350 ms; auditory, 170–300 ms), such as knocks on the laboratory door. We also recorded licking movement by means of a strain gauge (DPM-711B; Kyowa, Tokyo, Japan) fixed to the waterspout.

DATA ANALYSIS

Analysis of behavioral and spike data and statistical test were performed using a Visual Basic (Microsoft, Redmond, WA) and R statistical computing environment (Team RDC, Vienna, Austria).

Behavioral data analysis

For behavioral data analysis, we excluded the data of the initial eight correct trials during the transitional phase between blocks of trials with different action-reward associations. Error rates for each trial type were calculated in each block, and were averaged across blocks in each bias condition. The average error rate for each trial type was compared between bias conditions by two-sample *t*-test. Reaction times (RTs, time between GO and releasing the hold button) and movement times (MTs, time between releasing the hold button and pressing the target) in GO

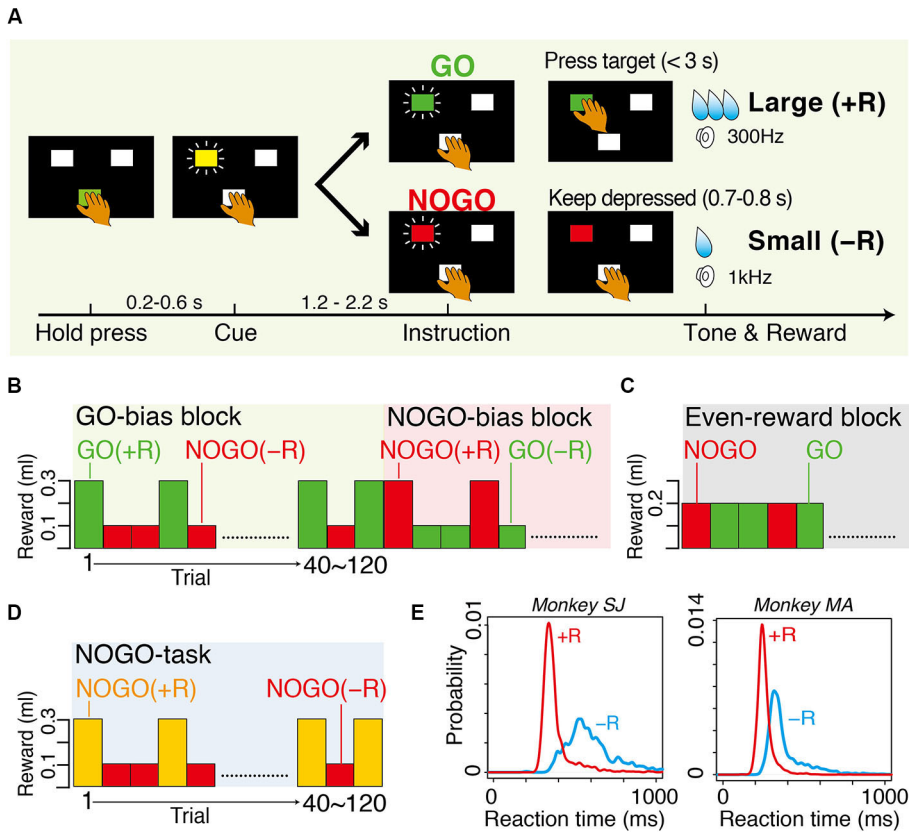

FIGURE 1 | Tasks and behavior. **(A)** Sequence of events in GO-bias block of GO-NOGO task in which GO and NOGO actions were followed by large reward (+R) and small reward (−R), respectively. **(B)** Action-outcome associations in GO-bias and NOGO-bias blocks. GO (green) and NOGO (red) trials were asymmetrically rewarded in each block. **(C)** Action-outcome associations in even-reward block where reward size was equal in GO and NOGO trials. **(D)** Action-outcome associations in NOGO task in which only NOGO action was requested. Successful trials were rewarded with either large reward (+R) or small reward (−R), which was assigned by colored instruction (yellow or red). Timing of events was the same as that of GO-NOGO task. **(E)** Smoothed histograms of occurrence probability of reaction time. Red and blue curves are for GO(+R) and GO(−R) trials, respectively. Histograms have bin width of 1 ms and are smoothed with a Gaussian kernel (SD = 10 ms).

trials were computed and compared between bias conditions by two-sample *t*-test.

Neural data analysis

For spike data analysis, we excluded the data of error trials and retrials after error trials, as well as eight successful trials after the block transition. Based on the previous study, we examined the discharge rates of each recorded neuron during two task epochs: (1) *Background*: the 250-ms period (500–750 ms) before pressing the hold button; and (2) *Post-instruction*: the 250-ms period (250–500 ms) after instruction onset. The statistical significance of changes in the discharge rate of the post-instruction activity for each of four trial types was evaluated by two-sample Wilcoxon test ($p < 0.05$) compared to the background activity. To quantify the preference of neural response, we performed receiver operation characteristic (ROC) analysis. For this analysis, we counted the number of spikes in the post-instruction period for each trial and constructed the distribution of spike numbers for each of GO(+R), GO(−R), NOGO(+R), and NOGO(−R) activity. Then we calculated the area under the curve of the receiver operating characteristic (ROC value) using a distribution set [e.g., GO(−R) and GO(+R)]. The ROC value gives us the general measure of selectivity; 0.5 indicates no preference while 0 and 1 indicate large- and small-reward preference, respectively. We examined the relationship between the latency of peak activation after GO instruction and RT in the same trial for each LLF neuron. First, we determined the peak activation after GO, although it was not detected in the remaining trials mostly because of the absence of spikes. To examine the relationship between neuronal activation and RT, we performed linear regression analysis on a trial-by-trial basis. For each trial, we determined the peak of activity (i.e., neural firing rate) smoothed with a Gaussian kernel (SD = 20 ms) during the period from the onset of GO instruction and 100 ms after GO reaction. Latency and magnitude of peak activity were used as regressors for multiple linear regression analysis of the GO RT.

IDENTIFICATION OF RECORDING SITES

At the end of all recording experiments, small electrolytic lesions were made at 8 and 16 locations along selected four and eight

electrode tracks in monkeys SJ and MA, respectively. Direct anodal current (20 μA) was passed for 30 s through tungsten microelectrodes. After all studies were completed, the monkeys were deeply anesthetized with an overdose of sodium pentobarbital (Nembutal, 80 mg/kg, i.p.), and perfused with 4% paraformaldehyde. Half of the coronal 50-μm-thick sections were stained with cresyl violet (Nissl). For monkey SJ, the other half of the sections were stained by thiocholine method to demonstrate acetylcholinesterase (AChE) activity. The anatomical boarders of thalamic nuclei were assessed on histological sections by referencing the histological criteria of the monkey thalamus in conjunction with the assessment of their AChE activity. Histological reconstruction of the microelectrode tracks in relation to the electrolytic lesion marks allowed us to verify the location of the neuronal recordings.

RESULTS

BEHAVIORAL BIAS AND ITS COUNTERACTION

Two macaque monkeys performed in biased blocks of GO-NOGO task. Both average RTs and average MTs were significantly shorter in GO(+R) trials than in GO(−R) trials in both monkeys (RT, $p < 0.001$, t-test, **Figure 1E**; MT, $p < 0.001$, t-test). The monkeys made an error (either failure of GO reaction within 3 s or releasing the hold button in NOGO trials) more frequently in small-reward trials than in large-reward trials (GO, $p < 0.01$, in monkey SJ; NOGO, $p < 0.01$, both monkeys; t-test). These results suggest that, while large-reward action is facilitated by internal motivational drive, slowing of small-reward action is due to the conflict between internal bias and the external demand to overcome to it.

LONG-LATENCY-FACILITATION (LLF) NEURONS PREFERENTIALLY RESPOND TO INSTRUCTION OF SMALL-REWARD ACTION

We recorded the activity of 107 LLF–type neurons from the central thalamus (40 in monkey SJ and 67 in monkey MA) while the monkeys performed in a biased block of GO-NOGO task. LLF neurons were identified as showing burst discharges after unexpected auditory and visual stimuli with long latencies (Matsumoto et al., 2001; Minamimoto and Kimura, 2002; Minamimoto et al., 2005). We histologically confirmed that the locations of all 107 LLF neurons were in the thalamic CM nucleus and its vicinity, including the PF nucleus and PFdl (**Figure 2**).

Figure 3A shows examples of the LLF response to GO and NOGO instructions. This LLF neuron showed phasic burst discharges after GO and NOGO instructions followed by small reward (−R trials; **Figure 3A**, blue shades and curves), whereas it showed almost no activation after instructions followed by large reward (+R trials; **Figure 3A**, red shades and curves). This was also evident in the population of activity; GO and NOGO responses of LLF neurons were higher in small-reward trials than in large-reward trials (**Figure 3B**). We quantified the reward preferences of GO and NOGO activity separately by using ROC analysis. Most recorded LLF neurons (78/107, 73%) showed small-reward preference for both GO and NOGO trials (ROC area > 0.5, **Figure 4A**). There was no significant correlation between small-reward preferences for GO and NOGO responses (**Figure 4A**, $r = 0.07$, $p = 0.45$). Collectively, these results indicate that LLF neurons preferentially respond to instruction for an action associated with a smaller reward.

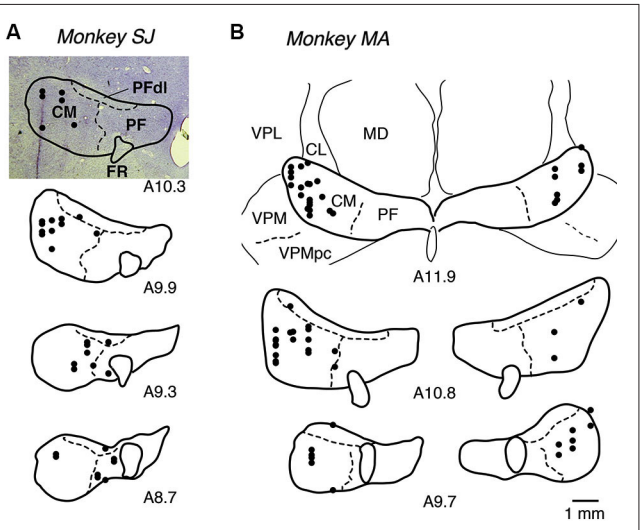

FIGURE 2 | Recording sites of LLF neurons. **(A, B)** Locations of recording sites for monkeys SJ and MA, respectively. Locations of recorded neurons are plotted in black dots on photograph of coronal Nissl-stained sections (A10.3) or on drawings of borders of nucleus, positioned from anterior to posterior as from top to bottom. A10.3 represents anterior 10.3 mm in Horsley-Clarke coordinates (i.e., distance from the plane having external auditory meatus). CL, centrolateral nucleus; FR, fasciculus retroflexus; MD, mediodorsal nucleus; PF, parafascicular nucleus; PFdl, dorsolateral parafascicular nucleus; VPL, ventral posterolateral nucleus; VPM, ventral posteromedial nucleus; VPMpc, ventral posteromedial nucleus pars compacta.

SMALL-REWARD PREFERENCE POSITIVELY CORRELATES WITH STRENGTH OF BEHAVIORAL BIAS

In GO-NOGO task, the action-reward association was stable within a block of trials (GO(+R)/NOGO(−R) or NOGO(+R)/GO(−R); 40–120 trials), inducing a behavioral bias as shown above. However, even under the same action-reward association, the degree of behavioral bias varied block-by-block. For example, the median RT of GO(+R), an index of behavioral bias of a block, ranged from 307 to 430 ms, and from 204 to 297 ms, in monkeys SJ and MA, respectively. This gave us the opportunity to test whether the LLF preference of small reward is modulated by the strength of behavioral bias; assuming that recorded LLF neurons were sampled from a homogeneous population, the small-reward preference would be stronger when the neuron was recorded under stronger behavioral bias. To test this, we examined a block-by-block relationship between NOGO(−R) preference of the LLF response and the median RT of GO(+R) action. As shown in **Figure 4B**, there was a significant negative correlation between the neuronal preference for NOGO(−R) indexed by the ROC value and the median RT of GO(+R) trials in the designated block in which the neuron was recorded (monkey SJ, $r = -0.59$, $p < 0.001$; monkey MA, $r = -0.40$, $p < 0.001$; **Figure 4B**). When we split the population neurons in half according to the median RT

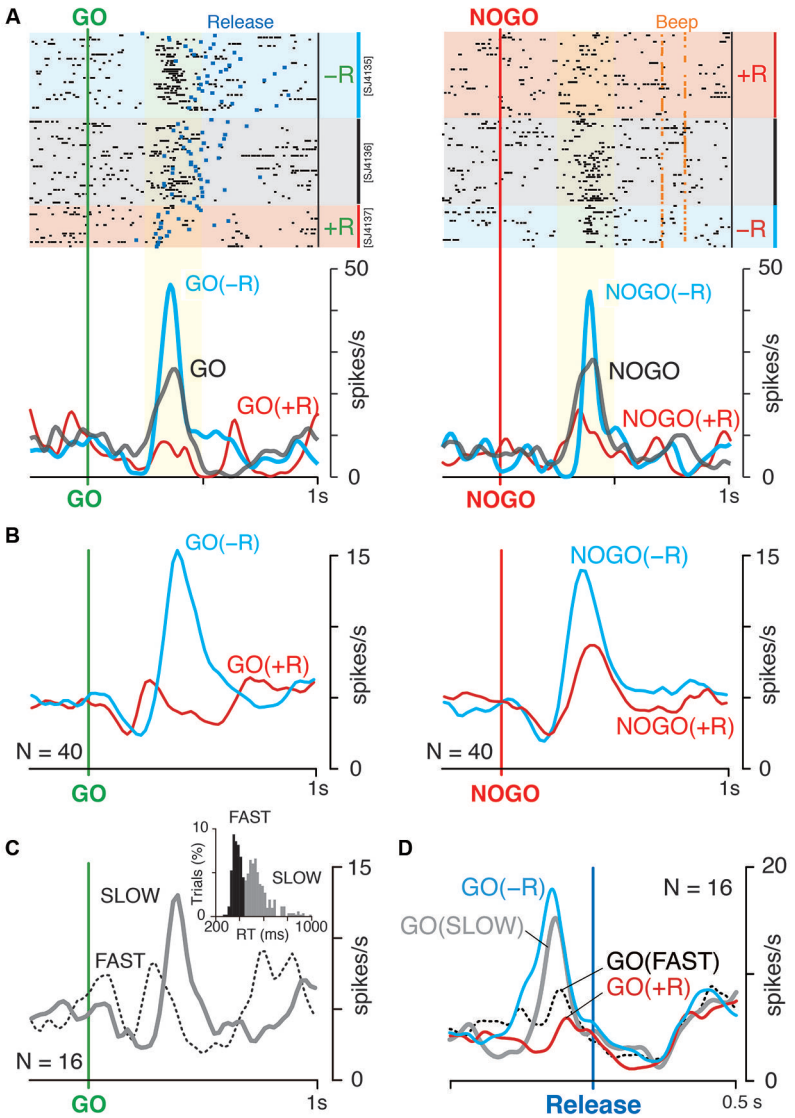

FIGURE 3 | LLF response to GO and NOGO instructions. (A) Representative activity of LLF neuron responding to GO and NOGO instructions. Raster displays of spikes for NOGO-bias, even reward and GO-bias blocks are shown in order of occurrence of trials from top to bottom. Red, blue and gray shades indicate trials with large (+R, 0.3 ml), small (−R, 0.1 ml) and medium rewards (0.2 ml), respectively. Blue and orange marks in the raster plot indicate the time of hold-button release (Release; left) and the time of correct signal (Beep; right), respectively. Smoothed histograms (SD = 20 ms) for −R (blue) and +R trials (red) in biased blocks, and for trials in even-reward block (gray). Yellow shades indicate the time window of neural activity for quantitative analysis in **Figure 4A**. **(B)** Population histograms (smoothed, SD = 20 ms) of 40 LLF neurons in biased blocks. Activities are separately plotted by reward condition (+R, red; −R, blue). **(C)** Population histogram of 16 LLF neurons in even reward blocks. Activities are separately plotted by mode of RT as shown in inset (Fast, dotted curve; Slow, solid curve), in which bimodal distribution of RT in even-reward block are shown. Black and gray histograms assign the trials to fast (<440 ms) and slow mode (>440 ms), respectively. **(D)** Population histogram of 16 LLF neurons in even-reward blocks and that of the same neurons in GO-NOGO task. Colors assigned are the same as in **B** and **C**. All data shown were obtained from monkey SJ.

in the block where the neuron was recorded, the NOGO(−R) response was much stronger in the fast-half blocks than in the slow-half blocks (**Figure 4C**, blue). However, the GO(+R) response did not differ between the two conditions (**Figure 4C**, red). Thus, when LLF neurons were recorded under high GO-bias, they tended to respond strongly to NOGO(−R) instruction.

We also examined the GO(−R)-NOGO(+R) block, where RT in GO(−R) trials was affected by the balance between pre-action bias and its counteracting. In this case, we could not find a consistent relationship; a significant negative correlation between GO(−R) preference and median RT was observed in monkey SJ ($r = -0.54$, $p < 0.0001$), but not in monkey MA ($r = -0.16$, $p = 0.19$).

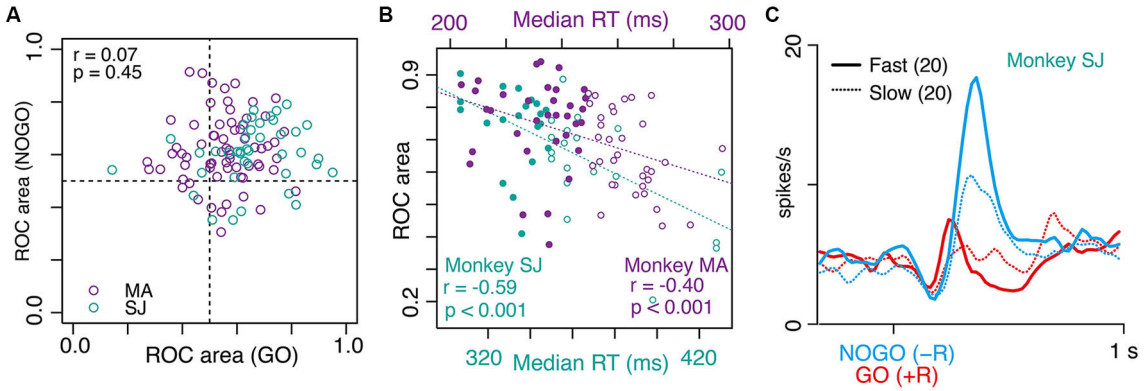

FIGURE 4 | Correlation between small-reward preference of LLF neurons and strength of behavioral bias. (A) Scatter plot of small-reward preference of LLF neuronal responses to NOGO instructions (*y* axis) vs. GO instructions (*x* axis) measured by a window 250–500 ms after each instruction. Each data point corresponds to the ROC value derived from one neuron. The ROC value quantifies the separation of distributions for neural responses to −R and to +R (0.5 indicates no preference while 0 and 1 indicate perfect +R and −R preference, respectively). **(B)** Correlation between small-reward preference of each neuron (ROC value) and median RTs of GO trials in GO(+R)/NOGO(−R) block. Each data point indicates the ROC value of one neuron's preference for NOGO(−R) relative to GO(+R) and median RT in the designated block. Filled and open circles indicate fast and slow half-blocks, respectively. **(C)** Population histogram (smoothed, SD = 20 ms) of LLF neurons (from monkey SJ) in GO(+R) (red) and NOGO(−R) (blue) trials in fast (solid line) and slow RT blocks (dotted line).

LLF ACTIVATION RELATED TO COUNTER-BIASED ACTION WITHOUT REWARD ASYMMETRY

We examined the activity of 16 LLF neurons when a monkey performed in an even-reward block, with both GO and NOGO actions being equally rewarded (monkey SJ, **Figure 1C**). This condition without reward asymmetry resulted in a bimodal distribution of RT with an antimode at 440 ms (**Figure 3C**, inset), suggesting that the monkey internally generated behavioral bias to GO action in some trials and to NOGO action in others. The example LLF neuron responded to both GO and NOGO instructions; the response was stronger than that in large-reward trials but weaker than that in small-reward trials (**Figure 3A**, gray curve). To examine whether the LLF activity reflects internally generated behavioral bias without reward asymmetry, we divided all even-rewarded GO trials into two groups according to their RT, either faster or slower than the antimode (**Figure 3C**, inset). LLF neurons responded to GO instruction stronger in slow trials than in fast trials (**Figure 3C**). This was also evident in the population histograms for 16 LLF neurons aligned at the onset of the behavioral GO response as shown in **Figure 3D**. Prominent activation in slow GO trials in the even-reward block occurred with its peak preceded by about 130 ms to the onset of release (**Figure 3D**, gray curve). In contrast, activation in fast GO trials was not clear, but was seen with a small dip of the peak just before release (**Figure 3D**, dotted black). The contrasting activations and their time course in slow and fast trials in the even-reward block resembled those observed in GO(−R) and GO(+R) trials in biased block. Activities of all four conditions were indistinguishable at the onset of release and afterwards. These results suggest that, when behavioral bias is generated without reward asymmetry, LLF neurons discharge strongly before execution of counter-biased option, as observed when behavioral bias is induced by reward asymmetry.

LLF RESPONSE DOES NOT REFLECT SMALL REWARD ITSELF

Although LLF activation after instruction for small-reward action seems to reflect behavioral bias as shown above, it could be a general signal related to small rewards. To examine this issue by dissociating small reward from counteracting process, we examined 19 LLF neurons in NOGO task (monkey MA, **Figure 1D**). In this task, the monkey was required to continue pressing the hold button in all trials, but it was informed by instruction that either large (+R) or small reward (−R) would be delivered. In GO-NOGO task, the monkey made stronger licking movements after NOGO(−R) instruction than after NOGO(+R) instruction (**Figure 5A**, top left). Similar patterns of licking were also observed in NOGO task (**Figure 5A**, top right), suggesting that the monkey recognized the rewarding condition by the instruction. An example LLF neuron showing strong response to NOGO(−R) in GO-NOGO task (**Figure 5A**, left) had similar discharge rates both after large- and small-reward instructions in NOGO task (**Figure 5A**, right). The population of 19 LLF neurons showed small-reward preference in GO-NOGO task (**Figure 5B**, left), but a similar discharge rate after two reward signals (**Figure 5B**, right), although timing of the activity was slightly different. These results suggest that the small-reward preference of LLF neuron activity does not reflect the general process regarding small reward.

TIMING OF LLF ACTIVITY EXPLAINS WELL THE TIMING OF OPPOSING ACTION

As shown in **Figure 3D**, bias-dependent LLF activations occurred before onset of the action opposed to bias. To determine the specific process that LLF discharges would contribute to, it is important to understand the temporal relationship between LLF response and the following action. We analyzed the trial-by-trial relationship between the magnitude or timing of LLF activity after

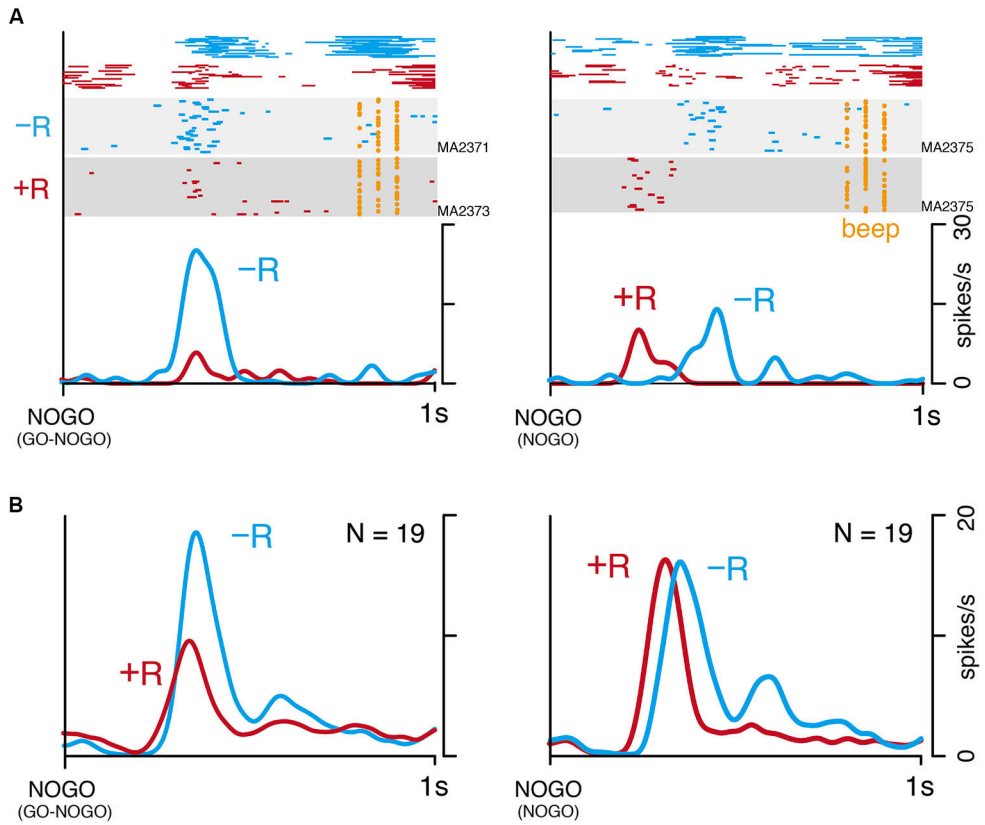

FIGURE 5 | Small-reward preference disappears when one action type is asymmetrically rewarded. (A) An example of single LLF neuron response to NOGO instructions in GO-NOGO task (left) and NOGO task (right). Licking movement (top), raster (middle), and smoothed histogram (bottom) are separately plotted by reward condition (−R, blue; +R, red). **(B)** Population histogram (smoothed, SD = 20 ms) of 19 LLF neurons responding to NOGO instructions in GO-NOGO task (left) and NOGO task (right). Activities are separately plotted by reward condition (−R, blue; +R, red).

GO(−R) instruction and the timing of the following small-reward action (GO(−R)). For this analysis, we tried to detect the peak response for each trial. It usually originated from phasic burst discharge, which was a cluster of several spikes at a 3–10 ms interval. For example, in the neuron shown in **Figure 6A**, we detected peak GO(−R) activity (**Figure 6A**, red dots) in 27 of 36 (75%) trials. We performed this analysis on 60 LLF neurons that showed significant higher discharge rate in GO(−R) trials than baseline ($p < 0.05$, two-sample Wilcoxon test). We detected a peak response in average 68% of GO(−R) trials, and defined the magnitude and latency of the peak activity (**Figure 6A**; see Section Materials and Methods). Then, we performed multiple linear regression analysis of GO(−R) RT with peak latency and peak magnitude of GO(−R) response as regressors. There was a significant positive correlation ($p < 0.01$) between peak latency of GO(−R) activity and RT (**Figure 6B**). We found significant correlation in the majority (40/60) of neurons (**Figure 6E**, gray) as well as at the population level ($r = 0.72$, $p < 10^{-15}$, **Figure 6C**). In addition, the regression line of the population ($b = 1.05$, intercept = 67 ms) indicated that the peak of LLF activity was constantly preceded to the following action (**Figure 6C**). In contrast, no neuron showed significant correlation ($p < 0.01$) between peak magnitude and RT (e.g., **Figure 6D**). This suggests that the timing of LLF activity for GO(−R) action can account for a trial-by-trial variance of RT among GO(−R) trials; the sooner LLF activity occurs, the sooner opposing action is executed.

We performed the same analysis on 35 LLF neurons that showed significant GO(+R) response in GO-bias block ($p < 0.05$, two-sample Wilcoxon test). We detected peak activity in relatively fewer trials (average 39%). We found significant correlation ($p < 0.01$) between peak latency of GO(+R) activity and RT less frequently (13/35, $p < 0.05$, χ^2-test). In even-reward block, 9/16 neurons showed significant GO response. Peak latency was detected in an average 56% of trials. Significant correlation was found in 7 of 9 neurons. Together, the timing of LLF discharges can predict the timing of the following action, and especially action that has not been biased.

Similarly, we examined the timing of LLF activity after NOGO(−R) instruction in GO-bias block. In **Figure 7**, we marked the timing of peak discharge of the same neuron as in **Figure 6A**. Peak latency varied from 200 to 800 ms within a session (**Figure 7**), as with the case of GO(−R) response (**Figure 6A**). On the other hand, temporal variance of biased action (i.e., GO(+R)) was relatively small, as indicated by blue dots in **Figure 7**. Although a temporal comparison between peak NOGO(−R) response and GO(+R) reaction was not possible

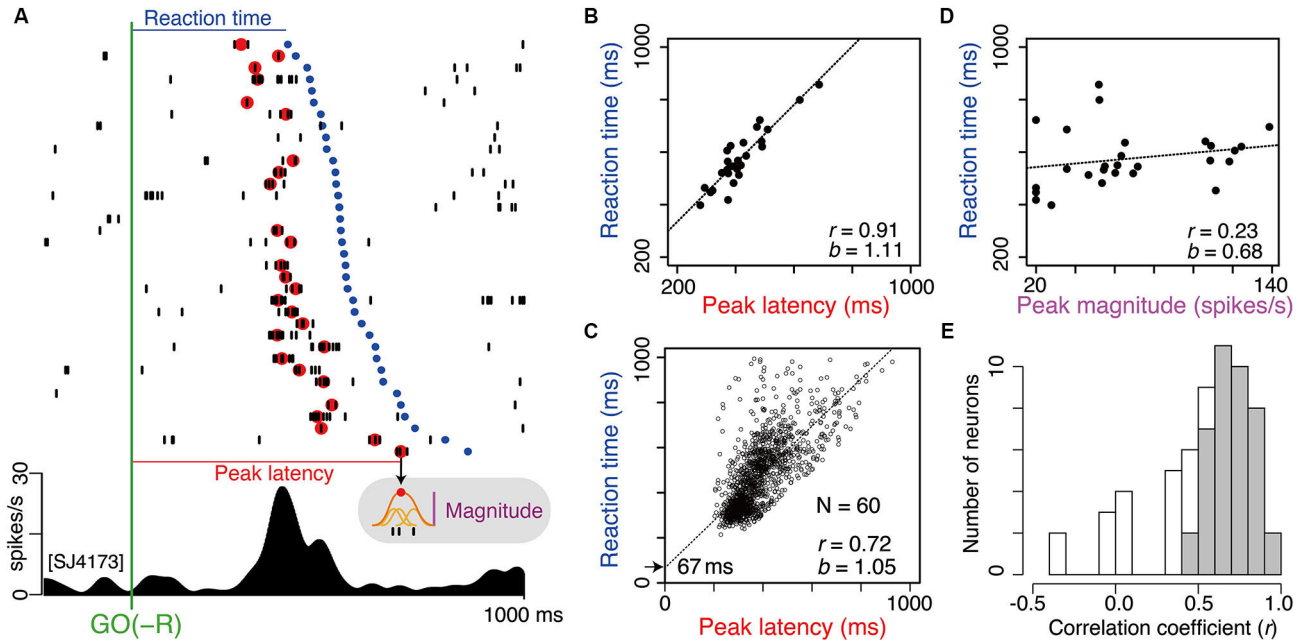

FIGURE 6 | Timing of GO(−R) activations well predict the timing of following GO(−R) action. (A) Example of GO(−R) response aligned according to GO(−R) onset. Raster displays of spikes are shown in order of shorter RT from top to bottom. Red and blue dots indicate time of peak activity and onset time of GO(−R) action (release of hold button), respectively. Gray shaded inset indicates the schematic illustration of measuring the peak magnitude. **(B)** Relationship between peak latency of GO(−R) response and RT for the example neuron shown in **A**. **(C)** Same as **B** but for all significant GO(−R) responsive neurons ($n = 60$). **(D)** Relationship between peak magnitude of GO(−R) response and RT for the example neuron shown in **A**. **(E)** Histogram of correlation coefficient between peak latency and RT. Gray bars indicate neurons with significant correlation coefficient ($p < 0.01$).

on a trial-by-trial basis, peak latency was relatively longer than the onset of GO(+R) in the same block (**Figure 7**). In 93 LLF neurons that showed significant NOGO(−R) response ($p < 0.05$, two-sample Wilcoxon test), median peak latency was significantly longer than the median RT of GO(+R) trials (t-test, $p < 0.001$). These results suggest that CM makes little or no contribution to the suppression of biased action.

DISCUSSION

In the present study, to investigate the neural mechanisms for counteracting pre-action bias, we tested monkeys performing GO-NOGO task, in which either GO or NOGO action was associated with large reward. The monkeys responded to instruction for large-reward action quickly and correctly, but reacted slowly to instruction for small-reward action. This suggests that, while large-reward action is facilitated by virtue of internal motivational drive (i.e., behavioral bias), slower small-reward action is due to a conflict between internal drive and external demand to overcome it (i.e., counteracting bias). LLF neurons, a subpopulation of neurons located mainly in the CM nucleus, exhibited phasic burst discharges after GO and NOGO instructions especially when associated with small reward. We found that the small-reward preference of the LLF response was positively correlated with the strength of behavioral bias toward large reward. A similar preference-bias relation was found in the block where both GO and NOGO actions were rewarded equally. When only one action type (i.e., NOGO) was requested with either large- or small-reward outcome, the small-reward preference disappeared. Furthermore, there was a positive temporal relation between LLF activation to GO(−R) instructions and the following GO(−R) actions on a trial-by-trial basis. LLF activations to NOGO(−R) instructions did not precede GO(+R) actions in the same block. Taken together, the results provide a better understanding of the role of CM in counteracting pre-action bias; CM neurons detect and signal external demand to overcome preset bias according to the degree of the bias.

As shown in a previous study (Minamimoto et al., 2005), most LLF neurons (>70%, **Figure 4A**) preferentially responded to instruction for small-reward action irrespective of action type. The preference for small-reward action was observed when actions associated with different magnitudes of reward. However, the differential activation of LLF neurons was also observed when two actions were equally rewarded; stronger activation occurred when instructions resulted in slow GO reaction trials compared to that in fast GO reaction trials in even-reward block (cf. **Figure 3C**). This suggests that the LLF response to instruction for an option is not a simple reflection of reward association in a categorical manner, but is also influenced by subjects' internal bias. Indeed, under the same reward-action association, the response was affected by the degree of preset bias across the LLF population; as preset bias is strong, the response to the option opposed to bias also gets strong (cf. **Figures 4B, C**). This is consistent with the previous observation that the magnitude of

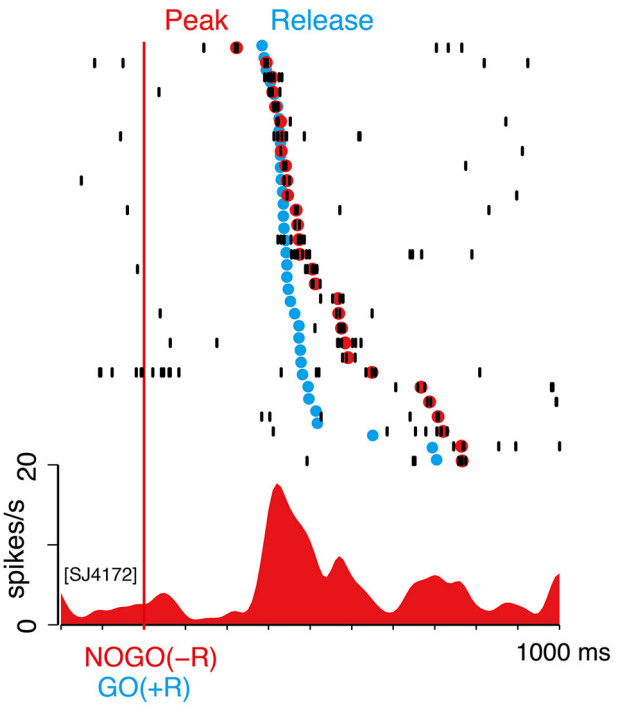

FIGURE 7 | NOGO(−R) activations did not precede GO(+R) action. Example of NOGO(−R) response of the same neuron in **Figure 6A**, aligned according to NOGO(−R) onset. Raster displays of spikes are shown in order of shorter peak latency from top to bottom. Red dots indicate time of peak activity. The trials in which peak activity was not detected are not shown. Onset time of GO(+R) action in the same block is superimposed on the raster display by blue dots.

the LLF response in a no-reward trial increases as expectancy of reward increases (Minamimoto et al., 2005). Together, these data suggest that neuronal response of CM reflects the discrepancy between internal preset bias and external demand for opposing action. Discrepancy signaling in the thalamic CM nucleus may be possible by integrating two sources of information from the basal ganglia and brainstem. The cortico-basal ganglia network has been implicated in a locus for creating pre-action bias (Hikosaka et al., 2006), and hence CM can gain access to pre-action bias by receiving axon collaterals of projections from the internal segment of the globus pallidus, the output nucleus of the basal ganglia, to the motor thalamic nuclei (Sidibe et al., 1997). In addition, CM receives projections from the brainstem pedunculo-pontine tegmental nucleus and the superior colliculus, both of which are considered to relay multi-modal aspects of sensory information (Pare et al., 1988; Grunwerg and Krauthamer, 1992; Krout et al., 2001). The thalamic CM nucleus thus appears to be located at an ideal position for coding discrepancy by monitoring pre-action bias and external events (Kimura et al., 2004; Minamimoto et al., 2009). Besides, CM may also receive discrepancy-related signal from the anterior cingulate cortex (Steriade et al., 1997; Hatanaka et al., 2003; Parent and Parent, 2005), which is suggested to play a role in conflict detection (Brown and Braver, 2005; Carter and Van Veen, 2007). Further studies are necessary to clarify how these inputs are integrated into discrepancy information and what the specific contribution of inputs from each brain structure to the integration is.

Discrepancy coding by CM neurons may raise the possibility that the CM contributes to the general process when a lesser reward than expected is assigned. One possibility is that the CM response might code the negative prediction error or negative motivational value, similarly to the neurons in lateral habenula (Matsumoto and Hikosaka, 2009). Another possibility is that the CM response may reflect disappointment or unpleasant process, since the CM-PF complex has been implicated in having a role in pain (Vogt and Sikes, 2000; Weigel and Krauss, 2004). However, those possibilities are inconsistent with our observation that LLF responses did not differ in magnitude between small- and large-reward trials when the same action was requested (in NOGO task, cf. **Figure 5**). It was also reported that LLF neurons similarly respond to salient stimuli irrespective of whether reward follows or not (Matsumoto et al., 2001). In contrast to magnitude, the latency of LLF activation was different between reward sizes in NOGO task (**Figure 5**). Although we do not have a good explanation for this result, it may not be a general property of LLF neurons since the latency difference was not found previously (Matsumoto et al., 2001). Collectively, our results suggest that CM does not have a general role regarding small reward.

Alternatively, discrepancy-related LLF discharges are likely to contribute to a specific process upon the request of opposing action. Discrepancy signaling by LLF discharges specifically occurred prior to the execution of opposing action regardless of with or without reward asymmetry (cf. GO(−R) and GO(SLOW) in **Figure 3D**). Although LLF neurons are activated by sensory stimuli even without motor response, phasic burst discharge after instruction for opposing action was not time-locked to the instruction, but temporally fluctuated trial-by-trial. Indeed, timing of the burst discharge predicted well the timing of the following GO(−R) action (cf. **Figure 6**). Given these action-related discharges, CM could have a direct role in the execution of opposing action. Still, this is unlikely because LLF neurons respond to instruction irrespective of action type. Given the above considerations, the most plausible interpretation for our results is that discrepancy-related LLF discharges mediate the counteracting process, which resets behavioral bias and leads to execution of opposing action.

Where does the counteracting process take place? The posterior putamen is a good candidate because it is the main target of the CM projections (Sadikot et al., 1992; Smith et al., 2004). Neurons in the striatum exhibit buildup activity toward an action instruction under asymmetrically rewarded condition (Lauwereyns et al., 2002; Takikawa et al., 2002; Hori et al., 2009), which is considered to be an underlying mechanism of creating advance bias for large-reward action (Hikosaka et al., 2006). The motivational bias is modulated by dopaminergic projections to the striatum (Schultz, 1998; Kawagoe et al., 2004). In the same GO-NOGO task, a subset of putamen neurons shows pre-movement activity specifically when one of two actions is associated with a large reward (Hori et al., 2009). When action opposing pre-action bias is unexpectedly requested, however, the striatal preset-bias-related activity becomes an obstacle to executing the requested action; the activity needs to be suppressed

and/or overridden by opposing-action-related activity. In support of this, subsets of putamen neurons exhibit post-instruction activity according to specific, or combinations, of reward-action association(s), where the small-reward types were prominent and activated prior to onset of small-reward action (Hori et al., 2009). These counteracting processes can be triggered by the CM's discrepancy signal transmitted through the thalamo-striatal projection. Concerning thalamic control of striatal activity, a potential substrate has been proposed by *in vitro* slice study (Ding et al., 2010). In brief, activation of thalamo-striatal axons induces burst activity in cholinergic interneurons, which leads to transient suppression of cortical input to medium spiny neurons (MSNs) and prolonged enhancement of responsiveness in striatopallidal MSNs. This suggests that thalamic burst activation can promote activity bias toward the "indirect-" over the "direct-pathway" of the cortico-basal ganglia circuit, which may lead to suppressing pre-action bias and unmasking opposing action. During GO-NOGO task, indeed, pre-GO action bias is diminished by electrical stimulation in CM, manifested as slower behavioral reactions in GO(+R) trials (Minamimoto et al., 2005).

In addition to the counteracting pre-action bias, CM burst discharges could also have a direct role in suppressing biased action. Although we could not test this hypothesis directly in a trial-by-trial manner, it is less likely because NOGO(−R) responses were not always ahead of time for initiation of GO(+R) action (cf. **Figure 7**). Instead, inhibition of the biased action may be accomplished by other brain systems, such as the subthalamic nucleus (STN), which is suggested to play a role in the inhibition of motor response (DeLong, 1990; Nambu et al., 2002; Isoda and Hikosaka, 2008).

As discussed above, our findings are consistent with the view that the CM-posterior putamen system complementarily operates between pre-action bias and counteracting it. This view can be extended to include PF and its connection with associative striatal regions (i.e., caudate nucleus and anterior putamen). Neurons in the caudate nucleus exhibit pre-movement activity that would create a motivational bias toward the contralateral space (Takikawa et al., 2002). On the other hand, neurons in the PF nucleus respond to salient sensory events especially when they appear in the contralateral location (Minamimoto and Kimura, 2002). Excitotoxic lesion or chemical inactivation of this nucleus impairs attentional orientating toward the contralateral hemifield (Mancia and Marini, 1995; Minamimoto and Kimura, 2002). Moreover, PF response to visual stimuli becomes stronger when it appears in unexpected places (Minamimoto and Kimura, 2002; Kimura et al., 2004). Thus, PF shares the same properties as CM in terms of counteracting internal bias, although it has not been tested in the context of motivational bias. Conversely, the contribution of CM may not be limited to counteraction to motivational bias. Indeed, when actions were equally rewarded, LLF discharges just before action depended on the strength of behavioral bias (cf. **Figure 3D**). As for eye-movement, Isoda and Hikosaka suggested that, while behavioral bias can originate from different domains (e.g., reflex, habit, motivational drive), the cortico-basal ganglia network is commonly involved in counteraction to it (Isoda and Hikosaka, 2011). In addition to the cortico-basal ganglia network, the counteracting process triggered by the CM-PF complex may also work for unexpected situations in general (Minamimoto et al., 2009). For example, when the subject unexpectedly detects salient stimuli or receives noxious stimuli, evoked CM-PF responses would contribute to resetting the on-going process in basal ganglia to facilitate impending behavioral reaction, such as attentional orienting or escape behavior. Future studies will have to investigate the significance of the CM-PF–striatal system in complementary operation of the counteraction to the pre-action bias originating from domains other than motivational drive.

Finally, our findings may also have a clinical significance, and especially for understanding cognitive deficits (e.g., set-shifting) in Parkinson's disease (PD). Specific and remarkable (30–40%) neuronal loss in the CM-PF complex was demonstrated by post-mortem brain studies in PD patients (Henderson et al., 2000a,b). The neuronal losses are selective to subpopulations of neurons: parvalbumin-positive neurons in PF and non-parvalbumin-positive neurons in CM (Henderson et al., 2000a). Anatomical tracing studies have shown that most of the CM neurons innervating the striatum are parvalbumin-containing (Sidibe and Smith, 1999), suggesting that CM-putamen projections are relatively intact in PD. Future study will have to identify the dysregulation of the CM-PF–striatal system caused by the degeneration of CM-PF in PD.

In summary, the present data demonstrated that neurons in the thalamic CM nucleus respond to external demand of action opposed to behavioral bias and signal the discrepancy between external demand and pre-action bias, the occurrence of which is followed by opposing action. The CM discrepancy signal may be used in its main target structure, the posterior putamen, to overcome its activity for the preset bias. This counteracting process seems to enable one to execute the opposite action, which is demanded externally but is not yet internally motivated or prepared. Interrelations between the basal ganglia and the thalamic CM-PF complex thus may allow us to switch our behavior properly and flexibly.

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The role of the anterior, mediodorsal, and parafascicular thalamus in instrumental conditioning

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The traditional animal model of instrumental behavior has focused almost exclusively on structures within the cortico-striatal network and ignored the contributions of various thalamic nuclei despite large and specific connections with each of these structures. One possible reason for this is that the thalamus has been conventionally viewed as a mediator of general processes, such as attention, arousal and movement, that are not easily separated from more cognitive aspects of instrumental behavior. Recent research has, however, begun to separate these roles. Here we review the role of three thalamic nuclei in instrumental conditioning: the anterior thalamic nuclei (ANT), the mediodorsal (MD), and parafascicular thalamic nuclei (PF). Early research suggested that ANT might regulate aspects of instrumental behavior but, on review, we suggest that the types of tasks used in these studies were more likely to recruit Pavlovian processes. Indeed lesions of ANT have been found to have no effect on performance in instrumental free-operant tasks. By contrast the mediodorsal thalamus (MD) has been found to play a specific and important role in the acquisition of goal-directed action. We propose this role is related to its connections with prelimbic cortex (PL) and present new data that directly implicates this circuit in the acquisition of goal-directed actions. Finally we review evidence suggesting the PF, although not critical for the acquisition or performance of instrumental actions, plays a specific role in regulating action flexibility.

Keywords: anterior thalamic nuclei, mediodorsal thalamic nucleus, parafascicular thalamic nuclei, corticothalamic disconnection, prelimbic cortex, instrumental conditioning

INTRODUCTION

The thalamus has been traditionally viewed as a sensory relay center, forming the interface between the sensory cortices and subcortical structures responsible for the execution of actions. In performing this role, several thalamic nuclei have been implicated in general processes such as arousal, attention, and voluntary movement. However, research within the last three decades has begun to focus more specifically on the role of the thalamus in instrumental conditioning. This has been driven, at least in part, by anatomical evidence that many thalamic nuclei have large and specific connections with the prefrontal cortex and dorsal striatum that now have well-established roles in the regulation of instrumental learning and performance.

In this review, we examine studies that have incorporated behavioral tasks in conjunction with various neural manipulations to assess the role of individual thalamic nuclei in instrumental learning and behavior. In particular we will consider the role of three thalamic nuclei: the ANT, mediodorsal (MD) and parafascicular thalamic nuclei (PF), the latter often referred to, in humans and primates, as the centromedian-parafascicular complex. In evaluating the evidence that any neural structure plays a role in some specific function, however, it is necessary to carefully evaluate, not only the anatomical but also the functional evidence. In the case of instrumental conditioning that requires evaluating the behavioral evidence that specific anatomical manipulations are influencing instrumental actions and not other forms of conditioned behavior and, in the current context, the chief alternative to instrumental action is, of course, the Pavlovian conditioned response.

Pavlovian conditioning occurs through pairings of an initially neutral stimulus, the conditional stimulus (CS), and a biologically relevant unconditional stimulus (US). Across repeated pairings, the CS comes to elicit a specific set of conditioned responses (CRs) indicative of the animal's expectancy of the impending US. By contrast, instrumental conditioning involves the animal learning to perform (or withhold) an action dependent on its consequences. Although the distinction between them may appear clear enough, in reality it is complicated by the fact that instrumental conditioning often takes place in the presence of stimuli any of which could form Pavlovian stimulus-outcome (S-O) relations. Under some circumstances, therefore, it might be difficult to separate whether it is the instrumental contingency or the Pavlovian S-O contingency that is guiding behavior.

There are two criteria that distinguish instrumental actions from Pavlovian CRs (cf. Dickinson and Balleine, 1994). Specifically, whereas an agent should be able to withhold and/or flexibly alter (e.g., reverse) the direction of an instrumental response to obtain an outcome (cf. Dickinson, 1994), the same is not true

of Pavlovian CRs. Thus, whereas it is clear that rats are capable of withholding a lever press response to receive a pellet outcome (Davis and Bitterman, 1971) and, further, that this response can be bidirectional; a lever can be pushed either up or down to gain a reward (Bolles et al., 1980; Dickinson et al., 1996), Pavlovian CRs are not open to such adjustment (e.g., Hershberger, 1986), nor can the response be withheld during the stimulus to gain the reward (Sheffield, 1965; Williams and Williams, 1969; Holland, 1979).

These examples demonstrate that Pavlovian CRs are controlled by S-O relations. In contrast, evidence suggests that, in instrumental conditioning, development of the instrumental action can be controlled by two other distinct forms of learning process. Considerable evidence suggests that instrumental actions can be goal-directed and controlled by the encoding of specific response-outcome (R-O) relationships. Much of this evidence has been provided by outcome devaluation studies (e.g., Adams and Dickinson, 1981; Colwill and Rescorla, 1985; Dickinson and Balleine, 1994). In such studies animals are trained to perform a response for a particular outcome, the value of which is subsequently reduced by feeding it to satiety or repeatedly pairing it with lithium chloride to induce illness. The animal is then tested for its propensity to make that response under extinction (i.e., in the absence of feedback from outcome delivery). If animals subsequently shows reduced performance of the response previously paired with the now devalued outcome this can be taken as evidence that it is goal-directed (Dickinson and Balleine, 1994) because it is governed by both: (1) a representation of the outcome as a "goal" and (2) a representation of the contingency between performance of the action and access to the outcome. The absence of feedback on test ensures that the second criterion is met because the animal can only rely on its prior knowledge of the R-O contingency to show the requisite reduction in performance.

Importantly, continuing performance on a lever after devaluation, as has been reported after extended training, demonstrates that performance is sometimes not guided by its relation with the outcome. Such demonstrations (Adams, 1982; Dickinson et al., 1995; Yin et al., 2004, 2006; Lingawi and Balleine, 2012) have been argued to reflect the behavioral development of habits. Habits are not guided by the R-O relation but, rather, reflect the role of the outcome as a reinforcer, strengthening the relation between prevailing stimuli (S) such as the context and the response (R). Behavioral and neurological evidence (Dickinson et al., 1995; Yin et al., 2004, 2005a,b) suggests that S-R and R-O relations are not mutually exclusive and develop in parallel with the influence over performance shifting across the course of training. Although the behavioral and neural processes that control habitual actions are important and of increasing interest, in this review we will refer primarily to goal-directed instrumental action whose performance is under the control of the R-O relation.

Finally, although the learning processes controlling the Pavlovian CR are distinct from those controlling instrumental actions, the latter actions can be influenced by specific retrieval-related effects of Pavlovian stimuli, an effect demonstrated using the Pavlovian-instrumental-transfer (PIT) paradigm. In such procedures, Pavlovian S-O and instrumental R-O relations are trained separately, and the ability of the Pavlovian stimuli to modulate instrumental performance is measured in an extinction test. The typical finding is that, on test, stimulus presentations promote responding on the instrumental action that was paired with the same outcome during training. For example, Colwill and Rescorla (1988) showed that a tone that had been paired with pellets promoted the performance of instrumental actions that had also been paired with pellets, relative to actions that earned a different outcome during training. This specific PIT effect requires the ability of the animal to retrieve specific R-O relations based on the ability of the Pavlovian stimulus to evoke a representation of the outcome. As a consequence, this effect is often characterized in terms of the formation of an S-O → R process in which the stimulus based retrieval of a specific outcome causes the animal to retrieve its specific associated action (see Balleine and Ostlund, 2007; Balleine and O'Doherty, 2010, for discussion).

In the remainder of the paper, we examine the aforementioned thalamic structures and their role in instrumental conditioning, focussing specifically on their role in goal-directed actions. With regard to the issues above, therefore, we will attempt to focus on actions that have been shown to be acquired and maintained by their contingent relationship to, and the value of, their consequences, rather than by antecedent stimuli. Where relevant, therefore, we will point to issues of behavioral control affecting interpretation and that may require clarification in future studies.

ANTERIOR THALAMIC NUCLEI

Several studies spanning the late 1970s–early 2000s proposed that the anterior thalamic nuclei (ANT: see **Figure 1B**) play a role in the regulation of behavior in discrimination tasks involving instrumental responding. In particular, a series of experiments by Gabriel et al. (1977, 1983, 1989) found several lines of evidence to suggest ANT involvement in the learning that underlies performance in a series of avoidance and appetitive discrimination tasks in rabbits.

The earliest of these studies examined unit recordings from the anterior cingulate cortex (AC), the reciprocally connected ANT, or both, during an aversive avoidance task. In this task the presentation of a tone stimulus (S+) preceded the presentation of a footshock. Rabbits also received presentations of a different frequency tone stimulus (S−) that did not predict shock. This procedure was carried out in a running wheel and the consequence of the rabbit performing a wheel turn during the S+ presentation was avoidance of the footshock as well as termination of the S+. Similar responses during S− presentations also terminated the S−. Behaviorally, rabbits learnt this task relatively well, taking between 4–5 sessions on average to reach a criterion of 9–10 responses to the CS+ and 9–10 non-responses to the CS− (Gabriel et al., 1977).

The first examination of the AC-ANT pathway using this task was conducted by Gabriel and colleagues (Gabriel et al., 1977). In this study it was found that neuronal activity increased from baseline in both the AC and ANT in the 15–25 ms following stimulus onset and decreased from 35–75 ms, then increased again at 75 ms where it continued until 200 ms when recording ceased. This response was greater in magnitude to the S+ than the S− in the first 100 ms and, as a consequence, the authors proposed

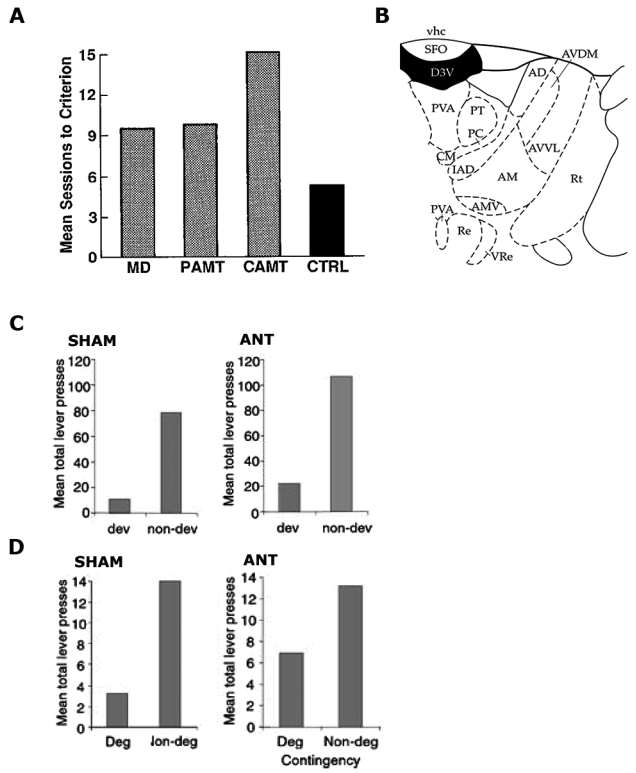

FIGURE 1 | (A) Reproduced from Gabriel et al. (1989). Mean sessions to criterion responding for rabbits with mediodorsal thalamus (MD), partial medial dorsal and anterior thalamic (PAMT), combined medial dorsal and anterior thalamic (CAMT) and control (CTRL) lesions. **(B)** Reproduced from Paxinos and Watson (1998). Schematic showing ANT at A/P: −1.4 from Bregma. **(C,D)** Reproduced from Corbit et al. (2003), examines Sham and ANT-lesioned animals. **(C)** Mean total lever-press responses for the outcome devaluation test. **(D)** Mean total lever-press responses for the contingency degradation test.

that these differential neural responses reflected discrimination learning and that this information was used to evoke a behavioral response to the S+ over the S−. This experiment was one of the first attempts to apply a psychological function to a thalamic region that could be separated from the regulation of some other general function. In particular, the authors claimed that arousal and body orientation could not have influenced the results because these states should have been the same prior to the onset of both the S+ and the S− such that any differential responding to each stimulus could only be elicited as a result of their differential relationships with the footshock.

A later study (Gabriel et al., 1989) demonstrated a causal role for the ANT in regulating the underlying learning in the discriminative avoidance task outlined above. Gabriel et al. (1983) had previously shown that bilateral ANT lesions eliminated excitatory responses to the S+ in the cingulate cortex and, as such, they hypothesized that lesioning the ANT might also affect behavior in this task. They found that rabbits with combined lesions of the MD and ANT were unable to reach criterion, whereas rabbits with only MD lesions did not differ from controls. Rabbits with MD lesions did show some impairment relative to controls when their percentage of correct responses to the S+ relative to S− was considered, but rabbits with combined ANT/MD lesions were more impaired than either group (see **Figure 1A**). Again, the authors claimed that these differences could not be attributed to deficits in the general processes of orienting or autonomic responses to the stimuli as these were intact in lesioned animals. Further, the aversive footshock was argued to be similarly effective in all of the rabbits. As a consequence, the authors attributed the impaired performance to a deficit in learning.

There have been several follow-up studies replicating and expanding on these earlier effects. A notable example is that of Smith et al. (2002) who used an appetitively motivated discrimination task to examine the role of ANT and MD in appetitive conditioning. For this task, a water reward was given after head extension and oral contact with a spout following a tone S+ presentation whereas no reward was given after the (alternate frequency) tone S−. Rabbits with limbic thalamic lesions (spanning ANT and MD) were severely impaired in their acquisition of the task, but did eventually reach criterion. Further, cingulate cortical neurons developed discriminative neuronal responses (S+ > S−) in controls but not lesioned rabbits. These results were interpreted as implicating the limbic thalamic-AC pathway in associative learning more generally, rather than aversive avoidance learning specifically.

These and other studies (e.g., Sparenborg and Gabriel, 1992; Gabriel et al., 1995) represent, therefore, a significant body of work implicating the ANT-AC pathway and to a lesser extent the MD, in discrimination learning. It should be emphasized that the authors did not claim a role for this pathway in the regulation of instrumental behavior *per se*, but rather referred to their discrimination task as requiring an instrumental response. However, none of these studies included a specific test of the bidirectionality or omission of these responses, so it remains open to question as to whether they were actually instrumental or subject to other, particularly Pavlovian, contingencies. The head extension response in particular (Smith et al., 2002) seems an unlikely candidate for an instrumental response as it comprises a food approach behavior, which cannot be withheld or flexibly performed to achieve a desired outcome. The wheel turn response, on the other hand, comprises a better candidate for an instrumental response as it has been shown to be sensitive to omission (Wilson et al., 1987). Although to our knowledge bidirectional performance of wheel turning has not been demonstrated, it is not unreasonable to think that if a rabbit can turn a wheel in one direction to avoid a shock it could turn it in the opposite direction for the same outcome.

What is not clear from these studies, however, is the type of relation governing performance in these particular tasks. Because footshock occurred only in the presence of the S+, it is possible that in spite of its potentially instrumental nature, wheel turn responding in the presence of the S+ simply constituted a conditional response governed by S-O relations. Indeed, if wheel-turning might be considered a form of escape, which is an unconditional response appropriate to footshock, then this response could even be seen to fulfil Pavlov's (1927) criterion of stimulus substitution. Even if we do accept that there was an instrumental contingency between wheel turning and shock

avoidance, the fact that performance of this response only led to the desired outcome (i.e., footshock avoidance) in the presence of the S+ creates the possibility that it was under Pavlovian control in a manner similar to that observed during PIT. If this were the case it would again imply that the ANT was mediating performance through the regulation of S-O or S-O-R relations, rather than the R-O relation, as discussed previously. In order to separate these possibilities it would have been necessary to show that the wheel turn was governed by its contingency with the footshock avoidance, *independent* of the S-O contingency. For example, Grindley (1932) showed that Guinea pigs who had learned to turn their head to the left or right every time a buzzer sounded to gain a carrot reward, would readily reverse the direction of head turning when the instrumental contingency was reversed but the S-O relation between the buzzer and carrot remained constant. Likewise if Gabriel et al. (1977, 1983, 1989) had shown that animals that had initially learned to turn the wheel in one direction to avoid shock and then learned to turn it in the opposite direction to avoid shock, independent of the continuing tone-shock contingency, this would suggest that the response was governed by the R-O, not the S-O contingency. Therefore, although elegant and among the first to assign a psychological function to a thalamic nucleus outside of general physiological functions, the research by Gabriel and colleagues leaves open the question of which type of relation governed behavior in these tasks and therefore which of these processes is regulated by the ANT.

A subsequent study by Corbit et al. (2003) specifically examined whether the ANT is required for the learning and expression of R-O relations. All of the behavioral tasks employed by Corbit et al. (2003) occurred in free-operant chambers of the kind described by Skinner (1932) meaning that no discrete stimuli were presented and the animal was free to emit (or omit) the behavior at any time in accordance with its expectation of receiving an outcome. Their first experiment employed the devaluation procedure described previously. Rats with sham lesions or ANT lesions were trained to make two instrumental responses (left and right lever presses) for two distinct outcomes (pellets and sucrose). Subsequently, one of these outcomes was fed to satiety to reduce its value, and rats were tested for their choice between levers in extinction. Both Sham control rats and rats with ANT lesions were able to preferentially choose the lever that had been associated with the non-prefed outcome during training (**Figure 1C**). As previously discussed, because no outcomes were delivered on test this result suggests that the performance of both the Sham and ANT lesioned rats relied upon the ability to recall the specific R-O contingencies. In their second experiment, Corbit et al. (2003) examined the effect of lesioning the ANT on the rats' sensitivity to degradation of the instrumental contingency. For this task rats were exposed to the same R-O contingencies trained in Experiment 1, but one of the outcomes was also delivered in a manner that was not contingent on its associated lever press action. Both ANT lesioned rats and Sham controls showed evidence of degradation and reduced their responding on the lever earning an outcome that was also being delivered in a manner that was not contingent on lever pressing (i.e., degraded lever), whilst maintaining their response rate on the lever that continued to contingently earn an outcome (i.e., nondegraded lever: **Figure 1D**). This pattern was observed both during training and on a 10 min choice extinction test. Together, these experiments demonstrate that, in free-operant conditions, the ANT does not play a critical role in the acquisition and/or expression of instrumental actions. Taken together with the body of work presented by Gabriel and colleagues, these results suggest that the role of the ANT is more consistent with the regulation of Pavlovian processes or the Pavlovian control of instrumental behavior, particularly in aversive avoidance tasks. This conclusion is bolstered by findings of c-Fos related activity in the anterior thalamus after fear conditioning (Conejo et al., 2007) and the fact that lesions of the anterior thalamus cause deficits in the ability of rats to use S-O relations to escape from a water maze (Warburton and Aggleton, 1999).

MEDIODORSAL THALAMUS

A second thalamic candidate that has been examined within the literature for its role in the regulation of instrumental behaviors is the MD (see **Figure 2E**). As mentioned above, in some of the experiments conducted by Gabriel et al. (1989) and Smith et al. (2002) the ANT was not the only thalamic target of some of their manipulations, as the MD was also targeted some of the time. Although the pattern of results seemed to suggest a greater deficit when the ANT and MD were both targeted than when the MD was targeted alone (Gabriel et al., 1989), rabbits with lesions of the MD alone did show some deficit relative to controls. However, because these tasks confound Pavlovian and instrumental processes, there is some difficulty extracting information about the involvement of the MD in regulating instrumental behavior from these results.

Another early attempt at examining the role of MD in instrumental conditioning also involved rabbits with MD lesions but examined performance in an eyeblink avoidance conditioning task (Buchanan, 1994). During this task, rabbits were required to perform an eyeblink response during a tone presentation to avoid a shock US delivered around the eye. MD lesions impaired acquisition but not asymptotic performance (see **Figure 2A**), leading the author to conclude that the MD influenced responding through its role in a general process of attention or arousal rather than the acquisition of the instrumental contingency. It must again be considered, however, whether there is any evidence that the eyeblink response required for this task was instrumental. Like the aversive avoidance task, this task confounds the Pavlovian and instrumental relationships as the animal's eyeblink response only achieves avoidance of the shock US when it occurs in the presence of the tone S+. Eyeblink responses that occur in the absence of the S+ bear no relation with the outcome such that, even if we accept that an eyeblink can be performed instrumentally, here it is controlled by the S+ in a manner that could be either S-O-R (implying no R-O control) or hierarchical S-(R-O). Thus, in the absence of any test to distinguish between these possibilities, the general depression in responding observed here in rabbits with MD lesions might reflect a general performance deficit but does not speak to the role of the MD in governing instrumental behaviors.

In the same series of experiments they used to examine the ANT, Corbit et al. (2003) provided an assessment of the MD's role

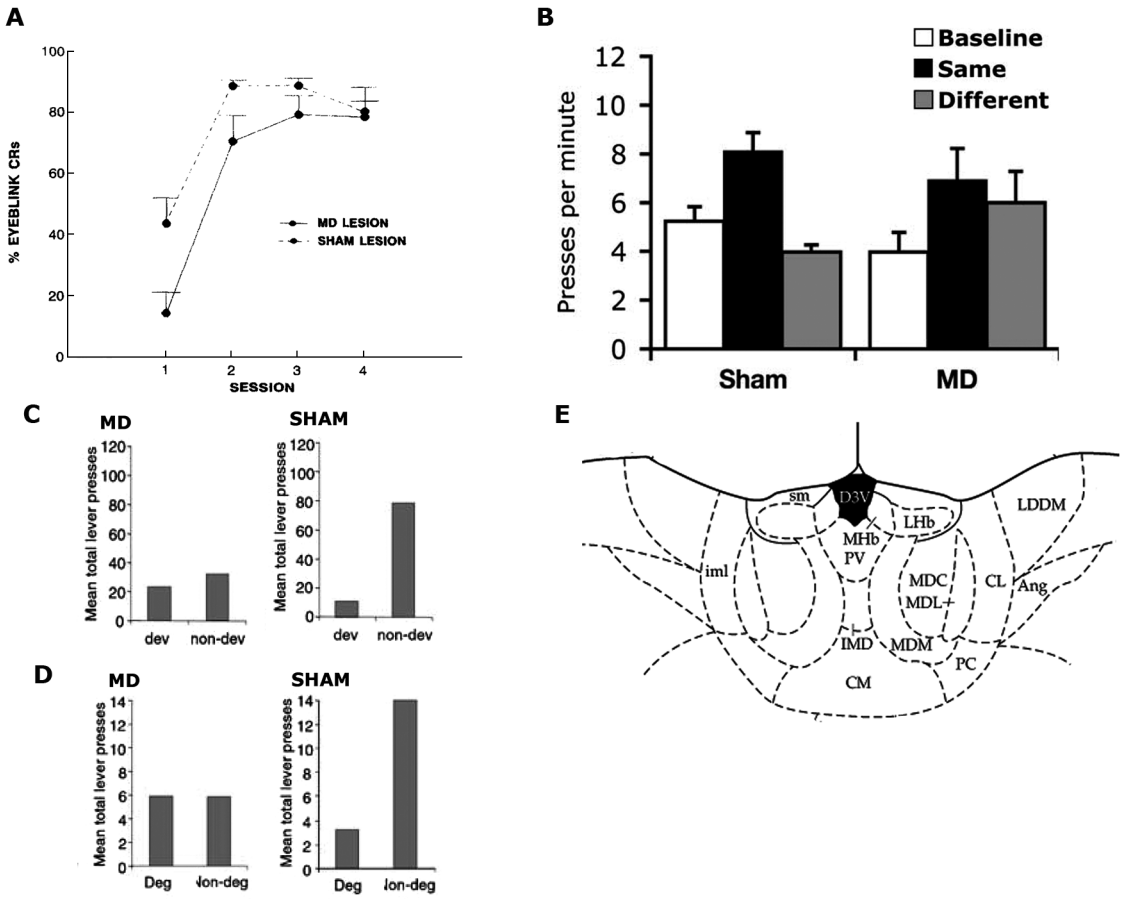

FIGURE 2 | (A) Reproduced from Buchanan (1994). Mean ± SEM percentage conditioned eyeblink responses in MD and sham-lesioned animals. **(B)** Reproduced from Ostlund and Balleine (2008). Mean lever presses per min (± SEM) during the precue period (baseline), the cue that signalled the same outcome as the action (same) and the cue that signalled the outcome paired with the other action (different) in Sham and MD lesioned animals. **(C,D)** Reproduced from Corbit et al. (2003), examines sham and MD-lesioned animals. **(C)** Mean total lever-press responses per min for outcome devaluation test. **(D)** Mean total lever-press responses for the contingency degradation test. **(E)** Reproduced from Paxinos and Watson (1998). Schematic showing MD at A/P: −3.6 from Bregma.

in regulating R-O relations. In marked contrast to the effects of ANT lesions, however, MD lesions did affect responding during outcome devaluation when tested in extinction (see **Figure 2C**). Importantly, when the outcomes were delivered on test, rats with MD lesions were able to choose the lever associated with the non-prefed outcome during training demonstrating they were able to discriminate between the two levers as well as encode the reduced value of the prefed food. This experiment also showed that the deficit observed in the extinction test could not be due to MD lesions affecting some kind of general process such as arousal or voluntary body movement, as such processes should have been equally affected during the rewarded test. A second experiment demonstrated that, again unlike ANT lesioned rats and controls, MD lesioned rats were not sensitive to selective reduction of the R-O contingency and responded similarly on both levers after degradation. This was observed both during training and test (see **Figure 2D**). Together these results clearly demonstrate a role for the MD in instrumental behavior. Moreover, they specifically suggest a role for the intact MD in regulating the acquisition of goal-directed instrumental behavior.

Ostlund and Balleine (2008) later re-examined the role of the MD in regulating instrumental performance. They again examined the effects of MD lesions but in this instance the lesions were performed after instrumental training. These post-training lesions produced a very different effect; although pre-training lesions abolished outcome devaluation it was unaffected by post-training lesions, suggesting that the MD plays a role in the acquisition of goal-directed behaviors but not their expression. This finding suggests that the MD might play a role similar to that of the prelimbic cortex (PL) which has been similarly found to mediate the acquisition but not expression of goal-directed behavior (Ostlund and Balleine, 2005), but differentiates it from the posterior dorsomedial striatum (pDMS) which has been shown to be mediate both acquisition and expression (Yin et al., 2005a,b).

In a second experiment, Ostlund and Balleine (2008) assessed PIT. In the Pavlovian training stage a tone stimulus was paired with pellets or sucrose and a white noise stimulus was paired with the alternate outcome. After eight days rats began the instrumental phase in which the left lever was paired with pellets or sucrose and the right lever paired with the other outcome. On

test, the Pavlovian stimuli were presented while the rats were allowed to press both levers in the absence of outcome delivery. As is typically found, the Pavlovian cues biased performance towards the lever delivering the outcome predicted by the stimuli despite the rats never previously experiencing the stimuli and levers in the same session (**Figure 2B**). Rats with post-training MD lesions were unable to perform this task and pressed both levers equally during stimulus presentations. This result suggests that the MD not only governs reward guided actions but also stimulus guided actions, a result that offers some explanation as to why MD lesions, that impair goal-directed performance in the absence of explicit Pavlovian cues (Corbit et al., 2003), also impaired performance in aversive avoidance tasks potentially governed by Pavlovian processes (Buchanan, 1994). In contrast, however, it appears that when the outcome, rather than a predictive stimulus, is used as cue, MD lesions leave performance intact. That is, Ostlund and Balleine (2008) found that, when a pellet or sucrose outcome was delivered to the magazine after a period of extinction, responding was selectively reinstated on the lever associated with that outcome during training and to a similar degree in both the control rats and rats with MD lesions. This effect differs from transfer, however, in that the governing relation is not between the stimulus and outcome but between the stimulus and response (in which the outcome functions as the stimulus).

The last experiment in the series conducted by Ostlund and Balleine (2008) examined whether MD lesions affected performance during a Pavlovian contingency degradation task that employs alterations in the predictive S-O relationship. For this task the rats continued to receive the same S-O pairings received in previous Pavlovian training, but one of these outcomes was also delivered unpaired with any stimuli. This served to degrade the contingency between the stimulus and that outcome as Sham rats selectively reduced time spent in the magazine during presentations of that stimulus. Rats with MD lesions, on the other hand, reduced responding to both stimuli, suggestive of a specific deficit in the encoding of S-O relations.

Taken together, these experiments demonstrate the complex nature of the MD's role in instrumental behavior. On the one hand, pre-training MD lesions impaired the acquisition of R-O contingencies and the selective degradation of one of these contingencies, suggesting that an intact MD is crucial for the acquisition of instrumental behaviors guided by R-O relations. On the other hand post-training MD lesions left outcome devaluation intact whilst impairing Pavlovian-to-Instrumental transfer and Pavlovian contingency degradation. Perhaps the simplest explanation for the multiple functions of the MD lies in the diverse connections it maintains with the frontal cortex. Connections between the MD and the prelimbic prefrontal cortex of the rat are, at least anatomically, the best studied (Groenewegen, 1988; Kuroda et al., 1993), but the MD also maintains strong connections with the orbitofrontal cortex (OFC) particularly its lateral regions (Krettek and Price, 1977). Recent studies have found that, whereas the prelimbic area is critical for the acquisition of goal-directed instrumental actions, it plays little if any role in appetitive Pavlovian conditioning or in the influence of Pavlovian cues on instrumental performance (Corbit and Balleine, 2003). In contrast lesions of lateral OFC, whilst sparing instrumental acquisition, abolish the outcome specificity of Pavlovian S-O relations (Schoenbaum and Roesch, 2005; Ostlund and Balleine, 2007) together with outcome-specific Pavlovian instrumental transfer (Ostlund and Balleine, 2007; Balleine et al., 2011). Hence, it seems likely that the diverse functions of the MD reflect the important role it plays in the distinct functions of the frontal cortical regions to which it projects.

PRELIMBIC-MEDIODORSAL THALAMUS INTERACTIONS: THE EFFECT OF DISCONNECTING THE THALAMO-CORTICAL PATHWAY ON GOAL-DIRECTED INSTRUMENTAL ACTIONS

The heavy interconnectedness of the MD and PL (Groenewegen, 1988) and their similar role in the acquisition of goal-directed instrumental actions led us to hypothesize that the encoding of the R-O contingency depends on the PL-MD pathway. In particular, we predicted that a functional disconnection of PL and MD would abolish goal-directed behavior. By contrast, we predicted that there would be no deficit in rats that received a functional PL/MD disconnection in outcome-induced reinstatement performance that tests the acquisition of O-R rather than R-O contingencies, particularly as bilateral PL lesions leave reinstatement unaffected (Ostlund and Balleine, 2005) as do MD lesions (Ostlund and Balleine, 2008).

Not only are the connections between PL and MD large and reciprocal, the PL projects to the MD in both the ipsilateral and contralateral hemispheres (Buchanan, 1994). Therefore, a traditional lesion disconnection study, in which rats might receive PL and MD lesions in contralateral hemispheres, should not be sufficient to anatomically or functionally disconnect these structures. That is, although it would disconnect these structures ipsilaterally, it would leave the contralateral PL-MD projections intact. For this reason, there have been few studies directly examining of the effect of disconnecting the PL with various sub-cortical structures. One notable attempt was that of Coutureau et al. (2009) who contralaterally lesioned the PL and basolateral amygdala (BLA) and found that although bilateral lesions of either structure abolished goal-directed responding their disconnection did not. It is possible that this failure to find an effect was because these structures communicated via the remaining contralateral projections, despite the authors arguing that these cross-connections are only weak. If it was not due to these connections then this finding is illustrative of the fact that disconnections do not always have the same behavioral consequences as bilateral lesions of those structures, demonstrating the necessity of testing disconnections in spite of the lesion data. In contrast to the PL-BLA pathway, PL-MD contralateral projections are substantial (Negyessy et al., 1998), so to ensure a full functional disconnection of PL and MD structures in the current study we included an electrolytic lesion of corpus callosum (CC) to specifically sever the contralateral projections. All experimental and surgical procedures were approved by the Animal Ethics Committee at the University of Sydney, and are in accordance with the guidelines set out by the American Psychological Relation for the treatment of animals in research.

First we demonstrated the efficacy of lesioning the CC in severing these contralateral PL-MD projections. After this lesion

had been made the retrograde tracer fluorogold (FG) was injected unilaterally into the MD of five Long-Evans rats. Brains were later examined for the extent of labeling in the PL in both hemispheres: that which was ipsilateral and that which was contralateral to FG injection. From **Figure 3A** it is clear that almost no FG labeling was observed in the PL contralateral to the MD injection site relative to that observed in a control rat that had no CC lesion. This suggests that the CC lesion was successful in severing contralateral projections between these structures. By contrast, it is also clear from this figure that ipsilateral projections were unaffected by the CC lesions: labeling in the hemisphere ipsilateral to the injection site looked similar in both lesioned rats and unlesioned control rats.

Once the efficacy of the CC lesion in severing these projections had been determined, 30 experimentally naïve Long-Evans rats received CC lesions combined with sham or excitotoxic PL and MD lesions with the aim of examining the effect of disconnecting these structures on outcome devaluation, and outcome-induced reinstatement. Eight of these had misplaced lesions or damage that extended beyond the CC and thus were excluded from the analysis. Twenty two rats were then used for analysis. There were three groups: Group Sham ($n = 8$), Group Ipsi ($n = 7$), and Group Contra ($n = 7$). Each rat in each group received a CC lesion. Rats in Group Ipsi received additional excitotoxic lesions of PL and MD in the same (ipsilateral) hemisphere such that these structures were disconnected in that hemisphere but an intact PL-MD pathway remained in the opposite hemisphere. Rats in Group Contra received additional excitotoxic lesions in alternate hemispheres such that the PL-MD pathway was disconnected in both. Therefore Groups Ipsi and Contra differed only in the hemispheric location but not the overall amount of damage. Rats in Group Sham controlled for the effects of receiving a CC lesion with sham PL and MD lesions (in which the needle was inserted but no excitotoxin injected). Half of the sham lesions were given ipsilaterally and half were given contralaterally. In addition, the hemispheres in which damage occurred were counterbalanced within each group (i.e., left vs. right).

For the next eight days rats received instrumental training. For half of the rats in each group the left lever earned pellets and the right lever earned sucrose. The remaining rats were trained on the opposite R-O contingencies. Acquisition of lever press responding is shown in **Figure 3B**. From this figure it is clear that all groups acquired lever press responding and that the groups did not differ (see Figure for statistical analysis). Subsequent to lever press training rats were tested for knowledge of these contingencies. There were two tests, one with pellets and one with sucrose (counterbalanced). Prior to each test rats received free access to either outcome to specifically satiate them on this outcome thereby reducing its value relative to the non-prefed outcome (cf. Balleine and Dickinson, 1998). As a result rats in the Sham and Ipsi control groups were expected to choose the lever that had been associated with the nondevalued outcome during training. As described previously, testing was conducted in extinction such that rats were required to rely on their knowledge of the R-O contingency to choose the nondevalued over the devalued lever. Test performance, averaged over the two tests, is shown in **Figure 3C**. As expected, rats in Groups Sham and Ipsi demonstrated evidence of having acquired the R-O contingencies (nondevalued > devalued) whereas rats in Group Contra did not (nondevalued = devalued, see figure caption for statistical analysis). This result suggests that the functional disconnection of PL and MD mimicked that of bilateral lesions of either structure; i.e., rats with functional disconnection of the PL-MD pathway demonstrated a decrement in goal-directed learning relative to Sham and Ipsi controls.

Finally, we examined whether rats in each group would selectively reinstate responding on the lever that had been associated with a particular outcome during training. Specifically, after 15 min of extinction on both levers, rats received four reinstatement trials separated by 7 min of extinction in which a pellet or sucrose outcome was freely delivered and responding recorded for the next 2 min. Outcomes were delivered in the order: pellets, sucrose, sucrose, pellets. It was expected that pellet delivery would reinstate responding on the lever that had earned pellets during training, and similarly sucrose delivery would reinstate responding on the sucrose lever. Results are shown in **Figure 3D**. It is clear from this Figure that all groups showed greater responding following outcome-delivery and that this increase in responding was selective for the reinstated lever (i.e., reinstated > other, see figure caption for statistical analysis). Although the bilateral lesions of PL and MD have no effect on outcome-induced reinstatement, it was important to demonstrate that the functional disconnection of these structures left reinstatement performance intact. This is because it rules out several potential explanations of the impairment in the outcome devaluation test, including a simple deficit in discriminating between levers and outcomes.

Together, these results show that disconnecting the PL-MD pathway creates a deficit in outcome devaluation performance whilst leaving outcome-induced reinstatement intact. The deficit observed during outcome-devaluation suggests that the MD does rely on inputs from the PL (or vice versa) for accurate performance in this task. Intact reinstatement suggests that this deficit was not a result of impaired discrimination, and the fact that there was no difference in lever-press acquisition suggests that the deficit in outcome devaluation performance cannot have resulted from a lack of opportunity to learn the R-O contingencies. Rather, the pattern of results suggests that this group suffered a specific deficit in using R-O contingencies to guide action selection such that they pressed both levers equally on test.

It is worth pointing out here that the success of the novel surgical technique involving electrolytically lesioning the CC in inducing a full functional disconnection of the PL and MD, as evidenced by the lack of FG labeling observed in the PL contralateral to the MD injection site as well as the behavioral deficit observed, could have wide-ranging implications. In particular, researchers who might have previously wished to examine the effect of disconnecting prefrontal cortical (and other cortical) structures from subcortical structures with which they share ipsilateral and contralateral connections now have a potentially viable technique with which to do so. For example, Hunt and Aggleton (1998) found that lesions of both regions produce similar deficits in shifting response rules during a radial arm maze task. Likewise, Balleine and Dickinson (1998) found that PL lesions, like MD lesions described above, reduced responding non-selectively on

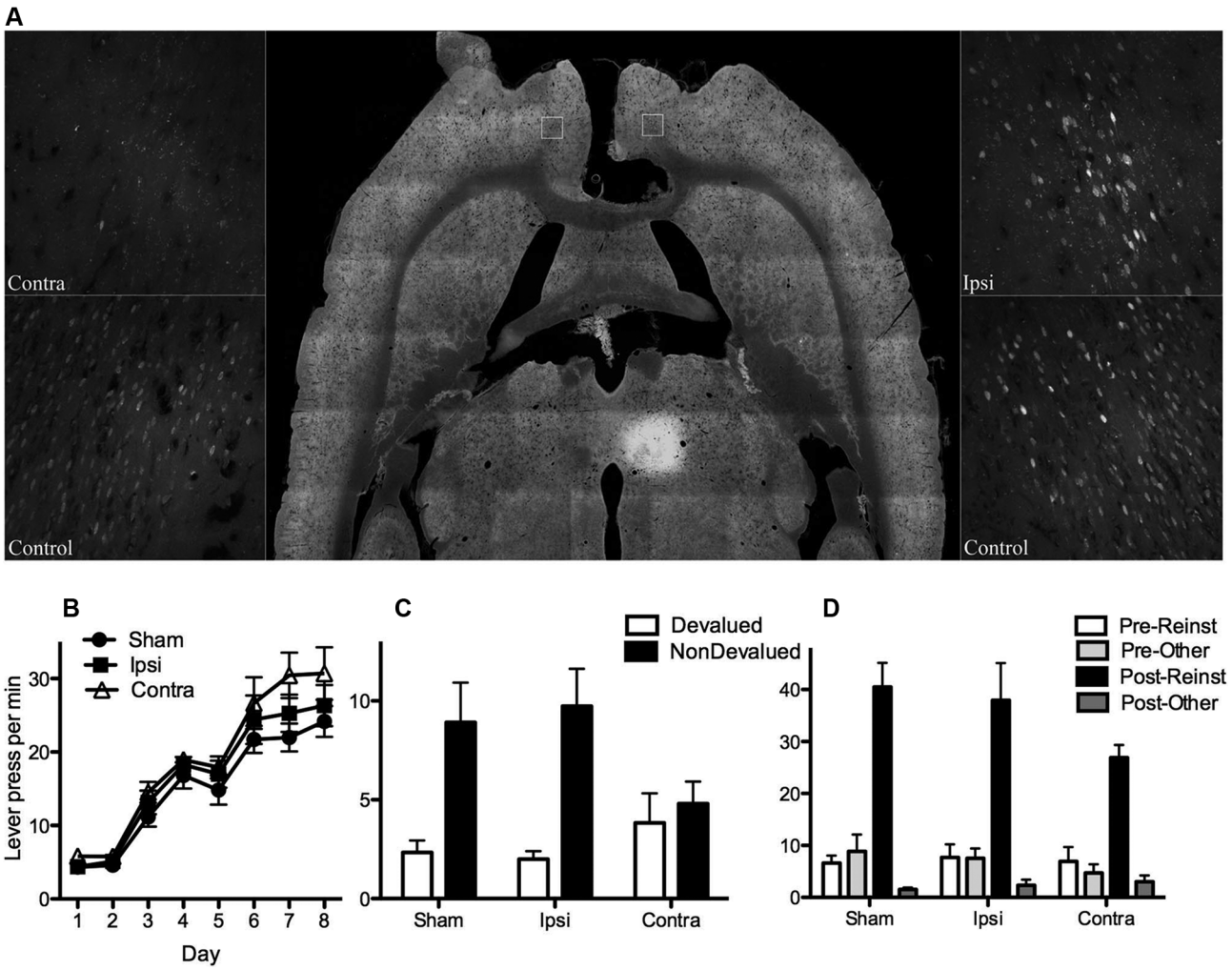

FIGURE 3 | (A) Shows the extent of fluorogold labeling in prelimbic cortex (PL) after receiving an injection of retrograde tracer FG into MD and either electrolytic (Contra and Ipsi) or sham (control) lesions of corpus callosum (CC). Horizontal section (middle panel) shows injection site in MD as well as CC lesion. CC lesions did not affect ipsilateral projections (no difference in labeling in Ipsi and control, right panel) but were effective in disconnecting contralateral projections (very little labeling in Contra relative to control, left panel). **(B)** Mean (± SEM) lever presses per min for the control groups (Groups Ipsi and Sham) and Group Contra that suffered a functional PL-MD disconnection (i.e., CC lesion plus contralateral N-methyl-D-aspartate (NMDA)-induced lesions of PL and MD). For all statistical analyses Group Sham and Ipsi did not differ on any measure (all $Fs < 1$) and therefore were averaged across for further analysis. All rats linearly acquired lever press responding, $F(1, 19) = 226.00$, $p = .00$, and groups did not differ on acquisition, $F(1, 19) = 2.194$, $p = .16$. **(C)** Mean (± SEM) lever press responding per min during outcome devaluation testing. Groups did not differ in overall responding, $F(1, 19) = 1.19$, $p = .29$, but there was a main effect of devaluation (averaged over group), $F(1, 19) = 18.54$, $p = .00$. There was a significant interaction, $F(1, 19) = 5.79$, $p = .026$, suggesting that both the control groups responded selectively on the nondevalued lever relative to the devalued lever (simple effects: Group Sham, $F(1, 19) = 10.08$, $p = .008$, Group Ipsi, $F(1, 19) = 14.76$, $p = .001$) but that Group Contra responded equally on both levers (simple effect: $F(1, 19) = .24$, $p = .63$). **(D)** Mean (± SEM) lever press responding per min during outcome-induced reinstatement testing. There was a main effect of reinstatement, $F(1, 19) = 105.38$, but no group x reinstatement interaction, $F(1, 19) = 3.88$, $p = .065$. Although this interaction might be considered marginal, simple effects show that rats in each group pressed the reinstated lever more than the other lever on test, Group Sham, $F(1, 19) = 54.31$, $p = .00$, Group Ipsi, $F(1, 19) = 39.6$, $p = .00$, and Group Contra, $F(1, 19) = 17.81$, $p = .00$.

both levers during a contingency degradation task. And, similarly, Ostlund and Balleine (2007, 2008) found similar effects on Pavlovian instrumental transfer induced by lesions of the MD and lateral OFC. Thus, given the similarity of these deficits produced by lesions of the MD and frontal cortical structures in behavioral tasks other than those reported here, it might be hypothesized that functionally disconnecting these structures will produce a similar deficit. Until now it has not been possible to explore such questions. Therefore, the surgical procedure described in the current study provides an exciting prospect for the study of these, and other potential functions of the thalamo-cortical pathway.

THE PARAFASCICULAR THALAMIC NUCLEUS

The final region we consider for its role in instrumental behavior was that of the parafascicular thalamic nucleus (PF; see

Figure 4C). The PF was one of the first thalamic regions to be assessed for its role in instrumental behavior. Delacour (1969) found that lesioning the PF did not affect learning during a passive avoidance or one-way avoidance task. Of some interest, however, were the findings of the second experiment showing that although PF lesioned rats were unimpaired relative to controls in learning to cross from shocked compartment A to the non-shocked compartment B, they did show a deficit when the shocked compartments were switched and rats had to learn to cross in the other direction (i.e., from B to A). This inability to reverse the previously learned contingency suggests a potential deficit in flexible performance. Unfortunately, in this instance it is not possible to separate the inflexibility of PF lesioned rats in learning a new Pavlovian relation (i.e., "stimulus" compartment A → "outcome" avoid shock) from inflexibility in learning a new instrumental action (i.e., "response" cross to A → "outcome" avoid shock).

The suggestion that the PF might regulate the flexibility of instrumental behavior was re-visited by Minamimoto et al. (2009) using primates as subjects. They recorded the responses of long latency facilitation (LLF) neurons in the centro-median parafascicular nuclear complex (CM-PF; the primate homologue of the PF) of two monkeys during a GO-NOGO task. This task requires monkeys to either respond ("GO") or withhold responding ("NOGO") to particular stimuli to receive a large or small water reward. LLF neurons in the CM-PF showed an interesting pattern of responding during the trial blocks when the GO response was paired with the large reward and the NOGO response paired with the small reward. Specifically, after several NOGO trials the likelihood of a GO trial increased, in parallel with the likely increase in the monkey's expectation of a GO response. When the NOGO stimulus was then unexpectedly presented LLF activity increased, but only when a NOGO response was produced. When the response was not produced LLF activity remained weak or silent, indicating that the presentation of an unexpected stimulus alone was not sufficient for this increase in LLF activity. The authors interpreted this as showing that CM-PF LLF neurons drive a kind of "rebias" process that occurs when the animal expects to produce one response but quickly changes to another. This, like Delacour (1969) study appears to point to a role for CM-PF in flexible responding, a requirement of instrumental conditioning. Again, however, it is difficult to make a solid conclusion about PF regulation of instrumental conditioning because the response measured in this task was stimulus-dependent, therefore already somewhat inflexible. Further, the activity of LLF neurons was purely correlative such that interpreting the activity of LLF neurons to be reflective the monkey's expectations was somewhat speculative.

More recently, Brown et al. (2010) conducted a series of experiments that they also interpreted as showing that the PF mediates behavioral flexibility, and does so by influencing acetylcholine (ACh) levels in the aDMS, with which it has large and specific connections. These experiments employed a T maze task in which rats were placed into the stem arm and learned to travel to one of the choice arms to retrieve a piece of cereal. Rats were trained to criterion (10 consecutive correct trials) in this phase of the task and then trained to enter the opposite arm ("reversal phase") the following day; i.e., the previously non-reinforced arm became the reinforced arm. Half of the rats received intra-PF infusions of baclofen-muscimol (Bac-Mus) prior to the initial acquisition and half received saline. PF inactivation did not affect initial acquisition because all rats took the same amount of time to reach criterion. However, rats that received Bac-Mus infusions prior to the reversal phase did take longer than saline-infused animals to reach criterion. In a separate experiment Brown et al. (2010) found that reversal learning of this kind increased ACh efflux in the DMS during reversal training, and that PF inactivation (using Bac-Mus) prevented this increase (see **Figure 4A**). They concluded that this increase in ACh efflux depended on PF inputs and reflected a facilitation in altering choice patterns and thus behavioral flexibility.

Although it is possible that this efflux in ACh did indeed reflect a facilitation of flexibility, this is not the only interpretation of these results. This is because behavioral flexibility implies an exclusively instrumental process, and it is particularly difficult to disentangle the Pavlovian and instrumental processes that might be employed during performance in T-maze tasks such as the one employed by Brown et al. (2010) (Dickinson, 1994; Yin and Knowlton, 2002; Yin et al., 2008). First, without a test session in which the outcome is absent it is not possible to conclude whether performance is governed by R-O contingency knowledge or whether the animal simply becomes better at detecting the presence of food over time. Second, without an evaluation of whether altering the value of the cereal also altered performance in the task there is no necessary demonstration that the cereal behaves as a "goal" of behavior. Brown et al. (2010) did not include either of these tests making it equally as likely that performance on this task was governed by S-O relations between maze cues and the cereal outcome. This conclusion holds even in spite of the maze being turned between trials to minimize the consistency of external cues; making extramaze cues ambiguous could have forced the rats to rely on intramaze cues (e.g., walls, floor). Superficially it might appear that the reversal learning assessed by Brown et al. (2010) addresses this problem by demonstrating that rats are able to flexibly alter responding in the manner required of an instrumental response. However, it is necessary to show that this occurs when the S-O relation is kept constant. In T-maze reversal learning, if the animal first learns to turn right on reversal, then the stimuli associated with turning left (i.e., the arm of the "T" that leads left) are no longer associated with reward, leading to extinction of that S-O relation. Instead, the animal forms a new S-O relation between the stimuli associated with turning right and the reward. In other words, it is not possible to show that animals can alter responding whilst keeping S-O relations consistent using a T-maze task.

A final point to be made about these experiments (Brown et al., 2010) is that the microdialysis probe placed in the DMS to measure ACh efflux was aimed aDMS whereas prior research has found that it is specifically the pDMS that mediates goal-directed instrumental conditioning (e.g., Yin et al., 2005a,b). Specifically, Yin et al. (2005a,b) used outcome devaluation and contingency degradation procedures similar to those described here and found that although the pDMS is critically involved in both the acquisition and expression of goal-directed behaviors,

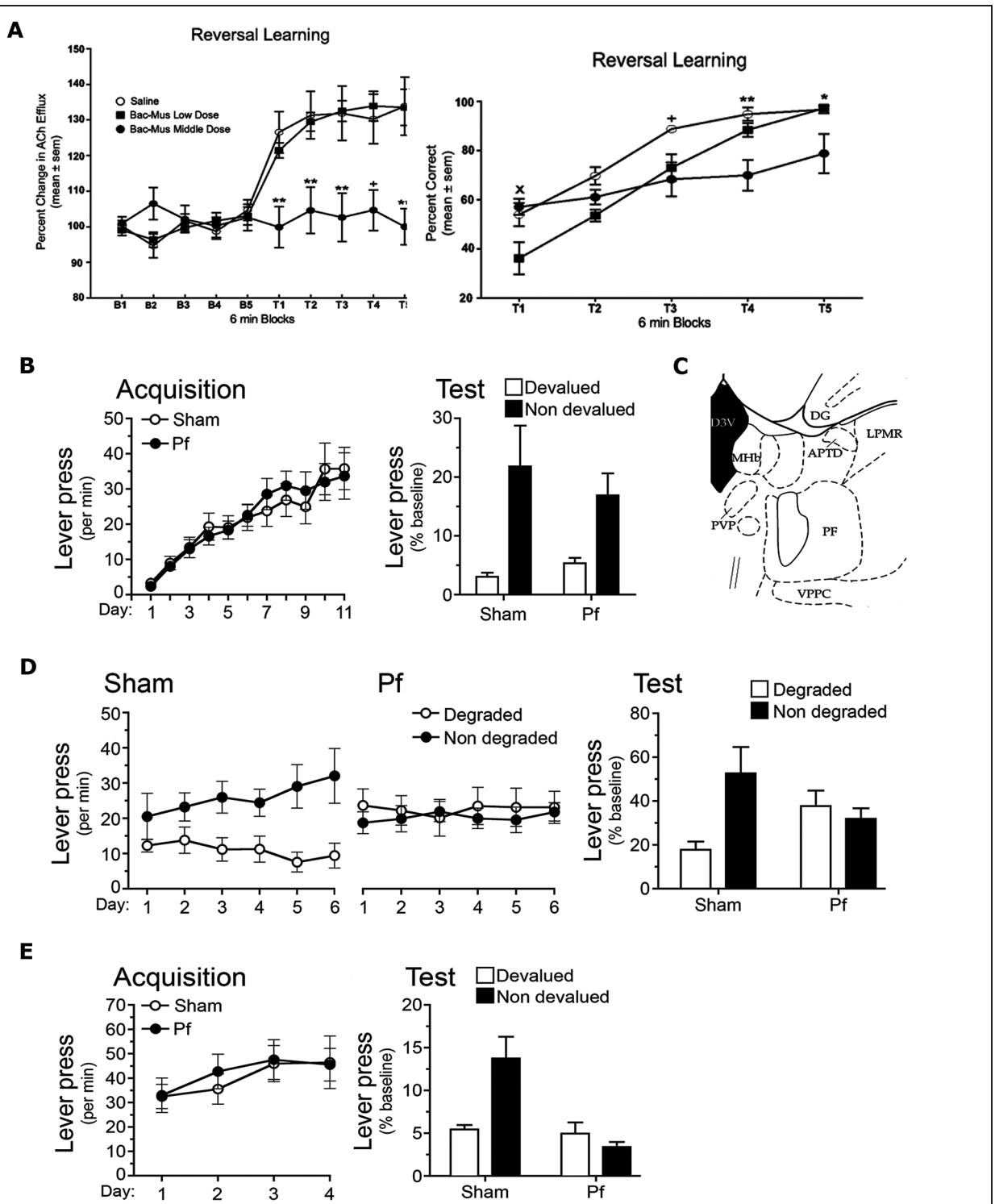

FIGURE 4 | (A) Reproduced from Brown et al. (2010). Acetylcholine (Ach) efflux in anterior dorsomedial striatum (aDMS; left panel) and behavioral performance (right panel) during 6 min blocks during the reversal learning phase of a T maze task (T1–T5). Left panel: the middle dose of $GABA_A$ agonist Baclofen-Muscimol (Bac-Mus) infused into the parafascicular thalamus (PF) was sufficient to reduce Ach efflux in the aDMS during reversal learning. Right panel: infusion of the low dose of Bac-Mus significantly reduced reversal learning performance relative to saline-infused controls at T1. The Middle dose reduced performance at T3, T4, and T5 relative to saline controls. **(B,D,E)** Reproduced from Bradfield and Balleine (2013), examines Sham and PF-lesioned animals. **(B)** Mean ± SEM responding per min during acquisition (left panel) and on an outcome devaluation test (right panel) of initial R-O contingencies. **(C)** Reproduced from Paxinos and Watson (1998). Schematic showing PF at A/P: −4.16 from Bregma. **(D)** Mean ± SEM responding per min during contingency degradation training (left and middle panels) and on the extinction test (right panel). **(E)** Mean ± SEM responding per min during acquisition (left panel) and test (right panel) of reversed R-O contingencies.

manipulations of aDMS had no effect. Furthermore, a separate study has suggested that, rather than governing instrumental behavior, the aDMS regulates the Pavlovian control of behavior (Corbit et al., 2007). On this basis, we suggest that the alterations in the behavior of PF-inactivated rats in the study by Brown et al. (2010) and the concomitant increase in ACh in aDMS, reflects the role of the PF-aDMS pathway in facilitating learning about alterations S-O rather than R-O relations.

More recently we have investigated whether the PF mediates behavioral flexibility via its afferents to the pDMS using unambiguous manipulations of the R-O contingency (Bradfield et al., 2013). In particular, we examined the role of PF-controlled tonically active pDMS cholinergic interneurons (CINs) in the interlacing of new and existing R-O contingencies. We first examined the effects of bilateral PF lesions on the same outcome devaluation and contingency degradation procedures outlined previously. Although PF lesions did not affect outcome devaluation (**Figure 4B**) and therefore did not interfere with the initial acquisition of goal-directed behaviors, PF lesioned rats did show a deficit relative to controls during contingency degradation (**Figure 4D**). Specifically, while the Sham control rats selectively reduced their responding on the degraded lever during training and test, PF lesioned controls continued to press both levers equally. One interpretation of this result is that once PF lesioned rats had learned the initial R-O contingency, the rats were unable to alter (reduce) their responding when the contingency changed. Because other interpretations of this result are possible, a third experiment was conducted to test this hypothesis. For this experiment the contingencies learned in the initial training phase were reversed, for example, if the left lever was previously paired with pellets it was now paired with sucrose, and if the right lever was previously paired with sucrose it was now paired with pellets. Sham rats demonstrated devaluation performance in line with the reversed contingencies because when they were prefed one of the outcomes to satiety and then tested in extinction, they preferentially chose the lever associated with the nondevalued outcome. PF lesioned rats, on the other hand, chose both levers equally (**Figure 4E**). This deficit was not limited to performance in a devaluation/extinction test. When the rats were treated to 15 min of extinction and then delivered two single pellet and two single sucrose presentations (separated by 7 min ITIs), Sham rats selectively reinstated responding on the lever associated with the relevant outcome according to the reversed contingencies, whereas PF lesioned rats pressed both levers equally. Together with the observed deficit in contingency degradation, this result suggests that an intact PF is necessary for true behavioral flexibility.

These behavioral tasks were repeated in later experiments to test the effects of functionally disconnecting the PF-pDMS pathway. Prior to these experiments we had injected the retrograde tracer FG into the pDMS and evaluated labeling in the PF. This confirmed that the PF does project to the pDMS and that the pathway is entirely lateralised. Rats were then administered either Sham, ipsilateral, or contralateral, PF/pDMS lesions. Rats with ipsilateral PF-pDMS lesions (group Ipsi) retained an intact PF-pDMS pathway in the opposing hemisphere, whereas contralateral PF and pDMS lesions (group Contra) ensured rats had no intact pathway in either hemisphere. Thus both the Sham and Ipsi groups controlled for the behavior of group Contra. Rats in this group (group Contra) showed the same pattern of results as bilaterally PF lesioned rats. That is, they showed intact initial acquisition of R-O contingencies, but impaired contingency degradation and acquisition of the reversed R-O contingencies. In contrast Sham and Ipsi rats showed intact performance in all tasks. After the rats were sacrificed their brains were sectioned and examined for examined p-Ser$^{240-244}$-S6rp intensity in cholinacetyltransferase (ChAT) immunoreactive neurons in the non-lesioned pDMS. p-S6rp was recently shown to reflect the activation levels of CINs particularly well (Bertran-Gonzalez et al., 2012). Analysis of the results showed that p-S6rp intensity was significantly reduced in Group Contra relative to Groups Ipsi and Sham, reflecting the reduced inputs from the lesioned PF in this group relative to the other two groups. A separate experiment using patch-clamp electrophysiology showed that removing PF inputs to the pDMS by lesioning the PF reduced the frequency of action potentials in pDMS CINs. A final experiment examined the effect of compromised CINs function on behavior. For this experiment all rats had a unilateral PF lesion, and then received an infusion of either saline or the M2/M4 muscarinic receptor agonist Oxotremorine-S (Oxo-S) into the contralateral pDMS prior to learning reversed R-O contingencies. On test, saline-infused rats demonstrated evidence of having learned the reversed contingencies (nondevalued > devalued) but Oxo-S-infused rats did not (nondevalued = devalued). Together, these results suggest that the activation of CINs in the pDMS is reliant on PF inputs, and is necessary for the flexible responding in the face of altered R-O contingencies.

Given that PF also innervates the aDMS, and that Brown et al. (2010) found that ACh increases in a manner that is dependent on PF inputs during a behavioral task, we also considered the effect of disconnecting the aDMS-PF pathway. Although aDMS lesions are known to have no effect on the initial acquisition of R-O contingencies, nor their degradation (Yin et al., 2005b), the effect of such lesions on learning reversed contingencies was unknown. Using the same asymmetrical lesion design, but substituting aDMS for pDMS lesions, we found that disconnecting this pathway left the acquisition of both initial R-O contingencies and their reversal intact, suggesting that any increases in aDMS ACh that are observed during a behavioral task either are functionally irrelevant for the interlacing of new and existing R-O contingencies, or that similar increases do not occur in tasks requiring flexibility of R-O contingencies.

This role of the PF (via inputs to the pDMS) differs from that of the MD in instrumental behavior in that the former is necessary for interlacing new and existing R-O contingencies, whereas the latter is necessary for the initial acquisition of R-O contingencies. Thus both of these thalamic regions play different but vital roles, however, whereas an intact MD is critical for a naïve animal to carry out various tasks to achieve an outcome, an intact PF is critical for animals to continue to perform these tasks when environmental contingencies change. Any animal that lacks either function would be at a distinct disadvantage.

The results regarding the PF are also consistent with another critical function: the regulation of what recent computational

views of instrumental conditioning have referred to as "state prediction errors". State prediction errors differ from reward prediction errors, that regulate learning during both Pavlovian and Instrumental conditioning and for which the neural mechanisms have been reliably established (Schultz and Dickinson, 2000; Waelti et al., 2001; Steinberg et al., 2013). The idea of "state" prediction has arisen with the recent increase in popularity of computational models (e.g., Daw et al., 2005) that model aspects of instrumental conditioning. These types of models suggest that model-based goal-directed behavior is observed when an animal experiences a series of transitions from one state (akin to a "situation") to another that ultimately results in the acquisition of a particular outcome. After encoding these state-to-state transitions the animal is then able to use its previous experiences to conduct a kind of forward search through the various states to ascertain whether their actions will lead to the acquisition of the outcome. State prediction errors are generated when the animal enters a state that is surprising given the probability with which they currently estimate their state-to-state transitions.

Experimentally, state and reward prediction errors tend to co-occur and are difficult to separate behaviorally (Schoenbaum et al., 2013). One experiment that does separate them, however, is the reversal of existing R-O contingencies. Upon entering the initial state during the reversal phase of the experiment, the animal expects that pressing the left lever (for example) will lead him to the state in which pellets are delivered to the magazine. When the animal is surprisingly transitioned into a different state in which sucrose is delivered instead, a large state prediction error is generated. If, however, it is assumed that rats value pellets and sucrose equally, then reward prediction error is zero because there is no discrepancy between the actual and expected reward. Therefore, the inability of rats with a compromised PF-pDMS pathway to accurately learn the reversed contingencies is consistent with an inability of these rats to effectively encode state prediction error. To be more specific, it is consistent with an inability to encode a reduction in contingency learning as a result of state prediction error. This is because the performance of PF-pDMS-compromised rats on this task was indiscriminate (i.e., they press equally on both levers at test, refer to figure). If these rats were incapable of encoding an increase in learning as a result of state prediction error, they should show no evidence of having learned the new contingencies (e.g., "left lever surprisingly leads to the state in which sucrose is delivered") and show greater responding on the now-devalued lever than the nondevalued lever on test. If, however, these rats were specifically incapable of encoding a reduction in learning that resulted from state prediction error (e.g., "left lever no longer leads to the state in which pellets are delivered") they would fail to unlearn the old contingencies whilst still learning about the new contingencies and their performance would be confused between the two on test. That is, they should show respond equally on the devalued and nondevalued levers, as observed.

Contingency degradation results also support this conclusion. PF-pDMS compromised rats, unlike controls, failed to reduce their responding on the degraded lever. State prediction error contributes to the reduction in learning about the degraded lever-outcome contingency during contingency degradation. Specifically, there is a state prediction error when an outcome that was previously paired only with lever press is also delivered outside of the lever press contingency. When the outcome was dependent on lever press alone, the animal learned that only pressing the lever in the initial state would transition them to the next state in which a pellet (for example) is delivered to the magazine. During contingency degradation they are surprisingly transitioned to this state without pressing the lever, generating a state prediction error. This state prediction error triggers an increase in learning (that favours learning about context-outcome relations) but also a reduction in learning about the contingency between performing the lever press in the initial state and entering the "food delivered" state. It is this reduction that leads to decreased responding on the degraded lever. Thus, the fact that the PF-pDMS compromised rats do not decrease responding on the degraded lever throughout training, is again consistent with an inability of those rats to process state prediction error in a manner that leads to a reduction in R-O contingency knowledge.

It is important to mention that, although broadly consistent with this view, Schoenbaum et al. (2013) have developed an alternative interpretation of these results. In a similar fashion to our interpretation (Bradfield et al., 2013), Schoenbaum et al. (2013) suggested that the PF-pDMS compromised rats primarily suffered a deficit in processing errors concerned with identity rather than reward. However, where we interpreted "states" in the manner assumed by model-based and model-free reinforcement learning models, Schoenbaum et al. (2013) offered an alternate but equally valid interpretation suggesting that the encoded states were more akin to a "context" or "latent cause". On this account the state refers to the phase of training that the animal enters when it encounters an alteration in contingency, such as in contingency degradation ("state 2") or reversal learning ("state 3"). It is Schoenbaum et al. (2013) suggestion that the PF-pDMS compromised animal suffers either a retrieval deficit such that multiple states are retrieved at one time causing confusion to the animal, or a state creation deficit in which the animal is incapable of forming a new state based on errors in identity prediction.

CONCLUSION

Research regarding the role of various thalamic nuclei in instrumental behavior has increased in recent years. One of the earliest regions considered were the ANT. Although early indications appeared to suggest that ANT did indeed mediate instrumental behavior, careful examination of these tasks revealed that the learning processes governing behavior confound Pavlovian and instrumental processes. By contrast, when rats with ANT lesions were tested in free operant instrumental conditions they showed no deficits in a range of tasks (Corbit et al., 2003) effectively excluding this region as a candidate for the regulation of instrumental behavior as governed by R-O relations.

Another region that has received attention for its role in regulating instrumental behavior is the MD. Again, early indications suggested a possible role for this region but did not employ tasks that clearly separate Pavlovian and instrumental relations. In contrast to the ANT, however, MD lesions were later found to affect performance in several free operant behavioral

tasks, highlighting a specific role for this region in the regulation of goal-directed instrumental behavior (Corbit et al., 2003). In addition, later research (Ostlund and Balleine, 2008) found that although the MD was important for the acquisition of goal-directed behavior, it was not important for its expression, as post-training MD lesions left goal-directed behavior intact. Finally, in the same study, it was found that an intact MD was important for the regulation of S-O as well as R-O contingencies, as MD lesions abolished PIT performance and Pavlovian contingency degradation.

Given that PL lesions regulate the acquisition but not expression of R-O contingencies in the same manner of MD lesions, we examined the effect of their disconnection in the current study. Because there are contralateral, as well as ipsilateral, connections between PL and MD, this required the adoption of a novel surgical technique that involved electrolytic lesions of the CC. Once the efficacy of this procedure in severing contralateral PL-MD connections had been established using the retrograde tracer FG, a functional disconnection of these structures was employed to examine the effect of this disconnection on various behavioral tasks. Specifically, all rats received Sham, ipsilateral or contralateral excitotoxic lesions of PL and MD in addition to a CC lesion. We found that outcome-induced reinstatement performance was intact in all groups, but that Group Contra showed a specific deficit in outcome devaluation testing. This suggests that the PL-MD pathway regulates learning of R-O contingencies in a manner that cannot be attributed to a deficit in discrimination or some other general process important to learning.

Finally, the role of the PF was examined, in particular for its role in flexible of instrumental behavior. Although several earlier studies implicated such a role for PF, again these tasks made it difficult to separate the influence of Pavlovian and instrumental processes. Our recent research by Bradfield et al. (2013) has shown, however, showed that the PF, via its control of the tonic activity of pDMS CINs, mediates the alterations in learning that occur when R-O contingencies change. This role is notably consistent with the possibility that PF-controlled pDMS CINs encode state prediction error, in particular when that error leads to reductions in contingency knowledge.

In summary, then, it is clear that there are multiple important and contrasting roles of various thalamic nuclei in the regulation of instrumental behavior. Given the wide connectivity of these nuclei with many striatal and cortical regions of interest, this is unsurprising. Future research will continue to uncover the specific role of these regions, particularly in the context of the complex interplay these regions enjoy with other structures in the brain.

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The anterior thalamus provides a subcortical circuit supporting memory and spatial navigation

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The anterior thalamic nuclei (ATN), a central component of Papez' circuit, are generally assumed to be key constituents of the neural circuits responsible for certain categories of learning and memory. Supporting evidence for this contention is that damage to either of two brain regions, the medial temporal lobe and the medial diencephalon, is most consistently associated with anterograde amnesia. Within these respective regions, the hippocampal formation and the ATN (anteromedial, anteroventral, and anterodorsal) are the particular structures of interest. The extensive direct and indirect hippocampal-anterior thalamic interconnections and the presence of theta-modulated cells in both sites further support the hypothesis that these structures constitute a neuronal network crucial for memory and cognition. The major tool in understanding how the brain processes information is the analysis of neuronal output at each hierarchical level along the pathway of signal propagation coupled with neuroanatomical studies. Here, we discuss the electrophysiological properties of cells in the ATN with an emphasis on their role in spatial navigation. In addition, we describe neuroanatomical and functional relationships between the ATN and hippocampal formation.

Keywords: anterior thalamus, memory, spatial navigation, theta rhythm, head direction cells

INTRODUCTION

That the hippocampal formation is vital for memory is undeniable. For this reason, understanding hippocampal learning mechanisms remains one of the principal objectives in neuroscience. However, this problem must be addressed from a broad perspective, i.e., one that includes the many connections of the hippocampal formation, some of which are now known to be critical for hippocampal mnemonic functions. The medial diencephalon is extensively connected with the hippocampal formation, damage to this area being frequently associated with anterograde amnesia (Aggleton and Sahgal, 1993; Aggleton and Brown, 1999). Within the medial diencephalon, the anterior thalamic nuclei (ATN) are an important part of the neuronal systems involved in spatial navigation (Clark and Taube, 2012), complementing their role in mnemonic functions (Buzsáki and Moser, 2013). This review will summarize some recent data concerning the anatomical and physiological properties of the anterior thalamic neurons, their role in spatial navigation, and their relevance to pathophysiological conditions associated with the ATN.

GENERAL ANATOMY OF THALAMUS

The thalamus is a bilateral, symmetrical structure comprising the majority of the diencephalon, with the medial thalamus being bordered, and in places split, by the third ventricle. The thalamus is classically divided into several groups of nuclei, described by their anatomical location: medial, lateral, ventral, and anterior, as well as the posterior (pulvinar) nuclei. This review focuses on the ATN, which is divided into the anterodorsal, anteroventral, and anteromedial nuclei, all located in the rostral part of the dorsomedial thalamus (**Figure 1**) (Morel et al., 1997; Wiegell et al., 2003). There is some uncertainty about the nuclei that comprise the ATN, with many authors regarding the lateral dorsal thalamic nucleus as part of the ATN due to its limbic associations (Morel et al., 1997). Some researchers have argued that the anteromedial nucleus is actually a part of the anteroventral nucleus (see Alelú-Paz and Giménez-Amaya, 2007), although in rodents and monkeys these two nuclei have clearly visible differences when examined in histological and immunochemical preparations. The three major nuclei within the ATN also have distinct patterns of connectivity.

HISTOLOGY

While the human anteroventral thalamic nucleus is distinguished by its homogenous and dense cell population (Morel et al., 1997), the neurons in anteromedial nucleus are larger and more widely dispersed. In contrast, the anterodorsal nucleus contains densely-packed small cells (Morel et al., 1997). All areas of the ATN show varying degrees of immunoreactivity to acetylcholinesterase, as well as the calcium-binding proteins calretinin, calbindin-D28K and parvalbumin (Morel et al., 1997; Fortin et al., 1998; Munkle et al., 2000; Alelú-Paz and Giménez-Amaya, 2007). In humans, the neuropil in ATN also stains variably in different areas for neuropeptides. These neuropeptide analyses reveal numerous substance P positive varicose fibers scattered throughout the ATN,

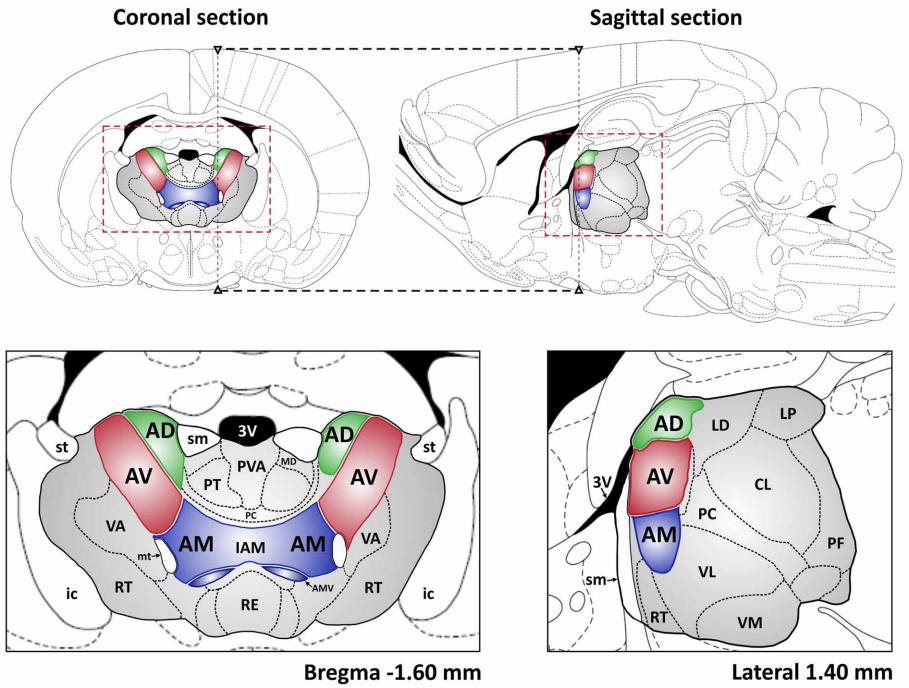

FIGURE 1 | The localization of the ATN in the rat brain. Top: coronal and sagittal sections of rat brain are shown (Paxinos and Watson, 1998) with the ATN indicated in green, red and blue and whole area of the thalamus in gray. The dashed black lines depict the spatial relation between presented sections. The dashed red rectangles denote the extent of coronal and sagittal sections, respectively, presented below. Abbreviations: 3V, 3rd ventricle; AD, anterodorsal thalamic nucleus; AV, anteroventral thalamic nucleus; AM, anteromedial thalamic nucleus; AMV, anteromedial thalamic nucleus, ventral part; CL, centrolateral thalamic nucleus; IAM, interanteromedial thalamic nucleus; ic, internal capsule; LD, laterodorsal thalamic nucleus; LP, lateral posterior thalamic nucleus; MD, mediodorsal thalamic nucleus; mt, mammillothalamic tract; PC, paracentral thalamic nucleus; PF, parafascicular thalamic nucleus; PT, paratenial thalamic nucleus; PVA, paraventricular thalamic nucleus, anterior part; RE, reuniens thalamic nucleus; RT, reticular thalamic nucleus; sm, stria medullaris of the thalamus; st, stria terminalis; VA, ventral anterior thalamic nucleus; VL, ventrolateral thalamic nucleus; VM, ventromedial thalamic nucleus.

in contrast to very few enkephalin positive varicose fibers (Alelú-Paz and Giménez-Amaya, 2007). Heterogeneity in morphological architecture and protein expression patterns within ATN may reflect regional differences in their functional organization with respect to the other thalamic nuclei and the cerebral cortex. Moreover, the varied morpho-chemical structure of the various ATN may underlie their different roles in the function of the limbic system.

CONNECTIVITY TO OTHER STRUCTURES

The ATN sits in the middle of a complex array of cortical and subcortical connections (**Figure 2**). Examples include the widespread links with frontal cortical areas, much of the cingulate cortex, and the hippocampal formation (Amaral and Cowan, 1980; Hicks and Huerta, 1991; Van Groen and Wyss, 1995). Many of these connections are reciprocal (Shibata and Naito, 2005). Especially dense inputs to the ATN arise from the retrosplenial cortex, the subiculum, and the mammillary bodies (Wright et al., 2010); the latter reach the thalamus via the mammillothalamic tract. The mammillary body inputs are particularly notable as it appears that almost every neuron within the structure projects to the ATN (Hopkins, 2005; Vann et al., 2007; Aggleton et al., 2010). However, the various projections to the ATN are often topographically specific (Wright et al., 2013). Previous rodent and primate studies had indicated that separate cell groups in the subiculum project to either the mammillary bodies or the anterior thalamus (Naber and Witter, 1998; Ishizuka, 2001; Aggleton et al., 2005). Wright et al. (2010) investigated this specificity and found distinct bands of projection to each area, i.e., the inputs are segregated. This same pattern of segregation extends to the inputs to the anteroventral and anteromedial nuclei, which often arise from the same structure but rarely from the same cells (Wright et al., 2013). The finding that the direct hippocampal projections to the mammillary bodies and ATN rely on the fornix (Aggleton et al., 2005, 2010; Saunders et al., 2005) is important as it has a direct bearing on how the impact of fornix damage upon cognition is interpreted (Tsivilis et al., 2008). A brief summary of some of the connections involving the different nuclei in the rodent anterior thalamus is summarized as follows (see also **Figure 2**):

ANTEROMEDIAL

Anteromedial nucleus receives projections from:

- medial mammillary bodies (Watanabe and Kawana, 1980; Seki and Zyo, 1984)
- rostral dorsal reticular nucleus (Shibata, 1992)
- prelimbic and medial orbital cortices (Shibata and Naito, 2005)

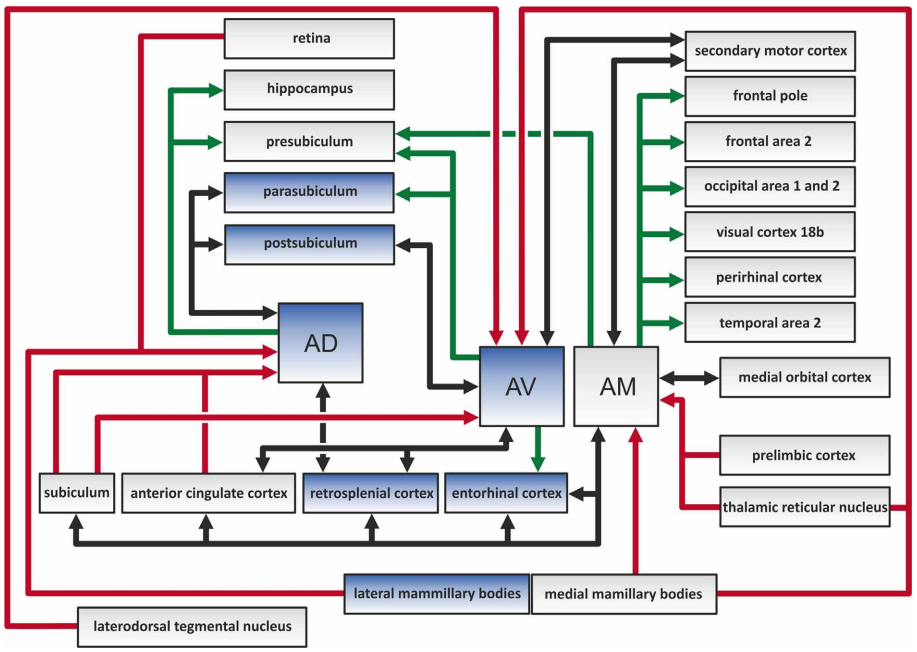

FIGURE 2 | The color-coded diagram presents the main direct connections of the anterodorsal (AD), anteroventral (AV), and anteromedial (AM) thalamic nuclei in the rat brain. Black arrows depict reciprocal connections, green efferents, and red afferents of the three anterior thalamic nuclei (ATN). Structures in blue contain head direction cells, and so constitute a part of the hierarchically organized head direction system (Clark and Taube, 2012). The various indirect connections of the ATN, along with the connections between other highlighted structures, are not included in this scheme.

- anterior cingulate and dysgranular retrosplenial cortex (Shibata, 1993b; Shibata and Naito, 2005; Wright et al., 2010)
- secondary motor cortices (Shibata and Naito, 2005)
- entorhinal cortex (Wright et al., 2010)
- subiculum (Wright et al., 2010)

Anteromedial nucleus projects to:

- frontal area 2 (Shibata and Kato, 1993), frontal polar and medial orbital cortex (Van Groen et al., 1999)
- anterior cingulate (Shibata and Kato, 1993) and dysgranular retrosplenial cortex (Shibata and Kato, 1993; Van Groen et al., 1999)
- entorhinal cortex (Shibata, 1993a; Shibata and Kato, 1993; Van Groen et al., 1999);
- perirhinal cortex (Shibata, 1993a; Van Groen et al., 1999)
- presubiculum, subiculum (Shibata, 1993a; Van Groen et al., 1999)
- visual cortex area 18 b (Van Groen et al., 1999)
- temporal area 2, occipital area 1 and 2 (Shibata, 1993a)
- (medial) secondary motor cortices (Shibata and Naito, 2005)

ANTERODORSAL

Anterodorsal nucleus receives projections from:

- lateral mammillary bodies (Watanabe and Kawana, 1980; Shibata, 1992)
- subiculum, para-and postsubiculum (Seki and Zyo, 1984; Van Groen and Wyss, 1990a,c; Wright et al., 2010)
- retina (Conrad and Stumpf, 1975; Itaya et al., 1981, 1986)
- anterior cingulate cortex (Shibata and Naito, 2005)
- granular retrosplenial cortex (Wright et al., 2010)
- caudal dorsal reticular nucleus (Shibata, 1992)

Anterodorsal nucleus projects to:

- pre-, para-, and postsubiculum (Van Groen and Wyss, 1990a,c, 1995)
- hippocampus (Wyss et al., 1979; Amaral and Cowan, 1980)
- granular retrosplenial cortex (Van Groen and Wyss, 1990b; Shibata, 1993b; Van Groen and Wyss, 2003)

ANTEROVENTRAL

Anteroventral nucleus receives projections from:

- medial mammillary bodies (Watanabe and Kawana, 1980)
- caudal dorsal reticular nucleus and laterodorsal tegmental nucleus (Shibata, 1992)
- subiculum and postsubiculum (Van Groen and Wyss, 1990c; Wright et al., 2010)
- anterior cingulate cortex, granular and dysgranular retrosplenial cortex (Van Groen and Wyss, 1990b, 2003; Shibata and Naito, 2005; Wright et al., 2010)
- secondary motor cortex (Shibata and Naito, 2005)

Anteroventral nucleus projects to:

- pre-, para-, and postsubiculum (Van Groen and Wyss, 1990c; Shibata, 1993a; Van Groen and Wyss, 1995)

- entorhinal cortex (Shibata, 1993a)
- anterior cingulate, granular and dysgranular retrosplenial cortex (Shibata, 1993b; Van Groen and Wyss, 2003)
- secondary motor cortex (Shibata and Naito, 2005)

FUNCTIONAL CONSIDERATIONS

The circuit outlined by Papez (1937) is still highly relevant when considering the functional and cognitive aspects of systems involving the anterior thalamus. This circuit highlighted the following projections: hippocampal formation > mammillary bodies > anterior thalamus > cingulate cortex > parahippocampal gyrus > hippocampal formation. Since then, the anatomical definition of Papez' circuit has been further refined (Shah et al., 2012). The ATN still occupy an important position as established by studies using traditional fiber dissection techniques (Shah et al., 2012), as well as *in vivo* diffusion spectrum imaging (Granziera et al., 2011) of Papez' circuit. Although Papez originally suggested that this pathway underlay emotional processing by the brain, our current understanding of Papez' circuit suggests that it has a particular and special role in supporting the neural substrates of explicit learning and memory (Vertes et al., 2001; Shah et al., 2012). Aggleton and Brown (1999) developed the idea of an extended hippocampal-diencephalic network for the integration of information, with the ATN at its core. Subsequent models have proposed that the individual ATN can be functionally divided, forming a series of three parallel sub-systems (Aggleton et al., 2010) (**Figure 3**): (1) The anteromedial nucleus is predicted to form part of a largely feed-forward system that conveys integrated information from the hippocampal-diencephalic network to prefrontal areas, thereby taking part in higher cognitive and executive functioning; (2) The anteroventral system largely comprises a return-loop, with the main purpose being to perpetuate rhythmic theta activity to the hippocampal formation; (3) The anterodorsal nucleus is considered to encompass the head direction system. This description arises because cells in this nucleus exhibit electrophysiological compass-like properties, so that they display tuning to specific head directions, but not to location (Taube, 2007; Clark and Taube, 2012). The proposal is that the combined properties aid both spatial and mental navigation, with a different emphasis in different species (Aggleton et al., 2010).

SPATIAL NAVIGATION ROLE OF ANTERIOR THALAMIC NEURONS—A CRITICAL PART OF THE HEAD DIRECTION SYSTEM

Investigations into the roles of anterior thalamic neurons in spatial navigation were triggered by the discovery of cells in

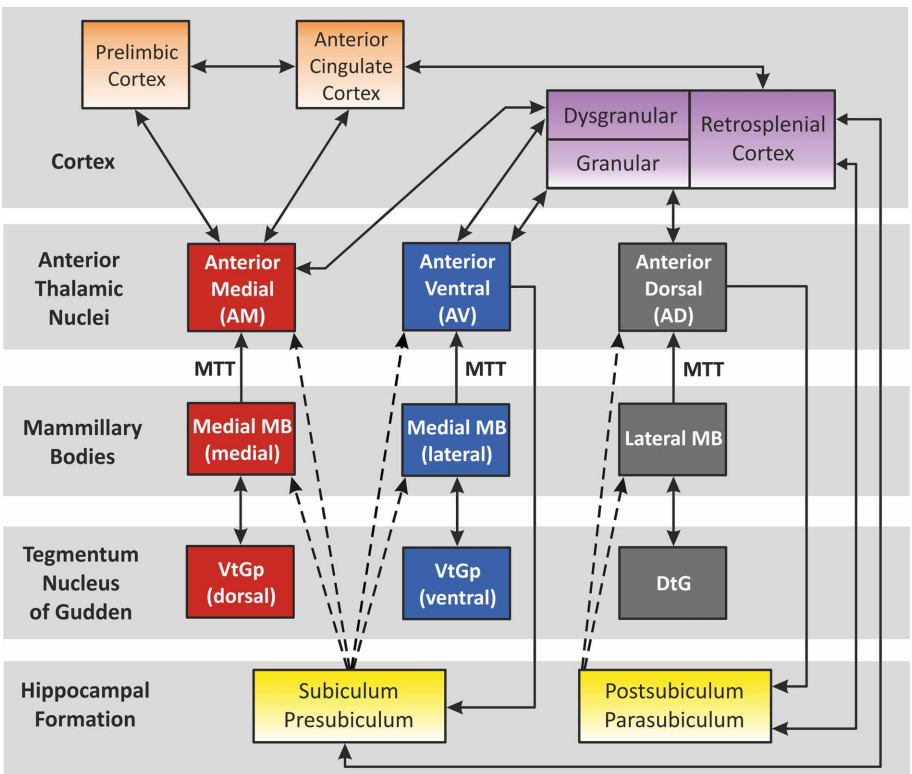

FIGURE 3 | The "extended-hippocampal system" proposed by Aggleton et al. (2010). Color-coded diagram depicts how, in the rat, the hippocampal formation is associated with three sets of parallel mammillary body—anterior thalamic connections. Connectivity studies in the monkey brain (macaque) support the same overall scheme for primates (e.g., Vann et al., 2007). The connections solely conveyed in the fornix are shown as dashed lines. Double-headed arrows depict reciprocal connections. Abbreviations: DtG, dorsal tegmental nucleus of Gudden; MTT, mammillothalamic tract; VtGp, ventral tegmental nucleus of Gudden, pars posterior. (Note, the lateral dorsal thalamic nucleus has not been included above as, unlike the anterior thalamic nuclei, it receives few, if any, mammillary body inputs. The interoanteromedial nucleus has not been included given its uncertain status in the primate brain).

the postsubiculum that discharge as a function of the animal's head direction in the horizontal plane, but independent of its behavior and location in the environment (Ranck, 1984; Taube et al., 1990). Knowing that the postsubiculum contains reciprocal connections with the ATN (anterodorsal nucleus in particular) led to the suspicion that the anterior thalamus might also possess head direction cells. In 1995, Taube reported that such cells, referred to as head direction cells (because they only discharge whenever the animal points its head in a particular direction), were indeed present in the ATN (Taube, 1995). Head direction cells are believed to encode primary information for spatial orientation in the environment, namely an animal's perceived directional heading with respect to its environment (for review see Taube, 2007; Clark and Taube, 2012). So far, the largest proportions of head direction cells in the thalamus have been found in the anterodorsal and lateral dorsal thalamic nuclei, with additional head direction cells in the anteroventral nucleus (Taube, 2007; Tsanov et al., 2011a; Clark and Taube, 2012). Moreover, head direction cells are also found in cortical structures such as the postsubiculum, parasubiculum, retrosplenial, and medial entorhinal cortex, as well as in subcortical brain regions like the lateral mammillary nucleus (LMN) and dorsal tegmental nucleus of Gudden (DTG) (Clark and Taube, 2012).

There is now considerable evidence that the ATN are part of an interconnected circuit, which is organized hierarchically and is responsible for the propagation of head directional signals in the central nervous system (Taube, 2007; Clark and Taube, 2012). Such a notion is supported by experiments in which lesions of the lower structures of this circuitry (e.g., anterodorsal thalamus) completely abolished head direction cell activity in higher components (e.g., postsubiculum, parasubiculum or superficial layers of medial entorhinal cortex), whereas destruction of postsubiculum did not disrupt head direction signals in subcortical structures (Goodridge and Taube, 1997; Clark and Taube, 2011, 2012). Moreover, damage to the postsubiculum or retrosplenial cortex disrupted anterodorsal nucleus head direction cell tuning to visual landmark cues, suggesting that these cortical structures are important for the visual regulation of head direction cells activity in the anterior thalamus (Goodridge and Taube, 1997; Clark et al., 2010; Yoder et al., 2011b). The medial entorhinal cortex seems to be at the top of this hierarchical head direction system because, after lesion, the discharge characteristics of anterodorsal head direction cells were only mildly affected. Furthermore, entorhinal cortex lesions did not cause clear deficits in landmark processing or angular path integration (neural integration of head angular velocity signals) by anterodorsal head direction cells (Clark and Taube, 2011). Further evidence for the hierarchical organization of head direction cell circuitry comes from experiments in which lesions in "lower" structures, e.g., bilateral damage of the dorsal tegmental nucleus of Gudden or the lateral mammillary nucleus, abolished head direction cell activity in the anterodorsal thalamic nucleus (Blair et al., 1998, 1999; Bassett et al., 2007). In contrast to this general pattern of hierarchical organization, lesions in lateral dorsal thalamic nucleus had little effect on the firing properties of head direction cells in postsubiculum (Golob et al., 1998), whereas an intact anterodorsal thalamic nucleus is necessary for the presence of head direction cell activity in the postsubiculum (Goodridge and Taube, 1997).

Thalamic head direction cells are influenced by both external and internal sources of information (Taube, 2007; Yoder et al., 2011a). Although external cues exert strong influences on anterior thalamic head direction cells, these cells can maintain directional firing preferences in the dark and in new environments (Taube and Burton, 1995; Goodridge et al., 1998). This observation suggests that head direction cells are strongly influenced by internal sources of information, i.e., vestibular, proprioception, or motor efference. One implication is that the vestibular system may be particularly important for this aspect of spatial navigation (Potegal, 1982). This hypothesis was verified experimentally by (Stackman and Taube, 1997), who recorded from head direction cells in the anterodorsal thalamus before and after neurotoxic lesions that destroyed the hair cells in the vestibular labyrinth. As a result, head direction cells in the anterior thalamus lost their directional specificity. Moreover, in lesioned animals, a new subset of neurons, characterized by intermittent firing bursts without specified directionality, was observed. The appearance of a new subset of cells in lesioned animals that were not recorded in intact animals suggests that head direction cells may alter their physiology in the absence of indirect vestibular input, and that other sensory systems (e.g., visual, somatosensory/tactile or olfactory) are unable to compensate for the loss of vestibular information in order to retain direction. The absence of head direction cell activity in animals with vestibular lesions persisted for up to 3 months post-surgery, indicating that indirect vestibular inputs remain crucial for anterior thalamic head direction cell function (Clark and Taube, 2012). However, in the anterodorsal thalamic nucleus of transgenic otoconia deficient *tilted* mice, which exhibit an impaired sense of linear acceleration and head tilt, directionally tuned cells were recorded (Yoder and Taube, 2009). Nevertheless, the head direction cells recorded in *tilt* mice often appeared to be unstable. These cells retained directional information for the duration of a single recording session, but often lost directionality across subsequent recording sessions. These experiments (Yoder and Taube, 2009) provided the first conclusive evidence that the otolith organs are important for maintenance of a robust head direction signal.

One of the main questions that emerged after the discovery that the anterodorsal head direction signal is dependent on indirect vestibular inputs was: Are anterodorsal head direction cells activated in the same manner during active and passive movement? Initially, (Knierim et al., 1995) and Taube (1995) both reported substantial reductions in firing rates during passive rotation, producing near or complete suppression of the anterodorsal head direction response when the animal's body was tightly restrained except its head. Reductions in firing rates during passive rotation were also observed in the postsubiculum and retrosplenial cortex (Chen et al., 1994; Golob et al., 1998). In contrast to these observations, (Zugaro et al., 2001) found only mild inhibition of anterodorsal head direction cell firing, with peak firing rates reduced by only 27% and no loss of directional responding during unrestrained passive movement.

(Bassett et al., 2005) found only a 23% reduction in the peak firing rates of anterodorsal head direction cells when the animals were passively moved while loosely restrained. The above observations suggest that the tight restraint of the animal may, in itself, be a factor which decreases firing rate of anterodorsal head direction cells. However, in the studies by Knierim et al. (1995) and Taube (1995), the head of the animal was not fully immobilized while the trunk was tightly restrained. Therefore, Shinder and Taube (2011) prepared a rotatable, horizontal plane platform that was equipped with an immobilizing tube for the trunk and holder for the head. Before the recording session, the rat was immobilized and its head fixed to the platform by a bar connected to the restraint bolt, which had been previously mounted to the skull. Experiments revealed that passive movement during head-fixed restraint did not reduce anterodorsal head direction cell firing, relative to active movement (Shinder and Taube, 2011). Moreover, anterodorsal head direction cell responses were also maintained during passive movement in the dark, suggesting that visual, motor, and proprioceptive inputs are not necessary to generate direction-specific responses in head direction cells. This experiment further supports the hypothesis that indirect vestibular input is crucial for head direction cell activity in the anterodorsal thalamus.

Another cell type relevant for spatial navigation is the "place cell." Place cells discharge when an animal is in a particular location in the environment (O'Keefe and Dostrovsky, 1971). So far, "true" place cells have only been recorded in the hippocampus (Clark and Taube, 2012). However, the anterior thalamus, as part of the limbic system and head direction system, may contribute to the function of hippocampal place cells. Several theories have suggested that place cells use the signal from the head direction system to establish and maintain place-field activity (McNaughton et al., 1996; Touretzky and Redish, 1996; Sharp, 1999). Calton et al. (2003) reported that, after lesions of the anterodorsal thalamic nucleus, place cells continued to exhibit location specific activity, but the place fields were somewhat degraded and cells were more directionally-sensitive. These observations suggest that input from anterodorsal head direction cells may be important for processing and integrating spatial information within the hippocampal circuits containing place cells.

THETA RHYTHM IN THE ANTERIOR THALAMIC NUCLEI

The nuclei within Papez' pathway that mediate head direction signals are closely paralleled by those adjacent nuclei mediating theta rhythm (a sinusoidal oscillation of 6–12 Hz). Theta rhythm is considered to play a critical role in spatial and non-spatial mnemonic functions of the limbic system (Burgess et al., 2002; Buzsaki, 2005). Both circuits (HD vs. theta) include the tegmental nuclei of Gudden (dorsal vs. ventral), the mammillary bodies (lateral vs. medial), the ATN (anterodorsal vs. anteroventral) and the subicular/entorhinal cortices (Swanson and Cowan, 1977; Witter et al., 1990; Shibata, 1993b; Van Groen and Wyss, 1995; Gonzalo-Ruiz et al., 1997; Van Groen et al., 1999). Electrophysiological studies in rats support this idea, because plasticity between sequentially-activated hippocampal place cells occurs during theta epochs (Mehta et al., 2000; Ekstrom et al., 2001), implicating the theta cycle as an information quantum (Skaggs et al., 1996; Buzsaki, 2002). Theta rhythm commonly modulates the spike trains of spatially-tuned neurons such as hippocampal place cells (O'Keefe and Dostrovsky, 1971), entorhinal grid cells (Hafting et al., 2005), and border cells (Savelli et al., 2008; Solstad et al., 2008). These neurons, together with HD cells, are believed to participate in computing the animal's location in the environment by integrating its movement velocity over time, the process referred to as path integration (McNaughton et al., 1996; Etienne and Jeffery, 2004).

So far, the anterodorsal thalamic nucleus is the best-described thalamic nucleus with respect to the electrophysiological properties of its neurons in freely moving animals. A particular focus on this nucleus stems from the fact that it contains high numbers of head direction cells (Taube, 2007; Clark and Taube, 2012). Single-unit recordings in other ATN (anteroventral and anteromedial) in urethane-anesthetized rats reveal that some anteroventral neurons tend to fire in theta-rhythmic manner (Vertes et al., 2001). This observation was confirmed by single-unit recordings both in freely moving rats foraging for food pellets and during naturally occurring sleep (Tsanov et al., 2011b). An identified subgroup of anteroventral neurons was strongly entrained by theta oscillations and synchronized their bursting activity in theta range. Moreover, theta and spindle oscillations differed in their spatial distribution within the anteroventral nucleus, suggesting that separate cellular sources are responsible for these oscillations. Approximately 23% of anteroventral neurons were assigned to the slow- and fast-spiking bursting units that are selectively entrained to theta rhythm (Tsanov et al., 2011b). Importantly, Tsanov et al. (2011a) also reported large subpopulation of head direction cells (39%) in the anteroventral thalamic nucleus that exhibit rhythmic spiking in the theta range. This class of units is termed head direction-by-theta cells, which discharge predominantly in spike trains at theta frequency whenever the animal is heading/facing in the preferred direction (**Figure 4**). Neurons possessing both theta and head-directional properties have been described earlier at the higher level of this circuitry, namely the presubicular/parasubicular region (Cacucci et al., 2004; Boccara et al., 2010). Tsanov et al. (2011a) showed for the first time that the integration of head-directional and theta information takes place at the level of the anteroventral thalamic nucleus. It is likely that this integrated information is sent in an ascending projection within Papez' circuit and so contributes to the complex firing properties of the presubiculum and parasubiculum as well as other parts of the extended hippocampal formation. Moreover, it is possible that non-directional theta cells from anteroventral thalamic nucleus may contribute to the priming of retrosplenial cells, thus magnifying the influence of anterodorsal head direction cells on neurons in retrosplenial cortex (Albo et al., 2003). Directional information may also be particularly important for animals engaged in locomotor/exploratory behaviors (theta states) and less during non-locomotor activities (non-theta states). This notion is supported by work of Zugaro et al. (2001), who reported that anterodorsal head direction cells fire at significantly higher rates during active, compared to passive, motion of rats. However, Shinder and Taube (2011), using their platform for full immobilization of the rat, found that the firing of anterodorsal head direction cells does not differ between active

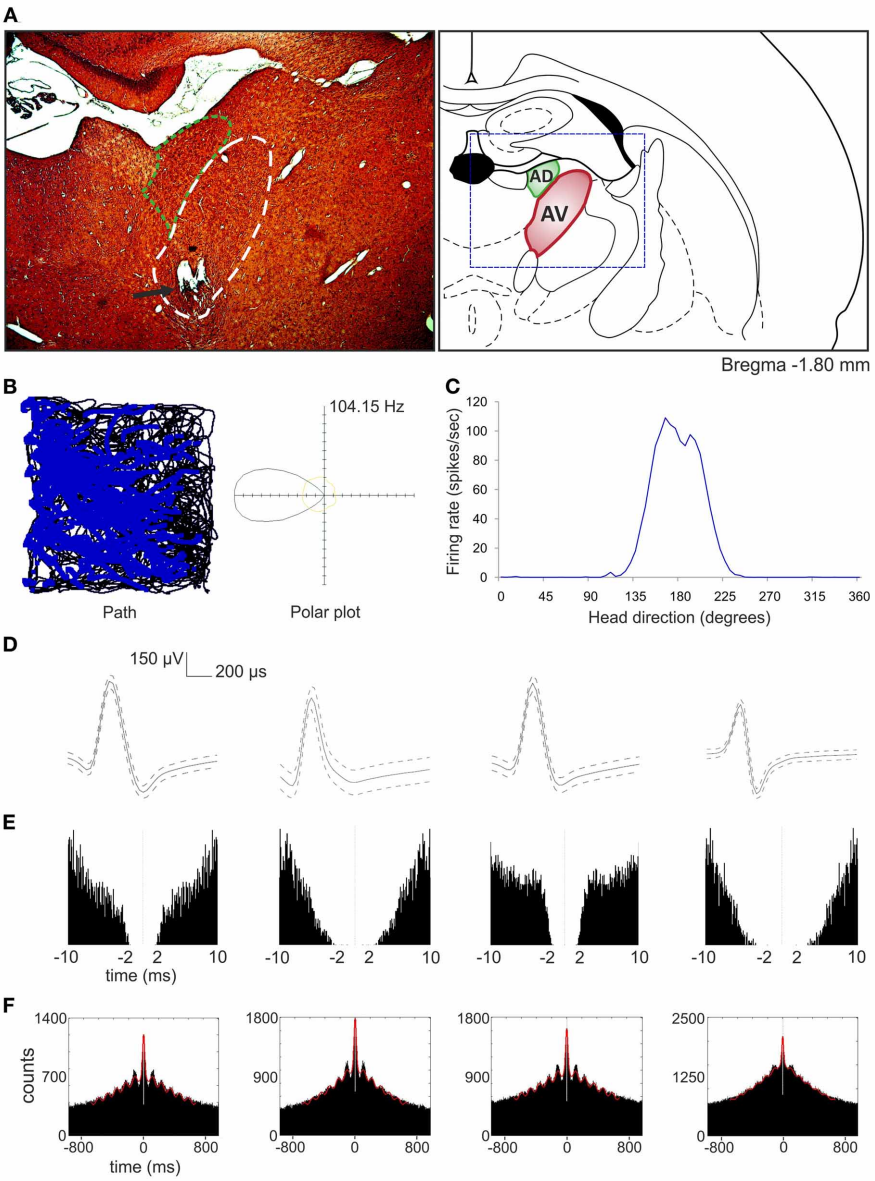

FIGURE 4 | Head direction-by-theta cells recorded in anteroventral thalamic nucleus (Tsanov et al., 2011a). (A) Anatomical location of chronically implanted tetrodes aimed at anteroventral nucleus (bundle of eight tetrodes). On the left, the histological slide showing the location of chronically implanted tetrodes marked with the black arrow. Area of anteroventral nucleus is indicated with white dashed line and anterodorsal nucleus with green dashed line. On the right, location of anteroventral and anterodorsal nuclei is shown on the modified section from the rat brain atlas (Paxinos and Watson, 1998). The dashed blue rectangle denotes the extent of the histological section on left. **(B)** On the left, the path of the animal (black line) with superimposed firing activity of head direction-by-theta unit (blue dots) recorded during 16-min session in a square arena (64 × 64 × 25 cm). On the right, the polar plot represents the distribution of time heading in different directions across all time bins of the trial (yellow) and the distribution of head directions for time bins when a spike was recorded from the cell (black). **(C)** The same signal can be plotted as firing rate vs. head direction tuning plot for head direction-by-theta units. **(D,E)** The spike waveform **(D)** and the autocorrelogram of spiking activity calculated for 10/10 ms **(E)** for four anteroventral head direction-by-theta units, respectively. For the spike waveform, the solid curve represents the mean, and the dashed curve represents the SD. The clear isolation of the neuronal extracellular response was identified by the absence of correlations within the first 2 ms of the refractory period. **(F)** The 1000 ms autocorrelograms of four head direction-by-theta units. The fitted vertical red line indicates the relative amplitude of the sinusoid component of the autocorrelogram, visualizing the degree of autocorrelogram rhythmicity.

and passive movement. The contradictions concerning the activity of HD cells in active vs. passive movement in fully vs. partially restrained animals still needs to be clarified. Available data suggest that HD cells from anterodorsal thalamic nucleus respond solely to the perceived head direction. However, the available data does not allow one to fully exclude the influence of other factors on HD cells activity such as theta oscillations or input information from other structures that may appear during active movement.

Clearly, the role of theta oscillations in the ATN on the function of head direction cells at all levels of the hierarchical head direction circuitry remains to be fully elucidated.

Vertes et al. (2001) initially reported that, in urethane-anesthetized rats, it was not possible to record theta modulated cells in the anteromedial and anterodorsal thalamic nuclei, as opposed to the anteroventral nucleus. However, in later experiments also performed in urethane-anesthetized rats, Albo et al. (2003) found theta-modulated cells in the anteromedial and anterodorsal thalamic nuclei. Our unpublished observations from recordings in freely-moving rats implanted with driveable microelectrodes confirm the presence of theta modulated cells in the anteromedial thalamic nucleus (see **Figure 5** for examples of recorded units). Moreover, in the ATN, (Welday et al., 2011) recorded theta-modulated cells with theta cell burst frequencies that varied as the cosine of the rat's movement direction, and this directional tuning was influenced by landmark cues.

NEUROPATHOLOGICAL CONSIDERATIONS

The importance of the ATN for memory was shown by Harding et al. (2000), who studied the post-mortem brains of Korsakoff's psychosis patients. This condition, which is typically seen in alcoholics, causes an amnesic syndrome characterized by persistent anterograde episodic memory loss, but with a relative preservation of semantic memory, intelligence, and procedural behavior. Harding et al. found that ATN atrophy was consistent with the amnesia in Korsakoff's patients, but was not found in other, closely-related alcoholic conditions (e.g., Wernicke's encephalopathy) that do not produce a persistent amnesia. Anterograde memory impairments (e.g., in delayed recall) were reported in twelve patients with infarcts involving the ATN (Ghika-Schmid and Bogousslavsky, 2000), while a review of thalamic stroke patients confirmed that damage involving the mammillothalamic tract was the best predictor of amnesia (Carlesimo et al., 2011).

Both lesion and stimulation studies have played a vital role in accruing knowledge about the function of certain brain structures. With regards to the ATN, the importance of these nuclei for spatial functioning and memory has been demonstrated in many experiments over the last two decades. One of the primary arguments for the functional significance of the hippocampus-diencephalic linkage is found in rodent studies, where discrete lesions in the hippocampus, mammillary bodies, fornix, and ATN all disrupt performance on spatial learning tests such as alternation, but with varied severity (Aggleton and Sahgal, 1993; Aggleton et al., 1995, 2010; Byatt and Dalrymple-Alford, 1996; Sziklas and Petrides, 1998; Vann and Aggleton, 2003). Deep-brain stimulation (DBS) of the ATN can also disturb spatial alternation performance by rats (Hamani et al., 2010). Moreover, lesions in the hippocampus, fornix, and ATN disrupt performance on tests of temporal order discrimination (Fortin et al., 2002; Charles et al., 2004; Wolff et al., 2006; Aggleton et al., 2010).

The functional importance of the ATN in some frequent neuropathological problems has been shown by applying DBS to these nuclei in epilepsy patients, a procedure of particular relevance for those who are not eligible for respective surgery (Hodaie et al., 2002). The world-wide prevalence of epilepsy is approximately 1% and approximately 30% of patients do not respond to current pharmaceutical interventions (Kwan and Brodie, 2000). Further clinical studies have shown significant reductions in event frequency (Lee et al., 2012) after DBS of ATN. Although the clinical study by Lee et al. also tested for effects on seizure types and for anticonvulsant actions, the low number of participants resulted in no significant results for these categories. The exact mechanism of the clinical benefit of DBS to the ATN is unclear, but it is more likely to concern a larger network effect involving several brain regions, rather than being simply a local effect within the ATN and hippocampal-diencephalic system. Evidence for this can be taken from the change in motor excitability seen in epileptic patients who received bilateral DBS in the ATN, while their TMS-evoked motor potentials were recorded (Molnar et al., 2006).

In the pilocarpine epilepsy rodent model, stimulation of the ATN reduced seizure activity (Fisher et al., 2010; Jou et al., 2013) and protected against status epilepticus (Hamani et al., 2004). In another rodent epilepsy model, where seizures were induced by electrical stimulation of the basolateral amygdala, low-frequency bilateral ATN stimulation significantly reduced the severity and incidence of seizures (Zhong et al., 2011). Application of bilateral high-frequency stimulation in rats to the ATN after amygdala-induced seizures (e.g., replicating clinical post treatment application) decreased the incidence and duration of subsequent seizures (Zhang et al., 2012a). Another study by the same group showed that unilateral high frequency stimulation of the ATN before amygdala-induced seizures inhibited the induced seizures, and was concluded to suppress susceptibility to seizures (Zhang et al., 2012b). However, Lado (2006) reported that the effects of DBS in acute chemoconvulsant model of seizures in rodent may differ from chronic epilepsy conditions. Lado used kainate-induced chronic seizures in rats and tested the effects of bilateral anterior thalamic DBS. In contrast to previously reported benefits, Lado (2006) showed a 2.5 times increase in seizure frequency, compared to their chronic baseline after DBS in the ATN. The author highlighted this difference in their results as important with regards to both the location of the epileptic focus, phenotype, neuronal injuries present, and the difference between species. Since then, several clinical studies have shown the benefits of applying DBS in the ATN in epileptic patients; the recent SANTE trial review (Stimulation of ATN for Epilepsy) concluded that bilateral stimulation of the ATN reduced seizures on average by more than 50% through two years of this study (Fisher et al., 2010).

SUMMARY

The ATN form a pivotal part of Papez' circuit, with widespread limbic connections forming an "extended hippocampal formation." Based on existing anatomical and electrophysiological data, we suggest there are, at least, three parallel hippocampal—anterior thalamic circuits (Aggleton et al., 2010). Studies of diencephalic amnesia reinforce the crucial role of the ATN for memory, although the ATN are also considered as important for the pathophysiology of epilepsy and serve as a possible target for DBS treatment in this condition (Aggleton et al., 2010; Fisher et al., 2010). The presence of slow- and fast-spiking bursting

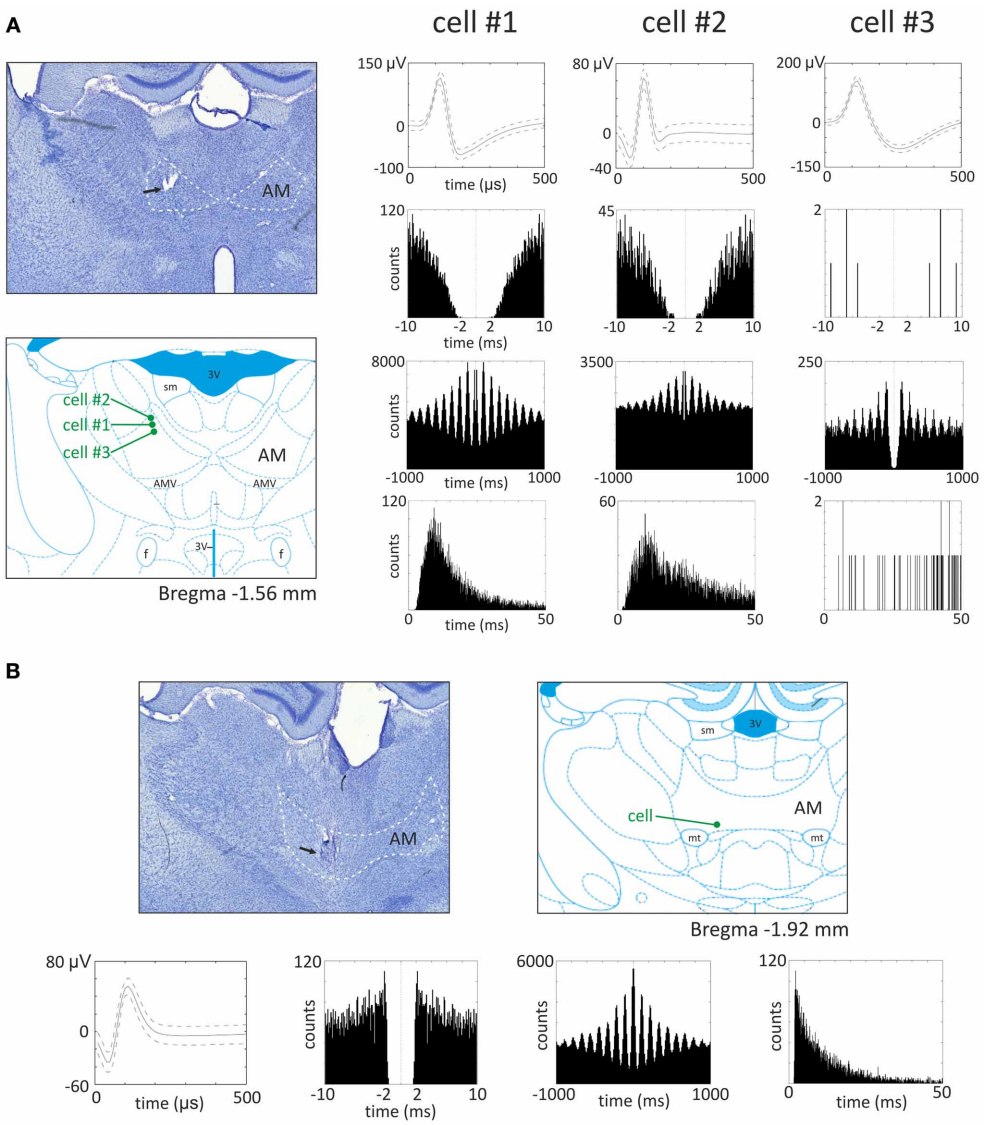

FIGURE 5 | Theta modulated cells from the anteromedial thalamic nucleus. (A) Recording sites and three examples of theta modulated cells recorded in the superficial part of anteromedial nucleus. On the left, the histological slide showing the location of chronically implanted tetrodes marked with the black arrow. In this case, three theta modulated cells were recorded in the superficial part of anteromedial nucleus. Estimated location of recorded cells is marked below by green dots on the section from rat brain atlas (Paxinos and Watson, 2006). On the right, parameters of three theta modulated cells recorded in this rat are presented. From the top for each cell, the waveform, autocorrelation for 10 ms, autocorrelation for 1000 ms and interspike interval histogram (ISIH) are presented. All three cells exhibit different firing rate and waveforms, but all are modulated in the theta rhythm frequency, which is visible as 6–10 peaks on 1000 ms autocorrelogram. The ISIH indicates that recorded cells were not bursting neurons (there is no peak of firing before 5 ms). **(B)** Recording site and example of theta modulated cell recorded in the bottom part of anteromedial nucleus. In the top, the histological slide shows the location of chronically implanted tetrodes, marked with the black arrow. In this case, a theta modulated cell was recorded in the bottom part of anteromedial nucleus (see also estimated position of the cell on the right). Below, the waveform, autocorrelation for 10 ms, autocorrelation for 1000 ms, and ISIH are presented. The 1000 ms autocorrelogram indicates that this cell was modulated in the frequency of theta rhythm and ISIH clearly shows that this cell is a bursting neuron. Recordings were performed in rats chronically implanted with driveable 32-channel microelectrodes organized in tetrodes. Each recording session lasted 20 min and was performed in freely moving rats foraging for food pellets in a circular arena (96 cm diameter). Abbreviations: AM, anteromedial thalamic nucleus; 3 V, third ventricle; AMV, anteromedial thalamic nucleus, ventral part; f, fornix; mt, mammillothalamic tract; sm, stria medullaris of the thalamus.

anterior thalamic units, which discharge within the theta frequency, suggest that the anterior thalamus is involved in the propagation of theta signals through Papez' pathway (Vertes et al., 2001; Tsanov et al., 2011b). Such theta propagation could have resulting mnemonic functions. The large populations of head direction cells recorded in the anterodorsal and anteroventral thalamic nuclei indicate that the anterior thalamus plays an important role in spatial navigation. Furthermore, the central

position of the anterodorsal and anteroventral thalamic nuclei in the hierarchically-organized head direction circuitry (Clark and Taube, 2012) and the apparent integration of theta and head direction information at the level of anteroventral thalamic nucleus (Tsanov et al., 2011a) underline the importance of this region for spatial orientation. Evidence to date suggests that the ATN serve as a subcortical gate for information used in path integration processes by cortical structures. A final point is that, by framing the contributions of the ATN within Papez' circuit, there is the strong implication that the functions of these nuclei are principally driven by the hippocampus. In fact, actions in the opposite direction may prove to be equally crucial. Just as the head direction system relies on inputs from "lower" sites within the tegmentum, i.e., inputs independent of the hippocampus, so there is reason to believe that other tegmental inputs (e.g., from the ventral tegmental nucleus of Gudden and from the lateral dorsal tegmental nucleus) will prove vital in understanding the broader role of these diencephalic nuclei in supporting memory (Vann, 2009). Consequently, these tegmental inputs may also prove to be of considerable importance for medial temporal lobe activity.

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ABL1 in thalamus is associated with safety but not fear learning

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In auditory fear conditioning a tone is paired with a footshock, establishing long lasting fear memory to the tone. In safety learning these stimuli are presented in an unpaired non-overlapping manner and enduring memories to the tone as a safety signal are formed. Although these paradigms utilize the same sensory stimuli different memories are formed leading to distinct behavioral outcome. In this study we aimed to explore whether fear conditioning and safety learning lead to different molecular changes in thalamic area that receives tone and shock inputs. Toward that end, we used antibody microarrays to detect changes in proteins levels in this brain region. The levels of ABL1, Bog, IL1B, and Tau proteins in thalamus were found to be lower in the group trained for safety learning compared to the fear conditioning group 6 h after training. The levels of these proteins were not different between safety learning and fear conditioning trained groups in auditory cortex. Western blot analysis revealed that the ABL1 protein level in thalamus is reduced specifically by safety learning but not fear conditioning when compared to naïve rats. These results show that safety learning leads to activation of auditory thalamus differently from fear conditioning and to a decrease in the level of ABL1 protein in this brain region. Reduction in ABL1 level in thalamus may affect neuronal processes, such as morphogenesis and synaptic efficacy shown to be intimately regulated by changes in this kinase level.

Keywords: safety learning, fear learning, thalamus, ABL1, memory

INTRODUCTION

Fear conditioning leads to long-term fear memory formation and is a model of psychopathologies conditions such as anxiety and post-traumatic stress disorders (e.g., LeDoux, 2000). On the other hand, in safety learning the subject learns the safety properties of a signal—a useful relief from a fearful situation and chronic stress (e.g., Rescorla, 1969). Although fear and safety learning can be formed by the same sensory stimuli different memories are created. We are therefore interested to unveil whether fear and safety learning paradigms activate different cellular processes during memory formation. Toward that end we aimed to identify molecular events initiated by fear conditioning or safety learning.

In fear conditioning a tone (conditioned stimulus; CS), is paired with a mild footshock (unconditioned stimulus; US) leading to long lasting fear memories, such that on subsequent occasions the CS comes to elicit behavioral, autonomic, and endocrine responses that are characteristically expressed in the presence of danger (Fanselow and LeDoux, 1999; LeDoux, 2000; Davis and Whalen, 2001; Sah et al., 2003; Maren, 2005). In safety learning the tone and shock are presented in an unpaired non overlapping manner and the tone is memorized as a safety signal that predicts the absence of the shock (Rogan et al., 2005; Pollak et al., 2008; Ostroff et al., 2010). Fear conditioning and safety learning elicit different cellular and molecular responses in lateral amygdala (LA) and Caudoputamen (CP) (Rogan et al., 2005; Pollak et al., 2008). Here we explored whether fear conditioning and safety learning lead to different molecular responses in the auditory thalamus which transfers information to both LA and CP during fear and safety learning (LeDoux, 2000; Rogan et al., 2005). Lesion to the auditory thalamus was shown to impair fear conditioning memory formation (LeDoux et al., 1986). Furthermore, fear conditioning induces frequency-specific receptive field plasticity in the medial geniculate body (Lennartz and Weinberger, 1992). In contrast, evidence show that the auditory thalamus is not involved in contextual fear conditioning. For example, pre-training intra-MGm (medial division of the medial geniculate body) thalamic infusion of the NMDA receptor antagonist (APV), which attenuates synaptic transmission in the thalamus, impaired the acquisition of auditory but not contextual fear conditioning (Webber et al., 1999; Maren et al., 2003). The auditory thalamus is also needed for safety learning. Lesion to the auditory thalamus post training impaired the ability to inhibit fear in the presence of the noise safety signal (Heldt and Falls, 2006) and changes in CS response after safety learning in LA and CP is consistent with modulation of CS information arriving via a direct thalamic projection from MGm/PIN (posterior intralaminar nucleus) (Rogan et al., 2005). Studies have shown that both tone and footshock arrive to the MGm, PIN, and SG (suprageniculate nucleus) area of the thalamus (Bordi and LeDoux, 1994). Convergence of auditory and footshock responses was also detected in these areas.

The aforementioned studies show that the auditory thalamus is needed for both fear conditioning and safety learning. The thalamus might serve as a passive sensory station not affected by different temporal activation of its neurons or be activated differently by fear and safety learning leading to alteration in cellular responses needed for the establishment of different memories. To explore this possibility we aimed in this study to identify changes in specific proteins levels in thalamus after fear conditioning and safety learning. Ample studies show a role for protein synthesis and degradation in synaptic plasticity and memory formation following different types of behavioral paradigms mediated by different brain regions (Davis and Squire, 1984; Steward and Schuman, 2003; Fioravante and Byrne, 2011; Gal-Ben-Ari et al., 2012). In auditory thalamus protein synthesis is needed for fear conditioning memory formation as injection of the protein synthesis inhibitor anisomycin into the thalamus 30 min before fear conditioning impaired long-term fear memory formation (Parsons et al., 2006). Moreover, intra MGm/PIN infusion of antisense ODN against EGR-1 90 min prior to fear conditioning impaired fear LTM (Overeem et al., 2010). Increasing CREB in MGm and PIN enhanced formation of an auditory conditioned fear memory (Han et al., 2008).

We utilized the antibody microarray and Western blot approaches to identify possible changes in proteins levels in thalamus between fear conditioning and safety learning.

MATERIALS AND METHODS

ANIMALS

Male Sprague Dawley rats (200–224 g) were used (Harlan Laboratories Jerusalem). Animals were housed individually in clear plastic cages and maintained at 22 ± 2°C in a 12 h light/dark cycle, with free access to food and water. Behavioral experiments were approved by the University of Haifa Institutional Committee for animal experiments in accordance with National Institutes of Health guidelines.

BEHAVIORAL PROCEDURES

Fear conditioning took place in a Plexiglas rodent conditioning chamber with a metal grid floor dimly illuminated by a single house light and enclosed within a sound attenuating chamber. Rats were habituated to the training chamber for 3 days (17 min/day) before training. Rats for the summation test were not habituated. The next day the rats were trained for fear conditioning and presented with five pairings of a tone (CS; 20 s, 5 kHz, 75 dB) that co-terminated with a footshock (US; 0.5 s, 1.3 mA). The inter-trial interval is random with average of 120 s. Safety learning took place in the same conditioning chamber. Rats received non-overlapping five presentations of the CS and US where the US preceded the CS by 60 s and at least 120 s was required between a tone CS and the next trial. Naïve group were introduced to the training cage with no CS or US. For the retardation test, rats were given two tone shock pairings (0.4 mA, 1-s shock, ITI = 180 s) one day after safety learning training.

Groups were tested in a different chamber with dark Plexiglas walls and Formica floor. In the summation test rats were tested in the same context where they were conditioned. Fear and safety responses were quantified by measuring the amount of time spent freezing during five CS presentations (20 s, 5 kHz, 75 dB) with average ITI of 180 s. The video images of rats during testing were transferred to a computer (Dell OptiPlex GXpro) equipped with an analysis program (Image) and a macroprogram (P. Schmid, Behavioral Neurobiology Laboratory, Swiss Federal Institute of Technology Zurich). The percentage of changed pixels between two adjacent 1 s images was calculated and if the percentage of change in images was <0.05%, the behavior of the rat was scored as "freezing" for the respective later second. In microarray experiments we tested a group of animals for fear conditioning or safety memory 24 h after training to verify that fear or safety learning occurred. This group was trained with the other animals that their tissue was processed for microarray. For Western blots analysis we tested all rats 6 h after training. Animals with percent freezing criterion of above 60% for Paired, below 45% for Unpaired and below 10% for Naïve groups were further sacrificed for Western blot analysis. Animals that did not reach criteria were removed from the experiments.

TISSUE DISSECTION

Six hours after training the brains were quickly frozen on dry ice and kept at −80°C until use. The brains were sliced at the thickness of 40 μm using Leica CM1900 cryostat until the thalamic area containing the PIL/MGm, was visualized. The brain area was micropunched from frozen brains with blunted 2 mm diameter sample corer (Fine science tools, CA, USA). For the microarray: tissue from fear conditioning trained animals ($n = 11$) or from safety learning trained group ($n = 11$) was combined to reach the protein level needed for the assay. For Western blots analysis: two thalamic regions from each rat were combined for analysis. Few slides were collected on Super/Plus Microscope Slides (Fisher Scientific, USA) for histology of dissection. All samples were stored at −80°C until further use.

HISTOLOGY

Brain slices were stained with methylene blue and punched areas were verified using Olympus IX81 microscope (×1.25 magnification). Brains with incorrect dissection areas were removed from the experiments.

ANTIBODY MICROARRAY

To identify changes in proteins level in thalamus between fear conditioning and safety learning we utilized the Clontech antibody array that consists over 500 individual antibodies spotted in duplicates. The protocol used was as recommended by the manufacturer. The brain tissue was rapidly transferred to a prechilled mortar containing Alumina, and immediately homogenized in iced cold homogenization buffer (Extraction/Labeling Buffer). Homogenate was centrifuged for 30 min at 10,000 g. Protein concentration was measured using Pierce's BCA Protein assay Reagent Kit. Cy3 and Cy5 were dissolved in 110 μl of Extraction/Labeling Buffer. The homogenate supernatants and Cy3 and Cy5 were mixed in four tubes as follows: A-Paired supernatant and Cy5; B-Unpaired supernatant and Cy3; C-Paired supernatant and Cy3; D-Unpaired supernatant and Cy5. The four tubes were incubated covered with foil for 90 min on ice. Four

microliters of blocking buffer was added followed by incubation for 30 min on ice. Unbound dye was removed by PD-10 desalting columns equilibrated with 3 × 5 ml of 1× Desalting Buffer. Protein samples were eluted and protein concentration was measured using Pierce's BCA. One hundred μg of proteins from samples were mixed as follows: Tubes A and B to mix 1 and tubes C and D to mix 2. Twenty μg of mix 1 was added to microarray 1 and 20 μg of mix 2 to microarray 2. Each slide was incubated with the samples in incubation chamber for 40 min at room temperature (RT), followed by washing procedure as described in details in Clontech protocol.

DATA ANALYSIS

Data analysis was done as instructed by supplier. The slides were scanned using Axon GenePix 4000B scanner. The sequence text files were analyzed with Clontech software to produce the scatter plots and correlation values. Subsequently the scanner files were analyzed with an AB Microarray Analyzing Workbook supplied by manufacturer to calculate internally normalized ratios (INR) using the conversion of fluorescence data to INRs for each coordinate in the array. The replicated values within each slide were averaged and INR was calculated as follows INR = $\sqrt{}$Ratio1/Ratio2 where ratios 1 and 2 correspond to slide 1 and 2. Ratio 1 = Paired-Cy5/Unpaired-Cy3. Ratio 2 = Unpaired-Cy5/Paired-Cy3. The average INR is calculated for each antibody. Values that are ≥1.3 or ≤0.77 × averaged INR indicate valid changes that signify differences in protein abundance.

WESTERN BLOT

Thalamus tissue was homogenized, in glass homogenizer using Teflon pestle in 300 μl homogenization buffer [(in mM: HEPES 10, EDTA 2, EGTA 2, DTT 0.5, 1% phosphatase inhibitor cocktail (Sigma), and 1% protease inhibitor cocktail (Sigma)].

After centrifugation at 10,000 g for 5 min at 4°C, 50 μl of lysates were kept for protein quantification and 200 μl of lysates were transferred to 1.5 ml eppendorf tubes containing 2× SDS-sample buffer, boiled for 5 min and stored at −80°C. Protein content of lysates was determined using the Bradford protein assay (Biorad). Proteins (total 10 μg for each sample) were separated by 7.5% SDS-PAGE and transferred to PVDF membrane (Millipore, immobilon-p 0.2 μm). Blots were incubated in blocking buffer [(in 5% non-fat dry milk or 3% BSA (depending on primary antibodies as recommended) in Tris buffered saline containing 1% Tween-20 (TBST)] for 1 h at RT, washed 3 × 10 min in TBST and incubated with primary antibodies to detect ABL1 (1:3000; over night in 4°C; BD Biosciences 554148), Bog (1:1000; over night in 4°C; Transduction laboratories B12520), Tau (over night in 4°C; BD Biosciences; 556319) or β-Tubulin (1:30000 for 1 h at RT; Sigma, T2200) in blocking buffer on rotating mixer. The blots were washed twice with TBST and incubated with either anti-mouse (1:2000 in 5% NFM), or anti-rabbit (1:10000 in TBST) secondary antibodies for 1 h at RT. After additional three washes in TBST, proteins were visualized using Ez-ECL Kit (Biological industries, 20-500-120).

QUANTIFICATION

The labeled protein bands in immunoblots were detected using a gel documentation apparatus (XRS; Bio-rad) and analyzed using the Quantity one (4.5.0.) software. Background was subtracted from measured band. The levels of ABL1, Bog, and Tau were calculated as the ratio between the signals from the proteins and the signal from the antibody directed against Tubulin. In order to enable a comparison between the three groups, we normalized the signals by dividing the protein (ABL1, bog, or Tau)/tubulin signal obtained above in each individual rat taken from the paired, unpaired or naïve groups by the average respective protein (ABL1, bog, or Tau)/tubulin value of the naïve group (the baseline value).

STATISTICAL ANALYSIS

Analysis of behavioral data between two groups was done by independent Student's *t*-test. In Western blot experiment significance between groups was assessed by one-way ANOVA for the three groups (paired, unpaired, and naïve) followed by *post-hoc* LSD test.

RESULTS

PAIRED CS-US TRAINING LEADS TO FEAR CONDITIONING WHEREAS UNPAIRED PRESENTATION OF CS AND US TO SAFETY LEARNING

We trained the animals with the fear conditioning or safety learning protocols (**Figure 1A**) and tested their response to the CS 24 h after training (these groups were trained together with the animals that were sacrificed for the microarray experiments). As shown in **Figure 1B** animals that were trained with paired stimulation ($n = 8$) froze significantly more ($p < 0.01$) during the tone when compared to the unpaired trained rat group ($n = 7$) showing that paired training leads to fear memory of the tone. We then used two standard tests, summation and retardation of acquisition, to establish that the unpaired trained animals memorized the tone as a safety signal. The summation test demonstrates that the tone can suppress freezing induced by the context which serves as the fearful stimulus (Rescorla, 1971; Williams et al., 1992). In summation test (Rescorla, 1971), animals were given safety training (unpairing of tone and shock) and 1 day later were returned to the shock context and freezing was assessed during ITIs and tone presentations. The animals showed significant suppression of context freezing during the tones when compared to their freezing during ITI ($p < 0.05$; **Figure 1C**). To rule out attentional or excitatory effects of the tone CS, we performed the retardation test (Rescorla, 1971). In the retardation paradigm rats were first trained for safety learning (unpaired presentation of US and CS) whereas control animals were not. Both groups were trained a day later for fear conditioning. When tested the next day, rats that were trained for safety learning showed less freezing to the tone than did control rats ($p < 0.03$; **Figure 1D**). Thus, in safety learning the tone acquires safety properties and excites fear less readily when subsequently paired with shock.

PROTEINS LEVELS IN THALAMUS DIFFER BETWEEN FEAR CONDITIONING AND SAFETY LEARNING TRAINED RATS

We were interested to screen changes in the level of proteins in auditory thalamus following fear conditioning or safety learning training. Toward that end we dissected thalamic areas that

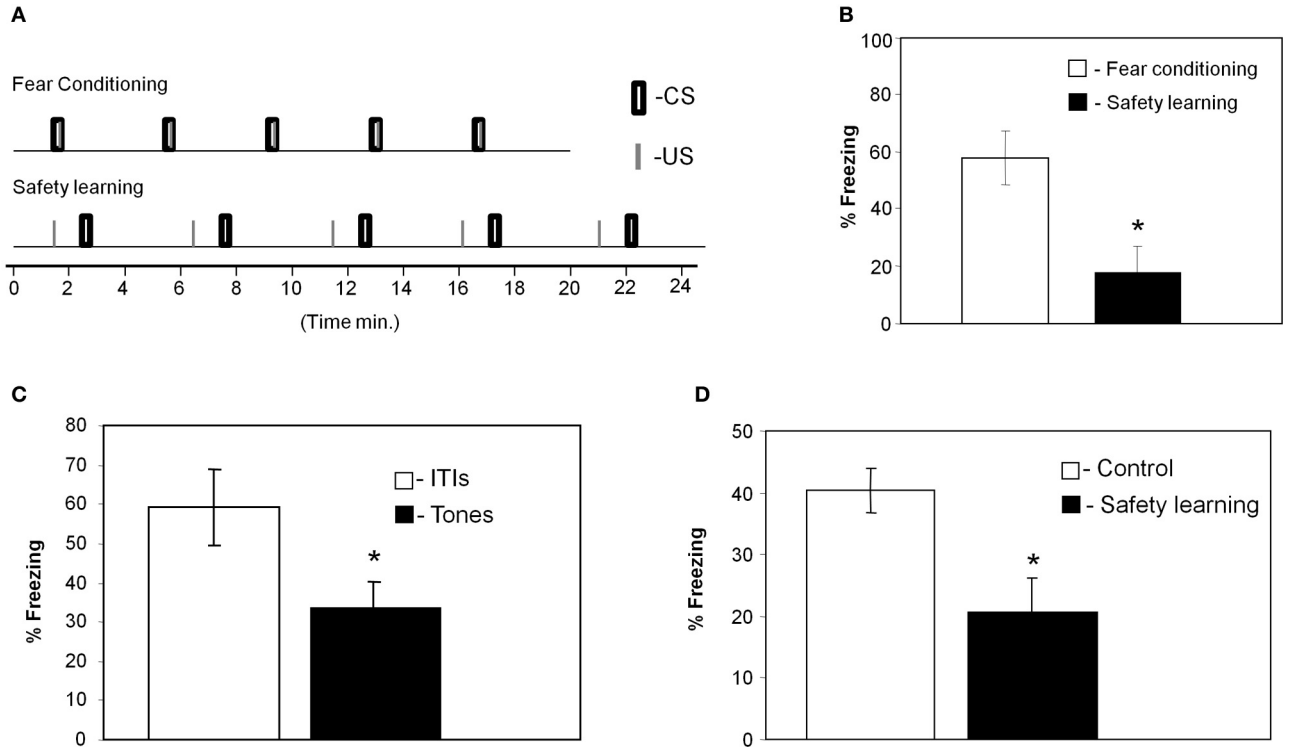
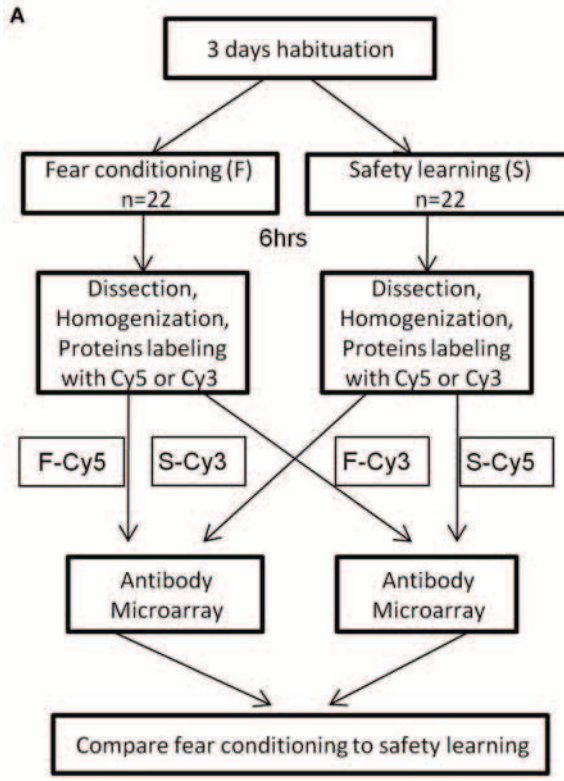


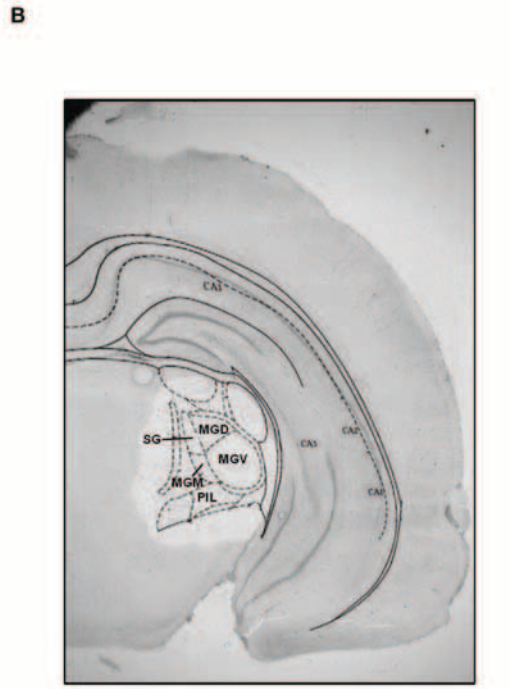
FIGURE 1 | Paired presentation of tone and shock leads to fear conditioning whereas unpaired presentation to safety learning. **(A)** Training protocols for fear conditioning and safety learning indicating the exact timing of tones and footshocks presentations. **(B)** Rats that received paired presentation of tone and shock froze significantly more during test tones when compared to animals that received unpaired presentation ($^*p < 0.01$) when tested 24 h after training indicating that they were fear conditioned to the tone CS. **(C)** In summation test animals that received tone and shock presentation in an unpaired manner froze significantly more during the ITIs than during the tone presentations when tested 24 h later in the same context where they were trained ($^*p < 0.05$; $n = 10$). This result indicates that the animals that received unpaired presentation of tone and footshock learned that the CS is safe and predicts the absent of the shock. **(D)** In the retardation test animals were first trained with unpaired CS and US whereas control rats were not. The next day both groups were trained with fear conditioning protocol. Animals were tested a day later for freezing during tones presentation. Unpaired rats froze less than controls ($^*p < 0.03$) showing that the tone acquires safety properties and excites fear less readily ($n = 11$ for safety group, $n = 12$ for control group).

receive auditory and shock stimuli (e.g., Bordi and LeDoux, 1994) 6 h after training (**Figures 2A**,**B**). Molecular changes (e.g., gene expression) occur after fear conditioning around this time point (Lamprecht et al., 2009). The proteins were extracted and subjected to antibody microarray for analysis. Proteins level was compared between fear conditioning ($n = 22$) and safety learning ($n = 22$) trained rats ($n = 11$ pooled in each group in two separate experiments). Analysis of microarray revealed reproducibility between duplicate spots containing the same antibody. ABL1, Bog, IL1B, and Tau proteins were the only proteins that their level was changed in all experiments. The INR of proteins was above the cutoff indicating that their level in the unpaired group is lower compared to the paired group (**Figure 2C**). The level of these proteins was not different in these animals in the auditory cortex (**Figure 2C**).

ABL1 LEVEL IN AUDITORY THALAMUS IS REDUCED FOLLOWING SAFETY LEARNING

We performed an experiment to monitor the level of Bog, Tau, and ABL1 in thalamus using the Western blot technique. The aims of this experiment were twofold. First, to verify the results detected in the microarray experiment and second to reveal whether the level of these proteins is reduced following safety learning or increased after fear conditioning. Toward that end we introduced an additional naïve group to monitor the basal level of the proteins in thalamus. The level of ABL1, Bog, and Tau was normalized to tubulin. Rats were scarified 6 h after fear conditioning, safety learning or naive training and brain area that includes the auditory thalamus was dissected (as in **Figure 2B**). Protein homogenate of each rat was monitored to detect the levels of ABL1, Bog, and Tau. As shown in **Figure 3** the level of ABL1 protein was significantly reduced in safety learning group ($n = 20$) [$F_{(2)} = 4.195$, $p < 0.03$] when compared with fear conditioning ($p < 0.009$; $n = 19$) or naïve group ($p < 0.04$; $n = 23$). The level of ABL1 in paired group was not different from its level in the naïve group ($p = 0.507$). The level of Bog and Tau showed similar trend in differences in protein levels as these observed in the microarray experiment [lower in unpaired (Tau $= 0.9 \pm 0.08$; Bog $= 0.86 \pm 0.07$) compared to naïve (Tau $= 1 \pm 0.06$; Bog $= 1 \pm 0.07$) and paired (Tau $= 0.96 \pm 0.08$; Bog $= 0.98 \pm 0.08$); $n = 21$; $n = 23$; $n = 19$ respectively] but these differences are smaller than these observed with ABL and are not significant





C

Thalamus

Protein	Experiment 1 INR>1.62 INR<0.95	Experiment 2 INR>1.86 INR<1.10
ABL-1	1.93	2.24
Bog	1.81	1.92
IL1B	2.08	2.12
Tau-5	1.76	2.88

Auditory Cortex

Protein	Experiment 1 INR>1.98 INR<1.17	Experiment 2 INR>1.42 INR<0.84
ABL-1	1.73	1.27
Bog	1.8	0.96
IL1B	1.88	1.11
Tau-5	1.24	0.98

FIGURE 2 | Proteins levels in thalamus are lower in unpaired compared to paired trained rats. (A) Rats were trained for fear conditioning [*F*; paired CS-US presentation ($n = 22$)] or safety learning [S; unpaired CS-US presentation ($n = 22$)]. Six hours after training the thalamus area, that includes the auditory and noniceptive areas was dissected, proteins were extracted, labeled, and subjected to antibody microarray. Differences between the level of specific proteins in the fear conditioning and safety learning groups were evaluated. **(B)** Representative brain section showing dissection of thalamus. **(C)** The levels of ABL1, Bog, IL1B, and Tau proteins in thalamus were found to be lower in the group trained for safety learning compared to the fear conditioning group 6 h after training. INR cut off indicates the upper and lower INR levels in which protein differences between fear conditioning and safety learning are taken into consideration. The levels of these proteins were not altered in auditory cortex. MGD, medial geniculate nucleus-dorsal; MGM, medial geniculate nucleus-medial; MGV, medial geniculate nucleus-ventral; PIL, post intralaminar thalamic nucleus; SG, Supragenicuiate thalamic nucleus.

[Tau $= F_{(2)} = 0.39, p = 0.6$; Bog $= F_{(2)} = 1, p = 0.37$]. The disparity in the Bog and Tau results between the microarray and Western blot studies could plausibly derive from the different methods used in the collection of the tissue and protein measurements. In the microarray experiments tissues from all animals were pooled to achieve the protein concentration needed, whereas in the Western blot the protein level was measured in individual rats: the latter methodology is necessary for quantification but it may introduce noise. We performed an additional experiment to explore whether the changes in ABL1 protein level occur in additional thalamic nuclei. We dissected a thalamic area more frontal and medial than the auditory thalamus that includes the

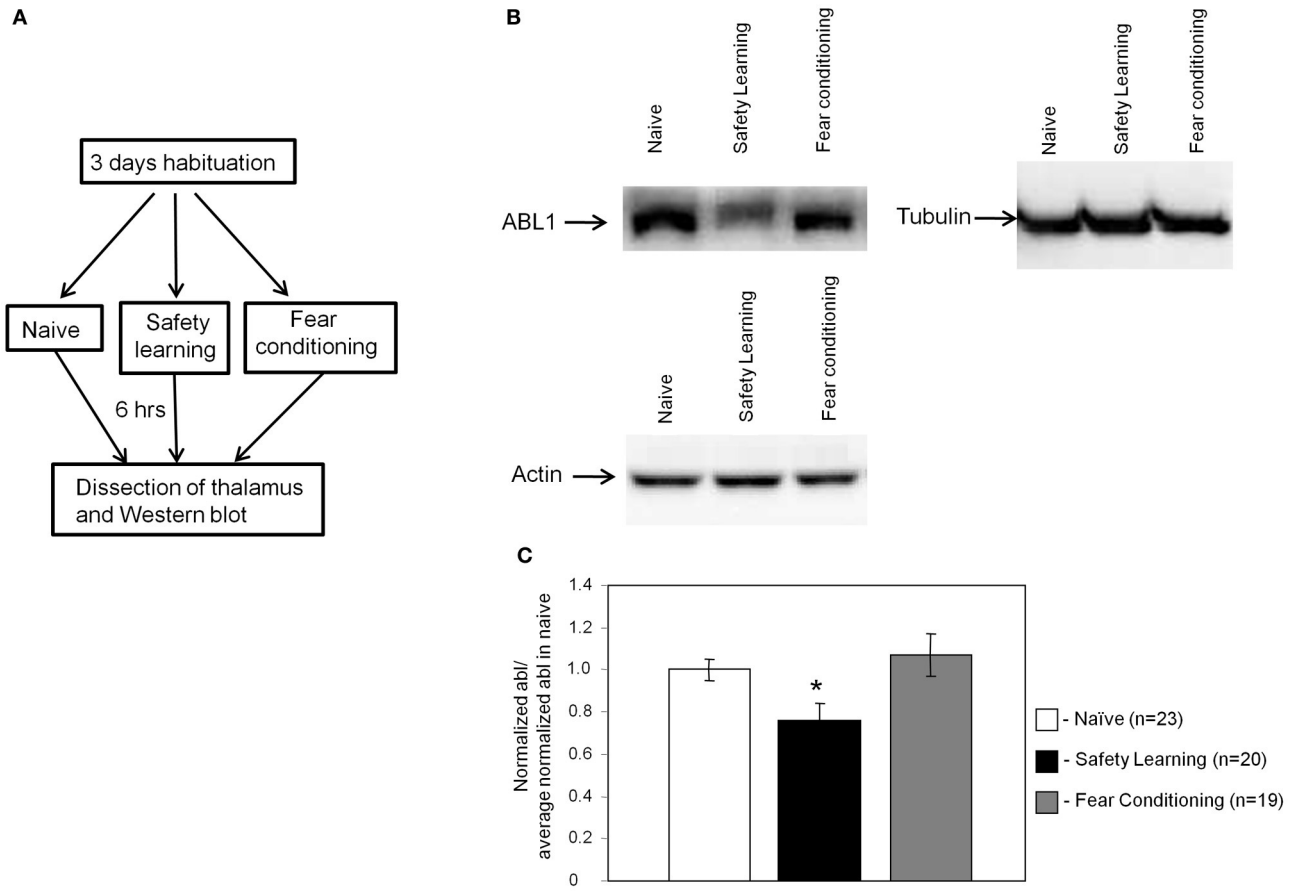


FIGURE 3 | ABL1 level in auditory thalamus is reduced following safety learning. (A) Animals were trained for fear conditioning ($n = 19$), safety learning ($n = 20$) or left naïve [exposed to conditioning chamber only ($n = 23$)]. Six hours after training the thalamus was dissected, proteins were extracted and subjected to Western blot analysis with the anti-ABL1 or the control anti-tubulin or anti-actin as primary antibodies. **(B)** Representative Western blots of ABL1, tubulin and actin in various animal groups. **(C)** The ratio of normalized ABL1 of various experimental groups to the averaged normalized ABL1 in naïve is shown. ABL1 protein level is lower in safety learning trained group [$F_{(2)} = 4.195$, $^*p < 0.03$] when compared to the fear conditioning ($p < 0.009$) or naïve ($p < 0.04$) groups. The level of ABL1 in fear conditioning group was not different from its level in the naïve group ($p = 0.507$).

ventral parts of the thalamus at the area of the ventrolateral and ventromedial thalamic nuclei and ventral posteromedial and posterolateral thalamic nuclei. There are no significant changes in the level of ABL1 between the paired, unpaired and naïve groups [$F_{(2)} = 0.006$, $p = 0.99$; $n = 4$ each]. Taken together the aforementioned results show that safety learning, but not fear conditioning, lead to reduction in the level of ABL1 in thalamus and that the thalamus is differentially activated by safety learning.

DISCUSSION

Paired tone-shock presentation leads to fear memory of the tone (Fanselow and LeDoux, 1999; LeDoux, 2000; Davis and Whalen, 2001; Sah et al., 2003; Maren, 2005) whereas unpaired training leads to safety learning where the rats remember the CS as a safety signal that predicts the absent of the shock (Rogan et al., 2005; Pollak et al., 2008; Ostroff et al., 2010). In this study we find that safety learning, but not fear conditioning, leads to reduction of ABL1 protein level in a thalamic region that includes areas that process the tone and shock information. Furthermore, ABL1 level was not different in auditory cortex between safety or fear learning. Thus, safety learning differentially activates the thalamus leading to modulation of ABL1 protein level in this brain area.

Studies have shown that the auditory thalamus is needed for safety learning. For example, rats were given feature-negative discrimination training in which a noise was conditioned to inhibit fear to a light that signals danger. Following training, rats were given lesions at the auditory thalamus and after recovery were tested for fear inhibition in the presence of the noise safety signal. Lesions of auditory thalamus impaired the ability of the noise inhibitor to inhibit fear indicating the need of the thalamus for detecting the safety properties of the auditory stimulus (Heldt and Falls, 2006).

The auditory thalamus transfers the auditory information to the amygdala. Safety learning in mice induces long-lasting depression of CS-evoked activity in the LA, consistent with

fear reduction (Rogan et al., 2005) whereas fear conditioning induces increase in CS-evoked responses in LA (Quirk et al., 1995; McKernan and Shinnick-Gallagher, 1997; Repa et al., 2004). Another study reported a decrease in amygdala response to an auditory CS− (unpaired with US) after discriminative CS+ (paired with US) training in the cat (Collins and Paré, 2000). The safety signal-driven inhibition of amygdala could mediate a shutdown of some aspects of amygdala function during the safety CS. It was shown that direct thalamic projection from MGm/PIN mediates the decreased CS-evoked activity in the LA after safety learning (Rogan et al., 2005).

What could be the implications of reduction in ABL1 protein following safety learning on cellular processes mediating memory formation? Abl is a tyrosine kinase that affects key neuronal function by regulating downstream effectors such as cytoskeletal proteins (Lanier and Gertler, 2000). Abl is localized in both the presynaptic terminals and dendritic spines in the hippocampus (Moresco et al., 2003). Within the presynaptic terminal, Abl localization is restricted to the active zone. In spines, Abl localization is prominent at the PSD. It was shown that chemical or genetic inhibition of c-Abl kinase activity reduces PSD-95 tyrosine phosphorylation, leading to reduced PSD-95 clustering and synapse number in treated cultured hippocampal neurons (de Arce et al., 2010). In addition, inhibition of c-abl activity reduced GluR1 cluster density in neurons (Lanier and Gertler, 2000). Furthermore, abl may have an effect on dendritic structure. Inhibition of Abl kinases in hippocampal culture leads to simplification of dendritic branching (Jones et al., 2004) and significant reduction in neurite branching and cortical neurons (Woodring et al., 2002). Such altered functions following reduction in abl activity may have a direct influence on synaptic efficacy in neurons. Abl protein may affect also presynapse functions. In $abl^{-/-}$ mice Paired-pulse facilitation (PPF), a transient form of presynaptic plasticity, is reduced in hippocampal slices suggesting that abl is required for optimal neurotransmitter release (Moresco et al., 2003). Basal synaptic transmission, posttetanic potentiation (PTP), long-term potentiation (LTP), and long-term depression (LTD) were similar between wild-type and $abl^{-/-}$ mice and in STI571-treated wild-type slices. These results indicate an important function of Abl in synaptic efficacy via a presynaptic mechanism during repetitive activation. Thus, since ABL1 may be involved in alterations in synaptic efficacy reduced ABL1 level after safety learning could contribute to changes in synaptic responses to the tone in thalamus and as a consequence alterations in activation of LA by the thalamus (Rogan et al., 2005).

What could be the mechanisms of rapid ABL1 protein level reduction observed after safety learning? Three mechanisms are suggested: (1) Ubiquitination dependent degradation: it was shown that activated c-abl is degraded by the ubiquitin-dependent proteasome pathway (Echarri and Pendergast, 2001); (2) Rapid increase in microRNA leading to reduction in ABL1 RNA and protein levels. Indeed, microRNA that reduces ABL1 levels, miR-203, was detected (Bueno et al., 2008). Moreover, microRNA can be induced rapidly after stimulation leading to synaptic plasticity (Park and Tang, 2009); (3) Repression of ABL1 gene expression.

The study shows that training leading to safety learning induces specific molecular changes different from fear conditioning in thalamic areas processing the tone and shock stimuli. Although both fear conditioning and safety learning utilize the same stimuli they may use different cellular mechanisms to form long-term memory. This observation is consistent with studies showing differential activation of gene expression (Pollak et al., 2008) and formation of spine morphology (Ostroff et al., 2010) in LA following safety and fear learning. Thus, memory formation of different sort may not engage identical cellular mechanism even if formed following the same sensory stimuli and in the same area. The temporal differences in presentation of the stimuli during safety or fear learning influence molecular activation following learning and may affect neurons differently to form distinct memories.

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What does the mediodorsal thalamus do?

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Dense amnesia can result from damage to the medial diencephalon in humans and in animals. In humans this damage is diffuse and can include the mediodorsal nuclei of the thalamus. In animal models, lesion studies have confirmed the mediodorsal thalamus (MD) has a role in memory and other cognitive tasks, although the extent of deficits is mixed. Anatomical tracing studies confirm at least three different subgroupings of the MD: medial, central, and lateral, each differentially interconnected to the prefrontal cortex (PFC). Moreover, these subgroupings of the MD also receive differing inputs from other brain structures, including the basal ganglia thus the MD subgroupings form key nodes in interconnected frontal-striatal-thalamic neural circuits, integrating critical information within the PFC. We will provide a review of data collected from non-human primates and rodents after selective brain injury to the whole of the MD as well as these subgroupings to highlight the extent of deficits in various cognitive tasks. This research highlights the neural basis of memory and cognitive deficits associated with the subgroupings of the MD and their interconnected neural networks. The evidence shows that the MD plays a critical role in many varied cognitive processes. In addition, the MD is actively processing information and integrating it across these neural circuits for successful cognition. Having established that the MD is critical for memory and cognition, further research is required to understand how the MD specifically influences these cognitive processing carried out by the brain.

Keywords: prefrontal cortex, memory, executive function, macaque, rodent, animal models, learning

INTRODUCTION

It is now more widely recognized that the episodic memory processes disrupted in anterograde amnesia involve interactions between the medial temporal lobes and the medial diencephalon (Aggleton and Brown, 1999). However, understanding how the medial thalamus contributes to memory and other cognitive functions has been much overlooked in cognitive neuroscience and neuropsychology. This mainly stems from the theoretical notion held over the past 50 years that the medial temporal lobes act exclusively as the brain's long-term declarative memory center. Despite this prevailing account, human patients can also suffer dense amnesia following damage in the medial diencephalon (diencephalic amnesia, thalamic amnesia). Brain damage that causes memory loss and other cognitive deficits in this region occurs after traumatic head injury, stroke, hemorrhage, thiamine deficiency, or chronic alcoholism (Korsakoff's syndrome). However, this brain damage is not circumscribed in clinical patients as many of the structures of the medial diencephalon (medial thalamus, mammillary bodies, and mammillothalamic tract) suffer combined damage due to their small size, close proximity to one another and fibers of passage coursing through the region. The medial thalamic structures most frequently identified as being critical for the memory deficits are anterior (AT), mediodorsal (MD), and the intralaminar (IL)/midline thalamic nuclei. The mammillary bodies and white matter fiber tracts, particularly the internal medullary lamina and the mammillothalamic tract, are also strongly implicated in human amnesic cases and animal models. Thus, the neural basis of the memory deficits associated with the medial diencephalon continues to be debated in the literature (Harding et al., 2000; Kopelman, 2002; Van der Werf et al., 2003a; Cipolotti et al., 2008; Aggleton et al., 2011; Carlesimo et al., 2011; Pergola et al., 2012; Vann, 2013).

Animal models of diencephalic amnesia are critical in helping to determine the structures that are important for memory and other cognitive processes as well as understanding the neural circuitry of this region. The emphasis of this review is on the experiments in animal models (monkeys and rodents mainly) that assess the role of the MD in memory and other cognitive processes. The review will show how this research can extend our understanding about the functions of the MD that when damaged cause some of the symptoms of the human amnesic syndrome. There is also a section on anatomy of the MD and its interconnections with other brain structures: detailing the communication within these regions is critical for understanding their overall functioning. It is important to remember that lesion studies do not show what the area of the brain that has been lesioned does, rather they show how the rest of the brain functions and compensates after brain injury to a particular region has occurred. Furthermore, we know that a single region of the brain does not act alone. Thus, the brain structures of the medial thalamus are interconnected with other brain structures, together forming integrated neural networks of cognition. The review concludes with an overview of some of the theories of MD involvement in

cognition and memory, current perspectives and possible future directions to investigate.

It is an exciting time to be studying the medial thalamus and its role in cognitive processing as the work of many is challenging the long held beliefs that the thalamus is only passively relaying information from the basal ganglia, midbrain and brainstem onto the prefrontal cortex (PFC). For example, more recent neuroanatomical and neuromodulatory studies highlight how the thalamus is providing a critical role in integrating communication between the basal ganglia, thalamus, and cortex, which is challenging many long standing theoretical ideas related to the passive role of the thalamus (Haber and McFarland, 2001; Guillery and Sherman, 2002; Sanchez-Gonzalez et al., 2005; Sherman and Guillery, 2005, 2011; Sherman, 2007; Haber and Calzavara, 2009).

In addition, with advances in neuroimaging and its analyses, and different electrophysiology techniques that can help investigate functional and anatomical connectivity, the medial thalamus and specifically the MD has now been shown to influence many cognitive processes including memory, decision-making, and executive functions with comparative data across numerous species. The MD is also a critical structure linked to many neurological disorders (e.g., stroke, dementia, schizophrenia, major depressive disorder, Parkinson's disease, and Alzheimer's disease). Clearly, further research is needed on the MD to develop greater understanding of the neural mechanisms of its functioning and how it contributes to many neurological disorders.

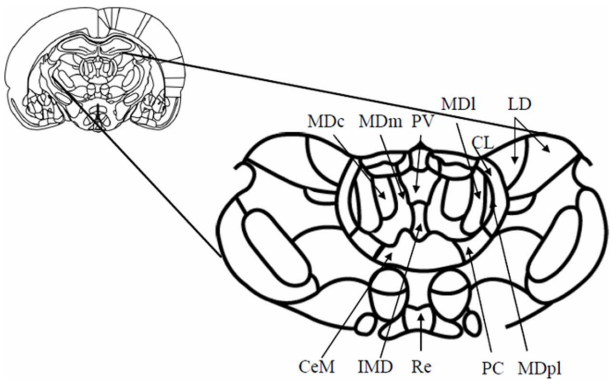

FIGURE 1 | Schematic diagram (and enlargement) of the medial aspects (Bregma −2.56 mm) of the medial thalamus in the rodent brain. Abbreviations: CeM, center median nucleus, part of the midline nuclei; CL, centrolateral nucleus, part of the intralaminar nuclei; IMD, intermediodorsal nucleus, part of the midline nuclei; LD, laterodorsal nucleus; MDc, central subdivision of mediodorsal thalamus; MDl, lateral subdivision of mediodorsal thalamus; MDm, medial subdivision of mediodorsal thalamus; MDpl, paralamellar subdivision of the mediodorsal thalamus; PC, paracentral nucleus, part of the intralaminar nuclei; PV, paraventricular nucleus, part of the midline nuclei; Re, reuniens. Adapted from Paxinos and Watson (1998).

ANATOMY OF THE MD

Many of the structures in the brain can go by several names and this is the case with the MD, which is also referred to as medial dorsal thalamic nuclei, nucleus medialis dorsalis, and the dorsomedial thalamus. For the purposes of this review, the structure will be referred to as the mediodorsal thalamus (MD) and at some points will be distinguished by some of its subdivisions, that is, the magnocellular mediodorsal thalamus (MDmc) or medial MD, the parvocellular mediodorsal thalamus (MDpc) or central MD, and a lateral grouping that will include the densocellular (MDdc) and pars multiforms (MDmf) mediodorsal thalamic nuclei or lateral MD (MDl).

CYTOARCHITECTURE

The MD is considered the largest of the nuclear structures in the medial thalamus, and it is most developed in primates, especially humans. The increase in the size of the MD in phylogenetic evolution parallels that of prefrontal, association and cingulate cortices (Bentivoglio et al., 1993; Jones, 1998). In rats, the MD is relatively heterogeneous with four main subdivisions identified (see **Figure 1**). These are the medial, central, lateral, and paralamellar segments (Krettek and Price, 1977; Groenewegen, 1988). The boundaries of each segment are somewhat well defined, especially between the central and lateral segments. The dendrites of the cells in each of these two segments tend to be confined to their respective regions and the lateral segment stains more heavily for acetylcholinesterase (Price, 1995). In primates, the four subdivisions are more easily recognizable (see **Figure 2**): a magnocellular subdivision (MDmc) occupies the most medial and rostral part of the MD and is considered equivalent to the medial segment in rats. The parvocellular (MDpc) subdivision is located within the central part of MD throughout the rostrocaudal extent. The other two subdivisions, densocellular (MDdc) and pars multiforms (MDmf) are located in the lateral part of MD with the MDmf situated in the rostral part and MDdc situated in the caudal part of the MD (Jones, 1985; Bentivoglio et al., 1993; Bachevalier et al., 1997).

NEURAL CONNECTIONS OF THE MEDIODORSAL THALAMUS

Prefrontal cortex afferents and efferents

In rodents and non-human primates, there are substantial reciprocal interconnections between the PFC and the MD (Krettek and Price, 1977; Goldman-Rakic and Porrino, 1985; Groenewegen, 1988; Ray and Price, 1993; McFarland and Haber, 2002; Xiao et al., 2009). Higher order thalamic structures, like the MD (and the pulvinar) receive inputs from different cortical layers. The majority of projection neurons to the MD originate from layer VI and V (Giguere and Goldman-Rakic, 1988; Yeterian and Pandya, 1994; Xiao et al., 2009); mainly from within the deep regions of these layers. The cortical layer V pyramidal neurons also have branches of long descending axons going to motor centers (Guillery, 1995; Guillery and Sherman, 2002). Guillery also proposed that these higher order thalamic nuclei play a key role in cortico-cortical communication and higher cortical functioning (Guillery, 1995). Thalamic neurons innervated by cortical layer VI project focally to the middle cortical layers and thalamic neurons innervated by cortical layer V project widely to the superficial cortical layers which are involved in cortico-cortical communications (Jones, 1985; Xiao et al., 2009). In addition, there are non-reciprocal components to the thalamo-cortical links, indicating a dual role for the MD in integrating basal ganglia outputs within specific cortical circuits (see below) (McFarland and Haber,

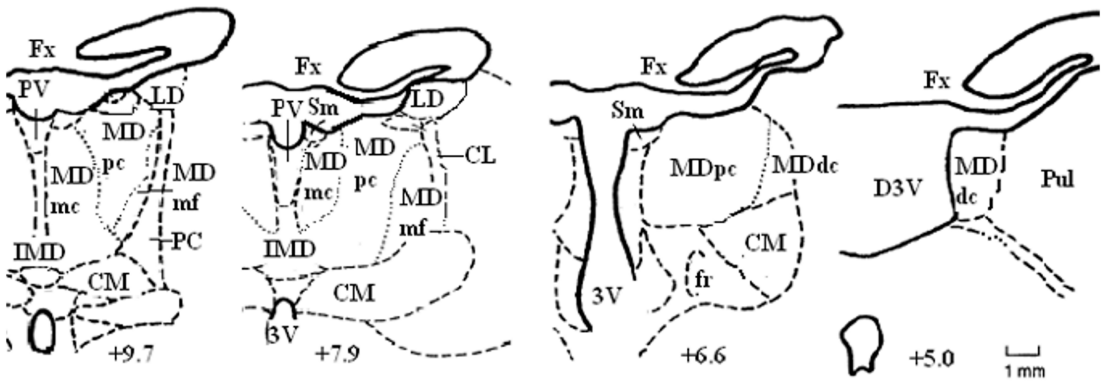

FIGURE 2 | Schematic diagrams of some of the coronal sections located approximately lA+9.7, +7.9, +6.6, and +5.0 through the rostrocaudal extent of the medial thalamus in the non-human primate brain. Abbreviations: CM, centromedian nucleus; Fx, fornix; Pul, pulvinar; Sm, stria medullaris. Adapted from the atlas of Olszewski (1952).

2002; Haber and Calzavara, 2009), as well as mediating information flow between cortico-cortical structures via this transthalamic route (Guillery and Sherman, 2002; Sherman, 2005, 2007; Sherman and Guillery, 2005). Glutamate is the main neurotransmitter of communication between thalamus and cortex (Sherman, 2013).

The major outputs of the MD are to the medial and lateral prefrontal and orbital frontal (OFC) cortices, and in some neuroanatomical tracing studies in rats, the medial PFC is said to be defined by the projections received from the MD nucleus (Groenewegen, 1988; Negyessy et al., 1998). Thus, these interconnections between the MD and PFC are segregated based on the subdivisions within the MD (see **Figures 3A–C**). The MDmc-PFC projections are almost exclusively reciprocal between the MDmc and the OFC and ventromedial PFC (vmPFC: areas 14, 25, 11, 13, and 12) but there is also a nonreciprocal input from ventrolateral PFC (VLPFC: area 45) and medial PFC (dACC: area 32 from the ventral and caudal aspects) (Preuss and Goldman-Rakic, 1987; Russchen et al., 1987; Barbas et al., 1991; Bachevalier et al., 1997; McFarland and Haber, 2002). Some of the midline nuclei [e.g., the intermediodorsal (IMD) and the paraventricular (PV) nucleus in rodents, see **Figure 1**] are also reciprocally connected to the OFC (Groenewegen, 1988). Thus, the MDmc and these midline nuclei have been regarded as a neuroanatomically functioning unit in rodents (Mitchell and Dalrymple-Alford, 2005). The MDpc has reciprocal connections with the dorsolateral PFC (DLPFC; areas 9 and 46) and area 10. There is also non-reciprocal inputs to MDpc from OFC (area 12, 13), VLPFC and the dACC (supracallosal area 24 and from the dorsal and rostral aspects of precallosal area 32 and 14) (Preuss and Goldman-Rakic, 1987; Russchen et al., 1987; Barbas et al., 1991; Bachevalier et al., 1997; Haber and McFarland, 2001; Erickson and Lewis, 2004). The most lateral parts of the MD that are combined with the ILn diffusely project to the PFC and dACC (supracallosal area 24) and exclusively to the frontal eye fields (FEF); the most prominent projection however is the topographically organized input to the basal ganglia (Preuss and Goldman-Rakic, 1987; Barbas et al., 1991; Bachevalier et al., 1997; Erickson and Lewis, 2004; Erickson et al., 2004).

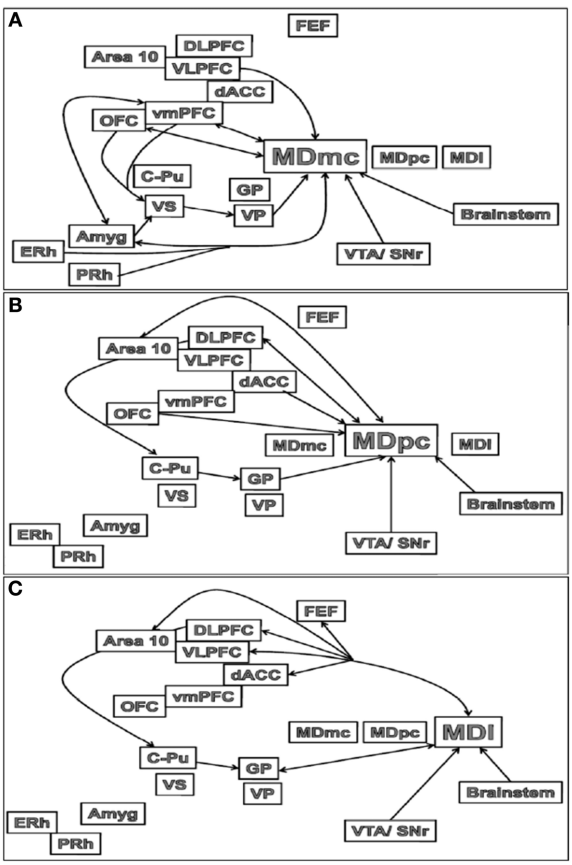

FIGURE 3 | Schematic illustrations of the main connections of the (A) MDmc, (B) MDpc and (C) MDl in the brain. Abbreviations are provided in the text.

Medial temporal lobes (MTL) afferents and efferents

In non-human primates there are connections from the association cortex of the temporal lobes [i.e., the entorhinal (ERh) and perirhinal (PRh) cortices] to the MDmc (see **Figure 3A**) and

midline thalamic nuclei (Aggleton et al., 1986; Russchen et al., 1987; Saunders et al., 2005). These mainly course through the ventroamygdalofugal pathway and the inferior thalamic peduncle. In the rodent brain, it appears that only the rostral portion of area 35 of the perirhinal cortex projects to the MD (Burwell et al., 1995).

There are also amygdala (Amyg) projections to the MD (see **Figure 3A**). The central nucleus and basolateral nuclei project densely to the MDmc in monkeys and medial segment of MD in non-primates (Aggleton and Mishkin, 1984; Groenewegen et al., 1990; Krettek and Price, 1977). These projections from the amygdala to the medial MD are much sparser than the amygdala projections to the striatum and PFC (Jones, 1985). Krettek and Price (1977) reported that the fibers from the caudal part of amygdala terminate rostrally in medial MD and those from the rostral part terminate more caudally and ventrally in the medial MD. In turn, it has been documented in rodents that medial parts of MD project back to the basal grouping and anterior cortical nuclei of the amygdala, while the midline nuclei project to the central nucleus and the rostral part of the basolateral nucleus of the amygdala (Groenewegen et al., 1990).

In contrast, the central MDpc and more lateral parts of the MD (see **Figures 3B,C**) do not directly interact with the MTL and amygdala.

SUBCORTICAL AFFERENTS AND EFFERENTS

Some of the thalamic projections to the PFC represent in many instances the final link in fronto-striatal-thalamic circuits (Alexander et al., 1986; Groenewegen et al., 1990, 1999a; Haber and McFarland, 2001; Haber and Calzavara, 2009; Haber and Knutson, 2010). There are no neuroanatomical tracing studies that document direct projections from the caudate-putamen (C-Pu) to the medial thalamus in rats or in primates. Instead the C-Pu projects to the output structures of the pallidum via either direct or indirect pathways and then onto the medial and ventral thalamus. The direct pathway comprises of striatal projections to the internal segment of the globus pallidus (GP) and the reticular part of the substantia nigra (SNr: located in the midbrain) then to the thalamus. The indirect pathway comprises of striatal projections to the external segment of the GP, then to the subthalamic nucleus (STN), which in turn project to the internal segment of the GP and the SNr, and then to the thalamus[1] (Haber et al., 1985; Groenewegen et al., 1990, 1993, 1997, 1999a,b; Tekin and Cummings, 2002; Haber and Calzavara, 2009). The internal segment of the GP projects predominantly to MDpc and MDl, while the ventral pallidum (VP) projects densely to MDmc. The most lateral subdivisions of the MD and many midline nuclei project to the basal ganglia (Berendse and Groenewegen, 1990; Groenewegen et al., 1990, 1999a; Gimenez-Amaya et al., 1995; Haber and McFarland, 2001; Haber and Calzavara, 2009).

From the brainstem in the rat, the locus coeruleus projects to all segments of the MD (Groenewegen, 1988). The median raphe projects most heavily to the MDl, whereas the dorsal raphe is strongly connected with the MDmc (Groenewegen, 1988).

The MDpc and MDl receive non-dopaminergic projections from the ventral tegmental area (VTA) and SNr (Groenewegen et al., 1990). The MDmc also receive projections from the VTA and SNr, but these projections are dopaminergic (Groenewegen, 1988). In addition, the reticular formation projects to all segments of the MD (Groenewegen, 1988).

A significant amount of thalamic neuromodulatory input is also received from the basal forebrain. Amongst many studies it is reported that the largest amount of basal forebrain inputs reaching the medial thalamus terminate in the reticular nucleus, with moderate terminal fields in the MDmc and sparse terminals in other sites (Hallanger et al., 1987; Groenewegen, 1988). These basal forebrain projections to the MD are predominantly GABAergic, while brainstem projections provide cholinergic inputs (Hallanger et al., 1987). For example, in cats, only 7–20% of basal forebrain neurons projecting to the MD are cholinergic (Bentivoglio et al., 1993).

Based on these differences in cortical-subcortical connectivity patterns among the MD, PFC, MTL, and basal ganglia, at least three separate MD thalamic neural circuits can be identified: a medial subdivision, including some of the midline nuclei and the MDmc, reciprocally connected to the OFC and vmPFC with further inputs from the VLPFC, rhinal cortex, amygdala, VS, and VP (Mitchell and Dalrymple-Alford, 2005); a central subdivision, the MDpc, reciprocally connected to the DLPFC and area 10 with further inputs from the OFC, dACC, dorsal striatum, and GP; and a lateral subdivision (Mitchell and Dalrymple-Alford, 2005; Lopez et al., 2009) including the intralaminar nuclei that is also interconnected to the dorsal striatum, GP and more diffusely to the PFC and FEF.

ANIMAL LESION STUDIES

Studying memory and cognition with animal models is extremely insightful, in addition to being a useful way to overcome some of the limitations that are inherent in the clinical evidence. There are many advantages to developing animal models of memory processing. Surgical lesions in animals can normally be somewhat more circumscribed and involve subtotal, complete or even contra-lateral neuronal damage to connected structures. These planned lesions, if produced with a high degree of selectivity to the target structures of interest, can encourage a greater certainty about identifying the critical locus and also the particular kinds of memory deficits than are evident in comparative human cases.

[1] In the direct pathway, the neurotransmitter GABA is activated, which inhibits pallidal and nigral neurons and consequently disinhibits the thalamus and midbrain targets. In the traditional model, it is proposed that this pathway facilitates thalamocortical activity and behavioral and motor outputs. The cells express mainly dopamine D1 receptors in the direct pathway. In the indirect pathway, the neurotransmitters GABA and glutamate are activated. The GABA inhibits the pallidal neurons, which leads to less inhibition at the subthalamic level where glutamate has stronger activity levels as a result. The glutamate then influences GABA in the output neurons of the internal segment of globus pallidus and pars reticulata of the SN, which results in stronger inhibition of the thalamic and midbrain targets. It is proposed this indirect pathway then exerts an inhibitory influence on the thalamus and midbrain, equating to suppression of behavioral and motor outputs. The cells express mainly dopamine D2 receptors in the indirect pathway. These two hypotheses on the direct and indirect pathway modulation are particularly relevant to theories of motor output problems associated with Parkinson's and Huntingdon's diseases. Tekin and Cummings (2002).

In addition, direct comparisons are possible between control and lesion animals, within pre- vs. post-operative testing or between subtotal lesions to one structure vs. another nearby structure.

Despite the benefits of experimental thalamic lesions, animal studies have, like the clinical evidence, also encountered difficulties and produced conflicting findings. This has resulted from the use of different techniques to create lesions in the MD, differences in the size and location of these lesions, and the extent of atrophy to surrounding target structures due to the inherent complexity of the medial and "non-specific" regions of the thalamus. Fortunately, the extent of brain damage in the medial thalamus has been minimized more recently by using neurotoxins that produce selective lesions to the individual structures that make up the medial diencephalon in animals. Thus, recent studies in rodents and non-human primates with very selective lesions to the mediodorsal thalamus using neurotoxins have been most insightful (Chudasama et al., 2001; Corbit et al., 2003; Mitchell and Dalrymple-Alford, 2005; Gibb et al., 2006; Mitchell et al., 2007a,b, 2008; Mitchell and Gaffan, 2008; Ostlund and Balleine, 2008; Pickens, 2008; Wolff et al., 2008; Lopez et al., 2009; Cross et al., 2012; Moreau et al., 2013).

Standardization of memory tasks and testing procedures for animals has also met with difficulties. Interpreting findings across studies and species can be problematic. Nevertheless, it is widely accepted that some cognitive tests provide adequate measures of animal memory that are analogous to human episodic recall tasks (Aggleton and Pearce, 2001). In addition, over the past few years, memory research has linked the work done in rats with the work of humans and non-human primates to a greater extent (Aggleton and Brown, 1999; Aggleton et al., 2000; Aggleton and Pearce, 2001; Morris, 2001; Uylings et al., 2003).

EXPERIMENTAL MEDIODORSAL THALAMUS LESIONS

Earlier work in animals focused on determining the one critical structure within the medial thalamus that was causing the memory deficits associated with thalamic amnesia. As mentioned, there are many candidates within the medial thalamus to fulfill this critical role. Neuropathological evidence reported in clinical cases of Wernicke-Korsakoff's syndrome supported a role for the MD in memory (Victor et al., 1971; Kopelman, 1995). However, Wernicke-Korsakoff's patients invariably suffer extensive neural damage due to the widespread effects of alcohol in the brain (Kril and Halliday, 1999), thus less equivocal evidence can only be obtained from experimental lesion studies involving circumscribed damage conducted in animal models. **Table 1** details what we believe to be the extent of the experiments that have investigated cognitive and memory impairments after MD lesions over the past 40 years in rodents and monkeys collected using searches on pubmed involving mediodorsal, medial dorsal, dorsomedial, dorsalis medialis, and thalam*. Some of these studies and their conclusions are discussed below.

Non-human primates

Monkey studies have demonstrated that aspiration lesions to the MD (i.e., typically including the magnocellular and the parvocellular subdivisions and other medial thalamic structures as well as potential fibers of passage passing through this region) cause impairments in recognition memory, deficits in new learning of object-in-place (OIP) discriminations and object-reward associations. These lesions also produce impaired performance in the spatial delayed alternation task and delayed response task but not in object reversal (associative memory task) and visual pattern discrimination (Isseroff et al., 1982; Aggleton and Mishkin, 1983a,b; Zola-Morgan and Squire, 1985; Gaffan and Murray, 1990; Gaffan and Watkins, 1991; Parker et al., 1997; Gaffan and Parker, 2000). Other studies have also highlighted how interactions between interconnected structures of the amygdala, vmPFC and MD are important for postoperative new learning of two-choice visual discriminations associated with differing amounts of food reward (Gaffan et al., 1993). Despite this extensive range of deficits linked to damage in the MD, it did not appear that MD lesions by themselves were the critical source of dense amnesia linked to cases of thalamic and diencephalic amnesia suffered in patients. For example, Parker et al. (1997) found that bilateral ablations to MDmc did not produce recognition memory deficits as severe as those reported after bilateral perirhinal cortex ablations, and the animals were also not as markedly impaired as amnesic patients with recognition memory deficits (Aggleton and Shaw, 1996).

Parker and Gaffan (1998) proposed that ablation of the MDmc in primates produces hypoactivity in the PFC and, therefore, the deficits in cognitive testing after MD lesions might be ascribed to frontal dysfunction. Given the extent of dense reciprocal connections between the MD and PFC, it makes sense to propose that damage to the MD may result in dysfunction within the PFC and that this disruption causes deficits in cognition and memory (Isseroff et al., 1982). The PFC is associated with higher order cognitive functioning, often labeled "executive functioning" in humans. It has been suggested that lesions to the MD could disrupt pathways leading to the PFC and may affect processes that are typically governed by the PFC, including attention, inhibition, planning, coordination, and strategy selection, which could then produce memory impairments on tasks (Gaffan and Parker, 2000). Certainly all of the above tasks that produce deficits after MD lesions are also sensitive to damage in the PFC (Fuster, 2008; Chudasama, 2011).

More recently, selective neurotoxic lesions to the MDmc have confirmed the importance of this medial subdivision in new learning of OIP discriminations and in a reward satiety devaluation task, as neurotoxic lesions of the MDmc produce impaired performance on these tasks (Mitchell et al., 2007a,b, 2008; Izquierdo and Murray, 2010). However, the same selective lesions to MDmc do not impair the retention of pre-operatively acquired information (Mitchell et al., 2007a; Mitchell and Gaffan, 2008). One such task that assesses retention of pre-operative information is the strategy implementation task (Gaffan et al., 2002). In this task, animals learn a specific strategy for responding to objects presented on a touchscreen in order to receive reward. Pre-operative performance for individual animals is compared with post-operative performance. Animals with crossed unilateral lesions that disconnect the whole of PFC in one hemisphere from inferotemporal cortex in the contralateral hemisphere (PFC × IT) cause impairments on this task (Gaffan et al., 2002) as do bilateral ablations to the VLPFC (Baxter et al., 2009). However, damage to

Table 1 | Summary of studies involving MD thalamic lesions assessing performance in an array of memory tasks over the past 40 years.

References	Lesion/Species/Type	Behavioral tasks	Training	Delay	Deficits reported
Moreau et al., 2013	Lateral MD + ILn rats: NMDA	Spatial water maze Visual water maze	Post-op		No No
Cross et al., 2012	MD rats: NMDA	Single item recognition Spatial location Object-in-place Recency memory	Post-op	5 m, 3 h 5 m, 3 h 5 m, 3 h 3 h	No No Yes Yes
Izquierdo and Murray, 2010	MDmc +Amyg + OFC macaques: NMDA	Reward devaluation	Post-op		Yes, neural circuitry important for reward based decision making
Chauveau et al., 2009	MD mice: ibotenic	Contextual serial discrimin Retention with stress variable	Post-op	24 h	With no stress MD only mildly impaired, with stress condition MD substantially impaired
Dolleman-van der Weel et al., 2009	MD rats: NMDA	Morris water maze	Post-op		Transient deficit only Some impairments with strategy shifting
Lopez et al., 2009		Morris water maze	Post-op		No acquisition deficits, impaired in remote (25d) but not recent (5d) retrieval of correct quadrant
Mitchell et al., 2008	MDmc + Fx macaques: NMDA/ibotenic + ablation	300 OIP discriminations 100 OIP discriminations	Pre-op Post-op		Yes Yes, combined lesions produced substantial new learning impairments
Mitchell and Gaffan, 2008	MDmc macaques: NMDA/Ibotenic	300 OIP discriminations 100 OIP discriminations	Pre-op Post-op		No Yes, new learning impairments
Ostlund and Balleine, 2008	MD rats: NMDA	Instrumental conditioning	Pre-op		Yes, disrupted influence of Pavlovian cues over action selection, no impact on selection of actions based on expected value
Pickens, 2008	MD rats: NMDA	Pavlovian devaluation Operant devaluation One vs. multiple reinforcers	Post-op Post-op		Impaired when switching from Pavlovian to operant contingencies but not when switching from one reinforcer to multiple reinforcer conditions
Wolff et al., 2008	Lateral MD + ILn Rats: NMDA	Allocentric spatial water maze Egocentric spatial Y water maze	Post-op		No No
Block et al., 2007	MD rats:	Task set shifting T-maze			No, only impaired on new learning of strategies
Mitchell et al., 2007a	MDmc macaques: NMDA/ibotenic	Strategy implementation OIP association	Pre-op Pre-op		No Yes, new objects-in-place post-op
Mitchell et al., 2007b	MDmc macaques: NMDA/ibotenic	Reward devaluation	Post-op		Yes

(Continued)

Table 1 | Continued

References	Lesion/Species/Type	Behavioral tasks	Training	Delay	Deficits reported
Gibb et al., 2006	Lateral MD + ILn Rats: NMDA	Odor-place associations Odor discriminations Place discriminations	Post-op		Yes No No
Mitchell and Dalrymple-Alford, 2006	Lateral MD + ILn rats: NMDA	Egocentric responding X-maze 8 arm radial maze	Pre-op Post-op		Impaired at matching body turn after delay No
Chauveau et al., 2005	MD mice: ibotenic	Sequential alt Go/ No-go temporal alt	Post-op	5–30 s 0–30 s	Only impaired when delays mixed (30-5) Impaired
Mitchell and Dalrymple-Alford, 2005	Medial MD; lateral MD + ILn rats: NMDA	Radial maze Go/No-go devaluation Single item (SOR) Recency memory (TOM)	Post-op Post-op Post-op Post-op	2 h	No Yes, MDmc No Yes, MDmc and MDpc+ILn
Ridley et al., 2005	MD + IT marmosets: NMDA + ablation	Spatiovisual conditioning Visuospatial conditioning retention and learning	Pre-op Post-op		Unilateral MD not impaired in retention. Combined crossed lesions caused mild impairments
Corbit et al., 2003	MD rats: NMDA	Instrumental conditioning Devaluation extinction tests	Post-op		MD acquired conditioning then deficits in selective devaluation effect during extinction
Ridley et al., 2002	MD+AT marmosets: NMDA	Visuospatial conditional task Visuovisual conditional Concurrent discriminations	Pre-op Post-op		Combined MD+AT impaired in retention but separate MD or AT lesions were not No No
Alexinsky, 2001	MD rats: ibotenic, excision	3/8 baited radial maze New Route—Pre-exp- Y/N Contextual light change	Pre-op		MD = less correct visits only; Pre-exposure –Y = MD deficits; MD adapted
Chudasama et al., 2001	MD rats: NMDA	Visual discriminations and reversals with touch-screen	Pre-op Post-op		MD = impaired at reversal of all three visual discriminations
Gaffan and Parker, 2000	MDmc macaques: aspiration	Visual scene memory Object-reward associations	Pre-op Pre-op		Yes Retention = No New Post-op Learning = Yes
Floresco et al., 1999	MD rats: bilateral lidocaine infusion	Delayed radial maze Non delayed random foraging radial maze Delayed radial maze and Pre-test infusion only	Post-op Post-op Post-op	30 min 30 min	Pre-test infusion severe deficits. Not impaired. MD/N Acc. not impaired. A PL/N Acc. group were also impaired
Kornecook et al., 1999	MD rats: electrode	Visual object discrimination	Pre-op Post-op		No deficits on retention of discriminations learnt pre-op up to 58 days prior to surgery No
Zhang et al., 1998	MD rats: NMDA	Go/no-go DNMTS odors Olfactory discrimination	Pre-op	4–20 s	MD mild and transient deficits; No

(Continued)

Table 1 | Continued

References	Lesion/Species/Type	Behavioral tasks	Training	Delay	Deficits reported
Burk and Mair, 1998	MD rats: NMDA	Place DMTS, operant boxes Serial reversal learning	Pre-op Post-op	1–13 s	No No
Hunt and Aggleton, 1998a,b	MD rats: NMDA	Standard radial maze Radial maze (45° rotation) T-maze Alt 8-arm radial maze SOR	Post-op Post-op	60 s 60 s 10 s 15, 60 min	No Yes No Yes, exacerbated by AT damage No
Hunt and Aggleton, 1998a,b	MD rats: NMDA	8-arm radial maze CCP Exploratory Activity T-Maze MTP T-Maze Reversal	Post-op	10–40 s	No No Yes, slower to acquired task but no delay deficits No, MD more perseverative errors than controls
Parker et al., 1997	MD macaques: ablations	DMTS Concurrent discriminations Rule reversal learning	Pre-op Post-op Post-op	0–30 s	Yes for large stimulus set size but not small set size No No
Peinado-Manzano and Pozo-Garcia, 1996	MD rats	Delayed alternation in operant boxes	Pre-op	0–80 s	Moderate and transient impairment for 0–40 s and severe impairment for 80 s
Young et al., 1996	MD rats: RF	DNMTS in operant boxes 8-arm radial maze	Post-op	1.8–8.8 s	MD produced deficits in acquisition of the radial maze task
Krazem et al., 1995	MD mice: ibotenic	T-Maze Spatial repetition T-Maze Reversal	Post-op	5 min, 24 h	No Yes, MD required more trials
Hunt et al., 1994	MD rats: NMDA	Object, concurrent and configural discrim	Post-op		MD mildly impaired on concurrent discriminations
Gaffan et al., 1993	MD + Amyg + VMPFC macaques: ablation	2-choice visual discrim task with food reward for correct choices	Post-op		Crossed lesions caused severe deficits in post-op acquisition
Mumby et al., 1993	MD rats: electrolytic	Visual object recognition DNMS	Post-op Pre-op	4 s acq. 4–300	Yes, more trials to learn, then delay dependent deficits 30–300 s Yes, more trials to reacquire
Neave et al., 1993	MD rats: NMDA	DNMTP Spatial discrim and Reversal	Post-op	0–32 s	No No
Gaffan and Watkins, 1991	MD macaques: ablation	Learning of visual stimuli associated with different amounts of food	Pre-op Post-op		Yes, impaired on retention of pre-op reward stimuli associations and impaired in new learning of further reward stimuli associations
Hunt and Aggleton, 1991	MD rats: RF, ibotenic	Y-Maze Object recognition T-Maze Delay alt	Post-op	0–60 s 10–60 s	Yes Yes, spatial memory deficits only a consequence of anterior thalamic involvement

(Continued)

Table 1 | Continued

References	Lesion/Species/Type	Behavioral tasks	Training	Delay	Deficits reported
M'Harzi et al., 1991	MD rats: electrolytic	Radial maze Place recognition Object recognition	Post-op		Yes No No
Peinado-Manzano and Pozo-Garcia, 1991	MD rats: electrolytic	Operant delay alt	Post-op	0–80 s	Yes
Gaffan and Murray, 1990	MD + Amyg + vmPFC macaques: ablation	2-choice visual discrim with food reward for correct choices	Post-op		Bilateral lesions to MD impaired Crossed unilateral lesions not as impaired as bilateral lesions to any of the single regions.
Stokes and Best, 1990a	MD rats: electrolytic	8-arm radial maze	Post-op		Yes, combined MD and AT damage
Stokes and Best, 1990b	MD rats: ibotenic	8-arm radial maze	Post-op		Yes, combined MD and AT damage
Winocur, 1990	MD rats: electrolytic	Memory for food preferences	Post-op Pre-op	0–8 d	No Yes, only if no delay btw acquisition and surgery Not impaired with 2 d between acquisition and surgery
Beracochea et al., 1989	MD rats: ibotenic	8-arm radial maze T-Maze temp alt T-Maze spatial reversal	Post-op	15, 45 s	No Yes = 15 s but not with 45 s delay No
Stokes and Best, 1988	MD rats: electrolytic	8-arm radial maze	Pre-op	0 s	Yes, combined MD and AT damage
Zola-Morgan and Squire, 1985	Posterior MD macaques: electrolytic	Visual DNMTS Pattern discrimination	Post-op	8–60 s, 10 min	Yes, delay independent No, analogous to preserved capacity for skill learning in human amnesic patients
Winocur, 1985	MD rats: electrolytic	Delayed alternation Passive avoidance	Post-op	0–21 d	Yes, impaired acquisition and impaired at all delays No
Aggleton and Mishkin, 1983a	MD macaques: ablation	Object recognition Object-reward associations	Post-op	120 s	Yes Yes
Aggleton and Mishkin, 1983b	MD +AT macaques: ablation	Object recognition Visual pattern discrim Spatial delayed response	Post-op	120 s	Yes No No
Isseroff et al., 1982	MD macaques: RF	Spatial delayed response Visual pattern discrim Delayed alternation Object discrim + reversals	Post-op	5 s	Yes No Yes No

Abbreviations: Alt, alternation; Discrim, discrimination; DNMTP, delayed non match to position; DNMTS, delayed non match to sample; Egocentric, egocentric discrimination; FX, fornix; RF, radiofrequency; Seq, sequential; SOR, spontaneous object recognition; post-op, post-operative; pre-op, pre-operative. For other abbreviations see elsewhere in the text.

the MDmc did not disrupt the animals' ability to implement the strategy that they had acquired pre-operatively (Mitchell et al., 2007a), despite the strong reciprocal interconnections with PFC and input from IT.

In the same study, another task, the OIP discrimination learning task, was also learnt pre-operatively although in this task animals learn 20 new pairs of OIP discriminations (see **Figure 4** for example stimuli of the OIP discriminations) during each session across eight concurrent repetitions of the set of 20 pairs of OIP discriminations. To assess impairments in this task, the performance of each animal is compared during a pre-operative test of 10 sessions and compared, after recovery from neurosurgery, to a post-operative test of 10 sessions. The neurotoxic MDmc lesions caused animals to make more errors during postoperative testing, so it could be concluded that deficits were linked to new learning of information as opposed to the retention of specific information acquired pre-operatively (Mitchell et al., 2007a). Critically though, this evidence demonstrated that the damage to the MDmc was not simply causing widespread PFC dysfunction to account for the observed cognitive deficits. Furthermore, the extent of the deficits on the OIP task were similar across two different lesion studies provided convincing evidence that the neurotoxin lesion technique used by Mitchell et al. (2007a) worked as effectively as the previously used ablation method (Gaffan and Parker, 2000).

In addition, the types of errors made in learning the OIP discriminations produced after bilateral MDmc lesions are not suggestive of problems with perseverative responding during learning (Mitchell et al., 2007a). However, bilateral ablations to the VLPFC do produce perseverative responding during new learning of OIP discriminations (Baxter et al., 2008). This evidence further confirms that damage to the MDmc does not simply produce a generalized impairment in memory by causing dysfunction of prefrontal functioning as had been previously proposed.

However, other studies (e.g., Parker et al., 1997) have shown that damage to the MD does not impair new learning or retention on recognition memory tasks when the stimulus set size is small. So it could also be argued that as the stimulus set size (four pairs of objects) is small in the strategy implementation task, no further learning is occurring. This theory was further tested (Mitchell and Gaffan, 2008) by comparing retrograde amnesia and anterograde amnesia within the same animals using the same types of OIP discrimination stimuli for both types of memory (see **Figure 4**) from a large sample size of 400 pairs of discriminations. In addition, a one-trial retention test was used to assess memory retention; this test is a pure measure of postoperative retention, uncontaminated by post-operative re-learning (Dean and Weiskrantz, 1974). Interestingly, damage to the MDmc using neurotoxins caused no impairment in the one-trial postoperative retention test. That is, the monkeys with bilateral MDmc neurotoxic lesions showed good retention (i.e., no retrograde amnesia) of the 300 pairs of OIP discriminations that they had acquired pre-operatively, when the errors made during their pre-operative retention test were compared with errors made during their post-operative retention test (Mitchell and Gaffan, 2008). In contrast, the same animals were markedly impaired in new postoperative learning (anterograde amnesia) of a further set of 100 novel pairs of OIP discriminations presented concurrently across sessions (Mitchell and Gaffan, 2008). It was concluded from this evidence that the MDmc is critical for the processing of new information more so than in the retention of information acquired prior to damage.

Further research from our laboratory has extended our understanding about some of the brain regions involved in retrograde amnesia and anterograde amnesia using this OIP retention and new learning task. The effects of lesions to different subcortical and cortical structures have been assessed (Mitchell et al., 2008; Mitchell and Buckley, submitted). One such study assessed the effects of combining neurotoxic MDmc lesions with bilateral fornix transection [a lesion that produces more widespread brain damage to medial diencephalic structures as well as disrupting interconnections with the PFC and medial temporal lobes (Mitchell et al., 2008)]. Interestingly these combined lesions produced dense amnesia for new learning as well as retention, yet still they confirmed that subcortical damage produces more severe deficits in anterograde amnesia than in retrograde amnesia.

Clearly animals with bilateral MDmc lesions have provided greater understanding of the critical role that the MDmc plays in differing forms of memory processing. Animals with MDmc lesions have also been assessed on tasks investigating other cognitive processes e.g., reward (satiety) devaluation. For example, animals with selective bilateral neurotoxic lesions to the MDmc are also impaired on a computerized version of a classic food satiety devaluation task (Malkova et al., 1997) demonstrating the importance of the MDmc within the neural circuit crucial for reward devaluation (Mitchell et al., 2007b) that also includes the OFC and amygdala (Malkova et al., 1997; Baxter et al., 2000; Izquierdo and Murray, 2010). Interestingly though, lesions to MDmc did not impair the animals' ability to learn the 60 pairs of object-reward associations presented concurrently over successive sessions during initial postoperative acquisition training before performing the reward satiety devaluation testing in this task. In this reward devaluation paradigm, the monkeys must first learn postoperatively to link one of the two pairs of objects in each presentation with a peanut or chocolate candy reward, 50% of one of the stimuli from the pairs of objects was rewarded for a correct choice with a peanut (while the other object was not associated

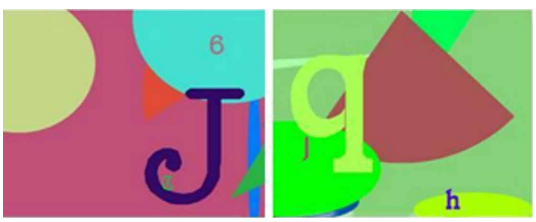

FIGURE 4 | Two examples of object-in-place (OIP) discrimination problems. Each discrimination problem had two different "objects" (one rewarded and one non-rewarded) embedded within a unique colored and patterned background akin to a "scene"; the objects are the differently colored typographic characters "B" and "m" in the left panel and "J" and "h" in the right panel.

with any food) and the other 50% of the pairs of objects with a chocolate candy. Presumably this lack of deficit in new learning during the initial acquisition was linked to the smaller set size of stimuli (Parker et al., 1997) as well as to the salience of the rewards [e.g., bilateral lesions to the OFC and the amygdala also do not impair the initial postoperative acquisition of the object-reward associations in this task (Malkova et al., 1997; Baxter et al., 2000)]. Other studies though have shown that bilateral MD lesions do impair the ability of the animals to associate pairs of stimuli with differing amounts of food rewards (Gaffan and Watkins, 1991).

In contrast, MD lesions do produce deficits in new learning of larger sized samples of concurrent object-reward association problems over sessions, although the lesion does not impair the retention of pre-operatively acquired object-reward associations (Gaffan and Parker, 2000). Damage to parts of the PFC (e.g., crossed unilateral disconnection of PFC × IT lesions) does not impair concurrent learning of visual object discriminations, where the animal learns to associate visually presented objects with food (or no) reward and the presentation of each object pair is separated in time by presentation of other pairs of objects (Gaffan et al., 2002). Interestingly, this same PFC × IT disconnection lesion does, however, severely impair serial learning of visual discriminations, where the animal learns to associate single pairs of objects with food (or no) reward and the presentation of each object pair occurs immediately after one another (Browning et al., 2007). Concurrent object-reward association learning is qualitatively different to learning serial presentations of visual discriminations (Murray and Gaffan, 2006). It remains to be fully tested whether bilateral MD lesions produce dissociable deficits in learning concurrent vs. serial visual discriminations, although as previously shown MD lesions produce deficits in within-session new learning of OIP discriminations (Gaffan and Parker, 2000; Mitchell et al., 2007a).

Rodents

In rats, many studies assess the rats' ability to forage for food using T-mazes, water mazes and radial arm mazes, taking advantage of their natural curiosity to explore novel environments for food. Many strategies can be used by the animals to complete these tasks successfully (Dudchenko, 2001). One strategy involves spatial navigation based on the use of extra maze cues (e.g., door, windows, lights, posters, experimenter, etc.) within the testing environment (spatial cues) to help guide their optimal exploration and ensure they do not return to the same location twice. Animals with selective neurotoxic lesions to the MD show comparable performance to control animals when they use spatial cues to guide their navigation in radial arm maze tasks (Beracochea et al., 1989; Hunt and Aggleton, 1998a; Mitchell and Dalrymple-Alford, 2005), unless they incorporate a delay (Harrison and Mair, 1996; Floresco et al., 1999) or produce more widespread damage that also includes the AT (Stokes and Best, 1988, 1990a,b; Hunt and Aggleton, 1991, 1998a). It has been proposed that MD deficits in delay tasks are presumably a consequence of widespread disruption to PFC functioning (Hunt and Aggleton, 1998b). Floresco et al. (1999) contrasted working memory performance using a spatial delayed responding task and non-delayed spatial tasks to show that the interaction between the PFC and the MD mediates "context-dependent retrieval and manipulation of recently acquired information." Furthermore, this study provided evidence, via lidocaine infusions into the MD, to show that MD alone is not sufficient to affect episodic-like memory processing on spatial memory tasks (Floresco et al., 1999). Instead, it is widely accepted that spatial memory processing deficits related to the medial thalamus are governed by the anterior thalamic nuclei and their interconnections to the extended hippocampal system, also known as the Delay-Bryon neural circuit (Aggleton and Brown, 1999).

Other researchers have observed in rats with bilateral MD lesions certain behavioral deficits that could result in memory impairments, for example, an inability to adopt different strategies, or changes in activity and exploration levels or deficits in withholding spatial responses (Hunt and Aggleton, 1998a,b; Floresco et al., 1999; Block et al., 2007; Ostlund and Balleine, 2008). All of these types of deficits are also observed in rats with damage to regions of the PFC (Chudasama, 2011).

Rodent studies have been instrumental in demonstrating the distinct, interdependent involvement of adjacent medial thalamic structures in memory and other cognitive deficits. Dissociable deficits between the MD and adjacent anterior thalamus (AT) have been reported (Chudasama and Muir, 2001; Chudasama et al., 2001; Corbit et al., 2003; Mitchell and Dalrymple-Alford, 2005, 2006). Corbit et al. (2003) assessed the effects of highly selective MD and AT lesions in rats on instrumental conditioning. Rats with either MD or AT lesions were both able to acquire the instrumental performance but during the degradation of the action-outcome contingency test, the rats with MD lesion were unable to demonstrate reliable devaluation effects. This deficit shown by the rats with MD lesions was distinct from the rats with AT lesions and controls, which did not differ, and suggests that the MD contributes to deficits in encoding and/or utilizing the action-outcome association (Corbit et al., 2003). Mitchell and Dalrymple-Alford (2005) have also demonstrated dissociable impairments in rats with lesions of the medial MD compared to the lateral MD or to the AT on various cognitive tests. The damage to the medial MD impairs go/no-go reward value discriminations and recency memory with a 2-h delay, but had no impact on spatial memory processing using an 8-arm radial maze or spontaneous object recognition (SOR) memory (see below). Lateral MD lesions produced mild deficits in 8-arm radial maze performance and recency memory but had no impact on go/no-go reward value discriminations or SOR memory (see below). In contrast, AT lesions produced deficits on 8-arm radial maze performance but they had no effect on recency memory using a 2-h delay. Interestingly, AT lesions do impair the ability to remember the pseudorandom order of six odors (Wolff et al., 2006). This deficit may be linked to the nature of the associative memory processing involving reward that is required in this particular task but that is not present in the spontaneous exploration paradigm used in the recency memory task (see below). Further dissociations in performance have been reported in rats with lesions to the lateral MD or to the AT, with only damage to the lateral MD impairing the rats' memory in a delayed-match-to-sample task using an egocentric (body-turn) response in a cross-maze; damage to the AT left performance intact (Mitchell and Dalrymple-Alford, 2006).

Further studies from the same laboratory have provided more insight into the dissociable effects of lesions to the AT and lateral MD combined with ILN lesions in learning and memory processing (Gibb et al., 2006; Wolff et al., 2008; Lopez et al., 2009; Moreau et al., 2013). These authors concluded from this and the above evidence that no single medial thalamic structure is critical for all of the memory and other cognitive deficits associated with thalamic amnesia. Instead many subdivisions of medial thalamic nuclei are contributing to independent neural networks via subcortical and cortical interactions and are integrating information for successful cognition (Mitchell and Dalrymple-Alford, 2005, 2006). Other research (e.g., Eleore et al., 2011) has also documented similar roles for other thalamic nuclei, namely the reuniens, in supporting the acquisition of associative learning using a classical eyeblink conditioning task with a trace paradigm, because high frequency train stimulation directed at the reuniens in behaving mice prevented the proper acquisition of the task.

The experiment demonstrating bilateral MD involvement in recency memory (Mitchell and Dalrymple-Alford, 2005) has been further confirmed by Cross et al. (2012). The medial PFC (mPFC) is involved in recency memory processing in rodents (Mitchell and Laiacona, 1998; Hannesson et al., 2004; Cross et al., 2012) and patients with Korsakoff's syndrome and frontal lobe damage have problems with temporal processing and recency discriminations (Kopelman et al., 1997; Kopelman, 2002; Fuster, 2008).

Cross et al. (2012) have demonstrated in rodents the importance of neural communication in MD-mPFC circuitry for successful recency recognition memory. After combining crossed unilateral lesions of the MD and mPFC, a lesion that disconnects the structures in both hemispheres, animals were impaired in the recency recognition memory task. In contrast, after a combined ipsilateral unilateral lesion of the MD and mPFC (essentially a control lesion of these two structures that leaves one hemisphere functioning) recency recognition memory performance was left intact. The authors proposed that "during associative or recency recognition memory tasks, the MD–mPFC connection might be necessary to direct ongoing behavior toward, for example, the novel object–place configuration" (Cross et al., 2012). This study highlights how the interplay of communication within and between MD-mPFC networks is clearly critical for cognition.

After neurotoxic lesions to MD, rodents are not impaired at SOR tasks (Hunt and Aggleton, 1998a; Mitchell and Dalrymple-Alford, 2005; Cross et al., 2012). As already noted above, conflicting evidence exists for the role of MD in various recognition memory tests. Several studies have reported deficits in object recognition using rats involving delay non-matching-to-sample tasks that involve object-reward associations (Hunt and Aggleton, 1991; Mumby et al., 1993), while others have reported no deficits on various unrewarded recognition memory tasks that rely on spontaneous exploration instead (M'Harzi et al., 1991; Hunt and Aggleton, 1998b; Kornecook et al., 1999; Mitchell and Dalrymple-Alford, 2005). The most parsimonious explanation is that the task demands related to reward are different, as SOR does not involve reward but rather relies on spontaneous exploration while delayed-matching or non-matching to sample tasks normally reward the animal for a correct response, thus engaging associative memory networks instead (Parker et al., 1997; Gaffan and Parker, 2000). In addition, it is now known that pre-operative training is a critical factor in learning and memory tasks, as damage to the MD does not impair retention of pre-operatively acquired information associating objects and rewards (Gaffan and Parker, 2000; Mitchell and Gaffan, 2008). Also, there may be cross species differences in neuroanatomy. That is, in macaques there is a distinct projection from the rhinal cortices (perirhinal and entorhinal) to the MDmc (Aggleton et al., 1986; Saunders et al., 2005), while a similar projection is not as robust in rodents (Burwell et al., 1995).

As in monkey studies, researchers have investigated the devaluation effects after bilateral MD lesions in rodents. Pickens (2008) has systematically assessed rats with MD lesions on many variants of devaluation testing using Pavlovian and operant contingencies, and single and multiple reinforcement paradigms. Pickens concluded from this series of experiments, that the MD is important in devaluation circuits only "in cases in which previous associations need to be suppressed in order for new associations to be learned and control behavior, otherwise the devaluation circuit does not require MD" (Pickens, 2008).

Thus, through experimental testing in both rats and non-human primates it has been shown that the different subdivisions of the MD provide critical contributions to successful cognitive processing in many different tasks. Principally, the MD in conjunction with its neuroanatomical connections is important for some forms of recognition memory, recency memory processing, and further prospective integration of the rewards associated with successful responses to govern additional responses, as well as new learning of OIP discriminations, but not their retention. The subdivisions of the MD provide key roles in helping integrate object/reward/response information for successful new learning and successful additional (future) responding. Furthermore, and most importantly, it has been demonstrated that the MD contributes to successful cognition, rather than causing memory and other cognitive deficits by simply causing a generalized dysfunction of the PFC.

ELECTROPHYSIOLOGY

A recent review of single unit recordings in macaques (Watanabe and Funahashi, 2012) provides insight into how the MD contributes to successful performance during working memory (delayed oculomotor response) tasks. The review highlights clear interplay between the MD and PFC, as suggested by other studies. For example, neurons in the MD have shown cue-, delay- and response-period activity, similar to the discharge patterns observed in DLPFC, although most neurons exhibited sustained excitatory response during the delay period (Tanibuchi and Goldman-Rakic, 2005; Sommer and Wurtz, 2006; Watanabe and Funahashi, 2012). One study (Alexander and Fuster, 1973) in particular showed attenuation in magnitude of the delay-period response following cooling of the DLPFC suggesting that the projection neurons of PFC control task-related activity of the MD.

Further experiments have shown that the MD seems to contribute to prospective encoding more so than DLPFC during the delay period (Funahashi et al., 2004; Watanabe and Funahashi, 2012). Watanabe and Funahashi (2012) have proposed that the MD is the major area that provides information regarding

impending behavior to the DLPFC. In contrast, retrospective sensory information is maintained during the delay period in the DLPFC and this could play an important role in helping to generate prospective motor information (Watanabe and Funahashi, 2012). The response-period active neurons were more frequent in MD than in DLPFC reflecting a bias toward processing motor aspects of the task by these thalamic nuclei, confirmed further by population vector analyses (Watanabe and Funahashi, 2012).

Other electrophysiology studies have shown that the MDmc of primates contain neuronal populations that signal information concerning prior stimulus occurrence (Fahy et al., 1993), that is linked to interconnected regions of the medial PFC and the perirhinal cortex (Brown and Xiang, 1998; Xiang and Brown, 2004), although the role of the MD within this neural circuitry is still uncertain.

Finally, another study has used single unit recording to demonstrate how the PFC and MD interact in cognitive tasks. Recent work by Kellendonk and colleagues (Parnaudeau et al., 2013) using a mouse model of cognitive deficits in schizophrenia has shown a subtle decrease in MD activity to disrupt the thalamic-PFC neural circuitry and cognition. They recorded single units in MD neurons during choice phase vs. reward phase of the T-maze task and demonstrated decreased MD activity interfered with task-dependent modulation of MD-PFC synchrony, which correlated with the cognitive deficits of the mice.

THEORIES ABOUT MD INVOLVEMENT IN MEMORY PROCESSING

Aggleton and Brown (1999) suggested that the MD, and the perirhinal cortex of the medial temporal lobe, may play a role in a system responsible for familiarity-based recognition processes. However, this proposal remains debated because the direct neural connections between the MD and perirhinal cortex are sparse and clinical evidence (Pergola et al., 2012) and animal lesion evidence (as detailed above) remains equivocal. While it is widely accepted that the perirhinal cortex contributes to recognition memory, the contribution attributed to the MD remains uncertain. The evidence in the clinical cases of deficits in recognition memory following damage in the MD is mixed (Cipolotti et al., 2008) with some researchers reporting no such impairments (Shuren et al., 1997; Edelstyn et al., 2002). However, given that the majority of evidence supports the MD being involved in memory, and that its role is not just confined to familiarity judgments, further models of MD functioning in memory processes are required.

Other researchers have proposed that the MD has a deferential role in memory processing caused by disruptions in executive functioning which is processed by the PFC. It has been suggested that the memory impairments resulting from lesions to the MD are secondary to the primary disruptions in executive functioning, e.g., deficits in attention or withholding responses/inhibition and perseverative responding in both humans and animals (Zola-Morgan and Squire, 1985; Hunt and Aggleton, 1998b; Floresco et al., 1999; Van der Werf et al., 2000; Schmahmann, 2003).

Van der Werf et al. (2003b) in a review of clinical evidence suggest that the AT and MD each has a functional role in declarative memory processes. The authors propose that the different nuclei of the thalamus play different roles at varying levels of declarative memory functioning, namely the AT and MD are involved in processing the contents of the stimuli for storage and recall. The AT influences the selection of material to be stored and remembered, whereas the MD is involved in the coordination and selection of strategies used to retrieve material. The intralaminar and midline nuclei maintain a necessary state of arousal amongst the cortical regions involved in the ongoing memory processes. These groupings of nuclei then work in parallel to mediate and allow memory functioning.

In contrast to these proposals, Gaffan, Mitchell and colleagues have proposed that the MD, in particular MDmc has an important integrative role in conjunction with the PFC in episodic-like declarative memory, due to the prominent interconnections among these structures (Gaffan and Parker, 2000). The MDmc has a specific role in supporting new learning of information, contributing to the successful acquisition rather than the retention of previously acquired information (Mitchell et al., 2007a, 2008; Mitchell and Gaffan, 2008). As highlighted above, the MD plays a key role in helping integrate object/reward/response information for successful new learning and successful additional (future) responding. Furthermore, Mitchell and colleagues have suggested that the role of MD in learning and memory is not simply a consequence of causing generalized disruption to PFC functioning (Mitchell et al., 2007a; Mitchell and Gaffan, 2008).

Aggleton et al. (2011) have revised their model of MD involvement in recognition memory. Their latest model, the multi-effect multi-nuclei model, asserts that the MD can contribute to both familiarity and recollective processes either directly via an interaction with the PFC or indirectly as a result of cortical diaschisis (Aggleton et al., 2011). This model is supported by recent findings regarding associative recognition (Cross et al., 2012), along with recent clinical results (Pergola et al., 2012) that point to contributions from the parvocellular MD for recollective aspects of recognition.

RE-EVALUATING MEDIODORSAL THALAMUS IN MEMORY AND WHERE TO FROM HERE

As indicated from the above survey of the contribution of the MD to specific forms of memory and decision-making, some conclusions have been drawn but much debate remains. Nevertheless, the evidence thus far provides some understanding and certainly helps with future directions. Thus, the animal evidence (and also the clinical evidence although not reviewed here) simply doesn't support the notion that there is a single structure within the medial diencephalon that is responsible for the extent of anterograde and retrograde memory deficits associated with diencephalic (or thalamic) amnesia. Furthermore, given the extent of variability in other cognitive deficits observed after damage to the MD it is not possible that one specific structure or subdivision of the MD is the critical locus of these deficits. Instead, the evidence suggests that the subdivisions of the MD, and subdivisions of other medial thalamic structures, are each functioning within independent but integrated neural circuits, all of which are important for specific aspects of cognitive processing, and together they form a group of critical networks in the brain that

are important for learning and memory as well as many other forms of cognition.

The current evidence points to the role of higher order thalamic structures, in our case the MD, in mediating the complex functioning within the PFC, via the transthalamic route (Sherman and Guillery, 2002). Neuroanatomical tracing studies have positioned the various subdivisions of the MD within separate but integrated neural circuits based on their respective interconnections. Moreover, as reviewed here, animal models of complete bilateral lesions to the MD as well as more selective lesions to individual subgroupings of the MD (i.e., medial MD, central MD and lateral MD) have demonstrated deficits in various tasks that assess new learning, recognition memory associated with reward, reward devaluation and recency memory processing, but not retention of previously acquired information. Manifestations of such deficits are often similar, but often can also be dissimilar to deficits seen after damage within the PFC (Fuster, 2008; Chudasama, 2011).

Thus, it may be proposed that the transthalamic connections linking the MD to the cognitive PFC are more important for supporting the learning of new information than for retention of previously acquired information (Mitchell et al., 2007a; Mitchell and Gaffan, 2008), perhaps by way of regulating cortical synchrony between regions of the PFC and MTL that support acquisition of new information. Others (Saalmann et al., 2012) have demonstrated how the pulvinar (another higher order thalamic relay structure) regulates cortico-cortical communication based on attention demands. This group combined simultaneous neural recordings in the pulvinar, V4 and area TEO (in the medial temporal lobes) while monkeys performed a visuospatial attention task. Precise interconnected target regions were identified via diffusion tensor imaging (DTI). The findings showed that the pulvinar regulates cortical synchrony between these connected structures according to the attentional allocation of the task (Saalmann et al., 2012).

In contrast to deficits in new learning, the evidence suggests that cortical structures are more important for the retention of information learnt prior to brain injury (retrograde amnesia). Impairments in retention are reported after restricted damage to selective cortical structures highlighting how some of these cortical regions are more important for memory of previously acquired information (Dean and Weiskrantz, 1974; Thornton et al., 1997; Mitchell et al., 2008). This evidence supports recent proposals that learning and retention are performed by different networks of the brain Thus, such memory processing may not require the regulation of cortical synchrony provided by the transthalamic pathways via the MDmc (at the least). Instead the direct cortico-cortical connections coursing within the PFC and across the medial temporal lobes are sufficient to support retention memory.

Widespread global amnesia associated with anterograde and retrograde memory deficits may be caused by widespread damage to subcortical structures. For example, the combined bilateral lesion damage to MDmc and fornix results in both retrograde and anterograde amnesia of OIP discriminations (Mitchell et al., 2008). This combined damage would have very likely resulted in extensive damage to interconnected regions of the medial diencephalon, medial temporal lobes, cingulate cortex and the PFC. In other primate animal models, similar types of global amnesia are also reported after combined lesions causing disconnection to the temporal stem, amygdala, and fornix (Gaffan et al., 2001; Easton et al., 2002; Gaffan, 2005). These lesions combining gray matter and white matter tracts disrupt widespread cortical—subcortical interconnections from basal forebrain, medial thalamus, and the midbrain, as well as cortico-cortical communication linking temporal and prefrontal cortices. Similar types of global amnesia are reported following widespread damage in the brain [e.g., in Korsakoff's syndrome patients (Kopelman et al., 1999; Harding et al., 2000)].

FUTURE DIRECTIONS

Further and combined behavioral, cognitive, and electrophysiology studies are required to gain greater understanding of the impact of disconnection lesions to the PFC, MD, and other interconnected structures. This research may also have clinical application in understanding the roles of the different subdivisions of the MD in many neuropsychological disorders (e.g., schizophrenia, obsessive compulsive disorder, and major depression). For example, recent studies across different species (Leal-Campanario et al., 2007, 2013; Cross et al., 2012; Parnaudeau et al., 2013) have highlighted the importance of MD-PFC communication within these interconnected neural circuits for successful cognition. Furthermore, many other studies have shown how different types of damage to brain structures interconnected to the MD can produce surprising results across species. Schoenbaum and colleagues (Stalnaker et al., 2007) have shown in rodents how the orbital frontal cortex (OFC) and amygdala interact in reversal learning tasks, with amygdala lesions abolishing the OFC dependent reversal impairments. Interestingly though, in macaques, amygdala lesions do not impair reversal learning (Izquierdo and Murray, 2007), nor do excitotoxic lesions to the OFC, however, transection of the white matter tract fibers leading into the OFC do disrupt reversals and inhibitory control (Rudebeck et al., 2013). It remains an empirical question about the extent of reversal learning deficits linked to the MD and how the MD interacts within this neural network.

There needs to be more research on the understanding of the functional consequences of the communication links between the MD and PFC related to this higher order information transfer (Guillery and Sherman, 2002). For example, how does the MD influence the neural circuitry involved for new learning yet appear to have little impact on retention. The importance of understanding the metabotropic glutamate communication between the MD and the PFC may be particularly relevant for answering this, given that glutamate invokes synaptic plasticity and potentially learning and memory due to the prolonged response of the metabotropic glutamate receptor activation (Sherman, 2013).

Finally, advances in neuroimaging are also illustrating the interconnections of the subcortical brain structures *in vivo*. For example, the fiber pathways from ventral PFC to MD have recently been documented using magnetic resonance scanning (Lehman et al., 2011). Recent DTI studies have started revealing structural connectivity of MD to PFC and limbic

cortical areas and the subcortical caudate nucleus suggestive of the existence of basal ganglia-thalamo-cortical circuits in humans *in vivo* (Draganski et al., 2008; Metzger et al., 2010; Eckert et al., 2012). These advances in neuroimaging and future research that combines different behavioral and cognitive neuroscience techniques in humans and in animal models will further advance our understanding of the key roles that the subdivisions of the MD contribute to cognition.

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Mediodorsal thalamus and cognition in non-human primates

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Several recent studies in non-human primates have provided new insights into the role of the medial thalamus in different aspects of cognitive function. The mediodorsal nucleus of the thalamus (MD), by virtue of its connectivity with the frontal cortex, has been implicated in an array of cognitive functions. Rather than serving as an engine or relay for the prefrontal cortex, this area seems to be more specifically involved in regulating plasticity and flexibility of prefrontal-dependent cognitive functions. Focal damage to MD may also exacerbate the effects of damage to other subcortical relays. Thus, a wide range of distributed circuits and cognitive functions may be disrupted from focal damage within the medial thalamus (for example as a consequence of stroke or brain injury). Conversely, this region may make an interesting target for neuromodulation of cognitive function via deep brain stimulation or related methods, in conditions associated with dysfunction of these neural circuits.

Keywords: thalamus, mediodorsal nucleus, retrograde amnesia, anterograde amnesia, hippocampus, prefrontal

INTRODUCTION

Midline thalamic nuclei are key elements of distributed neural circuits for many different aspects of cognitive function. The goal of this mini-review is to discuss several recent studies of the roles of one of these nuclei, the mediodorsal nucleus (MD), in cognitive function. In these studies, neurotoxic lesion experiments in non-human primates have suggested that MD is not simply a relay nucleus to/from the frontal cortex, but plays a distinct role in modulation of cognitive functions to the extent that damage to MD does not simply mimic the effects of damage to frontal cortex.

One goal of experimental lesion studies within the medial thalamus has been to dissect the neuropathological basis of diencephalic amnesia, following strokes or traumatic injuries to the thalamus and adjacent structures, or in conditions such as alcoholic Korsakoff syndrome. These have identified the contributions of multiple regions to various aspects of cognitive function, including anterior thalamic nuclei, the mammillary bodies, as well as MD. Impairments in executive function have also been reported following damage to the thalamus in humans, implicating thalamic nuclei in neural circuits beyond those critical for memory. Because monkeys exhibit a complex array of cognitive behaviors, and have a well-differentiated prefrontal cortex, they have been particularly useful models to help understand the functions of MD, with regards to its role in both memory and behavioral control by the prefrontal cortex.

MEDIODORSAL THALAMUS AND RETROGRADE/ANTEROGRADE AMNESIA

It is doubly difficult to understand the necessity of specific brain regions for memory consolidation and retrieval based on studies in human patients, because the lesions are rarely specific to a particular brain structure, and because levels of pre-injury memory have not been measured. Lesion-based symptom mapping and clever neuropsychological assessments can offset these problems to some degree, but lesion studies in animals provide an important complementary approach because both brain damage and pre-injury memory are under experimental control. Analyses in humans with thalamic damage have implicated the mammillothalamic tract, in particular, in impaired formation of new memories (anterograde amnesia) (Van der Werf et al., 2000, 2003). Individuals with Korsakoff syndrome (and widespread diencephalic degeneration) have extensive impairment in retrieval of memories formed before brain damage was sustained (retrograde amnesia), but retrograde amnesia is not associated with focal lesions of the thalamus (Kopelman et al., 1999, 2009). An initial investigation in monkeys reported no retrograde amnesia after focal neurotoxic lesions of the medial part of MD, but a significant anterograde amnesia (Mitchell and Gaffan, 2008), congruent to some degree with the clinical literature.

The focus on medial MD reflects its connectivity with the frontal cortex and networks involved in memory and cognitive function more generally. Four subdivisions of MD are recognized in the primate brain: the medial, magnocellular part (MDmc), a more lateral parvicellular part (MDpc), the most lateral multiformis portion (MDmf) that forms a band at the lateral edge of MD, and the densocellular portion (MDde) located caudally lateral to the MDpc and habenula (Goldman-Rakic and Porrino, 1985). The medial, magnocellular division may be further subparcellated (Ray and Price, 1993). Ventrolateral and orbital prefrontal cortex predominantly receive input from neurons in medial MD (MDmc) whereas dorsolateral prefrontal cortex mainly receives input from more lateral MD (MDpc) (Goldman-Rakic and

Porrino, 1985; Barbas et al., 1991). MD projections to the prefrontal cortex mainly target cortical layers III and IV, whereas projections back to the MD from prefrontal cortex originate from deep layers V and VI (Giguere and Goldman-Rakic, 1988; Xiao et al., 2009). The medial MD also receives input from the amygdala (Porrino et al., 1981) and rhinal cortex (Russchen et al., 1987; Goulet et al., 1998) and projects to the thalamic reticular nucleus, a key node for gating thalamocortical interaction (Zikopoulos and Barbas, 2012). The role of the MD in memory has been viewed mainly through interactions with amygdala/rhinal cortex and frontal cortex (Gaffan and Murray, 1990; Gaffan et al., 1993). The neurotoxic lesions of medial MD whose behavioral effects were investigated in the studies described below produced extensive damage to medial, magnocellular MD (MDmc) as well as unavoidable damage to midline thalamic nuclei located between the two halves of MD, including the rhomboid, centromedian, and paraventricular nucleus. Damage to these midline nuclei on their own cannot account for the behavioral effects of neurotoxic medial MD lesions (Gaffan and Murray, 1990; Mitchell and Gaffan, 2008) but could exacerbate the effects of bilateral MDmc damage.

We carried out a follow-up study to further explore the role of subcortical structures, including the thalamus, vs. cortical structures in retrograde and anterograde amnesia, using the same kind of stimulus material as Mitchell and Gaffan (2008). The stimulus material was object-in-place scene problems (Gaffan, 1994). These stimuli are presented on a large touch-sensitive screen and composed of a randomly colored background, a random number of randomly colored ellipse segments, a single large typographical (ASCII) character, and two small typographical characters. The two small characters are the "objects" and the remaining visual elements constitute the "scene." Monkeys are taught that within each scene, one of the two objects is correct (a touch to that object generates a reward) whereas the other is incorrect (a touch to that object generates no reward); a touch to any other element of the scene causes the screen to blank and the trial to repeat after a brief interval. Rhesus monkeys learned three sets of 100 object-in-place scene problems preoperatively, in sequential order, to a 90% performance criterion. They then received a single-trial retention test on each scene and were assigned to surgical groups balanced for preoperative performance. Postoperatively, each monkey received another single-trial retention test, received a number of retraining sessions on the preoperatively-learned scenes, and learned a new set of 100 scenes. The single-trial retention tests allowed for a sensitive within-subject measure of the degree of retrograde amnesia, and the postoperative acquisition of a new set of scenes allowed for a measure of anterograde amnesia with the same stimulus material. In the followup study, we tested two groups of monkeys (as well as an unoperated control group): one with focal ablations of the anterior entorhinal cortex, and one with neurotoxic lesions of the medial MD combined with transection of the fornix. This second group was intended to produce a widespread disconnection of subcortical networks involved in memory, including both projections from medial, magnocellular MD to ventrolateral and orbital prefrontal cortex (Goldman-Rakic and Porrino, 1985) and subcortical connections of the hippocampus (including, but not limited to, with the mammillary bodies). We found that entorhinal cortex lesions produced retrograde but not anterograde amnesia, whereas MD + fornix lesions produced both retrograde and anterograde amnesia (Mitchell et al., 2008).

Taken together with the earlier result with neurotoxic medial MD lesions using a slightly different test procedure (Mitchell and Gaffan, 2008) and other findings on cortical lesions and retrograde amnesia (e.g., Thornton et al., 1997) these findings suggest a general model in which subcortical damage primarily contributes to anterograde amnesia whereas cortical damage primarily contributes to retrograde amnesia (Mitchell et al., 2008). Of course, in the limit, extensive cortical or subcortical damage would be expected to produce both kinds of amnesia. Presumably this accounts for the combination of retrograde and anterograde amnesia observed after medial MD + fornix lesions, as well as for the complex patterns of retrograde and anterograde amnesia in humans after brain lesions that likely affect both cortical and subcortical areas, either by direct damage or by virtue of interruption of fibers of passage traveling adjacent to or through lesioned cortex. On this view, formation of new memories is much more sensitive to subcortical damage (anterograde amnesia) and retrieval of old memories is much more sensitive to cortical damage (retrograde amnesia), although the degree of both kinds of amnesia increases as the amount of brain damage increases (**Figure 1**). This may help explain, for example, why focal thalamic lesions tend not to cause retrograde amnesia, but the more widespread damage that occurs in Korsakoff's syndrome is associated with both retrograde and anterograde amnesia.

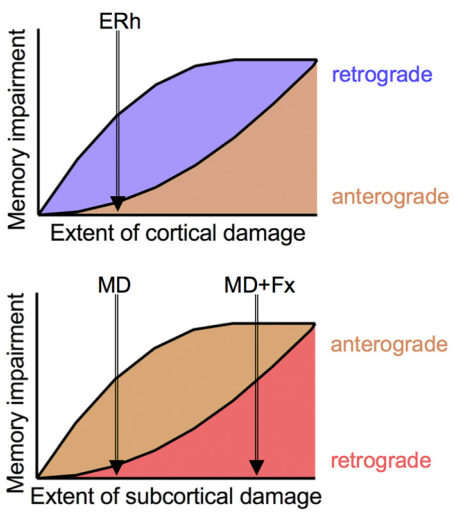

FIGURE 1 | Conceptual model of relationship between cortical and subcortical damage and degree of retrograde and anterograde amnesia. As degree of damage increases, so does severity of amnesia, but retrograde amnesia is more sensitive to cortical damage (**Top panel**) and anterograde amnesia is more sensitive to subcortical damage (**Bottom panel**). Small cortical lesions, as of anterior entorhinal cortex (ERh), produce retrograde amnesia but no anterograde amnesia; small subcortical lesions, as neurotoxic lesions of medial MD (MD), produce anterograde amnesia but no retrograde amnesia. More extensive subcortical lesions, as of MD and fornix (MD + Fx) produce both anterograde and retrograde amnesia.

MODULATION OF PREFRONTAL FUNCTION BY MEDIODORSAL THALAMUS

A previous study of medial MD lesions in monkeys, produced by direct surgical aspiration, concluded that the involvement of MD in memory reflected a disruption of prefrontal cortex function (Gaffan and Parker, 2000) because monkeys with aspiration lesions of medial MD were impaired in both scene learning and in acquisition of object-reward association problems, and this more generalized deficit is not seen in monkeys with lesions of the fornix-mammillary system or disconnection of prefrontal and inferotemporal cortex (Gaffan et al., 2001, 2002). Thus, medial MD ablations may have caused a widespread disruption of prefrontal cortex function, resembling effects of bilateral prefrontal damage (Parker and Gaffan, 1998). Based on the failure of neurotoxic lesions of medial MD to cause extensive retrograde amnesia (Mitchell and Gaffan, 2008), this issue was ripe for re-examination with neurotoxic lesions of medial MD. Although data from bilateral prefrontal lesions in the same retrograde amnesia paradigm are not available, it is worth noting that prefrontal-inferotemporal disconnection produces extensive retrograde amnesia for some kinds of visual discrimination problems that can be learned normally postoperatively (Browning and Gaffan, 2008), implicating the prefrontal cortex, as well, in some aspects of memory retrieval.

One approach to this question was to compare performance of monkeys with neurotoxic medial MD lesions on learning new scene memory problems, in this case a set of 20 problems presented within a testing day rather than sets of 100 problems learned across days (to facilitate comparison with earlier studies of aspiration lesions of medial MD), with performance on a complex strategy implementation task that is impaired by disconnection of frontal and inferotemporal cortex but not by extensive lesions of temporal lobe white matter tracts (Gaffan et al., 2002). In this task, monkeys learn about two classes of stimuli (cliparts), each class associated with a different strategy for obtaining reward. The first class, "persistent" (P), requires four consecutive choices of a P object on four consecutive trials in order to earn a reward. At any time after earning a reward for four consecutive P choices, a touch to the second class of stimuli, "sporadic" (S), generates a reward immediately, but another reward cannot be earned for choosing an S object until another reward is earned for four consecutive P choices. There are four pairs of these stimuli, each containing one P and one S stimulus, and they are randomly intermixed across trials. Thus, the monkey's optimal strategy is to choose PPPPSPPPPSPPPPS . . . across trials, neither interrupting sequences of P choices with an S choice before reward is earned nor continuing to choose S when a reward has already been earned for choosing S (and another reward for four consecutive P choices has not been earned yet). The ratio of trials worked to number of rewards earned provides a summary measure of how effective their implementation of the strategies is. Monkeys learn to perform this task very well, close to the perfect trials/reward ratio of 2.5, but their performance becomes disorganized after surgical disconnection of frontal and temporal cortex, such that the trials/reward ratio greatly increases, indicating the monkeys are not applying the choice strategies appropriately. Moreover, their behavior consists of both inappropriate S responses and a failure to make appropriate S responses as soon as they would be rewarded, so their deficit is not simply a failure to inhibit responding to the more attractive S stimulus (Gaffan et al., 2002; Baxter et al., 2009). Within the prefrontal cortex, performance on this task is significantly impaired by bilateral ablations of ventrolateral prefrontal cortex but not dorsolateral or orbital prefrontal cortex (Baxter et al., 2007, 2008b, 2009). Thus, loss of projections from medial MD to ventrolateral prefrontal cortex might be expected to impair performance on the strategy implementation task, if these projections are generally necessary for normal prefrontal cortex function.

Rhesus monkeys were preoperatively trained on both these tasks (object-in-place scene learning and strategy implementation), given a preoperative performance test, and received neurotoxic lesions of medial MD, followed by a postoperative performance test after post-surgical recovery. Remarkably, neurotoxic lesions of medial MD impaired scene learning to a similar degree as aspiration lesions, but were without significant effect on the strategy implementation task (Mitchell et al., 2007a). This indicates that damage to medial MD does not generally impair the function of its prefrontal targets. It also confirms the anterograde amnesia observed after medial MD lesions (Mitchell and Gaffan, 2008) extends to rapid, within-session learning of scenes, which also depends on an intact prefrontal cortex (Browning et al., 2005; Baxter et al., 2007, 2008a). We have proposed that the advantage in speed of learning conveyed by the unique background scenes (Gaffan, 1994) reflects the involvement of the prefrontal cortex in generating retrieval cues based on the unique background scenes to bridge successive presentations of the problems, creating an element of temporal complexity to this task that is not present in discrimination learning without unique background stimuli (Wilson et al., 2010). Thus, the MD may be involved in regulating plasticity within prefrontal cortex as these cues are acquired and generated. This loss of plasticity causes anterograde amnesia, while sparing execution of well-learned retrieval cues and behavioral strategies, allowing unimpaired retention of preoperatively learned scenes and performance on the strategy implementation task. Notably, frank prefrontal damage impairs all these behavioral domains, underlining the distinction between effects of selective MD damage and damage to the prefrontal cortex. The more discrete effects of neurotoxic lesions of medial MD, relative to aspirations of medial MD (Gaffan and Parker, 2000), presumably reflect damage to fibers of passage through medial MD caused by aspiration of the structure, perhaps including other divisions of MD and other regions of the thalamus.

Further insight into the functions of MD comes from a study of goal-directed choice behavior (Mitchell et al., 2007b). In this study, monkeys with neurotoxic lesions of medial MD learned a large set of object-reward association problems, in which half the rewarded objects (cliparts presented on a touchscreen) were rewarded with one distinct food (a half-peanut) whereas the others were rewarded with a different food (an M&M). Monkeys with neurotoxic lesions of medial MD acquired these problems at an equivalent rate to controls, again underscoring the selectivity of their memory impairment relative to that caused by aspiration lesions of medial MD (Gaffan and Parker, 2000). They were then confronted with sessions of critical trials in which they

chose between pairs of rewarded objects, one peanut-rewarded and one M&M-rewarded, composed of randomly re-pairing the rewarded objects from the discrimination problems. Before some of these sessions, monkeys were satiated on one of the two food rewards: they were allowed to consume as much of that food as they could before being brought to the touchscreen testing apparatus. Performance on these "devaluation" sessions was compared to baseline performance in the critical trials. Normal monkeys will adjust their choice behavior in devaluation sessions, avoiding choices of objects associated with the devalued food. Because they encounter each object only once in each critical trial session they do not have the opportunity to learn new associations between objects and the current value of the reward, so they must rely on their representation of the expected outcome of their choice in order to guide behavior. Devaluation performance is disrupted by lesions of orbital prefrontal cortex, amygdala, or surgical disconnection of these two structures (Málková et al., 1997; Baxter et al., 2000, 2009; Izquierdo et al., 2004) but not by damage to dorsolateral or ventrolateral prefrontal cortex (Baxter et al., 2008b, 2009). Monkeys with neurotoxic MD lesions were mildly, but significantly, impaired in their devaluation performance (Mitchell et al., 2007b). Surgical disconnections of medial MD from amygdala and orbital prefrontal cortex confirm that the participation of this structure in devaluation is via interaction with these two structures (Izquierdo and Murray, 2010).

This result suggests that projections from the medial MD to orbital prefrontal cortex may play a role in updating representations of expected outcomes of choices when the values of those outcomes change, in this case because of a change in the value of the food reward as a consequence of devaluation. Like object-in-place scene learning, this reflects a form of plasticity within prefrontal cortex, as compared to the retention of preoperatively learned scenes, the implementation of a well-learned strategy as in the strategy implementation task, or the gradual acquisition of associative strength by visual stimuli that presumably can be represented outside prefrontal cortex, as in the case of object-reward association learning.

IMPLICATIONS FOR FUTURE WORK AND THERAPEUTICS

Taken together, these experiments indicate that MD cannot simply be regarded as a relay nucleus for information to reach the prefrontal cortex, or a general source of modulation that supports all behavioral functions of the prefrontal cortex. Both of these points of view would imply a much greater correspondence between the effects of MD damage and prefrontal cortex damage than is observed experimentally. These data instead imply a role for MD in representational plasticity within prefrontal cortex, which would encompass some aspects of memory as well as dysexecutive syndromes associated with MD damage in humans (Van der Werf et al., 2000, 2003), a point of view supported by some related research with rats (Chudasama et al., 2001; Pickens, 2008).

This raises the possibility that neuromodulation of medial MD, for example via deep brain stimulation approaches, might be a potential target for improvement of prefrontal function in neuropsychiatric conditions and other disorders of cognition. A recent report of synchronization in the beta range between MD and frontal cortex in mice (Parnaudeau et al., 2013) during performance of a working memory task is congruent with our evidence for a critical role of MD-prefrontal interaction in cognition in non-human primates, and supports the notion that neuromodulation of MD may be therapeutic when prefrontal cortex function is impaired.

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Thalamic mediodorsal nucleus and its participation in spatial working memory processes: comparison with the prefrontal cortex

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Working memory is a dynamic neural system that includes processes for temporarily maintaining and processing information. Working memory plays a significant role in a variety of cognitive functions, such as thinking, reasoning, decision-making, and language comprehension. Although the prefrontal cortex (PFC) is known to play an important role in working memory, several lines of evidence indicate that the thalamic mediodorsal nucleus (MD) also participates in this process. While monkeys perform spatial working memory tasks, MD neurons exhibit directionally selective delay-period activity, which is considered to be a neural correlate for the temporary maintenance of information in PFC neurons. Studies have also shown that, while most MD neurons maintain prospective motor information, some maintain retrospective sensory information. Thus, the MD plays a greater role in prospective motor aspects of working memory processes than the PFC, which participates more in retrospective aspects. For the performance of spatial working memory tasks, the information provided by a sensory cue needs to be transformed into motor information to give an appropriate response. A population vector analysis using neural activities revealed that, although the transformation of sensory-to-motor information occurred during the delay period in both the PFC and the MD, PFC activities maintained sensory information until the late phase of the delay period, while MD activities initially represented sensory information but then started to represent motor information in the earlier phase of the delay period. These results indicate that long-range neural interactions supported by reciprocal connections between the MD and the PFC could play an important role in the transformation of maintained information in working memory processes.

Keywords: thalamic mediodorsal nucleus, prefrontal cortex, spatial working memory, delayed-response, retrospective information, prospective information

INTRODUCTION

Working memory is a dynamic neural system that includes neural processes for temporarily maintaining and processing information. Working memory is a fundamental neural component for a variety of cognitive functions, such as thinking, reasoning, decision-making, and language comprehension (Baddeley and Hitch, 1974; Baddeley, 2000). Therefore, working memory is an important concept for understanding the neural mechanisms of higher cognitive functions.

Working memory is an important concept for understanding the roles of the dorsolateral prefrontal cortex (DLPFC) in a variety of cognitive functions (Goldman-Rakic, 1987; Funahashi and Kubota, 1994; Funahashi, 2001; Funahashi and Takeda, 2002; Fuster, 2008). Brain imaging studies in human subjects have revealed that the DLPFC is activated whenever subjects perform behavioral tasks that require working memory (Stuss and Knight, 2012). Neuropsychological studies have also revealed that damage to the DLPFC impairs the performance of working memory tasks in human subjects (Stuss and Levine, 2002; Stuss et al., 2002). In animal studies, lesion of the DLPFC impaired performance in behavioral tasks that included an imposed delay period between cue presentation and response generation (e.g., delayed-response, delayed alternation, delayed matching-to-sample task) (Fuster, 2008). In neurophysiological studies, tonic sustained excitatory activity during the delay period (delay-period activity) has been observed in DLPFC neurons while monkeys performed behavioral tasks with a delay (Funahashi et al., 1989). These findings support the notion that the DLPFC plays an essential role in working memory processes.

However, the DLPFC is not the only brain area that participates in working memory processes. Neurophysiological studies using monkeys have shown that neurons in the parietal cortex (Gnadt and Andersen, 1988; Chafee and Goldman-Rakic, 1998), the temporal cortex (Fuster and Jervey, 1982; Miller et al., 1991, 1993), and the basal ganglia (Hikosaka and Sakamoto, 1986; Hikosaka et al., 1989) exhibit tonic sustained excitatory activity during the delay period. All of these brain areas have anatomical

connections to the DLPFC (Selemon and Goldman-Rakic, 1988; Fuster, 2008). Therefore, these brain areas also play important roles in working memory and might construct neural circuitries for working memory with the DLPFC.

The mediodorsal nucleus (MD) of the thalamus MD also has strong reciprocal connections with the prefrontal cortex (PFC) (Kievit and Kuypers, 1977; Goldman-Rakic and Porrino, 1985; Giguere and Goldman-Rakic, 1988; Ray and Price, 1993). Since the thalamus is the major relay structure that provides information to the cerebral cortex, it has been described as a gateway to the cortex (Sherman and Guillery, 2006). However, recent studies have indicated that, not only is the thalamus the gateway to the cerebral cortex, it also significantly contributes to cognitive functions. In fact, several lines of physiological evidence indicate that the MD participates in working memory processes in monkey experiments (Fuster and Alexander, 1971, 1973; Kubota et al., 1972; Tanibuchi and Goldman-Rakic, 2003). The experiment using rats also indicates that the MD participates in cognitive functions, such as prefrontal-dependent cognitive behaviors (Parnaudeau et al., 2013).

In this article, I will focus on the participation of the thalamus in cognitive functions. To demonstrate the importance of the thalamus in cognitive functions, I focus on working memory as an example of cognitive functions and the MD as a thalamic nucleus, and explain how the MD contributes to working memory processes. To explain the contribution of the MD to working memory, related findings obtained in prefrontal studies are helpful. Therefore, I will first explain findings regarding the neural mechanisms of working memory in the PFC, then explain the neural mechanisms of working memory in the MD, and finally consider the functions of the MD in a model of working memory.

WORKING MEMORY PROCESSES IN THE DORSOLATERAL PREFRONTAL CORTEX

MECHANISMS OF SPATIAL WORKING MEMORY IN THE DORSOLATERAL PREFRONTAL CORTEX

Since Goldman-Rakic (1987) proposed that working memory is an important concept for understanding the functions of the DLPFC in both humans and animals, the importance of the DLPFC in working memory has been demonstrated in a variety of experiments including lesion studies (see reviews by Goldman-Rakic, 1987; Petrides, 1994; Fuster, 2008), brain imaging studies using human subjects (see Stuss and Knight, 2012), and neurophysiological studies using non-human primates (see reviews by Funahashi and Kubota, 1994; Goldman-Rakic, 1998; Funahashi and Takeda, 2002; Fuster, 2008). Neurophysiological studies have shown that many neurons in the DLPFC exhibit tonic sustained activation during the delay period (delay-period activity) while monkeys performed spatial working memory tasks (Fuster, 1973; Niki, 1974; Niki and Watanabe, 1976; Kojima and Goldman-Rakic, 1984; Joseph and Barone, 1987; Funahashi et al., 1989; Hasegawa et al., 1998). Delay-period activity has been shown to have several important features regarding the neural mechanisms of working memory. First, the duration of delay-period activity can be prolonged or shortened depending on the length of the delay period (Fuster, 1973; Kojima and Goldman-Rakic, 1984; Funahashi et al., 1989). Second, this activity is observed only when monkeys perform correct behavioral responses (Fuster and Alexander, 1973; Funahashi et al., 1989). When the monkey made an error, delay-period activity was either truncated or not observed in that trial. Third, a great majority of delay-period activity exhibits a directional or positional preference (Funahashi et al., 1989), such that delay-period activity was observed only when a visual cue was presented at a particular area in the visual field. Many DLPFC neurons exhibited directional delay-period activity, and the preferred direction of this activity differed from neuron to neuron. Therefore, it has been proposed that neurons that exhibit directional delay-period activity have mnemonic receptive fields (memory fields) in the visual field (Funahashi et al., 1989; Rainer et al., 1998), analogous to visual receptive fields. Fourth, with the use of a delayed pro- and anti-saccade task, it has been shown that the great majority (about 70%) of delay-period activity represented information regarding the position of the visual cue (retrospective information), whereas the minority (about 30%) represented information regarding the direction of the saccade (prospective information) (Funahashi et al., 1993). Takeda and Funahashi (2002) used a conventional oculomotor delayed-response (ODR) task and a modified version (R-ODR task). In the ODR task, monkeys were required to make a saccade toward the direction of the visual cue after the delay, whereas in the R-ODR task, monkeys were required to make a saccade 90° clockwise from the direction of the visual cue. They compared the best directions of delay-period activity between these two task conditions. If the best directions of delay-period activity were the same in these two conditions, delay-period activity would encode the direction of the visual cue, since the best direction was depicted using the direction of the visual cue in their experiments. However, if the best directions of delay-period activity showed a 90° difference, delay-period activity would encode the direction of the saccade. They found that a great majority of delay-period activity (86%) encoded the direction of the visual cue, while a minority (13%) encoded the direction of the saccade. Similarly, Niki and Watanabe (1976) used a manual delayed-response task and a conditional position task, and reported that 70% and 30% of DLPFC neurons represented the spatial position of the visual cue and the direction of the response, respectively. Thus, delay-period activity represents either retrospective or prospective information, although most delay-period activity represents retrospective information in the DLPFC. Based on these observations, delay-period activity has been considered to be a neural correlate of temporary information-storage processes (Goldman-Rakic, 1987; Funahashi and Kubota, 1994; Miller, 2000; Funahashi, 2001; Funahashi and Takeda, 2002; Fuster, 2008).

Although the above observations were obtained using spatial working memory tasks, experiments with non-spatial working memory tasks (e.g., delayed matching-to-sample tasks and delayed conditional tasks) have also revealed that delay-period activity represents the active retention of non-spatial information, such as object shapes, patterns, or colors (Sakagami and Niki, 1994; Miller et al., 1996; Rao et al., 1997; Asaad et al., 1998; Rainer et al., 1999; Freedman et al., 2002). In addition, Romo et al. (1999) showed that differences in somatosensory information (e.g., frequency of mechanical vibrations) were encoded by the difference in the magnitude of

delay-period activity in DLPFC neurons. Further, delay-period activity has been shown to encode reward information and to be affected by the preference for the reward (Watanabe, 1996; Hikosaka and Watanabe, 2000; Kobayashi et al., 2002; Wallis and Miller, 2003). These results indicate that delay-period activity can represent not only spatial information but also non-spatial information, and confirm that delay-period activity observed in the DLPFC is a neural correlate of the mechanism for temporarily maintaining a variety of information (Funahashi and Kubota, 1994; Goldman-Rakic, 1998; Miller, 2000; Funahashi, 2001; Funahashi and Takeda, 2002; Fuster, 2008). Neurons with various task-related activities and neurons that exhibited various spatial and non-spatial features in task-related activity were distributed widely throughout the DLPFC with substantial overlap (Carlson et al., 1997; Quintana and Fuster, 1999; Rainer et al., 1999; Sakagami and Tsutsui, 1999). In addition, several neurons exhibited delay-period activity in both spatial and non-spatial working memory tasks (Rao et al., 1997). Therefore, neurons in the DLPFC can maintain various types of information as tonic sustained delay-period activity. Since each neuron exhibits a different preference for information and maintains it as delay-period activity, different information can be encoded by different groups of DLPFC neurons.

INFORMATION PROCESSING IN THE DORSOLATERAL PREFRONTAL CORTEX DURING SPATIAL WORKING MEMORY PROCESSES

Information processing in working memory can be considered as altering or transforming temporarily stored information in an appropriate way for accomplishing a particular purpose. Therefore, information processing could be achieved by dynamical and flexible functional interactions among mechanisms for temporarily storing information. Neurophysiological studies have provided evidence for the alteration or transformation of information by functional interactions among DLPFC neurons. Several studies have shown that the information represented by prefrontal activity changes as the task progresses. For example, in a paired association task with a delay, prefrontal activity represented the characteristics of the sample stimuli (sensory-related retrospective coding) in the early phase of the delay period, but began to represent the characteristics of anticipated targets (prospective coding) toward the end of the delay period (Rainer et al., 1999). Similarly, in a spatial delayed matching-to-sample task, spatial information was broadly tuned by delay-period activity in the early phase of the delay period. However, the proportion of neurons that exhibited sharper spatial tuning and high spatial discriminability increased in the later phase of the delay period (Sawaguchi and Yamane, 1999). Further, Asaad et al. (1998) showed that neural activity conveyed the direction of an impending eye movement progressively earlier along successive trials while monkeys performed arbitrary cue-response association tasks. Quintana and Fuster (1999) observed neurons attuned to the cue color and neurons attuned to the response directions while monkeys performed working memory tasks using color cues. They found that the discharge of neurons attuned to the cue color gradually diminished during the delay period, whereas the discharge of neurons attuned to the response directions gradually increased. All of these results indicate that the alteration of the neuron's discharge rate as the delay period progresses reflects the alteration of the information represented by the neuron. Thus, the temporal change in firing patterns observed in a population of neurons could reflect the progress of information processing during the delay period.

Takeda and Funahashi (2004) used a population vector analysis and demonstrated a temporal change in the preferred direction encoded by a population of DLPFC neurons as the delay period progressed in two ODR tasks (ODR and R-ODR tasks). In the ODR task, the monkey was required to make a saccade to the direction where the visual cue was presented, whereas in the R-ODR task the monkey was required to make a saccade 90° clockwise from the direction where the visual cue was presented. Takeda and Funahashi (2002) indicated two groups of DLPFC neurons with delay-period activity that encoded either the direction of the visual cue or the direction of the saccade, respectively. In the ODR task, since the direction of the visual cue is the same as the direction of the saccade, the preferred direction encoded by a population of DLPFC neurons would be maintained throughout the delay period. However, in the R-ODR task, the direction of the saccade is 90° clockwise from the direction of the visual cue. Therefore, the preferred direction encoded by a population of DLPFC neurons would change from the direction of the visual cue to the direction of the saccade during the delay period.

Figure 1-A1 shows population vectors calculated from a population of DLPFC activities in the 180° trial of the ODR task. Since the direction of the visual cue and the direction of the saccade were the same in the ODR task, population vectors were mostly directed toward the 180° direction. **Figure 1-B1** shows temporal changes in the directions of population vectors across all four conditions and confirms that the directions of the population vectors are the same as the direction of the visual cues and are maintained during the delay period. **Figure 1-A2** shows population vectors calculated for a population of DLPFC activities in the 180° trial of the R-ODR task. In this trial, the visual cue was presented at the 180° direction but the correct saccade was in the 90° direction. Population vectors were directed toward the 180° direction at the beginning of the delay period. However, the population vectors began to rotate in the middle of the delay period, continued to rotate slowly from the 180° direction to the 90° direction during the late half of the delay period, and were eventually directed toward the 90° direction at the response period (see **Figure 1-B2**). These results indicate that the information represented by a population of DLPFC activities changes from sensory information to motor information during the delay period, since the initial information is provided by sensory cues and must be transformed into motor information in these behavioral tasks. A population vector analysis can visualize the process for this transformation of information. Fuster (2008) stated that the delay period is the period for cross-temporal bridging when the transformation of sensory-to-motor information occurs, which is a dynamic process for the internal transfer of information as well as a process of cross-temporal matching. The present result indicates that the DLPFC plays a significant role in mediating the cross-temporal contingency. This

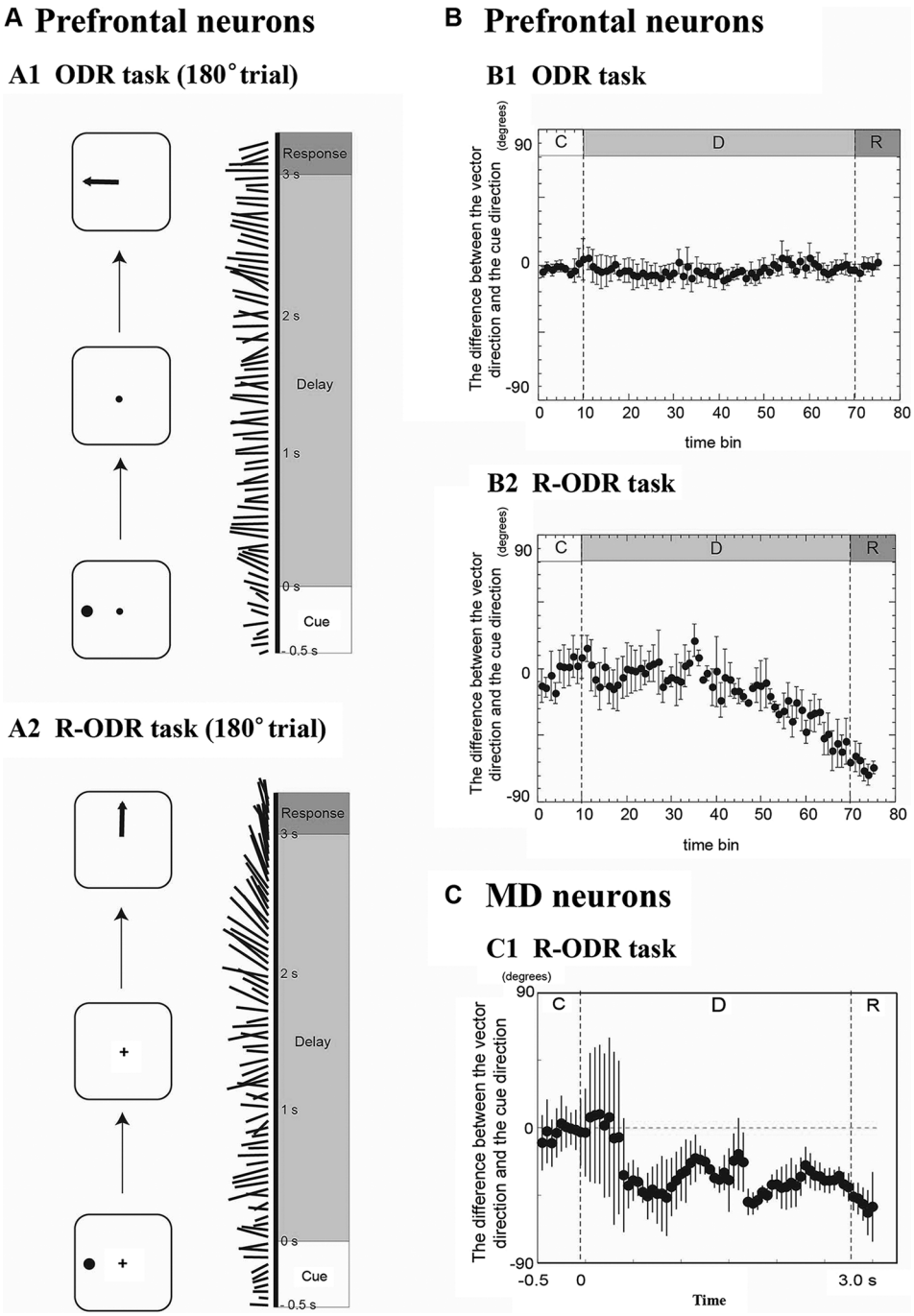

FIGURE 1 | Temporal changes in the directions of population vectors in prefrontal neurons (A and B) and MD neurons (C). **(A1)** Temporal changes in the directions of population vectors during the 180° trial of the ODR task. Most population vectors were directed toward the 180° direction. **(A2)** Temporal changes in the directions of population vectors during the 180° trial of the R-ODR task. The direction of the population vector gradually rotated from the 180° direction to the 90° direction during the delay period. **(B1)** The difference between the vector direction and the cue direction during the ODR trial. The population vector was directed toward the cue direction during the delay period. **(B2)** The difference between the vector direction and the cue direction during the R-ODR trial. The direction of the population vector gradually rotated from the cue direction to the saccade direction during the delay period. The timing of the change was start at 1.5 s after the start of the delay period (adapted from Takeda and Funahashi (2004)). **(C1)** Temporal changes in the differences between the directions of population vectors and the direction of the visual cue in the R-ODR task for MD neurons. The direction of the population vector rotated from the cue direction to the saccade direction during the delay period, similar as prefrontal neurons. However, the timing of the change was start at 0.5 s after the start of the delay period (Adapted from Watanabe et al. (2009)).

result also indicates that DLPFC neurons contribute significantly to dynamic neural processes for internal information transfer.

IMPORTANCE OF FUNCTIONAL INTERACTION IN WORKING MEMORY IN THE DORSOLATERAL PREFRONTAL CORTEX

When we consider the neural mechanism of information processes in working memory, the essential components must be dynamic and flexible functional interactions among neurons that exhibit different task-related activities, different types of activity, and different directional selectivity. In the DLPFC, Wilson et al. (1994) showed that the types of responses (excitatory or inhibitory) of pyramidal neurons were often opposite those of non-pyramidal neurons (e.g., when pyramidal neurons exhibited an excitatory response, non-pyramidal neurons often exhibited an inhibitory response). They also showed that the timing of excitatory and inhibitory responses appears to be anti-phased between pyramidal and non-pyramidal neurons. These results indicate the presence of functional interactions between pyramidal and non-pyramidal neurons in the DLPFC. Further, Rao et al. (1999) found inhibitory interactions between a pyramidal neuron and an adjacent non-pyramidal interneuron by cross-correlation analyses of neuronal firing in the DLPFC. Funahashi and Inoue (2000) also examined functional interactions between task-related DLPFC neurons by cross-correlation analyses. When both neurons of examined pairs exhibited delay-period activity, these neurons tended to have excitatory interactions and showed similar directional preferences. An examination of the temporal change in the strength of correlated firings revealed that functional interactions between task-related neurons with different directional preferences increased as the trial progressed. These observations suggest that the information represented by a population of neurons that exhibits directional delay-period activity gradually transforms into other types of information by these functional interactions, as indicated by a population vector analysis with a population of DLPFC activities.

The magnitude of activity of each neuron changes depending on the trial conditions, the temporal context of the trial, and the trial events. Therefore, the strength of functional interactions could change depending on the trial conditions or the temporal context of the trial. In fact, the strength of the cross-correlation calculated from the activities of two neurons recorded simultaneously changed dynamically depending on the cue conditions. Thus, dynamic and flexible changes in functional interactions among neurons are important components of neural mechanisms of information processing.

WORKING MEMORY PROCESSES IN THE THALAMIC MEDIODORSAL NUCLEUS

THE MEDIODORSAL NUCLEUS AND WORKING MEMORY

The thalamus consists of several thalamic nuclei, each of which has reciprocal connections with specific regions of the cerebral cortex. The MD is a major thalamic nucleus and is located at the midline of the thalamus. An important feature of the MD is that it has strong reciprocal connections, mainly to the PFC. Therefore, the MD could also play significant roles in a variety of higher cognitive functions in which the PFC participates, including working memory.

Animal studies have shown that the MD participates in working memory processes. Lesion of the monkey MD has been shown to impair performance in working memory tasks. For example, Isseroff et al. (1982) found that lesions in the monkey MD were associated with impairment in a spatial delayed alternation task and a delayed-response task, while there was no impairment in an object reversal task or a visual pattern discrimination task. Since spatial working memory capacity is required for the former two tasks, but not for the latter two tasks, they concluded that lesion of the MD impaired spatial working memory capacity. Lesion of the monkey MD also impaired performance in non-spatial working memory tasks including a delayed matching-to-sample task (Aggleton and Mishkin, 1983a,b; Parker et al., 1997) and a delayed non-matching-to-sample task (Zola-Morgan and Squire, 1985). Alexander and Fuster (1973) examined functional interactions between the DLPFC and the MD by cooling of the DLPFC in monkeys and found that the activities of most (63%) MD neurons were affected by cooling of the DLPFC. The cooling effects observed in MD neurons included the attenuation of delay-period activity, shortening of the duration of delay-period activity, and the inhibition of delay-period activity.

The human MD has also been shown to participate in working memory. Damage to the medial thalamus including the MD often produces syndromes similar to "prefrontal syndromes" in humans (Daum and Ackermann, 1994; Van der Werf et al., 2000, 2003). The impairment of executive function is a major symptom of "prefrontal syndromes" (see Stuss and Benson, 1986). Working memory is a fundamental neural process of executive function (Funahashi, 2001). Therefore, the impairment of executive function due to damage to the medial thalamus could be caused by the impairment of working memory. For example, Van der Werf et al. (2003) used four neuropsychological tests (Wisconsin card sorting test, Tower of London test, verbal category fluency test, and Stroop test) to assess executive function in 22 patients with thalamic infarction. They found that patients with damage in the MD exhibited impaired performance in all of these neuropsychological tests. Since all of these tests require working memory capacity, this result indicates that the human MD also participates in working memory. Zoppelt et al. (2003) also examined the relation between dysfunction of executive ability and the anatomical locus of the damaged area in the thalamus. For patients with thalamic infarction, the anatomical locus of the damaged area was identified by MRI. Among five patients with damage in the MD, two had damage predominantly in the medial MD and three had damage predominantly in the lateral MD. The capacity of executive function was assessed by the Stroop test, a verbal fluency task, and digit span tests (forward and backward reproduction). They found that patients with damage in the lateral MD exhibited more severe impairment in digit span tests with backward reproduction and in the phonemic condition of the verbal fluency test, whereas patients with damage in the medial MD did not exhibit impairment in these tests. These results indicate that the lateral MD is important for executive function. They also showed that, although patients with MD damage showed impaired memory processes such as recollection and familiarity, these memory impairments were more apparent when the damaged area included the medial MD. Anatomical studies have shown that

the lateral MD has anatomical connections mainly with the DLPFC, whereas the medial MD has anatomical connections mainly with the orbitofrontal cortex (Kievit and Kuypers, 1977; Goldman-Rakic and Porrino, 1985; Giguere and Goldman-Rakic, 1988). Thus, the participation of the MD in cognitive functions seems to depend on its anatomical relations to the PFC (Rovo et al., 2012). Since the lateral MD has anatomical connections with the DLPFC and since the DLPFC participates in working memory processes, the lateral MD could play an important role in executive functions and working memory.

Functional brain imaging studies have also demonstrated that the human MD participates in working memory processes. Activation of the human MD has been observed while subjects performed working memory tasks, such as delayed matching-to-sample tasks and delayed non-matching-to-sample tasks (Elliott and Dolan, 1999; de Zubicaray et al., 2001). In addition to the temporary maintenance of information in working memory, Monchi et al. (2001) showed that the MD participated in other aspects of information processing. They asked human subjects to perform the Wisconsin card sorting test and control tasks and examined thalamic activation using fMRI. They found that the MD was activated when the subjects received negative feedback. In the Wisconsin card sorting test, negative feedback signals the subject to shift the category for selection from that used in the preceding trial to a new one. Thus, the MD participates not only in the temporary maintenance of information but also in information processing, such as in the replacement of the content of working memory (current category) with new information (new category).

NEURAL ACTIVITY RELATED TO WORKING MEMORY IN THE MEDIODORSAL NUCLEUS

Neurophysiological studies with monkeys have demonstrated neural activity that was related to working memory, such as delay-period activity, in the MD. Fuster and Alexander (1971, 1973) first showed that about half of the recorded MD neurons exhibited sustained excitatory activity during the delay period (delay-period activity) while monkeys performed a delayed-response task. Watanabe and Funahashi (2004a) analyzed the characteristics of task-related activity of MD neurons while monkeys performed an ODR task. Since the same ODR task had been used to examine the neural mechanisms of working memory processes in the DLPFC (Funahashi et al., 1989, 1990, 1991, 1993; Takeda and Funahashi, 2002), it would be worthwhile to compare the characteristics of neural activities recorded using the same task in the MD and the DLPFC. Among recorded MD neurons, 26%, 53%, and 84% exhibited cue-, delay-, and response-period activity, respectively. Comparison of these values between the MD and the DLPFC indicated that more neurons exhibited response-period activity in the MD than in the DLPFC (**Figure 2A**). Among MD neurons with response-period activity, 74% showed pre-saccadic activity, while the remaining 26% showed post-saccadic activity. In contrast, a great majority (78%) of response-period activity was post-saccadic in the DLPFC (**Figure 2B**). Thus, the percentage of neurons with pre- or post-saccadic activity is an important difference in the functional characteristics of the MD and the DLPFC.

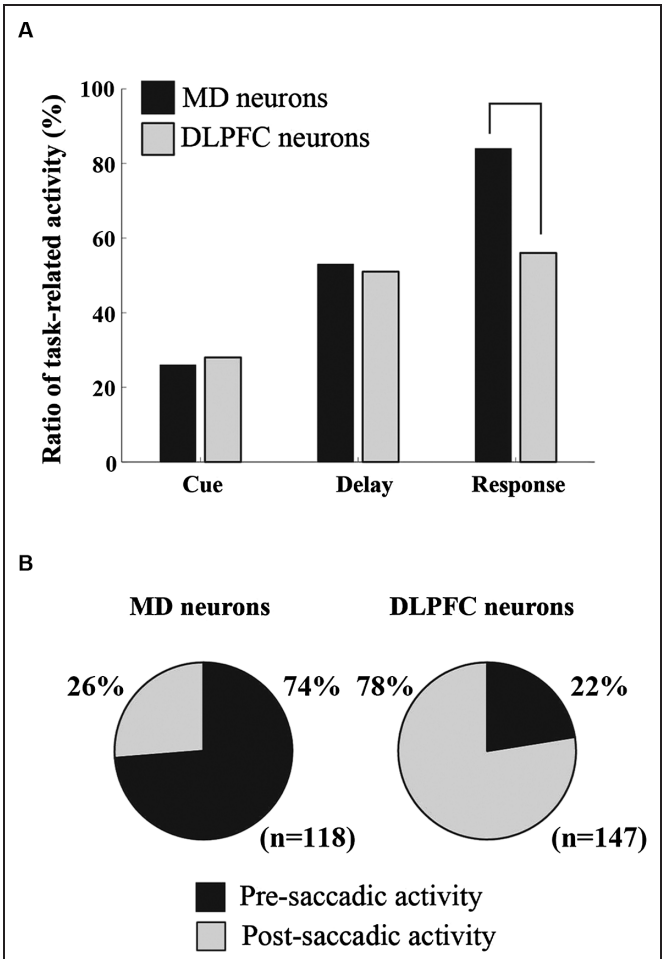

FIGURE 2 | Comparison of the characteristics of task-related activity between MD neurons and DLPFC neurons. (A) A comparison of the proportion of task-related activity between the MD and DLPFC. **(B)** A comparison of the proportion of pre- and post-saccadic activity between the MD and DLPFC. The data regarding DLPFC neurons and MD neurons are based on data obtained by Funahashi et al. (1989, 1990, 1991) and Watanabe and Funahashi (2004a), respectively.

Task-related activity observed in the ODR task showed directional selectivity in MD neurons. For example, all cue-period activity, 76% of delay-period activity, and 64% of response-period activity showed directional selectivity. A similar directional selectivity of MD neurons was reported by Tanibuchi and Goldman-Rakic (2003). Among response-period activities, 78% of pre-saccadic activity and 26% of post-saccadic activity was directionally selective (Watanabe and Funahashi, 2004a). The proportion of directionally selective task-related activity was similar in the MD and the DLPFC (Funahashi et al., 1989, 1990, 1991; Takeda and Funahashi, 2002). Most task-related activity showed directional selectivity in both MD and DLPFC neurons.

Since most task-related activity exhibited directional selectivity, we could determine a preferred direction for each task-related activity based on a tuning curve constructed by recorded neural activities. In MD neurons, statistically significant

contralateral bias in preferred directions was present in both cue-period activity and pre-saccadic activity, while significant contralateral bias was not observed in delay-period activity and most post-saccadic activity exhibited omni-directional selectivity (Watanabe and Funahashi, 2004a). In contrast, in DLPFC neurons, a statistically significant contralateral bias of preferred directions was observed in cue-period activity, delay-period activity, and pre-saccadic activity, while significant contralateral bias was not observed in post-saccadic activity (Funahashi et al., 1989, 1990, 1991; Takeda and Funahashi, 2002).

These results indicate that, while monkeys performed the ODR task, similar types of task-related activity were observed in similar proportions in the MD and the DLPFC. Directional delay-period activity was observed in the MD with similar characteristics and a similar proportion as in the DLPFC. Therefore, these findings strongly support the idea that the MD participates in spatial working memory processes. However, the MD and the DLPFC also show some differences, especially in response-period activity. Response-period activity was more frequently observed in the MD (84%) than in the DLPFC (56%), and the proportion of pre-saccadic activity in the MD (74%) was greater than that in the DLPFC (22%). Thus, although the MD and the DLPFC both participate in working memory processes, the MD contributes more to prospective aspects of working memory processes, such as motor or response preparation, compared to the DLPFC, which contributes more to retrospective aspects, such as sensory processes.

REPRESENTATION OF INFORMATION IN THE ACTIVITY OF MEDIODORSAL NUCLEUS NEURONS

Somewhat different contributions to working memory processes in the MD and the DLPFC are also observed when we examine the type of information that is encoded by delay-period activity. Watanabe and Funahashi (2004b) used the same ODR tasks as Takeda and Funahashi (2002) and examined the type of information encoded by the delay-period activity of MD neurons. They found that 56% of delay-period activity encoded the direction of the visual cue, while 41% encoded the direction of the saccade. Thus, more delay-period activity encoded the direction of the saccade in MD neurons than in DLPFC neurons. Together with the finding that more MD neurons exhibited response-period activity and most response-period activity showed pre-saccadic activity in the MD, these results support the idea that the MD participates more in motor aspects of working memory processes than the DLPFC and might provide impending motor information (prospective information) to the DLPFC.

POPULATION VECTOR ANALYSIS USING MEDIODORSAL NUCLEUS NEURAL ACTIVITIES

A population vector analysis was applied to MD activities to visualize information processes in the MD while monkeys performed spatial working memory tasks (ODR and R-ODR tasks) (Watanabe et al., 2009). After the authors confirmed that population vectors constructed by a population of cue- and response-period activities correctly represented information regarding the directions of the visual cue and the saccade, respectively, they calculated population vectors of MD activities during a 250 ms window which slid in 50 ms steps from the onset of the visual cue until 500 ms after the initiation of the response period (**Figure 1-C1**). In the ODR task, the directions of population vectors were maintained mostly toward the direction of the visual cue throughout the entire delay period. In the R-ODR task, the direction of the population vector was initially in the direction of the visual cue, then began to rotate toward the direction of the saccade in the early phase of the delay period, and gradually pointed toward the direction of the saccade as the trial progressed. These results indicate that the transformation from visual information to saccade information occurs during the delay period in the MD. In addition, comparison of the temporal change in the directions of population vectors of DLPFC neurons and MD neurons revealed that the rotation of the population vector started earlier in the MD than in the DLPFC (**Figure 1**). In addition, as we considered previously, more delay-period activity encoded the direction of the saccade and more response-period activity exhibited pre-saccadic activity in the MD compared with the DLPFC. These results indicate that the MD might be the major brain area that provides information regarding impending motor information to the DLPFC.

THE MEDIODORSAL NUCLEUS AND MOTOR ASPECTS OF INFORMATION PROCESSING

Although the MD participates in cognitive functions such as working memory, other results also support the idea that the MD contributes more to motor aspects rather than sensory aspects. For example, Sommer and Wurtz (2004) examined neural signals conveyed through an ascending pathway from the superior colliculus (SC) to the frontal eye field (FEF) via the MD. They used antidromic and orthodromic responses generated by electrical stimulation of the FEF to identify relay neurons in the MD. They examined the nature of the information that was transferred from the SC to the FEF while monkeys performed delayed-saccade tasks. They found that, although the SC sent visual as well as saccade signals to the FEF via the MD, pre-saccadic activity was prominent in MD relay neurons. Based on these and other results, they hypothesized that a major signal conveyed by the ascending pathway to the FEF is the corollary discharge that represents information regarding the direction and amplitude of an impending saccade (Sommer and Wurtz, 2002, 2004). In addition to the SC, the basal ganglia also project to the thalamus, including the MD, and provide information regarding saccades (Hikosaka et al., 2000). For example, an anatomical study by Ilinsky et al. (1985) showed that the substantia nigra has wide projections to the whole area of the MD. It has been known that neurons in the substantia nigra exhibit saccade-related activity (Hikosaka and Wurtz, 1983). High frequency tonic activity observed in the substantia nigra has inhibitory effect to thalamic neurons and this tonic activity temporarily suppresses thalamic activity in relation to the saccade performance. Therefore, thalamic neurons are disinhibited during saccade performance. Thus, activity of thalamic neurons is controlled by movement-related inputs from the basal ganglia.

Based on a comparison of the best directions of delay-period activity in the ODR and R-ODR tasks, most MD neurons encoded impending saccade information in delay-period activity.

A population vector analysis revealed that impending saccade information was generated in the earlier phase of the delay period in the MD, while the same information was generated in the later phase of the delay period in the DLPFC. More pre-saccadic activity was observed in the MD than in the DLPFC. In addition, the MD received corollary discharge that represented information regarding the direction and amplitude of an impending saccade from the SC and sent this signal to the PFC. These results indicate that the MD is one of the brain structures that provide forthcoming motor information (prospective information) to the DLPFC. While we do not yet fully understand how prospective motor information is generated and which brain structures provide prospective motor information to the MD, the SC is one of these structures. Retrospective sensory information maintained in the DLPFC may also play a role to produce prospective motor information in the MD. Further studies are needed to understand how prospective motor information is generated and which brain areas participate in this process.

CONTRIBUTIONS OF THE MEDIODORSAL NUCLEUS TO SPATIAL WORKING MEMORY PROCESSES IN THE DLPFC

We previously proposed neural components to explain spatial working memory processes based on our findings obtained from neurophysiological studies in the DLPFC (Funahashi, 2001). We hypothesized the presence of four basic neural components to execute working memory. These include a neural process for selecting appropriate information (selection process), a neural process for temporarily storing information (temporary storage process), a neural process for providing stored information to other neural systems (output process), and a neural process for appropriately processing the information (operation process). Working memory is defined as a system that includes both the temporary maintenance of and processing of information. Therefore, the temporary storage and operation processes are considered to be essential neural components of working memory. In addition to these neural components, the neural process for temporarily storing information can receive various kinds of information, including sensory, motor, motivational, emotional, cognitive, and perhaps somatic information. However, necessary and important information for executing the current task or achieving the current goal needs to be selected from among these varieties of information. Therefore, the neural process for working memory must include a neural process for selecting appropriate information from a variety of sources. In addition, stored and processed information should be used to perform the current task. For this purpose, the neural process for working memory must have a neural process to provide stored and processed information to other neural systems. Thus, when we consider a physiologically plausible model of working memory, the model should include at least these four neural processes.

We proposed four neural processes to explain how working memory function is executed in the DLPFC. However, it is hard to imagine how information processing could be a distinct neural component. Therefore, we hypothesize that information processing can be explained as a variety of functional interactions among temporary storage processes. The presence of various functional interactions among DLPFC neurons has been shown by neurophysiological studies. For example, excitatory as well as inhibitory interactions have been observed among task-related DLPFC neurons by a cross-correlation analysis of simultaneously recorded pairs of single-neuron activities (Funahashi and Inoue, 2000; Constantinidis et al., 2001). Dynamic and flexible interactions among neurons that depend on the progress of the trial have also been observed in the DLPFC by an analysis that used joint peri-stimulus time histograms (Vaadia et al., 1995; Funahashi, 2001; Tsujimoto et al., 2008). Thus, dynamic and flexible interactions among neural processes, especially among temporary storage processes, could play an essential role in information processing in working memory.

To further understand the mechanism of information processing in the DLPFC, we estimated information flow among DLPFC neurons during spatial working memory performance. Individual DLPFC neurons exhibit one or more task-related activities. Based on the temporal pattern of neuron activity, we could determine what task-related activity each DLPFC neuron exhibited, what information (*cue direction* or *saccade direction*) each task-related activity represented, and the preferred direction of each task-related activity for each neuron. While monkeys performed ODR tasks, DLPFC neurons exhibit task-related activities, such as cue- (C), delay- (D), or response-period (R) activity, or their combinations (C&D, C&R, D&R, or C&D&R). Takeda and Funahashi (2007) classified recorded neurons into nine groups based on which task-related activity the neuron exhibited and what information (*cue direction* or *saccade direction*) each task-related activity represented (C, D*cue*, D*sac*, CD*cue*, D*cue*R*cue*, D*sac*R*sac*, D*cue*R*sac*, CD*cue*R*cue* and CD*cue*R*sac*) (**Figure 3**). Preferred directions were compared between task-related activities in the same DLPFC neuron or in two different neurons. In groups of neurons that exhibited CD*cue*, CD*cue*R*cue*, and CD*cue*R*sac* activities, both cue- and delay-period activities represented the direction of the visual cue, suggesting that the directional selectivity of delay-period activity is affected by the directional selectivity of cue-period activity for these neurons. In groups of neurons that exhibited D*cue*R*cue*, CD*cue*R*cue*, and D*sac*R*sac* activities, both delay- and response-period activities represented either the direction of the visual cue (D*cue*R*cue* and CD*cue*R*cue*) or the direction of the saccade (D*sac*R*sac*), suggesting that the directional selectivity of delay-period activity affects the directional selectivity of response-period activity in these neurons. The temporal profiles of delay-period activity suggest that directional cue-period activity of C, CD*cue*, and CD*cue*R*cue* groups contributes to the initiation of directional delay-period activity of CD*cue*, CD*cue*R*cue*, D*cue*, and D*cue*R*cue* groups and that directional delay-period activity of D*sac* and D*sac*R*sac* groups affects directional saccade-related activity of D*sac*R*sac*. Thus, while monkeys performed ODR tasks, information flow from neurons that exhibit directional cue-period activity to neurons that exhibit directional saccade-related activity is present in the DLPFC through neurons that exhibit directional delay-period activity. During this information flow, visual information is gradually transformed into motor information.

As we mentioned above, all neurons with only cue-period activity represent visual information and most neurons with only response-period activity represent motor information in the

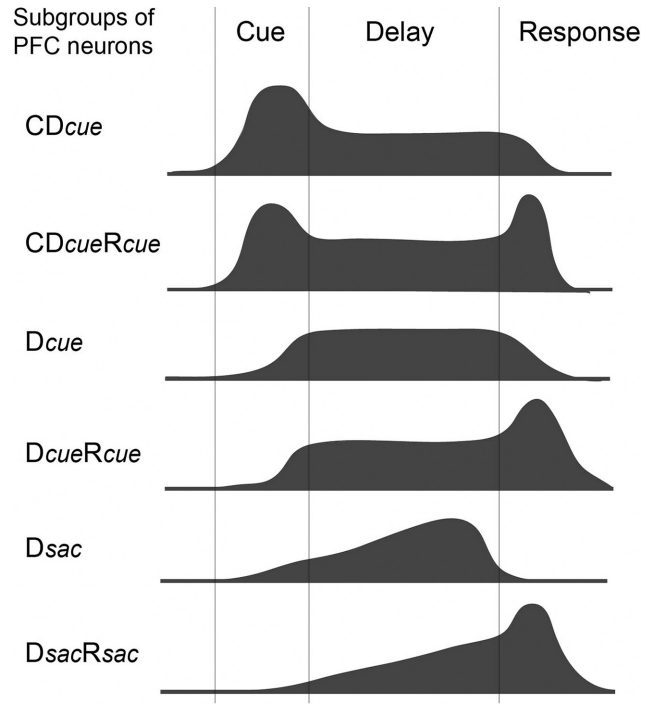

FIGURE 3 | Schematic drawings of the temporal profiles of activity for six groups (D*cue*, D*sac*, CD *cue*, D*cue*R*cue*, D*sac*R*sac*, and CD*cue*R*cue*) of DLPFC neurons (adapted from Takeda and Funahashi (2007)).

DLPFC. Therefore, based on these observations, an outline of the possible information flow during spatial working memory performance in the DLPFC is shown in **Figure 4**. Visual inputs first activate DLPFC neurons that only have cue-period activity (C*cue*). This activation is transferred to DLPFC neurons that have both cue- and delay-period activity (C*cue*D*cue*) and then to DLPFC neurons that have only delay-period activity (D*cue*). Since all of these DLPFC neurons receive visual inputs, both cue- and delay-period activities represent visual information. However, during the delay period, prospective motor information is generated and this information is maintained in DLPFC neurons that only have delay-period activity (D*resp*). This information is transferred to DLPFC neurons with both delay- and response-period activities (D*resp*R*resp*) and then to DLPFC neurons with only response-period activity (R*resp*). A comparison of the directional selectivity of delay-period activity between the ODR and R-ODR tasks revealed that delay-period activity encoded either visual information or saccade information in the DLPFC. No delay-period activity encoded both visual and saccade information simultaneously. Therefore, prospective motor information is necessary to generate delay-period activity that encodes saccade information in the DLPFC.

In this sense, the MD can be considered a candidate of brain structures that provide information regarding prospective motor information to the DLPFC. In the MD, a majority of neurons with delay-period activity encoded saccade information (D*sac* and D*sac*R*sac*). Therefore, these MD neurons might be candidates as sources for providing prospective saccade information to the DLPFC (**Figure 4**). To support this idea, we need further studies to show neural interactions between the DLPFC and the MD. For example, we need to examine whether DLPFC neurons with Dsac activity have direct interactions with MD neurons with Dsac or DsacRsac activities, whether MD neurons having pre-saccadic activity provide saccade information to DLPFC neurons with Dsac, DsacRsac, or Rsac activities, or whether MD neurons having saccade-related activities are the source of post-saccadic activity observed in many DLPFC neurons. Neurophysiological studies, such as which task-related MD neurons exhibit antidromic or authodromic responses by electrical stimulations in the DLPFC, could provide important information to interpret functional interactions between the MD and the DLPFC and construct more realistic neural circuitry for these interactions than that shown in **Figure 4**.

Although the MD is one important brain structure for providing prospective motor information to the DLPFC, other brain structures including the FEF, the supplementary eye field, the posterior parietal cortex are also needed to be considered as strong candidates for providing prospective motor information to the DLPFC (**Figure 4**). We need further experiments to elucidate what information is provided from these brain structures in working memory processes.

INVOLVEMENT OF OTHER THALAMIC NUCLEI IN WORKING MEMORY

Although the MD is one brain structure for providing prospective motor information to the DLPFC, other nuclei of the thalamus may also involve this process in working memory. For example, ventrolateral (VL) and ventroanterior (VA) thalamic neurons exhibit saccade-related activities and some of these neurons exhibited gradually increasing activities toward the initiation of the saccade (Schlag-Rey and Schlag, 1984). Tanaka (2007) also reported gradually increasing activity during the delay period of a memory-guided saccade task in the VL. Wyder et al. (2004) showed activities carrying spatial information throughout the instructed delay period of a visually guided delayed saccade task in the central thalamus. They observed two groups of delay-period activities in the central thalamus (VA and VL). One group of activity signaled the location of visible visual targets regardless of behavioral relevance, while other groups of activity signaled the locations of current goals of saccade. These activities are similar as retrospective and prospective activities observed in the DLPFC (Funahashi et al., 1993; Takeda and Funahashi, 2002) and the MD (Watanabe and Funahashi, 2004b), respectively. Recently, Kunimatsu and Tanaka (2010) examined saccade-related activities while monkeys performed either pro- or anti-saccade tasks and showed that activities of many VL and VA neurons were enhanced during the anti-saccade condition compared to the pre-saccade condition. In addition, inactivation of VL and VA nuclei by the local injection of muscimol produced an increase of error trials in the anti-saccade condition. In the anti-saccade condition, monkeys needed to maintain information regarding the location of the visual cue, but suppress an inherent response toward the visual cue. Therefore, enhanced prospective motor activity must be necessary to perform correct saccade responses by suppressing inherent reflexive responses. In human studies,

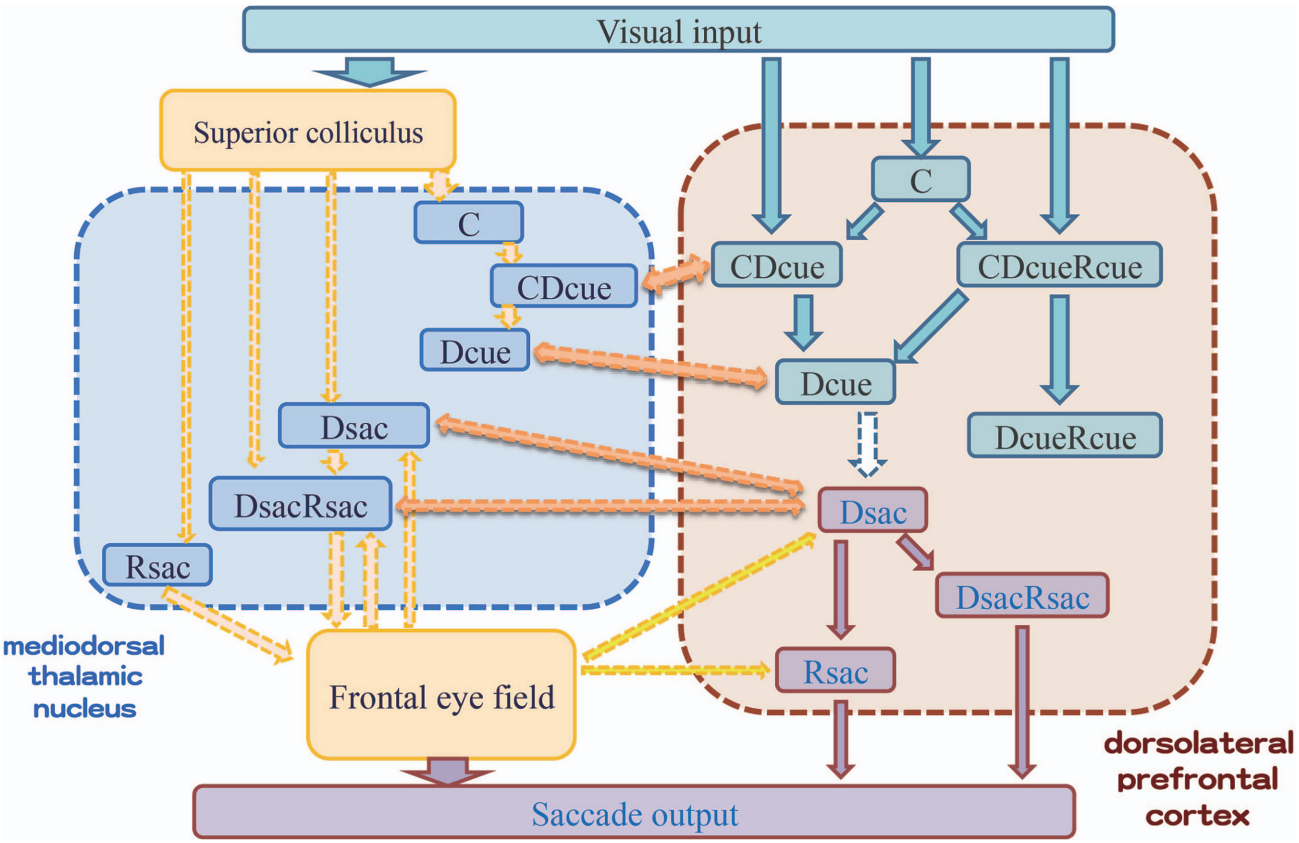

FIGURE 4 | Schematic drawing of information flow during delayed-response performance and possible interactions between DLPFC and MD neurons based on the characteristics of task-related activities of these neurons.

Bellebaum et al. (2005) showed that patients having VL and MD lesions exhibited impairment in performing a double-step saccade task. Since two targets were presented successively in this task, the retinal direction of the second target and the saccade direction of the second saccade were different. Therefore, the subjects could not use retinal information, but needed to use corollary discharge in order to perform the second saccade correctly. Their results indicate that the VL and MD participate in the processing of corollary discharge information, as had been indicated by Sommer and Wurtz (2002, 2004).

Thus, other nuclei of the central thalamus, such as the VA and the VL, also Participate in working memory processes. The VL and the VA have been shown to project to the DLPFC (Alexander et al., 1986; Middleton and Strick, 2001; McFarland and Haber, 2002). Therefore, the VL and the VA are also possible brain structures for providing prospective motor information to the DLPFC.

CONCLUSION

Working memory is a dynamic neural system that includes processes for temporarily maintaining and processing information. Working memory plays significant roles in a variety of cognitive functions, such as thinking, reasoning, decision-making, and language comprehension. Although the PFC has been known to play an important role in working memory, several lines of evidence indicate that the thalamic MD also participates in this process. Neurophysiological studies revealed that MD neurons exhibit directionally selective sustained delay-period activity while monkeys performed spatial working memory tasks. Sustained delay-period activity has been considered to be a neural correlate of the mechanism for the temporary maintenance of information. These studies also showed that most MD neurons that exhibit delay-period activity hold information regarding a motor response (prospective information), whereas a minority hold information regarding sensory cues (retrospective information). These observations suggest that the MD participates more in prospective motor aspects of working memory processes, in contrast to the PFC, which participates more in retrospective aspects such as the maintenance of sensory information. While monkeys perform spatial working memory tasks, spatial information provided by a visual cue must be transformed into motor information to perform an appropriate behavioral response. Both the MD and the PFC contain neurons that hold information regarding retrospective and prospective information, although the proportions of neurons that represent retrospective or prospective information are different between these two areas. In addition, the MD has strong reciprocal connections with the PFC. Therefore, these reciprocal connections between the MD

and the PFC could play an important role in the transformation of retrospective information into prospective information in spatial working memory processes. A population analysis of neural activities revealed that the transformation of sensory-to-motor information occurred during the delay period in both the PFC and the MD. This analysis showed that population activities in the PFC hold spatial information until the late phase of the delay period and then gradually represent motor information, while population activities in the MD initially represent spatial information but then start representing motor information in the earlier phase of the delay period. These results indicate that reverberating neural circuits constructed by reciprocal connections between the MD and the PFC could be an important structure for transforming retrospective information into prospective information in spatial working memory processes.

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Intralaminar and medial thalamic influence on cortical synchrony, information transmission and cognition

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The intralaminar and medial thalamic nuclei are part of the higher-order thalamus, which receives little sensory input, and instead forms extensive cortico-thalamo-cortical pathways. The large mediodorsal thalamic nucleus predominantly connects with the prefrontal cortex, the adjacent intralaminar nuclei connect with fronto-parietal cortex, and the midline thalamic nuclei connect with medial prefrontal cortex and medial temporal lobe. Taking into account this connectivity pattern, it is not surprising that the intralaminar and medial thalamus has been implicated in a variety of cognitive functions, including memory processing, attention and orienting, as well as reward-based behavior. This review addresses how the intralaminar and medial thalamus may regulate information transmission in cortical circuits. A key neural mechanism may involve intralaminar and medial thalamic neurons modulating the degree of synchrony between different groups of cortical neurons according to behavioral demands. Such a thalamic-mediated synchronization mechanism may give rise to large-scale integration of information across multiple cortical circuits, consequently influencing the level of arousal and consciousness. Overall, the growing evidence supports a general role for the higher-order thalamus in the control of cortical information transmission and cognitive processing.

Keywords: neural synchrony, memory, attention, reward, schizophrenia, anesthesia, reuniens nucleus, mediodorsal nucleus

INTRODUCTION

Information from the sensory periphery is first transmitted to the cerebral cortex via the primary sensory, or first-order, thalamic nuclei, such as the lateral geniculate in visual thalamus, ventral division of the medial geniculate in auditory thalamus, and ventral posterior nuclei in somatosensory thalamus. These first-order thalamic nuclei also receive feedback from the cortex, from layer 6. In contrast, higher-order thalamic nuclei, such as the pulvinar, mediodorsal (MD), intralaminar and midline nuclei (**Figure 1**), receive relatively little input from the sensory periphery. Instead, these higher-order thalamic nuclei receive major input from cortical layer 5 as well as cortical layer 6, and project to the cerebral cortex to form prevalent cortico-thalamo-cortical pathways (Guillery, 1995; Sherman and Guillery, 2002). This provides indirect connections between cortical areas via the higher-order thalamus, in addition to the direct cortico-cortical connections (Shipp, 2003; Sherman and Guillery, 2006). Although the direct cortico-cortical connections are commonly thought to convey detailed perceptual and cognitive information between cortical areas (but see Sherman and Guillery, 2006), the function of the higher-order thalamus and its connections with the cortex are poorly understood.

Lesions of higher-order thalamic nuclei have been shown to impair a number of cognitive functions, including memory, attention, perception and sensory-guided actions (Mitchell et al., 2008; Snow et al., 2009; Wilke et al., 2010). Although the underlying mechanism is unclear, recent evidence suggests that higher-order thalamic lesions perturb cortico-cortical information transmission (Theyel et al., 2010; Purushothaman et al., 2012). One possible mechanism may involve the higher-order thalamus modulating the degree of synchrony between different cortical neurons (Saalmann et al., 2012). Synchronizing cortical neurons can increase efficacy of information transmission. Synchronized pre-synaptic neurons are more likely to drive the post-synaptic neuron. Further, synchronized oscillatory activity of pre- and post-synaptic neurons, such that spikes from a pre-synaptic neuron arrive during periods of reduced inhibition of a post-synaptic neuron, increases the likelihood of spikes being relayed (Aertsen et al., 1989; Fries et al., 2001; Saalmann et al., 2007; Womelsdorf et al., 2007; Gregoriou et al., 2009; Tiesinga and Sejnowski, 2009). In this scenario, the higher-order thalamus may synchronize one network of cortical neurons and desynchronize other cortical networks, thereby selectively transmitting behaviorally relevant information between appropriately synchronized cortical neurons. This mechanism has the advantage of being able to dynamically route information across the cortex according to behavioral demands, by synchronizing different networks of neurons at different times. This review discusses how the relatively little-explored intralaminar and medial thalamic nuclei may influence the cortex. Although these higher-order thalamic areas, and even their subdivisions (**Figures 1B, C**), may contribute to different cognitive functions, they show similar

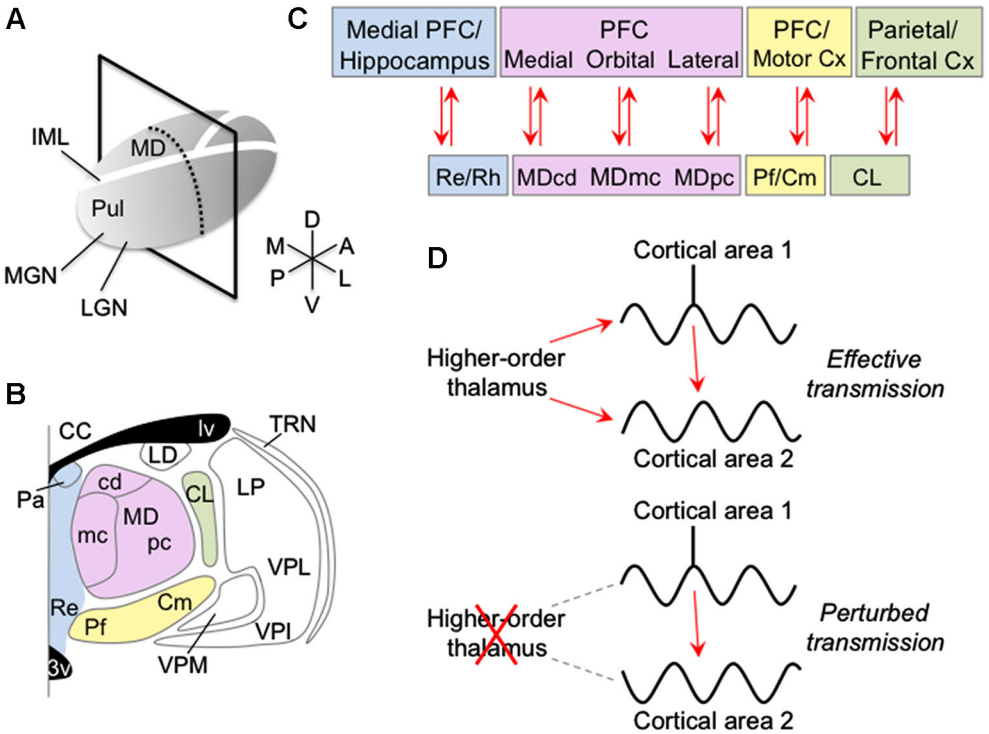

FIGURE 1 | Anatomy of the intralaminar and medial thalamic nuclei and their connectivity with the cortex. (A) Right thalamus overview, showing plane of section in **panel B**. **(B)** Coronal view of thalamus showing anterior intralaminar (green), posterior intralaminar (yellow), MD (pink) and midline (blue) nuclei. **(C)** Cortical connections of intralaminar and medial nuclei. **(D)** Schematic showing proposed mechanism of how the higher-order thalamus influences the cortex. The higher-order thalamus adjusts the magnitude and phase of synchrony between different groups of cortical neurons. Synchronizing cortical neurons, such that action potentials from pre-synaptic neurons arrive during phases of increased excitability of post-synaptic neurons, can increase the efficacy of their information exchange (top). In contrast, abnormal higher-order thalamic function can perturb cortico-cortical information transmission, either by reducing transmission efficacy with possible information degradation (bottom), or by erroneously routing information across cortex. Abbreviations: 3v, third ventricle; CC, corpus callosum; CL, central lateral nucleus; Cm, centromedian nucleus; Cx, cortex; IML, internal medullary lamina; LD, lateral dorsal nucleus; LGN, lateral geniculate nucleus; lv, lateral ventricle; MD, mediodorsal nucleus; MDcd, caudodorsal division of MD; MDmc, magnocellular division of MD; MDpc, parvocellular division of MD; MGN, medial geniculate nucleus; Pa, paraventricular nucleus; Pf, parafascicular nucleus; PFC, prefrontal cortex; Pul, pulvinar; Re, reuniens nucleus; Rh, rhomboid nucleus; TRN, thalamic reticular nucleus; VPl, ventral posterior inferior; VPL, ventral posterior lateral nucleus; VPM, ventral posterior medial nucleus.

thalamo-cortical connectivity principles. Here, I argue that this connectivity gives rise to common thalamic-mediated mechanisms for regulating cortical oscillation and synchronization patterns.

ANATOMY OF THE INTRALAMINAR AND MEDIAL THALAMUS

The internal medullary lamina contains myelinated fibers that course through the thalamus along its rostro-caudal axis (**Figure 1A**; this review focuses on thalamo-cortical networks in primates; references to cat and rodent data are noted below). The large MD nucleus, and adjacent midline structures, the paratenial, paraventricular, reuniens (Re) and rhomboid (Rh) nuclei, are located medial to the internal medullary lamina. Within the lamina, there are also several nuclei. These intralaminar nuclei can be classified into an anterior and a posterior group. The anterior group comprises the central medial, paracentral and central lateral nuclei, and the posterior group comprises the centromedian (Cm) and parafascicular (Pf) nuclei (**Figure 1B**).

The MD thalamic nucleus can be divided into at least two parts based on cytoarchitectonics: a magnocellular division, located antero-medially, and a parvocellular division, located more laterally. Based largely on thalamocortical connectivity, Ray and Price (1993) further divided the magnocellular division into a paramedian subdivision proximal to the midline, and a fibrous subdivision. Separate from the parvocellular division, there is a poorly myelinated caudodorsal division. These different MD nucleus divisions preferentially and reciprocally connect with different prefrontal cortical (PFC) areas. The magnocellular division preferentially connects with orbitofrontal cortex (Brodmann areas (BA) 11, 13, 47/12), the caudodorsal division connects with medial PFC (BA 14, 24, 32), and the parvocellular division connects with lateral PFC (BA 9, 45, 46). Each MD thalamic division is well positioned to influence distinct PFC circuits.

The midline structure, the Re nucleus, is reciprocally connected with medial PFC and the hippocampal formation,

subiculum and entorhinal cortex (rat: Vertes et al., 2006; Hoover and Vertes, 2012). Although it has been less studied, the Rh nucleus shows similar, possibly broader, connectivity. In addition, a number of Re/Rh neurons give collaterals to both PFC and medial temporal lobe (Cassel et al., 2013). It is important to note that the hippocampus directly projects to the PFC. In contrast, medial PFC directly projects to parahippocampal areas, but not to the hippocampus itself (Pandya et al., 1981; Vertes et al., 2007). Thus, information can only be indirectly routed from the medial PFC to the hippocampus, either via the Re/Rh or the parahippocampal areas (which themselves receive input from the Re/Rh). This anatomical connectivity suitably positions the midline thalamus to regulate communication between medial temporal and prefrontal areas.

The intralaminar thalamus has been classically viewed to non-specifically project to the cortex. However, more recent appraisals suggest that individual intralaminar nuclei each preferentially connect with particular regions of cortex (Van der Werf et al., 2002). In macaque monkeys, motor cortex and parietal cortex provide input to the central lateral nucleus, whereas the granular PFC (and medial limbic cortex) provides input to the central medial and paracentral nuclei (Künzle and Akert, 1977; Akert and Hartmann-Von Monakow, 1980). This anterior group of intralaminar thalamic nuclei also receives subcortical input from the cerebellum, brainstem and spinal cord (Jones, 2007). Evidence suggests at least the subcortical inputs from the cerebellum may predominantly synapse on intralaminar neurons that project to the striatum (see below; rat: Ichinohe et al., 2000). The anterior intralaminar nuclei project to frontal and parietal cortex. The central lateral and paracentral nuclei mainly project to the lateral cortical areas, whereas the central medial nucleus mainly projects to the medial and basal cortical areas. Projections to parietal cortex predominantly originate in the central lateral nucleus (cat: Macchi et al., 1984; Royce et al., 1989).

For the posterior group of intralaminar nuclei, the premotor cortex provides input to Pf and the motor cortex provides input to Cm (Künzle and Akert, 1977; Akert and Hartmann-Von Monakow, 1980; Chiba et al., 2001). The posterior intralaminar nuclei, predominantly Cm, receives a robust projection from the internal segment of the globus pallidus (Parent et al., 2001). Cm projects to motor cortex and Pf projects around rhinal sulcus and cingulate gyrus (cat: Macchi et al., 1984; Royce and Mourey, 1985). There is also a substantial projection from the intralaminar nuclei to the striatum, and it appears that more intralaminar neurons, especially in Cm, project to the striatum than the cerebral cortex.

The intralaminar nuclei project to most of the striatum, allowing modulation of striatal output (Smith et al., 2004). Generally speaking, cortical areas and intralaminar nuclei that are directly connected, also tend to project to overlapping parts of the striatum. Many cortical neurons projecting to the intralaminar nuclei have branched axons that project to the striatum as well (cat: Royce, 1983a; Paré and Smith, 1996). There is also a small number of Cm, Pf and central lateral neurons with axons that branch off to the striatum and cortex (cat: Royce, 1983b). Anterior intralaminar nuclei connections with the caudate and putamen mainly correspond with the location of cortico-striatal terminations from parietal and cingulate cortex. Considering the posterior intralaminar nuclei, there is a Cm connection bias towards the putamen and head of the caudate nucleus proximal to the internal capsule, where sensorimotor and premotor cortex projections terminate; and a Pf bias towards much of the caudate nucleus and anterior pole of the putamen, where PFC and parieto-temporal cortex projections terminate. That is, Cm projects to most of the sensorimotor area of the striatum (in dorsolateral caudate and putamen) and Pf projects to most of the cognitive and limbic areas of the striatum (in central caudate and putamen; Selemon and Goldman-Rakic, 1985; Sadikot et al., 1992). For more information on the thalamo-striatal pathway, see excellent recent reviews by Smith et al. (2004, 2011) and Minamimoto et al. (2014).

Summarizing the thalamo-cortical connectivity, the MD nucleus predominantly connects with the PFC, midline nuclei connect with medial PFC and medial temporal lobe, anterior intralaminar nuclei connect with frontal and parietal cortices, and posterior intralaminar nuclei connect with prefrontal and motor cortices (**Figure 1C**). The intralaminar and medial thalamic nuclei thus form important hubs in multiple frontal, parietal and medial temporal networks.

PULVINAR AS MODEL FOR HIGHER-ORDER THALAMUS

The pulvinar is the largest thalamic nucleus and higher-order part of the visual thalamus. The pulvinar is extensively and reciprocally connected with much of the cerebral cortex, especially visual and oculomotor areas. Generally speaking, directly connected visual cortical areas are also indirectly connected via the pulvinar. This pattern of pulvinar connectivity with the cortex ideally positions the pulvinar to influence information transmission between cortical areas (Shipp, 2003; Sherman and Guillery, 2006; Saalmann and Kastner, 2011).

Recent studies have shown that lesions of the pulvinar can greatly reduce cortical excitability (Purushothaman et al., 2012) as well as produce profound behavioral deficits, including deficits in attention and sensory-guided actions (Snow et al., 2009; Wilke et al., 2010). Simultaneous recordings from the pulvinar and cortex have shown these areas synchronize their activity during attention tasks (Wróbel et al., 2007; Saalmann et al., 2012). Furthermore, evidence suggests that the pulvinar modulates the neural synchrony between cortical areas, to regulate information transmission across cortex according to behavioral demands (Saalmann et al., 2012). Because of common cellular properties across higher-order thalamic nuclei and thalamo-cortical connectivity patterns, a general role for the higher-order thalamus may be to modulate neural synchrony between groups of cortical neurons, to control cortical information transmission (**Figure 1D**). This idea will be explored in separate sections for the MD, midline and intralaminar thalamic nuclei.

MEDIODORSAL THALAMUS PHYSIOLOGY AND FUNCTION

Macaque monkey studies suggest a role for MD thalamic neurons in working memory processes. In macaques trained in delayed response tasks, MD neurons have been shown to modulate their spike rate during the cue, delay and/or response periods. Around half of neurons in the parvocellular division of the MD nucleus showed increased spike rate during the delay period of the

task. Cells with delay period activity have been found in the magnocellular division as well, but the sample size is smaller (Fuster and Alexander, 1971, 1973; Watanabe and Funahashi, 2004). Such delay period activity has been proposed to play a key role in working memory processes. Many MD neurons also have shown direction selective activity reflecting the cue or upcoming response (Tanibuchi and Goldman-Rakic, 2003). The proportion of MD parvocellular neurons showing delay period activity and direction selectivity is similar to that in dorsolateral PFC (Takeda and Funahashi, 2002; Watanabe and Funahashi, 2004). Deactivation of the dorsolateral PFC reduced delay period activity in the parvocellular division of MD thalamus, and increased the number of MD thalamic neurons firing rhythmic bursts, typical of low vigilance states (Alexander and Fuster, 1973). This suggests that the PFC contributes to MD neuronal response characteristics.

In mice trained in a spatial working memory task (T maze delayed non-match to sample task), MD neuronal spiking synchronized with PFC local field potentials (LFPs) in the low beta frequency range (13–20 Hz), with MD spikes leading (Parnaudeau et al., 2013). During the task acquisition period, the beta frequency synchrony between the MD thalamus and PFC increased (measured as LFP-LFP coherence). Using a pharmacogenetic approach to hyperpolarize MD neurons, the reduced MD spiking activity corresponded to impaired performance of the mice in the delayed non-match to sample task (Parnaudeau et al., 2013). The reduced MD activity perturbed synchrony between MD and PFC. Importantly, the degree of MD-PFC synchronization correlated with task performance. Taken together, these results suggest that MD neurons influence PFC dynamics as well as working memory.

The PFC is vital for working memory as well as other executive brain functions, such as response inhibition, selective attention, and mental set shifting, which allow you to flexibly adapt your behavior according to current goals and context (Miller and Cohen, 2001; Diamond, 2013). Because different divisions of the MD nucleus connect with distinct regions of PFC (Ray and Price, 1993), which make differential contributions to executive processing, the MD nucleus may be involved in a variety of executive functions, not only working memory processes.

Because of the extensive reciprocal connections between the MD thalamus and PFC, one might expect that manipulating the MD thalamus will have an influence on the PFC, and vice versa. The above results are consistent with thalamo-cortical interactions playing an important role in working memory processes and perhaps executive processes more generally. The question posed here is how does the thalamus influence the cortex? Evidence suggests that directly connected PFC areas are also indirectly connected via the MD nucleus (Ray and Price, 1993). This connectivity pattern allows the MD thalamus to influence information transmission between PFC areas. Because this connectivity pattern is similar to that between the pulvinar and visual cortical areas, it is possible that the mechanism of MD influence on the cortex may also be similar to that of pulvinar influence on the cortex. That is, it is proposed that the MD thalamus normally modulates the degree of synchrony between different groups of PFC neurons, to regulate cortical information transmission. In this case, one would expect increased synchrony between the MD thalamus and PFC during working memory tasks, consistent with the Parnaudeau et al. (2013) study.

A critical test of the proposal would be to simultaneously record from the MD thalamus and two PFC areas during a working memory task. The prediction would be MD selectively synchronizing PFC neurons representing task relevant information (**Figure 1D, top**). *A second key test* would be deactivating MD thalamus to measure effects on synchrony and information transmission between PFC areas. The prediction would be abnormal cortical synchronization patterns and perturbed information transmission (**Figure 1D, bottom**). Interestingly, cortical synchronization patterns are altered in schizophrenia (Uhlhaas and Singer, 2010) and there is evidence of changes in MD thalamus as well (Andreasen, 1997; Popken et al., 2000; Alelú-Paz and Giménez-Amaya, 2008). One hypothesis consistent with these findings is that MD dysfunction in disorders such as schizophrenia may give rise to the observed changes in cortical synchronization patterns, which perturb information transmission and give rise to schizophrenic signs.

MIDLINE NUCLEI PHYSIOLOGY AND FUNCTION

Evidence from rat studies suggests a role for the midline thalamus in memory processes. Increased neural activity in Re/Rh, gauged by c-Fos expression, has been shown 25 days after learning the Morris water maze (but not after 5 days). When Re/Rh was lesioned, there was normal acquisition of the water maze task, but impaired memory retrieval after 25 days (Loureiro et al., 2012). This suggests that Re/Rh contributes to memory consolidation. Re/Rh may further contribute to recognition memory, because Re/Rh lesions interfered with performance in a delayed non-match to sample task (Hembrook et al., 2012). The Re nucleus has also been implicated in fear memory, and it is has been proposed that Re regulates the generalization of memory attributes, to facilitate responses to novel situations that share similar features with past experiences (Xu and Sudhof, 2013). The role of the midline thalamic structures may not be limited to memory-related functions. Lesioning Re/Rh also has been reported to affect strategy shifting (Dolleman-Van Der Weel et al., 2009; Cholvin et al., 2013).

There have been relatively few electrophysiological recordings from the midline thalamic nuclei. In rats, systemic ketamine dosing (an NMDA receptor antagonist, here used to mimic schizophrenia symptoms) that slowed movements, but did not produce unconsciousness, increased the spike rate of Re neurons, the power of delta (1–4 Hz) oscillations in the Re nucleus, and the modulation of Re spiking activity at delta frequencies (locally applied ketamine induced a similar electrophysiological effect; Zhang et al., 2012). It has also been reported that the spike rate of Re neurons increased during theta (4–8 Hz) oscillatory activity induced by tail pinch (Morales et al., 2007). This suggests state-dependent modulation of both spike rate and spike timing in the Re nucleus.

The Re nucleus can synchronize with the hippocampus and induce hippocampal oscillatory patterns (Zhang et al., 2012). Dolleman-Van Der Weel et al. (1997) showed that stimulation of the Re nucleus caused subthreshold depolarization of pyramidal

cells in hippocampus (CA1) and a suprathreshold excitation of inhibitory cells. Increasing Re output (with either neuroligin-2 knockdown or electrical stimulation) not only increased CA1 activity, but also increased medial PFC activity (measured using c-Fos expression: Xu and Sudhof, 2013; or evoked-potentials: Di Prisco and Vertes, 2006). Conversely, reducing Re output (tetanus toxin activation) reduced CA1 and anterior cingulate cortical activity (Xu and Sudhof, 2013). It has been shown that PFC neurons can synchronize their spiking to the hippocampal theta rhythm, with hippocampal activity leading PFC (Siapas et al., 2005). This prefrontal-hippocampal synchrony may be important for effective information transfer and spike timing-dependent plasticity. Because the Re nucleus has been shown to influence activity in both PFC and the hippocampus, as well as modulate oscillatory patterns in the hippocampus, it is possible that the Re modulates synchrony between the PFC and medial temporal lobe to regulate information transmission and storage.

ANTERIOR INTRALAMINAR NUCLEI PHYSIOLOGY AND FUNCTION

It has been proposed that the anterior intralaminar nuclei are part of an oculomotor thalamus (Schlag, 2009). At least three types of anterior intralaminar neurons can be differentiated during spontaneous eye movements: burst neurons that increase firing around saccades; pause neurons that stop firing around saccades, a number with post-pause rebound activity; and eye-position neurons, whose activity reflects orientation of the eye in the orbit (Schlag-Rey and Schlag, 1984). In a delayed saccade task, anterior intralaminar neurons responded to the visual cue, delay period and/or saccade (Wyder et al., 2003). Most neurons showed motor-related or both visual and motor-related responses. These neurons showed directional tuning, even during delay activity. Only a small number of sampled neurons showed solely visual-related responses. The latency of responses to the visual cue was usually 60–100 ms, and neurons showing pre-saccadic activity as well as neurons showing post-saccadic activity were common. The timing of these saccade-related activities suggests that the anterior intralaminar thalamus may be able to contribute to saccade generation as well as movement monitoring, possibly corollary discharge processing.

Behavioral context influences the activity of anterior intralaminar neurons. Central thalamic neurons, including central lateral and paracentral neurons, have shown increased spiking activity during the delay period in visually-guided and memory-guided delayed saccade tasks (Wyder et al., 2003, 2004). This delay period activity was modulated based on whether the cue signaled a distractor or the saccade goal in the response field. Error trials influenced delay period activity as well (Wyder et al., 2004; Schiff et al., 2013). In a human positron emission tomography study, increased attentiveness during visual and somatosensory stimulus detection tasks activated the intralaminar nuclei, likely the central lateral and Cm nuclei (Kinomura et al., 1996). Oscillatory activity in the central thalamus also depends on context. Increased gamma frequency (30–100 Hz) power of LFPs, and reduced power at lower frequencies (10–20 Hz), has been reported during the delay period in a variable foreperiod, reaction time task (Schiff et al., 2013). The limited evidence available is consistent with the anterior intralaminar nuclei contributing to attention-related processes.

A classical finding is that electrically stimulating (e.g., at 6–14 Hz) the intralaminar, and a number of other, thalamic nuclei induces the cortical augmenting response, that is, increasing amplitude of cortical field potentials, with activity synchronizing over large cortical regions and post-augmenting oscillatory activity (Morison and Dempsey, 1943; Castro-Alamancos and Connors, 1996b; Steriade et al., 1998). The magnitude of the augmenting response depends on behavioral state: increasing vigilance reduces the augmenting response (Castro-Alamancos and Connors, 1996a). This may mean that the widespread cortical synchronization that disrupts normal information transmission, for instance, during anesthesia and sleep, gives way to more spatially precise synchronization during waking activities. It has been shown that anterior intralaminar thalamic stimulation produces robust evoked potentials in medial frontal and parietal cortex (rat LFP: Kung and Shyu, 2002; human EEG: Schiff et al., 2007) and optogenetic activation of thalamo-cortical axons modulates responses of neurons in cortical layer 1 and layer 2/3 (Cruikshank et al., 2012). This suggests that, under normal conditions, the anterior intralaminar nuclei can influence the excitability of frontal and parietal cortical neurons and synchronize these cortical neurons with spatial precision (not just expansive augmenting responses).

The intralaminar nuclei play an important role in arousal regulation. Central thalamic damage is associated with disorders of consciousness, including acute coma after bilateral lesions and hemispatial neglect after unilateral lesions (Schiff, 2008). In minimally conscious patients, electrical stimulation of the central thalamus can improve behavioral responsiveness (Schiff et al., 2007). Moreover, particular parts of the cortex appear to be important contributors to conscious awareness, including certain areas of parietal (e.g., posterior cingulate), temporo-parietal and frontal cortex (Hudetz, 2012), to which the intralaminar thalamic nuclei are extensively connected (Van der Werf et al., 2002). However, it is unclear how the intralaminar thalamus contributes to mechanisms of consciousness. A neural correlate of consciousness is large-scale integration of processing across multiple cortical areas (Alkire et al., 2008). This integration appears to rely at least in part on neural synchronization between distributed groups of cortical neurons. One hypothesis that ties together the above findings is that the intralaminar thalamus may precisely synchronize ensembles of cortical neurons in multiple circuits, including those related to orienting, attention and memory processes (processes which have been shown to influence conscious awareness). As a secondary effect, this thalamic-mediated cortical synchrony may give rise to large-scale integration of information, influencing the level of arousal and consciousness.

POSTERIOR INTRALAMINAR NUCLEI PHYSIOLOGY AND FUNCTION

In macaque monkey studies, most Cm/Pf neurons show multimodal sensory activity, responding to auditory, visual and/or

somatosensory stimuli. Cm/Pf neurons can be categorized into two types based on response latency: short- and long-latency facilitation neurons, with mean latency less than 100 ms (as short as 30 ms or less to auditory clicks) and greater than 200 ms respectively (Matsumoto et al., 2001; Minamimoto and Kimura, 2002). The short-latency neurons have been found predominantly in Pf and the long-latency neurons predominantly in Cm. Cm/Pf neurons generated brief, phasic responses to a stimulus, and a number of long-latency neurons generated two or three repeat phasic responses. Cm/Pf neurons generally showed greater responses to unexpected sensory stimuli, and habituated to repeated stimulus presentations. Cm/Pf neurons responded to the sensory stimuli whether or not they were associated with reward, unlike (tonically active) striatal neurons recorded under similar conditions, which only responded to stimuli linked to reward. Inactivating Cm/Pf greatly reduced the striatal response to the reward-linked stimuli; the effect on the cortex is not known (Matsumoto et al., 2001; Minamimoto and Kimura, 2002). Considering that attention-demanding tasks modulate Cm activity (Kinomura et al., 1996; Minamimoto and Kimura, 2002), these results suggest that the posterior intralaminar thalamus provides information about behaviorally relevant sensory events to the striatum, and possibly the cortical targets of intralaminar neurons as well. The posterior intralaminar nuclei may thus influence cortical processing through the thalamo-striatal input to cortico-striatal-thalamo-cortical pathways or, more directly, through the Cm/Pf input to the cortex.

Human subjects after thalamic stroke affecting the Cm/Pf (as well as ventral MD thalamus) have been reported to perform poorly on the Wisconsin Card Sorting Test. It was argued that the intralaminar thalamic lesion impaired shifting of cognitive sets (Liebermann et al., 2013). In macaques performing a go-nogo task with the go or nogo instruction associated with either a large or small reward, long-latency neurons in Cm showed greater activity during small reward trials than large reward trials (Minamimoto et al., 2005). The Cm response preceded movement execution. This suggests that the Cm helped counter bias (bias, in this case, toward the high reward action) when responding to external demands, thereby contributing to flexible shifts of rule-guided behavior. This interpretation is supported by the behavioral effects of electrical stimulation of Cm during the go-nogo task, that is, slowed responses for high reward actions (Minamimoto et al., 2005). Both the Wisconsin Card Sorting Test and the go-nogo task require cognitive flexibility and response inhibition. Different groups of neurons will need to be activated based on the current behavioral rule. Dynamically shifting between different rule-guided behaviors may involve synchronizing different task-relevant groups of frontal cortical neurons (Buschman et al., 2012). Synchrony between different cortical areas has been reported during the Wisconsin Card Sorting Test (González-Hernández et al., 2002), and Cm/Pf stimulation has been shown to synchronize cortical activity (Starzl and Magoun, 1951). This opens the possibility of Cm/Pf, in concert with other higher-order thalamic nuclei like MD, modulating cortical synchrony based on the current relevant course of action.

CONCLUSION

Overall, the growing evidence supports important and specific roles for the intralaminar and medial nuclei, and higher-order thalamus more generally, in the control of cortical information transmission and cognitive processing. A critical mechanism may involve higher-order thalamus adjusting cortical synchrony and oscillatory patterns and thereby the efficacy of information transmission. However, further studies are needed to establish a causal role for the higher-order thalamus in regulating the synchrony between cortical neurons and consequently cognitive processing, particularly simultaneous neural recordings from thalamic and cortical areas of behaving primates as well as (pharmacological, electrical stimulation or optogenetic) manipulation of thalamocortical networks.

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