Title: Thalamocortical interactions in cognition and disease: the mediodorsal and anterior thalamic nuclei

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Abstract

The mediodorsal thalamus (MD) and anterior thalamic nuclei (ATN) are two adjacent brain nodes that support our ability to make decisions, learn, update information, form and retrieve memories, and find our way around. The MD and PFC work in partnerships to support cognitive processes linked to successful learning and decision-making, while the ATN and extended hippocampal system together coordinate the encoding and retrieval of memories and successful spatial navigation. Yet, while these distinctions may appear to be segregated, both the MD and ATN together support our higher cognitive functions as they regulate and are influenced by interconnected fronto-temporal neural networks and subcortical inputs. Our review focuses on recent studies in animal models and in humans. This evidence is re-shaping our understanding of the importance of MD and ATN cortico-thalamocortical pathways in influencing complex cognitive functions. Given the evidence from clinical settings and neuroscience research labs, the MD and ATN should be considered targets for effective treatments in neuropsychiatric diseases and disorders and neurodegeneration.

1.0 Introduction

The thalamus contributes to many varied cognitive processes, in addition to its widely acknowledged and pivotal roles in visual, auditory, somatosensory, and motor processes. For the purposes of this review, we focus on the mediodorsal (MD) and anterior thalamic nuclei (ATN). The association of the MD and ATN with higher order cognitive processes has long been recognized in clinical settings (Victor et al., 1971), although this is often attributed to the disrupted conveyance of information from distal brain regions to the cerebral cortex, via the thalamus. Fortunately, a shift has occurred in our view of the thalamus from a mere relay of peripheral and subcortical information to cortex, to that of a dynamic structure, working in partnership with the cortex, where it can influence and maintain cortical states (Mitchell, 2015; Halassa and Kastner, 2017; Halassa, 2018; Pergola et al., 2018).

In the past 5 years, it could be suggested that limbic, and dorsal, medial thalamic nuclei, including the MD and ATN, have finally received a share in the spotlight of our attention. Neuroscientists have further identified the neuroanatomical connections of these nuclei using transcriptional analyses, viral constructs, electron and light microscopy, and made inroads into defining the characteristics of MD and ATN cell populations using genotyping, phenotyping, and neurophysiology. These and other state-of-the-art techniques have been deployed to gather evidence of thalamocortical and corticothalamic contributions to cognitive functions including (1) neuronal recordings in primates and rodents, which are sometimes combined with chemogenetics or optogenetics. These have helped to identify the specific contribution of neural populations and/or pathways, or (2) discrete neuronal manipulations (drugs or excitotoxic lesions) combined with complex cognitive and behavioral assessments have provided causal evidence of the unique functional contributions of the MD and ATN. Clinicians too, have made use of advances in technology, particularly

developments in neuroimaging, to further define the involvement of the MD and/or the ATN in neuropsychiatric diseases and neurological and neurodegenerative disorders.

This review of the thalamocortical interactions in cognition and human diseases is divided into five main sections: Sections 2 and 3 provide updates on the neuroanatomical connectivity and the functional evidence identifying the influence of the MD and ATN in higher cognitive functions respectively, while Section 4 considers some of the latest clinical evidence implicating both the MD and ATN in neurological diseases and disorders. Finally, in Section 5, we focus on some of the models linking the MD and ATN to higher cognitive functions and consider future studies that build on our current understanding. In Section 3, for the ATN, we focus on recent electrophysiology and neuroanatomical studies that uncover the nature and functional significance of ATN-subicular complex interactions, with an emphasis on the pre-subiculum (PrS). The subiculum, the PrS, and the para-subiculum form the subicular complex. The dorsal part of the pre-subiculum (dPrS) is also termed post-subiculum in rats (Van Groen and Wyss, 1990c), and contains the largest proportion of cells tuned to head direction (Taube, 2007; Sargolini et al., 2006; Boccara et al., 2010; Winter et al., 2015a). Connectivity and electrophysiological properties of the other main cortico-thalamocortical pathway through the ATN, involving reciprocal ATN-retrosplenial cortex (RSC) connections in both rodents and monkeys, have been already reviewed in detail (Vann et al., 2009; Mitchell et al., 2018). Throughout the review, we share our thoughts on significant gaps in understanding the influence of the MD and ATN interactions with cortex in cognitive processes. Specifically, we aim to highlight the commonalities in how both the MD and ATN together influence the cortical mantle and thus, contribute significantly to higher cognitive functions, and neural diseases and disorders.

1.1 MD and ATN subdivisions

For the MD, each subdivision has dense and reciprocal connections to selective regions of frontal cortex that in combination span the entire frontal cortex area (see **Figure 1**). As previously detailed (Mitchell and Chakraborty, 2013; Mitchell, 2015), the MD comprises at least three distributed neural circuits, which in the primate center around the medial magnocellular (MDmc; for the rodent MDm), the central parvocellular (MDpc; for the rodent MDc) and the lateral MD (for the rodent MDl) subdivisions. As shown in **Figure 1**, the MDmc forms part of a fronto-temporal circuit connecting preferentially with more ventral regions of prefrontal cortex (PFC) including central and lateral orbital frontal cortex (areas 11, 12, 13 and 14) and agranular insular cortex; it also receives input from ventrolateral PFC (12, 45/47), amygdala, inferotemporal cortex, and the perirhinal, entorhinal, and piriform cortex (McFarland and Haber, 2002; Xiao et al., 2009). The MDpc forms a frontal circuit connecting primarily to dorsolateral PFC (areas 9 and 46) and the dorsal anterior cingulate cortex (ACC: areas 24, 32 and 14: see Mitchell 2015 for review). The lateral MD primarily connects to the frontal eye field and dorsomedial PFC in primates, and dorsal ACC in rodents. The subcortical connectivity to each of these subdivisions is also different (see Mitchell 2015 for review). There is also some degree of convergence of MDpc and MDmc cortical connections in primates, with both regions having reciprocal connections to frontal polar cortex (area 10), OFC (areas 12 and 13), and projections from dorsal ACC (area 32). However, differences between the MDpc and MDmc emerge from the efferent laminar (e.g., layer V and layer VI) origins of this cortical connectivity (Schwartz et al., 1991; Xiao et al., 2009; Timbie and Barbas, 2014). Evidence (as detailed in Section 2) suggests that these three circuits are involved in distinct aspects of higher cognitive processes.

The ATN, which sit more rostral in the dorsal thalamus than the MD, are comprised of three distinct nuclei, the anteroventral nucleus (AV), the anteromedial nucleus (AM) and

the anterior dorsal nucleus (AD: **Figure 2**). Each nucleus of the ATN is connected to the RSC and subicular cortex, but to different subregions (**Figure 2;** for review see: Jankowski et al., 2013; Aggleton et al., 2010; Mitchell et al., 2018; Perry and Mitchell, 2019) and contribute to different cognitive processes. The AV is connected to both granular and dysgranular RSC and posterior cingulate cortex in primates, whereas the AD is interconnected to granular RSC. The AM is widely linked to multiple regions of the PFC, the ACC, and dysgranular RSC. The overlap in connectivity between the MD and ATN is found within the PFC and ACC.

Communication with the subicular complex also define the ATN, as all three nuclei are reciprocally connected with at least one of its subregions, namely the subiculum, PrS, or para-subiculum (Canteras and Swanson, 1992; Shibata, 1993; Naber and Witter, 1998; Van Groen et al., 1999; Ishizuka, 2001; Wright et al., 2010). In rodents, the PrS can be further divided into dorsal and ventral subregions (Van Groen and Wyss, 1990c). Within the subicular complex, the subiculum sends projections to all three ATN nuclei via the fornix (Wright et al., 2010), with anatomically distinct cell populations projecting to the mammillary bodies or the ATN (Naber and Witter, 1998; Ishizuka, 2001; Aggleton et al., 2005; Wright et al., 2013). In addition to these subicular inputs, the AV and AD, but not AM, also receive projections from the para-subiculum and PrS (Van Groen and Wyss, 1990a,c; Wright et al., 2010). Both the AV and AD project back to para-subiculum and PrS (Van Groen and Wyss, 1990a,c; Van Groen and Wyss, 1995), and only the AM and AV reciprocate their anatomically segregated subicular inputs (Shibata, 1993; Van Groen et al., 1999; Canteras and Swanson, 1992).

2.0 Updates on the neuroanatomical and physiological basis of MD-PFC interactions

2.1 Rodent neuroanatomy

Although the global afferent and efferent connections from the MD to different areas of the PFC are well defined, much less is known about the local connectivity within the PFC micro-circuits to which the MD projects. Recent studies have attempted to close this gap in our understanding. In addition to the origin of their primary driving input, thalamic relays can also be divided by the organization of their efferent projections to cortex. “First order” thalamic relays conveying peripheral sensory information are suggested to form feedforward pathways by densely innervating layer IV of sensory cortex to drive activity in local cortical networks. By contrast, “higher order” thalamic relays, involved in complex cognition, are thought to form feedback pathways by sending inputs into superficial layer I of cortex where they form synapses on the apical dendrites of layer V pyramidal cortico-thalamic neurons (Sherman and Guillery, 2013).

For example, Delevich et al. (2015) showed that the organization of higher order MD inputs to the dorsal ACC (dACC), as predicted for a higher order thalamic nucleus, differ from those of first order thalamic inputs. Delevich et al. (2015) observed that inputs from the MD drive complex di-synaptic feedforward inhibition in the dACC, where axons arising from MD neurons directly synapse onto and excite parvalbumin (PV) interneurons that in turn mediate feedforward inhibition of pyramidal neurons in layer III of the dACC. This type of arrangement would allow for the greater flexibility required for higher order cognition in the dACC than the high-fidelity perceptual processing occurring in sensory cortex.

Further, using viral vectors and neural tracers in mice, Collins et al. (2018) found that the MDl preferentially targeted layer II/III dorsomedial PFC (dmPFC: prelimbic and ventral part of the dACC) neurons, which are known to receive inputs from both amygdala and hippocampus. Experiments using optogenetics showed that the cortico-thalamic neurons in dmPFC are strongly driving the neuronal firing in the thalamus, whereas MD only indirectly influences reciprocally connected neurons in the dmPFC (Collins et al. 2018). That is, local

circuits within the dmPFC connect the pyramidal neurons in layer II/III to the corticothalamic neurons in layer V, allowing a feedback loop.

Building on the work from Collins et al. (2018), Anastasiades et al. (2021) reported that thalamocortical neurons in the MDl target a distinct class of inhibitory interneurons in cortical layer 1b of the dmPFC. Axons from MDl neurons were found to engaged vasoactive intestinal polypeptide-expressing (VIP+) cells which, in turn, inhibit somatostatin expressing interneurons (SOM+). These SOM+ cells associated with the MDl circuit, then go on to form an inhibitory synapse on the dendritic tufts of layer V pyramidal neurons, forming a classical disinhibitory circuit (Anastasiades et al., 2021).

Other recent work has supported these findings by suggesting that the MD may have a critical role in maintaining the balance between excitation and inhibition in dmPFC (Ferguson and Gao, 2018). Using a chemogenetic approach, the authors showed that dampening MD activity caused a profound reduction of gamma amino butyric acid (GABA) signaling in the dmPFC. This resulted in an excitation/inhibition imbalance in the dmPFC and impaired performance on behavioral measures of cognition, social interaction, and anxiety (Ferguson and Gao, 2018). Critically, the excitation/inhibition balance appeared to be driving the behavioral deficits as increasing GABAergic signaling in cortex by selective activation of PV+ interneurons ameliorated all behavioral deficits.

Not only does it appear that MD thalamocortical neurons allow for considerable flexibility by activating and disinhibiting distinct cortical circuits, but also that single MD neurons within the subdivisions of rodent MD (MDm, MDc and MDl) send their axon fibres to multiple PFC regions concurrently (Kuramoto et al., 2017). In accordance with previous tracer work, Kuramoto et al. (2017) found that individual neurons in the MDm sent their axons abundantly to OFC, the MDl intensely projected to the dmPFC, while the MDc showed mixed projections innervating dmPFC, infralimbic cortex, OFC, and other frontal association

areas. The multiple area projection properties of single MD neurons strongly suggest that they can recruit distributed groups of cortical neurons, even in distant prefrontal areas, simultaneously.

Using a more traditional approach, Alcaraz et al. (2016) infused multiple retrograde tracers into the dmPFC, the infralimbic cortex, or OFC to clarify the location of the MD thalamocortical neurons projecting to each of these PFC subregions. Alcaraz et al. (2016) observed at least three separate populations of MD thalamocortical neurons that targeted different subregions of PFC. In general accordance with the pattern of findings observed in primates, cells located in the MDl preferentially projected to dmPFC, whereas cells in the MDm and MDc (MDmc and MDpc in primates) preferentially projected to ventromedial PFC and infralimbic cortex. Taken together with the findings of Kuramoto et al. (2017), these studies support the idea that there may be two distinct pathways, MDm and MDl, with a medial-ventral vs lateral-dorsal organization, respectively, and a third pathway, MDc, receiving overlapping information from a wider range of cortical regions.

Using a more global approach to classifying thalamic nuclei, Phillips et al. (2019) showed that in mice higher order thalamic relays, such as MD, can be dissociated using their transcriptional profile. Based on an analysis of gene markers, three major thalamic profiles emerged: primary, secondary, and tertiary nuclei. Importantly, these genes were found to be consistent with those found in human tissue suggesting this organizational logic likely applies more generally to mammals and is not specific to rodents. Nuclei conveying relatively unprocessed, first order sensory information fell into the primary category, this contained regions such as the AV, AD, and parts of the adjacent laterodorsal thalamic nucleus. By contrast, thalamic nuclei that received ‘driver’ inputs from layer 5 of cortex and showed broad arborization in cortical layer 1 formed the secondary category. As would be expected, the secondary cluster contained nuclei already proposed to be ‘higher order’ thalamic relays,

such as the MD and VM, but interestingly, the profile of the AM also belonged to this cluster (Perry and Mitchell, 2019). The tertiary cluster was primarily composed of those thalamic nuclei suggested to have a role in arousal along with dense frontal projections, such as the intralaminar thalamic nuclei.

2.2 Primate neuroanatomy

Along with dense inputs from PFC, the MD also receives inputs from many subcortical regions, including the substantia nigra, ventral tegmental area, basal ganglia, brainstem, and amygdala (for review, see Mitchell and Chakraborty, 2013). Elegant work from the Barbas' lab suggests that perhaps the greatest divergence in input to the subdivisions of the MD, at least in the macaque, might come from their subcortical inputs. Timbie et al. (2020) used neural tracers coupled with light and electron microscopy to show that a proportion of cells within the primate MDmc, but not MDpc, or the adjacent paraventricular thalamic nucleus, receive a potent, driving input from the amygdala. The strength, and likely importance, of this amygdala input to the MDmc can be seen by the similarity of the synaptic triads they form to those in the lateral geniculate nucleus by retinal axons. The authors speculate that this pathway may be involved in conveying signals forwarded to the OFC to monitor and update the status of the environment, specific to the MDmc circuit.

The differential subcortical input in the MDmc, compared to the MDpc is also reflected in an earlier immunohistochemical investigation of driving inputs in the primate thalamus by Rovo et al. (2012). Rovo and colleagues compared the distribution of vGluT1 and vGluT2 in the thalamus of macaque monkeys. The presence of vGluT1 is indicative of excitatory input from cortex, and vGluT2 is indicative of excitatory input from subcortical regions. Rovo et al. (2012) found a clear dissociation between MDmc and MDpc. The MDpc stained intensely for vGluT1 indicating predominantly cortical inputs, a large area of which

appeared to be large (driving) vGluT1 boutons from secondary motor cortex. By contrast, a substantial region of the MDmc showed dense staining for vGluT2 and the majority of these were large driving vGluT2 boutons. At the time it was suggested that the origins of these subcortical driving inputs may come from structures relating to nociception. We now know, however, that at least some of these large vGluT2 boutons originate in the amygdala, although this does not exclude additional sources of subcortical vGluT2 driving input to the MDmc (Timbie et al., 2015, 2020).

In combination, the rodent neuroanatomical studies provide fundamental information regarding the neuroanatomical basis of MD-PFC interactions, while studies in the non-human primate (NHP) compliment and extend this work by providing a more suitable analogue of the cortical development and cognitive complexity found in humans (Passingham and Wise, 2012). Moreover, evidence shows significant phylogenic divergences are present between rodent and primate thalamus. For example, comparative work across species has shown dense dopaminergic innervation of dorsal thalamus, especially within the MD of both monkeys and humans (Garcia-Cabezas et al., 2007). By contrast, incredibly sparse, almost non-existent, labelling was found in the rodent dorsal thalamus (Garcia-Cabezas et al., 2009). Interestingly, unlike the nigrostriatal or mesocortical dopaminergic systems, the origin of dopaminergic input in the primate thalamus was found to be incredibly complex, with sources in hypothalamus, periaqueductal gray, ventral mesencephalon, and the lateral parabrachial nucleus (Sanchez-Gonzalez et al., 2005). Recent work by the same lab has highlighted the possible importance of this dopaminergic innervation within the dorsal thalamus in the progression of Parkinson's disease (PD; Monje et al., 2020). Monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a model of gradual dopamine depletion, manifest some of the core symptoms of PD. Substantial reductions in axons positive for the dopamine transporter (DAT) were found in the MD and centromedian- parafasicular thalamic

nuclei in MPTP treated monkeys, both those with and without Parkinsonian symptoms, although the decrease was greater in the former. These reductions in DAT positive axons mirrored those observed in the ventral tegmental area, so may constitute a primary alteration that occurs early in disease progression. Interestingly, there appeared to be an increase in DAT in the thalamic reticular nucleus in both symptomatic and asymptomatic monkeys, with the greatest increase found in monkeys with persistent motor deficits, suggesting some form of compensatory modulation to account for the loss of direct dopaminergic innervation to other thalamic regions. What is not clear, and would be of great interest, is whether the loss of thalamic dopaminergic innervation contributes to the cognitive deficits observed in PD.

Further, in addition to the stark difference in thalamic dopaminergic innervation between rodents and primates, the dorsal thalamus of primates also differs markedly from rodents in the organization of inhibitory control within local thalamic circuits. In mammals, there are two primary mechanisms of inhibitory regulation of the dorsal thalamus. The first, present in all species of mammal, comes from the thalamic reticular nucleus (TRN; Pinault, 2004). The TRN develops embryologically from the ventral thalamus and forms a distributed cluster of GABAergic neurons that innervate the cells of dorsal thalamus (Arcelli et al., 1997; Pinault, 2004). The second form of thalamic inhibition comes from local GABAergic interneurons, of which, the soma, axons, and dendrites are contained entirely within a given nucleus of the dorsal thalamus. In primates, GABAergic interneurons are present, and often numerous, in all the dorsal thalamic nuclei (Arcelli et al., 1997). By contrast, these local interneurons are absent in rodents, except for the lateral geniculate nucleus (Arcelli et al., 1997). Thus, in rodents, it appears that inhibitory inputs to dorsal thalamus are provided, perhaps solely, by the TRN (Wang et al., 1999). Ultrastructural studies have shown that the presence of proximal GABAergic interneurons, like those found in the primate dorsal thalamus, adds further intricacy to the synaptology and circuitry of dorsal thalamic nuclei and

281 therefore, support a greater complexity in functional output. Interestingly, Arcelli et al.
282 (1997) observed a decrease in TRN cell density from rodents to humans that paralleled an
283 increase of intra-thalamic GABAergic local circuit neurons. This suggests that in more
284 behaviorally complex species, such as primates, the TRN might be taking on a more general
285 regulatory role, rather than providing a direct thalamic inhibition like that which occurs in
286 rodents.

287 With specific reference to the MD and ATN, a study by Wang et al., (1999) found no
288 evidence of GABA positive cell bodies in the AV or the AD of rats, only axon terminals and
289 myelinated fibers, predominantly from the TRN. The same structural arrangement is true for
290 the rodent MD (Arcelli et al., 1997). By contrast, in the macaque monkey, the AV, AM, and
291 MD all show moderate to high levels of GABAergic immunoreactive neurons. For example,
292 in the AM and AV, GABAergic neurons were found to be ~47% of neurons per volume, and
293 for the MD, ~49% in the MDl and ~35% in the MDmc (Hunt et al., 1991). Taken together,
294 these studies showing greater dopaminergic innervation and local circuit inhibition suggest
295 that the increases in cortical volume and complexity observed in primates are likely
296 paralleled by considerable changes in dorsal thalamus.

297 While tracer studies provide the gold standard in neuroanatomical connectivity, their
298 findings can be combined with those of newer techniques, such as probabilistic tractography
299 in magnetic resonance imaging (MRI) to provide a more complete understanding of neural
300 connectivity across species. For example, Rafal and colleagues (2015) located a previously
301 proposed although unidentified superior colliculus, pulvinar, amygdala pathway using
302 tractography in MRI in both humans and macaque monkeys. This new primate pathway was
303 subsequently confirmed using traditional tracer studies, which demonstrated overlapping
304 projections from the superior colliculus and lateral amygdala within the pulvinar (Elorette et
305 al., 2018). For the MD, a recent study used probabilistic tractography MRI in macaques to

investigate whether a unifying topographic scheme, which has been hinted at by multiple tracer studies, existed *in vivo* for MD-PFC connections across each of 19 architectonic areas of PFC (Phillips et al., 2019). One benefit of this approach is that all 19 cortical areas can be seeded simultaneously, and the paths followed in each individual, whereas the number of tracers that can be used in any given monkey is limited to the number of different fluorescent molecules that can be clearly differentiated within the tissue (typically 3-4). Importantly though, Phillips et al. (2019) used the verified findings from previous tracing work to calibrate their analysis pipeline increasing the validity of their approach. Like tracer studies, they found an orderly progression in the organization of the projections between PFC and MD. Ventromedial to posterolateral PFC were mapped onto anteromedial to posterolateral MD. Put another way, more lateral parts of the MD, like MDpc were more connected to dorsal regions of PFC, whereas the MDmc was more connected to ventral regions of PFC. Importantly, their data suggested a role for MD in coordinating communication across PFC. They found that functionally related, directly connected PFC areas have partially overlapping projection zones in MD. Such an arrangement is also observed in the pulvinar and is known as the replication principle (Shipp, 2003). Interestingly, cingulate area 24 appeared to provide an exception to the partial overlapping found in other cortical regions. Its' projection zone overlapped with projection zones of all other PFC areas, suggesting it may have privileged access to influence thalamocortical interactions involving all other PFC areas.

2.3 Animal models detailing the MD influence over cortical cognitive functions.

2.3.1 MD rodent cognition and behaviour

Two recent studies using advanced genetic techniques in mice have shown the MDl helps to sustain representations and disambiguate signals in the dmPFC when cognitive/attentional demands are high. Schmitt et al. (2017) found that spiking in the MDl

sustained neural activity in the dmPFC when representing two distinct task related rules, even though the MDl neurons themselves were not rule tuned. In a subsequent study, Rikhye et al. (2018) showed that a subset of MDl cells helped to sustain context relevant representation in the dmPFC, while a different subset suppressed context irrelevant ones. Consistent with these findings, Marten et al. (2018) found that selective disruption of dmPFC outputs to MDl with optogenetics, interrupted behavioral flexibility and prevented mice from switching from visual to auditory cues in a decision-making task.

Taking a different approach, this time in rats, Miller et al. (2017) found some key differences between MD and medial PFC (mPFC) action related neural responses while they performed a delayed non-matching to place task. In this study, Miller et al. (2017) recorded neurons in both MDl and MDm and compared task related responses to units previously recorded in mPFC using the same task. MD units (~50%) were found to be dominated by movement and reinforcement responses, compared to less than a third of mPFC units fitting this profile. Interestingly, no MD responses were related to preparation or memory delay as suggested by some previous studies. However, these responses accounted for 43% of event related activity in the mPFC. This finding may relate to differences in the structure of the behavioral task, or electrode location as Miller et al. (2017) sampled units across MD subdivisions, whereas previous studies have focused heavily on the MDl. A further group of MD cells (~22%) showed criterion event-related responses most of which were consistent with mPFC response types.

One powerful ability of viral vectors is that they allow researchers to target specified neural populations and hence pathways in the brain. These techniques have allowed the elucidation of the specific contributions of cortico-thalamic (PFC to MD) and thalamocortical (MD to PFC) pathways to learning, memory, and decision-making tasks. In one study, Bolkan et al. (2017) used optogenetics to produce temporally precise pathway specific

MD→dmPFC or dmPFC→MD inhibition while mice performed a spatial alternation task in the T-maze. Bolkan et al. (2017) found that inhibition of MD→dmPFC projections, but only during an extended inter-trial interval, resulted in impaired performance. By contrast, inhibition of dmPFC→MD projections only reduced performance during the subsequent choice phase of the task. These effects were specific to MD→dmPFC pathways as inhibition of MD→OFC pathways did not alter behavior in this task. Interestingly though, working memory deficits are not typically reported in rats, primates, or in humans with damage to the MD (e.g., Kopelman, 2015; Mitchell, 2015; Pergola et al., 2018). Thus, this performance deficit observed in mice is perhaps either linked to difficulties in implementing an optimal response strategy over time (see discussion below), or instead may be linked to specific deficits caused by temporary inactivation vs the ability of the system to adapt after permanent damage.

Using a different approach, Alcaraz et al. (2018) used chemogenetics to selectively inhibit projection defined neurons in the dmPFC or MDl during an instrumental learning task. Both pathways were found to participate in behavioral adaptions to the current goal value, but only MD→dmPFC neurons were required to integrate current causal relationships between actions and outcomes. Others have reported inactivation of the MD contributes to impaired timing of instrumental actions (Lusk et al., 2020). Taken together all these studies suggest, as previously observed: 1) interdependence between the MD and mPFC during spatial and adaptive decision-making tasks, and 2) that the MD provides a unique influence within the PFC in that task related neural activity in the MD does not simply replicate that of its efferent or afferent interconnected cortex with selective manipulations of corticothalamic and thalamocortical pathways resulting in differential outcomes.

Recently, renewed interest in thalamic contributions to olfactory processes combined with optogenetics have highlighted the contributions of the MDm, along with its connections

to piriform (PC) and orbitofrontal cortex (OFC), as the primary site of olfactory representation in the thalamus (Courtiol and Wilson, 2016; Courtiol et al., 2019). For example, Courtiol and Wilson (2016) found that the proportion of MDm units showed odorant selectivity during sampling when rats performed a two-odor discrimination task. Furthermore, and in agreement with subsequent findings, Miller et al. (2017) also observed that MDm units encoded spatio-motor aspects of the task. In terms of circuit wide functional interactions, a dissociation was found with MDm-PC showing enhanced spike-field coupling in the theta frequency during odor sampling, and MDm-OFC spike-field coupling enhanced in the beta frequency during decision/goal approach. In a further study, Courtiol et al. (2019) examined whether the increased MD-PC coupling had functional relevance. Selective optogenetic inactivation of the PC inputs to MDm during odor sampling did not affect performance accuracy but did increase the length of time rats spent sampling each odor. This finding suggests that to maintain an elevated level of performance the rats needed longer to pair the odor cue with the appropriate spatio-motor response to get rewarded. In combination these studies suggest the MD has a role in supporting the integration of task information, with inputs from the MD helping to disambiguate signals when attentional/ cognitive demands evolve because of changes within the task that necessitate the rapid updating of an optimal already established choice response strategy.

Finally, work in rats from our own lab has reported differential choice response impairments after excitotoxic lesions to combined MDm/MDc during an attentional set-shifting task (Ouhaz et al., 2021). Rats with permanent MD lesions required more trials to criterion to learn the initial sensory discrimination. However, once acquired, they were able to transfer this choice response strategy to further intra-dimensional shifts and reversals linked to the same sensory discrimination. This result provides a direct contrast to rats with excitotoxic lesions to the ATN (Wright et al., 2015) or nucleus reuniens (Linley et al., 2016)

– two neighboring thalamic structures to the MD. Furthermore though, in our recent study, when the rats with combined MDm/MDc lesion encountered the extra-dimensional shift later within the same test session, they required significantly more trials to criterion to learn that the previously unrewarded sensory dimension was now relevant. Our subsequent behavioral analysis of the choice responses of rats with MD lesions indicated that they made fewer correct second choice responses suggesting the MD inputs to mPFC influence cortical functioning when rapid updating of established response strategies must change. Evidence of learning deficits associated with impaired rapid updating of choice responses have been previously reported after excitotoxic MDmc lesions in macaque monkeys (Chakraborty et al., 2016) and in rodents involved in olfactory discriminations (Courtiol et al., 2019). Difficulties in altering response strategies have also been reported in other tasks after MD perturbations in rats (e.g., Hunt and Aggleton, 1998; Block et al., 2007). The conclusion from all this evidence suggests the MD, particularly the MDmc (MDm in rodents), contributes to monitoring and feedback to the cortex about the optimal task relevant choice response strategy. A related proposal has been made for the lateral MD in primates contributing to the internal monitoring and feedback of optimal sequences of eye movement (Sommer and Wurtz, 2008).

2.3.2 MD monkey cognition and behaviour

As mentioned above, anatomical evidence in both rodents and monkeys suggests MD subdivisions form distinct neural circuits, with a MDpc frontal cortical network and a MDmc fronto-temporal network. Preliminary evidence from our lab, suggests that these circuits support different forms of learning and decision-making (Chakraborty et al., 2019; Pelekanos et al., 2020). Previously, our lab has shown that monkeys with selective MDmc lesions were unable to rapidly acquire within-session pairings of a rewarded object with a specific place

embedded within a complex visual scene (Mitchell et al., 2007a). However, unlike MDmc lesions, lesions to MDpc did not impair new learning on this object-in-place task (Chakraborty et al., 2019). In a second cognitive behavioral task, monkeys had to learn a simple object discrimination across sessions, in which two of the objects were associated with two different highly valued rewards. Monkeys with bilateral lesions to either the MDpc, MDmc, or a contralateral combination of both were able to acquire this task to a prominent level of performance. However, in probe tests where one of the rewards was selectively devalued by satiation, all monkeys with MD lesions continued to show a weakened preference for the now devalued reward (Mitchell et al., 2007b; Chakraborty et al. 2019). This deficit could be attributed to an inability to rapidly monitor and update the optimal choice response when task conditions change. The deficit observed in the devaluation task is likely related to the convergent afferents both the MDmc and MDpc receive from OFC, as can be illustrated in a different pharmacological inactivation study described below, in addition to the thalamocortical connectivity from the MD to other cortical regions, e.g., ACC, frontopolar cortex, and dmPFC. Rather than using permanent excitotoxic lesions, Wicker et al. (2018) used pharmacological inactivation of the MDmc to selectively switch off the MD during specific aspects of the devaluation task. They found that the MDmc has unique roles in reward valuation and action selection that do not replicate either OFC or amygdala functions. Reward devaluation is thought to rely on an interactive network between the OFC, MDmc and amygdala. Previous studies have shown that the amygdala is required for adjusting the object representations to reflect the new value of the primary reinforcer but not necessarily for optimal action selection. Comparable results are seen for area 13 of OFC. By contrast, OFC, area 11 is critical for action selection. Like the amygdala, the MDmc was found to be necessary for adjusting the value of the objects to reflect the new value of primary reinforcers, and like area 11, when the MDmc was inactivated during the probe

session, it also appeared to be involved in action selection (Wicker et al., 2018). Therefore, the MDmc appears to represent a unique profile within this circuit differing from both the amygdala and two subregions of OFC.

In a different study, our lab showed that monkeys with MDmc lesions were also impaired on a more complex object-reward association task (Chakraborty et al., 2016). In this three-arm bandit task, monkeys had to track the probability of reward associated with three different objects. Critically though, midway through the session, there was an abrupt change in the object-reward contingency that switched reward probabilities across the objects. Monkeys with MDmc lesions could learn and track changing values in the object-reward associations over trials but were severely impaired when the object-reward contingencies were abruptly reversed or when there were multiple options associated with reward (Chakraborty et al., 2016). Using computational analyses, the behavioral data showed that the MDmc lesion group were unable to use their previous choice responses to guide their future optimal choice after switching to an alternative. These findings further suggest that the MDmc is necessary for the rapid updating and optimization of behavioral responses based on recent choice outcomes within a changing environment.

Few studies have to date recorded MD activity in behaving macaques and even fewer have obtained simultaneous recordings from both MD and PFC. Such recordings will be of critical importance to increase our understanding of both the functional role of MD and its interconnected regions and the role of MD→frontal, or MD→frontal and temporal dysfunctions in neurological disorders, such as schizophrenia. In a series of studies, Watanabe and Funahashi (2004, 2009) found that cells in the MDpc showed delay related activity and directional delay period activity in a spatial working memory task. More recently, Watanabe and Funahashi (2018) reported a key role for the MDpc in transforming visual information into motor information during spatial working memory performance. In

that study, monkeys performed two oculomotor delayed response tasks and the directional selectivity of the same MD neurons was compared between these two tasks to see whether MD represented cue direction or saccade direction. Of the 26 MD neurons that showed directional delay-period activity, 27% gradually altered their representation from the visual to the oculomotor domain, while the remaining kept their visual or oculomotor information throughout the delay period. These findings suggest that MDpc can alter incoming sensory information, by not only maintaining information at the single neuron level but may also participate in the transformation of visual information to motor information at the population level.

In a different study, the MDpc and dorsolateral PFC (dlPFC) were found to make clearly different contributions to cognitive control in macaques (DeNicola et al., 2020). The MDpc appeared to be specialized for decision making and response selection, whereas the dlPFC preferentially encoded the environmental state in which the decision was based. DeNicola et al. (2020) trained monkeys to perform a variant of the AX continuous performance task, which reliably measures cognitive control deficits in human patients. In the original version of this task, human participants were shown a string of letters presented one at a time in a random sequence and told to respond to the letter X, but only when it followed the letter A (Cohen et al., 1998). Therefore, the target 'X' must be bound within the context of the prior occurrence of 'A' to be correct. Patients with schizophrenia consistently make increased errors of omission on this task. Unlike other versions of this task, Cohen et al. (1998) added additional manipulations to isolate the influence of context on this cognitive deficit. To do this, target AX pairings were increased to 70% of the trials and the remaining 30% of trials were split evenly across three distractor conditions, a non-A followed by an X, an A followed by a non-X and a non-A followed by a non-X. Rather than using letters, the primate version of the task used by DeNicola et al. (2020; the dot expectancy task, DPX)

used patterns of dots to represent “A” and “X” target trials, and these were randomly interleaved with non-target dot patterns to represent distractor trials. During the task, the strongest coupling between MDpc and the dlPFC was observed when the decision as to which responses in the task to execute was being made, suggesting interactions between the MD and interconnected dlPFC are particularly important in supporting the integration of task relevant information to optimize choice response strategies.

Clearly further work, building on the evidence from these studies needs to determine the nature of the influence of the MD has on the frontal cortex during establishing vs re-establishing choice response strategies.

3.0 Neuroanatomical and physiological basis of ATN-PrS interactions

3.1 Head Direction (HD) cells in rodents

As is clear from our review of the functions of the MD in higher cognitive functions, the different subdivisions of the MD in both rodents and primates influence interconnected regions of the frontal cortex in specific ways during goal-directed tasks. We propose a similar influence from different nuclei of the ATN on interconnected cortical regions (subicular complex, extended hippocampal system, PFC, retrosplenial cortex (RSC) contribute to our ability to navigate effectively in our environment, given the head direction (HD) cell circuitry involves the ATN.

As already highlighted, substantial reviews have been written about the ATN-RSC connectivity and the influence of the ATN on RSC functioning, thus for this review, we focused on one of the other main cortical players that interacts with the ATN, the subicular complex. HD cells, which are neurons that preferentially fire when an animal is oriented towards a specific direction, were first discovered in the dorsal PrS (Taube et al., 1990). In subsequent studies, HD cells have been found in several interconnected cortical and

subcortical areas, including the RSC (Chen et al., 1994; Cho and Sharp, 2001; Jacob et al., 2017), medial entorhinal cortex (MEC; Sargolini et al., 2006), the AD (Blair and Sharp, 1995), AV (Tsanov et al., 2011), and AM (Jankowski et al., 2015) of the ATN, the nucleus reuniens (Jankowski et al., 2014), the dorsal tegmental nucleus (Sharp et al., 2001), and lateral mammillary bodies (Blair et al., 1998). In a seminal review, Taube (2007) proposed a distinct neural circuit for head direction signal providing a functionally relevant contribution to spatial navigation.

This HD cell system is a bottom-up network where vestibular information, which is required to generate HD cell signalling, ascends through hierarchically interconnected brain regions, and is then projected via the ATN to both the RSC and the subicular complex (Pergola and Suchan, 2013; Aggleton, 2014). As mentioned above, each ATN nucleus has a distinct profile of connectivity with the RSC and subicular complex. Differences within the ATN nuclei also appear to extend to the neurophysiological properties of neurons in each of the nuclei and provides additional support that each nucleus of ATN makes a distinct contribution to spatial navigation. For example, while the AD, AV and AM have been shown to contain HD cells, they all produce different neural signalling. The AD is an important node within the HD circuit responsible for propagating the HD signal from the lateral mammillary bodies on to its cortical targets in an ascending manner. In contrast, the AV has a more complex contribution to spatial navigation as, unlike the AD, this nucleus also contains theta-rhythmic cells (Tsanov et al., 2011a) and is a potential source of hippocampal theta (Vertes et al., 2001; Albo et al., 2003). Moreover, Tsanov et al. (2011b) found theta-modulated HD cells in the mediodorsal subregion of the AV. Previous studies (Cacucci et al., 2004) have suggested that HD information needs to be integrated into a theta-modulated spatial code that can be processed by the hippocampus to build a cognitive map. Theta-modulated HD cells in the AV might provide the very first step for this integration and send integrated theta and HD

information to the PrS, as described below. Conversely, the AM contains a small number of place cells and head direction cells, like the ones described in hippocampal and parahippocampal regions (see, for example, Savelli et al., 2008; Solstad et al., 2008; Lever et al., 2009), as well as cells that encode the perimeter/border of the environment (Jankowski et al., 2015; Matulewicz et al., 2019). The encoding of borders and perimeter in the AM has been suggested to complement the function of boundary-vector cells found in the subiculum (Barry et al., 2006; Lever at al., 2009), which respond to boundaries of a specific distance and direction from the position of the animal (Matulewicz et al., 2019).

3.2 HD cells in other mammalian species

HD cells have also been reported in similar brain structures in other mammalian species, including bats (Finkelstein et al., 2015; 2018) and primates (Robertson et al., 1999; Laurens et al., 2016). Neuroimaging studies have identified a HD signal in brain regions associated to the HD system in humans (Baumann and Mattingley, 2010; Chadwick et al., 2015; Chrastil et al., 2016; Shine et al., 2016).

A series of studies have shown that HD cells in the dorsal PrS of bats (Finkelstein et al., 2015; 2018) and in the AD of mice (Angelaki et al., 2020) and macaques (Laurens et al., 2016) encode head orientation not only in the horizontal plan (1D azimuth) but also 2D orientations relative to vertical planes (pitch and roll of the head), thus significantly extending our understanding of how HD cells can provide a 3D orientation signal. Interestingly, 3D HD representations in the bat dorsal PrS are modulated by angular velocity in a way that can optimize directional coding according to animal behavior. Many cells adjust their tuning dynamically, switching from pure to conjunctive (multidimensional) tuning as a function of angular velocity to optimize encoding strategy (Finkelstein et al., 2018). Moreover, the azimuth tuned HD cells show increased strength of the HD modulation at faster angular

velocity (Finkelstein et al., 2019).

AD and PrS gravity signals may allow HD cells to maintain spatial consistency during 3D motion, by updating the azimuth based on rotation signals around the three head axes. This process has been called the "dual-axis rule" in Page et al. (2018) and the 'tilted azimuth' model in Laurens and Angelaki (2019), and has now been confirmed experimentally by recordings from the AD of rats (Shinder and Taube, 2019). Finally, findings are also consistent with evidence from recent functional MRI evidence, showing azimuth and pitch responses in human RSC during virtual navigation (Kim and Maguire, 2019). This study found that the ATN and the subiculum only represent azimuth HD but this may be due to the visual (virtual reality while lying still in the MRI scanner) nature of the task, which would recruit the RSC.

3.3 Updates on ATN-PrS connectivity and the functional importance of laminar organisation

As indicated above, reciprocal communication between the ATN and PrS is necessary for optimising HD cell signalling (Goodridge and Taube, 1997). Further, the PrS contains the largest proportion of sharply tuned HD cells (Boccara et al., 2010; Sargolini et al., 2006; Winter et al., 2015a). In addition to ATN HD inputs, visual information reaches the dorsal PrS directly from both primary and secondary visual cortex (Vogt and Miller, 1983), and indirectly via the RSC, the laterodorsal thalamic nucleus, and associative visual cortex (Vogt and Miller, 1983; Van Groen and Wyss, 1990a; Shibata and Naito, 2005; Jones and Witter, 2007). In turn, HD representations in the ATN are updated based on visual information (Zugaro et al., 2003) through direct inputs from the dorsal PrS (Van Groen and Wyss, 1990a; Goodridge and Taube, 1997; Yoder et al., 2011; Huang et al., 2017) and indirect inputs from

603 the dorsal PrS via the lateral mammillary bodies (Yoder et al., 2011; Yoder et al., 2015) and
604 RSC (Clark et al., 2010).

605 In the past decade, evidence from tracing and optogenetic studies have shown that the
606 PrS exhibits layer-specific organisation of cell morphology and projections. In this
607 arrangement, layer III of the PrS appears to represent a crucial node for HD signal integration
608 and onward transmission to the grid cell network in the MEC. Grid cells, first discovered in
609 the MEC of freely moving rats, exhibit spatially modulated firing fields. However, contrary
610 to place cells that fire whenever the animal's position is in a specific location, grid cells are
611 arranged in a triangular structure spanning the entire surface of the environment (Hafting et
612 al., 2005). Most layer III PrS neurons have been classified as HD cells (Tukker et al., 2015) with
613 axons branching directly to layer III of the MEC (Tukker et al., 2015; Preston-Ferrer et al.,
614 2016; Huang et al., 2017), where grid cells projecting directly to the hippocampus are found
615 (Honda et al., 2008). Critically, HD cells from the ATN (Taube, 2007; Peyrache et al., 2015)
616 provide direct excitatory inputs to this layer (Nassar et al., 2018), suggesting the ATN may
617 have a vital role in driving the processing of head direction information within PrS-MEC
618 interactions. In contrast to layer III HD cells, layer II PrS neurons project exclusively to the
619 RSC, and contain theta rhythmic cells that are modulated by angular head velocity (Preston-
620 Ferrer et al., 2016). These layer II projection neurons are likely to be grid and border cells
621 (Boccara et al., 2010; Winter et al., 2015b), which is consistent with the lack of ATN inputs
622 to this PrS layer (Van Groen and Wyss, 1990b; 1995; Shibata, 1993). This overall laminar
623 specificity allows the segregated transmission of directional and non-directional information
624 represented in the PrS to other cortical regions of the spatial hippocampal system (i.e., MEC
625 and RSC). As we will highlight below, ATN to PrS to MEC projections appear to be crucial
626 for the integration of HD information and, these in turn support neural computations

627 performed by grid and place cells. Critically, both processes appear to depend on inputs from
628 the ATN.

629 Segregated organisation is also apparent within the PrS projections that feedback to
630 the HD network (Van Groen and Wyss, 1990a,b; Gonzalo-Ruiz et al., 1992; Ishizuka, 2001).
631 That is, calibrated HD information is either relayed to the RSC, directly from the PrS, or via
632 the ATN. For instance, projections from the PrS to the lateral mammillary bodies arise from
633 bursting layer IV pyramidal cells, while PrS neurons that target the ATN are regular-spiking
634 HD cells found in deeper layers V-VI (Huang et al., 2017). These feedback projections
635 convey important visual landmark information to the HD circuit (Goodbridge and Taube,
636 1997; Yoder et al., 2011). Together, these segregated projections can provide a fast and
637 efficient update of the subcortical HD signal by providing simultaneous convergent visual
638 information to the ATN (via direct PrS to ATN projections, and via an indirect PrS to lateral
639 mammillary bodies to AD route).

640 Finally, recent optogenetic and tracing studies in mice, have for the first time,
641 elucidated the mechanisms through which ATN inputs establish and refine HD tuning in
642 superficial PrS layers (Nassar et al., 2018). Nassar et al. (2018) found that within layer III of
643 the PrS, ATN inputs monosynaptically excite pyramidal HD cells, and disynaptically excite
644 somatostatin interneurons, through the recruitment of these pyramidal cells (Preston-Ferrer et
645 al., 2016; Simonnet et al., 2017; Nassar et al., 2018). Somatostatin interneurons, in turn,
646 provide feedback inhibition to the same ATN driven pyramidal cells. In addition, the same
647 ATN neurons monosynaptically excite fast-spiking parvalbumin (PV) interneurons in PrS
648 layer III (Nassar et al., 2018). Within this organisational framework, somatostatin
649 interneurons mediate precise feedback inhibition of ATN driven pyramidal cells and may
650 provide the mechanism to support HD firing during maintained head direction (Peyrache et

al., 2015; Simonnet et al., 2017; Nassar et al., 2018). Conversely, during head turns, ATN driven excitation, followed by disynaptic inhibition mediated by PV interneurons, may act to fine-tune changing ATN inputs transmitted to MEC. This idea is congruent with *in-vivo* studies, showing that activity of PV interneurons in the PrS increases with angular head velocity (Preston-Ferrer et al., 2016), as well as *in vitro* evidence (Nassar et al., 2018) showing adaptation in ATN inputs to PV interneurons during persistent stimulation (i.e., corresponding to similar times that an animal may maintain its head in a preferred direction).

3.4 ATN rodent cognition and behavior

Unlike the behavioral and cognitive evidence gathered in rodents and monkeys for the MD, to our knowledge, most of the cognitive and behavioral research focusing on the ATN is currently conducted in rodents, although as indicated, neuroscience research in bats, rodents, primates, and humans has helped confirm the ubiquitous nature of the HD neural circuitry. Prior to continuing our discussion on the contribution of the ATN to HD processing, it is important to highlight that the ATN also contributes to other higher cognitive functions in addition to supporting optimal spatial information integration (e.g., Aggleton et al., 1996; Henry et al., 2004; Mitchell and Dalrymple-Alford, 2006; Jankowski et al., 2013; Aggleton and Nelson, 2015). For example, evidence gathered from humans and rodents suggests the ATN contribute to nonspatial cognition via interactions with the amygdala, prelimbic cortex, and the ACC (Shibata and Kato, 1993; Shibata and Naito, 2005; Wright et al., 2013; Mathiasen et al., 2017). In rodents, lesion studies indicate a role for the ATN in "relational" processing. For example, ATN lesions spare recognition memory for single items (Mitchell and Dalrymple-Alford, 2005; Law and Smith, 2012) but impairments emerge when animals are required to combine memory about multiple items with their temporal and spatial properties (e.g., Parker and Gaffan, 1997; Wolff et al., 2006; Dumont and Aggleton, 2013). The ATN is also required for the processing of contextual memories (Carvalho-Netto et

al., 2010; Marchand et al. 2014; Law and Smith, 2012) with the ATN particularly important for recent, but not remote contextual fear memory retrieval (Lopez et al., 2018). Damage to the ATN also disrupts the ability of rats to form an attentional set during the attentional set-shifting task **(**Wright, et al., 2015) and abolishes latent inhibition (Nelson et al., 2018). Finally, the ATN is believed to play a role in learning associations between an odor/object and a spatial location (Sziklas and Petrides, 1999; Gibb et al., 2006), but not in non-spatial associations (Ward-Robinson et al., 2002).

Our focus for the rest of this review on ATN thalamocortical interactions via the subicular complex for processing spatial signals. Recent evidence (as detailed below) highlights the potential involvement of ATN-subicular interactions in supporting the formation of the grid cell firing patterns in the MEC.

3.5 Role of ATN-cortical pathways for hippocampal processing

The RSC and PrS are reciprocally connected (van Groen and Wyss, 1990) and as already mentioned, they have two distinct properties: they receive projections from all ATN nuclei, likely carrying HD information (Tukker et al., 2015), and project allocentric HD signals to the MEC grid cell system (Caballero-Bleda and Witter, 1993; Goodridge and Taube, 2007; Honda and Ishizuka, 2004; Clark and Taube, 2012; Winter et al., 2015a; Dumont and Taube, 2015; Preston-Ferrer et al., 2016; Clark et al., 2018; Mitchell et al., 2018; Simonnet and Fricker, 2018).

The ATN appears to provide the necessary information required to establish HD tuning in all its cortical targets (Goodridge and Taube, 1997; Clark and Taube, 2012; Winter et al., 2015a). For example, studies have shown that permanent disruption to the ATN by lesions in rodents leads to altered HD cell firing in the PrS **(**Goodridge and Taube, 1997), the para-subiculum, and superficial MEC layers (Clark and Taube, 2012; Winter et al., 2015a).

Furthermore, animals with ATN lesions are impaired in spatial learning and memory performance (e.g., Aggleton et al., 1996; Mitchell and Dalrymple-Alford, 2005, 2006). However, inputs from the PrS to the AD are also vital in supporting optimal HD cell firing (Goodridge and Taube, 1997).

However, to date, it is not well understood why this dual thalamo-cortical route exists and what unique contributions the ATN→PrS loop may add to what is the main HD signal, which ascends through the ATN→RSC loop via the cingulum bundle (Bubb et al., 2017). In this section, we will focus on the recently characterized neuroanatomical, electrophysiological, and functional properties of the thalamo-cortical ATN→PrS pathway, and discuss extant research arguing for a distinct contribution of these two ascending HD pathways through the ATN.

Unlike the RSC, which predominately contains HD cells, regions of the subicular complex and MEC contain a combination of spatial cells whose firing is modulated by theta oscillations, including grid cells (Hafting et al. 2005, Boccara et al. 2010) and boundary vector cells (Boccara et al., 2010). In addition, the subiculum, but not the MEC, contains place cells (Winter et al., 2015b). Furthermore, as the HD signal progresses along the ATN→PrS→MEC pathway, thalamic HD information becomes increasingly enriched with location, angular head velocity, speed, and theta signals. In this respect, compared to the more traditional HD coding observed along the AD→RSC pathway, integration of more complex spatial information along the ATN→PrS→MEC pathway is reflected by a greater functional distinction in activity profiles of cells in these regions (Sharp, 1996). The ATN contain theta-rhythmic neurons that increase theta burst frequencies with the cosine of the rat's running direction (Welday et al., 2011). In the AV specifically, theta-modulated HD cells integrate septo-hippocampal theta signals (Bland et al., 1995; Kirk et al., 1996) with HD

724 information descending from the RSC (Tsanov et al., 2011b). In the dorsal PrS, combined
725 theta and HD information ascending from the ATN becomes integrated for the first time with
726 positional information (i.e., from the whiskers; Peyrache et al., 2017). The diverse
727 populations of cells found in the PrS include HD cells modulated by environmental
728 boundaries (Peyrache et al., 2017), termed HD-by-border cells, theta modulated place-by-HD
729 cells (Cacucci 2004), and place-by-HD cells modulated by speed and angular head velocity
730 (Sharp, 1996).

731 Consistent with computational models (Burgess et al., 2007; Brandon et al., 2011;
732 Koenig et al., 2011), the integration of thalamic HD information into a theta modulated
733 spatial signal along the ATN→PrS→MEC pathway represents a necessary step for grid and
734 place cells generation (Burak and Fiete, 2006; McNaughton et al., 2006; Burgess et al.,
735 2007). Thus, it may be that the contribution of the ATN interacting within the MEC-
736 hippocampal system via the PrS is to support the formation of increasingly complex spatial
737 representations that can be used by the hippocampus for navigation. To support these models,
738 previous studies have shown that spatial representations in the subicular complex and MEC are
739 predominantly driven by ATN cell signalling, possibly mediated by AD/AV→PrS and
740 AV/AM→subiculum interactions, rather than being driven by hippocampal CA1 inputs. For
741 example, ATN lesions disrupt place and grid cell responses in the subiculum, leading to
742 severe spatial alternation deficits, while sparing CA1 place fields (Frost et al., 2020). In
743 contrast, CA1 inactivation leaves unaffected HD cells in the AD (Golob and Taube, 1997)
744 and MEC (Bonnevie et al., 2013), while MEC grid cells lose their periodicity, turning into
745 HD cells (Hafting et al., 2008; Bonnevie et al., 2013). Similarly, PrS lesions have only minor
746 effects on HD tuning in the AD and other subcortical HD regions (Goodridge and Taube,
747 1997, Yoder et al., 2011; Yoder et al., 2015). Finally, although hippocampal place cells could
748 still be recorded following ATN damage (Winter et al., 2015a), place fields become more

749 directionally sensitive because of AD and, to a greater extent, dorsal PrS lesions (Calton et
750 al., 2003), revealing a strong directional component to hippocampal place cell firing.
751 Crucially, the reversed manipulation has no impact on ATN HD cell firing (Golob and Taube,
752 1997), implying a unidirectional flow of HD signal from the ATN into the hippocampus via
753 the PrS and MEC.

754 Taken together, these experimental findings suggest that computations performed by grid and
755 place cells depend at least in part on ATN HD inputs and indicate a hierarchical progression
756 of information through these neural circuits (Dillingham and Vann, 2019). To further support
757 this hypothesis, bilateral and unilateral ATN damage reduces expression of the functional
758 gene markers, c-Fos and zif268, in the RSC (Jenkins et al., 2002a,b; Perry et al., 2018), and
759 zif268 in the ACC and CA1 (Perry et al., 2018). Further, Dupire et al. (2013) reported
760 reduced phosphorylated cAMP response element-binding protein (pCREB) immunoreactivity
761 in the hippocampal formation and in the amygdala for rats with ATN lesions after completion
762 of a contextual fear test. ATN lesions also impair synaptic plasticity, reducing dendritic spine
763 counts in hippocampal CA1 (Harland et al., 2015) Indeed, the role of ATN HD cells in
764 driving place and grid cell activity is also consistent with the formation of HD cells, which
765 precedes grid and place cells at the earliest stages of development (Langston et al., 2010;
766 Wills et al., 2010; Bjerknes et al., 2015). It is also relevant to mention that the convergence of
767 numerous behavioral, locational, and directional representations in PrS neurons might
768 provide the necessary mechanism for accurate calculation of the directional signal. This
769 signal partly depends on angular head velocity, speed, and locational signals, like the ones
770 integrated in the PrS (Sharp, 1996). For example, combining information about directional
771 heading and velocity at which the head is turning allows HD cells to calculate and predict the
772 future orientation (Blair and Sharp, 1995). In summary, the ATN and PrS may be part of a
773 neural network necessary to perform these integrative computations, which in turn represent

the building block for calculations of the HD signal supporting optimal spatial navigation. This proposal provides a perspective for understanding the neuronal changes observed in the entorhinal-hippocampal circuit following ATN lesions (Goodridge et al., 1997; Calton et al., 2003; Winter et al., 2015a; Frost et al., 2020). Disruption of the HD cell network impairs the parahippocampal grid cell signal having a direct bearing on how we interpret the impact of ATN damage on memory functions in both rodents and humans.

4.0 Recent clinical evidence of MD and ATN involvement in human neurological conditions

Clinicians have known for many decades now that the limbic, and dorsal, medial thalamic nuclei contribute to many neurological and neuropsychiatric conditions. These conditions involve symptoms where memory impairments and other cognitive abilities (e.g., decision-making, and executive functions) are typically impaired. For example, both the MD and ATN appear to have dissociable but complementary roles in Korsakoff's syndrome and Wernicke's encephalopathy (Harding et al., 2000; Pergola et al., 2018; Segobin et al., 2019). Additional studies examining patients with schizophrenia, for the MD (Pergola et al., 2015), or patients with localized thalamic infarcts, both for the MD and ATN, suggest that damage or dysfunction within either of these two thalamic nuclei contribute to distinct profiles of cognitive deficits (Carlesimo et al., 2015; Ouhaz et al., 2018; Parnaudeau et al., 2018; Pergola et al., 2018). Further, for the ATN, Braak and Braak (1991) identified changes in the AD and AV early in the progression of Alzheimer's disease. The subicular complex is also markedly changed in Alzheimer's disease patients but has received little attention in comparison to the hippocampus proper (i.e., CA1, dentate gyrus) and the entorhinal cortex.

More recently, researchers have also identified that neuronal loss occurs in the MD and ATN of individuals with Down's syndrome (DS) (Pakkenburg et al., 2014; Davidson et al., 2018; Perry et al., 2019). DS individuals have many medical complications, growth and

developmental delays, and intellectual disabilities because of a third copy of chromosome 21 (trisomy 21). In addition, these individuals have memory impairments and can start to accumulate amyloid plaques in their late teens (Annus et al., 2016). In addition, individuals with Down's syndrome have patterns of brain changes that are like those of individuals with sporadic or familial Alzheimer's disease (Annus et al., 2018; Davidson et al 2018). Individuals with Down's syndrome are also at higher risk of developing early onset dementia with the full neuropathology of Alzheimer's disease in their late 40s or early 50s (Davidson et al., 2018). Perry and colleagues (Perry et al., 2019) characterized the differences in neuronal loss compared to aged-matched controls, with the ATN showing a 68% reduction in neurons and a 37% reduction of glia cells. By comparison, the MD showed a 43% loss of neurons with little change in numbers of glia cells (Karlsen et al., 2014). Given this recent knowledge about the earlier build-up of amyloid plaques in individuals with Down's syndrome, it seems prudent for targeted drug treatments that could potentially slow down this build-up, with the hope of delaying the onset of cognitive impairment to improve their quality of life.

Individuals with frontotemporal dementia (FTD) also have thalamic atrophy, as measured by total thalamic volume reductions using structural MRI (Bocchetta et al., 2018). Specifically, the MD was the only thalamic nucleus significantly reduced by between 29-33% across all FTD sub-types including progressive non-fluent aphasia, behavioural-variant FTD, and semantic dementia (Bocchetta et al., 2020). When stratified by the genes (GRN, MAPT and C9orf72) linked to the diagnosis of FTD, thalamic volume was reduced in the MD by 21-32% in all subtypes, while thalamic volume in the AV was reduced by 17-24% (Bocchetta et al., 2020). Hornberger and colleagues have also identified thalamic volume reductions in the AV of individuals with FTD also diagnosed with episodic memory impairments (Hornberger et al., 2012).

FTD, schizophrenia, and other neurological disorders often have a co-morbidity with mood disorders. The neural circuitry linked to mood disorders includes the MD and ATN, although the traditional understanding is that cortical structures including the dorsal ACC, and orbitofrontal and subgenual cortex are typically involved along with the amygdala, ventral striatum, pallidum, and hypothalamus (Price and Drevets, 2010).

Finally, recent work in PD patients identified both ATN and MD as thalamic sites of additional iron deposits proposed to be linked to the cognitive deficits as measured using the Montreal Cognitive Assessment. Interestingly, the authors note that these 'tissue changes were strikingly seen where conventional measures of atrophy showed no relationship' (Thomas et al., 2020). To our knowledge, changes to the MD have not been well characterized in PD patients, although a recent neuroimaging study highlights connectivity changes between the cortex and MD (Harrington et al., 2020). However, in the NHP model of PD, monkeys also show reductions in dopamine in the MD and centromedian thalamus (Monje et al., 2020). Further, detailed immunohistochemistry studies in NHPs have identified there are abundant dopamine axon transporter receptor markers present in the MD (see Section 3.1.2 Updates on primate neuroanatomy). These DAT receptors indicate that the cells of the primate MD are capable of being regulated by dopamine neuromodulation.

5.0 Combining some of the MD and ATN circuitry into converging PFC - thalamic - extended hippocampal circuit networks

To account for the broad range of cognitive symptoms following dorsal thalamic damage, early cognitive models suggest that ATN and MD link medial temporal lobe with frontal lobe, and medial temporal lobe with OFC and amygdala, respectively (Warrington and

Weiskrantz, 1982; Wolff et al., 2015). However, these models neglect the significance of other subcortical inputs. For example, extra-hippocampal inputs to the ATN from the mammillary bodies are critical for sustaining episodic memory functions (Vann and Nelson, 2015). A particularly influential account was proposed by Aggleton and Brown (1999), stating that ATN and MD are critical parts of parallel temporal–thalamic systems, required for recollective and familiarity-based memory, respectively (Aggleton and Brown, 1999). However, this account does not fully capture the influence of the MD in cognitive functions (Mitchell, 2015; Wolff et al., 2015; Pergola et al., 2018). A recent model (Wolff and Vann, 2019) proposes the cognitive contribution of the MD and ATN are best explained by a general thalamic role in shaping mental representations, either by maintaining cortical representations or by updating existing ones based on ongoing evidence. This model considers the divergent and convergent nature of thalamo-cortical and cortico-thalamic loops, providing a common mechanism for all integrative thalamic functions, ranging from spatial cognition to cognitive flexibility.

A recent review of the rodent literature has highlighted evidence of input convergence between the midline thalamus, the hippocampal formation, and the mPFC (Bueno-Junior and Leite, 2018). While the influence of the ventral midline thalamus, namely the reuniens and rhomboid nuclei, in hippocampal-prefrontal circuits is widely accepted, the same cannot be said for the MD or the ATN. Yet, the MD is reciprocally connected to all the PFC, and the AM and the AV are interconnected to parts of the PFC (see **Figures 1 and 2**), in particular the mPFC that receives inputs from the subiculum, and CA1 (Swanson, 1981; Jay and Witter, 1991; Vertes et al., 2015). However, there are a few studies that have shown complimentary and/or converging function of MD and hippocampal connections to the PFC. For example, when direct comparisons were made between ventral hippocampal and MD-induced synaptic plasticity in medial PFC, opposite dynamics were found between the two afferent circuits.

Electrical stimulation in the MD increased the amplitude of the field post-synaptic potential in the mPFC, while electrical stimulation of the ventral hippocampus decreased it (Hugues and Garcia, 2007). Using a different approach (Kiss et al., 2011a, b) found that lidocaine MD inactivation reduced CA1/subiculum-mPFC paired pulse facilitation, another measure of synaptic plasticity, in an anaesthetized rat. Furthermore, recent evidence has suggested that suppression of activity in the MD may have a vital role in facilitating offline information processing from the hippocampal formation to the PFC, specifically in the memory domain. Yang et al. (2019) found that MD activity was transiently decreased around hippocampal ripple events. Hippocampal ripples are indicative of memory replay and hippocampal-cortical information transfer (Jones and Wilson, 2005). MD modulation correlated with ripple amplitude, differed across behavioral states, and depended on the dynamic of hippocampal-cortical population activity (Yang et al., 2019). Therefore, the authors suggested that MD suppression during spindle uncoupled ripples may facilitate memory replay by suppressing other sensory inputs to cortex. Given the few studies so far, a lot of questions remain as to the nature of MD involvement with, or modulation of, hippocampal-PFC communication. Along these lines, the AV and AM may also be worthy contenders of future research efforts involving hippocampal-mPFC communication (Kinnavane et al., 2019), given their connectivity patterns with the mPFC and ACC (see **Figure 2**).

5.1 Future Directions and Conclusions

Along with our increased understanding of the neuroanatomical substrates of thalamo-cortical and cortico-thalamic circuits, a growing number of studies have examined the role of these circuits in several aspects of cognition. In rodents, a combination of viral vector technology, transgenic models, electrophysiology, and cognitive behavioral testing has provided consistent evidence that the MD and ATN are critical in influencing cortical functioning

during complex cognitive processes. The ease of implementing these powerful techniques have made rodent studies indispensable, especially for dissecting neural circuits and understanding mechanistic function. It is, however, also worth noting that considerable progress has been made in the use of optogenetics and chemogenetics in NHPs (Galvan et al., 2018; Nagai et al., 2020). For example, with respect to optogenetics, researchers have previously struggled to deliver sufficient light intensity to opsin expressing neurons in the much larger structures of the macaque brain (Galvan et al., 2018). To overcome this significant limitation, a team of researchers have recently developed a step function opsin that is ultra-light sensitive and therefore requires much lower levels of illumination to be activated (Xin Gong et al., 2020). Incredibly, in a pilot study, Xin Gong et al. (2020) showed that they could activate regions of macaque cortex and consequently modulate neural oscillations, by placing the light source on top of dura. Furthermore, Xin Gong et al. (2020) showed it was even possible to activate deep brain structures in a mouse, by placing the light source on the cranium. In an analogous manner, researchers have continued to develop novel chemogenetic tools making ever more potent and selective ligands and their respective receptors as well as more selective actuators for use in NHPs (see Magnus et al., 2019; Nagai et al., 2020). Once these procedures have been further optimized, they will enhance our investigations, and hopefully increase our understanding of thalamocortical interactions and their specific influence on different classes of cortical interneurons and pyramidal neurons (e.g., Cobb et al., 1995) across the various interconnected areas of the MD and ATN. Furthermore, at least in primates, these technological advances will hopefully allow us to better understand the impact of the cortico-thalamic inputs to the MD and ATN. Another future direction that is important to explore and understand is the influence of changes in the cortex because of manipulations to the MD (e.g., Ouhaz et al., 2017; Ouhaz et al., 2018) and to the ATN during

different neurodevelopmental stages. As technology advances, we can use better ways to investigate the influence of the MD and the ATN in the control of cognitive functions.

To conclude, both the MD and ATN contribute to complex cognitive processing. These thalamic structures show changes in many neurological and neuropsychiatric disorders and neurodegenerative diseases. Optimal functioning in the MD supports our brain's ability to rapidly learn and update choice response strategies during value-based and sensory discrimination tasks. Optimal functioning in the ATN-subicular neural circuitry appears to support and critically influence the integration of different spatial signals that generate grid cell firing patterns further upstream in the MEC. Identifying how these neural networks together contribute to support rapid learning and updating of our whereabouts in complex visual environments presents one of the next challenges for neuroscience.

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Figure legends

Figure 1. Graphical illustration detailing some of the main cortical and subcortical connections of the main three MD subdivisions in coronal plates, in both the rat (left panel) and macaque (right panel). For the rat (A-F), the atlas plates have been adapted from Paxinos and Watson (1998) and the anterior-posterior coordinate given is relative to bregma. Plates A, B and C capture the anterior (A) to the posterior (C) regions of the rat prefrontal cortex. Plate D shows the important structures in the temporal and medial temporal lobe. Plate E shows the location and subdivisions of the rodent mediodorsal thalamic nuclei and plate F shows the location of lateral entorhinal cortex. The approximate location of each coronal plate in relation to the whole rat brain is indicated in the sagittal plane (not in alphabetical order) in the top right illustration of the left panel. The anatomical connectivity of the rodent MD is based on prior tracing studies described in Chakraborty and Mitchell (2013) and updated with recent work from Alcaraz et al. (2018), Kuramoto et al. (2017) and Courtiol and Wilson (2016). For the macaque (G-K), the relative anterior-posterior position of each coronal section is given relative to the anterior commissure (ac) based on the atlas of Paxinos et al. (2000). Plates G, H and I capture the anterior (G) to posterior (I) regions of the macaque frontal cortex. Plate J shows key regions of the temporal and medial temporal lobe, including the amygdala and plate K shows the location and subdivisions of the mediodorsal nuclei in the primate thalamus. The relative position of these coronal plates in the macaque brain is indicated on the sagittal plane in the top right illustration in the right panel. The anatomical connectivity of the MD is based on published works from the Barbas and the Goldman-Rakic labs. From Figure 1, it is apparent that across species, but especially in the macaque, the MDmc (1K; MDm in the rat, 1E) forms part of a distinct fronto-temporal circuit connecting with both perirhinal and entorhinal cortex (PRh, Erh, Lat.ERh) and subregions of the

amygdala (BLA in the rat, 1D; BL, BM, Co, Me, Ce in macaque, 1J). In terms of frontal connectivity, the MDmc primarily connects to more ventral and ventromedial regions of prefrontal (vmPFC in rats, 1B-C; area 25 in macaques, 1H and I) and orbitofrontal cortex (LO, VO, OFC in the rat 1A-C; areas 11, 13, 14, 47/12 in the macaque, 1G-I). Additional connections unique to the MDmc/MDm come from the insular cortex (GI, AID, AIV in the rat,1B-C; IA in the macaque, 1J). By contrast, both the MDpc/MDc and MDl tend to project to more dorsal regions, in the macaque dorsolateral frontal regions (1G-I) areas 9 and 46, and in the rodent (1A and C): secondary motor (M2), prelimbic (PrL), and dorsomedial prefrontal cortex (dmPFC). Interestingly, in the macaque at least, the anterior cingulate cortex areas 24a,b,c and 32 (1H and J) as well as the frontal pole areas: 10D and 10M (fig. 1G), appear to be a convergence point for all three MD subdivisions, indicating a special role for these regions in integrating thalamocortical and corticocortical information. These regions also connected to the AM and AV, as shown in the right panel of Figure 2(I and J). It is also worth mentioning the connections between the piriform cortex (PC) involved in olfactory processing and the MD that have been well defined in rodents (see Couritol and Wilson, 2016). The more anterior regions of piriform cortex (1B and C) connect to the MDc and the more posterior regions (1D) connect to the MDm.

Figure 2. Graphical illustration detailing some of the main cortical and subcortical connections of the three nuclei of the ATN: the AD, AV, and AM, in both rat (left panel) and macaque (right panel) coronal plates. For the rat (A-F), the atlas plates have been adapted from Paxinos and Watson (1998) and the anterior-posterior coordinate given is relative to bregma and the approximate location of each coronal plate in relation to the whole rat brain is

indicated in the sagittal plane (not in alphabetical order) in the top right illustration of the left panel. Plates A and B show the location of primary connections in more anterior (A) and posterior (B) regions of the rat prefrontal cortex. Plates C and D show the location of the retrosplenial, subicular and temporal connections of the rat ATN. Plate E shows the location and subdivisions of the rat anterior thalamic nuclei and plate F shows the location and subdivisions of the rate mammillary nuclei. The anatomical connectivity of the rodent ATN is based on prior tracing studies from the Aggleton lab described extensively in Bubb et al. (2017). For the macaque (G-M), the relative anterior-posterior position of each coronal section is given relative to the anterior commissure (ac) based on the atlas of Paxinos et al. (2000). Plates G, H and I capture the anterior (G) to posterior (I) regions of the macaque frontal cortex. Plates J and M show the location of the retrosplenial cortex and medial temporal lobes at a more anterior (J) and posterior (M) location in the macaque brain. Plate K shows the location and subdivisions of the ATN in the macaque thalamus and plate L shows the location and subdivisions of the mammillary nuclei in the macaque brain. The approximate position of these coronal plates in relation to the whole macaque brain is indicated on the sagittal plane (not in alphabetical order) in the top right illustration in the right panel. The anatomical connectivity of the ATN is again primarily based on the work of the Aggleton lab, with additional information about cortical connectivity coming from Barbas and colleagues (particularly Xiao and Barbas, 2002; Xiao et al., 2009). From Figure 2, it is apparent that the AM (regardless of species; 2E in the rat and 2L in the macaque) has a distinctive profile of cortical connectivity that is not apparent for either the AV or AD. In the macaque at least, the AM appear to be connected to nearly the entire frontal cortex including orbitofrontal (areas 14, 11, 13 and 47/12; 2H-J), ventromedial (25; 2I and J), frontal pole (10D, 10M; 2H), dorsolateral (areas, 45, 46, 9 and 8; 2H-J) and cingulate cortex (24a,b,c and area 32; 2I and J). In the rodent (see Fig. 2D), there appear to be considerable connections

between the AM and visual (V1 and V2), temporal association (TeA) and parahippocampal cortices (i.e., perirhinal (PrH) and lateral entorhinal (Lat.ErH). These connections are not apparent for the AV or AD. All three nuclei, however, connect to the entorhinal cortex (ERh; 2D). The prominence of AM connections with cortex, along with other evidence has led us (Perry and Mitchell, 2019) to consider whether the AM may be a 'higher' order thalamic nucleus. A defining feature of the ATN is their inputs from the mammillary bodies (2F in the rat and 2M in the macaque) as well as their connections to both the retrosplenial cortex (dysgranular: Rdg, and granular: Rgb and Rga areas in the rat; 2C and D) and areas 29a-d and 30, as well as posterior cingulate areas 23a-c and 31 in the macaque (2K and N) and the subicular complex (PaS, PrS, dPrS, Sub; dPrS not specified in macaques; 2C and D in the rat and 2K and N in the macaque). Although the AV, AM, and AD are all connected to the same structures, they are connected to different subregions within those structures, supporting the idea of each nucleus being involved in a different functional circuit.