



Review

The mediodorsal thalamus as a higher order thalamic relay nucleus important for learning and decision-making



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ABSTRACT

Recent evidence from monkey models of cognition shows that the magnocellular subdivision of the mediodorsal thalamus (MDmc) is more critical for learning new information than for retention of previously acquired information. Further, consistent evidence in animal models shows the mediodorsal thalamus (MD) contributes to adaptive decision-making. It is assumed that prefrontal cortex (PFC) and medial temporal lobes govern these cognitive processes so this evidence suggests that MD contributes a role in these cognitive processes too. Anatomically, the MD has extensive excitatory cortico-thalamo-cortical connections, especially with the PFC. MD also receives modulatory inputs from forebrain, midbrain and brainstem regions. It is suggested that the MD is a higher order thalamic relay of the PFC due to the dual cortico-thalamic inputs from layer V ('driver' inputs capable of transmitting a message) and layer VI ('modulator' inputs) of the PFC. Thus, the MD thalamic relay may support the transfer of information across the PFC via this indirect thalamic route. This review summarizes the current knowledge about the anatomy of MD as a higher order thalamic relay. It also reviews behavioral and electrophysiological studies in animals to consider how MD might support the transfer of information across the cortex during learning and decision-making. Current evidence suggests the MD is particularly important during rapid trial-by-trial associative learning and decision-making paradigms that involve multiple cognitive processes. Further studies need to consider the influence of the MD higher order relay to advance our knowledge about how the cortex processes higher order cognition.

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1. Introduction

Typically it is believed that direct cortico-cortical connections in the brain convey detailed perceptual, sensorimotor and cognitive information, while it has been customary to think of the thalamus as a relay of sensory information to the cortex (Guillery and Sherman, 2002a; Jones, 2007; Sherman and Guillery, 2011). However, anatomical evidence shows that different thalamic nuclei have quite distinct anatomical connections with the cortex and therefore likely quite distinct functional relay roles. The mediodorsal thalamus (MD) is a thalamic relay that contributes to cognitive processes. For example, humans and animals with damage to the MD demonstrate problems with learning and decision-making. Yet it remains to be determined how the MD thalamic relay contributes to cognition via its distinct interconnections with the cortex.

Based on many anatomical studies, mainly from the visual and somatosensory neural networks of the brain, different thalamic relays and their characteristic properties and potential functions have been identified (Guillery, 1995; Sherman and Guillery, 1996, 2006, 2013). At least two types of thalamic relays have been proposed, ‘first order thalamic relays’ (e.g. the lateral geniculate nucleus), which relay sensory inputs from the periphery via ascending pathways to their interconnected cortical targets (Guillery, 1995), and ‘higher order thalamic relays’. The ‘higher order thalamic relays’ (e.g. MD, and pulvinar) are reciprocally interconnected to the association cortex via cortico-thalamo-cortical connections (Guillery, 1995). Higher order thalamic relay nuclei receive very little, if any, sensory inputs. Instead their main ‘driver’ inputs are shown to originate from layer V of the cortex. These main ‘driver’ inputs are capable of relaying already processed cortical information onto other cortical areas. However, these cortical drivers represent a very small proportion of the inputs (possibly only 5%) that the higher order relays receive (Van Horn et al., 2000). Higher order thalamic relays also receive other cortical and subcortical inputs that have either an excitatory or modulatory function. These other ‘modulator’ signals include inputs from cortical layer VI, thalamic interneurons, the reticular thalamus, and other structures of the forebrain, midbrain and the brainstem (Rovo et al., 2012; Sherman and Guillery, 1996, 2002). The dual cortico-thalamic input to the MD from both layers V and VI of the PFC suggests that cortical input to the higher order thalamic relays regulates neural activity in a different way to that of the first order thalamic relays (Schwartz et al., 1991). In contrast, to the higher order thalamic relays, the main ‘driver’ input for first order thalamic relays is from the periphery (i.e. for the lateral geniculate nucleus, this input is from the retina, despite it representing less than 10% of the total inputs received, Van Horn et al., 2000). The lateral geniculate nucleus (like higher order relays as well) also receives other inputs that have a modulatory function. These other ‘modulator’ signals to the lateral geniculate nucleus include inputs from cortical layer VI, thalamic interneurons, the reticular thalamus, and the brainstem. These additional signals are proposed to regulate what ‘driver’ signals get relayed to cortex (Sherman and Guillery, 1996, 2002).

How generalizable this proposed categorization of ‘driver’ and ‘modulator’ inputs is for all thalamic nuclei still remains to be investigated. For example, recent evidence from anatomical

studies in rats suggests a lack of glutamatergic driver inputs from the cortex to the motor thalamus (Nakamura et al., 2014). Nonetheless, these proposals, based on extensive research of the visual and somatosensory systems of the brain, help to highlight that there are differing functional relay roles amongst the different thalamic nuclei (Theyel et al., 2010; Viaene et al., 2011a,b) (for review see Sherman and Guillery, 2013). Consequently, asking what signals are primarily responsible for driving thalamic relay neurons, how the other signals are modulating these relays, and investigating what messages these higher order thalamic relays are transmitting to influence the cortex is critical to understanding how the cortex is functioning (Sherman and Guillery, 2013). In relation to the MD, this endeavor is specific to beginning to understand its role in supporting the interconnected cortex during cognition.

In this review, I will provide an overview of the anatomy of the MD in the context of its proposed role as a ‘higher order thalamic relay’. In addition, there will be a summary of the impact on behavior and cognition after damage in the MD. Evidence from humans, rodents, and primates will be discussed to show how the importance of investigating the effects of MD as a possible higher order thalamic relay may further develop our fundamental understanding about the role of the cortex in cognition. Further sections will then focus on the underlying mechanisms that might be involved in these MD–PFC interactions and consider how the MD as a higher order thalamic relay might be supporting cortical processing of information. These sections suggest ideas for some future work combining various neuroscience techniques that could lead to further causal evidence that helps develop our understanding of the MD higher order relay functions in cognition.

2. The MD as a higher order thalamic relay

Sherman and Guillery have proposed that some of the cortical inputs to thalamic nuclei that originate in layer V are referred to as ‘driver’ inputs and are capable of transmitting an already processed cortical message across other cortical areas depending on the characteristics of the glutamatergic receptors (Sherman and Guillery, 2006, 2013). These ‘driver’ inputs represent a very small minority of connections originating from the cortico-thalamic pathways (Van Horn and Sherman, 2007; Wang et al., 2002). Instead, the majority of these excitatory cortico-thalamic inputs are modulators coming from layer VI of cortex. The relay functions of the higher order thalamic relays may help support cortico-cortical communication via this trans-thalamic route of transmitting the received message from layer V onto other interconnected areas of the cortex (Guillery, 1995; Guillery and Sherman, 2002a; Jones, 1998, 2007; Schwartz et al., 1991; Sherman and Guillery, 2011). The MD is classified as a higher order thalamic relay based on the inputs from layer V of prefrontal cortex (Guillery, 1995; Sherman and Guillery, 2006). Xiao et al. (2009) showed that about 20% of the PFC projections terminating in the MD are from layer V, mainly from the dorsal and medial PFC areas. In addition to these driver inputs, MD also receives excitatory inputs from many other brain structures in the medial temporal lobes, and modulator inputs from the pallidum, the reticular thalamus, MD interneurons, midbrain and brainstem, all of which are summarized below (Kuroda and Price, 1991a,b; Sherman and Guillery, 1996). All of these modulator inputs, rather

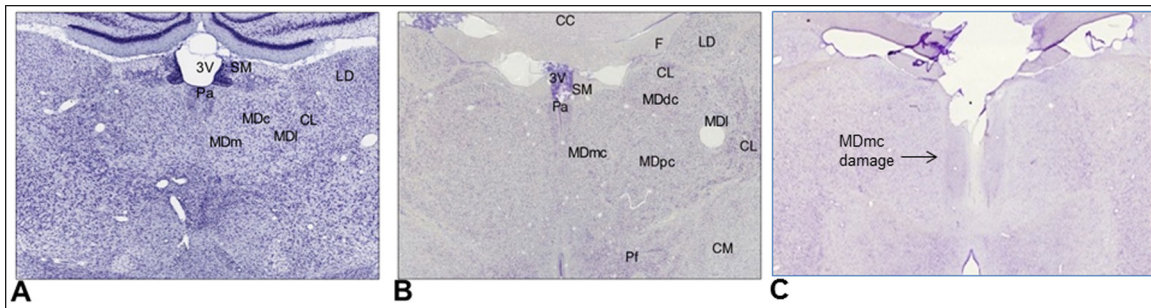


Fig. 1. Nissl stained photomicrographs of coronal slices of the mediodorsal thalamic nuclei in (A) the rat, *Rattus norvegicus* and (B) the monkey, *Macaca mulatta*. Adapted from BrainMaps: An Interactive Multiresolution Brain Atlas; <http://brainmaps.org> [October 2014]. (C) Bilateral neurotoxic lesion damage to the MDmc in monkey, *Macaca mulatta*. Abbreviations: 3V = third ventricle, CC = corpus callosum, CL = centrolateral intralaminar nucleus, CM = center median nucleus of the thalamus, F = fornix, LD = laterodorsal thalamic nucleus, Pa = paraventricular thalamic nucleus, Pf = parafascicular nucleus of the thalamus, SM = stria medullaris of the thalamus.

than providing a message for relay by themselves, are proposed to influence how and what ‘driver’ signals get relayed to the cortex, via this indirect trans-thalamic route through the MD. Mounting causal evidence from behavioral and electrophysiology studies in animals suggests that MD may influence how cortical regions communicate together during specific types of cognition and behavior (Cross et al., 2012; Jones, 2007; Kim et al., 2011; Mitchell and Gaffan, 2008; Mitchell et al., 2014, 2007b; Parnaudeau et al., 2013, 2015; Sommer and Wurtz, 2008a,b). Thus it remains imperative to consider the significance of these cortico-thalamo-cortical connections in combination with the lesion and electrophysiology studies to begin to further understand how the cortex is involved in higher order cognitive processes.

2.1. The anatomy of the MD as a higher order relay nucleus

2.1.1. MD morphology

Based on differing cell morphology, the MD has been divided into different subdivisions of nuclei. In rodents this division is typically characterized into three different parts including medial MD (closest to the midline), central MD, and lateral MD (bordering the rostral intralaminar nuclei and internal medullary lamina) (see Mitchell and Chakraborty, 2013 for review). In primates, there are further subdivisions within these broader three groupings (Fig. 1). The medial third of MD corresponds to the magnocellular subdivision (MDmc) with large cells that are evenly spaced and have extensive neuropil surrounding them. In Ray and Price (1993), MDmc has been further divided based on a plexus of fine myelinated fibers in its lateral part; this lateral part of MDmc is called pars fibrosa. There is also a poorly myelinated region, located medial to the pars fibrosa part of the MDmc that runs along the midline called pars paramediana. The pars fibrosa and pars paramediana subdivisions of the MDmc are further differentiated by differing anatomical connections as described below. The central MD lies adjacent to MDmc. The border between these two regions can be differentiated as the central part of MD has greater variability in the size of its cells and it also has reduced amounts of neuropil between cells. In primates, this central region (see Fig. 1) has also been divided further to include the pars caudodorsalis region (MDcd) that is located in the dorsal part of the central MD, and continues throughout the rostro-caudal extent of the MD. In the caudal pole of MD (MDmc is not present in this caudal pole region), the MDcd extends medially to the stria medullaris. MDcd is a poorly myelinated subdivision. This MDcd region is differentiated in the monkey atlas of Olszewski but is not labeled (Olszewski, 1952; Ray and Price, 1993). The cells in MDcd look very much like the large, uniform sized cells in the MDmc but have less neuropil between them. The other part of the central MD labeled pars parvicellularis (MDpc) is located ventral to the MDcd. It is a densely myelinated subdivision to a similar degree

as the pars fibrosa of the MDmc. Adjacent to MDpc at the lateral border of the MD nucleus is the lateral MD. Lateral MD lies adjacent to the intralaminar nuclei, and in primates it has been further subdivided into pars multiformis (which is the name given to the more rostral part of the nucleus) and pars densocellularis (which is the name given to the more caudal part of the nucleus). Lateral MD in primates is suggested to be indistinguishable for the rostral intralaminar nuclei that surround the MD (Jones, 1985, 2007).

2.2. Cortico-thalamo-cortical connections

The different subdivisions of the MD are interconnected to different regions of the frontal lobes (Fig. 2, adapted from Mitchell and Chakraborty, 2013). The pars fibrosa subdivision of MDmc is reciprocally connected with central and lateral orbital frontal cortex (Brodmann areas (BA) 11, 12 and 13); it also receives input from ventrolateral PFC (BA 12, 45/47) and piriform cortex (McFarland and Haber, 2002; Xiao et al., 2009). The pars paramediana subdivision of MDmc is reciprocally connected with caudal and medial orbital frontal cortex (BA 13 and 14) and agranular cortex; it also receives inputs from piriform cortex (Ray and Price, 1993). There are also inputs from the medial PFC (area 32) into the MDmc and layer VI inputs from BA 9/46 (see Fig. 1 of Xiao et al., 2009). The MDmc sends fibers to BA 10 in marmosets (Burman et al., 2011). In macaque monkeys, these projections are shown to be reciprocal (Petrides and Pandya, 2007).

MDpc is reciprocally connected with dorsolateral PFC (BA 9/46), BA 10 and BA 8 and receives inputs from layer VI of lateral areas 12 and 13 of orbital frontal cortex (Goldman-Rakic and Porrino, 1985; McFarland and Haber, 2002; Ray and Price, 1993; Xiao et al., 2009). MDcd is reciprocally connected with ventromedial PFC (BA 14, 24 and 32). The most lateral MD is reciprocally connected with diffuse areas of dorsal and lateral parts of the PFC and frontal eye fields. Dorsal anterior cingulate cortex (BA 24) also provides layer VI inputs to the MD subdivisions, especially MDcd (Giguere and Goldman-Rakic, 1988; Xiao et al., 2009). Evidence indicates that glutamate is the main form of communication between the cortex and the MD.

2.2.1. Underlying mechanisms of cortico-thalamic connections

The cortico-thalamic projections from PFC to MD subdivisions originate in layers V and VI of cortex. Given that there are two sources of input to MD from the PFC, it raises the possibility that there are different types of information transmitted from the PFC to MD (Schwartz et al., 1991). The largest outputs stem from layer VI coursing to the MD with collaterals to the reticular thalamic nuclei (Giguere and Goldman-Rakic, 1988; Schwartz et al., 1991; Zhang and Jones, 2004; Zikopoulos and Barbas, 2006). These cortical inputs to the thalamus from layer VI have a modulatory

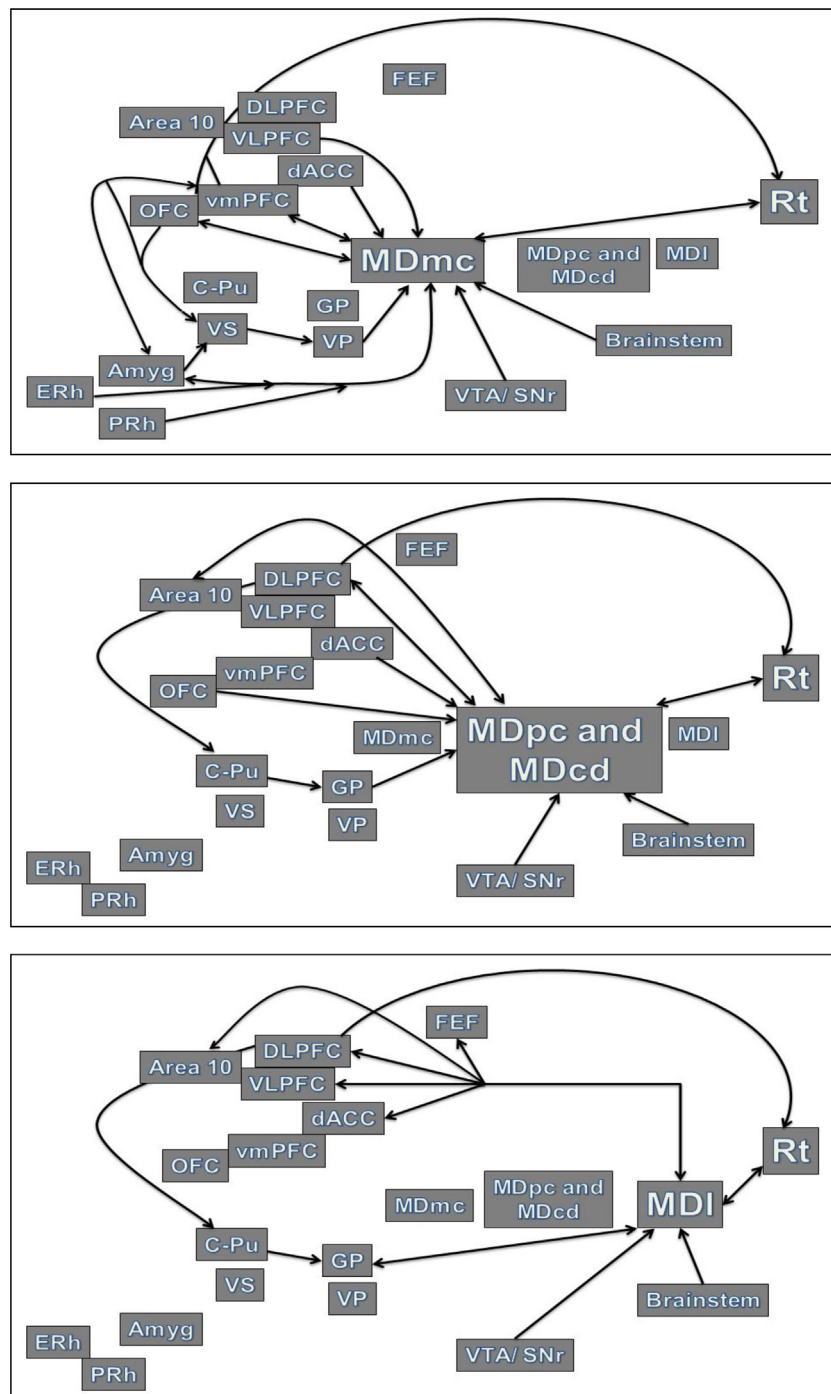


Fig. 2. Schematic diagrams of the identified anatomical connections between the MDmc (top), MDpc and MDcd (middle) and MDI (bottom) and the rest of the mammalian brain. Abbreviations: Amyg=amygdala, Area 10=pole of frontal cortex, C-Pu=caudate-putamen, dACC=dorsal anterior cingulate cortex, DLPFC=dorsolateral PFC, ERh=entorhinal cortex, FEF=frontal eye fields, GP=globus pallidus, OFC=orbital frontal cortex, PRh=perirhinal cortex, Rt=reticular thalamus, VLPFC=ventrolateral PFC, vmPFC=ventromedial PFC, VP=ventral pallidum, VS=ventral striatum, VTA/SNr=ventral tegmental area/substantia nigra pars reticulata.

function (Guillery and Sherman, 2002a, 2011; Sherman and Guillery, 2002). There are also fewer outputs from layer V pyramidal cells to the higher order thalamic relays (Guillery, 1995), in our case MD (Cavdar et al., 2011; Guillery, 1995; Schwartz et al., 1991; Xiao et al., 2009). These outputs from layer V of prefrontal cortex are described as ‘drivers’ – capable of relaying a message (Guillery and Sherman, 2002a, 2011; Sherman and Guillery, 2002). It is suggested that the cortex has already processed the messages that are relayed to the thalamic terminals. Then these thalamic relay cells transmit the message on to other cortical regions depending on

the influence of their modulators. These thalamo-cortical inputs ‘can provide information to higher order cortical areas not only about activity in other cortical areas, which can also be provided by direct cortico-cortical pathways if they are drivers, but in addition to this, they supply information about instructions that are currently on their way to subcortical centers from cortex, contributing information about future actions’ (Sherman and Guillery, 2013, p. 220).

In addition to these PFC to MD cortico-thalamic inputs, there are also inputs to the different subdivisions of the MD from the medial

temporal lobes (specifically the basolateral amygdala and entorhinal and perirhinal cortex to MDmc), insular cortex, piriform cortex, cingulate cortex (Aggleton and Mishkin, 1984; Goldman-Rakic and Porrino, 1985; Ray et al., 1992; Russchen et al., 1987; Saunders et al., 2005; Xiao et al., 2009) and the primary and supplementary motor cortex to MDpc (Rovo et al., 2012).

2.3. Underlying mechanisms of thalamo-cortical connections

In contrast, to the selective layer V and VI cortico-thalamic inputs to MD, the thalamocortical projections to layers of the prefrontal cortex are more diffuse. Like the cortico-thalamic projections, there are two types of thalamo-cortical inputs that stem from each of the different thalamic nuclei. A small minority of these ascending axons are 'drivers' – capable of carrying messages to the cortex – these are characterized by their large terminals and they relay information to middle cortical layers (Lee and Sherman, 2008; Sherman and Guillery, 2013; Viaene et al., 2011a,b; Zikopoulos and Barbas, 2007b). However, as yet, we still do not know what the messages are that are relayed from the MD to the prefrontal cortex. In addition to the driver inputs, the majority (90% or more) of cortical projections that are received from the thalamus have a modulatory function, with more diffuse projections to superficial PFC layers (Lee and Sherman, 2008; Sherman and Guillery, 2013; Viaene et al., 2011a,b; Zikopoulos and Barbas, 2007b). These dual thalamo-cortical projections potentially allow the thalamus to influence the cortico-cortical communication in several different ways (Jones, 2002, 2007; Sherman and Guillery, 2013).

In primates and humans (but not in non-primate species), across all of the thalamus, these 'driver' and 'modulator' thalamic relay neurons (i.e. those neurons that project to the cortex) react to one of two calcium binding proteins, either parvalbumin or calbindin (Jones and Hendry, 1989; Zikopoulos and Barbas, 2007b). These different calcium immunoreactivity proteins are widely used in primate anatomical immunohistochemistry studies to identify differences in thalamic neurons across the thalamus as well as their cortical projection sites (Jones, 2001; Zikopoulos and Barbas, 2007a). Specifically for the MD thalamic relay neurons (although many other thalamic relay neurons of the dorsal thalamus also have this specificity (see Jones, 2001 for details)), some of the neurons in the medial and central subdivisions that project to the cortex are characterized by parvalbumin-immunoreactivity. Their projections are to topographically ordered middle layers of specific cortical regions. It is proposed that they form part of the 'core' component of neurons that are believed to be involved in the propagation of 'driving' information within their respective cortical networks of connections (Jones, 2001). In contrast, other MD thalamic relay neurons (and other dorsal thalamic relay neurons) are characterized by calbindin-immunoreactivity. These thalamic relay neurons are proposed to form part of the 'matrix' component of thalamic neurons that project to small prefrontal terminals and provide a modulatory role with signals dispersed across superficial layers of widespread cortical regions (Jones, 2001). Jones (2001, 2007) suggested that these 'core' and 'matrix' neuronal groups of thalamic relay neurons are differentially involved with regulating the synchrony of neurons within the cortex leading to long-term potentiation and long-term depression.

Complementary evidence from animals and humans suggests that thalamic burst firing via calcium channels is involved in the generation of thalamocortical interactions. This low-threshold burst firing is dependent on thalamic calcium channels in response to hyperpolarizing membrane potentials elicited by inhibitory inputs (Crunelli and Leresche, 1991; Crunelli et al., 1989; Jeanmonod et al., 1996). It has been suggested that the inhibitory inputs are relayed from cortex via the reticular thalamus (Zikopoulos and Barbas, 2007b). These low-threshold spikes

are proposed to regulate neural oscillations, resonance, and synchrony (Crunelli et al., 1989; Jones, 2002; Kim et al., 2011). Sherman and Guillery (2013) suggest that at least three potential forms of relay can occur via the transthalamic route. Firstly, information transfer may be stopped completely, this being dependent on the thalamic relay mechanism being open or closed. Secondly, information transfer may occur in a linear form, with thalamic relay cells responding in a tonic mode of firing, in this form the thalamus would be providing the cortex with an accurate replication of the information that it received from other regions. Thirdly, information transfer may occur in a nonlinear form, with thalamic relay cells responding in a burst mode of firing that will allow for the opening of the calcium channels. This change in firing may generate a signal in the cortex that alerts it to novel or unexpected events (Sherman and Guillery, 2013). This complementary evidence from animal studies supports these proposals of the importance of the temporal dynamics of the thalamic calcium channels in the involvement of cortical processing. However, their specific role in supporting cortical processing has not yet been determined.

2.4. Subcortical connections of the MD

Thus far, the focus of this anatomy section has been on the MD interconnections with cortex. However, downstream inputs to the MD are also critical for determining how the MD higher order relay nucleus may be influencing the (prefrontal) cortex during learning and decision-making. Different subdivisions of the MD receive wide-ranging and distinct subcortical inputs as well (see Fig. 2). For example, the MDmc also receives excitatory inputs from the amygdala (Aggleton and Mishkin, 1984; Goldman-Rakic and Porrino, 1985; Ray et al., 1992; Russchen et al., 1987). The lateral MD receives inputs from the claustrum, superior colliculus and ventral midbrain (Erickson et al., 2004).

There are also fronto-striatal-pallidal-thalamic feedback loops that are proposed to govern different and independent cognitive processes and behavior, identified by Alexander and colleagues in rodents (Alexander et al., 1986). Within these loops, different subdivisions of MD provide the thalamic relay. Fig. 2 shows how different parts of the pallidum project to the subdivisions of the MD. Briefly, non-reciprocal inputs are received in the MDmc from ventral pallidum and in the MDpc from globus pallidus, while the MDl has reciprocal connections with globus pallidus. These inputs to the MD from the pallidum are inhibitory (GABAergic) signals as are inputs from different parts of the substantia nigra to all three subdivisions (Ray et al., 1992; Russchen et al., 1987).

The MD also has branching axons that extend into and from all sections of the reticular thalamus (Jones, 2002; Zhang and Jones, 2004; Zikopoulos and Barbas, 2012). These widespread interconnections between the MD and all parts of the reticular thalamus are unique to the MD, as other thalamic nuclei interact only with specific subregions of the reticular thalamus (Barbas et al., 2013). Interestingly, the PFC also has direct links with all subregions of the reticular thalamus via branches of corticothalamic axons coming from layer VI (Zikopoulos and Barbas, 2006). This anatomical evidence suggests that the MD may be able to 'modulate' the activity in other thalamic nuclei via its interactions with the PFC and also via its widespread interactions with the reticular thalamus. The MD nuclei also receive other inhibitory regulation from GABAergic interneurons, the zona incerta and pretectum.

Neuromodulatory regulation within the MD is received from neurotransmitters, like acetylcholine, dopamine, adrenaline and noradrenaline, projecting from the hypothalamus, midbrain and brainstem. These neurotransmitters act as neuromodulators for the release of glutamate in the MD (Bueno-Junior et al., 2012; Cavada et al., 1995; Ilinsky et al., 1985; Ray et al., 1992; Rico and Cavada,

1998; Russchen et al., 1987; Sherman, 2014; Velayos and Reinoso-Suarez, 1982).

2.4.1. Cross-species differences in the thalamus

Similarities of anatomical connections are being confirmed between primates and humans comparing well-established anatomical tracing studies in primates with in vivo tracing methods in humans using diffusion tensor imaging (Jbabdi et al., 2013; Klein et al., 2010). However, there are differences given that the human brain shows specializations not found in the macaque monkey brain (Neubert et al., 2014; Sallet et al., 2013).

In addition, there are some notable differences between primates and rodents. For example, there are distinct medial temporal lobe connections to the MDmc coursing from the rhinal cortex in monkeys, via the amygdalofugal pathway (Russchen et al., 1987; Saunders et al., 2005). However, similar connections in rodents are not as robust (Burwell et al., 1995). These differences in connectivity may help to explain some of the cross-species differences in performance of object recognition tasks in monkeys and rodents (Warburton and Brown, 2015).

Further, many rodent species do not have the extent of GABAergic interneurons in the thalamus – they are either sparse or absent in rodents apart from in the lateral geniculate nuclei, where they represent 20–25% of the total neurons (Arcelli et al., 1997; Spreafico et al., 1994). This lack of interneurons in rodents contrasts markedly with primates and many other mammals, whereby between 20 and 30% of the total neuronal population of thalamic neurons are interneurons (Jones, 2007, 2012; Steriade et al., 1997).

There have also been differences reported in levels of dopamine in the MD across primates and rodents. Dopamine transporter axons are readily found in the primate MD (Melchitzky and Lewis, 2001; Sanchez-Gonzalez et al., 2005). However, dopamine transporter axons are much sparser in the rat MD (Garcia-Cabezas et al., 2009). The MD thalamic interneurons are a main postsynaptic target of the dopamine transporter axon (Garcia-Cabezas et al., 2009). However as noted above there is a distinct lack of thalamic interneurons in the MD in rats (Arcelli et al., 1997). Furthermore, the pattern of innervation of dopamine across the different MD subdivisions is heterogeneous. For example, axons immunoreactive for dopamine transporters showed the highest density in the MDpc and MDmf (Melchitzky et al., 2006). Interestingly, the dopamine innervation of MDpc (Melchitzky et al., 2006) comes from the same source as the dopamine innervation to the cortex including the PFC (i.e. from the dorsal tier of ventral mesencephalon (ventral tegmental area, the dorsal portion of the substantia nigra pars compacta and the retrorubral area)), while the dopamine innervation to the striatum stems from the ventral tier of the ventral mesencephalon (Haber and Fudge, 1997). It has also been observed that dopamine innervation originating from the hypothalamus might go to the MDmc and not to the MDpc (Melchitzky et al., 2006; Sanchez-Gonzalez et al., 2005). Similar dopamine innervation patterns have been reported in macaque monkeys and in humans (Garcia-Cabezas et al., 2007).

Taking all of this anatomical evidence into account, it appears that the subdivisions of the MD are essentially different to each other based on their differing anatomy and innervation characteristics. Therefore they are highly likely to be functioning in quite distinctive roles with each subdivision providing distinct higher order thalamic relays of their respective thalamo-cortical and cortico-thalamic interconnections as well as via feedback and feed-forward signals coming through the telencephalon, diencephalon, midbrain and brainstem. This anatomical evidence suggests that when damage is sustained in the MD, that it may lead to widespread dysfunction in the prefrontal cortex.

3. Cognitive and behavioral effects of damage in the MD

Accumulating evidence in humans and in rodent and primate models of cognition indicates that damage to the MD impairs cognitive processes. However, consistent memory deficits are not found after damage to the MD. This includes variability in recognition memory (i.e. the ability to detect whether a stimulus has been encountered previously) and in learning (Aggleton et al., 2011; Markowitsch, 1982). Instead MD damage is reported to disrupt executive function leading to proposals that the MD contributes to cognition via influencing the role of the PFC in executive function (Carlesimo et al., 2011; Van der Werf et al., 2000, 2003a,b).

Many studies in monkeys and rats (Aggleton and Mishkin, 1983a,b; Hunt and Aggleton, 1998; Isseroff et al., 1982) have reported that damage to the MD causes similar cognitive deficits as seen in monkeys and rats with PFC damage. These studies have all produced damage to the whole of MD and in some cases adjacent medial thalamic structures as well, so given the different anatomical connections of these subdivisions of the MD, it may be concluded that extensive and widespread dysfunction has occurred in the PFC (and more widely in the brain) as a consequence of the loss of the whole MD higher order relay.

Conversely, there is some evidence to indicate that dissociable cognitive deficits occur after selective, circumscribed lesions to different subdivisions of the MD in rats (Mitchell and Dalrymple-Alford, 2005, 2006) and in humans (Pergola et al., 2012). This behavioral evidence indicates that MD, with its different subdivisions linked to heterogeneous brain regions operates across interdependent neural systems involved in several aspects of cognition. There are already detailed recent reviews of the impact of behavioral lesions to the MD in animal models including monkeys and rodents (Mitchell and Chakraborty, 2013), monkeys (Baxter, 2013) and instrumental conditioning paradigms in rodents (Bradfield et al., 2013). Further, in humans a recent detailed review has also been conducted (Pergola and Suchan, 2013). So the following discussion provides an overview of proposals about how the brain may be impaired as a consequence of the loss of the MD as a 'higher order thalamic relay' in animal models and humans. The aim of this review of studies is to highlight that with more selective damage restricted to the MD in monkeys, disruptions to executive function are not always apparent. Further the patterns of deficits found after selective MD damage suggests that widespread disruption to the prefrontal cortex may not actually occur. Instead the evidence suggests that the MD is particularly important for supporting the prefrontal cortex during its role in higher order cognitive processes.

3.1. Human cognitive deficits

In the human literature, the types of deficits that are reported after MD thalamic damage are often related to disruption of executive function rather than learning and memory deficits per se (Carlesimo et al., 2011; Van der Werf et al., 2000, 2003a,b). That is, patients that have sustained MD thalamic damage are reported to show similar deficits to patients with frontal cortex damage (Carlesimo et al., 2011; Van der Werf et al., 2003b). Frontal lobe dysfunction is typically characterized by a spectrum of cognitive and behavioral impairments such as hyperactivity, inattention, impulsiveness and working memory deficits. However, after damage in the MD, patients do not typically have problems during working memory assessments (von Cramon et al., 1985) or in recognition memory deficits (Aggleton et al., 2011; Markowitsch, 1982). Instead, patients with brain damage linked to the MD display certain types of learning deficits and problems with complex associative recognition memory but they do not have gross amnesia

(Aggleton et al., 2011; Aggleton and Shaw, 1996; Edeltyn et al., 2006, 2012, 2014; Pergola et al., 2012, 2013b; Pergola and Suchan, 2013; Van der Werf et al., 2003b; von Cramon et al., 1985; Zoppelt et al., 2003). Unfortunately patients also typically have damage to other adjacent medial thalamic nuclei, including the anterior thalamic nuclei, intralaminar thalamic nuclei and sometimes the mamillothalamic tract. More recently, using both neuroimaging to identify the extent of the damage within the medial thalamus and more complex neuropsychological testing, researchers have begun to elucidate the impact on cognition after more selective damage to the MD (Edeltyn et al., 2014; Pergola et al., 2012, 2013a,b). Consequently, these combined techniques may help to further illuminate how specific aspects of cognitive processes are linked to differing subdivisions of MD and their respective cortico-thalamo-cortical neural networks. However, it must also be noted that neuroimaging studies alone will not provide sufficient details about the messages that are relayed between the different layers of the prefrontal cortex and the MD.

Animal models of cognition have been extremely insightful at identifying dissociable cognitive and behavioral deficits linked to the MD. More selective damage to these different medial thalamic brain structures combined with pre-operative and post-operative assessments of cognitive ability have helped to understand the role of the medial thalamus in cognition, recently reviewed by (Aggleton et al., 2011; Mitchell et al., 2014). The animal studies have highlighted how these different medial thalamic structures each contribute to interdependent neural networks distinctively involved in different aspects of cognition (Bradfield et al., 2013; Mitchell and Chakraborty, 2013).

3.2. Do animals with selective MD damage show disruption of executive function?

As indicated from the human literature, MD damage (that includes damage to other medial thalamic structures or more widespread damage too) is suggested to cause disruption to executive function. However, in the animal literature, typically there is a lack of specific disruption to executive function and other behavioral deficits after more selective MD damage. Monkeys and rats with selective circumscribed damage to one of the subdivisions of MD do not typically show disruption to executive function during behavioral testing, unless the tasks are only introduced to the animals during postoperative testing (see Table 1: Mitchell and Chakraborty, 2013). Instead, animals with MD damage display learning and decision-making deficits specific to certain aspects of cognition (Mitchell and Gaffan, 2008; Mitchell et al., 2014). Further, in many cases, the cognitive deficits apparent after MD damage are dissociable to selective circumscribed damage produced in other areas of adjacent medial thalamic nuclei (e.g. anterior thalamic nuclei and intralaminar thalamic nuclei) in rodents (Chudasama et al., 2001; Corbit et al., 2003; Gibb et al., 2006; Mitchell and Dalrymple-Alford, 2005, 2006) for review see Mitchell and Chakraborty (2013).

Specifically, in non-human primates, after selective loss of the MDmc, cognitive deficits do not typically mimic the types of deficits to executive function observed in animals and in patients with frontal lobe pathology. For example, damage to the MDmc does not cause monkeys to respond in a perseverative manner during object-in-place scene discrimination learning. Instead monkeys alternate their choices sampling both stimuli in two-choice paradigms, although they do not respond randomly either (Mitchell et al., 2007a). In contrast, monkeys with ventrolateral PFC damage demonstrate perseverative responding (Baxter et al., 2008a). Additionally, damage to MD does not appear to make monkeys disinhibited in their responses. After small ablations

of MDmc, monkeys could still learn object recognition memory tasks using a small selection of stimulus objects, although these same monkeys showed poorer recognition memory performance for stimuli presented from a larger collection of objects (Parker et al., 1997). Interestingly though, the recognition deficits in these MD damaged monkeys were linked to a lack of improvement in performance over repeated testing when compared to the unoperated controls who showed improvements (Parker et al., 1997). Other monkeys with larger MD lesions that also involved the anterior thalamus or mamillothalamic tract had recognition memory deficits for objects presented within the session but the monkeys were able to learn visual pattern discriminations and the spatial delayed response task (Aggleton and Mishkin, 1983b). Another group of monkeys with more selective MDmc ablations were not markedly impaired in object recognition but they did show extensive deficits in object-reward associative learning during within session testing (Aggleton and Mishkin, 1983a). Other monkeys with large MD ablations showed impaired recognition memory with postoperative testing only (Zola-Morgan and Squire, 1985). Further, after neurotoxic damage to the MDmc, monkeys could learn 60 pairs of distinct object-reward associations across sessions (Mitchell et al., 2007b) and showed good memory retention for 300 object-in-place scene discriminations that they had learnt prior to thalamic brain injury (Mitchell and Gaffan, 2008). All of this combined evidence showing specific deficits in some cognitive tasks but not in others suggests that the cognitive and behavioral deficits linked to damage of the MD are not always simply due to disruption of executive function that is typically observed after damage to the PFC.

Further, the cognitive deficits that are apparent after MDmc damage cannot be attributed to problems with motivation to complete the tasks or from a lack of arousal. For example, evidence of time spent completing testing in the computerized cognitive paradigms involving non-human primates and MD damage has demonstrated similar preoperative and postoperative performance measures (Gaffan and Parker, 2000; Mitchell et al., 2007a,b; Parker et al., 1997).

In some rat studies, researchers have concluded that cognitive deficits that are apparent after MD damage, although this damage is to the whole of MD, are linked to problems with behavioral flexibility (Hunt and Aggleton, 1998) or to a general impairment in developing new behavioral strategies to obtain rewards (Block et al., 2007; Yu et al., 2010).

However, it is also apparent that the cognitive deficits shown in animals with loss of MD, and specifically MDmc in primates, seem to be associated with tasks that require information from multiple cognitive processes to be linked together for successful, optimal performance (especially when the learning has to occur on a trial-by-trial rapid basis). These cognitive processes (such as information about objects, their whereabouts, context, feedback (rewards), temporal order, and other modalities of information) arrive in the cortex from many other brain regions directly involved in their processing. Therefore given the widespread anatomical connections with all areas of the PFC, the MD may be involved in cognition by contributing to the underlying mechanisms that enable the higher order regions of the prefrontal cortex to link together these multiple cognitive processes at the same time (on a trial-by-trial basis) in order for the animal (or human) to optimally perform the current task.

A similar kind of functional role has been suggested for the pulvinar during tests of selective attention (Saalmann et al., 2012). As mentioned earlier, the pulvinar is also classified as a higher order thalamic relay linked to the visual system with its main driver inputs originating in layer V of area 17 (Guillery, 1995; Sherman and Guillery, 2006; Van Horn et al., 2000).

3.3. Tasks involving multiple cognitive processes

One of the tasks used in primates and in humans that requires multiple cognitive processes to be integrated together for successful performance on a trial-by-trial basis is the object-in-place scene discrimination task (Aggleton et al., 2000; Gaffan, 1994; Murray and Wise, 2010). Successful performance on this associative learning task requires the integration of object and place information within a unique complex background visual scene on a trial-by-trial basis. In this task, the stimuli are all different colored typographic characters and they are randomly assigned on each trial so the stimulus information from the previous trial will not provide clues for successful performance on the current trial. Similarly, the unique background visual scenes are comprised of differently colored, randomly generated shapes and the information from the previous trial will not provide clues for successful performance on the current trial. In some forms of this associative learning task, learning of 20 unique object-in-place scene discriminations occurs rapidly *within* a single session involving 8 repetitions of the concurrently presented discriminations. Monkeys with loss of MDmc are impaired on this version of the task (Gaffan and Parker, 2000; Mitchell et al., 2007a). The object-in-place scene discrimination task has also been modified to assess *across* session learning of 100 object-in-place scene discriminations. In this version of the task, learning of the complex object-in-place scene discriminations occurs across sessions with only one presentation of each of the 100 unique discriminations in each session (Mitchell and Gaffan, 2008). Monkeys with loss of MDmc are also impaired on learning these discriminations *across* sessions (Mitchell and Gaffan, 2008). Monkeys with MD damage are also impaired in other cognitive and behavioral tasks that involve associative learning that incorporates the integration of multiple cognitive processes rapidly. Some examples of these tasks include within session *serial* presentations of object-reward associations using different list lengths of stimuli or different amounts of reward associated with different stimuli (Gaffan and Murray, 1990; Gaffan and Watkins, 1991; Parker et al., 1997).

In rodents, cognitive and behavioral tasks that involve associations of several different cognitive processes, including temporal order recognition memory (a task that requires rats to distinguish between the more recent presentation of two familiar objects within the same session) and object-in-place recognition memory. These associative learning tasks involve spontaneous exploration paradigms so they provide an important comparison with other associative learning tasks that also involve food rewards to be associated with correct performance (Warburton and Brown, 2015).

3.4. MD deficits on cognitive tasks involving multiple cognitive processes

The following discussion represents an overview of animal studies in monkeys and rodents that use behavioral tasks that require multiple cognitive processes to be integrated for successful performance. These translational cross-species approaches have demonstrated the extent of cognitive deficits on these tasks even after selective damage in the MD. As expected, the evidence from these studies shows that the loss of MD causes cognitive deficits but typically it does not suggest the disruption of executive function. Therefore these studies in animals can be extremely helpful in extending our understanding about how the higher order MD thalamic relay may be supporting the prefrontal cortex in its role to integrate various multiple forms of information together that contribute to normal cortical functioning.

After selective damage to the MDmc in primates, cognitive deficits can occur in learning many types of information (Aggleton and Mishkin, 1983a,b; Gaffan and Murray, 1990; Gaffan et al., 1993;

Gaffan and Watkins, 1991; Mitchell et al., 2007a, 2008; Mitchell and Gaffan, 2008; Parker et al., 1997). In many of these studies though, monkeys are also able to learn other information presented in different ways (as illustrated below). It has also been observed that damage to the MDmc is not always producing similar deficits as PFC damage (Mitchell et al., 2007a; Mitchell and Gaffan, 2008). For example, in animal models of amnesia, monkeys that have damage in the MDmc are unable to learn 20 new object-in-place scene discriminations, either rapidly *within* a single session (Gaffan and Parker, 2000; Mitchell et al., 2007a; Mitchell and Gaffan, 2008) or slowly *across* several sessions (Mitchell and Gaffan, 2008). However, the same monkeys are able to remember 300 object-in-place scene discriminations that they learnt prior to their thalamic brain injury (Mitchell and Gaffan, 2008). These dissociable cognitive deficits suggest several important points about the effects on the brain after the loss of MD. Firstly, it appears that communication between the MDmc and its cortical targets is particularly important for learning certain types of object-reward associations, but not for their retention (Mitchell et al., 2008; Mitchell and Gaffan, 2008). Secondly, this evidence indicates that the animals' ability to scan these complex visual 'scenes' and recognize the previously rewarded stimuli appear to remain intact. Finally, in contrast to intact retention after MDmc loss, monkeys with widespread damage to the PFC have impaired retention of object discriminations that they learnt prior to brain injury (Browning and Gaffan, 2008).

In these complex object-in-place scene discrimination paradigms, differing levels of severity are also reported after damage to the MD or damage to interconnected structures of the PFC. As mentioned, monkeys with MDmc damage are severely impaired during learning new object-in-place scene discriminations (Gaffan and Parker, 2000; Mitchell et al., 2007a). In contrast, selective bilateral ablations to orbital frontal cortex or to the ventrolateral prefrontal cortex cause milder deficits in learning (Baxter et al., 2007, 2008a) but selective bilateral ablations to the dorsolateral PFC do not impair learning of this complex object-in-place scene discrimination task (Baxter et al., 2008b). Interestingly, selective bilateral damage to frontopolar cortex (BA 10) impaired rapid one-trial learning on the object-in-place scene discriminations only (Boschin et al., 2015). This evidence shows the crucial contribution of the MDmc in this rapid associative learning task and suggests that the MDmc contributes to specific aspects of cognition via its interconnections to the PFC rather than causing widespread cortical dysfunction.

Further, monkeys with bilateral MDmc damage are able to implement a strategy for obtaining rewards that they had acquired prior to brain injury (Mitchell et al., 2007a). However, monkeys with bilateral selective damage to the ventrolateral PFC are impaired at the strategy implementation task (Baxter et al., 2009). This evidence suggests that the MDmc higher order thalamic relay supports communication across the cortex during some forms of associative learning but not during memory retention. Other complementary monkey lesion studies have demonstrated that direct cortico-cortical routes of information transfer are important for retention memory in non-human primates. For example, Gaffan and colleagues have shown that the integrity of interactions between the prefrontal cortex and medial temporal lobes are important for retention of previously acquired information (Browning et al., 2007; Gaffan et al., 2002; Wilson and Gaffan, 2008). Interestingly though, in a different monkey lesion study, memory retention deficits for object-in-place scene discriminations can occur when the loss of MDmc is combined with fornix transection (Mitchell et al., 2008). The extensive deficits after the combined MDmc and fornix damage are suggested to occur due to the more widespread disconnection of subcortical structures from their cortical targets within the respective neural networks of the MDmc

and fornix spanning both the frontal lobes and the medial temporal lobes (Mitchell et al., 2008).

Finally, rapid within-session learning of object-reward associations can also be disrupted after MD damage. For example, monkeys with MD damage were impaired during object-reward association learning when stimulus pairs were presented rapidly using serial presentation (Gaffan and Murray, 1990). Monkeys with MD damage were also impaired in serial presentations of object-reward associations when different objects were associated with different amounts of rewards (Gaffan and Watkins, 1991). The serial presentation of information forces the rapid learning of object-reward associations within a single session. Consequently, with the loss of MD, rapid serial presentation of the object-reward associations may not provide sufficient time for the cortex to produce adaptive responses to be implemented prior to the next successive trial (see more details below). However, this proposal has not yet been explicitly tested in monkeys with MD damage.

3.5. Associative learning tasks in rats with MD damage

Evidence in rat models of amnesia supports these findings too. For example, rodents with selective bilateral neurotoxic damage to either the medial MD or lateral MD are impaired on two-item temporal order recognition memory but not on single item spontaneous object recognition memory in open field exploration paradigms (Mitchell and Dalrymple-Alford, 2005). Rodents with medial PFC damage are also impaired in two-item temporal order recognition memory (Mitchell and Laiacina, 1998). These testing paradigms use spontaneous exploration tasks that do not involve food reward for correct responses. Cross et al. (2012) confirmed similar dissociable results of impaired performance on two or more item temporal-order recognition memory and intact performance on single item recognition memory after more extensive MD damage in rodents. Furthermore, additional evidence from these experiments showed that rodents with unilateral damage to all of MD or contralateral MD–PFC functional hemisphere disconnections show intact single item recognition but marked impairments on associative object-in-place recognition memory and two-item recency discriminations in open field exploration paradigms (Cross et al., 2012). Similar results on these tasks are also apparent in rodents with medial PFC damage (Barker et al., 2007). All of this evidence suggests that the MD higher order relay is supporting the prefrontal cortex in tasks that require the association of multiple cognitive processes.

3.6. MD deficits and interference effects

As discussed so far, monkeys with MDmc damage are impaired on complex associative learning tasks including the object-in-place scene discrimination task and serial presentations of object-reward associations that require the rapid integration of objects and rewards within a session (Gaffan and Murray, 1990; Gaffan and Parker, 2000; Mitchell et al., 2007a). In contrast, monkeys with MDmc damage are not impaired at learning object-reward associations across sessions (Mitchell et al., 2007b). Further, monkeys with MDmc ablations are only mildly impaired using small sets sizes of object-reward associations when pre-operative learning rates are compared to post-operative learning rates (Gaffan and Parker, 2000). Similarly MDmc damage did not impair object recognition with small set sizes (Parker et al., 1997).

This evidence indicates that dissociable deficits in postoperative learning can occur if learning is spread out across sessions. The underlying mechanism that may support successful learning across sessions may be linked to a reduction in the amount of interference with these longer epochs between trials that occurs to support separate representations of these associations of multiple cognitive

processes. Similar conclusions have been made to account for the differences in learning abilities of monkeys with perirhinal cortex ablations (Buckley and Gaffan, 2006).

This proposed account of increases in interference may also explain the mild deficits in learning after MD damage across sessions when the level of complexity of the task increases. This effect is apparent in rewarded recognition memory paradigms, whereby MD lesions show no improvement in performance across sessions when larger set sizes are encountered (Parker et al., 1997). In the small set size condition of the recognition memory paradigm, the monkeys encountered the same objects more frequently, so it was not a very demanding condition, resulting in less interference, compared to the large set size condition (Parker et al., 1997). Parker and colleagues noted that the extent of the deficits produced after MDmc ablations were also not as extensive as the deficits they observed after perirhinal cortex ablations (Parker et al., 1997). As mentioned, perirhinal cortex sends inputs to the MDmc in primates and humans but these connections are not as robust in rodents (Burwell et al., 1995; Saunders et al., 2005). This increase in interference may also help to explain the extent of new learning deficits in monkeys with MDmc damage in the across session learning of the object-in-place scene discrimination task (Mitchell and Gaffan, 2008).

3.7. The loss of MD and decision-making

In addition to the dissociable deficits encountered in learning, retention and recognition memory tasks after MD damage, consistent evidence suggests that the MD also provides a functional role when animals are required to make adaptive decisions. For example, after MD lesions, monkeys and rats are impaired at establishing the current value or desirability of a reward (Corbit et al., 2003; Izquierdo and Murray, 2010; Mitchell et al., 2007b; Mitchell and Dalrymple-Alford, 2005; Ostlund and Balleine, 2008; Parnaudau et al., 2015), and therefore, are unable to utilize this information to establish the appropriate goal-directed action (Bradfield et al., 2013). During adaptive decision-making, evidence suggests that the MD may facilitate the interaction between the orbital prefrontal cortex and amygdala (Izquierdo and Murray, 2010; Ostlund and Balleine, 2008). This proposal suggests that the MD thalamic relay is particularly important for providing support to cortical communication between the amygdala and the orbital frontal cortex (Mitchell et al., 2014; Murray and Rudebeck, 2013). The anatomical links of these regions suggest a triangular anatomical interaction of these three structures. The orbital frontal cortex and the basolateral amygdala have a direct route of communication (Carmichael and Price, 1995). In addition, anatomical evidence shows that there is a trans-thalamic route of communication running between the amygdala and the orbital frontal cortex via the MDmc higher order thalamic relay nucleus (as mentioned in Section 2). Adaptive decision-making paradigms require the cortex to integrate task relevant information on a trial-by-trial basis for optimal decisions to occur. The MD higher order relay may contribute a functional role supporting the prefrontal cortex during these higher order cognitive processes in a similar way to the role it contributes to the prefrontal cortex during learning. The effects of decision-making deficits in humans with MD damage have thus far not been widely investigated.

4. Mechanisms for MD relay in cortico-cortical communication

4.1. Electrophysiology in rodents

Electrophysiology recordings from animals can provide some insights into the underlying mechanisms of MD higher order

thalamic relays impacting on the PFC. Recent work in mice (Kim et al., 2011; Parnaudeau et al., 2013, 2015) has provided evidence that shows how the MD relay may interact in PFC cortical communication. Firstly, this review will establish how the MD relay might be altered after frontal lobe dysfunction in a PFC-specific hypoxic-like damage model (Kim et al., 2011). In the study of Kim and colleagues, coherence between the MD and PFC in the theta frequency was abnormally enhanced and low threshold burst spikes were increased in MD neurons as a consequence of the hypoxic damage in PFC (Kim et al., 2011). It remains to be determined how local excitability of PFC neurons occurs in this hypoxic-model, which in turn stimulates MD neurons via cortico-thalamic interactions and might alter the signaling of calcium MD channels. However, Kim et al. (2011) have suggested that the inhibitory mechanisms leading to the deactivation of the calcium channels in MD may be generated via feedback mechanisms activated between the PFC and reticular thalamic nuclei (Groenewegen, 1988; Zikopoulos and Barbas, 2006).

Subsequently, after genetic knockdown or knockout of the MD calcium channels, Kim et al. (2011) recorded decreased theta frequency coherence between MD and PFC and decreased frontal lobe-specific seizures as well as locomotor hyperactivity in the mice. Kim and colleagues suggest their results demonstrate a two-step model of dysfunction caused by the PFC hypoxic lesions, which resulted in abnormal cortico-thalamocortical feedback interactions that altered the MD calcium channels, leading to the onset of neurological and behavioral abnormalities (Kim et al., 2011).

Further work in mice has studied how synchrony of the PFC is affected during learning before and after temporary inactivation of MD (Parnaudeau et al., 2013, 2015). In this research, mice were trained in a spatial working memory task (T-maze delayed non-match-to-sample). During task acquisition increased MD neuronal spiking synchronized with PFC local field potentials (Parnaudeau et al., 2013). Further with temporary inactivation of the MD, changes in synchronization were recorded in the PFC and these changes correlated with errors in learning (Parnaudeau et al., 2013). Since the proposals of Hebb (1949), extensive evidence has demonstrated that synchrony in cortical oscillations enhances binding, with the greater the degree of synchrony in the cortex the better the information transfer between synchronized structures (Uhlhaas and Singer, 2013). As mentioned earlier, Jones (2001, 2007) and others (Sherman and Guillery, 2013) have proposed that signaling from differing groups of thalamic relay neurons are supporting the modulation of synchrony in cortical neurons. Thus, from these electrophysiology studies it may be suggested that the MD higher order thalamic relay is supporting cortico-cortical communication by simultaneously increasing synchrony in cortical neurons for appropriate behavioral responses during new learning. Thus in relation to the cognitive and behavioral lesion studies, it may be suggested that after damage to MDmc, normal processing of information by the interconnected cortical regions is dysfunctional causing noisy signaling that leads to disorganized behavioral responses (i.e. errors). In addition, in the dysfunctional PFC, cortico-thalamic feedback mechanisms entering the reticular thalamus and MD may be controlling the hyperpolarization of the calcium MD channels that leads to increased low-burst spiking causing abnormal coherence to occur (Kim et al., 2011).

4.2. Electrophysiology in monkeys

Other electrophysiology studies in monkeys have suggested that the trans-thalamic route of information transfer could also be an important route for constructing prospective information in the cortex. Several researchers suggest that a component of the signals relayed to the cortex via the thalamus are copies of motor outputs, or corollary discharge signals (Guillery, 2005; Guillery and

Sherman, 2002b, 2011; Wurtz et al., 2011). The corollary discharge signal is generated simultaneously with a movement and is relayed to allow other brain areas that take the prospective movement signal into account when planning future movements (Sommer and Wurtz, 2002). This evidence for corollary discharge signals relayed via the thalamus has been shown in the lateral subdivision of MD during visual sensorimotor processing from the superior colliculus (Sommer and Wurtz, 2002, 2004, 2006, 2008a,b), recently reviewed (Mitchell et al., 2014). These conclusions indicating a corollary discharge signal is relayed via the thalamus may also be supported by research of Watanabe, Funahashi and colleagues investigating prospective information processing from working memory studies in monkeys involving the central subdivision of MD, recently reviewed (Funahashi, 2013). MD neurons, like their projection targets in dorsolateral PFC, exhibit sustained delay activity. It had been assumed that these MD neurons were involved with prospective information processing in a similar way to that of dorsolateral PFC. However, using a population vector analysis of the transformation of sensory-to-motor information, Watanabe and colleagues (Watanabe et al., 2009) revealed that this transformation occurred earlier during the delay period in the MD compared to the dorsolateral PFC. This combination of results suggests that the MD provides information regarding forthcoming (prospective) information to the dorsolateral PFC (Watanabe and Funahashi, 2012). It may be extrapolated from these studies in lateral and central subdivisions of the MD, that MDmc also receives corollary discharge of prospective information that it relays onto cortex. However, this still remains to be determined.

The anatomical, lesion and electrophysiology evidence in animal models suggests possible functional roles for the MD higher order thalamic relays in learning and decision-making. During normal behavioral and cognitive demands, the MD may be involved in relaying processed messages onto other cortical regions via excitatory signals from its cortical layer V inputs. These excitatory signals are being modulated by other signals received via the cortex, reticular thalamus, MD interneurons, pallidum, midbrain and brainstem. These signals that modulate the main glutamatergic MD–PFC interactions may occur as a consequence of a mismatch in the feedback received after the completion of a trial or action (Sherman and Guillery, 2013). This mismatch of signals may then generate a change in the firing of the neurons, which is relayed across the cortex to indicate that a change is going to occur. These signals of information are then transferred via the MD onto other higher order cortical regions involved in the current task demands. Thus with damage to the MD, there is no longer appropriate mechanisms to regulate the rapid flow of information transfer that helps to update the association cortex and supports its integration of information across multiple cortical regions via the MD trans-thalamic route.

5. Conclusions and future directions

Patient lesion studies and animal models of cognition, combined with complex cognitive neuropsychological testing continue to offer great insights into our understanding about cortico-thalamo-cortical functions and their underlying neuronal mechanisms linked to cognition. Combining these techniques together with detailed anatomy, electrophysiology and neuroimaging methods, will further advance our understanding about the interactions between the cortex and the thalamus that are important for cognition and behavior. This review has highlighted how the MD may contribute to learning and decision-making processes. The MD may help support the prefrontal cortex to do its job of integrating several task relevant signals together on a trial-by-trial basis for optimal higher order cognitive processing. When MD is damaged, some of

the signals linked to the integration of this information may no longer pass via the MD trans-thalamic route resulting in distorted information transfer across widespread but specific cortical regions leading to abnormal behavioral outputs (errors).

Since we now know that no structure in the brain works alone or independently and that there are multiple cortical areas involved in complex cognitive processes, we need further research studies that investigate how the MD and PFC brain regions function together and what messages are transmitted across these interconnected regions. As this review has highlighted, both long-range and short-range communication between and within these brain regions is clearly important. Newer methods of producing temporary lesions and inactivation studies, in addition to the already widely successful lesion techniques can together contribute further advances in determining the influence of the MD higher order thalamic relays on cortical functions. However, it is important more than ever to understand the anatomy of these brain regions and recognize the importance of subcortical influences on the cortex to fully understand how the brain is functioning in normal and abnormal states.

This review has highlighted how the role of the MD defined as a higher order thalamic relay may be influencing the cortex in certain aspects of cognition. Evidence in animal studies and in humans implicates the MD as contributing to learning and decision-making. However, these functions are typically considered to be the domain of the PFC and the medial temporal lobes. This review has detailed how the anatomy of the MD is highly complex and that its influence on the brain is widespread but distinct. Consequently, the MD thalamic relay can facilitate communication between multiple brain regions involved in complex cognitive processes. But the specific mechanisms and the messages that the MD relays linked to learning and decision-making remain to be determined. In order to understand this influence, future studies must focus on the functional anatomy of the MD, considering its inputs, identifying which ones are drivers and which ones are modulating the signals being relayed to the projection targets in different layers of the prefrontal cortex. Then we may be able to understand further how the cortex processes higher order cognition.

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