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The Mediodorsal Thalamus: An Essential Partner of Prefrontal Cortex for Cognition

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Abstract

Deficits in cognition are a core feature of many psychiatric conditions, including schizophrenia, where the severity of such deficits is a strong predictor of long-term outcome. Impairment in cognitive domains, such as working memory and behavioral flexibility, have classically been associated with prefrontal cortex (PFC) dysfunction. However, there is increasing evidence that the PFC cannot be dissociated from its main thalamic counterpart, the mediodorsal thalamus (MD). Since the causal relationships between MD-PFC abnormalities and cognitive impairment, as well as the neuronal mechanisms underlying them, are difficult to address in humans, animal models have been employed for mechanistic insight. In this review, we discuss anatomical, behavioral, and electrophysiological findings from animal studies that provide a new understanding on how MD-PFC circuits support higher-order cognitive function. We argue that the MD may be required for amplifying and sustaining cortical representations under different behavioral conditions. These findings advance a new framework for the broader involvement of distributed thalamo-frontal circuits in cognition and point to the MD as a potential therapeutic target for improving cognitive deficits in schizophrenia and other disorders.

Keywords

Mediodorsal Thalamus; Prefrontal Cortex; Thalamo-Cortical Connectivity; Working Memory; Behavioral Flexibility; Schizophrenia

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INTRODUCTION

The thalamus is a heterogeneous structure located deep in the brain, which has been traditionally viewed as a simple gateway for relaying information from the sensory periphery to the cortical end-station(1,2). This concept has roots in the 19th century when neurologists used clinical or experimental brain lesions to map cortical areas onto sensory and motor abilities. Subsequently, histology and lesion-induced retrograde degeneration of cortical targets were employed to parcel the thalamus into subnuclei with distinct projection patterns to circumscribed cortical areas. Placed just several synapses from the sensory and motor periphery, and exhibiting a relatively homogenous cellular structure in comparison to cortex, the computational power of the thalamus was considered limited(1,2).

While the effects of sensory and motor cortex lesions or stimulations were relatively easy to interpret, the consequences of frontal lobe ablations were more complicated to describe. Decades of work were needed to establish what would eventually be termed the prefrontal cortex (PFC) as an important center for personality, emotion and cognitive function(1). This classical work paved the way for the first reports showing striking resemblance between the cognitive deficits observed in patients with frontal lesions and schizophrenia(3,4). In the last 30 years, modern brain imaging techniques confirmed the association between altered prefrontal function and cognitive deficits leading to the influential hypothesis that cognitive symptoms, especially in the executive function domain, arise from a dysregulation of PFC activity(5–7).

Yet, just as with sensory and motor cortical areas, the PFC receives dense innervation from anatomically prescribed thalamic counterparts, most prominently from the mediodorsal thalamus (MD)(8). However, unlike sensory and motor thalamic nuclei, the MD exhibits minimal connectivity with either sensory or motor pathways and instead receives its driving input directly from various PFC areas. Moreover, lesions of the MD typically induce cognitive dysfunctions that are reminiscent of those observed following prefrontal lesions(9,10). These observations indicate that PFC function cannot be divorced from that of its interconnected thalamo-frontal circuitry. While it has been proposed on anatomical grounds that the MD serves as a relay station between distinct prefrontal areas(2,11), the unique contributions of the MD towards PFC-dependent cognition remains largely enigmatic.

An understanding of how MD-PFC circuitry contributes to cognition is of growing clinical interest. Recently, studies have reported MD dysfunction along with abnormal thalamo-frontal connectivity in several mental disorders including schizophrenia (12,13). Thus, a clearer anatomical and functional understanding of thalamo-frontal circuitry appears essential in order to elucidate how their alteration may contribute to cognitive dysfunction in psychiatric conditions. Here, we provide an overview of recent behavioral and electrophysiological findings in primates and rodents, giving new insights on how MD-PFC circuits interact in order to support higher-order cognitive function. We then review the evidence for altered thalamo-frontal circuitry in mental disorders and discuss how this may contribute to cognitive deficits.

ANATOMY OF MD-PFC CIRCUITS

Based on anatomical and functional data, dorsal thalamic nuclei have been categorized into two types(14). First order thalamic nuclei are characterized by their functional response patterns to sensory stimuli or motor activity, consistent with their close connectivity with the sensory periphery and primary motor pathways. In contrast, higher-order thalamic nuclei receive few or no sensory inputs from the periphery but can be anatomically defined by its driving afferents from the cortex(14). These thalamic structures are thereby linked to the higher-order processing that has classically been attributed to cortex alone. Higher-order thalamic nuclei include the MD, the pulvinar, and the posterior, the intralaminar and the midline nuclei (but see Rovo et al.(15)). In this review, we will focus on the MD that displays a unique set of topographically organized interconnections with the PFC. Since excellent and detailed reviews of MD-PFC anatomy exist(2,16,17), we just depict here the main components of these circuits in Figure 1.

THALAMO-FRONTAL CIRCUITS AND WORKING MEMORY: BEHAVIORAL AND ELECTROPHYSIOLOGICAL STUDIES

Patients with thalamic lesions often exhibit amnesic syndromes similar to those observed in patients with hippocampal lesions, likely due to damage to the mammillothalamic tract or anterior thalamic nucleus(18,19). However, more circumscribed lesions to the MD have been associated with deficits in executive functions similar to those observed in patients with frontal lobe dysfunction(19–21). Unfortunately, patients often exhibit damage to several thalamic areas, thus limiting inferences about the precise role of the MD. Therefore, research has turned to animal models in which MD function can be directly manipulated. Those studies implicate a role for the MD in working memory, behavioral flexibility, and goal-directed behavior(10).

Behavioral evidence for a role of MD-PFC circuits in working memory

Working memory is defined as a transient holding, processing, and use of information on the scale of seconds. Based primarily on work in humans, Baddeley and Hitch proposed an influential model of working memory defined by two independent subsystems – a visual-spatial sketch pad and a phonological loop – that are coordinated by a central executive controlling the flow of information between them(22). For obvious reasons, it is challenging to apply this model across species. In animal research, working memory can be defined as a delay-dependent short-term memory of an object, a stimulus or a location that is used within a testing trial, but not between trials, as opposed to reference memory that is typically acquired with repeated training and persists for days(23).

Classical studies in primates have shown that MD lesions diminish performance in delayed response tasks, a standard assay for working memory(24,25). Although not always consistent(26–32), rodent literature also supports a role for the MD in working memory. Rodent studies have typically employed spatially guided delayed response tasks, in which the animal is required to retain a memory trace of a recently sampled maze location during a delay period and then prompted to select the opposite location in order to receive a reward

(delayed non-matching-to-sample (DNMS)). Many studies have reported deficits after lesions or inhibition of the MD using variants of the DNMS task(33–41). Although in some of these studies lesions may have extended to adjacent regions, including the anterior thalamus(33–35), the MD, unlike the anterior thalamus, does not seem to play a role in spatial reference memory(42). Moreover, deficits in DNMS working memory tasks following MD lesions have also been observed in operant settings, where spatial requirements are more limited(37,40,43–45). Several studies have also found that DNMS deficits were dependent on the length of the delay(37,41,44,45), suggesting the MD may be particularly involved in the maintenance of representations critical for task performance as opposed to general task learning.

Spatial working memory in rodents is known to depend on medial PFC (mPFC) function(46–48). Analogous deficits observed following MD lesions could therefore be due to a disconnection of MD-mPFC circuitry(39), thus raising questions regarding the unique contributions of each structure to working memory processes. Using optogenetic tools, a recent study examined the involvement of MD-to-mPFC and reciprocal mPFC-to-MD pathways in a DNMS T-maze task(49). Inhibition of either pathway led to a decrease in performance in a delay-dependent manner, while inhibition of MD-to-lateral orbitofrontal cortex (OFC) projections had no impact on behavior. The temporal resolution of optogenetic inhibition further allowed assessing the significance of reciprocal MD-mPFC circuits during discrete phases of the DNMS spatial working memory task. While initial spatial sampling did not require MD-mPFC activity in either direction, spatial choice specifically required the mPFC-to-MD pathway but not the MD-to-mPFC pathway. In contrast, the delay period relied on reciprocal interactions across both structures(49). This observation is strikingly circuit-specific as inhibition of ventral hippocampal (vHip) inputs to the mPFC during the sample phase, but not the delay phase, robustly impaired performance(49,50). Together, these data suggest that while the direct vHip-to-mPFC pathway is involved in the encoding of the spatial location during the initial sample phase, reciprocal activity between MD and mPFC supports short-term maintenance of working memory during the delay. Moreover, top-down inputs from the mPFC-to-MD guide successful memory retrieval and/or choice selection (Figure 2A).

Thalamo-frontal synchrony during working memory

The above data point to functional interactions between the MD and the PFC in working memory. But how do both structures interact at the physiological level? In the DNMS T-maze working memory task, MD-mPFC synchronous local field potential activity in the theta (4–12Hz) and beta (13–20Hz) frequency ranges increases hand in hand with task learning(41). Moreover, in trained mice, the spiking of individual MD neurons have been shown to synchronize with mPFC local field potentials in the beta range during the choice phase of the task when working memory demand is highest(41).

Two findings support the functional relevance of MD-mPFC beta-synchrony in working memory processes. First, decreasing MD activity delays both task acquisition as well as the increase of MD-mPFC synchrony. Second, decreasing MD activity disrupts the choice phase-specific enhancement of MD phase-locking to mPFC beta oscillations(41).

Interestingly, a more refined task phase-specific analysis of MD-PFC beta synchrony suggests bi-directional information flow going from MD to mPFC during the delay and from mPFC to the MD during the choice phase(49). This dynamic shift in directionality of MD-PFC synchrony suggests that choice phase beta synchrony may serve the retrieval or selection of motor-related working memory information via mPFC to MD connections, consistent with the behavioral impact of inhibiting this projection.

Modulation of thalamo-frontal synchrony has also been observed in other cognitive tasks(51,52). In a two-alternative discrimination task in which rats must discriminate between two odors and use this information to guide subsequent decision-making, synchronous activity between the MD and piriform cortex (PCX) and MD-OFC circuits dynamically shifts according to task demands. During initial odor sampling, MD neurons exhibited enhanced phase-locking to both PCX and OFC theta oscillations, followed by a strikingly specific increase in phase-locking to OFC beta oscillations immediately preceding the subsequent choice(53). These findings suggest that the MD, as has been proposed before, may be a critical subcortical node for linking cortical areas involved in processing cognitive information(11). The choice-specific modulation of MD-OFC beta synchrony is also reminiscent of the above described MD-mPFC beta synchrony during working memory guided spatial selection, potentially indicating that thalamo-frontal beta synchrony is a general circuit mechanism supporting working memory guided action selection.

The MD sustains delay-elevated activity in the mPFC

The fact that inhibiting MD inputs to the mPFC during the delay phase impairs later choice performance in the DNMS task, suggests that mPFC activity during the delay carries information critical for short-term memory maintenance in an MD-dependant manner. Almost 50 years ago Joaquin Fuster proposed a potential neural correlate for short-term memory maintenance when he recorded neurons in the dorsolateral PFC (dlPFC) of monkeys whose activity remained elevated across the entire delay period of a delayed response task(54). In a subsequent study, Alexander and Fuster revealed the same neural signature in MD neurons. Employing PFC cooling, they further showed that delay activity in MD neurons, along with behavioral performance, depended on PFC activity. This pioneering paper provided the first evidence of functional interactions between both structures and led to the hypothesis that the maintenance of PFC activity during working memory requires reverberatory activity within the MD-PFC circuit(55).

Two recent rodent studies examined the impact of MD inhibition on PFC delay period activity in a two-alternative forced choice (2AFC) task and the above-described DNMS T-maze task. Both studies uncovered populations of mPFC neurons with elevated spiking during the delay. Rather than being active during the entire delay, individual neurons exhibited brief bouts of elevated activity much shorter than the total delay length. As each neuron displayed elevated activity at distinct temporal offsets from the delay onset, ordering of neurons according to peak time of firing within the delay revealed a sequential activation across the population that spanned the entire delay duration(49,56). This population-distributed delay activity has been observed in several previous studies using both monkey

and rodent models(49,56–61) and is interpreted to reflect the encoding of memory in synaptically connected populations of neurons(59).

In both studies, elevated mPFC activity indicated correct performance during the subsequent choice phase, and was critically dependent on MD inputs for its sustained maintenance across the delay(49,56). Strikingly, the impact of MD inhibition on elevated mPFC delay activity was temporally specific in both studies. While mPFC neurons with elevated spiking during the early delay period were not impacted by manipulations of MD activity, mPFC neurons with peaks later in the delay were highly dependent on MD inputs(49,56). This suggests that delay period activity is unlikely to derive from the MD. Instead, the MD may serve as a substrate for the amplification and maintenance of delay representations first generated in PFC.

Findings from Schmitt et al. further support this model. First, temporally restricted inhibition of PFC activity at distinct delay time points equivalently disrupted behavioral performance, while inhibition of MD activity had diminished impact on behavior at early time points. In addition, similar to the PFC, MD neurons also displayed elevated delay activity. However, unlike the PFC, MD delay activity was critically dependent on PFC activity even at early delay time points(56). Altogether, these findings suggest that the MD, and perhaps other higher-order thalamic nuclei(62), may be recruited by the PFC in order to amplify or sustain cortical representations as memory decays across time, or in particularly demanding cognitive tasks (Figure 2B). Indeed, both global MD inhibition and pathway-specific MD-to-mPFC inhibition only impaired performance in the DNMS T-maze at longer delays, while leaving behavior intact at shorter delays(41,49). Further supporting this hypothesis, broadly enhancing MD excitability not only improved performance in both the DNMS T-maze and the 2AFC tasks(49,56), it also enhanced the connectivity within local PFC circuits, and increased PFC delay period information in the 2AFC task(56).

Although the above-discussed studies are broadly in agreement regarding this proposed model of thalamo-frontal interactions during working memory, there are still inconsistencies. For example, previous primate studies(63–66) observed explicit stimulus or spatial representations in thalamus delay period activity, while Schmitt et al. provide compelling evidence for MD representations that lack information content(56). The reasons for these differences are sure to be manifold, ranging from species, sub-circuit and task design differences. More studies including MD single-unit along with cortical electrophysiological recordings during working memory tasks, will be required to clarify the role of thalamo-prefrontal interactions in working memory.

THE ROLE OF MD IN GOAL-DIRECTED AND FLEXIBLE BAHAVIORS

The role of MD in behavioral flexibility

Behavioral flexibility reflects the ability of an individual to respond and adjust to changes in the environment. It can be tested using reversal learning or set shifting tasks. Both behaviors require adaptation by switching stimulus-outcome and/or response-outcome associations, yet have been shown to depend on distinct prefrontal areas. Reversal learning has been linked to lateral OFC function. OFC lesions in primates and rodents(67–71) generally induce

perseveration in reversal learning tasks (though see(72)), meaning that lesioned animals tend to stick to a previously learned rule or strategy that is no longer relevant. In contrast, set-shifting tasks requiring multiple associations within different sensory sets, instead rely on mPFC in rodents and on dlPFC in primates(73).

Although the literature concerning the role of MD in behavioral flexibility is conflicting(24,26,74,75), one repeatedly reported finding is an increase in perseverative behavior following lesions or manipulations of MD activity similar to that observed following OFC lesion. Perseveration has been observed in many task contexts, including water maze learning(76), strategy reversal(28,77), and operant reversal learning tasks(41). MD and OFC may therefore work in concert to act on or update old strategies during reversal learning.

Of note, some studies reporting impairments in reversal learning did not attribute the deficit to perseverative behavior(78,79). In a probabilistic reward-guided task involving three different stimuli, monkeys with lesions of the magnocellular portion of MD exhibited a maladaptive switching strategy upon reversal in reward contingency. That is, monkeys did not perseverate in responding to the previously rewarded stimulus, but instead shifted their selections across all stimuli and were unable to persist in selecting the best-rewarding option, unless having an extended choice history on that option(79). These findings suggest that the magnocellular potion of MD may support the representation of recent stimulus choices and thus facilitate rapid stimulus-outcome contingent learning.

In tasks involving multiple stimuli and outcomes, the ability to keep track of recent choices and their associated outcomes is crucial, especially during reversal when a rapid update of stimulus-outcome is needed. In monkeys, some neurons in the magnocellular and parvocellular MD have been shown to increase firing when the animal was making cue-guided actions and when receiving feedback post-response(65). Thus, in behavioral flexibility tasks, the MD may stabilize an online representation of stimuli-outcome associations within the cortex, possibly OFC, similar to the findings described above involving MD-mPFC circuits in working memory. Future neurophysiological studies monitoring both MD and OFC activity during reversal learning tasks combined with temporally-precise optogenetic manipulations could directly test whether amplifying and sustaining cortical representations is a general principle by which the MD supports cognition.

The role of MD in goal-directed behavior

Behavioral flexibility is not a unitary process and involves several potentially dissociable cognitive components. For example, flexible behavior often requires an animal to integrate the relationship or contingency between actions and their outcomes, which additionally entails an accurate representation of the outcome value. The sensitivity to changes in action-outcome contingencies can be tested in contingency degradation tasks during which the outcome is presented independent of the action. The representation of the outcome value on the other hand can be tested in outcome devaluation tasks, in which action-outcome associations remain intact while only the value of the outcome is diminished(80–83). In rodents there is strong evidence for deficits in contingency degradation tasks following MD

manipulations, suggesting that the MD is important for the representation of action-outcome associations and/or the updating of such representations following changes in the environment(84–86).

Whether the MD also supports an accurate representation of the outcome value is still unsettled. Some studies in rat and in monkey reported deficits in outcome devaluation tasks when the MD was lesioned before learning the action-outcome contingency but not when it was ablated just before devaluation of the outcome(84,87,88). However, several studies failed to find any deficit following MD lesion or inhibition(86,89). These discrepancies are likely due to the different task designs and MD manipulations methods. Further work will therefore be needed to determine whether the MD and its related networks support outcome value representation.

Associative learning and flexible adaptation frequently also involves environmental stimuli that need to be associated with the outcome. The ability of environmental stimuli to influence action can be tested in a Pavlovian-to-instrumental transfer (PIT) paradigm. PIT includes three phases: 1) Pavlovian training where stimuli are associated with specific outcomes, 2) Instrumental training where the same outcomes are associated with specific responses, and 3) a Pavlovian-to-instrumental transfer (PIT) in which the conditioned stimulus is tested for its ability to trigger the action that shares the same outcome. Pharmacogenetic inhibition of the MD in mice restricted to the PIT testing phase did not impair instrumental transfer(86), suggesting that the MD is not involved in retrieval of stimulus-outcome or action-outcome associations (but see:(87)). Strikingly, inhibition of MD restricted to the Pavlovian training phase did not affect learning of the association between the stimuli and the outcomes, yet it later impaired instrumental transfer(86). MD activity during Pavlovian training may therefore be important for assigning incentive properties to the conditioned stimulus, which is later required to bridge the learned stimulus-outcome association across contexts. Such a role has been hypothesized for the basolateral amygdala (BLA) which shares, as the MD, reciprocal projections with the PFC(90–92).

DISTINCT MD-PFC CIRCUITS FOR DISTINCT COGNITIVE FUNCTIONS

Overall, work over the past 15 years demonstrates a role for the MD in distinct cognitive behaviors that rely on different prefrontal regions. As such, we described above that in rodents, MD inhibition alter both working memory and reversal learning two functions that are supported by the mPFC and the OFC respectively. Based on the predominately parallel nature of thalamo-frontal circuits, it may be inferred that OFC function is tightly linked to central MD (magnocellular MD in monkey), dorsal mPFC function is tightly linked to lateral MD, and ventral mPFC tightly linked to medial MD (parvocellular MD in monkey) (Figure 1A). Different thalamo-cortical circuits may therefore regulate different behaviors.

Nevertheless, a key question to resolve is the extent to which these parallel thalamic circuits support an overarching, common function, such as sustaining cortical representations for instance, or whether their processing is more singular to the cognitive processing carried out by their cortical partners. Future studies with refined targeting of individual MD subregions will be needed to address this question. Moreover, it is still unclear which cortical layers and

cortico-thalamic projections are critical for these different behaviors. Is a close-loop deep layer-MD circuitry sufficient for amplifying and sustaining cortical representations or is there a requirement of additional processing through superficial layers? Layer specific targeting of inhibitory opsins using transgenic Cre mouse lines in combination with layer specific imaging or in vivo physiology will be able to address such questions.

RELEVENCE FOR CLINICAL RESEARCH

Numerous studies have found anatomical and/or functional abnormalities in either the thalamus or thalamocortical circuits of patients with psychiatric disorders including major depression(93,94), obsessive-compulsive disorder(95), eating disorders(96), post-traumatic stress disorder(97), bipolar disorders and schizophrenia(13,98). Cognitive dysfunction is a common feature of most if not all psychiatric diseases(99).

In schizophrenia, cognitive symptoms are considered core to the disease and have been linked to the functional outcome of patients(100). While in healthy subjects, the MD is activated during cognitive testing in tasks that involve working memory and attention(101,102) this activation has been shown to be decreased in patients with schizophrenia(103–106). However, localizing thalamic dysfunction to thalamic nuclei such as the MD using imaging methodologies is challenging due to lack of contrast and resolution.

More recent evidence also suggests abnormal functional connectivity between the MD and its prefrontal counterparts in patients with schizophrenia. Decreased correlation in MD and dlPFC activity has been measured under resting conditions, an observation also made in individuals at risk for psychosis(98,107–109). Strikingly, the decrease in functional connectivity was most prominent in those subjects that later converted to full-blown illness, suggesting a role in the pathogenesis of the disease(108,110). Of note, decreased functional connectivity may have a structural basis (110–112) however, the exact relationship between the alterations in functional and anatomical connectivity still needs to be clarified.

Decreased functional MD-PFC connectivity has also been measured in patients during cognitive testing(106,113,114). In this context Marenco et al. recently described that thalamo-frontal white-matter connectivity was reduced in patients and this reduction correlated with the level of dlPFC functional activation and performance in a working memory task(111) (see also Giraldo-Chica et al.(115)). This finding may so far be the strongest evidence for an involvement of decreased anatomical connectivity in cognitive deficits.

It is important to note that thalamo-cortical disturbances in schizophrenia likely extend beyond a simple MD-PFC dysconnectivity. Indeed, reduced thalamo-prefrontal connectivity has been associated with thalamic hyperconnectivity to sensory and motor cortices, raising the possibility of a general dysfunction of thalamo-cortical circuits(98,108). In addition, the thalamic reticular nucleus, which is a key inhibitory node for the entire thalamo-cortical system has also been implicated in schizophrenia(116–118). Since imaging studies are largely correlative, it is difficult to determine the origin of these circuit abnormalities. Future

longitudinal clinical studies tracking functional and structural connectivity in high-risk subjects will provide insight into the primary structure(s) involved in the pathogenesis of thalamo-cortical abnormalities. Furthermore, animal studies will be critical for establishing causality and could address questions such as whether decreased MD-mPFC connectivity induced during development triggers hyperconnectivity to sensory cortices.

Regardless of the proximal causes of thalamo-frontal dysconnectivity, the animal studies described here suggest its possible involvement in cognitive deficits. Enhancing MD function may stabilize cortical representations critical for working memory and other cognitive functions and thus be a promising therapeutic approach for improving cognition in mental disorders. New technologies aimed at localized or circuit specific interventions such as focused ultrasound induced blood-brain barrier opening(119) and non-invasive deep brain stimulation(120) could offer an opportunity to achieve this goal in humans.

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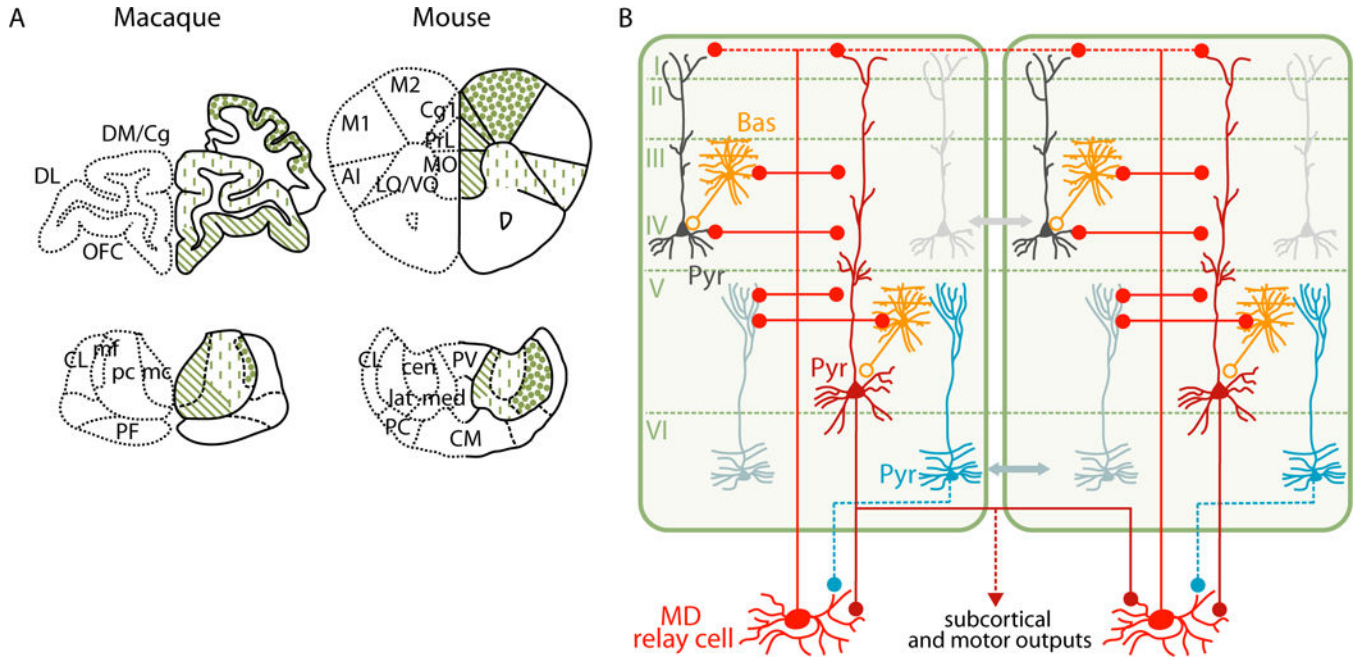

Figure 1. Thalamo-prefrontal circuitry non-human primates and mice

A) Schema of MD-PFC circuits topographic organization in the monkey (left panel) and in the mouse (right panel) (based on Jones EG, the thalamus(2). In non-human primates, the medial magnocellular region is interconnected to the orbital cortex (OFC), the central parvocellular region with the dorsolateral PFC, and the lateral multiform part with the premotor cortical area. In rodents, the medial segment of MD shares connections with the ventral-medial PFC (prelimbic and infralimbic cortices, medial OFC). The central part of the MD is interconnected with the lateral OFC, and the lateral MD with the dorsal-medial PFC (anterior cingulate and accessory motor cortices).

AI: agranular insular; cen: central MD; Cg1: cingulate cortex 1; CL: centrolateral thalamic nucleus; CM: Centromedian thalamic nucleus; DL: dorsolateral PFC; DM/Cg: dorsomedial/ cingulate cortex; lat: lateral MD; LO: lateral orbitofrontal cortex; M1 and M2: primary and secondary motor cortex; mc: magnocellular MD; med: medial MD; mf: multiform MD; MO: medial orbitofrontal cortex; pc: parvocellular MD; OFC: orbitofrontal cortex; PC: paracentral thalamic nucleus PF: parfascicular nucleus; PrL: prelimbic cortex; PV: paraventricular thalamic nucleus; TRN: talamic reticular nucleus; VO: ventral orbitofrontal cortex.

B) Schema of the ultrastructural organization if MD-PFC circuits. MD relay cells send widespread projection to cortical layer I and topographic projections to layers II/III/V and possibly VI (although see Kuramoto et al.(121)). MD terminals make contacts with pyramidal projection neurons (Pyr) as well as inhibitory interneurons including parvalbumin-expressing basket cells (Bas)(122–125). In primates, most cortical input to the MD stems from layer VI pyramidal cells that send projections to topographically interconnected MD regions(126,127). In contrast, layer V pyramidal neurons, so-termed driving inputs, appear to innervate the MD in a non-reciprocal manner, with one prefrontal area innervating several MD subregions(128). Overall, this organization suggests that MD-

PFC circuitry functions in intimately interconnected open loops rather than strictly parallel and independent units.

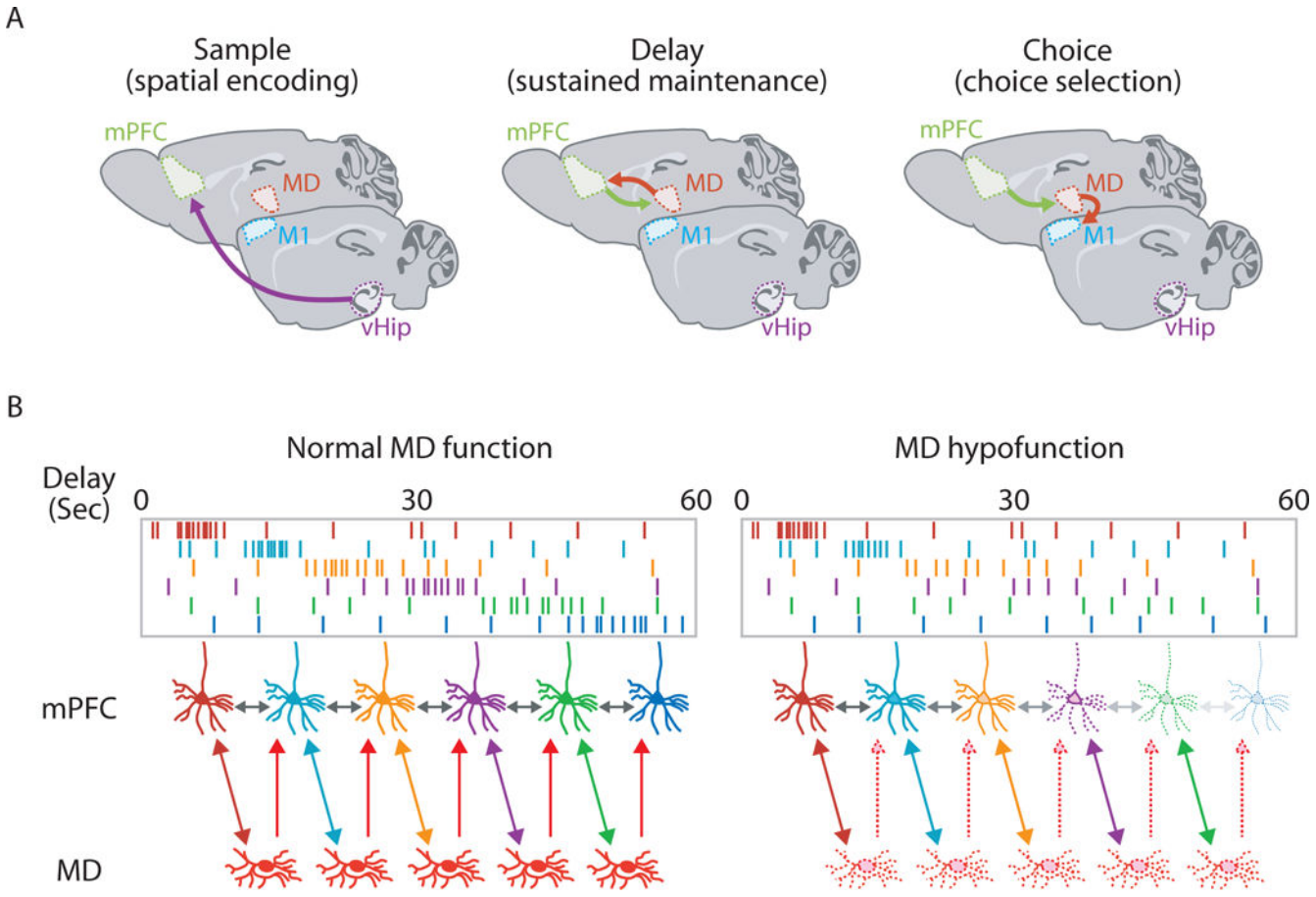

Figure 2. Thalamo-Prefrontal interactions during working memory

A) Schematic depictions of thalamo-prefrontal interactions during a T-maze DNMS working memory task in the mouse. (Left) During the sample phase, spatial encoding is supported by inputs from ventral hippocampus (vHip) to mPFC (based on Spellman et *al.*[50]). (Middle) Upon its recruitment by the mPFC, the MD is critical for amplifying and sustaining cortical activity during the delay, which is critical for task performance (based on Bolkan et *al.*[49]). (Right) mPFC to MD projections participate in memory retrieval or choice selection (based on Bolkan et *al.*[49] and Schmitt et al.[56]) and may serve as a relay station to areas involved in motor function such as the primary motor cortex (M1).

B) Sustained cortical activity during the working memory delay relies on a crosstalk between the MD and mPFC. (Left) Schematic depiction of six mPFC neurons exhibiting sequential increased activity across the delay phase (0–60 sec). Elevated activity is dependent on local cortical connectivity as well as on thalamo-cortical input (Right). Inhibiting MD to mPFC projections reveals that local cortical circuits may not be sufficient to maintain mPFC neuronal activity across the entire delay period. This sustained activity of mPFC neuron across delay requires MD inputs (right panel).