Disentangling the influences of multiple thalamic nuclei on prefrontal cortex and cognitive control

*Jessica M. Phillips[a], Niranjan A. Kambi[a], Michelle J. Redinbaugh[a], Sounak Mohanta[a], *Yuri B. Saalmann[a,b]

a. Department of Psychology, University of Wisconsin-Madison, 1202 W Johnson St., Madison, WI, 53706, United States.
jphillips7@wisc.edu; kambi@wisc.edu; mredinbaugh@wisc.edu; smohanta@wisc.edu; saalmann@wisc.edu

b. Wisconsin National Primate Research Center, University of Wisconsin-Madison, 1202 Capitol Ct., Madison, WI, 53715 United States.

* Corresponding authors:
saalmann@wisc.edu
Brogden Building 518
1202 W Johnson St.
Madision, WI, 53706, USA

jphillips7@wisc.edu
Brogden Building 619
1202 W Johnson St.
Madison, WI, 53706, USA

Abstract

The prefrontal cortex (PFC) has a complex relationship with the thalamus, involving many nuclei which occupy predominantly medial zones along its anterior-to-posterior extent. Thalamocortical neurons in most of these nuclei are modulated by the affective and cognitive signals which funnel through the basal ganglia. We review how PFC-connected thalamic nuclei likely contribute to all aspects of cognitive control: from the processing of information on internal states and goals, facilitating its interactions with mnemonic information and learned values of stimuli and actions, to their influence on high-level cognitive processes, attentional allocation and goal-directed behavior. This includes contributions to transformations such as rule-to-choice (parvocellular mediodorsal nucleus), value-to-choice (magnocellular mediodorsal nucleus), mnemonic-to-choice (anteromedial nucleus) and sensory-to-choice (medial pulvinar). Common mechanisms appear to be thalamic modulation of cortical gain and cortico-cortical functional connectivity. The anatomy also implies a unique role for medial PFC in modulating processing in thalamocortical circuits involving other orbital and lateral PFC regions. We further discuss how cortico-basal ganglia circuits may provide a mechanism through which PFC controls cortico-cortical functional connectivity.

Keywords: cognitive control, prefrontal cortex, thalamus, mediodorsal nucleus, ventroanterior nucleus, intralaminar nuclei, anteromedial nucleus, pulvinar, thalamocortical, corticothalamic, basal ganglia

1. Cognitive control

Optimal human behavior, from the most complex of reasoning and decision-making to the mundane, yet critical, daily tasks on which our survival depends, is fundamentally dependent on cognitive control. Generally speaking, cognitive control refers to the management of mental resources to align ongoing behavior with current goals and context (Miller and Cohen, 2001). Several sub-component executive functions, such as manipulation and monitoring of information in working memory, inhibition of prepotent actions, and the ability to focus or shift our current behavioral strategies, together form the basis of cognitive control (Miyake et al., 2000). Moreover, most of our actions are geared toward the pursuit of goals, ultimately serving to achieve rewarding outcomes; and actions that lead to rewards are remembered and repeated. As such, our ability to act in accordance with learned values of actions and stimuli highlights the involvement of affective and mnemonic processes in goal-directed behavior and cognitive control (Barbas, 2000). There is also a system in the primate brain which monitors ongoing behavior and achieved outcomes. When unintended or unexpected consequences surprise us, this system is proposed to recruit additional control mechanisms toward the optimization of future outcomes (Phillips and Everling, 2014; Ridderinkhof et al., 2004).

Most patients suffering from psychiatric disorders experience disruptions of cognitive control (Millan et al., 2012), and accumulated

functional brain data detail abnormalities in control-related neural circuits in these populations (Aggleton and Brown, 1999; Lewis et al., 2001; Llinas et al., 1999; Llinas and Steriade, 2006; Rubenstein and Merzenich, 2003; Van der Werf et al., 2003). Since we rely heavily on cognitive control for much of what we do, these symptoms create severe challenges in the daily lives of patients (Shallice and Burgess, 1991). For example, a disturbance in cognitive control, and abnormalities in its neural substrate, represent a core symptom of schizophrenia (Green et al., 2000). It is thus an important imperative of cognitive neuroscience to better understand how these circuits operate in healthy individuals, which should ultimately yield more optimally targeted therapeutic interventions for clinical populations.

1.1 Neural basis of cognitive control

Clinical populations with disrupted cognitive control provided the first clues about brain regions that are vital for such functions. The first obvious key players were the frontal lobes (Fuster, 1980; Luria, 1966; Shallice and Burgess, 1991). The term “Frontal lobe syndrome” was commonly used to describe the constellation of behavioral changes, including disinhibition, impaired judgment, unpredictability, altered emotionality, apathy, loss of motivation, and abnormal executive function that follow frontal lobe damage (e.g., Luria, 1973; Meyer, 1974). Schizophrenia patients also show symptoms that resemble frontal

dysfunction. The role of the prefrontal cortex (PFC), the sizeable and heterogeneous anterior sector of the frontal lobe (Figure 1A), has now been rigorously studied using a wide array of available methodologies in healthy humans, clinical populations and animal models for over a century (Yeterian et al., 2012).

The PFC integrates motivational, emotional, mnemonic, sensory, and motor information, ultimately facilitating the organization of goal-directed behavior (Barbas, 2000; Fuster et al., 2000). Although the many distinct PFC subregions likely participate cooperatively in multiple aspects of cognitive control together with other PFC, posterior cortical and subcortical regions, specialization of function for broad PFC subdivisions has emerged across the relevant scientific literature: Investigations of orbital regions on the ventral surface of the PFC have converged upon a role for this zone in economic decision-making and value assessments (Murray and Rudebeck, 2018; Padoa-Schioppa and Conen, 2017); The lateral surface of the PFC has a main role in rule- and strategy-guided action, monitoring and manipulation of information in working memory, preparation of goal-directed behaviors, and resolution of competing response alternatives (Duncan, 2010; Miller and Cohen, 2001); The medial PFC (including anterior cingulate) is active during a large assortment of situations where cognitive control is required, and appears to have a main function in monitoring the need for cognitive control, and recruiting it when necessary (Kolling et al., 2016; Shenhav et al., 2013).

Each of these PFC zones has dense connections with subcortical structures, which suggests that an accurate account on the neural basis of cognitive control needs to include the contributions of these deeper brain regions, since this anatomical arrangement (and accumulated brain data) strongly implies that PFC also works with posterior cortical and subcortical regions to carry out its functions. The goal of this review is to describe the anatomical relationship of PFC with its assortment of connected thalamic nuclei in primates, as well as the available functional information on the contributions of these thalamocortical circuits toward cognitive control. First, we will briefly review some general thalamocortical principles, which will lay the foundation for our subsequent discussion of the multiple thalamic nuclei that have connections with PFC.

1.2 Macaque monkey: Ideal model system to study neural basis of cognitive control

Much of what we have learned, about the contribution of the PFC toward cognitive control, comes from electrophysiology and lesion studies in alert, behaving nonhuman primates. The macaque monkey is an excellent animal model to study the neural basis of cognitive control, with a very similar basic organization of PFC cytoarchitecture (Figure 1B) as compared to that found in humans (Figure 1A; Petrides and Pandya, 1994). Comparative anatomical efforts have demonstrated that primate PFC is comprised of at least 19 distinct cytoarchitectonic regions (Petrides

et al., 2012). There is some order to this heterogeneity, in that the level of laminar differentiation shifts gradually across the PFC, ranging from the least differentiated dysgranular cortices – in posterior orbital regions and the medial cortex surrounding the rostral corpus callosum (Figure 1A, B, lightest gray shading) – to the most differentiated granular eulaminate cortices in posterolateral PFC zones (Figure 1A, B, deepest gray shading). Between these two extremes, graded changes in cytoarchitectonic features are observed. For example, the prominence and cellular density of granular layer 4, and the size of pyramidal cells in layers 3 and 5, are elevated with increasing architectonic differentiation (Barbas and Pandya, 1989). Collectively, this additional complexity in middle and superficial layers causes the prominence of deep layers to decrease, with increasing laminar definition. PFC architectonic regions share the greatest (reciprocal) connections with their architectonic neighbors (Barbas and Pandya, 1989; Yeterian et al., 2012). Importantly, this work has highlighted the evolutionary cognitive advantage of monkeys and humans, credited to the presence of specialized zones of granular prefrontal cortical tissue that are not found in lower species, such as rodents (Figure 1A,B, “evolved in primates”). These primate-specific regions of PFC include the more differentiated ventral, dorsal and lateral regions, and converging evidence heralds these cortices as critical for the expression of the complex cognitive control abilities of primates (Wise, 2008).

One important way that studies in nonhuman primates have enriched our understanding of the neural basis of cognitive control, is by illuminating the patterns of afferent and efferent connections of PFC regions using modern tract-tracing methodologies (e.g., Barbas et al., 1991; Siwek and Pandya, 1991; Yeterian et al., 2012). Like cortical cytoarchitectonic features, the direct monosynaptic connections between two cortical regions show a striking regularity. Specifically, the laminar sources and targets of projections depend on the structural laminar differential between the two connected regions. In the PFC, regions with less laminar definition issue “feedback” projections to regions that have greater laminar definition, with this pattern most extreme when the architectonic differential between two connected regions is large (and vice versa for “feedforward” projections, Figure 1C; Barbas and Rempel-Clower, 1997; Goulas et al., 2018). Interestingly, in this framework, evolutionarily ancient brain circuitry, which is conserved across mammalian orders, may be equipped to exert an influence over the newer brain circuitry that has evolved in primates to endow us with enhanced cognitive abilities, although a hierarchical organization for the PFC remains a controversial topic (e.g., Badre and Nee, 2018; Goulas et al., 2014; Haber and McFarland, 2001).

Tract tracing studies in primates have also shown that each PFC subregion has a unique fingerprint of connections with other cortical regions, both within and outside of PFC (Yeterian et al., 2012). All PFC

regions have connections with posterior cortical (parietal or temporal) regions involved with the processing of high-level sensory and multi-modal information, and some regions also have access to the premotor and cingulate motor cortices. In addition, each PFC region has dense connections with subcortical structures, deep within the brain (Calzavara et al., 2007; Haber and Calzavara, 2009; Haber and Knutson, 2010). Thus, cognitive control is likely enacted through PFC interactions with other cortical and subcortical brain areas.

2. Subcortical structures contribute to PFC processing and cognitive control

As introduced above, there is an ordered pattern to the mode of connections across PFC zones having differing laminar characteristics. In detail, neurons in the deeper layers of cortex issue “feedback” signals to more differentiated cortical regions (Figure 1C). Cells in layers 5 and 6 also issue dense projections to subcortical structures. Specifically, layer 5 projects prominently to the striatum (the main input nucleus of the basal ganglia; Arikuni and Kubota, 1986) and most thalamic nuclei, and the entire thalamus also receives innervation from cortical layer 6 (Guillery, 1995; Xiao et al., 2009; Yeterian and Pandya, 1994). Although the thalamus is widely known for its role in “relaying” signals from the sensory periphery to primary sensory cortices, this function is only carried out in a minor volume of the thalamus, comprised of what are commonly known as

"first-order" nuclei (Guillery, 1995). By contrast, many thalamic nuclei (commonly known as higher-order nuclei) are doing something different, receiving dual innervation from cortex: driving inputs from cortical layer 5, in addition to the modulatory inputs from layer 6. In return, thalamocortical projections preferentially target specific cortical laminae. Higher-order thalamic nuclei thus have dense reciprocal projections with the cortex, forming prevalent cortico-thalamo-cortical loops (Jones, 2007; Saalmann, 2014). Below, we will describe some basic general principles for higher-order thalamic nuclei and their connections with cortex, which will lay the foundation for discussion of the assortment of PFC-connected thalamic nuclei and their contributions to cognitive control. Although the evidence leads us to roughly map a specific sub-component of cognitive control onto a specific thalamic nucleus, we do not mean to imply that any aspect of cognitive control is carried out by a discrete brain region; rather cognitive control appears to arise through the cooperation of large networks of nearby and distant cortical and subcortical brain regions. In fact, the contribution of the higher-order thalamic nuclei toward cognitive control appears to be critically dependent upon their diverse sources of inputs and influences on their diverse assortments of targets; and each nucleus is endowed with a distinct fingerprint of cortical and subcortical connectivity.

2.1 Distinct types of corticothalamic projections

In higher-order thalamic nuclei, layer 5 corticothalamic neurons issue signals at high conduction velocities, terminate in giant boutons, and exert effects on thalamic neurons through actions on ionotropic glutamate receptors (Rouiller and Welker, 2000; Zikopoulos and Barbas, 2007). Because of these features, this corticothalamic projection is considered a “driving” pathway. The layer 5 inputs usually represent a minority of the corticothalamic projection (Guillery and Sherman, 2002a). As mentioned above, cortical layer 6 issues a prominent diffuse projection to the entire thalamus. These projections are modulatory, associated with smaller boutons, with actions on AMPA, NMDA and metabotropic glutamate receptors (Rouiller and Welker, 2000; Zikopoulos and Barbas, 2007).

Driving inputs in most thalamic nuclei participate in a synaptic arrangement known as the triadic synaptic junction, or triad for short. Glial sheaths enclose complex glomeruli, bringing together driving inputs – from sensory periphery in first-order nuclei and layer 5 of cortex in higher-order nuclei – presynaptic to both the proximal dendrites of a thalamocortical “relay” cell, and an interneuron, which in turn inhibits the same relay cell (Guillery, 1995; Guillery and Sherman, 2002a). This is thought to produce a rapid excitation (from the corticothalamic input) that is followed closely by inhibition (indirectly, driven by this same input to the interneuron) in the relay cell; with the balance between excitation and inhibition of the relay cell dependent on the driving input (Sherman, 2017; Steriade and Deschenes, 1984). Although the precise functional significance of triads is

not known, they afford an opportunity for context-dependent gain control (e.g., contrast gain control in the lateral geniculate nucleus).

Modulatory inputs from layer 6 of cortex mostly innervate distal dendrites of thalamocortical projection neurons, more often located in the neuropil outside of the glomeruli, and never participate in triads (Guillery and Sherman, 2002a). These projections from layer 6 of cortex issue a branch to the thalamic reticular nucleus (TRN), a thin sheet of neurons encapsulating the dorsal thalamus, which has an inhibitory influence on thalamic neurons (Guillery, 1995). Layer 6 corticothalamic projections are mostly reciprocal, meaning that they form synapses with thalamocortical neurons that project back to the originating site of the corticothalamic input (Guillery, 1995; Jones, 1998b; Rouiller and Welker, 2000; Shipp, 2003). Thus, these circuits are proposed to have a role in sustaining circuit activation (Figure 2, “Local” in blue, representing corticothalamic inputs to reciprocating thalamocortical neurons; McFarland and Haber, 2002).

Moreover, there is not strict reciprocity between the thalamocortical and more massive corticothalamic projection systems. Instead, the corticothalamic projection system usually has an unreciprocated component, innervating a thalamic territory that has a reciprocal relationship with another cortical architectonic region (Figure 2, “Long-range” in red representing corticothalamic inputs issued from layer 5 to unreciprocating thalamocortical neurons that innervate another cortical region, e.g., corticothalamic influence originating in “PFC A” targeting

"PFC B"; Guillery, 1995; Jones, 1998b). This has been demonstrated to be the case wherever it has been investigated: in the visual, somatosensory, auditory, and motor systems in rats, cats and monkeys (Rouiller and Welker, 2000; Sherman and Guillery, 1996). Unreciprocated corticothalamic projections have also been observed in the PFC-thalamic system of monkeys (Erickson and Lewis, 2004; Giguere and Goldman-Rakic, 1988; McFarland and Haber, 2002; Romanski et al., 1997; Xiao and Barbas, 2002a, 2004). Thus, this long-range "transthalamic" pathway links one cortical area to another, indirectly through the thalamus. With this anatomical arrangement, higher-order thalamic nuclei therefore contain zones where connections with multiple cortical areas overlap. These overlapping projection zones have been observed in many higher-order corticothalamic projection systems in many species, thus it might represent a general principle of higher-order thalamic nuclei (Phillips et al., 2019a; Saalmann, 2014; Shipp, 2003). In addition, some thalamocortical loops involving inputs from cortical layer 6 may link nearby cortical locations within the same architectonic region (Rouiller and Welker, 2000; "local transthalamic" route not shown in Figure 2). To summarize, there are multiple types of pathways originating in cortex and projecting to the thalamus, one that is reciprocal with the cortex, another that provides local links (within an architectonic area), and another linking multiple distinct cortical architectonic regions. In return, there are also multiple types of projections from the thalamus to the cortex.

2.2 Duality of the thalamocortical projection system

The thalamocortical projection is focused on specific laminar targets in cortex, depending on the area and nucleus. Some thalamic neurons influence the middle layers (deep layer 3 and layer 4) of cortex, which also receive feedforward inputs from “lower” cortical areas (Figure 2, green and orange components). This projection is considered to be a driver of cortical neurons (Sherman and Guillery, 1998). Other projections have a modulatory influence in layer 1 (Figure 2, purple components; Jones, 1998a, b; Sherman and Guillery, 1998), which also receive cortico-cortical “feedback” innervation (Barbas and Rempel-Clower, 1997; also see Figure 1C). In some nuclei, this type of projection also targets deep layers, suggesting a more direct influence on cortico-subcortical interactions (Timbie and Barbas, 2015). The superficially focused component of the thalamocortical projection system provides an additional means by which the thalamus could influence cortico-cortical communication: the thalamocortical axons in superficial layers can branch and spread over substantial horizontal distances, crossing architectonic borders (Figure 2, purple trifurcating arrows; Erickson and Lewis, 2004; Jones, 1998b). Thus, superficially projecting thalamocortical neurons can simultaneously modulate multiple cortical architectonic regions, and information may be transferred from the corticothalamic source region to one or more other cortical regions via a projection onto this type of

thalamocortical neuron (McFarland and Haber, 2002; Xiao et al., 2009). These projections are also well-positioned to impose synchrony between cortical regions (Jones, 1998b; McFarland and Haber, 2002; Xiao and Barbas, 2004), through the establishment of effective phase relationships for the efficient transfer of cortico-cortical signals (Akam and Kullmann, 2010; Buzsaki and Draguhn, 2004; Fries, 2005). This mechanism may allow the thalamus to synchronize one distributed ensemble of cortical neurons while desynchronizing others, according to current behavioral relevance (Saalmann, 2014). The predominant operating frequency of oscillatory mechanisms can vary depending on the thalamocortical system and function/state, and we describe such available details in forthcoming sections on functional details of the PFC-connected thalamic nuclei (see section 3.2 for anteromedial thalamic nucleus (AM), section 4.2.2 for mediodorsal nucleus, parvocellular compartment (MDpc), section 6.1.2 for anterior intralaminar group (aIL), and section 7.2 for the medial pulvinar (PULm)).

In primates, the thalamocortical neurons projecting to middle layers usually have a topographic relationship with their connected cortical areas (meaning there is an ordered pattern related to functional gradients), and stain positively for the calcium binding protein parvalbumin (PV; Figure 2, orange components, but also see green components). Jones referred to this as the “core” of the thalamocortical system (Jones, 1998b). On the other hand, thalamocortical neurons projecting diffusely to superficial

layers stain positively for the calcium binding protein D 28K calbindin (CB), and are referred to as the thalamic “matrix” (Figure 2, purple components; Jones, 1998b). Staining for CB and PV in the primate thalamus has a striking complementary pattern, and the prominence of each type of thalamocortical neuron varies across the nuclei (Jones and Hendry, 1989). However, the available evidence suggests there is likely yet another type of thalamocortical projection in primates (calretinin neurons – explanation forthcoming; Timbie and Barbas, 2015;), which is represented by the green components in Figure 2.

To summarize, there are multiple types of corticothalamic and thalamocortical projections, with unique influences on their targets, implying involvement in distinct types of computations. In addition, the brain appears to mix and match the various types of driving and modulatory corticothalamic and thalamocortical projections, which adds a layer of complexity to these circuits. An example of this is illustrated in Figure 2: The ventroanterior nucleus, magnocellular compartment (VAmc) and PULm use CB neurons in different ways, in their respective circuits (Shipp, 2003; Zikopoulos and Barbas, 2007). We will next shift our focus onto these projection systems involving the PFC, but first, we introduce some general mechanisms, which we propose equip the higher-order thalamus with an ability to contribute to cognitive control and PFC function in several important ways.

2.3 Thalamic contributions to sensory transformations and decision-making

The higher-order thalamus may be endowed with several mechanisms by which its thalamocortical neurons can shape cortical activity and thus contribute to cortical processing and cognitive control. For one, it plays an essential role in controlling the gain (excitability) of cortical neurons, sustaining activity of cortical neurons as well as flexibly routing information between cortical neurons according to context (Bolkan et al., 2017; Guo et al., 2017; Purushothaman et al., 2012; Saalmann et al., 2012; Schmitt et al., 2017). Sustained cortical activity is important for decision-making, including working memory – linking the recent past to future plans – evidence accumulation, and representation of decision variables (Curtis and Lee, 2010; Shadlen and Kiani, 2013). Gain control and flexible routing of information between cortical neurons enable transformations; most famously sensorimotor transformations, but also others, including those which must take place between different perceptual reference frames. Such transformations require mechanistic support to enable the flexible differential weighting of sensory, mnemonic and value information according to context (Makin et al., 2013; Pouget and Snyder, 2000). Further, adaptive selection of relevant rules (Buschman et al., 2012) and other information for decision-making relies on flexible routing of signals or dynamic functional connectivity (Voloh and Womelsdorf, 2016). In addition, there is growing evidence from studies in

rodents that higher-order thalamus may be a highly plastic source of feedback information to the cortex, through thalamocortical targeting of various interneuron types (resulting in disinhibition) and NMDA-receptor dependent mechanisms, such as long-term potentiation and depression (LTP and LTD; Audette et al., 2019; Joffe et al., 2020; Mukherjee et al., 2020; Pardi et al., 2020; Williams and Holtmaat, 2019; Yamawaki et al., 2019). These mechanisms may provide the crucial capacity for the learning of input to output mappings, to enact the aforementioned transformations that are critical for successful cognitive control.

2.4 Prefrontal-connected thalamus

It is well established that the PFC has a strong relationship with higher order thalamus, especially MD, with which it shares many reciprocal anatomical connections (Phillips et al., 2019a). In fact, a classic definition of PFC was the portion of cortex innervated by MD (Rose and Woolsey, 1948). And yet, for decades, the role of MD in cognitive control had been overlooked or largely ignored, with intense interest in thalamo-PFC circuit function only emerging in recent years. Further, anatomical investigations have shown the PFC has substantial connections with many other thalamic nuclei, including AM, VAmc, MD, IL, and PULm (in addition, some smaller midline nuclei, which are beyond the scope of this review; Barbas et al., 1991; Goldman-Rakic and Porrino, 1985; Kievit and Kuypers, 1977; Romanski et al., 1997; Xiao et al., 2009; Figure 3, Figure

4, A-D), which clearly demonstrates that the PFC has a much more complex relationship with the thalamus than is generally appreciated. Thus, a comprehensive understanding of cognitive control and PFC function is likely to be greatly prohibited by ignoring these thalamic circuits.

For example, using diffusion MRI with probabilistic tractography, we recently demonstrated that PFC projection zones in primate MD show substantial overlap for directly connected cortical regions (Phillips et al., 2019a), a pattern referred to as the “replication principle” (Shipp, 2003). Importantly, this anatomical arrangement may enable MD to influence cortico-cortical communication across PFC architectonic regions, and ultimately to support cognitive control through these mechanisms (Saalmann, 2014). As many anatomical principles appear to be conserved across different types of thalamocortical projections, it is quite possible that the intriguing overlapping representations in MD may reflect conserved mechanistic principles for other higher order thalamic areas. To help shed more light on the relationship between thalamus and PFC, and to contextualize their relevance and potential contribution to cognitive control, we will discuss the various PFC-connected thalamic nuclei in the remainder of this review. We will address their cortical (laminar, architectonic) and subcortical sources of inputs, which enables anatomically constrained speculation regarding the computation a region may perform, and use their laminar and architectonic targets to suggest

their possible impact on cortical computations. In addition, we will consider observations from lesion and electrophysiological studies if available, towards delineation of the distinct contributions of each nucleus to PFC processing and cognitive control.

2.5 Multiple thalamic relationships

By and large, the thalamic nuclei with connections to PFC are uniquely positioned between the PFC and basal ganglia. Specifically, they represent a common link involved with both the prominent PFC-thalamic circuits on the one hand, and PFC-striatal circuits on the other, having direct and indirect reciprocal connections with PFC and the basal ganglia, respectively (Haber and McFarland, 2001; Figure 3). It is well known that the basal ganglia modulate the cortex by influencing thalamocortical projection neurons, but these thalamic nuclei also issue projections directly to the striatum (Gimenez-Amaya et al., 1995; McFarland and Haber, 2001; Sadikot et al., 1992; Smith and Parent, 1986), with the most prominent projection arising from IL (although detailed discussion of the thalamostriatal projection from IL nuclei is beyond our scope, we refer the reader to Galvan and Smith, 2011; Smith et al., 2004), and thus thalamic neurons also modulate the information coursing through basal ganglia. The cortex, basal ganglia and thalamus have undergone substantial evolutionary expansion in comparison to other central nervous system components, such as the hypothalamus (Butler and Hodos, 2005; Xie and

Dorsky, 2017), and because of this, they are considered most important for variability on cognitive capacity across species (Lefebvre et al., 2004).

These circuits feature a topography that is maintained through parallel channels traversing the involved subcortical structures (Alexander et al., 1986), with the PFC architectonic regions approximately mapping onto affective, mnemonic (low laminar differentiation, Figure 3, warmer colors), cognitive and motor-related territories (high laminar differentiation, Figure 3, cooler colors Haber, 2003, 2016; Haber and Knutson, 2010; Yeterian and Pandya, 1991b). Critically, although the circuits can broadly be described as parallel and segregated, on a finer level there is potential for much integration through convergence of striatal inputs from distinct, but functionally related cortical regions, as well as interaction between circuits through directed, unreciprocated projections across them (Choi et al., 2017; Greene et al., 2019; Haber, 2003; Haber and Calzavara, 2009; Haber et al., 2000; Parent and Hazrati, 1993; Selemon and Goldman-Rakic, 1985).

Despite decades of empirical research aimed at demystifying the precise role of the basal ganglia, a clear grasp remains out of reach. Basal ganglia outflow from ventral pallidum (VP), substantia nigra, pars reticulata (SNr) and globus pallidus, internal segment (GPi) is focused on thalamocortical neurons. Signals coursing through the striatum and downstream nuclei can suppress or reinforce this outflow (to thalamocortical neurons), which is known to be inhibitory (Graybiel, 1990;

Hikosaka, 2007b; Mink, 1996; although the case for an inhibitory projection from VP to its thalamic target, the magnocellular compartment of MD (MDmc), is less clear: while there is some support (Smith et al., 1987), another study failed to find any such evidence (Russchen et al., 1985), and yet another demonstrated stimulation in rat VP resulted in 1) long-latency (multisynaptic) EPSPs – driven by VP-mediated inhibition of the TRN – in non-MD thalamic nuclei of rats, and 2) short-latency IPSPs in MD, driven through monosynaptic VP influences (Lavin and Grace, 1994)). As such, the basal ganglia circuits are mostly concerned with modulating activity in the thalamocortical projection systems involving the entire frontal lobe, as well as higher-order parietal and temporal cortical regions (Alexander et al., 1986; Clower et al., 2005; Haber and Calzavara, 2009; Middleton and Strick, 1996b).

Although rarely emphasized, anatomical studies of thalamo-PFC circuits have collectively demonstrated that a prominent band of PFC representation is found in the medial thalamus along its anterior-to-posterior extent, without any regard for nuclear borders (Akert and Hartmann-von Monakow, 1980; Barbas et al., 1991; Barbas and Mesulam, 1981; Cavada et al., 2000; Draganski et al., 2008; Jacobson et al., 1978; Kievit and Kuypers, 1977; Kunzle and Akert, 1977; Phillips et al., 2019a; Pribram et al., 1953; Yeterian and Pandya, 1988; Figure 4E shows example of probabilistic tracts connecting MD with orbital area 11 and posterolateral area 8ad, estimated using diffusion MRI). In addition, PFC

neurons projecting to VA, MD and AM nuclei were found to overlap in the same cortical columns (Xiao et al., 2009). These findings suggest significant interaction between extended PFC circuits comprising different thalamic nuclei.

Why are there multiple thalamic nuclei that project to PFC? We argue that each nucleus contributes to a subset of component processes that collectively facilitate the cognitive control functions supported by the PFC, which are quite diverse and must be smoothly integrated for efficient, optimal behavior. The evidence suggests that a common mechanism, by which these nuclei contribute, is through their ability to modulate cortico-cortical communication.

In addition, based on the reviewed information, we highlight a possible main function of cortico-basal ganglia circuits in controlling inter-areal functional connectivity in the cortex, through their impact on thalamocortical neurons which form the long-range transthalamic pathways (Figure 2, red arrows, can involve either superficially projecting CB, or middle projecting PV, thalamocortical neurons, but always involves layer 5 corticothalamic projections), and possibly through their ability to modulate gain of cortical pyramidal neurons through their subset of projections targeting layer 1 (Larkum et al., 2004). Moreover, the medial PFC regions (including anterior cingulate) seem well poised to control thalamocortical processing and functional connectivity across other PFC regions through their unique capacity to influence thalamic and striatal

circuits involving lateral and orbital PFC regions. These lateral and orbital PFC circuits, in turn, are equipped to exert a top-down influence over thalamic and striatal circuits involving posterior cortical regions.

3. Anteromedial nucleus

3.1 Anatomical details of AM

As the name indicates, this nucleus occupies a medial (and ventral) position relative to the other two nuclei belonging to the anterior nuclear group, the anterodorsal and anteroventral nuclei. AM continues dorsolaterally into the anteroventral nucleus, the two nuclei being separated by a thin fibrous lamina in monkeys (Jones, 2007; Figure 4A). AM is uniquely positioned in the thalamus, since it receives projections related to memory, emotions, reward value and interoceptive sensations from the entire midline region, spanning from medial PFC at the genu of the corpus callosum, to retrosplenial cortex in the splenium of corpus callosum. It also receives inputs from nearly all PFC architectonic regions (Figure 3, arrows connecting AM with PFC; Xiao and Barbas, 2002b).

The regions from which AM receives the most robust inputs lie in the medial (including anterior cingulate) and orbital PFC (areas 24, 25, 32 and 13) with minor to moderate projections from medial area 9 (Xiao and Barbas, 2002a, b; Yeterian and Pandya, 1988; Figure 3, bold red arrow). Further, moderate projections to AM come from additional orbital, polar and lateral regions (areas 10, 11, 12, 14, and 46) conveying information

about stimulus value and value-to-action transformation signals (Cavada et al., 2000; Xiao and Barbas, 2002a, b; Yeterian and Pandya, 1988; Figure 3, thin lime arrow connecting AM to PFC). Substantial projections from medial (including anterior cingulate) PFC regions arise from layer 5 (25-30%), as compared to the orbital and lateral PFC, which project mostly from the layer 6 (80-95%; Xiao and Barbas, 2002a; Xiao et al., 2009). Many of these projections are bilateral (Xiao and Barbas, 2002a). AM, in turn, sends projections mostly to orbital, polar and anterolateral PFC regions (areas 10, 11, 12 and 46), and to a minor extent, medial/anterior cingulate areas 32 and 24. Thus, several medial PFC regions (areas 9, 14, 24, 25 and 32) issue unreciprocated or asymmetrically dominant projections to AM (Barbas et al., 1991; Dermon and Barbas, 1994; Goldman-Rakic and Porrino, 1985; Xiao and Barbas, 2002a).

The pattern of cortical projections to AM places it in an intermediate position between the PFC-connected thalamic regions at one end and the medial temporal lobe-connected thalamus (i.e., anteroventral and anterodorsal) at the other. Among non-PFC afferents, AM is a major recipient of mnemonic inputs from the hippocampal formation (specifically, anterior subicular complex and CA3; Christiansen et al., 2016; Xiao and Barbas, 2002b). In addition, AM receives minor inputs from the entorhinal, perirhinal and parahippocampal cortices (Aggleton and Mishkin, 1984; Xiao and Barbas, 2002b). In return, AM issues a minor projection to the

subicular complex in the hippocampal formation (Amaral and Cowan, 1980). Subcortical inputs to AM mostly arise from the amygdala (basolateral, basomedial and lateral nuclei), medial mamillary bodies and the medial GPi (output nucleus of basal ganglia; Xiao and Barbas, 2002b), presumably carrying affective information, mnemonic information and affective-related basal ganglia outflow, respectively.

CB positive neurons are scattered throughout AM, while PV staining is absent (Jones 2007). Thus, its projection to the middle layers of cortex likely originates from an unidentified (in terms of calcium binding protein) thalamocortical projection (i.e., Figure 2, green components). In the context of the laminar origins of inputs from the medial PFC regions, AM showed punctate terminal patches resembling the earlier documented axonal endings of layer 5 driving inputs (Xiao and Barbas, 2002b).

Overall, AM collects control-related (from medial PFC) and mnemonic (from the medial temporal lobe) information, and to a lesser extent, affective and cognitive information (from amygdalar inputs as well as orbital and lateral PFC inputs), and issues it mostly to orbital, polar and anterolateral PFC regions, with some influences on medial PFC and hippocampal circuits, as well.

3.2 Functional data on AM

The nature of functional properties of AM neurons in primates remains unknown, as there are no electrophysiological studies from AM in

primates while performing cognitive or memory tasks. Furthermore, in primate lesion studies of AM, there is almost always an involvement of neighboring nuclei, so the unique contributions of AM to cognition have been difficult to assess. For example, lesions to anterior and medial thalamus, including AM, in monkeys showed deficits in visual recognition and associative memory tasks (Aggleton and Mishkin, 1983a, b; Parker and Gaffan, 1997; Ridley et al., 2002). In humans, damage to anterior thalamic regions including AM caused anterograde amnesia (Ghika-Schmid and Bogousslavsky, 2000), while in Alzheimer's disease patients, anterior thalamic nuclei show progressive neurodegeneration and deposits of neurofibrillary tangles (Braak and Braak, 1991a, b).

Clues to the functional properties of AM neurons come from rodent studies (Albo et al., 2003; Jankowski et al., 2015). One study exploring the electrophysiological properties of AM cells in rats showed a small proportion of cells (~6-10%) with head direction sensitivity and place cell-like responses. Further, a similarly small proportion of these cells were modulated by 6-12 Hz oscillations, indicating the frequency range which cells in this nucleus may use for communicating with other connected brain regions (Jankowski et al., 2015). These results also hint at the nature of mnemonic and spatial signals in AM during its interactions with the hippocampal system and PFC circuits, as described below.

AM seems to be well suited for mediating communication between the hippocampus and orbital, frontopolar and anterolateral PFC regions.

The connections from hippocampus proper (dentate gyrus, CA and subicular regions) to the PFC regions are mostly unidirectional or unreciprocated, and since there has been no reported direct projections from any PFC region to the hippocampus proper (Cavada et al., 2000; Goldman-Rakic et al., 1984), AM appears to be unique among the higher-order thalamic nuclei, as it provides an indirect route of information from the PFC (which otherwise does not have a direct projection) to the hippocampus. In providing inputs to the hippocampal system from PFC circuits, AM may contribute to the various cognitive challenges that primates face during navigation. Specifically, AM might be a key thalamic nucleus by which PFC regions influence hippocampal activity to minimize interference in spatial navigation tasks by retrieving appropriate goal and contextual information as well as updating the existing memories with new information (Alonso et al., 2020; Patai and Spiers, 2021). Hence, PFC inputs might reach hippocampus via AM to exert executive influence to select relevant spatial and mnemonic information for current cognitive demands.

Moreover, in addition to direct projections (Barbas and Blatt, 1995), the hippocampus, by virtue of its innervation of AM (Aggleton et al., 2010), has indirect access to specific and larger parts of PFC, possibly providing mnemonic information to these PFC regions. This hippocampal innervation of the PFC through AM may in turn support cognitive control and decision-making processes which depend on retrieval of learned

memoranda. Furthermore, the projections of the CA3 region of the hippocampus to AM also provide another indirect pathway between the autoassociative networks in CA3, which have been shown to play a role in encoding and recall of short-term memory (Kesner, 2007), and functionally related circuits in orbital, polar, and lateral PFC regions.

Regarding the role of AM with its connections with the PFC circuit, the medial PFC regions that connect with AM are also implicated in processing of visceral and affective signals from the body (Azzalini et al., 2019). The mnemonic information in AM may in fact be integrated with motivational and visceral information that AM receives from these medial PFC regions, before it is issued to orbital and anterolateral PFC regions.

These proposed functions of AM may partly explain the memory deficits seen after lesions to anterior thalamic nuclei (Aggleton and Mishkin, 1983a, b; Parker and Gaffan, 1997; Ridley et al., 2002). Taken together, we suggest that the major role of AM involves transformations (see section 2.3) between mnemonic (i.e., episodic memories), and possibly motivational, information and cognitive control signals for optimal decision-making, including those required during spatial cognition and navigation.

4. Mediodorsal nucleus

MD is one of the largest nuclei of the thalamus, well known for its close anatomical relationship with the entire PFC (as described in section

2.4), and lesions involving MD in human patients often result in “prefrontal-like” dysexecutive syndromes (Van der Werf et al., 2003; Van der Werf et al., 2000). Based on cytoarchitectonics, MD can be broadly subdivided into an anteromedial MDmc, which contains large evenly spaced cells, a central zone, MDpc, with increased variability in cell size and dense myelination, and a lateral paralamellar zone that can be divided into an anterior multiform (MDmf) and a caudal densocellular (MDdc) zone (Jones, 2007; Olszewski, 1952; Walker, 1940; Figure 4 B-D). The cells in MDmf and MDdc bear strong resemblance to the neighboring IL nuclei that surround the lateral aspect of MD (Jones, 2007). Each of these subregions has unique preferential connections with PFC, and unique subcortical inputs (Figure 3, see unique pattern of PFC connected arrows directed to/from MDmc, MDpc and MDdc/mf). More detailed topographic schemes, going beyond broad divisions of PFC (e.g., lateral, orbital) and MD, have been proposed by anatomists (Barbas et al., 1991; Goldman-Rakic and Porrino, 1985; Kievit and Kuypers, 1977; Pribram et al., 1953; Siwek and Pandya, 1991). However, proposed schemes failed to converge, which is likely due to the limitations of tracer injections to reveal complete topographic patterns, and the complex converging and diverging connections associated with MD and its connections to the PFC (Erickson and Lewis, 2004; Phillips et al., 2019a).

To complement that body of work, diffusion MRI with probabilistic tractography allowed for the investigation of the projection zones for all 19

architectonic PFC regions in MD, within each hemisphere of 8 macaque monkeys. This work showed that across the horizontal axis of MD, there is an ordered topographic gradient of PFC projection zones: the anteromedial extreme of MD connects preferentially with ventromedial and orbital PFC regions, while the posterolateral extreme of MD connects preferentially with posterolateral PFC regions, and intermediate PFC regions occupy the zones in between (Phillips et al., 2019a; Figure 4F). We found that this pattern roughly approximates the gradually shifting architectonic features across PFC (Figure 1B), although it showed a stronger relationship to ventromedial-to-posterolateral location of architectonic regions in PFC (Figure 4F). This gradient was characterized by substantial overlap of projection zones (for nearby, directly connected cortical regions) with representations shifting gradually across the horizontal axis of MD (Phillips et al., 2019a; Figure 4F). Critically, this observation implies that MD is well suited to coordinate cortico-cortical communication in the PFC (Nakajima and Halassa, 2017; Saalmann, 2014). The distinct anatomy and innervation of MD subregions suggest that they each contribute to different aspects of cognitive control (Mitchell, 2015; Watanabe and Funahashi, 2012).

4.1 Mediodorsal nucleus, magnocellular compartment

4.1.1 Anatomical details of MDmc

MDmc occupies the anteromedial portion of MD (Figure 4B). It has reciprocal connections with nearly all PFC architectonic regions, but its strongest relationship is with the orbital PFC regions known to play a role in stimulus evaluation and economic decision-making (areas 11, 13, 14), which are recipient to highly processed multimodal sensory information, and inputs from the amygdala (Timbie and Barbas, 2015; Figure 3, bold orange arrow). In addition, MDmc has a moderate relationship with the principle sulcus in the lateral PFC (area 46), and orbital area 47/12 (Figure 3, thin lime arrow connecting MDmc with PFC); there is also an unreciprocated projection from dorsal anterior cingulate (medial) area 24, and an asymmetrically dominant input from medial area 32 and ventromedial area 25 (Barbas et al., 1991; Cavada et al., 2000; Goldman-Rakic and Porrino, 1985; Ray and Price, 1993; Russchen et al., 1987; Siwek and Pandya, 1991; Tobias, 1975; Yeterian and Pandya, 1988). The corticothalamic projection from the orbital and ventromedial regions is bilateral (Goldman, 1979; Preuss and Goldman-Rakic, 1987), with corticothalamic fibers decussating via the massa intermedia at the level of the thalamus (Preuss and Goldman-Rakic, 1987). Ray and Price (1993) further divided MDmc into a lateral and fiber rich “pars fibrosa”, and a medial, poorly myelinated “pars paramediana” with preferential connectivity to specific OFC subregions.

MDmc receives inputs from temporal polar, olfactory, entorhinal, perirhinal cortices, and the subiculum, which supply sensory- and

memory-related information (Russchen et al., 1987; Saunders et al., 2005; Webster et al., 1993). Premotor cortex also issues some projections (Akert and Hartmann-von Monakow, 1980). MDmc also receives topographic inputs from the basal amygdala nuclei in its rostral third (also a target of olfactory inputs; Bachevalier et al., 1997; Russchen et al., 1987), providing affective information to this subregion of MD. Finally, MDmc receives input from the basal ganglia, mostly via the VP, but also partially via the medial SNr, which convey outflow of the affective basal ganglia circuits (Francois et al., 2002; Haber et al., 1993; Ilinsky et al., 1985; Jones, 2007; Russchen et al., 1987; Figure 3). The SNr transmits information to the thalamus that originates in PFC (Goldman-Rakic and Friedman, 1991; Tanibuchi et al., 2009a). There is also a complex and prominent dopaminergic innervation to MDmc from the hypothalamus, periaqueductal gray, and ventral mesencephalon (Sanchez-Gonzalez et al., 2005). MDmc is thus a hub that receives highly processed visual information, as well as olfactory, affective and mnemonic information.

MDmc contains PV-positive “core” neurons, which project focally to middle layers, but also a relatively large proportion of CB-positive “matrix” neurons (Jones, 2007; Timbie and Barbas, 2015), which have been shown to project expansively to superficial cortical layers. In addition, a novel calretinin pathway was reported by Timbie and Barbas (2015), although no details on its laminar targeting were available. MDmc neurons also target deep layers, similarly to the IL nuclear projection (Timbie and

Barbas, 2015). The prominent CB neurons, postulated to mediate the long-range transthalamic projections between PFC areas, likely gives rise to the very prominent overlap in anteromedial MD for ventromedial and orbital PFC connections, demonstrated using diffusion MRI (Phillips et al., 2019a; Figure 4G, lower corner).

4.1.2 Functional data on MDmc

There is relatively little information available about the response properties of MDmc neurons in alert, behaving primates. Fortunately, there is a wealth of data from lesion studies, which have provided clear evidence that MDmc makes distinct contributions toward cognitive functions in comparison to the PFC regions with which it has connections (Baxter, 2013). This is because the effects observed following lesions to MDmc and those following lesions to its connected PFC regions produce dissociated behavioral impairments (Baxter, 2013; Mitchell and Chakraborty, 2013).

Problems following MDmc damage cannot be explained as a reduction in motivation or arousal (Mitchell, 2015), nor do they simply cause a hypofunction in PFC (Mitchell and Chakraborty, 2013). Monkeys subjected to targeted neurotoxic lesions of MDmc retain pre-operatively learned object-in-place discrimination problems (which test episodic-like memory) but are impaired at learning post-operatively (Izquierdo and Murray, 2010; Mitchell et al., 2007a). In stark contrast, disruptions of

cortico-cortical communication involving PFC regions, to which MDmc connects, have been shown to severely perturb retention (Browning and Gaffan, 2008). Deficits are not caused by an increased tendency to perseverate, an effect which is observed following ventrolateral (area 47/12) PFC lesions (Baxter et al., 2008; Mitchell et al., 2007a). MDmc thus seems to have an important role in processing of new memories and learning new associations toward optimal decision-making, but not in their retention (Mitchell and Gaffan, 2008). Dissociation of effects for MDmc and ventrolateral PFC lesions are also observed when monkeys need to discover sequences of object touches to earn rewards: this ability remains intact following MDmc lesions, while it is severely impaired following bilateral ablations of ventrolateral PFC (Baxter et al., 2009; Mitchell et al., 2007a).

In addition, MDmc has an important role in evaluating rewards and formation of object-reward associations for large stimulus sets. Animals with MDmc lesions do not show normal devaluation behavior following reward satiation, indicating a disruption in value monitoring (Gaffan and Parker, 2000; Izquierdo and Murray, 2010; Mitchell et al., 2007b) or reward-guided action selection (Wicker et al., 2018). They also show abnormal behavior during adaptive decision-making (Murray and Rudebeck, 2013). All of these deficits reflect its close association with the orbital PFC, amygdala and affective orbital PFC-striato-pallidal circuits (Baxter, 2013).

Importantly, the relationship of MDmc with the medial temporal lobe structures is strongest in primates (Mitchell, 2015), suggesting that evolution of these circuits endowed primates with enhanced cognitive abilities related to memory and learning that are not available to lower mammals, such as rodents (Gray and Barnes, 2019; Hara et al., 2012; Mustafar et al., 2018; Phillips et al., 2014; Schmitt and Halassa, 2017; Wise, 2008; Although rodents certainly have a capacity for learning and memory, and can provide valuable mechanistic insights as animal models for human cognition, studies have shown that these abilities are superior in primates (Mustafar et al., 2018; Phillips et al., 2014). This may be a consequence of key adaptations in vision and anatomy, including granular frontal cortex in primates (Buffalo et al., 2019; Christel, 1994; Phillips et al., 2014)). Mitchell and colleagues have proposed that MDmc has an important integrative role, in conjunction with PFC, in episodic-like declarative memory, combining object, reward and response information for successful new learning and future responding (Mitchell and Chakraborty, 2013). To this end, MDmc may enable value-to-choice transformations (see section 2.3) and contribute to memory consolidation. The mechanism may involve the regulation of plasticity within PFC (Baxter, 2013). For example, work in rodents has demonstrated that MD is capable changing synaptic efficacy (LTP and LTD) in the rodent PFC homologue through NMDA-dependent mechanisms (Zhou et al., 2017), a physiological change which was paralleled by changes in a behavioral

assay. In addition, it has been proposed that MDmc may impose synchrony between medial PFC and medial temporal lobe regions during acquisition of new information (Mitchell and Chakraborty, 2013), or between orbital PFC and amygdala for value assignment and updating (Timbie and Barbas, 2015).

4.2 Mediodorsal nucleus, parvocellular compartment

4.2.1 Anatomical details of MDpc

The parvocellular compartment of MD occupies its anterior pole (a thin section just anterior to the anterior pole of MDmc), along with its central and lateral portions (MDpc, Figure 4B,C). MDpc is reciprocally connected with most PFC architectonic regions, but has the strongest relationship with anterior, mid-dorsal and mid-lateral regions of the PFC known to be critical for many cognitive processes including rule-guided behavior and working memory functions (areas 10, 46, 9 and 9/46; Barbas et al., 1991; Erickson and Lewis, 2004; Goldman-Rakic and Porrino, 1985; Jacobson et al., 1978; Kievit and Kuypers, 1977; McFarland and Haber, 2002; Siwek and Pandya, 1991; Tanaka, 1976; Yeterian and Pandya, 1994; Figure 3, see pattern of arrows connecting MDpc with PFC). The posterior portion of MDpc has a reciprocal relationship with anterior cingulate regions in the medial wall (areas 24, 32), and there is an unreciprocated projection from these same medial PFC regions onto more anterior MDpc zones (Baleydier and Mauguiere, 1980; Barbas et al., 1991;

Goldman-Rakic and Porrino, 1985; McFarland and Haber, 2002; Vogt et al., 1987; Vogt et al., 1979; Yeterian and Pandya, 1988, 1994).

Outside the PFC, MDpc also has some reciprocal connections with posterior parietal cortices, involved in visuospatial attentional processes (Kasdon and Jacobson, 1978; Schmahmann and Pandya, 1990; Taktakishvili et al., 2002). There are also some reciprocal connections with the supplementary motor and premotor cortices, and minor connections with motor cortex (Akert and Hartmann-von Monakow, 1980; Kultas-Ilinsky et al., 2003; Rouiller et al., 1999; Rouiller et al., 1998). In addition, patches of MDpc receive basal ganglia outflow through the lateral SNr (Francois et al., 2002; Ilinsky et al., 1985; Tanibuchi et al., 2009a). MDpc also receives minor ascending innervation from the midbrain superior colliculus (SC; Erickson et al., 2004; Harting et al., 1980), a critical node in the control of gaze and more generally, orienting behavior in primates (Moschovakis, 1996; Schiller and Tehovnik, 2005). Lateral MD, including MDpc, also receives inputs from the periaqueductal gray and zona incerta (Erickson et al., 2004). Finally, MDpc receives intense dopaminergic innervation from multiple hypothalamic and brainstem sources (Sanchez-Gonzalez et al., 2005). Taken together, MDpc appears suited as a node gathering and integrating cognitive and attention related information.

Electron microscopic investigation of MDpc showed that, like most other thalamic nuclei (Steriade and Llinas, 1988), the neuropil of MDpc

can be divided into glomerular regions and extraglomerular regions. In addition, most terminals were of the “SR” (small terminal, round vesicle) type, having relatively few vesicles, no mitochondria and asymmetric (putatively excitatory) synapses. These were found almost exclusively in the extraglomerular neuropil, contacting small-medium dendrites (putatively thalamocortical neurons) and local circuit neurons, which fits the description for layer 6 inputs. Inside glomeruli, “LR” (large terminal, round vesicle) asymmetric terminals dominated, possessing a greater number of vesicles and also, mitochondria, likely originating in cortical layer 5. Thus, it has been confirmed that cortical inputs synapse in a “dual mode” onto MD thalamocortical neurons (Schwartz et al., 1991), consistent with the dual corticothalamic projection systems described in section 2.1, and supporting this arrangement as a general principle across higher-order thalamic nuclei.

MDpc receives roughly 80% of its cortical inputs from layer 6, and roughly 20% from layer 5 (Xiao et al., 2009). These numbers map nicely onto the proportions of extraglomerular SR terminals and glomerular LR terminals described above (Schwartz et al., 1991). Based on the core/matrix framework of Jones (1998b), one may predict that a similar proportion of targeting by MDpc to middle (more projections) and superficial (less projections) layers in PFC, would be accompanied by greater PV and less CB labeling in MDpc. It has been reported that MDpc thalamocortical neurons have few superficial projections to layer 1, with

the majority of fibers issued to deep layer 3 and layer 4 (Figure 2; Erickson and Lewis, 2004; Giguere and Goldman-Rakic, 1988; McFarland and Haber, 2002); and consistent with this, there is only a sparse scattering of labeled CB positive cells in MDpc (Jones and Hendry, 1989). However, MDpc is completely devoid of PV labeling (Jones, 2007; Jones and Hendry, 1989), so there must be a different type of thalamocortical projection (i.e., non-PV) to the middle layers from MDpc (Figure 2, green components). Timbie and Barbas (2015) identified a novel calretinin thalamocortical projection in MDmc, and so it seems reasonable to speculate that this type of thalamocortical projection, which would preferentially target middle cortical layers, may dominate in MDpc. This possibility is supported by prevalent calretinin staining in primate MDpc (Mikula et al., 2007). Moreover, as described above, AM also lacks PV positive neurons, but like MD, its neurons also stain positively for calretinin (Jones and Hendry, 1989; Mikula et al., 2007). Therefore, AM and MDpc may use a calretinin pathway to influence the middle cortical layers in its PFC target regions. Of course, this is speculative, and more information is required on this “unidentified” thalamocortical pathway.

These anatomical features for MDpc align with our diffusion MRI work investigating degree of overlap for PFC projection zones (Figure 4G). The central zone (putative MDpc, representing mostly areas ranging from 46v to 9/46v on Figure 4G) was associated with overlapping projection zones for anterior and mid-PFC regions, but the degree of overlap usually

did not reach the intense levels observed for ventromedial (including anterior cingulate) and orbital PFC (in putative MDmc) and posterolateral PFC zones (in putative MDmf/MDcd; Phillips et al., 2019a). These observations suggest that there is a greater prominence of the long-range transthalamic pathway (see Figure 2) linking orbital/ventromedial PFC architectonic regions in anteromedial MD, and posterior PFC architectonic regions in posterolateral MD. MDpc may instead play a more key role in influencing local processing in anterior and mid-lateral PFC neural ensembles, which may involve layer 6 corticothalamic projections that issue unreciprocated relationships more locally, within a cortical zone, through prominent projections to the middle layers (local transthalamic route between neighboring columns; Rouiller and Welker, 2000). This notwithstanding, the less prevalent long-range transthalamic pathways would likely contribute to information transmission or functional connectivity across anterior and mid-PFC regions. The unique cortico-thalamocortical circuit configuration in MDpc (compared to other subregions) may be related to the nature of the representations encoded flexibly by multiplexing lateral PFC neurons (Rigotti et al., 2013).

4.2.2 Functional data on MDpc

Lesions that are localized to the lateral half of MD, which should map onto MDpc, give rise to impairments in working memory and executive function in humans and monkeys (Isseroff et al., 1982; Zoppelt

et al., 2003). Physiology studies in macaques also point to a role for MDpc in working memory, the transient holding, processing and use of information on the scale of seconds. Working memory is critical for thinking, planning, reasoning and decision-making, ultimately allowing integration of retrospective information, information pertaining to ongoing goals and internal states, and prospective information on behavioral output (Baddeley, 2000; Baddeley and Hitch, 1974; Watanabe and Funahashi, 2012). The mid-dorsal and mid-lateral PFC regions, with which MDpc is prominently interconnected, have a well-established role in supporting the selection and manipulation of working memory representations (Funahashi et al., 1989; Funahashi and Kubota, 1994; Fuster, 2008; Goldman-Rakic, 1987; Petrides, 1994).

In fact, pioneering macaque physiology studies demonstrated that MDpc neural activity resembles that observed in lateral PFC, during spatial working memory tasks. Lateral PFC and MDpc neuronal populations both show cue, maintenance and response-related activity (Funahashi et al., 1989; Fuster and Alexander, 1971, 1973; Takeda and Funahashi, 2002). The delay period activity is thought to represent a neural correlate of maintained information, because it often shows directional selectivity (reflecting maintained location information), its duration matches that of the delay period, and is markedly reduced or missing on error trials (reviewed in Watanabe and Funahashi, 2012). In addition, task-related neuronal modulations in many MDpc neurons (63%)

were critically dependent on lateral PFC neural activity (Alexander and Fuster, 1973), because suppression of spiking activity in lateral PFC, through cryogenic deactivation, attenuated the delay period modulations of MDpc units, and promoted bursting activity commonly associated with low arousal states. Turning to thalamocortical mechanisms, mouse studies have reported that the thalamus can enable sustained activity of neuronal ensembles in frontal cortex (Bolkan et al., 2017; Guo et al., 2017; Schmitt et al., 2017). The functional interactions between MD and frontal cortex may operate in the beta frequency range (Bolkan et al., 2017).

Evidence suggests the role of MD extends beyond working memory to other cognitive control functions, such as rule-guided action. A projection to the ventral principal sulcus from the caudal SNr via anterolateral MD was demonstrated using combined orthodromic and antidromic stimulation methods during electrophysiological recordings. This pathway was reported to convey rule-related ("go/no-go") information to ventrolateral PFC from the basal ganglia (Tanibuchi et al., 2009b). Another physiological study demonstrated that lateral MD neurons show selectivity for pro- and anti-saccades near the time of response generation (Kunimatsu and Tanaka, 2010). The anti-saccade rule requires the suppression of an "automatic" saccade toward a peripheral stimulus, and generation of a volitional saccade toward its mirror position, requiring both rule-guided action and inhibitory control.

Lateral PFC and MD neural activity have shown some important differences when recorded during the same task. Specifically, during working memory tasks, lateral PFC and MD neuronal populations have differing proportions of preferences for task-related information, with MD populations tending to reflect prospective information about forthcoming saccade directions, while lateral PFC populations tend to carry more retrospective information about remembered cue locations (Takeda and Funahashi, 2002; Watanabe and Funahashi, 2004a, b; Watanabe et al., 2009). Consistent with this, a recent study, utilizing the dot-pattern expectancy task that tests context processing, found that MD neurons played a larger role in action selection, while lateral PFC neurons were more involved with encoding the environmental state (relating to the need to cancel a prepotent response; DeNicola et al., 2020). Interaction between MDpc and lateral PFC appeared to be strongest around the time of decision-making. In other words, use of tasks which required the application of rules facilitated observations that MD neurons likely support a transformation from contextual information (encoded predominantly in PFC) to an appropriate response, suggesting rule-to-action transformation (see section 2.3) could occur through the vital participation of MD.

To summarize, the few studies involving physiological recordings of putative MDpc neurons have shown that, similar to those in lateral PFC, these populations carry signals related to several aspects of cognitive control, such as spatial working memory and inhibitory control, as well as

signals related to simple rules and decisions, consistent with a possible role for MDpc in shaping local PFC neural ensembles, which are well known to encode this type of information. However, the differential activity recorded in MD and PFC suggests that MD also performs transformations of PFC input, linking contextual information in the recent past to appropriate action plans e.g., rule-to-action; but the precise nature of putative transformations need to be clarified by recordings from “matched” or interconnected MDpc and lateral PFC sites.

4.3 Mediodorsal nucleus, multiform/densocellular

4.3.1 Anatomical details of MDmf/MDdc

The lateral paralamellar or multiform portion (MDmf) has a strong relationship with the postero-lateral PFC regions (Barbas et al., 1991; Barbas and Mesulam, 1981; Goldman-Rakic and Porrino, 1985; Lynch et al., 1994; Siwek and Pandya, 1991; Figure 3, see bold deep violet arrow). This includes the frontal eye fields (FEFs) of area 8a, in the anterior bank of the arcuate sulcus, which play a critical role in covert selective attention and overt orienting behavior in primates (Armstrong et al., 2006; Moore and Armstrong, 2003; Moore and Fallah, 2004; Schafer and Moore, 2007). There are also connections with posterior parietal cortices, which are involved with similar attentional and oculomotor functions (Schmahmann and Pandya, 1990). Relative to MDpc, MDmf has a greater density of reciprocal connections with supplementary motor, premotor and primary

motor cortices (Kultas-Ilinsky et al., 2003; Rouiller et al., 1999; Rouiller et al., 1998).

MDmf also receives prominent inputs from the lateral SNr (Francois et al., 2002; Ilinsky et al., 1985), and thus likely participates in a basal ganglia pathway which innervates posterior PFC regions (Ilinsky et al., 1985). This same lateral portion of the SNr also conveys oculomotor-related basal ganglia outflow to the midbrain SC (Hikosaka and Wurtz, 1983), which itself issues ascending projections to MDmf (Harting et al., 1980). As such, MDmf represents a central hub in the oculomotor system, and it also likely interacts with the functionally related frontoparietal attention network. Considering the anatomical relationship with non-PFC motor-related frontal lobe areas, its role in attention and oculomotor control may generalize to motor intention involving other effectors. MDdc has a strong relationship with the motor control system, having connections not only with motor, supplementary motor and premotor areas, but also inputs from the spinal cord (Jones, 2007; Kultas-Ilinsky et al., 2003; Rouiller et al., 1998; Rouiller and Welker, 2000).

To our knowledge, the ratio of laminar sources of corticothalamic input or laminar targeting of thalamocortical output has not been directly investigated for MDmf or MDdc. However, PV labeling abounds in these regions, with CB notably absent in MDmf, and minimally expressed in MDdc (Jones, 2007). Interestingly, in our diffusion MRI work, we observed a posterolateral zone of MD that was characterized as having intense

overlap for posterior PFC regions, which tend to have greatest laminar definition of the PFC regions, and are likely more involved in concrete aspects (i.e., closer to specification and preparation of action) of behavior control (Phillips et al., 2019a; Figure 4G, upper-right hand corner). In addition, posterolateral PFC area 8 was shown to issue an outsized proportion of layer 5 projections to the thalamus (Xiao et al., 2009), and PV “core” neurons, which dominate in MDmf/dc, are thought to issue projections to middle layers with a topographic organization, directly influencing cortico-cortical inputs. Taken together, the evidence suggests that layer 5 corticothalamic projections in posterolateral PFC regions (i.e., those that comprise the long-range transthalamic route) may contact the prevalent PV positive neurons in MDmf, which would indirectly issue signals between cortical sites in the posterolateral PFC regions through an influence on middle layers. These projections may contribute to action selection, gaze shifts, or report on issued premotor and motor commands. This type of circuit arrangement, where the transthalamic route (from cortical layer 5) uses PV neuron-mediated thalamocortical projections to middle cortical layers, is seen for the indirect pathways between sensory cortices via the ventral pulvinar (Shipp, 2003) as well as between sensory and prefrontal cortex via PULm (Romanski et al., 1997; Figure 2). The two regions of elevated overlap in MD (Figure 4G, bright yellow zones at opposite ends of the figure) may reflect thalamic zones (putative MDmf and MDmc) having strong relationship with the “cognitive” motor control

system, in the posterolateral PFC, and the “emotional” motor control system, in the ventromedial PFC (Barbas et al., 2003). These circuits at opposite ends of the PFC architectonic spectrum may rely heavily on the transthalamic route to coordinate and sequence movements using multiple effectors.

4.3.2 Functional data on MDmf/MDdc

Consistent with the anatomical connections for MDmf, a series of elegant physiological studies demonstrated that a corollary discharge signal, regarding oculomotor commands, is relayed from SC to FEFs through MDmf (away from more peripheral, direct control of the oculomotor muscles), which facilitates the re-mapping of retinotopic receptive fields in cortex during eye movements (Sommer and Wurtz, 2002, 2004, 2006). These findings support the proposal of the higher-order thalamus as a monitor of motor actions (Guillery and Sherman, 2002b), and MDmf specifically as enabling motor-to-sensory transformations (see section 2.3). Corollary discharge signals likely contribute to the percept of a stable world during ongoing gaze shifts (Sommer and Wurtz, 2008). To our knowledge, there have been no physiological investigations precisely targeting MDdc.

Guillery and Sherman (2002) proposed that higher-level thalamic nuclei all share a common function of relaying copies of motor commands to “higher” cortical areas. In this view, cortical projections from layer 5

branch to issue a synapse, onto higher-order thalamocortical neurons, on their descent to motor-related targets in the brainstem, but it is unclear whether this arrangement maps onto PFC-thalamic circuits. Importantly, it has not been demonstrated that layer 5 corticothalamic neurons in primate PFC architectonic regions in fact branch off projections destined for motor structures.

4.4 MD summary

Overall, MDmc, MDpc and MDdc/mf have their strongest relationships with mostly non-overlapping, complementary PFC regions and extra-PFC sources. As a whole, MD contains a functional gradient, with its subregions having involvement in a wide range of circuits and computations. Specifically, medial zones are involved with affective and mnemonic processing, central zones with rules and working memory manipulation, and lateral zones with contributions to more concrete sensorimotor and attentional processes. The limited available functional evidence suggests that each of these MD divisions may contribute to specific types of transformations (see section 2.3), such as value-to-choice for MDmc, rule-to-choice for MDpc, and motor-to-sensory for MDmf. In addition, MD is connected with widespread regions of the TRN, which may suggest that MD has a special role in modulating corticothalamic circuits involving posterior cortices (Jones, 2002; Zhang and Jones, 2004; Zikopoulos and Barbas, 2012) since other nuclei only

interact with restricted subregions of TRN (Barbas et al., 2013). PFC areas 46, 13 and 9 have also been shown to have widespread TRN innervation, projecting to regions through which low level sensory circuits pass (Phillips et al., 2016; Zikopoulos and Barbas, 2006). These innervation patterns emphasize the important role of PFC-MD circuits in top-down control over sensory circuits.

5. Ventroanterior thalamic nucleus, magnocellular compartment

VA is classically considered part of the “motor thalamus”, along with the ventrolateral nucleus (VL; Haber and McFarland, 2001; Ilinsky and Kultas-Ilinsky, 1987; Xiao and Barbas, 2004). Most, if not all thalamocortical neurons in these zones are under the control of cerebellar (VL) and basal ganglia (VA) outflow (Ilinsky and Kultas-Ilinsky, 1987). VA and VL are generally positioned anterior and lateral to MD and the internal medullary lamina (Figure 4A, B). There are different opinions on how the medially situated VAmc (Figure 4A) should be categorized. It has been speculated that VAmc may in fact be an anterior extension of IL (Jones, 2007). This suggestion is based on its architectonic characteristics, its projection to the striatum (but we now know that many non-IL thalamic nuclei issue projections to the striatum, see section 2.5), and early studies showing that a short latency cortical recruiting response could be elicited by stimulation of VAmc. Otherwise, VAmc is commonly grouped instead with the “motor” nuclei in the thalamus, since anatomists have usually

positioned it as a subregion of VA (Jones, 2007). Indeed, VA and VAmc are the main targets of basal ganglia outflow in the thalamus. However, the habit of, in our view, inaccurately classifying VAmc with the “motor” nuclei is likely due to the historical reputation of the basal ganglia as a structure mostly concerned with motor control. This view has been challenged or corrected in recent decades, since there is ample evidence that the basal ganglia also process affective and cognitive information (Eisinger et al., 2018). VA proper (i.e., the portion of VA outside of VAmc, comprised of VApc and VAdc; Ilinsky and Kultas-Ilinsky, 1987) and VL thalamocortical neurons do not project to the PFC (Jones, 2007; McFarland and Haber, 2002; Nakano et al., 1992), unlike VAmc, which has connections with most if not all PFC architectonic regions (Figure 3, see pattern of arrows connecting VAmc with PFC; Erickson and Lewis, 2004; Goldman-Rakic and Porrino, 1985; Jones, 2007; Xiao and Barbas, 2004). As such, VAmc will be the primary focus of our discussion. For the ventral nuclei, we adhere to the designation system of Ilinsky and Kultas-Ilinsky (Ilinsky and Kultas-Ilinsky, 1987)

5.1 Anatomical details of VA and VAmc

VA proper projects mostly to frontal lobe regions outside of the PFC: primary motor, supplementary motor and pre-supplementary motor area, premotor, and cingulate motor cortices (McFarland and Haber, 2002; Rouiller et al., 1999; Rouiller et al., 1998), although there are some

projections to posterolateral PFC areas (which contain the FEFs). Its thalamocortical neurons are under the control of the inhibitory projection from the GPi (Ilinsky and Kultas-Ilinsky, 1987; Ilinsky et al., 1993; Jones, 2007). The motor-related basal ganglia circuits pass through these pallidal and thalamic zones (Haber and McFarland, 2001). By contrast, VAmc participates in cognitive and affective circuits mediated through the anteromedial SNr, in addition to the motor-related basal ganglia circuits mediated through the caudolateral SNr (Kitano et al., 1998), since the entire SNr projects densely to VAmc (Ilinsky et al., 1985; Jones, 2007; Tanibuchi et al., 2009a; Xiao and Barbas, 2004). In fact, VAmc is the main target of basal ganglia outflow among the PFC-connected nuclei (Xiao and Barbas, 2004). As mentioned above, VAmc thalamocortical neurons are connected to nearly all architectonic regions of PFC (Barbas et al., 1991; Cavada et al., 2000; Dermon and Barbas, 1994; Erickson and Lewis, 2004; Goldman-Rakic and Porrino, 1985; Xiao and Barbas, 2004), with massively converging corticothalamic inputs onto zones overlapping with more sparse reciprocating thalamocortical projections (Figure 3, see pattern of arrows connecting VAmc with PFC).

Anatomical studies have described mostly inconsistent crude topographic relationship for VAmc with PFC (Dermon and Barbas, 1994; Goldman-Rakic and Porrino, 1985; Xiao and Barbas, 2004). For example, orbital regions (areas 11, 13, 47/12) do appear to consistently connect with its ventral sector. More consistent across studies seems to be a large

degree of overlap for PFC representation in VAmc, which may obscure efforts to extract a topography using tracer injections (Phillips et al., 2019a). One study reported VAmc had the strongest relationship with areas 12, 32 and 14 (i.e., regions on each of the lateral, orbital and medial surfaces of PFC; Barbas et al., 1991). However, there was no injection in areas 24 or 9 in that study, and others observed a preferential relationship with dorsal and medial PFC areas, such as areas 8a/b, 9, 32 and 24 (Goldman-Rakic and Porrino, 1985; Jones, 2007; Xiao and Barbas, 2004), but these studies grouped VAmc together with VA proper. One study found that, although the entire PFC projected to VAmc, the largest proportion of inputs originated in area 46 (Erickson and Lewis, 2004). Studies employing bidirectional tracer injections in cortex have showed that there is a large territory with an unreciprocated projection from areas 24 and 32 and (McFarland and Haber, 2002; Xiao and Barbas, 2004) and although the projections from other PFC areas (14, 11, 10, 9, 12, 46) were reciprocated, the corticothalamic projection is more massive, encroaching on territory outside the reciprocal thalamic zone (Xiao and Barbas, 2004). Overlapping projections from PFC architectonic regions were noteworthy for VAmc (Xiao and Barbas, 2004), which contrasted with the segregated cortical representations observed in VA. Complementary to this observation, electrophysiologically identified VAmc neurons (which “relay” information from the SNr to the PFC) projected to an assortment of PFC

architectonic regions, while similarly identified MD neurons projected to only one architectonic region (Tanibuchi et al., 2009a).

VAmc also has some reciprocal connections with posterior parietal cortices (Asanuma et al., 1985; Divac et al., 1977; Kasdon and Jacobson, 1978), and an unreciprocated projection to the temporal pole (Markowitsch et al., 1985), suggesting its involvement in modulating high-level perceptual processes. There is also a reciprocal relationship with the dorsal premotor cortex (Rouiller et al., 1998), but apparently not with the supplementary motor area or motor cortex (Kultas-Ilinsky et al., 2003; Rouiller et al., 1999). VAmc thalamocortical neurons are uniformly under the control of inhibitory input from the SNr (Ilinsky et al., 1985; Kultas-Ilinsky and Ilinsky, 1990, Figure 3). It was suggested that SNr inputs are the most powerful influences contacting VAmc thalamocortical dendrites, based on their size and strategic location on proximal dendrites. Thus, any message transmitted from VAmc to PFC likely needs to coincide with a pause in SNr-mediated inhibition. The lateral SNr also projects to the SC, in a pathway that has been thoroughly dissected to understand its role in eye movement control (Hikosaka, 2007a; Wurtz and Hikosaka, 1986). However, the nigrothalamic projection to VAmc is larger than the nigrocollicular projection (Parent et al., 1983), yet very few studies have investigated the function of this main nigral projection (Tanibuchi et al., 2009a; Yasuda and Hikosaka, 2019). VAmc is considered to be the main route by which SNr influences reach more rostral PFC regions (Erickson

and Lewis, 2004; Goldman-Rakic and Porrino, 1985; Xiao and Barbas, 2004) although in rodents, basal ganglia influences from the GPi and SNr reach the PFC through MD (Groenewegen, 1988; Groenewegen et al., 1990). In primates, the GPi does not appear to influence the PFC through VA or MD, but it has been reported to instead have a minor influence via projections to the posterior IL group and AM (Sidibe et al., 2002; Xiao and Barbas, 2002b; Figure 3). Similar to MD, VAmc receives complex and dense dopaminergic inputs (Sanchez-Gonzalez et al., 2005). Thus, VAmc thalamocortical neurons appear to be involved with affective and cognitive processing in the PFC, with a contribution that is under the supervision of basal ganglia outflow.

Ultrastructural studies have highlighted that VAmc has relatively simple synaptic arrangements (Kultas-Ilinsky and Ilinsky, 1990), with no hint of glomerular packaging or triadic synaptic arrangements that organize the driving inputs in most other nuclei (Guillery, 1995). Complex synaptic arrangements are found in VA proper (which conveys GPi inputs to cingulate motor, supplementary motor, premotor and motor cortices) (Ilinsky et al., 1993; Ilinsky et al., 1997; McFarland and Haber, 2002), VL (which conveys cerebellar inputs to motor-related cortical regions; Kultas-Ilinsky and Ilinsky, 1991) and MDpc (Schwartz et al., 1991), but not VAmc.

The “motor” nuclei, including VAmc, receive outsized proportions of layer 5 driving inputs from the cortex, with this pathway contributing nearly 50% of corticothalamic inputs (compared to ~20% proportion of the

corticothalamic pathways projecting to other nuclei such as AM and MD; Xiao et al., 2009). This suggests that VA and VAmc may possess elevated capacity for the long-range transthalamic route. Corroborating evidence for this comes from the observation that medial PFC (including anterior cingulate; architectonic regions which prominently innervate VAmc; Jones, 2007; McFarland and Haber, 2002; Xiao and Barbas, 2004), are known to issue large proportions of layer 5 inputs to the thalamus in comparison to other PFC architectonic regions (Xiao et al., 2009). VAmc thalamocortical projections are focused preferentially on cortical layers 3 and 4, with a smaller proportion issued to layers 5 and 1 (McFarland and Haber, 2002; Xiao and Barbas, 2004; Zikopoulos and Barbas, 2007), although terminals can be found in all cortical layers (Zikopoulos and Barbas, 2007).

In VAmc, evidence suggests that modulatory inputs from small layer 6 projection neurons contact PV thalamocortical neurons, which have been shown to project back up to middle cortical layers. Driving and modulatory inputs from large layer 5 projection neurons contact CB thalamocortical neurons, which modulate superficial layers, branching and travel large horizontal distances (Zikopoulos and Barbas, 2007). However, the separation for the multiple parallel corticothalamic and thalamocortical pathways is not necessarily so clear cut, since both small and large terminals from cortical layer 5 were observed. Moreover, because VAmc thalamocortical projection neurons target all cortical layers, the patterns of corticothalamic pathways linking with thalamocortical projection neurons

likely involve additional complex relationships that need deeper exploration. Nonetheless, this relationship between corticothalamic and thalamocortical projections observed by Zikopoulos and Barbas (2007) fits reasonably well with the core/matrix framework (Jones, 1998b).

In addition, layer 5 projections to AM and MD were found to reside in the deep sublamina, while those to VA/VAmc were found to reside in upper layer 5, which is also populated by the PFC-striatal neurons (Xiao et al., 2009). Projection neurons in upper layer 5 are generally large, with long apical dendrites ascending to layer 1, long horizontal dendrites stretching many millimeters along these layers (Castro-Alamancos and Connors, 1997; Mountcastle, 1997) and axonal branching patterns that target the entire cortical column above. In addition, influences on cortical layer 1 have been shown to increase the gain of these layer 5 projection neurons in rats (Larkum et al., 2004). By contrast, it has been suggested that pyramidal neurons in superficial layer 5 (which project to MD and AM) have less expansive dendrites and axonal branching patterns (Xiao et al., 2009). Therefore, VAmc projection neurons seem positioned to participate in the relatively large-scale recruitment of cortical columns and circuits, in comparison to AM and MD projection neurons, which may have a more localized span of reception and influence.

Taken together, the evidence highlights many ways that VAmc, the PFC and basal ganglia have close anatomical links: (1) VAmc and the striatum receive projections from all PFC architectonic regions; (2) VAmc

is the main thalamic target of SNr (basal ganglia) outflow that conveys signals originating in PFC; (3) corticothalamic neurons projecting to VAmc are comingled with corticostriatal neurons in superficial layer 5 of PFC; and (4), VAmc projections impact PFC-striatal and PFC-VAmc projection neurons, both proximally through targeting of layer 5, and distally through targeting of layer 1; (5) PFC-striatal and PFC-VAmc projection neurons (but less so PFC-MD or PFC-AM projection neurons) are directly modulated by superficially-projecting thalamocortical neurons – which are thought to play a role in interareal recruitment through their long horizontal spread across PFC architectonic regions – through their long ascending dendrites reaching layer 1. A similar relationship may exist with premotor and supplementary cortices, VA proper, and the basal ganglia circuits involving the GPi (McFarland and Haber, 2002).

5.2 Functional data on VAmc

We know very little about the response properties of VAmc. However, it is a primate-specific thalamic nucleus (Ilinsky et al., 1985; Jones, 2007), and therefore likely a relatively new and important addition to the cognitive control circuitry, similar to the granular PFC regions (Wise, 2008). We do know that when monkeys perform a simple task involving generation of saccades toward rewarding stimuli, VAmc neurons showed selectivity for stable stimulus values (Yasuda and Hikosaka, 2015, 2019). This characteristic was also observed for lateral MD neurons. In addition,

SNr-recipient PFC projecting VAmc neurons sent information to the PFC about stimuli, carried the information across the delay, and specified rules, but again, this was also observed for similarly identified MD neurons (Tanibuchi et al., 2009b). What is the unique function of VAmc toward processing in PFC? Based on several lines of anatomical information discussed above, it seems reasonable to propose that VAmc may represent a critical node in a distributed system involved with the coordination of large-scale inter-areal neural ensembles involving PFC and more posterior cortical regions. This may occur through the representation of learned value information that could rapidly engage the appropriate thalamocortical circuits, and thus behavioral responses, to stimuli of varying values (Yasuda and Hikosaka, 2019). Of course, additional functional data will be necessary to test this possibility.

5.2.1 Cortical network control hypothesis for PFC, VAmc and the basal ganglia

Overall, the thalamic locations associated with (1) increased layer 5 inputs from PFC and (2) projections to superficial PFC layers, appear to be correlated with those that receive basal ganglia outflow. As reviewed above, these are the components that would endow the thalamus with an ability to influence interareal cortico-cortical communication in PFC circuits. VAmc is the main target of basal ganglia outflow destined for all PFC regions, although MDmc and anterior IL thalamocortical neurons also

seem to express these characteristics (see sections 4.1.1 for MDmc and 6.1.1 for anterior IL). The striatum, the main input nucleus of the basal ganglia, is privy to contextual information from all of cortex (except primary sensory areas), with functionally related cortical regions issuing converging inputs (Calzavara et al., 2007; Choi et al., 2017; Haber et al., 2006; Haber et al., 1995; Kunishio and Haber, 1994; Middleton and Strick, 1996a; Saint-Cyr et al., 1990). Thus, the SNr seems equipped to gather and convey internal state- and goal-related information together with external contextual information, which VAmc (and to some extent, other thalamic nuclei) may use to help establish functional connectivity in the currently relevant regions of PFC, premotor cortex, and the involved parietal and temporal areas. Although other basal ganglia-recipient thalamic zones may play a similar role with their projections to PFC, thus far only VAmc-targeting corticothalamic neurons have been reported to reside in superficial layer 5, which suggests VAmc may be particularly well equipped to carry out this function as outlined above.

The PFC may ultimately exert control over network functional connectivity in at least 3 ways: (1) through direct monosynaptic “top-down” influences in posterior cortices (Yeterian et al., 2012), (2) through influences over their related striatal circuits (Calzavara et al., 2007; Choi et al., 2017; Haber et al., 2006; Jarbo and Verstynen, 2015; Saint-Cyr et al., 1990) – which may help recruit these functionally relevant network assemblies, according to internal goals and preparatory sets, reinforcing

the appropriate configurations through the basal ganglia circuits converging onto VAmc – and (3) through its direct projection to VAmc (and other thalamic nuclei). The VAmc thalamocortical projections – controlled directly by PFC projections and indirectly by PFC projections to the basal ganglia – would reinforce or help to shift the activated ensembles through a dual impact on superficial layer 5 neurons: first, by modulating their dendrites in layer 1, and second, by direct projections to pyramidal cell bodies in superficial layer 5. These layer 5 projections in turn impact striatum and VAmc. Thus, there may be robust feedback mechanisms linking PFC, basal ganglia and VAmc, which may establish network configuration based on internal goals and context.

As cognitive operations progress over time, circuits influencing VAmc thalamocortical activity could possibly help the PFC shift the currently engaged (but no longer relevant) corticocortical motif to a new relevant configuration, by either permitting, blocking or shifting thalamocortical selection of the appropriate cortico-cortical circuits (Haber and Calzavara, 2009; McFarland and Haber, 2002; Xiao et al., 2009) involving distributed prefrontal, parietal and temporal regions. The spatiotemporal features of the appropriate configured networks may be shaped and reinforced through the plastic learning mechanisms involving dopaminergic projections to the PFC, thalamus and striatum (Haber et al., 2000; Ott and Nieder, 2019; Sanchez-Gonzalez et al., 2005).

6. Intralaminar nuclear group

There are several nuclei within the internal medullary lamina – the myelinated fibers that run along the rostro-caudal axis through the thalamus. These IL nuclei have been classified into an anterior group (aIL), comprising the central medial, paracentral and central lateral (CL) nuclei, and a posterior group (pIL), comprising the centromedian (CM) and parafascicular (Pf) nuclei (subset of IL depected in Figure 4B, C). Although the IL thalamus, as a whole, projects broadly across the cortex, giving rise to the classical view of non-specific IL projections, individual IL nuclei each preferentially connect with specific cortical areas (Saalmann, 2014; Van der Werf et al., 2002). The IL also substantially project to much of the striatum; and striatal projections from directly connected IL and cortical areas tend to overlap (Smith et al., 2004). That said, IL neurons that project to the cortex, and those that project to the striatum, likely represent different subpopulations, for the most part. Here we focus on the relationship between the IL thalamus and extended PFC circuits (we again refer the reader to Galvan and Smith, 2011 and Smith et al., 2004 for excellent review of the thalamostriatal projections from the IL nuclei).

6.1 Anterior intralaminar group

6.1.1 Anatomical details of anterior intralaminar group

Lateral and medial PFC project to aIL. The central medial and paracentral nuclei receive input from granular PFC and medial limbic

cortex. In comparison, CL receives input from posterolateral PFC (including FEFs), premotor and motor cortex as well as parietal cortex (Akert and Hartmann-von Monakow, 1980; Kunzle and Akert, 1977; Figure 3, see pattern of arrows connecting aIL with PFC). Projections from the cortex originate from small pyramidal cells in layer 5, and to a lesser extent from layer 6 (Deschenes et al., 1998). aIL also receive subcortical input from the brainstem reticular activating system, SNr, SC, deep cerebellar nuclei and spinal cord (Jones, 2007; May, 2006). The cerebellar, and possibly other subcortical, input may preferentially synapse on striatum-projecting IL neurons (Ichinohe et al., 2000). Taken together, aIL have access to a breadth of attentional, arousal and sensorimotor information.

Much of the work delineating projections of the aIL group has been done in cats, which indicates that the aIL project to much of the PFC from which they receive input. CL and the paracentral nucleus mainly send output to lateral frontal cortical areas, whereas the central medial nucleus mainly sends output to medial and basal frontal cortical areas (Figure 3, arrows connecting aIL with PFC). CL additionally projects to parietal cortex, including the parietal eye fields (Macchi et al., 1984; Royce et al., 1989). There is evidence for thalamocortical terminations in both superficial (layer 1 and possibly 3) and deep (layers 5 and 6) cortical laminae (Kaufman and Rosenquist, 1985; Towns et al., 1990). These projections have been proposed to arise from different subpopulations of

IL cells (Molinari et al., 1994). While more work confirming laminar targets in macaques is required, we do know that aIL cells predominantly stain for CB (although there are fewer such cells in posterior parts of CL and central medial nucleus). There are some cells that stain for PV, in the dorsolateral part of CL (Jones, 2007), but the predominance of CB-immunoreactive aIL is consistent with terminations outside cortical layer 4. The projections from aIL to superficial and deep layers, but not middle, contrasts with the laminar termination patterns of other thalamic nuclei, such as MDpc and PULm (see Figure 2).

6.1.2 Functional data on anterior intralaminar group

The limited available electrophysiological and lesion evidence suggests that aIL contribute to attentional, oculomotor and arousal functions (Saalmann, 2014; Schiff, 2008; Schlag, 2009), in line with their cortical and subcortical connectivity. These inter-related functions are important for selective attention, a key component of cognitive control. In a visually-guided saccade task, when monkeys shifted their gaze to a cued target in the presence of a distracter, the spiking activity of CL and paracentral neurons differentiated the target from distracter (Wyder et al., 2004). Further, a memory-guided task variant showed that CL and paracentral neurons maintained elevated activity specific to the target across the delay period (Wyder et al., 2004). This suggests a role in

cognitive control for aIL that may extend beyond attention to working memory and planning.

Causal evidence for an attentional role derives from deep brain stimulation focused on CL, which improved the behavioral performance of macaques in a phasic alerting paradigm requiring a time-limited manual response to a go cue (Baker et al., 2016). Additionally, clinical data suggest that unilateral lesions including aIL can give rise to hemispatial neglect, a deficit in attention and awareness affecting one side of space (Schiff, 2008). Further, bilateral lesions including aIL can produce acute coma, further supporting a role regulating arousal and level of consciousness. Accordingly, deep brain stimulation of IL thalamus of a patient in a minimally conscious state improved their behavioral responsiveness (Schiff et al., 2007). In rats, optogenetic stimulation of CL and the paracentral nucleus (at 40 and 100 Hz) caused a transition from sleep to wakefulness (Liu et al., 2015). In our recent macaque study, CL electrical stimulation – at 50 Hz frequency, mimicking the firing rate of the fast-spiking subpopulation of CL neurons during wakefulness – roused monkeys from continuous anesthesia with propofol or isoflurane (Redinbaugh et al., 2020). This arousal effect decreased markedly when the stimulating array was moved away from the center of CL (e.g., into pIL or MD), which shows the effect was specific to manipulating the aIL. Moreover, it was likely mediated via thalamocortical (rather than thalamostriatal) projections, considering the lack of arousal effect during

stimulation of the CM (which has strong striatal projections but limited cortical projections (Smith et al., 2004)).

Towards a mechanistic understanding of how aIL influences PFC, stimulating CL at 50 Hz reinstated wake-like cortical dynamics, including increased functional connectivity within a frontal cortical column as well as between frontal and parietal cortex (Redinbaugh et al., 2020). In particular, CL stimulation increased coherence, at frequencies greater than 4 Hz, between superficial and deep layers within the FEFs. CL stimulation also increased coherence at alpha (8-15 Hz) and gamma (>30 Hz) frequencies in the feedforward pathway from parietal to frontal cortex, as well as increased coherence at alpha frequencies in the feedback pathway from deep frontal layers to superficial parietal layers. This is consistent with human (Schiff et al., 2007) and rat (Kung and Shyu, 2002) studies that showed electrical stimulation of aIL elicited strong evoked potentials in frontal and parietal cortex; as well as an optogenetic functional MRI study (Liu et al., 2015) showing widespread activation of rat frontal (and more posterior) cortex during CL and paracentral stimulation. These findings align well with the anatomy, as described above. The dominance of CB neurons in aIL, and their tendency to project to both superficial and deep layers of multiple cortical areas, suggests that they can enhance cortical synchrony and facilitate fast and efficient transfer of information both within and between cortical areas. In the context of cognitive control, this mechanism could facilitate balanced processing of feedforward sensory

information with feedback signals reflecting attentional demands, rules, and contextual information. In summary, it seems that overall aIL can influence not only intra-PFC processing, but also sensorimotor information transmission to PFC as well as PFC feedback to sensorimotor areas, which may have consequences for ongoing conscious state.

6.2 Posterior intralaminar group

6.2.1 Anatomical details of posterior intralaminar group

The major output of pIL is to the striatum. pIL projects to much of the caudate and putamen, with Pf projections having some overlap with PFC projections in the caudate nucleus, and CM projections overlapping mainly with sensorimotor projections in the putamen and dorsolateral caudate (Sadikot et al., 1992; Selemon and Goldman-Rakic, 1985). pIL contains few cells staining for CB. Rather, there are higher numbers of PV-staining cells; and some CM cells stain for calretinin (Jones and Hendry, 1989). The PV-staining cells of pIL likely project to the striatum (Sidibe and Smith, 1999). However, Pf also projects to PFC, including the cingulate gyrus, as well as to parietal cortex; and CM projects to motor cortical areas (Kasdon and Jacobson, 1978; Kievit and Kuypers, 1975; Vogt et al., 1979). Thus, pIL, like aIL, can influence cognitive control-related processes via the thalamostriatal or thalamocortical pathway; but

in the case of pIL, influence via the thalamocortical pathway is likely to be relatively minor.

Cortical input to pIL originates mainly from frontal cortex, with premotor areas projecting to Pf and motor cortex projecting to CM (Akert and Hartmann-von Monakow, 1980; Chiba et al., 2001; Kunzle and Akert, 1977). There is also substantial subcortical input to pIL, particularly from the basal ganglia. But unlike aIL, which receives basal ganglia input via the SNr, the GPi provides significant input to pIL, especially CM (Parent et al., 2001). Overall, the anatomical connectivity suggests that the pIL can influence different stages of processing from planning to action, Pf earlier and CM later, closer to action execution.

6.2.2 Functional data on posterior intralaminar group

The available electrophysiology and lesion evidence suggests that pIL contributes to cognitive flexibility and response inhibition, key components of cognitive control. Thalamic stroke involving damage to Pf and CM negatively impacted patients' ability to perform the Wisconsin Card Sorting Test (WCST), presenting as perturbed rule maintenance and set shifting; but this may have been in part due to MD, as the damage included its ventral part (Liebermann et al., 2013). Another lesion study (Van der Werf et al., 2003) reported impaired response inhibition (measured using a number of cognitive control tasks including the WCST),

after damage to ventral parts of IL, which appears to include the posterior group, and MD. While consistent with the posterior group contributing to set shifting and inhibitory control, the extent of the clinical lesions makes it difficult to distinguish the contribution of MD.

Single-neuron recordings in behaving macaques have helped clarify the role of pIL in cognitive control. In a go-nogo task, in which different reward sizes corresponded to the go and nogo options, CM neurons were more active after the go/nogo cue (prior to any response execution) on small reward trials compared with large reward trials (Minamimoto et al., 2005). Electrical stimulation of CM in this task slowed behavioral responses in high reward trials. This suggests that CM can counter bias towards a particular action (i.e., the high reward action in this study), and in doing so, enable set shifting according to context. Inactivation studies have been performed to probe the influence of pIL on the striatum. Inactivating CM/Pf, using the GABAa receptor agonist, musimol, markedly decreased both striatal activity and behavioral responses to stimuli linked to reward (Matsumoto et al., 2001; Minamimoto and Kimura, 2002). Thus, the thalamostriatal pathway may enable the contribution of the pIL toward countering response bias and set shifting.

7. Pulvinar

The pulvinar is the largest thalamic nucleus and located most caudally among the PFC-connected thalamic nuclei (Figure 4D). The brachium of the SC provides a useful landmark to roughly divide the pulvinar into dorsal and ventral parts. The dorsal and ventral pulvinar differ in anatomical connectivity and functional properties (Saalmann and Kastner, 2011; Shipp, 2003). Cortical connections of the dorsal pulvinar include frontal, parietal and temporal cortical areas, whereas the ventral pulvinar has connections with visual and inferior temporal cortex. The dorsal pulvinar can be further subdivided into medial and lateral portions (Olszewski, 1952), based on an increased cellular density in the medial portion and a paucity of large fiber tracts, which traverse the lateral section (Romanski et al., 1997). There are two clearly organized retinotopic maps of space in the pulvinar, one map inferior and the other lateral, thus forming the ‘visual pulvinar’. These subdivisions have been a focal point of the research to date. Instead, in this review, we will focus on the dorsal pulvinar, particularly its medial portion (PULm), because of its association with the PFC (for reviews of ventral pulvinar, see, e.g., Bourgeois et al., 2020; Saalmann and Kastner, 2011; Shipp, 2003). Similar to several other PFC-connected thalamic nuclei we have discussed, PULm is connected with most if not all architectonic PFC regions (Barbas et al., 1991; Dermon and Barbas, 1994; Goldman-Rakic and Porrino, 1985; Romanski et al., 1997; Figure 3, see pattern of arrows connecting PULm with PFC).

7.1 Anatomical details of PULm

Tract tracing studies in nonhuman primates have demonstrated a topography of connections between PULm and PFC, with lateral and central PULm projecting to different PFC regions, relative to more medial (and caudal) PULm. Generally speaking, lateral/central PULm projects to lateral and orbital PFC, whereas medial PULm projects to medial PFC (including anterior cingulate; Barbas et al., 1991; Romanski et al., 1997). The most robust of these lateral/central PULm projections appear to be to areas 46v and 8a (including the FEFs; see also Barbas and Mesulam, 1981; Stanton et al., 1988), with additional projections to areas 45, 11, 12 and 13. In comparison, there are fewer medial PULm projections to PFC. Medial PULm issues projections to areas 9 and lateral 12, as well as weaker projections to areas 10, 24, 25 and 32. In return, the PULm receives input from almost all of the PFC regions to which it projects.

There is also topographic specificity for PULm when considering its connections outside of PFC. Unlike the medial PULm, the central/lateral PULm also has reciprocal connections with the insular and posterior parietal cortex (especially the parietal eye fields); and unlike the central/lateral PULm, the medial PULm projects to lateral and basal nuclei of the amygdala. Both PULm subregions connect with the posterior cingulate cortex and superior temporal cortex, in addition to some minor connections with medial anterior cingulate area 24 (Homman-Ludiye and Bourne, 2019; Romanski et al., 1997). The medial PULm may have a

greater influence on the temporal pole than central/lateral PULm. In addition, limbic regions such as area 23, retrosplenial cortex and posterior parahippocampal areas (TH and TF) have reciprocal connections to central and caudal PULm (Baleydier and Mauguiere, 1985). The PULm also receives ascending input from the SC, especially from its multisensory deep layers (Benevento and Standage, 1983; Shipp, 2003). When considering the thalamic nuclei which have connections with the PFC, PULm is conspicuous in that no projection from basal ganglia output nuclei has been demonstrated using tract tracing in monkeys. It is possible that the basal ganglia influences PULm indirectly, through their projections to the SC.

Layer 6 is the origin of the great majority of input from PFC, with very few projections arising from layer 5. The PULm projections terminate in deep layer 3 and layer 4 of PFC, while very few terminated in layer 1 (Romanski et al., 1997; Figure 2, connections with “PFC B”). In contrast with input from PFC, the input from insular and parietal cortex originates, to a significant degree, from both layers 5 and 6 (Romanski et al., 1997; Figure 2 connections with “sensory” cortex). This suggests that like indirect pathways between visual cortical areas via the ventral pulvinar, PULm may form an indirect pathway originating in layer 5 of sensory cortex which terminates in middle layers of PFC (although this needs to be confirmed with double labeling experiments; Figure 2, “Long-range” from “sensory” cortex to “PFC B”). Central/lateral PULm has slightly elevated

staining for PV in comparison to medial PULm. However, the PV stain is a little patchy across PULm (i.e., a little lighter or darker in places), and complementary to CB stain intensity (respectively, darker or lighter; Gutierrez et al., 2000).

In line with the replication principle (Shipp, 2003), directly connected cortical areas have overlapping connections in PULm. However, the widespread connectivity of PULm (with cortical areas associated to varying degrees) leads to some non-overlapping projections in PULm, giving rise to what has been described as a modular organization (Gutierrez et al., 2000). Within the PULm, there are interneurons with widespread collaterals – hence differing from the typical thalamic interneurons with smaller dendritic arbors and very localized axonal distributions – which may allow interactions among the cortical modules within the PULm (Imura and Rockland, 2006). Overall, this suggests that PULm has the potential to integrate information from, and regulate information flow to, much of higher-order cortex spanning frontal, parietal, temporal and limbic areas. This differentiates PULm from other PFC-connected thalamic nuclei, in that PULm can route a wealth of behaviorally relevant information from sensory cortex to PFC.

7.2 Functional data on PULm

The PULm contains both unimodal and multimodal neurons, activated by visual, auditory and/or somatosensory stimulation. The

response properties of most PULm neurons seem to reflect the inputs they receive from higher-order cortical neurons, insofar as they have relatively large visual or somatosensory receptive field size and respond to complex stimulus attributes. In visual experiments, PULm neurons show selectivity to faces (including their emotional valence), hands and geometric shapes as well as threatening stimuli like snakes (Nguyen et al., 2013; Nguyen et al., 2016; Van Le et al., 2013). Coarse stimulus representations can emerge with short latency (≤50ms after stimulus onset), which may reflect input from the SC (Nguyen et al., 2013; Nguyen et al., 2014; Nguyen et al., 2016). Auditory experiments have shown that PULm neurons can signal repeating patterns and contribute to pattern segmentation in sound sequences (Barczak et al., 2018). Further, many PULm neurons have multisensory properties, again reflecting their input from various sensory and multimodal areas, including those in the superior temporal cortex (upper bank of the superior temporal sulcus; Yeterian and Pandya, 1991a) and ventrolateral PFC (lateral area 12 and area 45a; Diehl and Romanski, 2014; Hwang and Romanski, 2015; Romanski, 2012; Sugihara et al., 2006). For these PULm neurons, different modalities could modulate activity in either the same or different direction. For example, in the case of the latter, somatosensory excitation and auditory inhibition (Gattass et al., 1978; Yirmiya and Hocherman, 1987). Finally, dorsal pulvinar neurons, including in PULm, can show activity related to intentional, goal-directed

movements, both eye and limb movements (Acuna et al., 1983; Robinson et al., 1986; Yirmiya and Hocherman, 1987).

The aforementioned multimodal response properties suggest a role for PULm in selective attention, sensory-guided action (including in response to threatening stimuli) and social cognition, which interact/overlap in our daily lives. Selective attention modulates evoked and delay period activity of PULm neurons (Fiebelkorn et al., 2019; Petersen et al., 1985). An attentional role is further substantiated by lesions involving PULm in both macaques (Petersen et al., 1987; Wilke et al., 2010) and humans (Danziger et al., 2004; Karnath et al., 2002; Snow et al., 2009). PULm neurons also have been shown to represent perceptual confidence (Komura et al., 2013). Monkeys reported the direction of motion in a random dot motion task, in which the relative proportion of upward and downward moving dots could be manipulated. Monkeys also reported confidence in each decision using an opt-out option. When monkeys are less confident in their perceptual decision, choosing an opt-out option lets the animal abandon perceptual discrimination and get a small but guaranteed reward. The activity of PULm neurons better correlated with the confidence of the monkey than the content of perception (i.e., the reported motion direction). When monkeys chose the opt-out option, likely indicating that the monkeys were less confident, PULm neurons showed reduced responses. Moreover, deactivation of PULm using muscimol increased the opt-out rate, as if this

manipulation reduced the monkeys' confidence. This suggests that the PULm can signal stimulus reliability, which may inform attentional prioritization and appropriate multimodal integration, as well as contribute to predictive coding (Kanai et al., 2015).

PULm appears to contribute to planning, rather than strictly motor aspects, of sensory-guided actions. PULm activity starts before the onset of, and continues throughout, an action, suggesting a contribution to planning and/or execution (Acuna et al., 1983; Robinson et al., 1986; Yirmiya and Hocherman, 1987). Causal evidence from both lesion and stimulation experiments supports a contribution to planning and sensorimotor coordination. Dorsal pulvinar, including PULm, deactivation (using muscimol or THIP) perturbed target selection and visually-guided reaches in the presence of multiple food targets (Wilke et al., 2010). Specifically, there was a significant bias towards ipsilesional targets. This was not due to a primary sensory or motor deficit, because monkeys could saccade or reach to a single target in either ipsi- or contralesional space after dorsal pulvinar deactivation (Wilke et al., 2010), see also (Bender and Baizer, 1990). Further, electrical stimulation of dorsal pulvinar has been shown to influence saccadic planning, distinguishable from action execution (Dominguez-Vargas et al., 2017). The deactivations of PULm give rise to behavioral deficits resembling those following lesions of frontal and posterior parietal areas to which it projects, suggesting PULm

interactions with fronto-parietal networks are important for planning and coordination of sensory-guided actions.

A subset of PULm neurons are sensitive to face orientation and gaze direction (Nguyen et al., 2013), important cues for social behavior (Emery, 2000). PULm neurons have also been reported to respond to emotional expressions of human faces (Maior et al., 2010). The latency of these responses could be relatively short (<100ms) or long (>300ms). Such short latency responses are consistent with a subcortical path from the SC to amygdala via the pulvinar, supporting fast processing of facial information (LeDoux, 2000; McFadyen et al., 2019). Indeed, pulvinar lesions in human subjects perturb implicit processing of fearful stimuli (Bertini et al., 2018). Short latency pulvinar responses could also contribute to the colliculo-pulvinar route to dorsal cortical areas (although available evidence suggests this may predominantly route through inferior pulvinar; (Berman and Wurtz, 2010; Lyon et al., 2010), providing low spatial frequency information for rapid orienting to faces and social prediction (Bar, 2007). However, the long latency PULm responses are more in line with contributions to conscious face processing along the ventral cortical pathway (Pessoa and Adolphs, 2010). Because PULm is connected with the upper bank of the superior temporal sulcus, PFC area 45a and lateral area 12, PULm is well positioned to contribute to the integration of faces and vocalizations that occurs in these cortical areas (Diehl and Romanski, 2014; Hwang and Romanski, 2015; Romanski,

2012; Sugihara et al., 2006). Further work is needed to probe the involvement of PULm and pulvino-PFC interaction in social cognition and communication.

At a mechanistic level, evidence suggests that the other subregions of the pulvinar, specifically inferior and lateral parts, can regulate the gain of cortical neurons, to modulate stimulus-evoked responses and delay period activity (Purushothaman et al., 2012; Saalmann et al., 2018; Zhou et al., 2016). Further, the pulvinar can regulate the functional connectivity between cortical neurons, within and between areas, according to attentional demands (Saalmann et al., 2012; Zhou et al., 2016). The pulvino-cortical network has been shown to predominantly operate at alpha and gamma frequencies during selective attention. Recent work suggests that a number of these mechanisms extend to interactions between PULm and FEFs (Fiebelkorn et al., 2019). Based on its connectivity with much of PFC, PULm may regulate the gain of PFC neurons and their functional interactions to enable not only selective attention, but also other cognitive control functions. Consistent with this, computational modeling work suggests that a network consisting of the pulvinar and two cortical areas can reproduce several empirical observations in attentional, working memory and decision-making studies (Jaramillo et al., 2019; Quax et al., 2017). This includes changes in pulvinar excitability supporting sustained and ramping cortical activity as well as controlling cortico-cortical connectivity.

Overall, the PULm is well-connected with many associative cortical areas, including superior temporal, posterior parietal, cingulate and insular cortex as well as the PFC. Connectivity differences between the lateral/central PULm and medial PULm suggest different functional roles. The connections of the lateral/central PULm with lateral PFC and posterior parietal cortex suggest contributions to selective attention and sensory-guided action; whereas the medial PULm connections with medial PFC and amygdala suggest contributions to social and affective processing. Generally speaking, the PULm not only bridges higher-order sensory areas and PFC, but can also weight information based on the reliability of sensory evidence (Komura et al., 2013). This would be useful for multi-modal integration, selective attention and perceptual decision-making, i.e., sensory evidence accumulation to the choice threshold (Curtis and Lee, 2010; Shadlen and Kiani, 2013). Considering the additional evidence that PULm deactivation impairs target selection (Wilke et al., 2010), it suggests that the PULm is involved in sensory-to-choice transformations (see section 2.3), i.e., the PULm helps integrate and prioritize information to enable goal-directed action. Such transformations would rely on PULm supporting sustained cortical activity and flexible functional connectivity between cortical neurons (Fiebelkorn et al., 2019; Jaramillo et al., 2019; Quax et al., 2017; Saalmann et al., 2018; Saalmann et al., 2012; Zhou et al., 2016)

8. Conclusions: Thalamus regulates information transmission and performs transformations necessary for cognitive control

Cognitive control requires integrating information about the current context, goals, learned rules, episodic memory, expected rewards and action outcomes, to optimize behavior. Different thalamic nuclei, each endowed with its own unique fingerprint of PFC, posterior cortical and subcortical connections to support the necessary computations across their respective networks, contribute differentially to the processing of these various forms of information. In line with their patterns of anatomical inputs and outputs, functional evidence suggests AM contributes to mnemonic processing, MDmc to learning and value appraisal, MDpc to rule processing, VAmc to action values, aIL to more general arousal mechanisms, pIL to response inhibition, PULm to selective attention, and MDdc/mf to sensory consequences of movements; but not exclusively, and there appears to be some overlap between the roles of thalamic nuclei. More specifically, the reviewed information suggests that AM may have a main role in conveying mnemonic information from hippocampal systems to the orbital and anterolateral PFC zones, while MDmc may mostly coordinate information exchange between entorhinal and amygdalar systems with these same PFC zones. AM and MDmc may thus contribute to the integration of mnemonic information and affective information with highly processed multimodal sensory information; MDpc may have a main role in coordinating the local ensembles in anterior and

mid-PFC regions for flexible encoding of contextual information necessary for the guidance of goal-directed behavior; VAmc may have a key role in coordinating longer range inter-areal communication through influences on functional connectivity across distributed PFC-PFC and PFC-temporal/PFC-parietal networks; MDmf was shown to have a prominent role in overt and covert attentional and overt orienting shifts, including informing the cortex about issued motor commands; PULm selects and transmits behaviorally relevant sensory information to PFC; and CL maintains cortical gain and connectivity according to arousal level.

These thalamic nuclei do not simply relay information between PFC (and other) areas. Rather, through extensive converging inputs, thalamocortical neurons are well positioned to contribute to transformations of incoming information to enable effective decision-making (see section 2.3). Such transformations may include rule-to-choice (MDpc), value-to-choice (MDmc), mnemonic-to-choice (AM), and sensory-to-choice (PULm). At a mechanistic level, higher-order thalamic nuclei can influence the gain of cortical neurons and ongoing cortico-cortical communication (Fiebelkorn et al., 2019; Nakajima and Halassa, 2017; Purushothaman et al., 2012; Saalmann et al., 2012; Zhou et al., 2016). This functional connectivity can be adjusted via local reciprocal, local transthalamic or long-range transthalamic routes (Figure 2), and may involve oscillatory or non-oscillatory schemes (Jaramillo et al., 2019; Jones, 1998b; Saalmann, 2014; Schmitt et al., 2017). It is also possible

that thalamocortical projections induce longer-term plastic changes in the cortex (Baxter, 2013; Zhou et al., 2017). Thus, the thalamic nuclei clearly make major and complex contributions to PFC processing and all aspects of cognitive control.

Converging evidence suggests that there is more to the primate thalamocortical projection system than the core and matrix components (Jones, 1998b), with the existence of a hitherto unidentified component, based on the calcium binding protein profiles in AM and MDpc. Possibly relevant to this is the novel calretinin projection recently reported in MDmc (Timbie and Barbas, 2015). CB positive thalamocortical neurons project to superficial layers, and AM and MDpc are known to issue some projections to superficial layers through scattered CB projection neurons. But these nuclei focus most of their projections onto middle cortical layers, therefore we tentatively propose that the calretinin pathway targets middle layers in AM and MDpc, similarly to the PV positive thalamocortical neurons found in other thalamic nuclei (Figure 2, green components).

Anatomical information has converged to suggest that medial PFC (including anterior cingulate) regions may have privileged access to modulate processing in subcortical circuits involving other PFC regions through (1) their prevalent unreciprocated projections to AM, MDmc, anterior MDpc, and VAmc (Figure 5), and (2) their projections to striatal territories involving orbital and lateral PFC circuits. Evidence for this comes from precise results of bidirectional tract tracer injections in the

cortex and thalamus, and in addition, from observations from a large-scale investigation of the entire PFC using diffusion MRI (Haber and Calzavara, 2009; Haber et al., 2006; Phillips et al., 2019a). The projection zone for medial area 24 uniquely showed prominent overlap with those of all other PFC regions (Figure 4G,H, solid black outlines). In addition, medial area 32 showed prominent overlap with orbital, ventrolateral and other medial regions, as well as elevated overlap with posterolateral regions; and dorsomedial area 9 showed overlap with other medial and posterolateral regions (Figure 4G,H dashed black outlines; Phillips et al., 2019a). This suggests that medial PFC regions may occupy a privileged position in the frontal lobe hierarchy, which fits well with its proposed role in monitoring the need for cognitive control, and in alerting distributed PFC circuits to recruit them, when necessary. These subcortical considerations have not been a feature of proposed hierarchical schemes for PFC (for discussion, see Badre and Nee, 2018), which tend to focus on cortico-cortical influences. The presence of a performance monitoring signal in thalamocortical circuits involving lateral PFC would be consistent with a prominent widespread signal broadcast from medial PFC regions to the entire PFC-thalamic system, toward adjustment of control to optimize future outcomes (Kolling et al., 2016; Ridderinkhof et al., 2004; Shenhav et al., 2013).

Studies in mice have provided vital mechanistic details on thalamocortical operations such as showing that: persistent patterns of

frontal cortical activity depend on thalamic inputs (Bolkan et al., 2017; Guo et al., 2017); thalamic activity sustains local functional connectivity in frontal cortex (Rikhye et al., 2018; Schmitt et al., 2017); and mouse MD effects longer-term plastic changes in the cortex (Zhou et al., 2017). But mice have relatively primitive cognitive control circuitry and abilities, and thus findings in this model organism may not always extend to findings in primates. This is exemplified when considering rule-related modulations, rules being an important means of implementing cognitive control. Specifically, mouse MD neurons have been reported to carry little/no categorical rule information (Schmitt et al., 2017; which may relate to the relatively low proportion of rule-selective neurons in mouse frontal cortex cf. monkeys), while preliminary evidence suggests it is a prominent feature of MD neurons in monkeys (Phillips et al., 2019b), suggesting possible stark differences in function across rodent and primate cognitive thalamocortical circuits.

Since a major goal of basic neuroscientific research is an eventual translation to the clinic, we will need to acquire more information about these circuits in monkeys. Specifically, multi-areal recordings involving (1) multiple PFC regions and multiple thalamic nuclei, (2) complex cognitive tasks, (3) use of laminar probes, to enable investigation of layer-specific thalamocortical interactions and (4) use of causal manipulation techniques, such as microstimulation, opto- and chemogenetics will be critical. Studies employing these methods can investigate how higher-

order thalamic nuclei uniquely contribute to the functions supported by their networks, and interact with other network nodes and cortical microcircuitry. Specific examples include: How do AM and MDmc uniquely contribute to learning and implementation of mnemonic-to-action transformations? How do MDpc and VAmc uniquely contribute to goal-directed behavior? How does the pulvinar contribute to decisions based on sensory evidence and confidence? In addition, studies employing such electrophysiological methods can be used to probe the purpose of medial PFC/anterior cingulate inputs overlapping with inputs to the thalamus from other PFC regions, and their influence over ongoing thalamo-PFC interactions. Simultaneous recordings in PFC and at least two of VAmc, MD and AM can be used to investigate the functional significance of a corticothalamic neuron occupying superficial (projecting to VAmc and striatum) vs deep (projecting to MD and AM) layer 5. Moreover, anatomical work could shed light on the plausibility of key hypotheses we have outlined: Are the thalamocortical neurons which receive basal ganglia outflow the same thalamocortical neurons which receive inputs from layer 5 of PFC? In addition, information on preferential laminar targeting of the layer 5/basal ganglia recipient thalamocortical neurons (if they are indeed overlapping populations) could provide key insights into the overall purpose of the basal ganglia. We could also benefit from more information about the non-CB thalamocortical projections from MD and AM. Is this indeed a calretinin pathway? Which layers are preferentially

targeted by this pathway? Addressing these questions will help us to better understand the complex relationship between the thalamus and PFC. Such mechanistic details are vital to understanding the neural basis of cognitive control, and critically, what goes wrong in a pathological situation, opening up new avenues for targeted therapeutic techniques.

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Figures

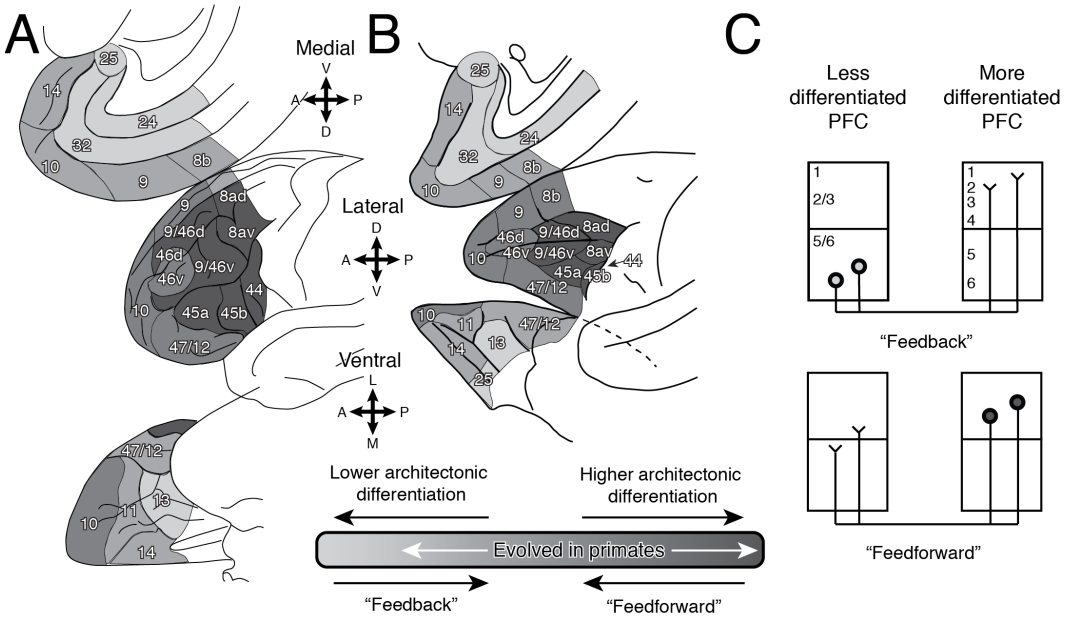

Figure 1. *PFC cytoarchitectonic parcellations in humans and monkeys with laminar patterns of cortico-cortical connections A.* Architectonic regions of human PFC. *B.* Architectonic regions of macaque PFC. Both A and B according to Petrides and colleagues (Petrides et al., 2012) and modified with permission from Elsevier. Orbital (ventral) regions are involved in value assessments and economic decision-making; lateral areas are involved with rule-and strategy guided action, including selective attention and working memory; and medial regions are involved in monitoring the need for cognitive control, and when necessary, alerting lateral and orbital regions to recruit them to optimize behavior. The level of architectonic differentiation is lowest in the tissue closest to the corpus callosum (periallocortices and proisocortices, also known as agranular and

dysgranular, represented in the lightest shade of gray), and gradually increases in anterior, dorsal and lateral regions, with the greatest architectonic differentiation in posterolateral PFC regions (granular isocortices also known as eulaminate; Barbas and Pandya, 1989). Architectonic regions found intermediate to these medial PFC and posterolateral PFC regions are characterized as having gradual shifts between these two “extreme” architectonic profiles. 4 levels of architectonic differentiation are shown; the top 3 levels (i.e., darkest 3 shades) have only evolved in primates, and are thus not found in lower orders such as rodents. *C.* Architectonic differences are a proxy for the laminar patterns of sources and targets for cortico-cortical connections (Barbas and Rempel-Clower, 1997; Goulas et al., 2018). Specifically, if a (prefrontal) cortical region projects from its deep layers onto the superficial layers of another, this is known as a feedback connection from a “higher” region to a “lower” one. Conversely, when a region projects from its upper layers (layers 2/3) to the middle and deep layers of another, this is called a feedforward projection from a “lower” region to a “higher” one (Barbas and Rempel-Clower, 1997). This pattern is similar in sensory cortices, although the feedforward projections target only middle layers (Felleman and Van Essen, 1991; Rockland and Pandya, 1979; Rockland and Virga, 1989; Shipp & Zeki 1989; Spatz 1977). This laminar-based hierarchy was first clearly demonstrated in the posterior sensory cortices, and so the terms feedforward and feedback make more intuitive sense in that context. For

example, in the visual system, primary visual cortex is at the bottom of the cortical hierarchy, having feedforward projections to, and receiving feedback projections from “higher” cortical areas. In A/B, L – lateral; M – medial; D – dorsal; V – ventral; A – anterior; P – posterior.

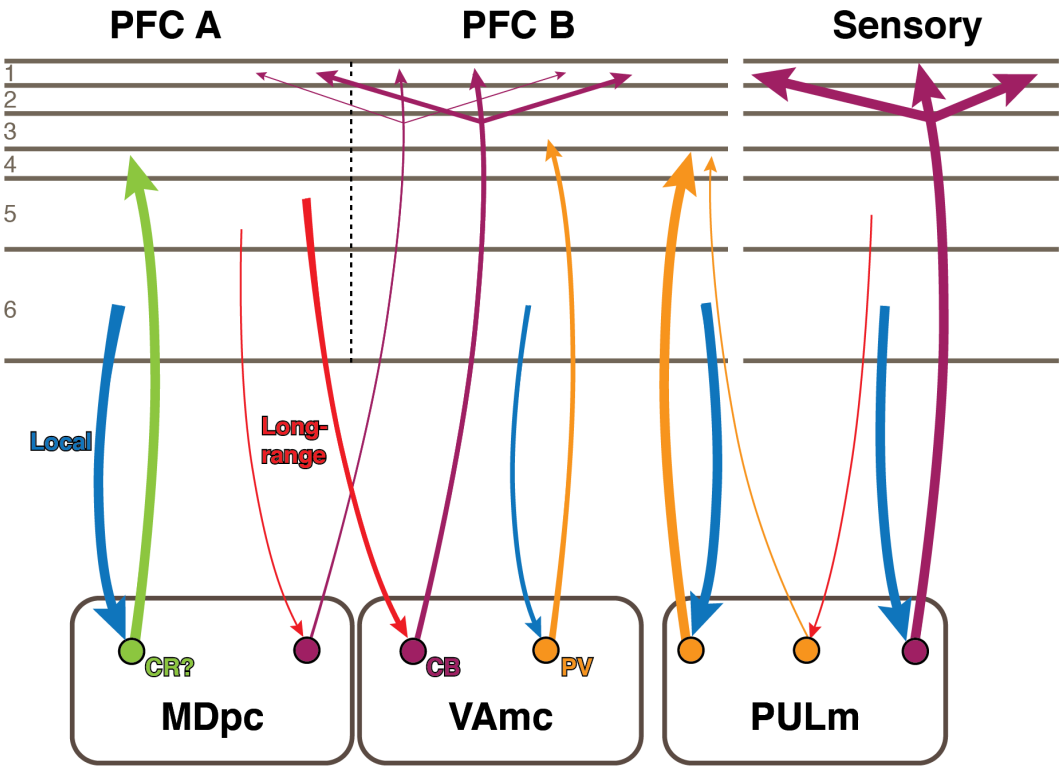

Figure 2. *Schematic showing multiple types of corticothalamic and thalamocortical projections.* Along the top is a representation of the cortical laminae, vertical dashed line representing border between distinct architectonic regions. *Corticothalamic projections*: Blue arrows represent modulatory corticothalamic projections from layer 6. Inputs from layer 6 contact thalamocortical neurons that project back to the same cortical zone ("Local" reciprocal), or to a distinct but local cortical zone in the same architectonic region (not shown, "Local" transthalamic). Red arrows represent (mostly) driving corticothalamic projections from layer 5, which involve projections from a cortical region to a thalamic zone outside its reciprocating thalamic territory, which has reciprocal connections with another cortical architectonic region ("Long-range" transthalamic). The layer 5 corticothalamic projections represent one way that the thalamus

can influence information transmission between distinct architectonic cortical regions. *Thalamocortical projections:* Orange components represent the PV positive thalamocortical neurons that project in a punctate, topographic manner to middle layers, with a driving effect on cortical neurons. Jones referred to this component of the thalamocortical projection system as the “core”. Purple components represent the CB positive thalamocortical neurons that project diffusely and broadly to superficial cortical layers, with axons often traveling great horizontal distances, and modulating large cortical territories that often involve multiple architectonic regions. This type of projection represents an additional way that the thalamus can spread modulatory influences from one architectonic cortical region to others. Jones referred to this component of the thalamocortical projection system as the “matrix”. Green components represent the unidentified thalamocortical projection to the middle layers in AM and MDpc, which may involve calretinin (CR?), since such a projection has recently been identified in MDmc, although its laminar targeting was not reported (Timbie and Barbas 2015). The corticothalamic and thalamocortical pathways can be combined in distinct ways, as exemplified by the patterns of corticothalamic and thalamocortical projections to CB neurons involving VAmc in comparison to those involving PULm. Circuits involving VAmc send layer 5 projections to CB thalamocortical neurons, thus having the driving corticothalamic (transthalamic) pathway influence the modulatory thalamocortical

pathway. In contrast, circuits involving PULm send layer 6 projections to CB thalamocortical neurons, thus having the reciprocating modulatory corticothalamic pathway influencing the modulatory thalamocortical pathway. Pathway combinations can result in a dominant thalamocortical influence on middle layers (e.g., MDpc or PULm to PFC) on the one hand, or a dominant thalamocortical influence outside middle layers (e.g., the intralaminar groups) on the other, and these relationships may exist along a continuum when considering all higher-order thalamic nuclei. Arrow thickness indicates the proportion of projection density for corticothalamic and thalamocortical pathways (thinnest, moderate and thickest indicate approximately 20%, 50% and 80% projection density, respectively).

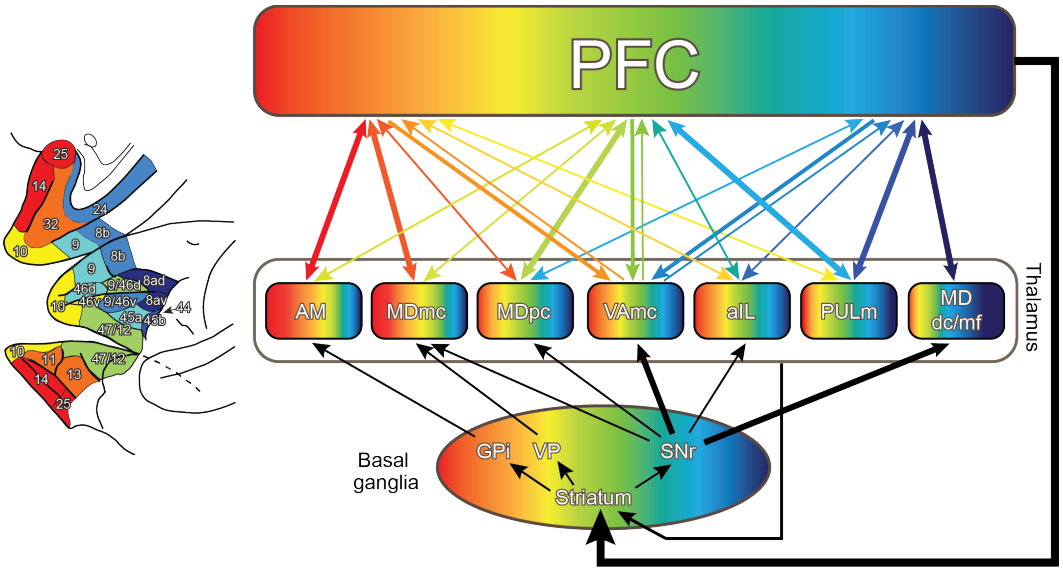

Figure 3. *Schematic summarizing PFC-thalamic connections, featuring PFC-striatal, thalamostriatal and basal ganglia-thalamic projections*. Left, PFC architectonic regions color-coded according to their position in VM-PL gradient of representation in MD (see Figure 4F), which reflects the ventromedial to posterolateral position in PFC, and roughly approximates level of architectonic differentiation (Phillips et al., 2019a). Right, schematic of corticothalamic, thalamocortical, thalamostriatal and cortico-basal ganglia-thalamic circuits, with associated cortical architectonic regions color-coded throughout PFC and striatum. Central level represents PFC-connected thalamic nuclei, with ordering and colored gradients approximating preferential PFC connections of the nuclei (closer to the left, a stronger relationship with warm colored PFC zones; closer to the right, a stronger relationship with cool colored PFC zones). Arrow thickness approximates density of projections. Thalamic nuclei have direct reciprocal connections with PFC and commonly both direct and indirect

connections with the striatum (main input nucleus of basal ganglia, includes nucleus accumbens, caudate nucleus and putamen). Note that IL, especially pIL, has a particularly strong projection to the striatum. However, because pIL has relatively few direct connections with the PFC, we did not include it in this schematic.

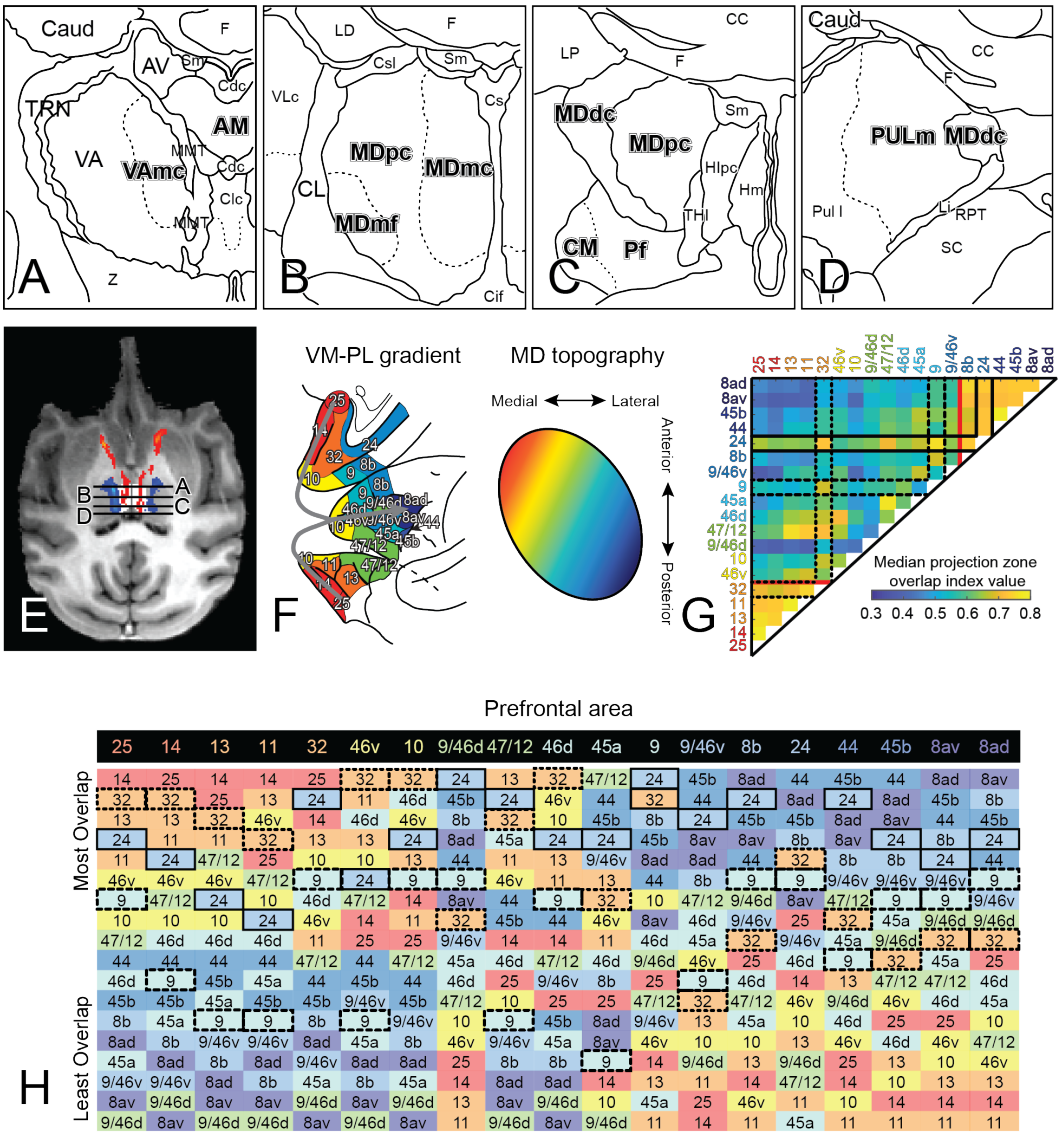

Figure 4. *Anatomical location of thalamic nuclei and summary of relevant probabilistic tractography results. A-D.* Coronal sections illustrating the locations of VAmc, AM, MDmc, MDpc, MDmf, MDdc, CL, CM, Pf and PULm in the macaque thalamus. E. Probabilistic paths (estimated with diffusion MRI) connecting orbital area 13 (red/orange) and posterolateral area 8ad (blue) with MD (white), in macaque brain, viewed in axial plane at the level of the thalamus. Paths occupy longitudinal bands passing

through medial thalamus and crossing nuclear borders. Anterior-to-posterior level of coronal slices shown in A-D indicated on horizontal slice in E. Illustrations in A-D modified from Goldman-Rakic and Porrino, 1985, with permission from John Wiley and Sons. *F*. The VM-PL (ventromedial to posterolateral) gradient describing the topographic relationship between PFC and MD. This work demonstrated a gradient of PFC representation across the horizontal axis of MD: the anteromedial extreme of MD connects preferentially with ventromedial and orbital PFC regions, while the posterolateral extreme of MD connects preferentially with posterolateral PFC regions (Phillips et al 2019a). Intermediate PFC regions have a gradually shifting overlapping representation spanning this axis of MD, with ventromedial, to anterior, to mid, to posterolateral PFC mapped across the anteromedial to posterolateral axis of MD. *G.* Summary of median pairwise overlap indices (based on dice coefficient) across all PFC architectonic regions. Prominent overlap at VM and PL extremes, overlap present but reduced for intermediate PFC architectonic regions (i.e., areas 46v through 9/46v). The pairwise median projection zone overlap index for a given PFC area, with all other PFC areas (in MD), is represented by a single trajectory along the grid. Deeper blue colors indicate less projection zone overlap, while brighter yellow colors indicate greater projection zone overlap. Red lines delineate group of ventral and anteromedial PFC areas having a robust overlap with each other, and the group of posterior PFC areas having robust overlap with each other at

opposite extremes in MD. Solid lines highlight overlap profile for medial area 24. Dashed lines highlight overlap profile for anteromedial area 32 and dorsomedial area 9. *H.* Table depicts, for each PFC architectonic region, the mean pairwise projection zone overlap indices sorted by rank. Each column shows, for the sample PFC area, the rank order of other PFC architectonic regions for mean pairwise overlap index, with most overlap at the top and least overlap at the bottom. The color-coding is taken from the pattern observed in F, with ventromedial and orbital PFC regions in warm colors, and posterolateral PFC regions in cool colors. The ranks for area 24 is shown in solid outlines, while those for ventromedial area 32 and dorsomedial area 9 are shown in dashed lines. Anteromedial area 32 shows very high overlap with other orbital and anterior PFC architectonic regions, and substantial overlap with posterolateral regions. Area 9 also shows substantial overlap with posterolateral regions. Projection zones of medial regions also have prominent overlap with each other. E-H are reproduced or modified with permission from Elsevier.

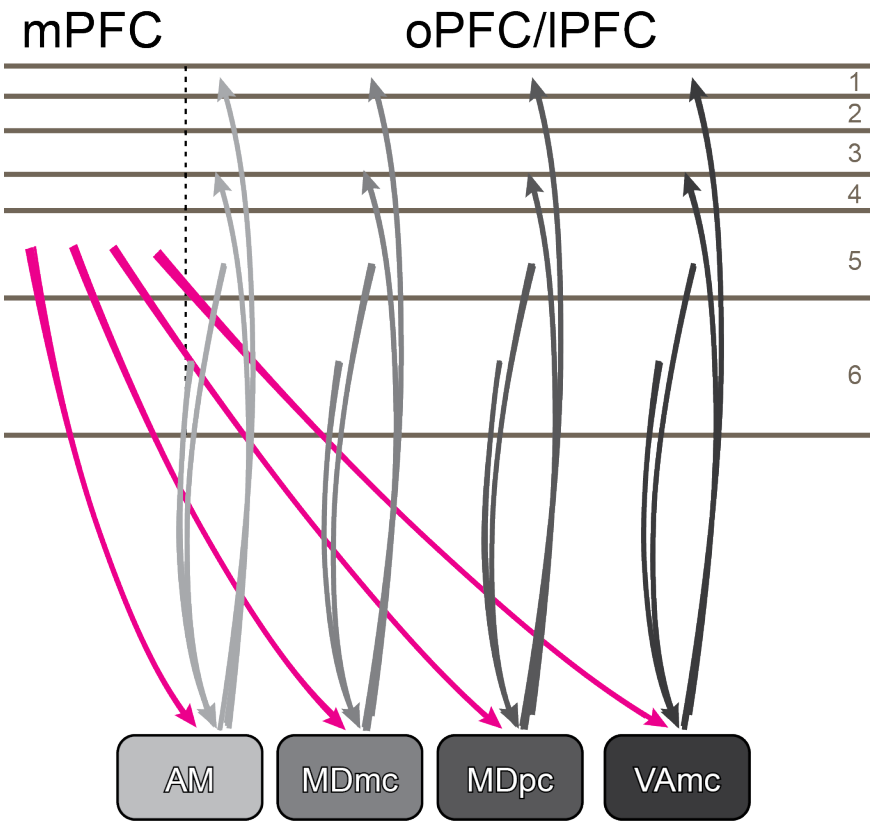

Figure 5. *Medial PFC regions can modulate thalamocortical circuit activity involving orbital and lateral PFC.* Medial PFC can act through unreciprocated projections to thalamic zones having reciprocal connections to orbital and lateral PFC in AM, MDmc, MDpc and VAmc. Pattern identification requires use of bidirectional tracer injections in cortex and/or thalamus. Medial PFC regions issue a relatively large proportion of their corticothalamic projections from layer 5, which participate in the long-range transthalamic route linking cortical areas, and prominently innervate thalamic zones that do not reciprocate the projection (but have a reciprocal relationship with other orbital and lateral PFC architectonic regions). This may endow medial PFC regions a unique ability to control thalamocortical processing in lateral and orbital PFC circuits. Medial PFC

has a similar arrangement for projections into the striatum, the input nucleus of the basal ganglia. While the medial PFC controls processing in lateral and orbital PFC, these lateral and orbital PFC regions can control processing in posterior sensory cortices through direct cortico-cortical projections, and through subcortical projections to the relevant zones in the thalamus and striatum.