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The rostromedial tegmental (RMTg) "brake" on dopamine and behavior: a decade of progress but also much unfinished work

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Abstract

Between 2005–2009, several research groups identified a strikingly dense inhibitory input to midbrain dopamine neurons in a previously uncharted region posterior to the ventral tegmental area (VTA). This region is now denoted as either the rostromedial tegmental nucleus (RMTg) or the "tail of the VTA" (tVTA), and is recognized to express distinct genetic markers, encode negative "prediction errors" (inverse to dopamine neurons), and play critical roles in behavioral inhibition and punishment learning. RMTg neurons are also influenced by many categories of abused drugs, and may drive some aversive responses to such drugs, particularly cocaine and alcohol. However, despite much progress, many important questions remain about RMTg molecular/genetic properties, diversity of projection targets, and applications to addiction, depression, and other neuropsychiatric disorders.

Introduction:

By now, a vast literature has arisen describing roles of dopamine (DA) in motivated behavior, reward-seeking and addiction (Marsden, 2006; Wise and Robble, 2020). Much of this work has focused on downstream targets of dopamine in striatum, cortex, and other sites, while functions of upstream inputs to dopamine neurons have been much less investigated (Tian et al., 2016), despite their importance in regulating this critical neurotransmitter system. One striking example of just how much remained to be discovered occurred between 2005–2009, when multiple research groups simultaneously described a dense GABAergic input to dopamine neurons arising from an unmapped region posterior to the ventral tegmental area (VTA) and extending caudally the border of the acetylcholine-rich pedunculopontine nucleus (Figure 1) (Jhou, 2005; Perrotti et al., 2005; Colussi-Mas et al., 2007; Jhou et al., 2009a; Jhou et al., 2009b; Kaufling et al., 2009; Barrot et al., 2012; Bourdy and Barrot, 2012). Now denoted as either the rostromedial tegmental nucleus (RMTg), or the tail of the ventral tegmental area (tVTA), these GABA neurons are recognized as a genetically distinct group of neurons providing a major "brake" on motivated behavior. For example, RMTg inactivations or lesions produce marked hyperactivity and severe deficits in punishment learning (Bourdy et al., 2014; Lavezzi et al., 2015; Vento et al., 2017), along with a loss of conditioned avoidance responses

to cocaine (Jhou et al., 2013). The RMTg also receives a prominent excitatory afferent from the lateral habenula (LHb), a region whose stimulation had been known to inhibit dopamine neurons (Christoph et al., 1986; Ji and Shepard, 2007), but which had been largely neglected until breakthrough recording studies of the LHb revealed that they encode motivational valence in a manner inverse to dopamine neurons (Matsumoto and Hikosaka, 2007; Geisler and Trimble, 2008; Matsumoto and Hikosaka, 2009). From these auspicious beginnings, the past decade has seen important new work characterizing the RMTg, particularly its genetic expression profiles, interactions with the LHb and other brain structures, encoding of aversive "prediction errors", and responses to drugs of abuse. However, many challenges remain, including a need for further characterization of RMTg genetic and cellular properties, its downstream targets, its responses to drugs of abuse, and possible translational applications.

Early challenges: visualizing RMTg neurons

Early studies of the RMTg utilized a combination of immunohistochemical and tracing techniques to identify these neurons as a distinct population based on their expression of GABAergic markers, innervation of midbrain dopamine neurons, and expression of immediate early genes (IEGs) such as c-Fos after psychostimulant exposure (Scammell et al., 2000; Jhou, 2005; Perrotti et al., 2005; Jhou et al., 2009b; Kaufling et al., 2009; Kaufling et al., 2010). However, the variability and incompleteness of these methods posed considerable early challenges. For example, psychostimulant-induced cFos occurs in only a subset (typically 30–50%) of RMTg neurons in rats, and is largely ineffective in the commonly used C57BL6 mouse strain (Lavezzi and Zahm, 2011; Smith et al., 2019), while GABA markers are more expressed more universally within RMTg neurons, but are also present at high levels in adjacent regions. Hence, the exact boundaries of the RMTg were open to debate, including questions about whether the RMTg is distinct from classical VTA GABA interneurons.

An important advance in defining the RMTg occurred in 2015, when Partanen and colleagues at the University of Helsinki examined the distribution of various transcription factors in and around the VTA (Lahti et al., 2016). In general, transcription factors play critical roles in neuronal development and cell fate determination, and within the VTA and RMTg, different subsets of GABA neurons were found to express different subsets of these factors. In particular, Lahti et al. found three transcription factors (FoxP1, Sox2, and Sox14) expressed at high levels in RMTg neurons, relative to immediately adjacent regions. Among these, FoxP1 has been particularly useful in corroborating and refining earlier delineations of the RMTg (Figure 2), as it strongly labels almost all RMTg neurons, is strongly expressed in both rats and mice, and is readily detectable using commercially available antibodies and RNAscope probes (Lahti et al., 2016; Smith et al., 2019). The expression pattern of FoxP1 not only corroborates previous delineations of the RMTg, but reveals surprisingly sharp boundaries, as FoxP1 is found in >90% of neurons within these boundaries, and <5% of neurons immediately lateral (Smith et al., 2019). FoxP1 shows a very similar expression pattern in mice, and furthermore, in VGAT-Cre mice crossed to a ZsGreen reporter strain, essentially all (~98%) of FoxP1 neurons within the RMTg boundaries expressed ZsGreen reporter (Smith et al., 2019), confirming an overwhelmingly, if not exclusively, GABAergic

identity. FoxP1 is hence increasingly used across multiple labs to define the RMTg (Taylor et al., 2019; Castillo-Rolon et al., 2020; St Laurent et al., 2020; Zhao et al., 2020; Pradel et al., 2021).

In addition to transcription factors noted above, RNA sequencing experiments identified dozens of additional genes enriched in RMTg relative to the adjacent VTA (Smith et al., 2019). Some of these genes, such as GABAergic markers, were already known, but others were novel, including genes encoding prepronociceptin (PNOC) and the serotonin 2C receptor (5HT2CR), which were previously shown to influence reward-seeking (Maillet et al., 2008; Parker et al., 2019), but whose function in RMTg is unexplored. Hence, these genes, among others, represent major areas for further investigation. Notably, genes encoding PNOC and FoxP1 are either absent or present at greatly reduced levels in VTA GABAergic interneurons, again suggesting differential origins and functions of RMTg versus classical VTA GABA neurons.

RMTg “brake” on dopamine firing and motor behavior:

Anatomic studies using light and electron microscopy show that even small anterograde tracer injections in the RMTg give rise to a remarkably dense innervation of dopamine neurons in VTA and substantia nigra (SN), and possibly the retrorubral dopamine fields as well (Jhou et al., 2009a; Balcita-Pedicino et al., 2011; Bourdy et al., 2014). Hence, the RMTg likely influences almost the entire dopaminergic system, with over half of all RMTg neurons innervating the VTA in rat, and nearly 70% innervating at least one of the VTA or SN (Smith et al., 2019). Surprisingly, the RMTg neurons innervating the SN are mostly distinct from those innervating the VTA, and arise preferentially from more lateral RMTg neurons (Smith et al., 2019). Hence, this suggests the possibility of differential modulation of different dopamine neuron subsets from different subsets of RMTg neurons.

Anatomic findings have been corroborated via electrophysiological studies showing that the RMTg indeed exerts a massive “braking” effect on dopamine neuron firing. Single brief pulses of electrical stimulation in the RMTg inhibit 95% and 94% of SN dopamine neurons in rat and monkey, respectively, with these stimulations typically causing total cessation of firing at short latency (Hong et al., 2011; Bourdy et al., 2014), indicating an overwhelming inhibitory influence. Stimulations of the LHb is similarly powerful, with single pulses of electrical stimulation inhibiting 85–97% of dopamine neurons in the SN, and 91–97% in the VTA of rats (Christoph et al., 1986; Ji and Shepard, 2007). Interestingly, one study found a lower proportion of VTA dopamine neurons inhibited by RMTg stimulation - 53% (Lecca et al., 2012), than after LHb stimulation.

In awake rats or monkeys, or urethane-anesthetized rats, RMTg neurons exhibit fast basal firing rates of 14–20 Hz (Jhou et al., 2009a; Hong et al., 2011; Lecca et al., 2011; Melis et al., 2014), that would presumably exert continuous ongoing inhibition of dopamine firing. Such a high “basal” activity is consistent with findings that acute inactivation of the RMTg increases both tonic and burst firing of SN dopamine neurons to roughly 200% of baseline (Bourdy et al., 2014), indicating a strong disinhibitory effect. Similarly, excitotoxic lesions of the RMTg produce long-lasting increases in SN dopamine firing rates, albeit to a slightly lower degree (148% of baseline) than acute inactivation (Bourdy et al., 2014).

This tonic influence likely varies between individual dopamine neurons, as three different groups report that VTA dopamine neurons having slower basal firing rates exhibit more prolonged inhibitory responses to single-pulse RMTg stimulation (Lecca et al., 2012; Melis et al., 2014), and show larger increases in firing after RMTg inhibition via opioids (Jalabert et al., 2011). Hence, RMTg activation might have stronger inhibitory influences on some dopamine neurons than others, leading to lower basal firing in those neurons.

The inhibitory physiological RMTg influence on dopamine is also consistent with numerous behavioral finings. For example, whereas dopamine invigorates motoric activity, RMTg activation suppresses it (Jhou et al., 2013; Lavezzi et al., 2015), while conversely, RMTg lesions or inactivations can produce large increases in locomotion, reaching 2 to 10-fold over baseline (Jhou et al., 2013; Lavezzi et al., 2015; Vento et al., 2017). Notably, these increases appear much larger in novel environments than in animals' home cages, where RMTg lesions have relatively less effect on locomotion (Jhou et al., 2009a). This would be consistent with a disinhibitory effect, in which removal of the RMTg "brake" is permissive for dopamine firing, but with such firing still requiring dopamine activation via other excitatory inputs driven by external stimuli.

What is the RMTg role in aversive learning and behavior?

Of course, dopamine neurons influence much more than locomotor behavior, with particular roles in learning of motivated behaviors. Over a century ago, Thorndike characterized such learning according to the "law of effect" (Thorndike, 1911), positing that animals' actions that lead to desirable outcomes are reinforced, and hence more likely to occur in similar situations in the future. Conversely, actions leading to undesirable outcomes are punished, becoming less likely to occur. Increasing evidence suggests that dopamine and RMTg neurons appear to play opposing roles in this phenomenon. In particular, optogenetic activation of dopamine neurons reinforces operant behavior, increasing its likelihood of future occurrence (Adamantidis et al., 2011; Saddoris et al., 2015), while activation of the RMTg or of its LHb afferents just after an operant action biases animals' choices away from that action (Shumake et al., 2010; Stamatakis and Stuber, 2012; Proulx et al., 2018; Elmer et al., 2019). Activation of the RMTg also produces aversive effects in non-operant tasks, such as condition place preference tests (Smith et al., 2019; St Laurent et al., 2020).

Although exogenous activation of the RMTg produces clear behavioral effects, inactivation studies are needed to assess whether these neurons are necessary for normal motivated behavior. And indeed, inactivations or lesions of the RMTg produce profound "resistance to punishment" in rats trained to lever press for food pellets followed by a very brief (30ms) footshock. Specifically, RMTg lesions produce a 3 to 4-fold increase in the shock amplitude required to suppress food-seeking (Vento et al., 2017), demonstrating a marked insensitivity to the suppressive effects of footshock punishment. Although this effect might be seen as secondary to the motoric disinhibition induced by RMTg impairment, several lines of evidence weigh against this interpretation. First, these animals show no increase in pressing of an adjacent inactive lever, nor do they show increased pressing during normal extinction learning (i.e. when food is no longer delivered). Hence, RMTg lesioned rats are not impaired in their ability to withhold behavior *perse*, but show a selective deficit in inhibiting behaviors

that are followed by punishment (Vento et al., 2017). Additional evidence comes from optogenetic tests in which RMTg inhibition is confined to the few milliseconds of shock delivery itself. This very brief RMTg inactivation also increases shock breakpoints, without any motoric disinhibition at the time of lever pressing (Vento et al., 2017).

Despite evidence from multiple labs for an RMTg role in aversive processing, it would also be erroneous to equate RMTg activity with all aversion (just as dopamine activity is not equivalent to all reward). For example, RMTg-lesioned rats still run away from acute footshocks, and do so at similar latencies as intact rats (Vento et al., 2017; Elmer et al., 2019). RMTg lesioned rats also still exhibit defensive responses to predator odors (Jhou et al., 2009a), and are still motivated to avoid falling on a rotarod test, where they even show enhanced motoric performance (Bourdy et al., 2014). In general, despite the RMTg's critical role in inhibitory responses to aversive stimuli, it does not appear necessary for many *active* responses to the same stimuli. In one particularly striking example, RMTg lesioned and unlesioned rats exposed to predator odor showed equal similar durations of defensive behavior, but intact rats almost exclusively exhibited behavioral inhibition (freezing), while lesioned rats almost exclusively exhibited active responses such as defensive treading/burying (Jhou et al., 2009a). Given these results, it might be tempting to ascribe to the RMTg a role in motoric behavior but *not* punishment or aversion, but this too would be an oversimplification, as RMTg lesioned rats are not globally disinhibited in all behaviors, and as noted above, they exhibit normal ablility to inhibit reward-seeking under non-punishment conditions, such as extinction. A parsimonious description for the RMTg role is that it mediates neither inhibition nor aversion exactly, but rather drives the *learning* that allows aversive stimuli to translate into subsequent behavioral inhibition. In other words, the RMTg is the "effector" in Thorndike's law of effect, at least for punishment learning, a role symmetrically opposed to that of dopamine in reinforcement learning.

RMTg and dopamine phasic firing patterns:

The profound influence of RMTg in punishment and avoidance learning suggest that these neurons might encode information about the stimuli in such tasks. Again, RMTg encoding patterns are in many ways symmetrically opposite to dopamine firing. Of course, the latter is a complex topic, as dopamine neurons are increasingly recognized to encode complex and diverse types of information (Berke, 2018; Saddoris et al., 2018; Collins and Saunders, 2020), but considerable evidence from Pavlovian conditioning paradigms nonetheless indicates that dopamine activity encodes information about whether rewarding and aversive stimuli are "better" or "worse" than expected (Schultz, 2007, 2016). This encoding pattern became widely recognized in the mid-1990s, when a large proportion (albeit not all) of dopamine neurons were found to be phasically activated *not* by rewards per se, but by cues predicting upcoming rewards, or by rewards that are "surprisingly" delivered when none was expected (Montague et al., 1996; Schultz et al., 1997). Further, many dopamine neurons are phasically inhibited by cues predicting aversive outcomes, or by outcomes that are smaller than expected (or entirely absent). This response pattern was termed a "reward prediction error" (RPE), and was quickly recognized for its remarkable resemblance to learning signals developed years earlier in theoretical and computational learning models (Sutton, 1988; Tesauro, 1994; Montague et al., 1996; Schultz et al., 1997). This convergence

of biology and theory infused new ideas into the study of dopamine function, including the recognition that *unexpected outcomes* are major drivers of learning, and that dopamine neurons are ideally poised to broadcast "teaching signals" that indicate such unexpectancy. Accumulating optogenetic evidence indicates that phasic dopamine activation indeed drives new learning about environmental stimuli that alters future behavior (Tsai et al., 2009; Adamantidis et al., 2011; Steinberg et al., 2013; Saddoris et al., 2015; Chang et al., 2016; Hamid et al., 2016). Conversely, inhibition of dopamine activity produces aversive learning in many paradigms (Shippenberg et al., 1991; Danjo et al., 2014), suggesting that dopamine can encode a bidirectional signal, with positive and negative changes in firing signaling that stimuli are "better" or "worse" than expected.

Consistent with opposing roles for RMTg and dopamine, many RMTg neurons across rats, mice, and non-human primates exhibit an inverted version of the canonical dopamine RPE signal (Hong et al., 2011; Li et al., 2019a; Li et al., 2019b) (Fig. 3). Among RMTg neurons that respond phasically to motivation-related stimuli, clear majorities (65–70%) are inhibited by reward-predictive cues and activated by negatively valenced stimuli such as shocks, shock-predictive cues, or unexpected reward omission (Jhou et al., 2009a; Hong et al., 2011; Li et al., 2019a; Li et al., 2019b). This aggregate pattern is inverse to the canonical dopamine response, and similar to patterns seen in the LHb, a major RMTg afferent (Matsumoto and Hikosaka, 2007, 2009; Hong et al., 2011). Hence, both RMTg and dopamine neurons encode a bidirectional valence signal indicating whether stimuli are "better" or "worse", but in opposite directions.

However, not all aspects of the RMTg and dopamine signal are perfectly symmetric. For example, after selective ablation of RMTg projections to the VTA in rats, dopamine neurons in the VTA are no longer phasically inhibited by footshocks, shock-predictive cues, or reward omission, but are still activated by reward predictive cues (Li et al., 2019b) (Fig. 3). Hence, RMTg activation may drive dopamine phasic inhibition to negative motivational stimuli, but surprisingly, RMTg phasic inhibition by positive motivational stimuli does not seem to contribute to dopamine neuron activation (Li et al., 2019b). This may seem paradoxical, but is consistent with observations that RMTg inhibitions by reward predictive cues occur *after* dopamine activation by the same stimulus (Fig. 3). Hence, even though the RMTg encodes information about both positive and negative motivational stimuli, transmission of this information is preferentially weighted toward the latter.

"Surprising" differences between LHb and RMTg function:

As noted above, RMTg and LHb neurons show similar phasic responses to environmental stimuli, leading us and others to initially assume the LHb is the main driver of responses in RMTg. However, emerging evidence suggests this is true only in specific (but potentially very important) circumstances. Most surprisingly, after optogenetic inactivation of its LHb afferents, RMTg neurons are still strongly activated by footshock and shock-predictive cues, and inhibited by reward predictive cues (Li et al., 2019b). In contrast, LHb inactivation abolished RMTg activation by surprising reward omission (Li et al., 2019b), indicating a highly selective LHb influence on RMTg. Interestingly, this parallels the LHb influence on dopamine firing seen by Uchida and colleagues, in which LHb ablation impairs dopamine

phasic inhibitions to reward omission, but not other motivational stimuli (Tian and Uchida, 2015).

Additional experiments suggest that the LHb influence on RMTg drives a broad signaling of “negatively surprising” events. For example, RMTg phasic activations by predicted footshocks are brief - about ~30ms - but become prolonged to ~100ms if the footshock is surprising, for example if it is given without prior predictive cues (Li et al., 2019b). LHb inactivation eliminates the surprise-driven prolongation, without affecting the initial 30ms response. Like the responses to footshock, RMTg responses to auditory cues predicting shock are also prolonged if they are surprising (not preceded by other cues), but become shorter if expected (due to a second preceding predictive cue). Again this prolongation depends on the LHb. Meanwhile, “positively surprising” events do not seem to depend on the LHb, and the LHb’s main contribution to RMTg firing may be to augment its responses to “surprisingly worse” stimuli, whether these are cues, shocks, or reward omission (Li et al., 2019b).

These differences in LHb and RMTg influences on dopamine have several implications. First, they indicate that despite the LHb being a particularly prominent input to the RMTg, other inputs should not be overlooked, and indeed, RMTg responses to footshocks and shock cues were found to depend on inputs from the parabrachial and prefrontal cortical regions, respectively (Li et al., 2019b) (Fig. 4). Secondly, these results could also explain some of the differences reported in LHb versus RMTg behavioral effects. Multiple labs have shown that LHb influences on behavior are particularly strong in tasks involving quickly changing outcomes, or during acquisition of new learning, or reversal learning, all situations that would generate particularly large prediction errors (Stopper and Floresco, 2014; Laurent et al., 2017; Li et al., 2019b; Trusel et al., 2019; Durieux et al., 2020). In contrast, the RMTg role in punishment tasks appears critical both in situations when outcomes are changing rapidly, or when they are static or changing only slowly (Vento et al., 2017).

Astute readers may note that some RMTg responses described above deviate from mathematically idealized RPEs. In particular, whereas majorities of dopamine, LHb and RMTg neurons show no significant changes in firing to rewards that are fully predicted, RMTg neurons still respond, albeit more briefly, to fully predicted footshocks, and retain this response even after extensive training (Li et al., 2019b). This response deviates from an idealized error signal that should disappear entirely, rather than simply being attenuated, when an outcome is fully predicted by prior cues. While seemingly at odds with theory, similar deviations had been reported by Hikosaka and colleagues in the LHb, again for aversion-related but not reward-related RPEs (Matsumoto and Hikosaka, 2009), while VTA dopamine neurons also show attenuation, but not elimination, of inhibitory responses to fully predicted airpuffs (Tian and Uchida, 2015). Hence, all three types of neurons deviate from the idealized RPE signal for predicted aversive stimuli, but not predicted rewards. The significance of this deviation is not known, but given the roles of these phasic responses in associative learning, their selective persistence for predicted aversion but not predicted reward, even after extensive training, suggests a bias toward “loss aversion” over “reward-seeking”. Such an asymmetry has indeed been seen in human decision-making (Kahneman

and Tversky, 1979), although it is unknown whether these decision biases are related to reported encoding biases.

Responses to cocaine and alcohol:

In addition to their responses to sensory stimuli, RMTg neurons are also strongly influenced by many drugs of abuse (Table 1). Acute withdrawal from cocaine, morphine, or alcohol markedly increases firing and IEG expression in the LHb and/or RMTg (Jhou et al., 2013; Glover et al., 2016; Sanchez-Catalan et al., 2016; Glover et al., 2019; Li et al., 2019a). These findings are consistent with long-standing observations that withdrawal from many drugs of abuse leads to suppression of dopamine activity (Rossetti et al., 1992; Diana et al., 1999; Melis et al., 2005), and suggests the possibility that this suppression is driven by RMTg activation. Notably, increases in RMTg activity often parallel the time course of aversive effects of abused drugs. For example, single intravenous cocaine infusions in rats produce an initial euphoric phase lasting ~5–10 minutes followed by aversive effects beginning 15 minutes after infusions (Ettenberg et al., 1999; Jhou et al., 2013). Paralleling this time course, LHb and RMTg firing rates in awake behaving rats are suppressed for the first few minutes after single intravenous cocaine infusions, but show a rebound activation starting around 15 minutes later, paralleling cocaine's aversive phase (Jhou et al., 2013; Li et al., 2019a; Parrilla-Carrero et al., 2021). Furthermore, optogenetic RMTg inactivation overlapping the aversive (but not rewarding) phase abolishes conditioned avoidance of cocaine in a runway operant cocaine-seeking task, indicating that this activation causally drives avoidance behavior (Jhou et al., 2013).

Interestingly, avoidance responses to cocaine show considerable variability between individual rats, with some rats being "high-avoiders" of cocaine while others are "low-avoiders". Furthermore, high-avoiders show greater RMTg "rebound" firing 15–30 minutes after individual cocaine infusions (Parrilla-Carrero et al., 2021), suggesting a possible protective effect of RMTg activity against acquisition of cocaine-seeking. At a cellular level, this differential RMTg activation by cocaine may be due to downregulated calcium-permeable AMPA receptors in RMTg neurons of "low-avoiders", in concert with increased presynaptic release from glutamatergic afferents in "high-avoiders" (Parrilla-Carrero et al., 2021). It is not known why these neuroplastic changes occur in some rats but not others, but their elucidation could shed new light on differences in addiction vulnerability between individuals.

In addition to cocaine, several studies have also examined RMTg responses to ethanol. In one study comparing Sardinian alcohol-preferring (sP) versus non-preferring (sNP) rats, RMTg neurons (in anesthetized rats) showed a dose-dependent increase in firing in response to intravenous alcohol in sNP but not sP rats (Melis et al., 2014). Analogous to findings with cocaine, this result is consistent with a possible protective effect of RMTg activation in sNP rats, though that hypothesis remains to be directly tested. A separate study examined rats exposed to chronic intermittent ethanol (CIE) for 14 weeks via vapor chamber, and then withdrawan, and found marked RMTg cFos activation (Glover et al., 2019) peaking 12 hours after removal from vapor chambers, coinciding with the peak of withdrawal-induced reductions in reward sensitivity measured by intracranial self-stimulation (ICSS).

RMTg inactivation via muscimol further reduced measures of withdrawal-induced anxiety-like behaviors on a battery of tests (Glover et al., 2019), although RMTg inactivation interestingly did not prevent reductions in reward sensitivity measured by ICSS. This study also did not examine influences of RMTg on alcohol consumption *per se*, but a different group examining depressive-like behavior after 48 hours of withdrawal from 6 weeks of alcohol drinking (2 bottle free-choice procedure) showed that RMTg inactivation relieved a variety of depressive-like behaviors, but did not reduce drinking in withdrawn rats (Fu et al., 2019). Numerous other studies indicate that lesions or inactivations of either the RMTg or LHb increase voluntary alcohol intake in non-withdrawn rats (Haack et al., 2014; Fu et al., 2016b; Fu et al., 2016a; Sheth et al., 2016; Fu et al., 2019).

In a preponderance of studies, increased RMTg activity is associated with *reduced* drug-seeking, suggesting a mechanism by which aversive effects of drugs protect against drug-seeking. However, aversive effects of abused drugs can also *increase* drug-seeking, as when the dysphoria of acute drug withdrawal drives individuals to alleviate the discomfort via resumed drug taking (Solomon and Corbit, 1974; Koob and Le Moal, 2008). This latter phenomenon is known as negative reinforcement, and evidence gathered so far indicates that the RMTg does not contribute to this effect, as inhibiting the RMTg during acute ethanol withdrawal does not reduce intake (Fu et al., 2019), and actually increases reinstated cocaine-seeking after extinction (Huff and LaLumiere, 2015). Interestingly, LHb inactivation reduces yohimbine-induced reinstatement of ethanol-seeking (Haack et al., 2014), suggesting the LHb may drive some negative reinforcement type behaviors that the RMTg does not (Stamatakis and Stuber, 2012; Trusel et al., 2019).

Responses to other drugs of abuse:

In addition to cocaine and alcohol, multiple labs have described RMTg responses to many other classes of abused drugs (Lecca et al., 2011). For example, in anesthetized rats, intravenous morphine inhibits RMTg firing to roughly half its baseline rate (Lecca et al., 2012), and in electrophysiological slices mu opioid agonists reduce by 60–75% the magnitude of IPSCs induced in dopamine neurons by RMTg optogenetic stimulation (Matsui et al., 2014; St Laurent et al., 2020). Both effects would be expected to acutely disinhibit dopamine release, producing rewarding effects. Interestingly, mu opioid-mediated disinhibition of dopamine had long been assumed to be mediated by VTA interneurons, but unexpectedly, mu opioid modulation of VTA interneuron effects on dopamine neurons were much weaker than those driven by the RMTg (Matsui et al., 2014). Hence, the prevailing wisdom may have been a case of mistaken identity – i.e. mu opioid effects thought to be mediated by VTA interneurons are more likely mediated by the RMTg residing immediately posterior. Consistent with these electrophysiological results, rats self-administer mu opioid agonist into the RMTg more avidly than into the VTA or other surrounding regions (Jhou et al., 2012), while RMTg inactivation entirely blocked the ability of intra-VTA morphine to disinhibit dopamine neurons (Jalabert et al., 2011). Because RMTg inactivation influences dopamine via disinhibition rather than direct activation, the ability of mu opioids to increase dopamine firing likely requires concomitant activation of glutamatergic or cholinergic inputs to these neurons (Jalabert et al., 2011; Steidl et al., 2017; Buie et al., 2020). Prolonged opioid withdrawal may also produce adaptations in RMTg projections, although the latter

result varies between studies, as one study noted tolerance of RMTg responses to mu opioid agonists in morphine dependent animals (Matsui et al., 2014), while another did not (Kaufling and Aston-Jones, 2015).

Similarly to mu opioid agonists, agonists at CB1 cannabinoid receptors also directly inhibit RMTg firing to about half its baseline rate in anesthetized rats, while also markedly reducing by 78% the ability of RMTg electrical stimulation to inhibit dopamine firing (Lecca et al., 2011; Lecca et al., 2012). Again, both of these cannabinoid effects would disinhibit dopamine neurons, presumably producing rewarding effects. The latter of these effects is further consistent with presynaptic effects on RMTg axons in the VTA, and CB1 receptors at this location also mediate depolarization-induced suppression of inhibition (DSI), which could further disinhibit dopamine neurons (Melis et al., 2014). Interestingly, the latter effect was larger in Sardinian alcohol preferring (sP) relative to non-preferring rats (Melis et al., 2014), again suggesting that RMTg activation could be protective against drug-seeking in sNP rats, but again this has not been directly tested.

Lastly, nicotine appears to increase RMTg firing to about double its baseline firing in anesthetized rats (Lecca et al., 2011), an effect mediated by alpha 7 nicotinic receptor subunits, possibly located on glutamatergic inputs to the RMTg (Castillo-Rolon et al., 2020). The functional significance of this is unknown, but one obvious hypothesis is that it could contribute to aversive effects of nicotine, analogous to aversive effects of nicotine mediated via alpha 5 receptor subunits located on medial habenula circuits (Bierut et al., 2008; Fowler et al., 2011; Morton et al., 2018).

Future challenges:

After its initial description 15 years ago, the last decade has seen considerable progress in elucidation of RMTg function, but much work remains in both basic science and translational areas. RMTg roles in individual differences in addiction may be a particularly ripe area for study. For example, RMTg activation may protect against acquisition of drug-seeking, as animals with stronger RMTg activation by cocaine or alcohol are slower to acquire addiction-like behavior, while RMTg inactivation conversely accelerates intake of abused substances. Hence, potential therapeutic approaches might seek to selectively enhance RMTg activation by cocaine or alcohol.

In addition to translational goals, many basic science questions also remain unanswered. For example, inverse RPE-like encoding is present in 60–70% of cue-responsive RMTg neurons, a clear majority, but one that also leaves a substantial minority encoding other patterns that are not well understood. Similarly, almost 70% of RMTg neurons project to dopamine neurons in either the VTA or SN, but once again substantial minorities project to other targets, such as the dorsal raphe and pedunculopontine (PPTg) nuclei (Lavezzi et al., 2012), which are enriched in serotonin and acetylcholine neurons respectively. However, RMTg projections may not target serotonin or acetylcholine neurons directly (Lavezzi et al., 2012; Sego et al., 2014), and the function of these pathways is largely unexplored, aside from one study noting that RMTg projections to the raphe may encode salience rather than valence (Li et al., 2019a).

In addition to heterogeneity in the RMTg itself, there is likely heterogeneity in its influence on dopamine neurons. While RMTg axons innervate a very high percentage of midbrain dopamine neurons (likely >90%), they avoid minor but potentially important subsets of dopamine neurons in both the VTA and SN (Lecca et al., 2012; Vento et al., 2017). The significance of such heterogeneity is unknown, but would be consistent with a growing literature on diversity in dopamine anatomy and function (Ikemoto, 2007; Schultz, 2007; Brischoux et al., 2009; Root et al., 2014; Schultz, 2016; Berke, 2018; Gardner et al., 2018; Saddoris et al., 2018; Engelhard et al., 2019; Lee et al., 2019; Heymann et al., 2020; Hughes et al., 2020; Root et al., 2020).

Finally, in addition to roles in addiction, recent work has uncovered possible RMTg roles in an increasing range of neuropsychiatric disorders. For example, RMTg ablation alleviates motor deficits in a rat model of Parkinson's disease (Faivre et al., 2020), alleviates learned helplessness in a depression model (Elmer et al., 2019), and also influences sleep-wake regulation (Yang et al., 2018) in a manner inverse to recently uncovered dopamine roles in sleep regulation (Eban-Rothschild et al., 2016). These models have received much less study relative to addiction, but could be highly fruitful given the strong dopaminergic influences on these disorders, particularly Parkinson's disease and major depressive disorder (Belujon and Grace, 2017). Clearly there is much yet to do.

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Highlights:

- The RMTg provides major GABAergic inputs to midbrain dopamine neurons
- Many RMTg neurons are selectively activated by aversive stimuli and their predictors
- RMTg inactivation profoundly impairs punishment but not reward or extinction learning
- RMTg neurons contribute to aversion during withdrawal from abused drugs
- A minority of RMTg neurons project to non-dopamine targets of unknown function

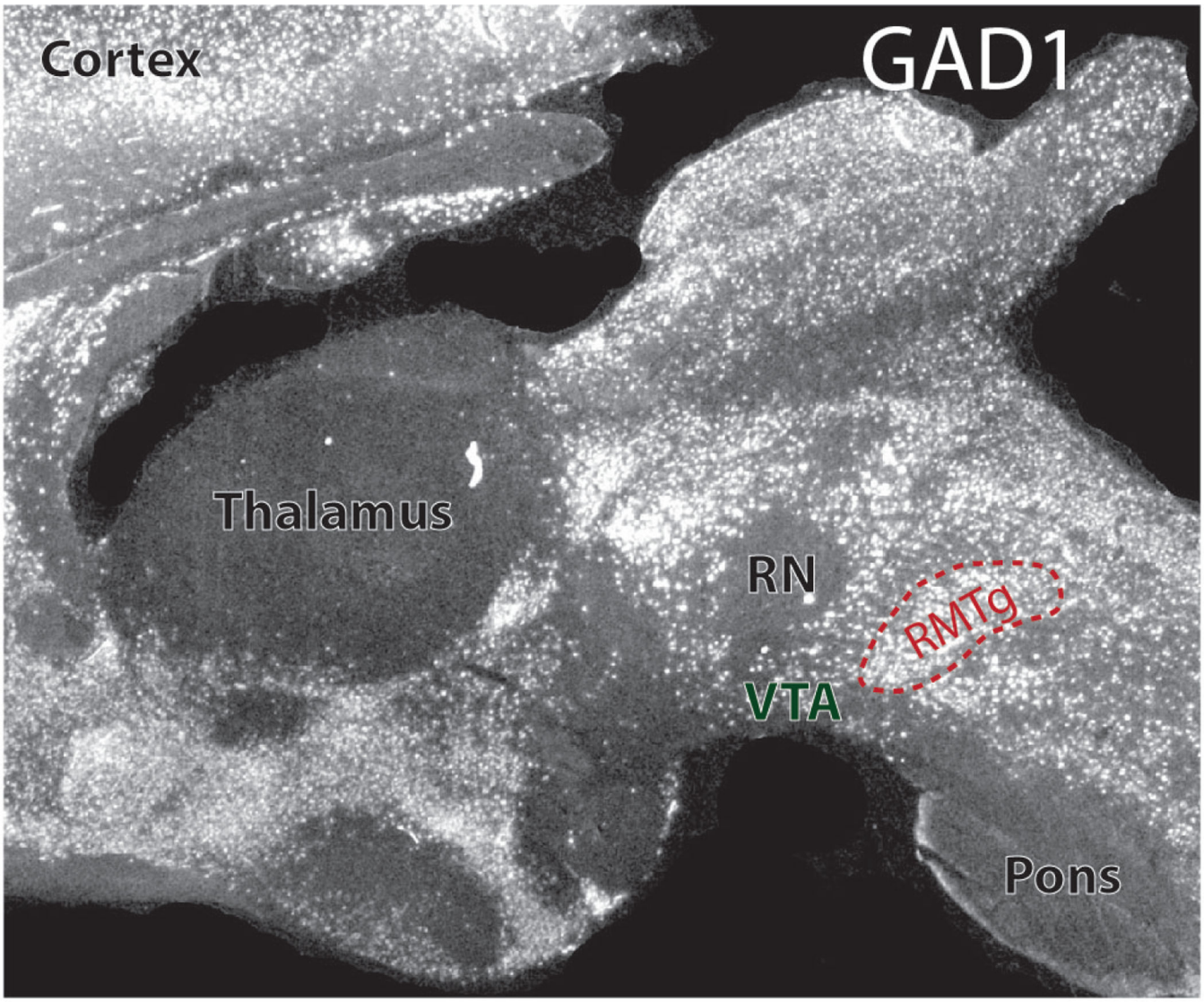

Figure 1.

Sagittal rat brain section (~0.5mm from midline) showing in situ hybridization for GAD1. The RMTg is outlined in red, and other nearby landmarks are denoted, including the ventral tegmental area (VTA), red nucleus (RN) and pons. In rats, the stereotaxic coordinates of the RMTg center are roughly 7.5mm posterior to bregma, 7.4mm ventral to dura, and 0.6mm lateral from the midline, albeit with some variation between individual animals.

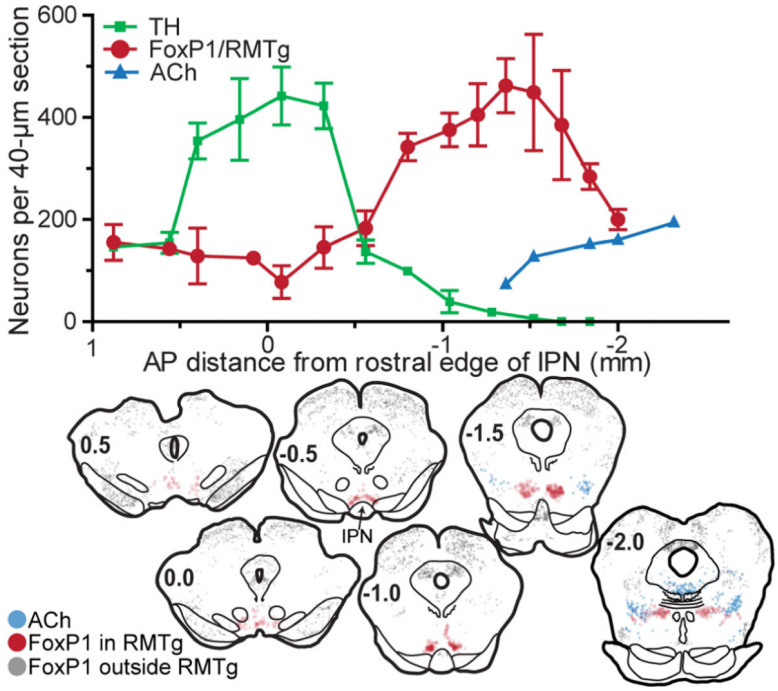

Figure 2.

Distribution of FoxP1/RMTg neurons at various rostro-caudal levels in coronal rat brain sections. (A) Counts of neurons in 40-micron sections plotted versus anterior-posterior distance from rostral edge of IPN. RMTg neurons, as identified by FoxP1 immunostaining, reside caudal to the majority of VTA dopamine neurons, identified via tyrosine hydroxylase (TH), and rostral to many cholinergic neurons of the pedunculopontine nucleus. (B) Coronal rat brain sections show distribution of FoxP1 neurons inside RMTg (red symbols), which are distinct from FoxP1 neurons outside the RMTg (grey symbols). Cholinergic neurons of the PPTg are denoted by blue symbols.

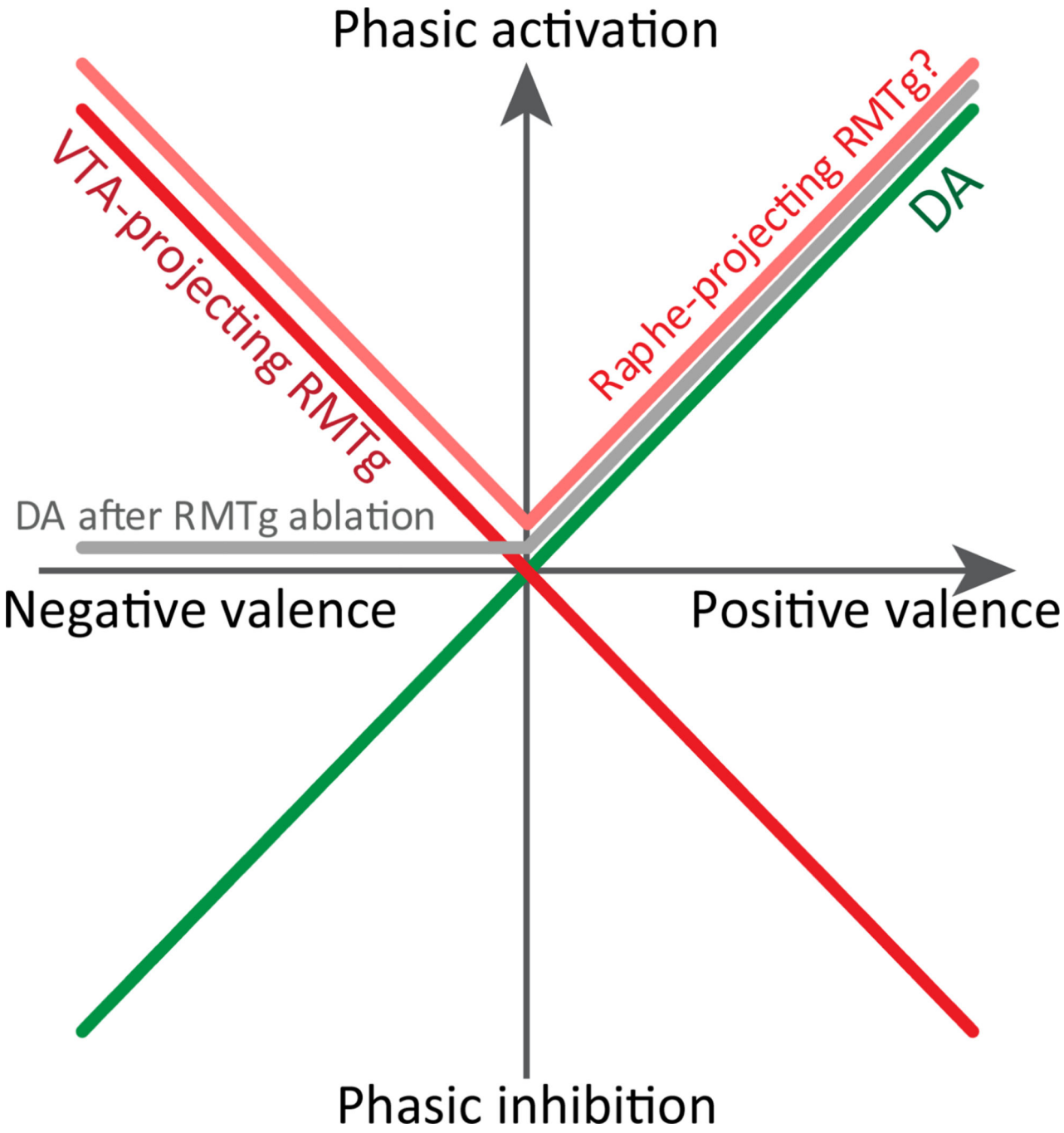

Figure 3.
Simplified depiction of RMTg and DA responses to stimuli of positive and negative valence. Responses of dopamine neurons are shown in both intact rats (green trace) and after ablation of RMTg (grey trace). Responses to RMTg neurons projecting to VTA versus raphe are adapted from (Li et al., 2019a).

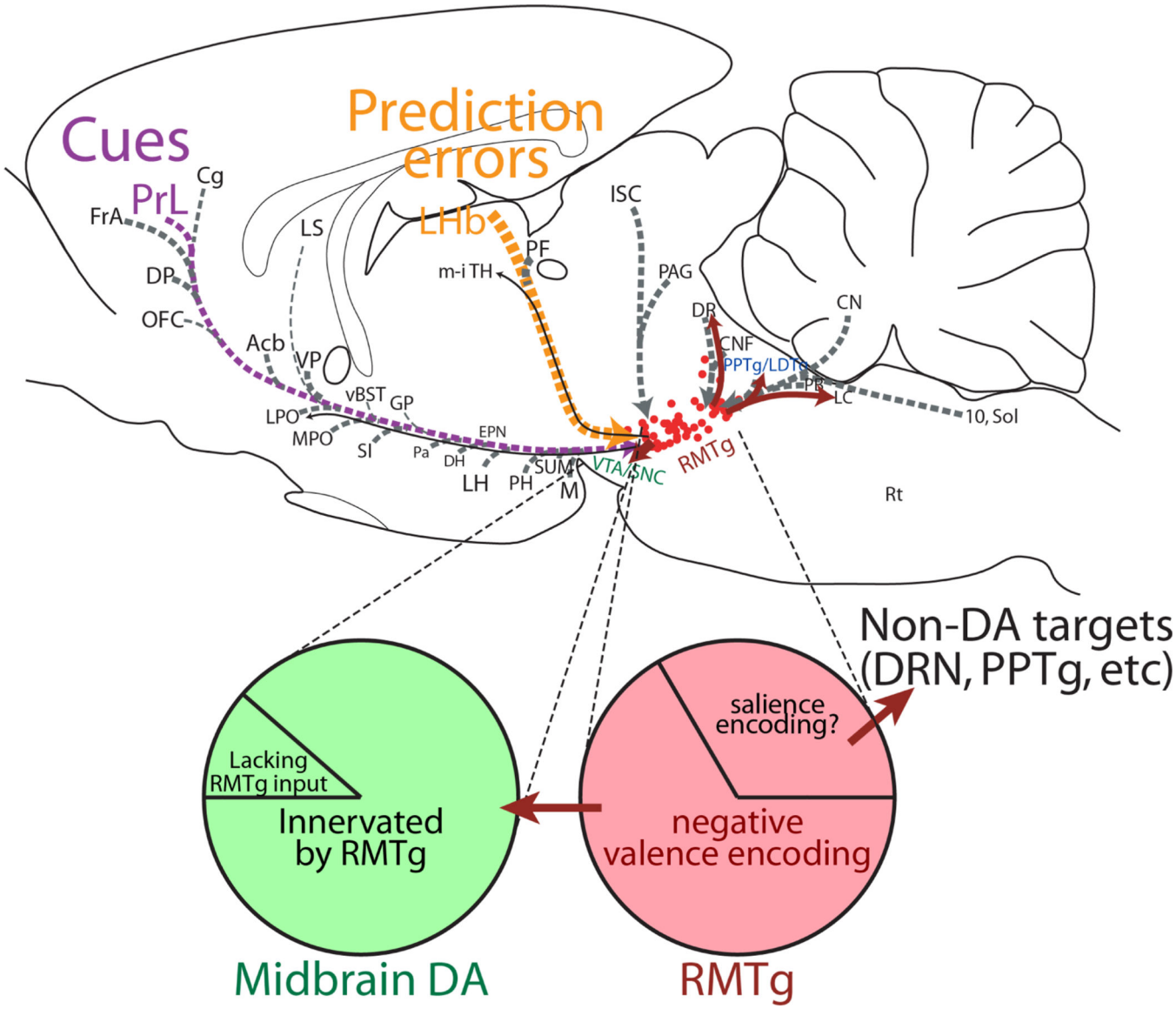

Figure 4.

Sagittal drawing of RMTg efferents (red) and afferents (grey). Afferents with verified electrophysiological influences on RMTg are indicated with colored lines and text: prelimbic cortex (PrL, purple), and lateral habenula (LHb, orange). RMTg and dopamine neuron populations are further dissected in pie chart diagram, showing diversity of neuron subtypes with proportions approximated by areas of pie chart. Roughly one-third of RMTg neurons may project to targets outside the midbrain dopamine system, while a minority of dopamine neurons may lack an RMTg input.

Table 1:

At least six categories of abused drugs strongly influence RMTg activity. Among these, cocaine is the most widely studied, but other drugs, particularly opioids and cannabinoids, appear to have large acute effects. In several cases, activity appears protective against acquisition of drug-seeking, but this topic is overall relatively understudied.

Drug	RMTg neural response:	Relevant receptors	References
Cocaine	Biphasic: reduced firing for several minutes, followed by excitation in some neurons 15–30 min after exposure. Marked cFos seen at 1–2 hours.	CP-AMPARs, 5HT2CR	(Colussi-Mas et al., 2007; Geisler et al., 2008; Jhou et al., 2009; Lavezzi et al., 2010; Jhou et al., 2013; Li et al., 2019; Parrilla-Carrero et al., 2021)
Methamphetamine	Firing rate unknown, but cFos increased at 2 hours.	Unknown.	(Lecca et al., 2011)
Morphine	Large acute reduction in firing. Increased cFos during withdrawal in dependent rats. Morphine blocks RMTg's ability to suppress DA firing.	Mu opioid receptor	(Jalabert et al., 2011; Lecca et al., 2011; Lecca et al., 2012; Kaufling and Aston-Jones, 2015)
Nicotine	Acute increase in firing.	Alpha-7 nicotinic receptors on presynaptic glutamate inputs to RMTg	(Lecca et al., 2011; Castillo-Rolon et al., 2020)
Alcohol	Modest acute firing increase in firing, large cFos increase during withdrawal in dependent rats.	Unknown	(Melis et al., 2014; Glover et al., 2016; Glover et al., 2019)
Cannabinoids	Large acute firing inhibition, also blocks RMTg-induced suppression of DA firing	CB1 receptors on RMTg and presynaptically on its projections to VTA	(Lecca et al., 2011; Lecca et al., 2012; Melis et al., 2014)