



Pallidal circuits for aversive motivation and learning

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The basal ganglia are a group of subcortical nuclei that play a critical role in goal-directed behaviour by setting motivation, adjusting the vigour of actions, and driving reinforcement learning. Detailed knowledge exists of how these nuclei contribute to the different aspects of goal-directed behaviour in the context of reward-seeking, but far less is known about how they work in a framework of avoiding threats. This review will highlight recent work that has begun exploring how the non-motor output of the basal ganglia, from the ventral pallidum (VP) and the habenula-projecting globus pallidus (GPh), are essential in driving the motivation to avoid punishment and the learning from aversive outcomes. We consider the VP and GPh in turn and discuss the circuitry and neural encoding that support their functions, while underscoring the unanswered questions in the field.

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Introduction

A prominent trait of animals is their ability to predict rewards and punishments, and to change their behavior accordingly, such that they can obtain reward and avoid threats. In response to stereotyped rewarding and threatening cues animals display a range of hard-wired species-specific behavioral responses. Equally animals can learn to flexibly adapt their behavior to obtain rewards and avoid threats. The basal ganglia play a key role in flexibly adapting behavior to obtain reward [1–3]. Electrophysiological recordings have identified neurons in the basal ganglia that encode the value of actions [4,5]. These representations develop with learning and are thought to provide the basis for selecting the most valuable action [6–8]. These values are learnt through experience, with

dopaminergic input to the basal ganglia providing a reinforcement signal that strengthens the representation of actions that lead to reward [9,10].

In the case of avoiding threats, it is equally important for animals to flexibly adapt their behavior but the mechanisms that support this are less well known. Evidence is emerging that the basal ganglia are vital for driving the motivation to avoid threats as well as for learning from aversive outcomes. In this review we discuss the evidence that two basal ganglia output nuclei the VP and GPh play complimentary roles in avoiding threats, with a subset of VP neurons driving avoidance behavior by encoding motivational state value and the GPh encoding punishment prediction errors to update action values.

Ventral pallidum

The VP is the major output structure of the ventral basal ganglia [11]. It receives GABAergic projections from the nucleus accumbens (NAc) and transmits information to multiple brain regions involved in motor control and motivation such as the ventral tegmental area (VTA), lateral habenula (LHb), thalamic mediodorsal nucleus and pedunclopontine tegmental nucleus [12]. This connectivity places the VP in an ideal location to transform information about the expected value of stimuli into motivation [13] and has led to proposals that it forms the ‘final common path’ for drug seeking [14] and for reward processing more generally [15]. Indeed, a large body of work, comprehensively reviewed by others [15–17], has identified the VP as a crucial driver of reward-seeking behaviour. For example, the VP is important for the normal hedonic reactions to sucrose [18], and lesions to the VP decrease an animal’s willingness to work for reward [18,19]. Conversely, rats will work to electrically self-stimulate their VP [20,21] and pharmacological activation and disinhibition can both trigger feeding in sated animals [22].

In addition to seeking reward an at least equally important motivational drive is the desire to avoid punishment. Experimental evidence suggests that the VP also plays a role in this motivational processes as pharmacological disruption of intra-VP mu-opioid activity is sufficient to drive conditioned place aversion [23] and activating mu-opioid receptors in the VP can impair conditioned taste avoidance [24]. In a similar manner, disinhibiting the VP through injections of the GABAergic antagonist bicuculline induce anxiety-related behaviours and increase avoidance in an approach/avoidance task in primates [25,26]. Conversely, reducing the glutamatergic input to the VP can reduce anxiety and despair-like behaviours

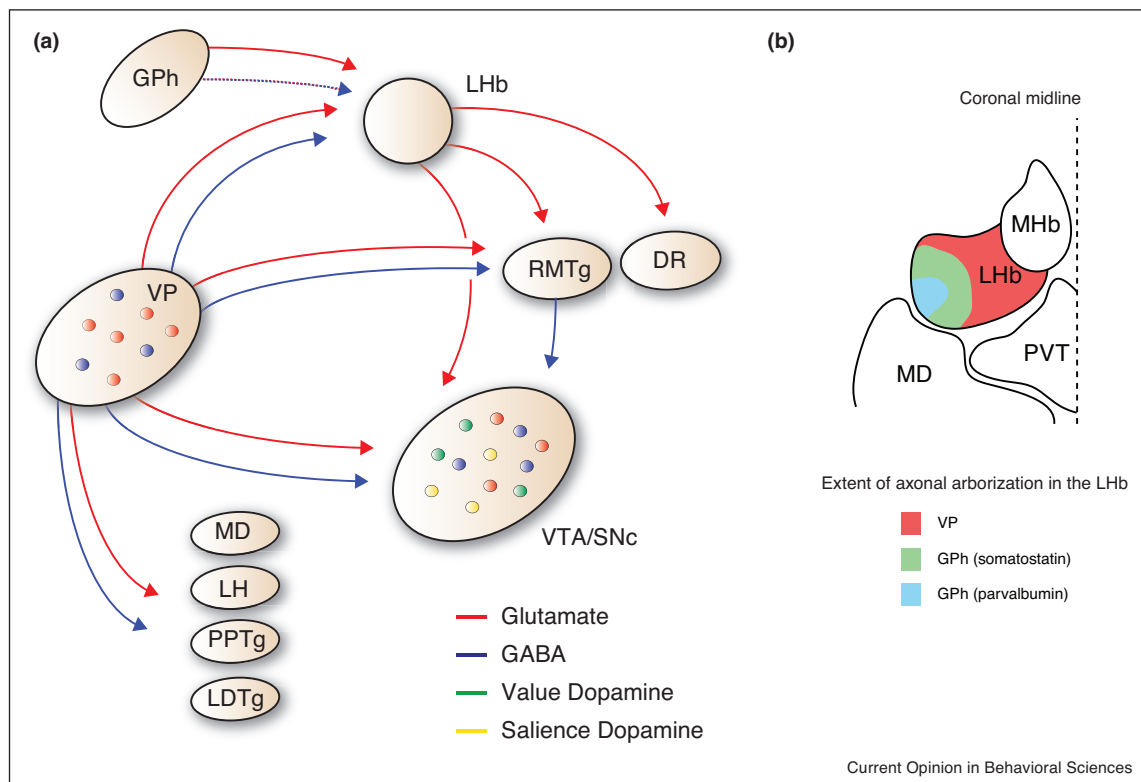
in rats [27]. D1 receptor agonists injected into the VP can also enhance inhibitory avoidance learning [28]. Together this suggests that the VP plays a role in the motivation to both seek reward and avoid punishment.

Theoretical work has suggested that the motivation to obtain reward or the desire to escape a threat are driven by the same process as in both cases the incentive is a positive outcome, that is obtaining reward or safety [29–31]. However, in the case of the VP recent work has shown that approach and avoidance are controlled by genetically distinct populations of neurons. Optogenetic activation of GABAergic neurons in the VP, as with non-specific VP stimulation, can drive self-stimulation and real-time place preference [32**,33**]. In contrast, optogenetic activation of glutamatergic VP neurons has an opposing effect and drives real-time place avoidance [32**,33**]. The glutamatergic VP neurons also adaptively constrain reward seeking as they are necessary for limiting the effort expended to obtain a reward and for learning to avoid sucrose rewards that are paired with nausea inducing lithium chloride [33**]. As the glutamatergic VP neurons can drive avoidance behavior it is possible that

the GABAergic and glutamatergic VP neurons may also work in concert in an aversive setting with the GABAergic neurons adaptively constraining avoidance behavior when there is potential for reward. This suggests that glutamatergic and GABAergic VP populations may encode the drive for approach and avoidance respectively with the balance between their activity determining the overall behavioral strategy.

Interestingly, the projection pattern of these two VP populations is qualitatively similar, suggesting that they exert their motivational effects through opposing roles on common downstream structures (Figure 1). Both the GABAergic and glutamatergic neurons project to the lateral habenula, VTA and rostromedial tegmental nucleus (RMTg) [33**]. Indeed, stimulating the GABAergic or glutamatergic axons in the VTA drives reward or aversive responses respectively [32**]. In contrast, while optogenetic stimulation of the glutamatergic VP terminals in the LHb is aversive [32**,34*] optogenetic stimulation of the GABAergic input to the LHb has not been reported to be rewarding [32**]. In both the LHb and the VTA the GABAergic and glutamatergic neurons make

Figure 1



(a). Schematic of the major GABAergic and glutamatergic projections from the ventral pallidum and the GPh as well as some selected additional circuitry. This schematic highlights the circuitry discussed in the review and is by no means exhaustive. (b). Schematic of the axonal arborization pattern of the VP and the GPh in the LHb. Abbreviations not used in the manuscript: DR, dorsal raphe; LH, lateral hypothalamus; LDTg, laterodorsal tegmental nucleus; MD, mediodorsal thalamus; MHb, medial habenula; PPTg, pedunculopontine tegmental nucleus; PVT, paraventricular thalamus.

synaptic connections with greater than fifty percent of the neurons recorded suggesting that they may synapse on the same population of neurons [32**]. If this is indeed the case it would provide a simple integrative mechanism for downstream targets to determine the balance between the GABAergic and glutamatergic VP activity.

In the VTA the VP glutamatergic projection neurons synapse directly onto both dopaminergic and GABAergic neurons, while the net effect of activating the glutamatergic VP neurons *in vivo* is to excite putative VTA GABA neurons and inhibit putative DA neurons [33**]. This inhibition of dopamine neurons could contribute to the aversive responses driven by the glutamatergic VP input, since optogenetic inhibition of the VTA DA neurons alone induces real-time place avoidance and drives negative prediction error [35,36]. However, the dopaminergic response to glutamatergic VP input is likely more complex. For one, dopamine release increases in a number of brain areas in response to aversive stimuli, including in the dorsal lateral striatum [37], medial prefrontal cortex [38,39], the medial shell of the NAc [40] and the tail of the striatum [41]. In addition, dopaminergic activity is needed for active avoidance, and blocking dopamine receptor activity in the medial shell of the NAc can impair avoidance behaviour and promote passive defensive strategies [29,42]. Therefore, if glutamatergic VP neurons are needed for motivating active avoidance this population cannot simply suppress dopamine. One possibility is that the glutamatergic VP input to the VTA differentially affects subpopulations of dopamine neurons [39,43–45], inhibiting the classic value-coding dopamine neurons, that are inhibited by aversive stimuli, and exciting dopamine neurons that are activated by aversive stimuli. This suggests that aversive and appetitive motivation could be implemented in part by the different target regions that are modulated by dopamine in an appetitive or aversive context.

The aversive nature of the glutamatergic VP input to the VTA may also be mediated by non-dopaminergic neurons in the VTA. Recent experiments have shown that a population of glutamatergic neurons in the VTA project to the medial shell of the NAc and that photoactivation of this pathway drives aversion [46]. This effect is due to excitation of parvalbumin interneurons that in turn inhibit spiny projection neurons in the NAc [46].

Consistent with a role in both appetitive and aversive motivation, *in vivo* recordings in the VP have identified two main types of neurons that are activated by the prediction of either reward or punishment [25,47]. A subset these of VP neurons are active in a sustained manner from the time of a cue predicting a rewarding outcome until the outcome occurs, while a second population are inhibited in a sustained manner in response to appetitive outcomes [19,25,47,48]. While it has not been

demonstrated it is tempting to speculate that these functional classes correspond to the GABAergic and glutamatergic VP neurons. These activity patterns led Hikosaka and colleagues to propose that the VP neurons encode the current value of a given state rather than the difference between the actual and expected values, which is calculated by reward prediction error-coding dopamine neurons [43,47]. Interestingly, such sustained activity in response to reward- and punishment-predictive cues has also been observed in the dorsal raphe [49]. Furthermore, this sustained activity has been observed in optogenetically-identified serotonergic neurons and was shown to change dynamically with the motivational state [50]. This could be driven in part by the VP as the VP projects to the medial portions of the LHB, a region that in turn project strongly to the dorsal raphe [16]. The sustained activity in the VP and dorsal raphe would be useful for maintaining motivation in either a rewarding or aversive setting. Indeed, during reward-seeking the activity of the VP neurons is predictive of response latencies and the vigor of animal behaviour during instrumental tasks [19,47,48].

Another hallmark of VP neuronal activity is that neurons are only excited by reward predictive cues when the available reward is ‘wanted’ [15,26,51]. For example, high concentration salt solutions are normally aversive for rats but when a rat is salt depleted, high salt concentration solutions become appetitive. Correspondingly VP neurons are not activated by cues predicting unpalatable salt solutions but after salt depletion cues gain an incentive value and VP neurons are robustly activated by the prediction of the salt solution [51]. This coding of incentive salience or ‘wanting’ may be encoded by GABAergic VP neurons and raises the possibility that glutamatergic VP neurons in contrast could encode aversive salience. Together the recording data suggests that ventral pallidal neurons dynamically track the incentive and aversive value on both long and short timescales to set the motivational state.

Together there is emerging evidence that the VP plays a fundamental role in driving the motivation to not only seek reward, but to also avoid punishment. These motivational states are driven by GABAergic and glutamatergic neurons, which may encode incentive and aversive state values respectively. It is tempting to speculate that these two populations work together to balance the behavioural requirements, constraining reward seeking when there are risks/costs involved and limiting avoidance behavior when there is potential for reward.

Habenula-projecting globus pallidus (GPh)

Another key aspect of evading threats, in addition to motivating avoidance, is the ability to learn what actions to choose in order to avoid a threat [30,31]. The LHB is an important area of the brain involved in learning from

aversive outcomes [52]. Neurons in this nucleus encode negative prediction errors, such they are phasically excited by the prediction of punishment or when an outcome is worse than expected [53,54]. Activation of the LHB is aversive and can promote negative reinforcement [55] and leads to inhibition of reward prediction error coding dopaminergic neurons through a di-synaptic connection including the RMTg [56,57]. Tian and colleagues showed with lesions of the LHB and *in vivo* recording of dopamine neurons that inhibition of dopamine when an outcome is worse than expected is dependent on the LHB [58]. These dips in dopamine when an outcome is worse than expected are sufficient to drive negative reinforcement [36].

This role in learning from negative outcomes may at least in part be driven by the basal ganglia. The LHB receives a large excitatory projection from basal ganglia output neurons located in the globus pallidus interna (GPi) (also called the entopeduncular nucleus in rodents) [59,60,61,62]. These GPh neurons are located in the rostral two thirds of the GPi in mice and in the border region between the GPi and globus pallidus externa (GPe) in primates [59,63,64]. A subpopulation of GPh neurons encode negative reward prediction error signals and this activity precedes the activity in the LHB [60,63,64]. Optogenetically stimulating the GPh can drive activity in the lateral portion of the LHB and is aversive [61]. In a probabilistic switching task excitation of the GPh is necessary for mice to use negative feedback to guide their decisions [60]. Together this suggests that the GPh is crucial for aversive learning as it drives the activity in the LHB when an outcome is aversive or when it is worse than expected.

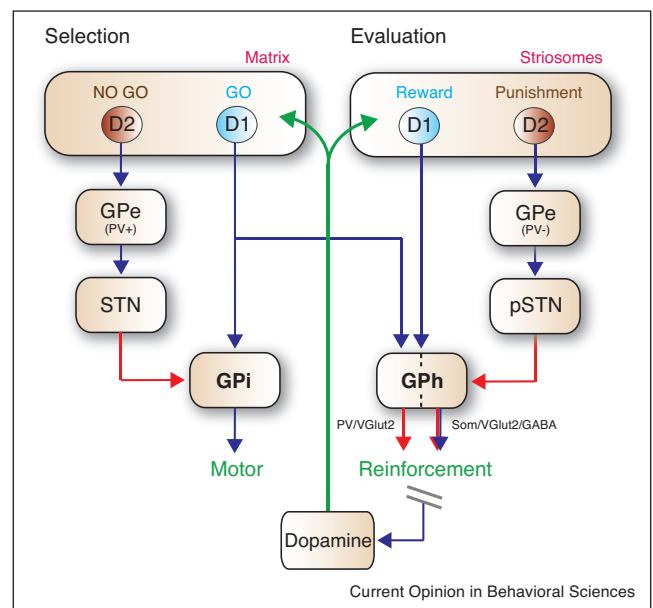
Beyond learning to avoid punishment, the GPh and LHB neurons play a broader role in reinforcement learning. Neurons in both nuclei are also inhibited by the prediction or unexpected delivery of reward [60,63] and optogenetic inhibition of the GPh or inhibition of the LHB is rewarding and can reinforce actions [60,65]. In line with this inactivation of the LHB does not merely impair the processing of aversive information but rather prevents mice from forming a preference between choices with different subjective value [66].

Recent single cell sequencing data has revealed that the GPh is actually composed of two genetically distinct populations [67]. One type of GPh neurons expresses somatostatin and co-releases glutamate and GABA, a second population expresses parvalbumin and are exclusively glutamatergic [67]. Interestingly in primates two functional classes of GPh neurons have also been identified, a reward negative type that bi-directionally encodes prediction errors and a reward positive type that display sustained activation to reward predictive information [63]. How these genetic and functional populations relate

to each other still needs to be determined as does their individual roles in behaviour.

As the GPh bi-directionally responds to cues of opposing valence it suggests the GPh is able to integrate reward and punishment information to evaluate whether an action was better or worse than expected. Indeed cell-type-specific synaptic manipulations in mice have demonstrated that inhibitory and excitatory inputs to the GPh are necessary for mice to appropriately learn from positive and negative feedback, respectively [60]. This suggests that reward and punishment information is encoded in separate circuits upstream of the GPh, with the GPh representing the key point of convergence for information of opposing valence. Rabies tracing from the form the GPh and GPi has demonstrated that the circuits that control the motor output of the basal ganglia are distinct from the circuits that regulate the GPh [60,67] (Figure 2). Both types of GPh neurons receive direct inhibitory input from both striosome and matrix compartments of the striatum, while the GPi receives inhibitory input exclusively from the matrix [60,67]. As GABAergic inputs to the GPh are necessary for processing of positive feedback [60], the direct inhibitory input from the striatum to the GPh may provide the information

Figure 2



Schematic showing the proposed selection and evaluation circuits within the basal ganglia (adapted from Ref. [60]). Here the direct and indirect pathway striosomal neurons are proposed to independently encode reward and punishment information. The information of opposing valence is then integrated in the GPh. For brevity the circuit linking the GPh and the dopaminergic neurons is left out. This circuit contains a projection to the LHB and then direct projection from the LHB to dopaminergic neurons as well as di-synaptic connections to dopamine neurons via the RMTg.

about predicted rewards. One candidate for this inhibition are striosomes as striatal neurons provide direct inhibitory input to the GPh [60^{••},67^{••}] and striosomes have been proposed to play a role in reinforcement learning [68,69]. Indeed, striosomal neurons are crucial for the rewarding effect of opioid drugs [70] and loss of the mu opioid receptors on striosomes prevents both the rewarding effect of morphine and abolishes the induced dopamine release in the NAc [70].

Until recently, directly testing the function of striosomes has been hampered by the lack of methods to specifically target these neurons. The development of non-inducible and embryonically inducible transgenic mouse lines that specifically express GFP or Cre-recombinase in striosomal neurons now permits an investigation of their function [71,72^{••}]. The role of striosomes in encoding predicted rewards was directly tested for the first time in two recent studies, each using *in vivo* calcium imaging but different genetic strategies to specifically record from striosomal neurons. Both studies showed that striosomal neurons encode information about the expected reward that develops with learning [72^{••},73[•]]. Striosome neurons are therefore excellent candidates for inhibiting the GPh when an outcome is predicted to lead to reward.

The best candidates for exciting the GPh when an outcome is aversive or when it is worse than expected are distinct circuits associated with the 'indirect pathway'. The GPi receives excitatory input from the core of the subthalamic nucleus (STN) and input from parvalbumin-positive prototypical GPe neurons [67^{••}]. The GPh receives glutamatergic input from the subthalamic cells located in the 'limbic' region of the STN, on the medial border of this nucleus and in the surrounding parasubthalamic nucleus (pSTN) as well as input from mainly parvalbumin-negative GPe neurons [60^{••},67^{••}] (Figure 2). The pSTN is a good candidate for providing information about negative valence to the GPh as glutamatergic input to GPh neurons is needed for mice to process negative feedback [60^{••}]. Furthermore, a subpopulation of subthalamic cells are activated by aversive outcomes or when an outcome is worse than expected [74]. This suggests information of about predicted rewards and punishments may be carried by the direct and indirect pathway inputs to the GPh respectively. This hypothesis is supported by optogenetic experiments, where stimulating the direct and indirect pathways not only influences movement parameters but also drives reward and punishment respectively [75]. Interestingly predicted punishment activity is also over represented in striosomes as compared to matrix and may be encoded by indirect pathway striosomal neurons [73[•]]. These indirect striosomal neurons could provide the input to the indirect limbic pathway consisting of the PV-ve GPe neurons and the pSTN to convey information about predicted punishment to the GPh (Figure 2).

Together this model suggests that direct and indirect striosomal neurons encode the predicted benefits and costs associated with certain stimuli. This information of opposing valence would then be integrated in the GPh to give the total predicted value of how good or how bad an outcome is expected to be. In line with this hypothesis, individual striosomal neurons independently encode information about predicted rewards or punishments [73[•]]. Furthermore, *et al.* prefrontal cortical inputs to striosomes play a specific role in decision making when there are both costs and benefits associated with particular choices [76[•],77]. The GPh is a likely candidate for where information about costs and benefits is combined to predict the relative value of choices or determine whether the outcome was better or worse than expected.

Conclusion

Theories of avoidance have noted that there are two separate types of learning that occur in active avoidance [29,78–80]. First animals need to learn the value of states so that threatening situations can be predicted and avoided as well as motivating escape if threats are encountered. Second, in case an animal does encounter a threatening situation it needs to learn which actions to choose to escape the threat. Interestingly the VP and the GPh could fulfill these different roles. VP glutamatergic neurons can drive avoidance by encoding negative motivational states. If these neurons not only encode the current state value but also serve as a teaching signal to learn the predicted value of an aversive state, then animals could learn to avoid negative states before encountering a threat. In contrast, GPh neurons encode reward and punishment prediction errors. In classic reinforcement learning models RPE's are used to update the value of actions such that in any given context animals are able to choose the most valuable action [9,81,82]. Indeed, manipulations have shown that RPE signaling in the GPh can bias action selection by updating action values [60^{••}]. In this way if an animal were to avoid a threat, the outcome would be better than expected and the resulting GPh RPE signal could positively reinforce the action that led to the threat being avoided. Taken together, the VP and GPh could have complementary roles in learning, with the VP learning motivational state values and the GPh updating action values. Such a dichotomy may also occur within subpopulations of dopamine neurons as a recent study has shown that VTA and SNc dopaminergic neurons are able to respectively reinforce general motivation or invigorate specific actions [83]. This suggests that the VP and GPh could be nodes of two extended reinforcement systems: one for learning state value and another for learning action value.

Conflict of interest statement

Nothing declared.

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- of special interest
- of outstanding interest

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