

The Basal Ganglia

Caveats. (1) These are my part II notes and I've done little to make them more accessible, so ask me if there are unclear abbreviations or you want references/more info. (2) This is a very active research area – I hope this gives you better insight into the field than the IB course, but many aspects are genuinely unclear and open to several interpretations at present; also, this was the 1996 picture. (3) The diagram seems to have gone horribly wrong, see Kandel & Schwartz (I think) for the original.
RNC, 24 Feb 99.

Segregated loops

	Motor	Oculomotor	Association	Limbic
Cortex	somatosensory cortex primary motor cortex premotor cortex SMA	posterior parietal cortex prefrontal cortex FEF	posterior parietal cortex premotor cortex prefrontal cortex	med. / lat. temporal lobe hippocampus anterior cingulate cortex orbitofrontal cortex
Striatum	putamen	caudate (body)	caudate (head)	ventral striatum caudate (head)
Pallidum	GPi, SNr	GPi, SNr	GPi, SNr	ventral pallidum, GPi, SNr
Thalamus	VL	VA, MD	VA, MD	VA, MD
Cortex	SMA	FEF	prefrontal cortex	anterior cingulate cortex orbitofrontal cortex

Input

- Other important inputs are from the intralaminar thalamic nuclei, DA from the midbrain and serotonin from the midbrain raphe neurons. Note neocortex innervates dorsal striatum, while allocortex innervates ventral striatum.
- Every cortical area has a 'private line' through the neostriatum; the "funnel" metaphor is incorrect.
- Recent work suggests that "the shell of the nucleus accumbens is part of an extended amygdala system while the core resembles more the corpus striatum" (Koob, 1992). This view can be taken too far!

Output

- Dorsal striatal output consists of a '**direct**' path (with excitatory D1 receptors) and an '**indirect**' path (with inhibitory D2 receptors), see figure. **The GPi and SNr have high spontaneous discharge rates:** tonic inhibition of the thalamus. The striatum works by disinhibition; phasic decreases in GPi/SNr discharge gate or facilitate cortically initiated movements. The gating hypothesis is most likely; experimental inhibition of the SNr does not trigger oculomotor saccades, but merely produces a strong tendency to saccade towards the disinhibited place. [Enabling particular movements, controlling their sequencing...] **The GPe also** has a high spontaneous discharge rates, which has the opposite effect. In the ventral striatum, this direct/indirect separation is not so clear. **Striatal output neurons are quiescent** at rest (and, by the way, they are medium spiny neurons).
- Do the direct and indirect pathways project to the same GPi/SNr neurons ('braking' or 'smoothing' the cortical motor pattern) or to different sets (reinforcing the currently selected pattern and suppressing others)?
- In cats and rodents, GPe projects to the reticular nucleus of the thalamus; no such projection exists in primates.

Interneurons

- **ACh** has clinical effects that are generally antagonistic to those of dopamine. This might be because large, ChAT⁺ striatal interneurons preferentially excite the GABA/enkephalin neurons of the indirect pathway.
- There are interactions between D₁ and D₂ striatal neurons. (1) A few neurons may express both receptors. (2) Local axon collaterals between the two populations may exist. (3) Striatal interneurons may mediate the interactions; for example, D₁ striatonigral neurons release SP, which activates cholinergic interneurons that act on D₂ striatopallidal neurons.

Patches and matrix

- The striatum consists of **patches**, rich in μ opiate receptors, neurotensin and AMPA receptors, and **matrix**, rich in AChE, somatostatin and calbindin. The matrix contributes to the main pallido-thalamic circuitry shown above. Cortical neurons in the deep parts of layer 5 and layer 6 project to the patches, while superficial layer 5 and supragranular layer neurons project to the matrix [certainly this is true for dorsal striatum; I expect the ventral striatum is broadly similar]. The patches of the dorsal striatum project mainly to the SNc (dopamine neurons) [feedback modulation of the striatum?] but also to cholinergic neurons in the pallidum, and the patches of the ventral striatum project mainly to the nucleus basalis (cholinergic neurons).¹ Graybiel (1990) states that the patches (striosomes) receive limbic input, as does the ventral striatum. She suggests

¹ The primary neurodegeneration in Huntingdon's disease may involve the patches. This would lead to dysregulation and increased firing of the SNc, causing chorea. There is also an early, selective loss of the GABA/enkephalinergic striatal projection to the GPe. Rigid akinetic signs in advanced HD are associated with loss of GABA/SP neurons projecting to GPi.

that the limbic system may split its striatal projections into a hippocampus–matrix system and an amygdala–patches system; a similar division has been found for the nucleus accumbens. The best summary is in Gerfen (1992).

- Of the midbrain DA cells, the SNc (A9) projects mainly to the patches and A8 (retrosubthalamic n.) projects to the matrix.
- There appear to be ‘matrixomes’ as well as striosomes – modules in the matrix, but little is known about them yet.

Dopamine systems: overview

- Different DA systems (mesocortical², mesolimbic, mesostriatal) have different roles, depending on their target systems. The nigrostriatal system (caudate–putamen) is involved in the activation of behaviour to particular stimuli, particularly those of endogenous origin (PD...); the mesolimbic (VTA, nucleus accumbens) system is involved in incentive motivation. The stereotypy induced by high-dose amphetamine is blocked by 6-OHDA lesions of caudate–putamen, whereas the locomotor hyperactivity induced at lower doses is blocked by similar DA depletion of the nucleus accumbens (“consummatory versus incentive motivational function”). So MFB lesions cause severe aphagia/adipsia because (1) sensorimotor integration is disturbed [dorsal striatum]; (2) incentive motivation properties of primary rewards are disturbed [ventral striatum].

Single unit recording of dopamine neurons (Schultz, 1992)

- Mesencephalic dopamine neurons fire mainly to significant phasic environmental events. Most respond to visual, auditory and somatosensory stimuli, but only in specific behavioural contexts. In any given situation, 50–80% show stereotyped responses to the same stimulus or stimuli while the rest do not fire. Responses consist of a 100–150ms burst at a latency of 60–130ms, regardless of the stimulus. They do not habituate.
- Dopamine neurons respond specifically to primary food/fluid rewards when reward-predicting CSs are absent. They respond to incentive stimuli predicting reward, but this abolishes the response to the primary reward itself: the response is transferred from the primary reward to the CS during learning (and, while recording from the same neuron, when the behavioural task is changed from self-initiated movements with no CS present to stimulus-triggered movements).
- Dopamine neurons also respond to stimuli occurring in association with incentive stimuli and to which animals need to pay attention in order to detect the incentive stimulus. (For example, an empty box opens in random alternation with a food box, in a go–no-go task; this box elicits a response but does not predict reward. Dopamine neurons do not respond when the box opens outside of the task.)
- The responsiveness of dopamine neurons decreases during the performance of well established habits (unlike striatal neurons!). The effect is task-specific. (It is possible that responses of dopamine neurons are particularly important when new behavioural reactions are learned.)
- Dopamine neurons respond to novel and unexpected stimuli, and subside as the orienting reactions do following repeated presentation.
- If the offset of an auditory stimulus predicts reward, none of the dopamine neurons that respond to other incentive stimuli respond to tone offset, though behavioural activation occurs.
- Neuron responses are quite similar in A8, A9 and A10. Exceptions: the medial SNc and the VTA respond more frequently to external stimuli, while the lateral midbrain areas respond more often during movement, and medial neurons respond more than lateral to primary reward during acquisition of a delayed response task.
- **So**, the induction of behavioural reactions is neither a necessary nor a sufficient condition for the activation of dopamine neurons. Neither the receipt of reward nor the prediction of reward are necessary conditions for activating dopamine neurons. Nor are they sufficient (the stimulus offset task, and that dopamine neurons respond little to incentive stimuli after overtraining, though one could argue that overtrained behaviour is driven by a stimulus–response habit rather than by the expectation of reward).
- **Suggested function.** Dopamine systems may be involved in determining the probability and speed of responding to salient stimuli and in motivational arousal. Dopamine neurons respond specifically to salient stimuli that have alerting, arousing and attention-grabbing properties (distinct from the cognitive process of directed/selective attention, which requires a central representation of the target, and distinct from startle responses). Salient stimuli leading to motivational arousal are a large, albeit not comprehensive set of stimuli that activate dopamine neurons.
- **Information carried.** Dopamine neurons fire as a fairly homogeneous group, responding to a stimulus in the same manner or not at all. They respond to the most significant stimuli for the behaviour of the subject in a given situation, determining the probability and intensity of behavioural reactions, the basic measure of motivation. [Note other indications of little information, like 70% of SNc DA cells must die for PD symptoms, exogenous DA fixes things, etc.]
- **Inputs.** Though the striatum projects to dopamine neurons, they respond mostly with longer latencies and without homogeneous and salience-specific characteristics. Short latency, complex excitatory input may arrive from the reticular formation, particularly the nucleus pedunculopontinus.
- **Contradictions.** Whereas PD patients show a reduced speed of movement, only some dopamine neurons are active during the task. Although delayed response tasks are impaired by intracortical dopamine antagonists, and delay-related activity depends on D₁ receptors, dopamine neurons do not show sustained activity during delays. Explanations? (1) A major effect of dopamine appears to be a focusing effect by which postsynaptic structures are restricted to processing of the most prominent input; this function could be enabled by spontaneous dopamine release. (2) Presynaptic influences of cortical input on striatal dopamine varicosities may affect dopamine release phasically. (3) Dopamine released in response to salient stimuli may have long-lasting effects.

² VTA → prefrontal cortex

- **Stress.** Baseline firing rates are little affected by homeostatic challenges or stress. However, stressors can transiently reverse akinetic states produced by striatal dopamine depletion; furthermore, stress increases forebrain dopamine utilization and turnover. One possibility is that stressors affect the presynaptic regulation of dopamine at the terminal by glutamatergic cortical or thalamic afferents, without affecting the firing rate. However, the effects of stress on dopamine function are affected by neuropeptides at the cell bodies, which may differentially modulate the three projection systems. For example, footshocks alter dopamine turnover in prefrontal cortex and nucleus accumbens but not in caudate–putamen, while tail pinch elevates dorsal striatal activity but does not affect prefrontal cortical dopamine. (This may reflect the appropriate avoidance behaviour.) Chronic stressors affect tonic dopamine levels: chronic social isolation in rats elevates dorsal and ventral striatal dopamine but depresses it in the frontal cortex. These animals are hyperactive, perseverative, and have an elevated response to amphetamine, acute stressors and conditioned signals of reward. So the tonic state of the striatal dopamine system may help determine its response to phasic events. Another ref. (Jaskiw & Weinberger, 1992): “in rodents, increased stimulation-induced mesolimbic dopamine release following chronic mild stress is associated with a blunting of the reinforcing properties of rewarding stimuli and has been proposed as an experimental analogue of anhedonia” (seems a bit contradictory!).

Dopamine in the dorsal striatum: evidence

- **Nigrostriatal DA pathway** runs in **medial forebrain bundle** (MFB), through **lateral hypothalamus** (LH). 6-OHDA lesions cause aphagia and adipsia, recovery but residual deficits, hypokinesia and catalepsy, sensory neglect. (LH lesions also cause somnolence, rats are more finicky, deficits in taste aversion learning and thermoregulation, and produce the full syndrome with only 50% DA depletion, whereas 6-OHDA lesions require >90% depletion to cause all these symptoms. So the LH syndrome does involve more than just forebrain DA depletion).
- Unilateral 6-OHDA lesions cause an asymmetric posture (twisted to the side of the lesion) which recovers. At this point **amphetamine-induced rotation** will occur (towards the side of the lesion)³. Note that amphetamine releases DA presynaptically, so more on the intact side. Apomorphine (a direct DA agonist) produces *contralateral* turning (away from the side of the lesion). Ungerstedt’s explanation: DA receptors are made ‘supersensitive’ by DA denervation (an increase in DA receptor number has been found).
- The defect is not a sensory neglect of the contralateral side (Carli *et al.*, 1985), or an inability to complete the movement (reaction time data), but a problem of **initiation** of the movement.
- “A general activational system, turned on to boost behavioural output in certain motivational situations”?

Hypotheses of dorsal striatal function

- The striatum is implicated in motor plasticity (procedural memory, ‘habits’); the striatum contains many NMDA_R.
- The “gain control” that the striatum seems to perform might provide fluctuating activity levels to scale movements in time and space... or as part of a program-selection mechanism. In this context, the competitive queuing models (Houghton & Hartley, 1995) seem particularly relevant.
- The **motor loop** may participate in the preparation, as well as the execution of movement, by producing a ‘**response set**’. Activity in specific cells that is dependent on the environmental context is sustained until a stimulus that triggers movement occurs. Dopamine activity contributes to the speeding of responding that occurs as the animal waits for the signal, but does not drastically affect the precise programming of its responses. Striatal dopamine asymmetry in the rat leads to an exaggeration in preference to use the paw governed by the side with greater dopamine activity. The response set that striatal dopamine contributes to includes several different parameters of responding (which limb, which side of space, what precise instant, probably the force to be applied).
- The **oculomotor loop** appears to operate in producing saccades to attractive and remembered targets, not in reflexive saccades. (Defects seen in PD.)
- **Cognitive functions.** Deficiencies in striatal dopamine may contribute to the problems of establishing and switching set shown by PD patients (e.g. Wisconsin Card Sorting Test). [“Impairment of cognitive processes involved in deciding what to do on the basis of prior concepts in a sequence – one concept of mental action should lead to the next, within an overall cognitive plan.” Similar to the basal ganglia’s motor function; “thought is mental movement without motion”; Marsden, 1992.] PD patients take an excessive time to make the first move in the Tower of London puzzle, but subsequent thinking time is not prolonged (with the motor problems there is also delay of initiation, but subsequent execution of thoughts is normal while motor sequencing is impaired). However, early PD spares the dopamine content of the caudate relative to the putamen, and untreated early PD patients are not impaired at all on the Tower of London task. In multiple system atrophy there is much greater caudate pathology, and here there is no increase in initial thinking time but subsequent thinking time is prolonged. This is the pattern seen in frontal lobe lesions (it’s suggested, of course, that lack of caudate dopamine causes impaired frontal processing). A similar defect may underlie the defects in attentional set shifting and spatial working memory seen in early PD, multiple system atrophy and frontal lesions. However, striatal dopamine has not clearly been shown to be the cause of these problems.

³ Think carefully – this is a bit odd. Lesion LHS, give amphetamine. Should activate striatum on RHS more. Therefore RHS cortex should be activated. Therefore LHS musculature should be more active. Therefore (you’d think) rat should turn to RHS. The fact that it doesn’t implies a problem initiating movements *to the contralateral side* (i.e. motor neglect), not *with the contralateral musculature* – rats with left striatal dopamine depletion are impaired at initiating movements to the right-hand side of space, so they turn left, and this is accentuated by boosting right striatal dopamine. [Checked with BJE, 25 Feb 99.]

- Dorsal striatal dopamine may also contribute to the initial **learning and consolidation of stimulus–response habits** (e.g. depletion considerably impairs acquisition/retention of a visual discrimination task that involved the learning of two decision rules). It appears likely that activity at dopamine receptors after initial training may contribute to the consolidation or strengthening of the learned response (e.g. injecting amphetamine or dopamine agonists into the dorsal striatum after training leads to superior retention of a learned response).

Dopamine in the ventral striatum: evidence

- ICSS is most prominent to the VTA. Beware the interpretation: reward or motor effects? DA neurons probably are not the only mediators of ICSS.
- Dopamine depletion from the ventral striatum does not impair consummatory behaviour (eating, sex) in the presence of primary reinforcers (food, a mate), but it may reduce the incentive motivational properties of those goals (for example, investigative and pre-copulatory, i.e. appetitive, behaviours are reduced).
- Dopamine is released in the ventral striatum in the presence of food, sexual partners and stimuli predictive of them. DA neurons respond to CSs, and then do *not* respond to the US.
- Mesolimbic DA is involved in mediating behaviour controlled by conditioned reinforcers (stimuli that have gained predictive significance through association with primary reward); e.g. amphetamine to ventral striatum enhances control of behaviour by CS, specifically. **Incentive motivation.** Drugs that activate this system somehow facilitate the process whereby reinforcers gain significance.
- The mesolimbic system may also have a role in **attention**: destruction of the dopamine projection to the nucleus accumbens produces a syndrome of perseveration, with reduced distractibility and a decrease in behavioural switching and flexibility. In learning tasks, such animals are impaired at spontaneous alternation, acquisition of spatial habits and difficulty in reversing previously learned habits. A **filter**, gating motivational drives competing for control of behaviour? Why would that be reinforcing? Because attention is necessary for reinforcement?
- By the way, α -flupenthixol is a dopamine antagonist.

Drug addiction

- Mesolimbic DA certainly seems important in stimulant addiction⁴ (self-administration reduced by DA depletion from ventral striatum⁵, amphetamine is self-administered to n. accumbens, cocaine and amphetamine increase extracellular DA in n. accumbens, etc.). Its role in opiate addiction is more controversial. *For* – heroin place preference attenuated by DA depletion from ventral striatum; self-administration of morphine to VTA occurs and this increases VTA firing. *Against* – DA blockers may not lead to compensatory increases in heroin self-administration⁶; Koob *et al.* (1989) found that DA depletion from the ventral striatum doesn't affect heroin self-administration much, while naloxone to the same site does block it; DA depletion from the ventral striatum does block amphetamine/cocaine self-administration while the opiate antagonist has no effect. They argue that stimulant and narcotic reward are both mediated by the ventral striatum, but DA has only a small role in the latter. (Oh, and by the way, ICSS can survive destruction of the mesolimbic DA system, and an established heroin habit survives it too, while cocaine self-administration is severely attenuated.)
- **Opiates and opioids.** Opiate reinforcement is via μ receptors. However, δ -opioid receptors have an important role in opioid motor stimulation that is D_1 -dependent. Note the difference between opiates and opioid peptides. Opioids excite the VTA indirectly (local GABAergic interneurons are inhibited by μ receptors). Opiates relieve pain when applied to the spinal cord by hyperpolarizing cells in the substantia gelatinosa where nociceptive afferents terminate.
- **Aversive effects of drugs.** Withdrawal symptoms are not necessary to account for dependence: (i) self-administration can be maintained at doses that don't cause withdrawal; (ii) self-administration of morphine to VTA does not cause withdrawal on naloxone challenge, whereas (iii) in the **periaqueductal grey**, it does. Locus ceruleus also implicated in opiate withdrawal. (iv) Psychomotor stimulants don't have an obvious physical withdrawal syndrome. On the other hand, Koob *et al.* propose an “opponent motivational process” – a rebound ‘low’ – largely within n. accumbens. Evidence: (i) post-amphetamine/ cocaine depression exists and is linked to depletion of central catecholamines; (ii) intra-accumbens naloxone in morphine-dependent rats produces (a) conditioned place aversion, without physical signs of withdrawal, (b) disruption of an operant baseline of food-rewarded behaviour; (iii) following a cocaine binge, ICSS ‘reward’ thresholds are raised and a place aversion can be conditioned. **Anhedonia?** [Following withdrawal, natural stimuli that once held important motivational power lose it.] Withdrawal from morphine or cocaine results in a profound reduction in VTA activity (the neurons are dependent!).
- Corticosteroids facilitate the acquisition of a speed habit.
- **Incentive-Sensitization Theory of Addiction** (Robinson & Berridge, 1993).
 1. Addictive drugs share the ability to enhance mesotelencephalic dopamine neurotransmission.
 2. One psychological function of this system is to attribute ‘incentive salience’ to representations of events associated with activation of the system. Incentive salience makes a stimulus ‘wanted’.
 3. In some individuals the repeated use of addictive drugs produces incremental neuroadaptations in this system, rendering it increasingly and perhaps permanently hypersensitive (‘sensitized’) to drugs and drug-associated stimuli. The sensitization of dopamine systems is gated by associative learning, which causes excessive incentive salience to

⁴ Note also that dorsal striatal dopamine may facilitate the attentional-motor systems for approach behaviour.

⁵ In particular, D_1 receptors in the nucleus accumbens may be particularly important for the reinforcing properties of cocaine.

⁶ Hmm. I think the incentive-sensitization theory would predict this!

be attributed to the act of drug taking and to stimuli associated with drug taking. It is the sensitization of incentive salience that transforms 'wanting' into 'craving'.

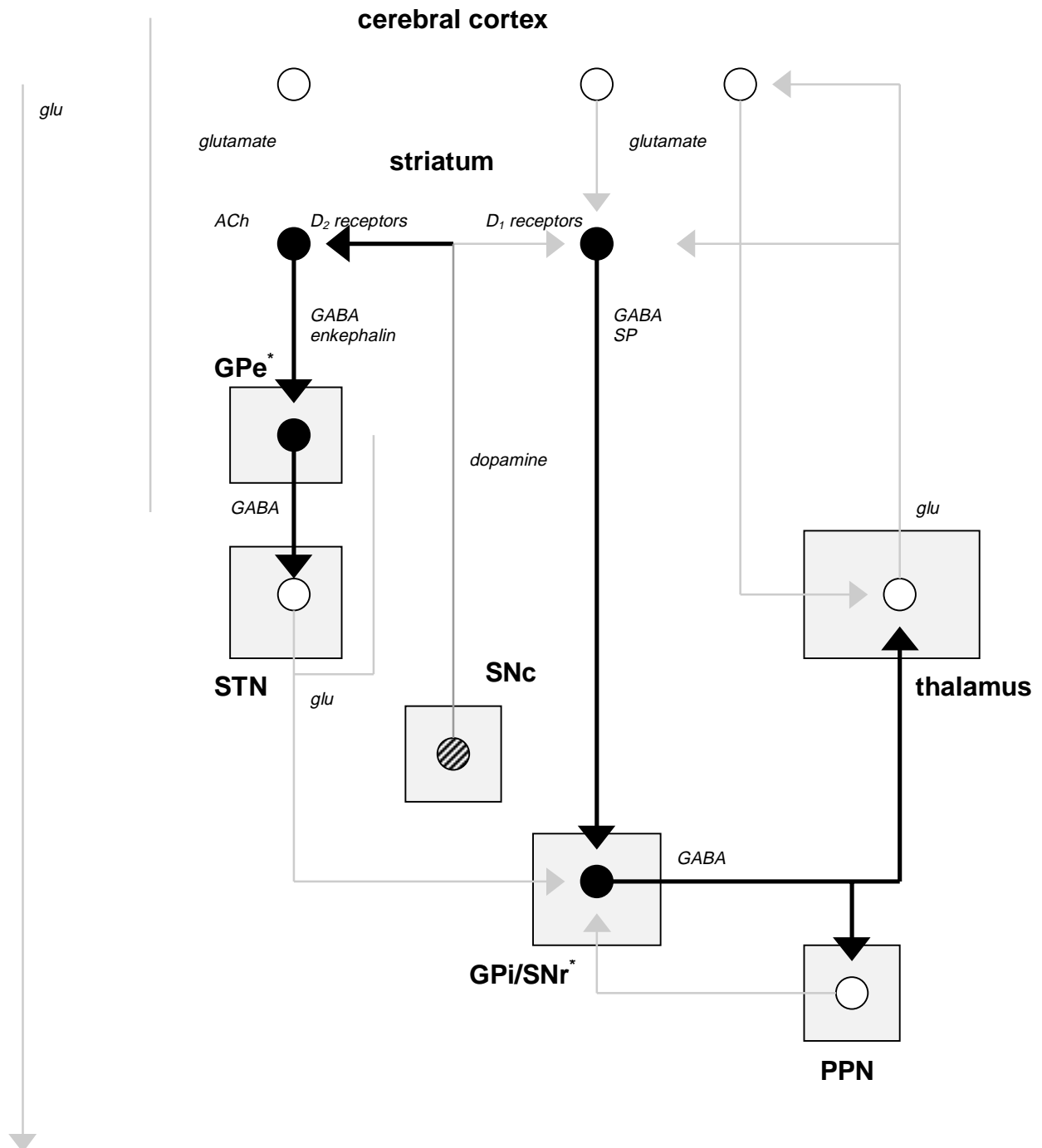
4. Sensitization of the neural systems responsible for incentive salience ('wanting') can occur independently of changes in neural systems that mediate subjective pleasure ('liking') and of neural systems that mediate withdrawal.

- ◇ Negative reinforcement theories of addiction: escape from distress. *Problems:*
 - * people and animals self-administer opioids in the absence of withdrawal or physical dependence
 - * maximal periods of self-administration do not coincide with periods of maximum withdrawal distress
 - * many drugs which produce withdrawal symptoms are not self-administered (e.g. tricyclic antidepressants, anticholinergics, κ -opioid agonists)
 - * relief of withdrawal is minimally effective in treating addiction
 - * there is a high tendency to relapse, even after withdrawal symptoms have subsided
 - * craving for some drugs (cocaine) is highest immediately after drug administration (withdrawal symptoms weakest)
 - * animals will self-administer drugs that do not produce withdrawal; infusion of these drugs can 'prime' or reinstate responding in animals in which responding has been eliminated.
- ◇ Positive reinforcement theories: pleasure seeking. *Problems:*
 - * Poor relationship between euphoric and addictive properties of drugs. Addiction can persist while drug euphoria diminishes and the consequences of drug use are highly unpleasant (social, emotional).
 - * Theory doesn't adequately explain drug craving or relapse elicited by environmental stimuli associated with drug taking. Reports of 'conditioned highs' are rare. A 'cognitive memory of past pleasure' explains this but fails to explain why addicts manage months or years of abstinence, for they certainly think of drugs in that time.
 - * addicts will reliably choose and work for stimulant and narcotic drugs despite being consciously unable to discriminate them from the vehicle, i.e. in the absence of subjective pleasure. (Lamb *et al.*)
- ◇ More supporting evidence... Behavioural sensitization is seen to many drugs, as is cross-sensitization between drugs and between drugs and stress (e.g. stress facilitates acquiring a speed habit). Behavioural sensitization is accompanied by increases in mesotelencephalic dopamine activity, and by increased postsynaptic sensitivity in the nucleus accumbens. This sensitization can last for at least a year in rats (lifespan 3y). The sensitization is amenable to conditioned stimulus control (p259). The proposed sensitization will enhance vulnerability to addiction, both to the drugs themselves and to conditioned reinforcers.
- ◇ Incentive motivation directed towards particular stimuli is the result of a three-stage process (p280). First, the neural substrates for pleasure are activated by the consequences of a particular act or event. Second, pleasure is associated with stimuli by associative learning. Third, salience is attributed to subsequent perceptions/mental representations of the stimuli (incentive salience, involving dopamine). Incentive salience assigned to CSs is 'boosted' when paired again with salience activation (block of this, as by neuroleptics, leads to 'extinction mimicry' or decay of incentive value.
- ◇ A query: negative reinforcement. Dopamine "does not seem to be critical for associative learning, i.e. for forming stimulus-stimulus associations" (p262). Dopamine antagonists do not block learning of associations between a stimulus and electric shock. Dopamine neurons are activated by pleasant and unpleasant significant stimuli. But I'm unclear on the role of incentive motivation in negative situations (because I'm unclear on its nature: approach? attention?).

Hypotheses of ventral striatal function

- Stimuli associated with primary goals gain **incentive value** because they predict those goals. Mesolimbic dopamine subserves this specific behavioural function by promoting appetitive behaviour in the presence of both conditioned and unconditioned incentive stimuli. (Contrast the flexible appetitive behaviours that serve to bring the animal into contact with the goal, with the later consummatory behaviours dependent on the dorsal striatum.)
- The association of stimuli with primary reward presumably depends on higher-order associative processes known to occur in the limbic forebrain. The **mesolimbic DA system mediates the control of behaviour by conditioned reinforcers** ("the activating effects of reward"). The potentiative effect of ventral striatal DA release on behaviour controlled by conditioned reinforcers is greatly diminished by lesions to limbic afferents, particularly the **basolateral amygdala**.

Basal ganglia circuitry



brainstem
spinal cord

*GPi/SNr and GPe fire tonically.
Striatum is normally quiescent.

excitatory

inhibitory

Patches (striosomes) and matrix, not shown above

Matrix receives sensorimotor input and projects to the pallidum as shown.

Patches receive limbic input.

Dorsal striatal patches project to the SNc and/or its immediate surrounds. Ventral striatal patches project to the NBM.

Of the midbrain DA cells, the SNc (A9) projects mainly to the patches and A8 (retrosubthalamic n.) projects to the matrix.

There is probably dendritic release of dopamine from SNc to SNr.

There appear to be 'matrixsomes' as well as striosomes – modules in the matrix, but little is known about them yet.