Special issue paper

Impulsivity and apathy in Parkinson's disease

Nihal Sinha[1,2,3], Sanjay Manohar[1,2,3] and Masud Husain[1,2,3]*

[1]Nuffield Department of Clinical Neurosciences and Department of Experimental Psychology, Oxford University, Oxford, UK
[2]Institute of Cognitive Neuroscience, University College London, UK
[3]Institute of Neurology, University College London, UK

Impulse control disorders (ICDs) and apathy are recognized as two important neuropsychiatric syndromes associated with Parkinson's disease (PD), but as yet we understand very little about the cognitive mechanisms underlying them. Here, we review emerging findings, from both human and animal studies, that suggest that impulsivity and apathy are opposite extremes of a dopamine-dependent spectrum of motivated decision making. We first argue that there is strong support for a hypodopaminergic state in PD patients with apathy, as well as for an association between dopamine therapy and development of ICDs. However, there is little evidence for a clear dose-response relationship, and great heterogeneity of findings. We argue that dopaminergic state on its own is an insufficient explanation, and suggest instead that there is now substantial evidence that both apathy and impulsivity are in fact multi-dimensional syndromes, with separate, dissociable mechanisms underlying their 'surface' manifestations. Some of these mechanisms might be dopamine-dependent. According to this view, individuals diagnosed as impulsive or apathetic may have very different mechanisms underlying their clinical states. We propose that impulsivity and apathy can arise from dissociable deficits in option generation, option selection, action initiation or inhibition and learning. Review of the behavioural and neurobiological evidence leads us to a new conceptual framework that might help understand the variety of functional deficits seen in PD.

Apathy and impulsivity are two debilitating neuropsychiatric syndromes that commonly occur in Parkinson's Disease (PD; Oguru, Tachibana, Toda, Okuda, & Oka, 2010; Voon, Sohr *et al.*, 2011). Recently, it has been proposed that these conditions exist at opposite extremes of a spectrum of motivated behaviour dependent on dopaminergic dysfunction (Volkmann, Daniels, & Witt, 2010; Voon, Mehta, & Hallett, 2011). Specifically, impulsivity is interpreted as a *hyper*dopaminergic state within cortico-striatal systems, whereas apathy is viewed as a *hypo*dopaminergic state in this circuit. However, there is now substantial evidence that both conditions are in fact multi-dimensional syndromes, with

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Correspondence should be addressed to Masud Husain, Nuffield Department of Clinical Neurosciences and Department Experimental Psychology, Oxford University, Oxford OX3 9DU, UK (e-mail: masud.husain@ndcn.ox.ac.uk).

separate, dissociable mechanisms underlying their 'surface' manifestations. Such a conceptual framework questions whether there exists a single axis stretching between two extremes of global impulsivity and apathy. Here, we consider the evidence for the view that these conditions are multi-dimensional, and ask which specific dimensions of impulsive and apathetic decision making might be modulated by dopamine and which are dysfunctional in PD. But we start briefly by considering how impulsivity and apathy have been defined to clarify some current difficulties with interpretation.

Defining impulsivity and apathy is not straightforward

A simple definition of impulsivity is the tendency to act prematurely without forethought (Dalley, Everitt, & Robbins, 2011), whereas apathy is a reduction in self-generated, purposeful behaviour (Levy & Dubois, 2006). Clearly, from these definitions, impulsivity will be observed as excessive action and apathy as reduction in action. However, such broad definitions provide little explanatory power and could reflect very diverse underlying mechanisms. More specific definitions of impulsivity tend to differ widely according to the behaviour under investigation: acting without gathering sufficient evidence, inability to wait, preference for immediate over delayed rewards, risk seeking, inability to inhibit actions and preference for novel stimuli (Basar *et al.*, 2010; Dalley *et al.*, 2011).

Clinical studies, in contrast, classify individuals using either self-report questionnaires or diagnostic criteria. Questionnaires include the Barratt Impulsiveness Questionnaire (BIS-11, Patton, Stanford, & Barratt, 1995), which importantly is multi-dimensional with subscales for attention, motor, self-control, cognitive complexity, perseverance, and cognitive instability. By contrast, diagnostic criteria flag the presence of specific behaviours in the classification of 'impulse control disorders' (ICDs). The prevalence of ICDs in PD is ~13%, and includes pathological gambling (5%), hypersexuality (3.5%), binge eating (4.3%), compulsive shopping (5.7%), hoarding, and kleptomania (Weintraub, Koester *et al.*, 2010). At present, the only ICD included in the Diagnostic and Statistical Manual IV is pathological gambling, which requires the presence of 5 of 10 features (see Table 1).

Apathy, in contrast, does not yet have DSM-IV criteria. It has been considered to be a syndrome consisting of loss of motivation not attributable to disturbances in emotion, intellect, or consciousness (Marin, 1991). Subsequently, a range of instruments for diagnosis have been proposed including the Apathy Evaluation Scale (Marin, Biedrzycki, & Firinciogullari, 1991), Lille Apathy Rating Scale (LARS; Sockeel *et al.*, 2006), and the Apathy Scale (Starkstein *et al.*, 1992) which is specifically validated in PD (Leentjens *et al.*, 2008). Other widely used scales also document apathy such as the Neuropsychiatric Inventory (Cummings, 1997) and item 4 of the Unified Parkinson's Disease Rating Scale (UPDRS). More recently, apathy has been defined as a disorder of motivation with reduced self-initiated and responsive behaviour, thought, or emotion that persists over time and meets the requirements listed in Table 1, now validated for use in PD (Robert *et al.*, 2009; Drijgers, Dujardin, Reijnders, Defebvre, & Leentjens, 2010; but see Starkstein, 2012 for criticism). Note that this allows for dissociable types of apathy according to different domains or axes, defined in this system as 'behavioural', 'cognitive' and 'emotional' (Table 1).

The frequency of apathy reported in PD varies from 7% to 70% (Drijgers *et al.*, 2010; Dujardin *et al.*, 2007; Kirsch-Darrow *et al.*, 2006; Oguru *et al.*, 2010; Pedersen, Larsen, Alves, & Aarsland, 2009; Sockeel *et al.*, 2006; Starkstein *et al.*, 2009). This wide variability arises from the use of different criteria, as well as differences in severity of PD and incidence of co-existing depression in different studies. Up to 36% of patients with apathy

Table 1. Comparison of criteria used to diagnosis apathy and two impulsive control disorders – pathological gambling and compulsive shopping

Diagnostic criteria for apathy (Robert *et al.*, 2010)	Diagnostic criteria for pathological gambling (DSM-IV)
For a diagnosis of Apathy, the patient should fulfil the criteria A, B, C, and D A) Loss of or diminished motivation in comparison with the patient's previous level of functioning and which is not consistent with his age or culture. These changes in motivation may be reported by the patient himself or by the observations of others B) Presence of at least one symptom in at least two of the three following domains for a period of at least four weeks and present most of the time *Domain B1 – Behaviour:* Loss of, or diminished, goal-directed behaviour as evidence by at least one of the following: Initiation symptom: loss of self-initiated behaviour (e.g., starting conversation, doing basic tasks of day-to-day living, seeking social activities, communication choices) Responsiveness symptoms: loss of environment-stimulated behaviour (e.g., responding to conversation, participating social activities) *Domain B2 – Cognition:* Loss of, or diminished, goal-directed cognitive activity as evidenced by at least one of the following: Initiation symptom: loss of spontaneous ideas and curiosity for routine and new events (i.e., challenging tasks, recent news, social opportunities, personal/family and social affairs) Responsiveness symptoms: loss of environment-stimulated ideas and curiosity for routine and new events (i.e., in the person's residence, neighbourhood or community)	A) Persistent and recurrent maladaptive gambling behaviour as indicated by five (or more) of the following: 1. Is preoccupied with gambling (e.g., preoccupied with reliving past gambling experiences, handicapping or planning the next venture, or thinking of ways to get money with which to gamble) 2. Needs to gamble with increasing amounts of money to achieve the desired excitement 3. Has repeated unsuccessful efforts to control, cut back, or stop gambling, is restless or irritable when attempting to cut down or stop gambling 4. Gambles as a way of escaping from problems or of relieving a dysphonic mood (e.g., feelings of helplessness, guilt, anxiety, depression) 5. After losing money gambling, often returns another day to get even ("chasing" one's losses) 6. Lies to family members, therapist, or others to conceal the extent of involvement with gambling 7. Has committed illegal acts such as forgery, fraud, theft, or embezzlement to finance gambling 8. Has jeopardized or lost a significant relationship, job, or educational or career opportunity because of gambling 9. Relies on others to provide money to relieve a desperate financial situation caused by gambling B) The gambling behaviour is not better accounted for by a Manic Episode **Diagnostic criteria for compulsive buying (McElroy *et al.*, 1994)** A) Maladaptive preoccupation with buying or shopping, or maladaptive buying or shopping impulses or behaviour, as indicated by at least one of the following:

Continued.

Table 1. (*Continued*)

Diagnostic criteria for apathy (Robert *et al.*, 2010)	Diagnostic criteria for pathological gambling (DSM-IV)
Domain B3 – Emotion: Loss of, or diminished, spontaneous emotion, observed or self-reported (e.g., subjective feeling of weak or absent emotions, or observation by others of a blunted affect) Responsiveness symptoms: loss of emotional responsiveness to positive or negative stimuli or events (e.g., observers-reports of unchanging affect, or of little emotional reaction to exciting events, personal loss, serious illness, emotional-laden news) C) These symptoms (A–B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning D) The symptoms (A–B) are not exclusively explained or due to physical disabilities (e.g., blindness and loss of hearing), to motor disabilities, to diminished level of consciousness, or to the direct physiological effects of a substance (e.g., drug of abuse, a medication)	1. Frequent preoccupation with buying or impulses to buy that is/are experienced as irresistible, intrusive, and/or senseless 2. Frequent buying of more than can be afforded, frequent buying of items that are not needed or shopping for longer periods of time than intended B) The buying preoccupations, impulses, or behaviours cause marked distress, are time-consuming, significantly interfere with social or occupational functioning, or result in financial problems (e.g., indebtedness or bankruptcy) C) The excessive buying or shopping behaviour does not occur exclusively during periods of hypomania or mania

are also depressed (Drijgers *et al.*, 2010), with development of apathy being increased in individuals with depression and dementia (Pedersen *et al.*, 2009). Although apathy is dissociable from both these conditions, including in PD (Kirsch-Darrow, Marsiske, Okun, Bauer, & Bowers, 2011; Leroi, Pantula, McDonald, & Harbishettar, 2012), their co-occurrence raises the question of shared neural substrates, and may often cloud clinical diagnosis (Bogart, 2011).

In summary, it is now acknowledged that both impulsivity and apathy can manifest in different ways. These considerations suggest that clinical diagnoses do *not* define a single spectrum ranging from apathy at one extreme to impulsivity at the other. Recognition that some neurological patients, including those with PD, can display elements of both conditions (Leroi, Andrews, McDonald, Harbishettar, Elliott, *et al.*, 2012; Rosenblatt, 2007; Voon *et al.*, 2011) also suggests that a single axis of dysfunction might be too simplistic.

Apathy and impulsivity in PD: Evidence for the role of dopamine at a syndromic level

Is dopamine the critical factor controlling impulsivity and apathy in PD? If ICDs occur due to a hyperdopaminergic state, then giving exogenous dopamine would be expected to cause ICDs. Indeed, treatment with dopamine agonists is now recognized as the strongest risk factor for ICDs in PD (Driver-Dunckley, Samanta, & Stacy, 2003; Grosset *et al.*, 2006; Voon *et al.*, 2006; Weintraub *et al.*, 2006), while l-dopa may confer an independent risk (Weintraub, Koester *et al.*, 2010; but see Grosset, Cardoso, & Lees, 2011). ICDs typically develop a few months after initiating dopamine agonists, suggesting that either duration of treatment or cumulative dosage is critical (Evans, Strafella, Weintraub, & Stacy, 2009; Voon *et al.*, 2006). Furthermore, when dopamine agonists were discontinued in patients undergoing subthalamic nucleus deep brain stimulation (STN DBS), ICDs fell from 27% to zero over a year (Thobois *et al.*, 2010).

In contrast, if dopamine deficiency is critical for apathy, we might expect it to occur in early, untreated PD. Consistent with this prediction, apathy is found in >11% of early, untreated PD patients (Aarsland *et al.*, 2009). However, there is no simple correlation between apathy and motor deficits (Dujardin *et al.*, 2007). This lack of an association is not straightforward to interpret, however, as considerable evidence (reviewed later) points to the existence of distinct cortico-striatal circuits for motor and cognitive functions, which are differentially affected at different disease stages.

A few case series have also demonstrated that dopaminergic drugs may reduce apathy (see Czernecki *et al.*, 2002), and in a large meta-analysis, pramipexole improved motivational apathy indexed by item 4 of UPDRS (Leentjens *et al.*, 2009). Moreover, cholinergic, serotoninergic, or noradrenergic drugs have not been shown to improve apathy (Grace, Amick, & Friedman, 2009; Levin, 2007; Weintraub, Mavandadi *et al.*, 2010). It is harder to find evidence that reducing dopaminergic treatment increases apathy. After STN DBS, a significant reduction in dopaminergic therapy is mandatory (Kempster *et al.*, 2007). Eleven case series have now reported increased apathy after DBS (Funkiewiez, 2004; Volkmann *et al.*, 2010). Yet, several others have failed to find direct evidence (Drapier *et al.*, 2006; Kirsch-Darrow *et al.*, 2011; Le Jeune *et al.*, 2009; Thobois *et al.*, 2010). One way to reconcile these conflicting data involves considering underlying, neurobiological individual differences between patients (Thobois *et al.*, 2010), an issue which we discuss later.

A very recent study (Leroi *et al.*, 2012) is the first to directly compare both apathy and ICDs in PD. Apathy was associated with lower dopamine agonist use, older age of disease

onset, and higher levels of depression. ICDs were associated with a complementary pattern: higher overall dopamine intake, younger age, with higher levels of anxiety and greater motor complexity (fluctuations, dystonia, freezing). Furthermore, there is now clear evidence that PD ICD patients have altered brain states – either at rest, in response to dopaminergic challenge or to reward cues – compared with controls (Cilia *et al.*, 2011; Frosini *et al.*, 2010; O'Sullivan *et al.*, 2011; Steeves *et al.*, 2009; Van Eimeren *et al.*, 2010). Overall, these findings support the role of a hyperdopaminergic state in ICDs and a hypodopaminergic state in apathy.

Behavioural and neurobiological evidence: Towards a multi-dimensional spectrum

The studies discussed so far have used qualitative, subjective measures to diagnose apathy and ICDs. One possible reason why these data do not support a dose-response relationship for dopamine in impulsivity and apathy is that only some components of these syndromes might be dopamine-dependent. To dissect out these components, behavioural experimental measures – rather than questionnaire or clinical ones – have been used. These have the potential advantage of being more objective and quantifiable. Importantly, some of them also have direct analogues in the animal experimental literature, and can be used in conjunction with neuroimaging to relate brain structures to specific neurobiological mechanisms.

Perhaps the strongest evidence for the existence of dissociable neurobiological components of impulsivity comes from lesions in rats. For example, STN lesions cause impaired cancellation of planned responses ('stopping'), but do not affect premature responding in a waiting task, whereas lesions to the core of the nucleus accumbens (NAc) show the opposite pattern (Eagle, Bari, & Robbins, 2008). Findings such as these have raised the possibility that impulsivity might be multi-dimensional (Basar *et al.*, 2010; Dalley *et al.*, 2011). Here, for the sake of ease of exposition, we conceptualize motivated decision making as occurring in different stages, based on experimental findings in animals (Figure 1; see Kalis, Mojzisch, Schweizer, & Kaiser, 2008) including:

- option generation (first column, Figure 1)
- option selection (second column, Figure 1)
- action initiation and inhibition (third column, Figure 1)
- learning (fourth column, Figure 1)

In reality, of course, these processes might occur in parallel. Nevertheless, for the purposes of developing an accessible conceptual framework, we consider each in turn. We suggest several different, empirically dissociable components of impulsivity and apathy that might lie at different ends of different, conceptually distinct cognitive axes (Figure 2). We envisage that normally optimal function is centred along each of these axes. However, in a labile environment, it might be adaptive for an animal to become more exploratory and sample their surroundings more widely, even if there is a risk of poor returns. Thus, there might be a shift towards the right of the axes shown in Figure 2. However, in more stable situations, it might be better to alter decision making towards the other extreme (leftwards on these axes), so that behaviour is geared to exploiting – making the most of – what the environment has to offer.

Each of these axes might also be differentially vulnerable to alteration by neurodegeneration that occurs in PD. Thus, impulsive behaviour might arise from rightward shifts along
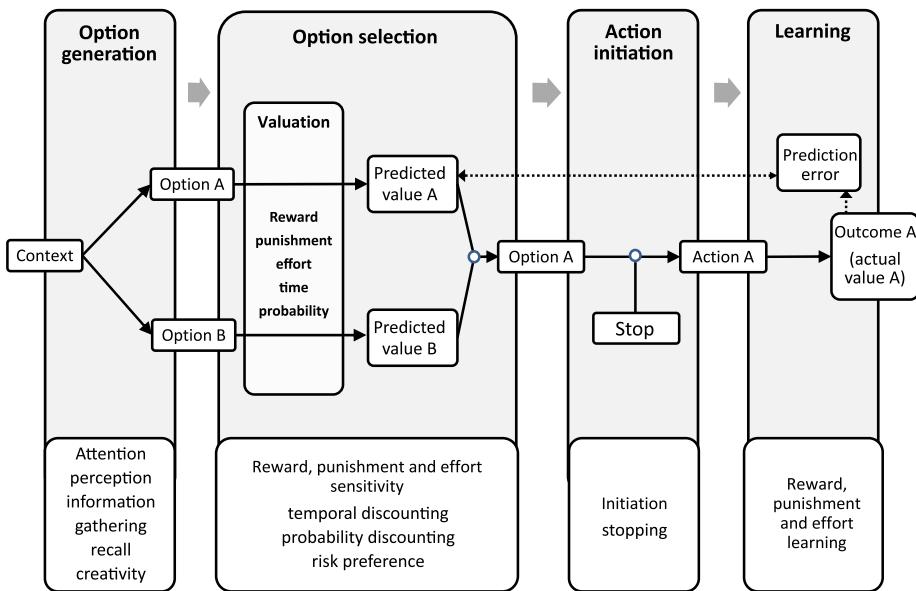
Figure 1. Highly schematic depiction of processes involved in motivated behaviour implicated in impulsivity and apathy. Animals and humans use, among other things, perceptual and attentional mechanisms to generate possible behavioural options. These options are then valued and compared based on features including predicted reward, punishment, effort required, time involved to outcome delivery, and probability of outcome. Following such option selection, the chosen option is then linked to the appropriate action – but critically, actions can also be cancelled by signals arriving from a change in context, for example, changes in the environment, which might mean that a behaviour is no longer optimal. Finally, the outcomes of motivated behaviours are compared with predictions made prior to making these actions. Such comparisons play a key part of learning and feeding back on option selection mechanisms. There is evidence that each of these processes might be modulated by dopamine. (Developed from Kalis *et al.*, 2008).

any one or more of these axes, without any change in the environment, leading to different manifestations of impulsivity (see rightward ends of axes in Figure 2). In contrast, different manifestations of apathy might arise from shifts in the opposite direction, again without any alteration in the external world (see leftward ends of axes in Figure 2). As we shall see below, dopamine levels might modulate such shifts of decision making in PD, at least for some of these axes. Finally, although these axes are shown as independent in Figure 2, it is possible – perhaps even likely – that in reality, they interact (Niv, Daw, Joel, & Dayan, 2007).

In PD, motor deficits result from degeneration of dopaminergic neurons in the substantia nigra, which project predominantly to dorsal striatum. The traditional model of how basal ganglia dysfunction results in motor deficits proposes competing activity between direct and indirect pathways (see Figure 3). However, the aetiology of cognitive and motivational deficits in PD is less clear. Early accounts emphasized cortical degeneration. However, the failure to find a correlation between cortical Lewy body deposition, the pathological hallmark of PD, and severity of cognitive impairment (Parkkinen, Kauppinen, Pirttilä, Autere, & Alafuzoff, 2005; Weisman *et al.*, 2007) suggest that other mechanisms are likely to be important.

Substantial evidence from human and animal research now implicates the striatum itself in cognitive processes such as option selection, action initiation, and inhibition.
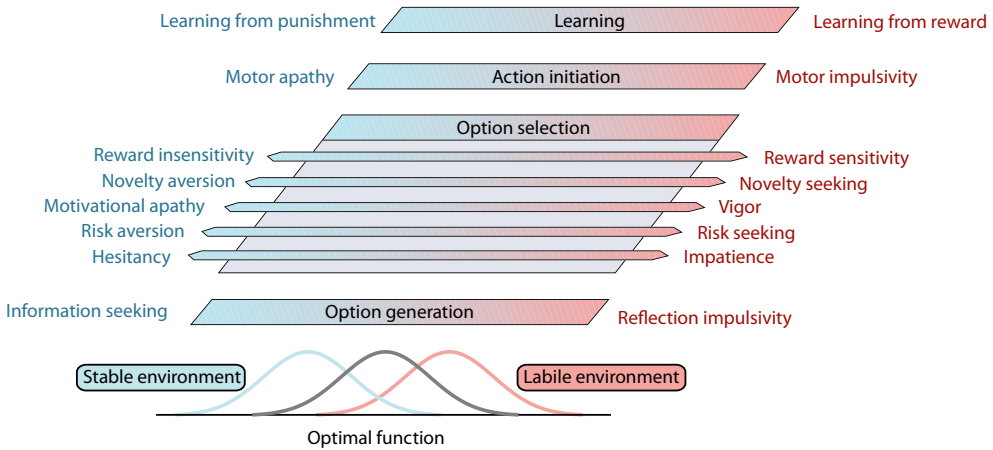
Figure 2. Hypothetical relationships between distinct facets of impulsivity and apathy. This schematic illustrates how dysfunction resulting in impulsive and apathetic behaviours can occur at multiple levels of processing, often leading to superficially similar behavioural phenotypes. Optimal function along each axis will be in part determined by the behavioural context at a given point in time, for example, whether opportunities for rewards are likely to remain stable for the immediate future, or whether their availability is highly time-sensitive. This schematic is not meant to be exhaustive, but serves to illustrate the principle.
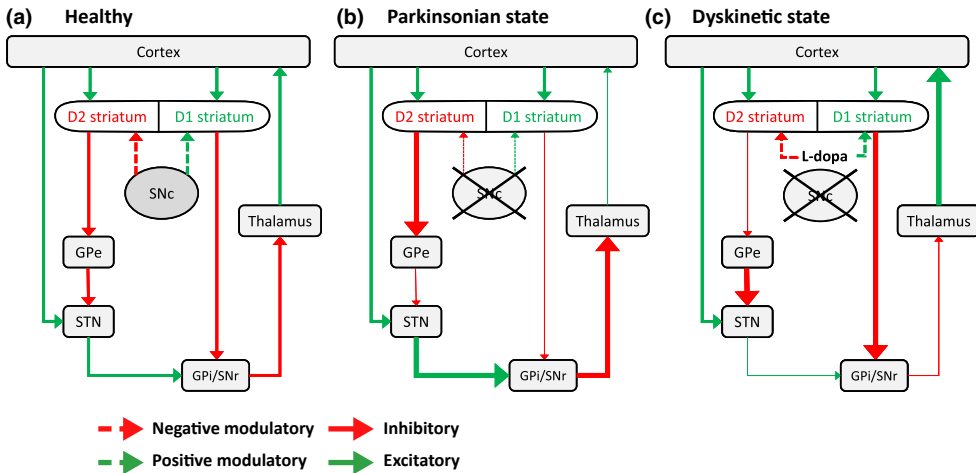
Figure 3. Classical model of basal ganglia pathophysiology in healthy, Parkinsonian, and dyskinetic states. The input to BG is from most cortical areas. Output is via GPi/SNr, which provides inhibitory input to the thalamus. The direct pathway expresses D1 receptors while the indirect pathway expresses D2 receptors. In health, GPi output is modulated by competing influences from both direct and indirect pathways. In Parkinson's Disease, death of SNc neurons results in overactivity in the indirect pathway and underactivity in the direct pathway leading to heightened GPi output. The converse pattern is thought to account for dyskinesia induced by l-dopa therapy. Adapted from Rodriguez *et al.,* 2009

Several studies support functional distinctions between cortico-striatal circuits for reward (limbic), association (cognitive), and motor control (Alexander, DeLong, & Strick, 1986; Chudasama & Robbins, 2006). Anatomically, regions implicated in reward, motivation and
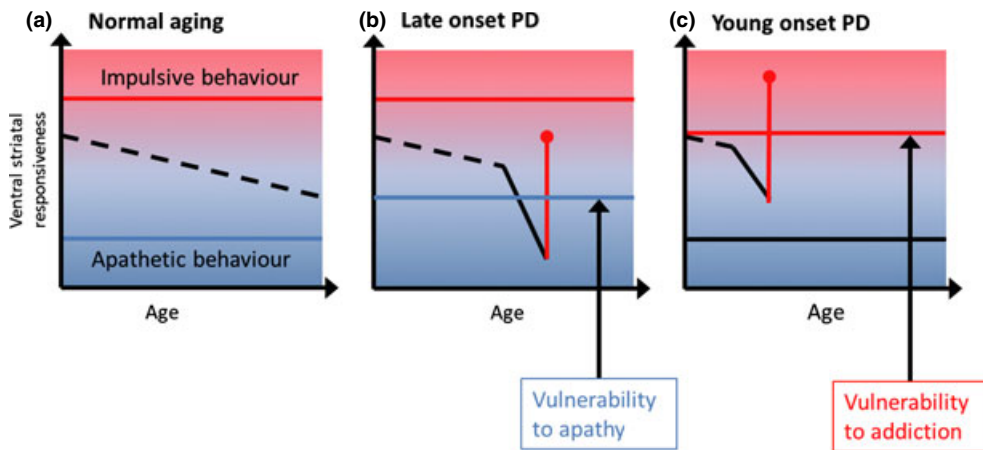
Figure 4. Highly schematic and speculative depiction of changes that might account for age differences, behavioural findings, and occurrence of apathy and impulsivity in PD. (a) Ventral striatal responsiveness (indexed by reward sensitivity, reward learning, effortful responding, and novelty seeking) decreases with age (dashed line). (b) In late-onset PD, degeneration of dopaminergic projections to ventral striatum occurs when ventral striatal responsiveness is already at a low level causing apathy (solid black sloping line). Potentially, vulnerability mechanisms for apathy, such as deficits in option generation due to executive dysfunction, lower the threshold for the expression of apathetic behaviour. Treatment with dopaminergic medication restores ventral striatal function (solid red vertical line). (c) However, if PD occurs at a young age when ventral striatal deterioration is limited, then administration of dopaminergic medication can cause pathologically enhanced ventral striatal responsiveness (solid red vertical line). Additionally, vulnerability mechanisms, such as decreased response inhibition, reduce the threshold for expression of impulsive behaviours.

affect regulation – such as ventromedial prefrontal cortex, hippocampus and amygdala – project primarily to the ventral striatum (including NAc). In contrast, sensorimotor cortical areas project more to dorsal striatum. Functionally, ventromedial striatum is implicated in reinforcement learning in rodent studies of drug self-administration, whereas dorsolateral striatum is considered important in mediating drug seeking after prolonged exposure when drug use becomes habitual (Everitt & Robbins, 2005).

Thus, a dominant view is that dorsal striatum, which receives predominantly sensorimotor afferents and has greater dopaminergic innervation, facilitates habit-formation and association of stimuli to rewards (Balleine & O'Doherty, 2010). In contrast, ventromedial striatum, which has limbic connections and relatively sparse dopaminergic input, is implicated in goal-directed behaviour via acquisition of stimulus-action-outcome associations.

In terms of our schema for motivated decision making (Figure 1), one might consider ventral striatum as a crucial node in option selection in the early stages of learning, but this later becomes bypassed via dorsal striatum, when habits have formed, with a direct connection between option generation and action initiation. However, studies in humans paint a more complex picture: dorsal striatum is also implicated in selective attention, task switching, category judgements, visuospatial processing, and complex planning, whereas ventral striatal activity also reflects salient, novel, and rewarding stimuli (MacDonald & Monchi, 2011). These considerations suggest a role of human dorsal striatum in option

selection and action initiation, whereas ventral striatal structures have a major role in general learning of stimulus associations (MacDonald *et al.*, 2011).

The distinction between dorsal and ventral striatal areas is highly relevant to understanding the motivational and cognitive deficits observed in PD. Dopaminergic input to these structures differ, and critically degenerate at different rates and to different extents during the disease, across individuals. In early PD, dopaminergic loss is more pronounced in dorsal than in ventral striatum (Kish, Shannak, & Hornykiewicz, 1988). Therefore, l-dopa doses that restore dopamine levels in the dorsal striatum to improve motor function might paradoxically lead to dopamine 'overdose' of the less affected ventral striatum, thereby disrupting goal-directed action (Cools & Robbins, 2004).

These considerations lead us to propose the following conceptual framework. With advancing age, ventral striatal responsiveness normally decreases (Figure 4a). In late-onset PD, degeneration of dopaminergic projections to ventral striatum occurs when ventral striatal responsiveness is already at a low level, leading potentially to apathy (Figure 4b). Risk factors such as dementia and depression might similarly lower the threshold for apathetic behaviour, whereas treatment with dopaminergic medication would tend to restore ventral striatal function. However, if PD occurs at a younger age, when the ventral striatum is relatively intact, administration of dopaminergic medication might be appropriate for dorsal striatum, but 'overdose' ventral striatum, leading to pathologically enhanced ventral striatal responsiveness and impulsive behaviours (Figure 4c). With this background in mind, we now consider each aspect of motivated decision making in PD in turn, and the evidence for their modulation by dopamine.

Option generation

Of the four stages considered here, we know least about the first: option generation (first column of Figure 1). Intuitively, one might imagine that a failure to produce options might lead to a paucity of actions, manifest as apathy. On the other hand, generating too many options might theoretically also lead to a poverty of behaviour by increasing procrastination. Thus, apathy might potentially be due to extremes on the same axis. Producing only one option and acting on it immediately without considering other possibilities, however, might be associated with a 'surface' manifestation of impulsive behaviour.

Exactly how brains produce decision options is, of course, not easily observable, but a crucial component is likely to be obtaining sufficient information prior to making a decision. A failure to collect enough information has been referred to as 'reflection impulsivity', investigated, for example, using the Information Sampling Task (Crockett, Clark, Smillie, & Robbins, 2012). In this paradigm, participants are exposed to a grid of grey boxes on a touch screen. Touching a box results in it opening and revealing one of two possible colours. The task is to decide which of the colours is in the overall majority on the grid. There are two conditions. In the 'free' condition, participants win or lose 100 points on each trial regardless of the number of boxes opened. Whereas in the 'costly' condition, opening each grey box decreases the available win from 250 points in steps of 10 points. As the inter-trial interval is kept constant irrespective of decision time, this paradigm enables quantification of the amount of information that a participant requires prior to making a decision.

Perhaps surprisingly, in a recent study, trait impulsivity (measured using BIS) was positively correlated with information sampling in the free but not the costly

condition (Crockett *et al.*, 2012). One reason for this might be that a gain of information leads to reduced uncertainty, so risk-aversion promotes information seeking. Thus, sampling information when it is free reflects impulsivity, whereas when it is costly, information trades off with reward. Indirect evidence for a role of dopamine comes from the observation that chronic amphetamine use is associated with reduced threshold for information prior to option selection (Clark, Robbins, Ersche, & Sahakian, 2006). In PD, a recent study has demonstrated that individuals with ICDs make decisions with far less information than controls, in a manner similar to drug users (Djamshidian *et al.*, 2012). It remains to be determined how such decision-making is affected in PD apathy.

Attentional and executive mechanisms are also likely to be important factors in option generation (Figure 1). While inattentiveness and distractibility are features of impulsivity (Arnsten, 2006), a failure to engage attention might potentially be a feature of apathy. There is substantial evidence for a variety of deficits in PD in tests of executive function (Kudlicka, Clare, & Hindle, 2011). However, perhaps the closest existing index of option generation is random number generation and, to some extent, the Hayling sentence completion task, which requires participants to suppress the obvious word that normally completes a sentence and generate instead a novel ending. PD patients can be impaired on such tasks (Obeso *et al.*, 2011) but, to the best of our knowledge, this has not been tested specifically in subgroups of PD ICD and apathetic patients.

An influential model for considering deficits in executive function has been the concept of an 'inverted U'-shaped relationship between the level of dopamine and a cognitive function (Cools, Altamirano, & D'Esposito, 2006). Thus, both too little and too much dopamine might result in sub-optimal 'executive' processing, and thereby impact option generation. PD ICD patients have been shown to have significantly reduced executive function (Kudlicka *et al.*, 2011). It is possible that this relates to relative dopaminergic overdosing, but this remains to be definitively established. One study has reported that dopamine-mediated abnormalities in cognitive control in PD ICD (as assessed using the Simon task) may be related to baseline performance on the task, consistent with an inverted U function (Wylie *et al.*, 2012). The same group has also found evidence that STN DBS can both increase premature, erroneous responses on this task, as well as improving later inhibitory control (Wylie *et al.*, 2010). Investigating the link between executive functions and option generation, and their potential modulation by dopamine or STN DBS remains a crucial goal for future research in this area.

Option selection

In our decision schema, impulsive and apathetic behaviour might also potentially reflect extremes of behaviour involved in option selection (second column, Figure 1). This is a stage of motivated behaviour that involves attributing values to options prior to selecting the one with the highest value. The process of valuation reflects more than just a cost–benefit comparison, that is, weighing up the benefits against potential effort required to obtain them. It is now appreciated that several factors affect the subjective utility attributed to an option including: its predicted reward value, salience or novelty, the likely effort required to achieve the goal, risk involved and the time to outcome delivery. These factors (summarized in Table 2) have been implicated in both impulsive and apathetic behaviours, and importantly, dopamine has been proposed to play a key role in each of these functions, as we discuss below.

Table 2. Behavioural functions and processes suggested to be involved in impulsivity and apathy together with relevant evidence-implicated excesses and deficits of dopamine in dysfunction. The four different shades of grey indicate processes involved in option generation (top), through option selection, motor response initiation and inhibition, to learning from rewards and penalties (bottom)

Behavioural function	Evidence that dopamine excess causes impulsivity in this function	Evidence that dopamine deficit causes apathy in this function
Information gathering	• PD ICD patients make decisions with less information	• *No studies of information sampling in apathy*
Reward sensitivity, Incentive salience	• Microdialysis studies of rats with repeated psychostimulant exposure show progressive augmentation of drug induced dopamine release in ventral striatum after drug withdrawal – a change proposed to account for compulsive drug seeking • PD patients with ICDs show enhanced signals in these regions when viewing gambling/rewarding stimuli	• 'Wanting' behaviour decreased on dopamine depletion but 'liking' (hedonic) responses intact • Reduced reward sensitivity in patients with trait 'anhedonia' or healthy controls who have been exposed to medication reducing dopaminergic transmission
Effortful responding	• Intertrial reaction time correlated with average rate of reward delivery – consistent with Niv *et al.*'s (2007) model	• Striatal dopamine depletion reduces high effort/high reward responding in rodents • Dopamine antagonists reduce effortful responding • PD patients are impaired in exerting effort for reward in grip task
Temporal discounting and waiting	• Lesions of NAc cause increase premature responding on 5CSRTT in rodents. This is dopamine dependent effect • PD ICDs have increase discount rate • Levodopa administration in healthy controls increases discount rate	• A profoundly apathetic patient with bilateral GPi lesions did not make functional anticipations on task of waiting. Administration of dopamine agonist increased anticipatory responding • However the dopamine antagonist haloperidol did **not** reduce discount rate in humans

Continued.

Table 2. (*Continued*)

Behavioural function	Evidence that dopamine excess causes impulsivity in this function	Evidence that dopamine deficit causes apathy in this function
Novelty seeking	• Increased novelty induced motor activity following dopamine microinjections to NA and ventral pallidum in rodents • Increased in PD ICDs • Increased with dopamine agonists in healthy controls • Ventral striatal activity correlates with novelty seeking behaviour	• *No specific investigations of novelty seeking in apathy in humans* • There is a reduction in novelty seeking behaviour in animals following dopamine-depleting lesions • Rodents bred for reduced novelty-seeking locomotor activity, which is known to be associated with reduced nucleus accumbens dopaminergic tone compared to rats bred with higher novelty seeking, developed more severe anhedonia
Risk seeking	• Tonic dopamine levels encode reward uncertainty • Increased in PD ICDs • Increased in healthy controls administered dopamine agonists	• *No specific investigations of risk seeking in apathy in humans* • Patients with depression are better than controls on the IGT and more risk averse
Motor response initiation and inhibition	• Drugs enhancing dopaminergic transmission (e.g., methylphenidate and d-amphetamine) improve SSRT in ADHD (de Wit, 2009) – an effect which has been linked to DRD2 gene expression • D2/D3 receptor bioavailability and BOLD signal in dorsal striatum are positively correlated with SSRT speeding	• D1 antagonists delivered to dorsal striatum speed SSRTs in rodents
Learning from rewards/penalties	• PD patients ON l-dopa have increased reward learning (and decreased punishment learning) compared to age matched controls • PD ICD patients have increased reward learning compared to PD patients without ICDs when on DA treatment	• PD patients OFF l-dopa have decreased reward learning (and increased punishment learning) compared to age matched controls

Reward sensitivity, incentive salience, and novelty

Early hedonic theories of dopamine in reward have been replaced by a concept of 'incentive salience' – a process in which dopamine is involved in conversion of a neutral stimulus into an attractive, 'wanted' incentive that becomes perceptually salient (Berridge & Robinson, 1998). Evidence that dopamine is important in 'wanting' – as opposed to simply 'liking' – comes from studies in rodents involving dopaminergic depletion of striatal structures. In such animals, there is preservation of hedonic responses (such as orofacial reactions associated with liking a stimulus), but a deficit in (instrumental) behaviour needed to obtain primary rewards (Berridge, 2007).

Incentive salience has been proposed to be an important mechanism in drug addiction, with compulsive drug use arising from excessive attribution of 'wanting' drug rewards and their cues because of alterations in dopaminergic projections to the ventral striatum (Robinson & Berridge, 1993). Importantly, in recent years several investigations using PET have provided evidence that similar dysfunction occurs in PD ICD patients.

PD patients with dopamine dysregulation syndrome (DDS), a condition characterized by increased l-dopa usage and craving, exhibit enhanced l-dopa-induced ventral striatal dopamine release compared with PD cases without DDS. Furthermore, this enhanced ventral striatal dopamine transmission correlates with subjective reports of drug 'wanting' but not 'liking' (Evans *et al.*, 2006). PD patients with pathological gambling also show greater BOLD responses to gambling cues in ventral striatum and cingulate cortex than control PD cases in fMRI experiments (Frosini *et al.*, 2010). Two PET studies have further demonstrated that these areas show greater decreases in binding potential in ICD patients with diverse behavioural addictions, probably reflecting greater dopamine release to rewarding cues (O'Sullivan *et al.*, 2011; Steeves *et al.*, 2009).

On the other side of the spectrum, no studies to date have specifically investigated ventral striatal dopamine release to rewarding cues in PD with apathy. However, one study of depression in PD has reported that the severity of apathy symptoms is inversely correlated with RTI-32 (2β-Carbomethoxy-3β-(4-tolyl)tropane) binding in the ventral striatum, which is considered to reflect dopaminergic denervation (Remy, 2005).

Given the similarities in neural disturbance observed between drug addiction and ICDs, it is interesting to consider whether drug addiction might provide an important model for the relationship between apathy and ICDs. Dopaminergic neurons are tuned to respond in a phasic manner to salient stimuli in the environment and under normal conditions play a key role in motivation and learning (Schultz, 1998). Addictive drugs cause dopamine release within ventral striatum, associated with self-reports of euphoria (Volkow, Fowler, Wang, Baler, & Telang, 2009). Supra-physiological activation by drugs is experienced as highly salient and, with repeated use, raises the threshold for dopamine cell activation and signalling such that drug abusers have reduced D2 receptors and dopamine release, associated crucially with apathy in periods of drug abstinence (Volkow *et al.*, 2009).

A recent study measured depression and apathy scores in previously non-apathetic patients whose dopamine agonists were stopped after DBS STN. Remarkably, over half the patients (34 of 63) developed apathy at some point over the following year. For most, this lasted only a few months. PET imaging demonstrated that development of apathy was associated with increased dopamine D2/D3 binding bilaterally in orbitofrontal cortex, posterior cingulate cortex, dorsolateral prefrontal cortex, bilateral striatum, thalamus, and right amygdala. The findings suggest that apathy is more likely in patients with lower tonic dopamine levels, which could in turn correspond to the degree of background mesocorticolimbic dopaminergic degeneration (Thobois *et al.*, 2010).

The role of dopaminergic activity in ventral striatum is likely to go beyond just the rewarding properties or incentive salience of stimuli. Short latency dopaminergic responses in rodents may mediate attentional and behavioural shifts towards important, unexpected stimuli (Redgrave, Prescott, & Gurney, 1999). In humans, striatal activity elicited by new stimuli predicts novelty-seeking behaviour (Wittmann, Daw, Seymour, & Dolan, 2008). A recent study of novelty seeking in PD ICD patients found they chose novel options significantly more often than healthy or PD controls (Djamshidian, O'Sullivan, Wittmann, Lees, & Averbeck, 2011). Intriguingly, at the other end of the spectrum, dopaminergic depletion in rodents reduces novelty-induced motor activity (Pierce, Crawford, Nonneman, Mattingly, & Bardo, 1990), and low novelty seeking has been reported as a common feature in the premorbid personality of PD patients (Glosser *et al.*, 1995).

Effortful responding

In addition to its role in reward, incentive, and salience processing, dopamine appears to modulate effort of responding. Depletion of dopamine in rodents reduces choice of high effort/high reward options, but importantly does not affect choice of the most rewarding option when the effort required is made equivalent (Salamone, 2007). Humans show increased striatal activity in anticipation of responses requiring effort (Croxson, Walton, O'Reilly, Behrens, & Rushworth, 2009). Other studies report higher dorsolateral striatal activity when choosing low compared with high effort options (Kurniawan *et al.*, 2010), providing support for the importance of striatum in effort-related processes. Consistent with these findings, PD patients are impaired at exerting effort in a task linking reward to effort (Schmidt *et al.*, 2008).

From the above, one might expect that dopaminergic signals in the striatum will reflect some form of cost-benefit integration. However, a study using voltammetry which allows detection of dopamine transients (Gan, Walton, & Phillips, 2010) found otherwise. Rats chose the high reward option when effort was matched, and the low effort option when reward was matched. But when tested on 'forced choice trials' in which only one option was presented, dopamine release correlated with reward but not effort. There is clear evidence, however, that dopamine depletion reduces effort (Salamone, Cousins, & Bucher, 1994). Moreover, amphetamine can abolish haloperidol-induced reductions of effortful responding in rodents (Bardgett, Depenbrock, Downs, Points, & Green, 2009) while low-dose amphetamine increases effortful choice; however, high doses paradoxically decrease it (perhaps because of an 'inverted-U' type of relationship between drug and effort).

Basal ganglia dysfunction can also impair effortful responding. One theory of apathy proposes that it results from a disconnection of the representation of anticipated reward (option value) and the action required (Kurniawan *et al.*, 2011). Indeed, it has been suggested that this accounts for the profound apathy that has been reported following bilateral basal ganglia lesions. Interestingly, a recent study of a rare patient with bilateral globus pallidus lesions and profound apathy, in the absence of motor deficits, reported that administration of a dopamine receptor agonist could reverse apathy clinically, and as measured by a speed-incentivised task (Adam *et al.*, 2012). Importantly, there have been no studies to date investigating PD patients with syndromically defined apathy on such tasks.

But how do the data on effort relate to dopamine's proposed role in incentive salience, reward learning and effort? A recent computational model has gone some way towards reconciling the different strands of research. It proposes that costs of delayed and missed

rewards are compared with costs of effortful, rapid responding. In this scheme, tonic dopamine levels encode 'vigour', which is directly related to the average rate of reward in the environment (Niv *et al.*, 2007). Following this line of reasoning, apathy might reflect low tonic dopamine and thus reduced vigour, whereas heightened tonic dopamine levels might cause increased vigour, potentially leading to impulsive behaviour. Note that this role of tonic dopamine levels is to be contrasted with role of phasic dopamine providing a prediction error signal in reinforcement learning (see section on Learning below) and in responding to salient stimuli (Schultz, 1998).

Risk and outcome probability

Risky behaviour is often associated with impulsivity. It can be considered to reflect potential for loss or outcome variance – the higher the variance of potential outcomes, the higher the risk. The results of some neurophysiological studies suggest that tonic dopaminergic neuronal responses might encode risk (Fiorillo, Tobler, & Schultz, 2003). In healthy people, administration of dopamine agonists can increase risk taking (Riba, Krämer, Heldmann, Richter, & Münte, 2008) and ventral striatal activity may track risk (Preuschoff, Bossaerts, & Quartz, 2006).

Many tasks have been used to investigate risk in clinical populations, including the Iowa Gambling Task (IGT), Cambridge Gambling Task, Balloon Analogue Risk Test (BART) and a variety of others (Bechara, Damasio, Damasio, & Anderson, 1994; Lejuez *et al.*, 2002; Rogers *et al.*, 1999). Early PD patients paradoxically show risky decision making despite having relatively good overall cognitive function (Pagonabarraga *et al.*, 2007; Perretta, Pari, & Beninger, 2005). However, a review of 13 studies of the IGT in PD found mixed results, perhaps due to very different study populations (Poletti *et al.*, 2010). A recent investigation of *de novo* PD patients showed no impairment on the IGT, suggesting that deficits observed in previous studies might potentially have arisen as a result of the influence of dopaminergic overdosage of mesolimbic pathways in treated cases (Poletti *et al.*, 2010).

A study of PD ICD patients using the BART also found that OFF medication, they were similar to PD controls in risk-taking behaviour. However, ON medication, they showed an increased tendency to try to gain more money by taking greater risk, (Claassen *et al.*, 2011), although previous investigations did not report this pattern (Van Eimeren *et al.*, 2009). Importantly, ICD patients had no problems adjusting their behaviour following negative outcomes, suggesting that they are able to respond appropriately to feedback (Claassen *et al.*, 2011). This finding was replicated in a separate fMRI study, which found decreased ventral striatal signal in anticipation of risk. It was suggested that this was due to decreased coupling of ventral striatal activity to action, rather than reflecting risk *per se* (Voon *et al.*, 2011).

No studies to date have specifically investigated risk-taking in patients with apathy. However, it is worth noting that a study of depressed patients found that they were more risk averse and actually performed better on the IGT than controls (Smoski *et al.*, 2008). Whether a similar result would obtain in PD apathy remains to be determined.

Temporal discounting and waiting

In parallel with risk impulsivity is the inability to delay gratification by putting off smaller, immediate rewards to obtain larger rewards at a longer delay (Dalley *et al.*, 2011). In an unstable environment, one rationale for temporal discounting is that delayed rewards

might be risky as greater temporal distance equates to greater uncertainty of receipt. Although often referred to as 'impulsive choice', such delay discounting could be seen as adaptive (Figure 2). In humans, an individual's observed choice preferences are well fitted by a hyperbolic decay of value over time (Peters & Büchel, 2011). A high discount rate means that subjective value of a certain reward falls off rapidly with delay.

Recordings from midbrain dopaminergic neurons in a temporal discounting task have revealed increased phasic activity with increasing delay (Kobayashi & Schultz, 2008). Increased ventral striatal response to reward as a function of delay has also been demonstrated in humans using fMRI (Gregorios-Pippas, Tobler, & Schultz, 2009). Rats with pre-existing higher discounting rates display greater propensity to drug addiction (Perry, Larson, German, Madden, & Carroll, 2005), while patients with substance abuse disorders and pathological gambling also show greater temporal discounting (Bickel & Marsch, 2001). Rodent studies of temporal discounting suggest a pivotal role for the core region of the NAc in impulsive choice, with NAc-lesioned rats demonstrating increased preference for immediate rewards (Cardinal, Pennicott, Sugathapala, Robbins, & Everitt, 2001).

Intriguingly, in healthy people, it has been shown that l-dopa can increase the number of sooner choices relative to placebo, with an associated alteration of activity in the striatum (Pine, Shiner, Seymour, & Dolan, 2010). PD ICD patients also show higher rates of discounting compared with PD cases without ICDs (Housden, O'Sullivan, Joyce, Lees, & Roiser, 2010; Voon *et al.*, 2007). The former study also reported that higher dopamine doses increased impulsive choice in PD ICD, but not in PD controls. In contrast, there has been little investigation of temporal discounting in apathy or dopamine depleted states.

These studies on temporal discounting have suggested a key role of controlling 'waiting'. However, the ability to wait longer to obtain a larger reward intuitively seems to entail inhibiting a potent response plan, that is, to obtain the immediate reward. The question arises therefore whether there is overlap of this cognitive axis with inhibition of actions (see next section). However, the discovery of a double dissociation in rodents between the role of the STN in stopping and NAc in tasks that require waiting suggests that these processes might in fact be neurally distinct (Dalley *et al.*, 2011; Eagle & Robbins, 2003a,b).

Motor response initiation and inhibition

In terms of the schema of motivated behaviour suggested here (Figures 1 and 2), motor apathy occurs when, despite appropriate option valuation and selection process, there is failure of action. Motor impulsivity, on the other hand, could represent either a failure of response inhibition when context dictates, or a heightened signal from the option selection stage resulting in over-vigorous responding. A significant body of research has investigated response inhibition or 'stopping' behaviour using methods including the stop signal, go/nogo and antisaccade tasks. Here, we focus on the stop signal task (SST), which has arguably received the most attention.

In the SST, participants respond to a GO signal, usually a visual stimulus that indicates whether a right or left manual response is required. On a proportion of trials, this is followed after a delay – the stop signal delay – by a stop cue, often in the form of an auditory tone, which instructs the participant to withhold the response. As the stop signal delay is increased, it becomes increasingly difficult to cancel the GO response. Performance on this task can be modelled successfully as a race between two linearly rising signals – GO and STOP – moving towards a response activation threshold (Logan, Cowan, & Davis, 1984). The time taken for completion of the stop process can be

estimated by adjusting the stop signal delay such that an individual participant can successfully inhibit responses on half of the trials. This stop signal delay is taken as the stop signal reaction time (SSRT).

Consideration of the classical model of direct and indirect pathways (Figure 3) might suggest that activation of the indirect pathway could inhibit behavioural responses (striatal activation would lead to inhibition of the GPe, which in turn releases STN inhibition, thereby increasing excitation of the GPi and inhibiting movement). But is there any evidence that these structures play an important role in reactive motor inhibition? In a rodent version of the SST, lesions to dorsal striatum slow SSRTs (Eagle & Robbins, 2003a,b). Crucially, administration of D2 antagonists to dorsal – but not ventral – striatum slows SSRTs, whereas D1 antagonists speed SSRTs (Eagle *et al.*, 2011).

This finding invites an extension of the classical model (Figure 3). In that model, dopamine promotes action plans delivered by the cortex through positive modulation of D1 receptors, and inhibits competing actions via D2 receptors, consistent with the finding that D2 antagonists increase SSRT. However, why should D1 receptor antagonism speed SSRT? An intriguing possibility is that action and inhibition processes might compete in a race towards threshold with the 'winning' process becoming the expressed behaviour and D1 receptor stimulation promoting action by inhibiting a competing inhibition process. (For an alternative model of competition between GO and NoGO systems in the direct and indirect pathways, which is differentially altered by dopamine agonists, see (Cilia & Van Eimeren, 2011)).

Studies of healthy people also suggest that dorsal striatum and its dopaminergic function are important. Both dorsal striatal BOLD signal and D2 bioavailability correlate with shorter SSRTs (Ghahremani *et al.*, 2012). Furthermore, there is evidence across species that reduced D2 receptor expression correlates with poor control of behaviour (Dalley *et al.*, 2007; Hamidovic, Dlugos, Skol, Palmer, & De Wit, 2009). Humans with drug addiction have decreased striatal D2 receptor availability (Lee *et al.*, 2009), while enhancing dopaminergic transmission (e.g., with methylphenidate) improves SSRT in ADHD (De Wit, 2009), an effect linked to DRD2 gene expression.

Rats with lesions to the STN demonstrate an increase in SSRT, whereas NAc lesions do not affect it (Eagle & Robbins, 2003a,b). Studies of STN DBS in PD suggest that the relationship of STN activity with response inhibition is complex. DBS high frequency stimulation disrupts STN activity slowing the SSRT, consistent with the model presented above (Ballanger *et al.*, 2009; Ray *et al.*, 2009). In addition to externally triggered stopping, STN stimulation prevents the normal slowing observed in high-conflict decisions that allow better choices (Frank, Samanta, Moustafa, & Sherman, 2007). However, in contradiction to these, two other studies which included only patients with bilateral STN DBS, reported the opposite: SSRT was significantly speeded ON stimulation compared to OFF (Swann *et al.*, 2011; Van den Wildenberg *et al.*, 2006).

In fact, if response inhibition depended linearly on activation of the indirect pathway, then untreated PD patients, who are hypodopaminergic, and known to have increased STN activity and decreased GPe activity, should be improved on tasks of response inhibition. However, several studies have shown this is not the case. PD patients are impaired on the SST compared with age-matched controls independently of global cognitive impairment (Gauggel, Rieger, & Feghoff, 2004), even after correcting for GO reaction times (Obeso *et al.*, 2011), both ON and OFF levodopa treatment (Obeso,

Wilkinson, & Jahanshahi, 2011). These findings suggest that PD is a disorder of inhibition as well as activation, and that the mechanism through which STN stimulation improves response inhibition might reflect an improvement in the fidelity of information transfer in cortico-basal-ganglia circuits (Swann *et al.*, 2011).

Overall, our reading of the literature is that the mechanism of disrupted stopping observed in PD is unlikely to be mediated by dopamine changes in the indirect pathway, but rather reflects diffuse dysfunction in fronto-striatal timing, affecting both response initiation and response inhibition. Consequently, it does not appear that there is a simple dopamine-dependent spectrum of response inhibition behaviour. Rather, differences in response inhibition between people – possibly caused by differences in D2 bioavailability – reflect a vulnerability trait to addictive behaviours. Further evidence for this comes from findings of impaired executive function in PD ICDs (Voon *et al.*, 2009). Importantly, these response inhibition behaviours tested in PD ICD cases did not vary in a dopamine-dependent manner (Djamshidian, O'Sullivan, Lees, & Averbeck, 2011).

Learning from rewards and penalties

The final process we consider is learning. A prominent, theoretical account of dopaminergic function suggests that it is important in reward learning and interprets midbrain phasic dopaminergic activity as the reward prediction error used in temporal difference models of reinforcement learning (Schultz, Dayan, & Montague, 1997). Administration of l-dopa to healthy people improves learning about rewarding stimuli but not punishing ones, with a standard reinforcement learning algorithm modelling choice behaviour well as a dopamine-mediated change in size of reward prediction error (Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006).

An influential computational model (Frank, Seeberger, & O'reilly, 2004; Frank *et al.*, 2007) has suggested a link between the direct and indirect pathways (Figure 3) with midbrain phasic dopaminergic activity signalling reward prediction error. In this model, the basal ganglia modulate selection of actions under consideration in frontal cortex including the pre-supplementary motor area. Activity in the direct pathway facilitates execution of a particular response, whereas activity in the indirect pathway inhibits competing responses. Phasic dopaminergic responses to positive and negative feedback have opposite effects on the two pathways via D1 and D2 receptors. The consequence is that dopamine bursts during positive reinforcement activate the direct pathway and inhibit the indirect pathway such that rewarded responses are subsequently facilitated. Conversely, decreases in dopamine during negative reinforcement inhibit the direct pathway and activate instead the indirect pathway leading to subsequent suppression of responses to that option.

Investigations in PD patients have provided some support for this model. In the hypodopaminergic OFF state, individuals with PD are better at learning from punishment than from reward, whereas in the ON state, they are better at learning from reward than from punishment (Frank *et al.*, 2004, 2007). Moreover, PD patients in the OFF state are better than healthy controls at learning about punishment, and in the ON state are enhanced at learning about reward. These findings support the contention that reward learning critically depends on dopaminergic state within the striatum.

Voon *et al*. (2010) compared PD ICD cases with matched PD controls ON and OFF dopamine agonists. They found that dopamine agonists increased reward learning rate only in PD patients with pathological gambling. Dopamine agonists might also impair learning from negative feedback on a roulette-based task. After pramipexole, there was

loss of normal deactivation of orbitofrontal cortex with negative reward prediction error, consistent with the view that dopamine agonists prevent pauses in dopaminergic release necessary for negative reinforcement learning (Van Eimeren *et al.*, 2009).

At the opposite end of the spectrum, what evidence is there that apathy might be caused by deficiency in reward learning? Unfortunately, to date, studies investigating reward learning in PD have not recorded apathy status and there have been no specific behavioural studies addressing this question. However, there is evidence that reward learning is impaired in patients with major depression and healthy individuals with trait anhedonia (Bogdan & Pizzagalli, 2006) or after administration of a dopamine autoreceptor agonist, which reduces dopamine levels (Pizzagalli *et al.*, 2008). The study of reinforcement learning in PD patients with apathy is clearly an area that would be of interest to develop in future.

Conclusions

The findings reviewed here demonstrate that, at a syndromic level, there is strong evidence for a dopamine-dependent spectrum of decision making from ICDs to apathy in PD. At a behavioural level, there is evidence that excessive dopamine can lead to specific forms of impulsivity, whereas a paucity of dopamine has been associated with apathy. However, there is comparatively little work on exactly how alterations in dopamine level produce such effects. Here, we have attempted to provide a conceptual framework to understand these syndromes. Our strategy has been to fractionate aspects of decision making (see Figures 1 and 2 and Table 2 for a summary of the evidence), attempting to integrate a very large body of experimental data that spans animal models, research in healthy humans, and patients with PD.

We have focused on dopaminergic modulation of option generation, option selection, motor response initiation or inhibition and learning. Our review suggests that there might be several cognitive axes that might potentially be affected, theoretically in an independent manner (Figure 3). Normally, optimal function might be centred along each of these axes. However, in a labile environment, it might be adaptive to shift towards the right of the axes shown in Figure 2 so that behaviour is more exploratory, whereas in more stable situations, it might be better to shift towards the other extreme, so behaviour is more exploitative. In pathological states, impulsive behaviour might arise from rightward shifts along these axes, without any change in the environment, whereas apathy might arise from shifts in the opposite direction.

The degree of shift on each axis might be influenced by different factors. The amplitude of endogenous phasic dopamine bursts might influence impulsivity and apathy in terms of reward sensitivity and learning rates. Tonic ambient dopamine (which may be modulated by exogenous factors) might modulate shifts in effort discounting and risk seeking. The extent of degeneration of critical ventral striatal regions may determine motor impulsivity, but this also interacts with dopamine in generating shifts in option generation and temporal discounting, by determining 'overdosing'. Additional factors such as genetics, depression, and dementia may each influence the axes differentially. That some neurological patients, including those with PD, can display elements of both impulsivity and apathy (Leroi *et al.*, 2012; Rosenblatt, 2007; Voon, Sohr *et al.*, 2011) directly supports such a contention.

Although the experimental data reveal that axes that constitute the impulsivity-apathy spectrum are dissociable – both at a behavioural and at a neural level – it is also evident that there are strong links between some of these axes. Indeed, as we have seen, dopamine

appears to modulate several of them, suggesting there may be mechanistic parallels between dimensions. Indeed, one recent model brings together evidence concerning dopamine's role in incentive salience, reward learning and effort by proposing that costs of delayed and missed rewards are compared with costs of effortful rapid responding. According to this hypothesis, tonic dopamine levels encode 'vigour' (how much effort is spent), which is directly related to the average rate of reward in the environment (Niv *et al.*, 2007). Thus, reward sensitivity might be considered a determinant of effort. Such considerations show that the axes we have considered might not, in reality, be totally independent and dissociable. Nevertheless, we would argue that the framework we have advanced here provides a useful means to begin to understand the mechanisms underlying impulsivity and apathy in PD.

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