Trends in Neurosciences

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Review

Understanding disrupted motivation in Parkinson's disease through a value-based decision-making lens

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Neurobehavioural disturbances such as loss of motivation have profound effects on the lives of many people living with Parkinson's disease (PD), as well as other brain disorders. The field of decision-making neuroscience, underpinned by a plethora of work across species, provides an important framework within which to investigate apathy in clinical populations. Here we review how changes in a number of different processes underlying value-based decision making may lead to the common phenotype of apathy in PD. The application of computational models to probe both behaviour and neurophysiology show promise in elucidating these cognitive processes crucial for motivated behaviour. However, observations from the clinical management of PD demand an expanded view of this relationship, which we aim to delineate. Ultimately, effective treatment of apathy may depend on identifying the pattern in which decision making and related mechanisms have been disrupted in individuals living with PD.

Highlights

Loss of motivation (apathy) significantly affects the lives of many people living with Parkinson's disease (PD), and neural evidence links it to systems crucial for goal-directed behaviour.

Decision-making neuroscience, informed by work across species, provides a mechanistic framework within which to examine how rewards and costs of actions underpin goal-directed behaviour.

Decision-making experiments in people with PD demonstrate distinct behavioural signatures of apathy, whilst also advancing understanding of the role of neuromodulators like dopamine.

Specific cognitive processes, including executive functions, may modulate the relationship between apathy, neuromodulators, and decision making.

Applying more complex models of decisions to the behaviour and neurophysiology of people living with PD are exciting research avenues that promise to deepen understanding of this important clinical area.

Applying decision neuroscience to motivational disruption in PD

PD is the second most common neurodegenerative disorder worldwide. It has traditionally been considered a disorder of movement, but a plethora of other (so-called 'non-motor') features characterise this condition [1]. Prominent amongst these are neurobehavioural disturbances, of which **apathy** (see Glossary), a pathological loss of motivation that manifests as reduced goal-directed behaviour, stands out in terms of its common occurrence and impact on quality of life and mortality [2–4]. Other changes in (motivated) behaviour such as **impulsivity** also occur, particularly in relationship to dopaminergic therapies that form the backbone of PD management [5,6]. Motivational problems can be notoriously difficult to treat effectively, which in part can be attributed to limitations in understanding of the mechanisms driving their emergence. However, advances in understanding of normal motivated behaviour, led by the research domain of decision-making neuroscience, have provided a framework within which these clinical problems can be investigated [7–9]. In turn, the unique situation that PD presents has provided an important model to better understand normal motivated behaviour, from drug manipulations to recording human neural activity in the form of local field potentials during motivated tasks [10,11].

In this review, we discuss recent progress in understanding disordered motivation in PD – chiefly apathy – within a framework of disrupted **value-based decision making**. We underscore core issues arising from the clinical management of apathy in PD that are not well explained by current conceptualisations. We further highlight how these same issues overlap with evolving – and often controversial – areas of decision-making neuroscience, including evidence accumulation in decision making, the importance of decision context, and the role of dopaminergic and other neuromodulatory signals as both primary mediators of goal-directed behaviour and secondary

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influencers via impact on key executive functions. Based on these discussions, we outline an updated model of motivational disruption in PD that synthesises these ideas, and which we hope will drive ongoing research into this fundamental problem of human behaviour.

What are the disorders of motivation that occur in PD?

We start by briefly describing the main disruptions to motivated behaviour that occur in PD (Figure 1). Apathy is broadly defined as a pathological loss of motivation that manifests as reduced goal-directed behaviours. Apathy has long been understood as a feature of PD, but full appreciation for its prevalence and impact has emerged relatively recently, both in the clinical and scientific spheres [2,3,12,13]. Apathy can occur at any disease stage and in some patients precedes the development of the motor symptoms that typically lead to a PD diagnosis [3,14–16]. Estimates of prevalence have varied widely, in part because of variation in assessment tools and subpopulations that are studied, but a figure of around 30–40% seems to be representative of most current estimates [2,13]. Apathy is a strong determinant of quality of life, to the point that, in individuals experiencing it, interventions that demonstrably improve the motor symptoms of PD but have little effect on apathy fail to improve quality of life [15,17,18]. Furthermore, the occurrence of apathy at any stage of PD is associated with higher mortality [3]. Although it can occur in the absence of any of the following factors, at a group level apathy in PD is associated with cognitive impairment and dementia, higher levels of depressive symptoms, increasing motor symptoms, and increasing age. It is also more common in males [2,3,13]. As we discuss later, the association between apathy and cognitive impairment in some, but not all, studies seems especially related to executive dysfunction [3,13,19]. Apathy can also emerge or remit following deep-brain stimulation (DBS) to the subthalamic nucleus, with the exact placement of electrodes in the context of an individual's brain connectivity likely driving this complex relationship [20–22]. It is worth mentioning that the nosological relationship between PD and dementia with Lewy bodies is undergoing substantial debate, with prominent proposals to formally unite these conditions based on their shared underlying pathological substrates [23,24]. Apathy is also a prominent

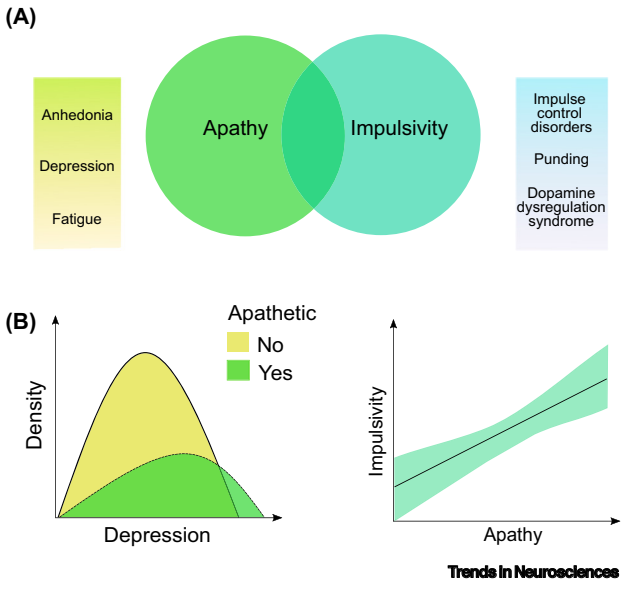

Figure 1. Apathy and impulsivity are common syndromes of disrupted behaviour seen in people with Parkinson's disease (PD), and are distinct from, but overlap with, other neurobehavioural and neuropsychiatric conditions. (A) For apathy, this includes in particular anhedonia, depression, and fatigue. For impulsivity, associated conditions can include the specific impulse control and behavioural disorders of impulse control disorder, punding, and dopamine dysregulation syndrome. However, some of these conditions occur in the context of dopaminergic treatment and may be more directly linked to compulsivity, differentiating them mechanistically from impulsivity *per se*. (B) Apathy and depression can sometimes be confused in the setting of a PD patient with reduced behavioural output. Although these two conditions have overlapping features, particularly in the domain of anhedonia, they are clearly distinct syndromes. Specifically, apathy can occur across the spectrum of depressive symptoms, although at a group level, apathy in PD is associated with higher levels (left panel). Apathy and impulsivity are correlated in PD and many other neurological disorders (right panel).

Glossary

Apathy: broadly defined as an observable reduction in goal-directed behaviour compared with the previous level of functioning. Apathy has been considered to have behavioural, cognitive, social, and emotional dimensions.

Dopamine dysregulation syndrome: the overuse of dopaminergic medication beyond the necessity of controlling motor symptoms. Some patients may experience withdrawal symptoms similar to those observed in addiction, requesting further increases in their drug regimen, even when motor control remains satisfactory.

Drift diffusion model: a single-process decision-making model whereby evidence is assumed to accumulate towards a decision bound in a noisy manner. Latent parameters include drift rate (rate of evidence accumulation towards a decision bound), threshold (distance between two decision bounds), non-decision time (information encoding and motor processes), and bias (starting point of evidence accumulation).

Impulse control and related behavioural disorders (ICBDs): failure to resist impulses to perform certain behaviours, which are repeatedly executed and have a negative effect on an individual's functioning. Impulse control disorder behaviours include compulsive shopping, binge eating, pathological gambling, compulsive hobbyism, and hypersexuality. Because impulse control disorders are not related directly to disease progression but indirectly, via dopamine (particularly D3 receptor agonist) prescribing practices, they can occur at any time in the disease course. Punding is a stereotyped behaviour characterised by excessive non goal-oriented, repetitive activities such as sorting things, tidying, taking objects apart, or collecting objects.

Impulsivity: broadly defined as the tendency to act rashly without forethought, impulsivity is a multidimensional construct. Motor impulsivity refers to both premature actions and reduced ability to stop an already initiated action, whilst decisional impulsivity refers to choice preferences for risk, and for smaller, immediate rather than larger, delayed reward. Reflection impulsivity refers to making a decision prior to sufficient gathering of information.

feature of dementia with Lewy bodies and its occurrence is associated with similar associations to those seen in PD, while both conditions show evidence for a treatment effect of cholinesterase inhibitors on apathy [25–27].

Perhaps counterintuitively, evidence points to the co-occurrence of impulsivity with apathy, both in PD and in other conditions [28–33]. This tendency to act rashly, without appropriate forethought, is increased in people with PD relative to the general population [34]. Within the umbrella of impulsive behaviour, **impulse control and related behavioural disorders (ICBDs)** have been a high-profile side effect of, in particular, dopamine agonists with high D3 receptor affinity [5,35,36]. ICBDs encompass compulsive shopping, eating and gambling, hypersexuality, **dopamine dysregulation syndrome** and punding [36]. Whilst ICBDs clearly represent disruptions of motivated behaviour, in this review we will not focus on this interesting group of disorders, given that their aetiology is probably more related to changes in habitual brain systems that give rise to compulsive behaviours, in a similar way to addictive disorders [36,37].

Value-based decision making as a framework for understanding disorders of motivation

Over the past two decades, frameworks for understanding normal goal-directed behaviour have been increasingly applied to the study of clinical disorders of motivation, including apathy [9,38,39]. The mechanisms underlying goal-directed behaviour in humans are complex, but a central element is the relationship between actions and their outcomes. Work in people with PD to understand apathy has mainly focused on decision-making approaches that probe this relationship, and particularly how loss of motivation may be associated with changes in sensitivity to rewarding outcomes and/or the costs of the actions required to obtain them [8,40]. Value-based decision making can be conceptualised as occurring across multiple phases. These include generation of potential options for behaviour, choice between options, perseverance with the chosen option to the goal, and learning about the value of choices to update future behaviour [8,38]. A large body of evidence spanning rodent, non-human primate, and human neuroscientific investigation has demonstrated these processes are dissociable but interlinked components of goal-directed behaviour, and are instantiated neurally in similar brain regions [41,42]. Importantly changes in these regions, which include the ventral striatum, thalamus, anterior cingulate cortex, medial and lateral orbitofrontal cortex, and supplementary motor areas are also associated with apathy in PD, and can even predict its future development (Figure 2) [39,43,44].

Reductions in dopaminergic function are a core feature of PD. Although classically described within nigrostriatal pathways, it is clear there are also variable changes within mesolimbic dopaminergic systems. In healthy individuals, the mesolimbic dopaminergic neuromodulatory system is central to the different phases of value-based decision making [42,45–49], and there is clear evidence linking disruption of this system to apathy in PD [40,50–53]. There is therefore a strong anatomical and pathological backdrop to suggest that motivational deficits in PD could be due to disruption of value-based decision-making processes, and that changes in dopaminergic signalling may have a key influence on this. In the next section, we review empirical evidence from studies conducted in people with PD that have tested this broad hypothesis, probing decision-making mechanisms and motivation.

As a side note, in both the decision making and clinical literature alternative terms to value-based decision making are also used. In fact, much of the investigation of apathy mechanisms in PD has used the terminology of disrupted effort-based decision making. In trying to add clarity to the terminology, we note, first, that neural signals associated with reward, cost (effort or time) and value (i.e., reward discounted by cost) can be clearly dissociated in human and non-human studies

Value-based decision making: a framework within which to understand motivated behaviour. It includes the cognitive processes needed to identify and evaluate potential options for behaviour, select and persist with actions to a chosen goal, and learn from the outcomes of these actions, whilst also monitoring for alternative better courses of action. This enables adaptive behaviour in the context of a changing environment.

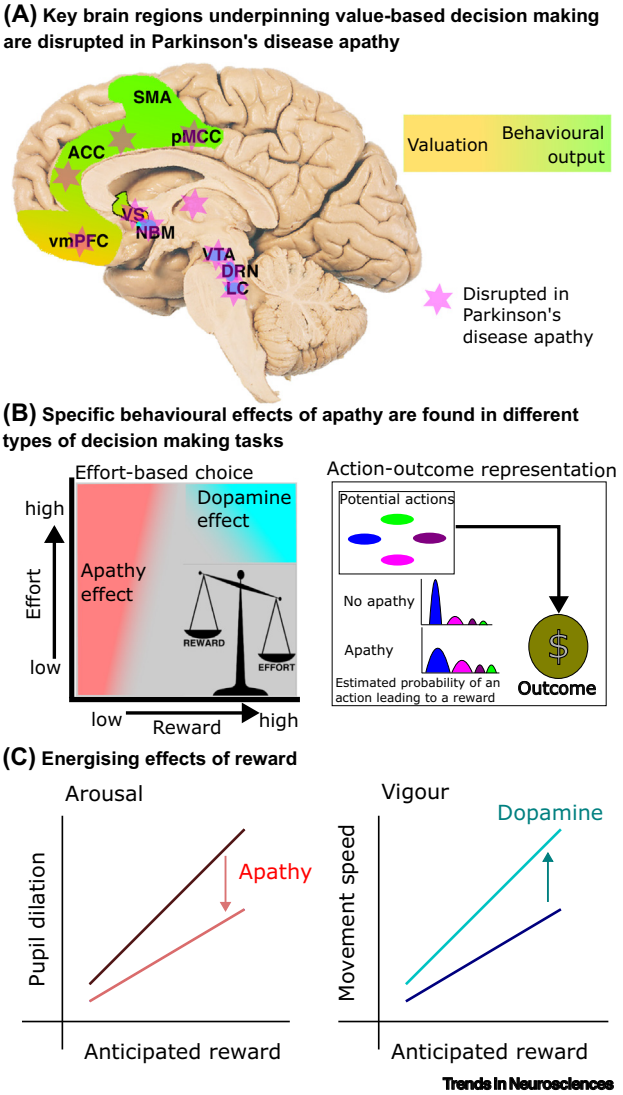

Figure 2. The anatomical and neuromodulatory correlates of value-based decision making show substantial overlap with the correlates of apathy in Parkinson's disease (PD). (A) Substantial work in rodents, non-human primates, and humans has highlighted key brain regions underpinning value-based decision making. These include the medial frontal cortex, as well as subcortical areas, including the ventral striatum (VS), anterior cingulate cortex (ACC), and ventromedial prefrontal cortex (vmPFC), supported by dopaminergic, cholinergic, noradrenergic, and serotonergic neuromodulatory systems. In the schematic, the relative weighting of regions towards valuation (of reward and effort) and behavioural response is implied by the gold–green colour gradient. Disruption (functional or structural) of these same areas is associated with PD apathy (depicted by pink stars) across imaging studies (see main text for more details). (B) Left panel: PD apathy and dopamine show distinct effects on effort-based choice. When weighing up rewards against the effort costs to obtain them, PD apathy is associated with reduced incentivisation by low-reward offers, while dopamine increases acceptance of offers requiring high effort for higher rewards for both apathetic and non-apathetic patients. Right panel: Apathetic behaviour may also result from disrupted linking between possible actions (here button presses) and their outcomes (e.g., a reward). In such experiments, the probability of each button (when pressed) leading to reward varies across the task, and participants must keep track of these likelihoods (or action–outcome representations) in order to perform well. Computational models can be used to estimate the precision of these representations in individuals, based on their choices. (C) Reward has primitive energising effects in the brainstem. Pupillary dilation in response to reward, which may index noradrenergic function, is blunted in PD and further in PD apathy (left), while vigour (motor speeding with reward) may rely on nigrostriatal dopamine release. Abbreviations: DRN, dorsal raphe nucleus; LC, locus coeruleus; NBM, nucleus basalis of Meynert; pMCC, posterior mid-cingulate cortex; SMA, supplementary motor area; VTA, ventral tegmental area. (A) Adapted from [8], (B) from results in [11] (left) and [85] (right).

[41,54–57]. Secondly, historically the term value-based decision making has tended to refer to situations where reward is devalued by uncertainty or time, or where value must be learnt. However, in the more recent literature, the term is often used in a broader meaning that also encompasses effort-based decisions (where the value of an action includes an effort cost).

Distinct apathy- and dopamine-related effects on decisions in PD

A clear pattern of altered choice behaviour, associated with apathy, has been demonstrated by experiments in which people with PD make decisions about whether or not to incur costs to obtain rewards. Individuals with apathy are less willing to exert physical effort for low rewards but,

once reward levels are high enough, even as required effort levels increase, people with PD apathy are just as likely to accept offers as their no-apathy counterparts (Figure 2) [11]. Such altered responding is often described as reward insensitivity and is also reflected in physiological responses of PD patients with apathy to rewards [58]. The general pattern of these findings extends to cognitive (rather than just physical) effort [59], and to more 'real-world' effort exertion situations [60]. Importantly with these experiments, performance of no-apathy people with PD, at least on choice and when ON dopaminergic medications, does not differ from healthy controls, suggesting that changes in decision making are indeed specific to apathy, rather than being more generally disease related.

The natural next question, in the context of PD pathophysiology and the importance of dopaminergic signals for normal motivated behaviour, is whether the apathy pattern of choice behaviour is related to altered dopamine signalling. Two relatively large studies in patients with apathy have addressed this question via a counterbalanced ON–OFF dopamine medication design [11,59]. Somewhat surprisingly, although dopamine state clearly influenced the decisions of people with PD, it did so irrespective of their motivational status. People with PD, both with and without apathy, ON their medications were more likely to accept offers of medium/high reward that required high physical or cognitive effort (Figure 2). These results – the mobilisation of higher effort levels for higher rewards – are also consistent with the effects of dopamine on choice behaviour in no-apathy PD patients [61,62].

Therefore, although both apathy and dopamine manipulations change effort-based decisions in people with PD, they each affect different aspects of the reward/effort decision space – which presumably correspond to different situations in daily life – and do not seem to interact with each other in this context. One potential caveat to interpretation of these ON–OFF studies is that dopaminergic treatment in PD is generally titrated to motor symptoms and therefore may not ameliorate potential deficits in the mesolimbic pathways that are closely tied to motivated behaviour. An experimental design that included 'OFF', 'ON', and 'Supra-ON' states could theoretically resolve this question.

Despite these important differences in effort-based choice, there remains significant evidence within other components of value-based decision making linking dopaminergic functioning to apathy in PD. More broadly, it has been suggested that the motor deficits of PD are closely related to reduced motivation [62,63]. Accordingly, dopamine increases motor energisation and reward responsiveness in healthy people, and in PD it increases motivation for action-contingent rewards [64,65]. This dopaminergic energisation ('vigour') is coupled with increased autonomic arousal in response to rewards, which is blunted in apathy [58] and is also selective to situations where actions are required to attain rewards [66]. Finally, to add to these findings, a recent study in early, untreated people with PD (albeit without high levels of apathy), found that reduced reward incentivisation (indexed by choice of force exerted to gain rewards at different levels) was linked to both changes in motivation and levels of striatal dopaminergic binding [50].

Overall, the work discussed in this section suggests a complex relationship between apathy, dopamine, and decisions to exert effort for reward in PD. A possible way to explain the patterns of findings discussed earlier is that dopaminergic disruption is more directly related to motivational disturbance before an apathy phenotype is established, driving changes in motivation that lead to apathy via shifts in a combination of effort-based choice, vigour, and learning. By contrast, once apathy is established, the effects of dopamine manipulations on effort-based choice may dissociate from those of apathy. The stage of PD at which apathy develops may also be important in terms of the relative contribution of dopaminergic systems. Finally, there is also the important

possibility that dopamine and apathy are linked in PD via mechanisms not probed by effort-based decision-making tasks, such as executive functions, which we discuss later in this review.

Probing the physiological mechanisms underlying altered decision patterns in PD apathy

While this behavioural work discussed in the previous section has yielded insights into the nature of cost–benefit disruption in PD apathy, an open question remains regarding the physiological underpinnings of these changes (Figure 3). The use of computational analysis techniques (discussed in the next section) may give access to latent cognitive processes that animal work has demonstrated underpin both perceptual and value-based decisions, providing the next step in understanding how a change in dopamine (for example) leads to the observed changes in decision making described in the previous section [67–69]. However, crucial to advancing understanding is the ability to relate these models – and more basic analyses of behaviour – to neuronal activity. Studies in humans have provided some insights in that regard. Studies using surface electroencephalography (EEG), for instance, have shown that PD apathy is associated with altered spectral power at the time of reward cues and during incentivised movement [70,71]. Further, the use of DBS as a treatment for motor symptoms of PD has provided an important new avenue for exploring neural changes in PD via intracranial recordings during decision making [10,72–75]. Although currently limited by the targets of these systems (which in PD is most often the subthalamic nucleus, but in some cases also the globus pallidus and other brain regions), these studies have revealed neural signals associated with the value of options during decision-making tasks, and changes in these signals when reward and effort requirements are manipulated. As a potential caveat to this line of research, it should be noted DBS itself has in some studies been associated with the development of apathy [20]. Better understanding of this association and the reasons for it represents an important goal for future work. Possibly the

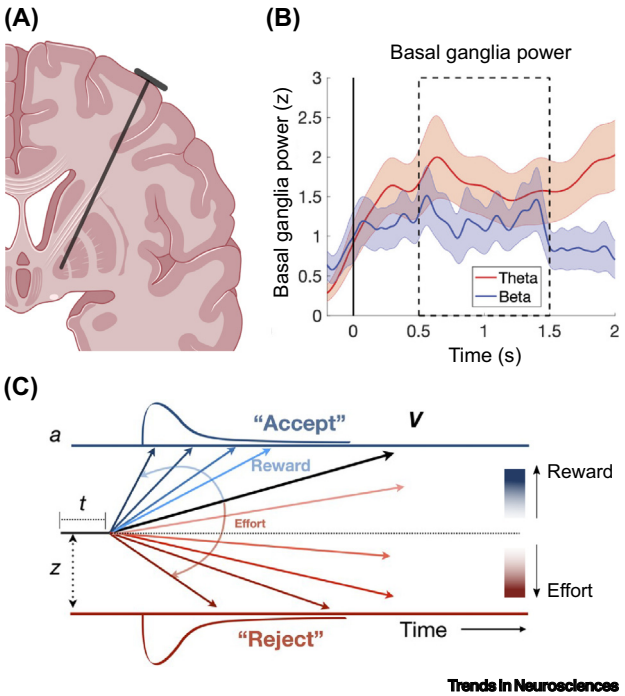

Figure 3. Recording local field potentials (LFPs) via implanted deep-brain stimulation (DBS) units can offer insights into the neurophysiology of motivational disruption. (A) Implanted DBS units are used to treat motor symptoms in a subgroup of people with Parkinson's disease (PD). (B) These can be used to record LFPs as patients perform decision-making tasks – here a demonstration of changes in LFP power in response to varying effort requirements. (C) Models of choice behaviour can be used to enhance the utility of LFP recordings to inform questions about motivational disruption. One example is the drift diffusion model, which conceptualises the cognitive processes underlying value-based decisions as an accumulation of evidence towards a bound, which when reached corresponds to a decision to act. Key parameters include the rate of this accumulation, drift rate (*v*), the threshold or bound (*a*), bias towards one response (*z*), and non-decision-related time (*t*). Here, both increasing reward and increasing effort are shown as increasing the drift rate (*v*) towards the accept threshold (reward) or reject threshold (effort). (B) Adapted from [10], (C) from [69].

greatest utility from approaches incorporating DBS for deeper physiological understanding of apathy will come from studies in people whose apathy predates DBS insertion, or else develops at a future timepoint distant from the procedure.

Decision-making models for studying disrupted motivation in PD

Models of decision making can take different forms, and are used to identify and quantify latent cognitive processes that may align with the neural processes underlying value-based decisions [67]. Sequential sampling models – a class of models that includes the **drift diffusion model** – share the same core principle that evidence accumulates towards a bound that, when crossed, corresponds to a decision being made [76]. By contrast, reinforcement learning models capture a simplified decision process but allow expected decision values (reward and costs) to update within subjects across an experiment, reflecting the learning process. Combinations of these approaches exist as well; for example, the reinforcement learning drift diffusion model [77]. Depending on the specifics of the behavioural task at hand, some models may be better aligned with the experimental context. As an example, some of the tasks that have been applied in neurological populations (e.g., the Apple Gathering Task; Figure 2) minimise learning requirements, and aim to examine primarily the choice phase of decision making. This type of task renders sequential sampling models more suitable. Conversely, reinforcement learning or combination models would be more suited for tasks examining specifically learning processes, as are sometimes used to study dysregulated motivation in PD. Use of computational models allows fine-grained analysis of experimental manipulations. For example, in the case of the drift diffusion model, cholinergic contributions to apathy may affect the rate of evidence accumulation (drift rate) or its variability. Given the connections between cholinergic signalling and attention, this reflects the idea that attention may guide or bias the accumulation of value signals as a decision evolves [78,79]. Dopamine may modulate the cost for controlling decision noise, leading to improved speed and accuracy when individuals are motivated [80]. While these models remain to be applied to PD apathy, it should be noted that more generally in PD, both dopamine (ON vs. OFF) and subthalamic nucleus DBS stimulation affect drift rate and threshold (respectively) [81]. Work in other disorders also suggests the potential utility of these approaches, with changes in drift rate at different levels of reward and effort varying as a function of motivational status in both Huntington's disease and cerebral small vessel disease [68,69].

A range of other computational models relevant to motivation exist, each with strengths and limitations. For example, the growing urgency to reach a decision as time elapses, independent of evidence accumulation, can be captured by the urgency-gating variation of the drift diffusion model [82]. Models can also index attention and curiosity using the attentional drift diffusion model, acceptance of the status quo using single-bound models, cognitive effort using models with a cost of control, and fatigue using cumulative cost models [7,67,78,80]. Overall, leveraging decision-making models in conjunction with the neurophysiological manipulations provided by clinical advances in the treatment of PD provides an allée to advance understanding of the brain mechanisms giving rise to motivational disruption in PD (Figure 3C).

Beyond choice: multiple mechanisms contributing to motivational disruption?

Inspection of any raw effort-based choice dataset shows significant variation in responses between individuals with apathy, suggesting that more than one mechanism might be important for the final observed phenotype of reduced goal-directed behaviour. To date, less work has examined other components of value-based decision making in the context of pathological loss of motivation in PD, and further defining apathy associated disruptions in these is an important priority for the field. This is particularly so given that apathy in PD, as with other neurodegenerative conditions, develops slowly, and subtle shifts in learning processes or environment evaluation in a

person with initially normal motivation could, across time, lead to the reduced reward incentivisation associated with a clinically apathetic state. Indeed, a study utilising EEG to measure an event-related potential associated with learning demonstrated a blunted response in PD apathy to outcomes of choices [83]. Furthermore, a recent study utilising a probabilistic bandit-style decision-making task and fMRI in a sizeable PD population, many with clinical apathy, provided some evidence that representation of the association between actions and their outcomes is disrupted in those who have lost motivation [84]. This fits with recent work that has used Bayesian methods to examine how beliefs about action/outcome relationships might be altered in apathy, and demonstrated an influence of noradrenergic modulation on this weighting in PD apathy [85,86]. Outcomes or goals usually require perseverance across time to reach them. A robust literature associates such perseverance with dopamine signalling [46,47]. This overlaps with another class of decisions often referred to as foraging, after the behaviours they are classically important for [87]. Here the problem is often not whether to choose one of a limited set of options, but rather whether to persist with a current behaviour or switch to a potentially more rewarding one. For these types of decisions, an estimate of the background environmental reward rate is a crucial signal of the relative value of options and the opportunity cost of the chosen behaviour [87]. As with associating actions and their outcomes, a breakdown in representation of this reward signal could disrupt goal-directed behaviour [88]. Looking ahead, it will be important to understand how processes such as action–outcome representation and background reward rate estimation relate to each other, and also whether changes in these processes are important at specific stages of apathy development.

In sum, the clinical phenotype of apathy in PD has multiple potential underlying neurobiological contributors, which will differ in importance between patients. Because perturbations of different biological components may be best treated by differing pharmacological or non-pharmacological approaches, selecting the best treatment for an individual person with apathy will depend on robust ways to assess the mechanistic underpinning of a person's loss of motivation. One general limitation of studies investigating apathy mechanisms in PD (and elsewhere) has been the use of group-level analysis strategies that effectively average across individual differences. While undoubtedly this approach has led to important mechanistic insights, and is appropriate in the setting of relatively low numbers of participants, a crucial next step will be to apply decision-making tasks to larger groups of people with PD with a range of motivational states, ideally longitudinally. Utilising online resources/testing is one way of reaching a wider spectrum of people. Collecting sufficiently large datasets should allow comprehensive dissection of the PD apathy phenotype, which may then be used as a springboard to inform treatment stratification for clinical trials (see Outstanding questions). Indeed, such a general approach has recently been applied to better understand which cognitive processes respond to particular psychotherapy interventions used for treatment of mental health disorders [89]. In this recent study, the specific mechanistic effects of cognitive and behavioural therapy interventions were investigated using computational analyses of decision-making tasks administered to individuals via online platforms.

Important observations from the clinic

Theoretical frameworks and empirical findings from healthy human and from preclinical animal model studies do not always translate directly into real-world patient settings. In this section we highlight the gaps in existing knowledge, revealed through the study and management of people with PD, and where current frameworks require revisiting.

Apathy and impulsivity co-occur in humans

Historically, especially in animal work, a reduction or absence of action has been denoted as apathy, whereas premature action has been construed as impulsivity [90,91]. That is, the two exist

at opposite ends of a behavioural spectrum – often suggested to be mediated by dopaminergic tone. However, in PD and other disorders, apathy and impulsivity are in fact strongly associated, frequently coexisting in individual patients, which suggests a closer aetiological link [29–33,92]. Notably, decision context – which is harder to manipulate in animal work – may determine whether disruptions to value-based decision-making mechanisms manifest as an impulsive action or lack of action. For example, lack of persistence during an effortful task may seem impulsive when other tasks are available to switch to (premature switching), but may seem apathetic when no other tasks are available in the immediate environment. Similarly, within a foraging context, impaired ability to estimate environmental reward availability could lead to a decision maker relying on salient 'foreground' features rather than the background in which these are embedded, again potentially manifesting in impulsive or apathetic behaviours.

More broadly, it is important to note that observable traits in non-humans, such as reduced or early lever pressing, may not accurately reflect the constructs of apathy or impulsivity seen in humans – but merely show superficial resemblance (e.g., as discussed in [93]). Indeed, there are many possible ways to measure 'apathy' in humans, each with benefits and drawbacks, and defining precise measures for apathy represents a major research challenge (Figure 4). Furthermore, anatomical differences between species are particularly prominent in some key regions for goal-directed behaviour (e.g., prefrontal and anterior cingulate cortex), with inconsistent nomenclature and challenges in defining homologous brain regions rendering translation of findings between species challenging [94,95]. Overall, human decision-making experiments that concurrently examine both apathy and impulsivity are an important gap in the literature. The view that apathy and impulsivity occupy opposite ends of a behavioural spectrum joined by a dopaminergic axis – whilst appealing – is not fully consistent with empirical data. Neuromodulatory systems beyond dopamine also play crucial roles in motivated behaviour, and in the following section we turn to these other systems relevant to understanding altered motivation in PD.

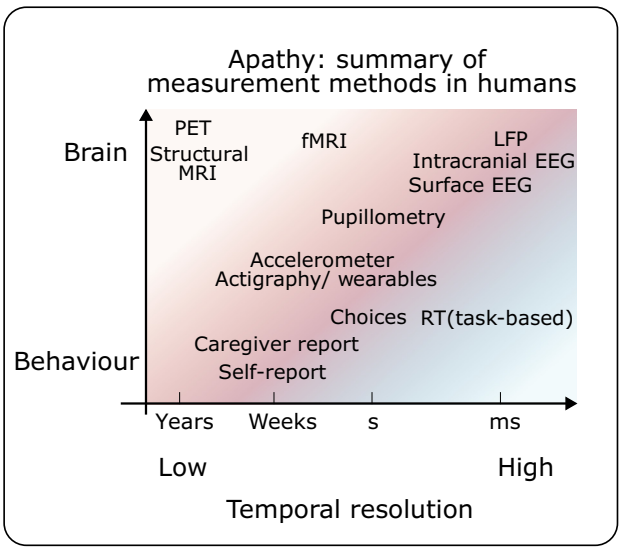

Figure 4. Different methods for measuring motivational disruption in humans. Methodological approaches for studying motivation disruption include: questionnaire-derived measures of a person's motivation; performance on behavioural tasks; objective measures of activity and physiological changes to reward; imaging techniques assessing the structural, functional, or neuromodulatory correlates of apathy's presence; and electrophysiological recordings during decision making or at rest. These vary in both the dimension of measurement (behavioural outputs or brain mechanisms) and time to change (temporal resolution). As such, it is not always clear that they are tapping the same constructs, which is a challenge for apathy research. Furthermore the neural signalling of immediate cost and benefit may not translate to longer-term measures of neurodegeneration. These differences between behavioural and neural measures, and between timescales, may account for some conflicts in the literature, and further work is needed to connect the dots between these disparate measures. Abbreviations: EEG, electroencephalography; LFP, local field potential; PET, positron emission tomography; RT, reaction time.

Pharmacological treatments for apathy in PD suggest multiple neurotransmitter systems contribute to amotivation

As it has become clear that dopamine's contribution to motivational disruption is more nuanced than initially thought, several other neurotransmitters have been studied as modulators of motivation, including acetylcholine, noradrenaline, and serotonin. Limited evidence and significant variability in response between patients means there are currently no FDA-approved treatments for apathy in PD, but nevertheless medications can sometimes substantially improve motivation [96].

Although reductions in apathy in PD can be observed with dopaminergic medications [97], including dopamine agonists, perhaps most intriguing is that significant benefits can also be seen with cholinesterase inhibitors, which act to increase synaptic acetylcholine levels [25,26,98–100]. This may align with the finding in animals that acetylcholine is critical for motivation [101]. One potential mechanism for this is that acetylcholine release in the striatum facilitates dopamine release via nicotinic receptors driven by corticostriatal glutamatergic input [102], which is in turn inhibited by dopamine via D2 receptors [103]. This may generate local 2-Hz waves [104,105] that effectively decouple axonal dopamine release from firing at the soma [106]. Emerging work in healthy humans supports this, with cholinergic antagonists decreasing vigour while increasing willingness to exert effort [107,108]. This could fit with a distinction that has been made in substance and mood disorders, between 'activational' motivation, which describes energisation of action, and 'directional' motivation, which describes effects on decision making [42].

However, it would be overly simplistic to suggest that dopamine and acetylcholine are the only neuromodulatory systems related to apathy and decision making in PD (Figure 5). Noradrenergic systems are crucial for supporting effort production and energisation of behaviour, and facilitate expectation of outcomes [86,109]. Their disruption has been associated with PD apathy, whilst methylphenidate (which has noradrenergic as well as dopaminergic actions) improved apathy in a small sample of individuals with PD [110,111]. There is also a relationship between apathy and serotonergic changes, possibly mediated via decision-making mechanisms [112–115]. Importantly, the baseline state of any given neuromodulatory system associated with apathy

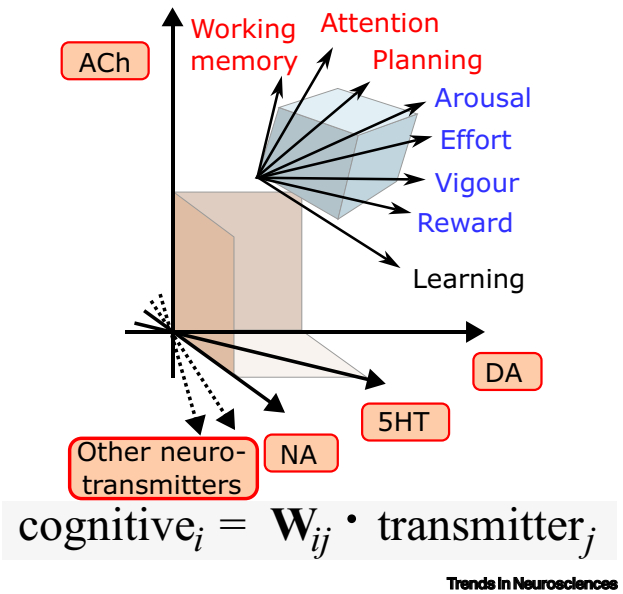

Figure 5. Complex interplay of neuromodulators in motivated behaviour. An important direction in recent work has been to map neurochemical axes onto the dimensions of cognition that contribute to apathy in Parkinson's disease (PD). Work has centred on four core neurotransmitter systems: acetylcholine (ACh), dopamine (DA), serotonin (5HT), and noradrenaline (NA). The solution is a many-to-many mapping between cognitive and neurotransmitter multidimensional spaces. The figure's equation formalises this notion, where each cognitive component of motivation may load differently onto the pattern of neurotransmitter function. Future integrative work should identify the matrix weights based on meta-analysis of human and animal studies.

presence seems crucial for the degree of response to subsequent drug manipulation [86,113,116]. Clinically, this emphasises the importance of considering each person's behavioural phenotype and neurochemical profile when selecting medications that act on these systems [115]. Along these lines, studies have begun to use medications with multiple actions; preliminary evidence from a small open-label study in people with PD who have depression suggests that the combined serotonin-dopamine-noradrenaline agent vortioxetine improved apathy [117]. Cognitive behavioural therapy may also be a viable option either by itself or coupled with pharmacological treatments [118]. Other psychological therapies such as positive affective therapy are also emerging as methods to target motivation and reward sensitivity [119], and mindfulness, exercise, music, and transcranial magnetic stimulation have all been proposed (reviewed in [120]). Overall the clinical experience of treating apathy in PD emphasises the complexity of both the disease and the normal process of goal-directed behaviour it is affecting, and underlines the need for better understanding of each.

Executive dysfunction as a link between dopamine and amotivation

Traditionally apathy has been conceptualised as a neuropsychiatric symptom, lying outside the scope of clinical neuropsychological testing. Until recently, cognitive assessments in PD have typically focused on memory, executive and visuospatial function, and language rather than 'hot' or affective symptoms or reward processing. More generally, though, cognitive neuroscience treats reward as a central aspect of cognition; for example, in learning and goal-directed behaviour, and in studying goal representation and computation. As such apathy, defined more broadly as a deficit in goal-directed behaviour, involves more than just value-based decision deficits. Directing action towards goals involves planning ahead – which is also disrupted in PD [121,122]. Indeed, several dimensions of executive function, such as attention, working memory, planning, and creativity are crucially modulated by dopamine and altered in people with PD [123–125]. Dopamine also plays a role in stabilising working memory in PD [126,127] and facilitates cognitive effort [128], although in healthy people these relationships are less clear [129]. Overall, though, executive dysfunction is a core feature of PD strongly linked to changes in dopamine signalling [130–132]. Considered together, these observations suggest that dopamine might mediate apathy via its effects on executive function, independent of any association with reward sensitivity. This view is supported by correlation between apathy and both cognitive decline and executive dysfunction [3,13,19]. Executive function may also be important in patients' being unaware of their own apathy [133,134]. More broadly, these links between motivational disturbance, specific cognitive functions and dopamine suggest that a broader view of value-based decision making and apathy is required. This expanded framework should include the cognitive processes required to both prepare for and support decision making, as well as successfully enact goal-directed behaviour (Figure 6, Key figure).

Concluding remarks

Disrupted motivation is one of the most significant contributors to impaired quality of life in PD. Human goal-directed behaviour is a complex, multifaceted entity, and the disruption of any of multiple different components that underpin it can lead to the final observable phenotype of apathy. Furthermore, despite significant advances, current understanding of core neuroscientific issues such as how the brain makes a value-based decision, or how different neuromodulatory systems interact to support cognitive processes crucial for goal-directed behaviour, remains incomplete. However, translating current theories of one crucial aspect underpinning normal goal directed behaviour – value-based decision making – to the clinical sphere has led to significant progress in understanding the motivational problems encountered by many people with PD. Already, this provides a schema within which to discuss these problems with affected people and their families in the clinic, and the importance of this should not be underestimated.

Outstanding questions

Can mechanistically different subgroups of PD apathy be identified using decision-making tasks applied (possibly online) to larger groups of patients than most studies to date?

Which computational models of decision-making tasks best capture the latent cognitive constructs pertaining to motivation, and which ones are altered in individuals with motivational loss?

Can computational outputs derived from decision-making tasks be used to individualise treatment selection, and as endpoints in clinical trials of PD behavioural treatments?

Neural recordings from PD patients treated with DBS have rarely been obtained from those with apathy. What neurophysiological signatures characterise patients with normal motivation versus those with apathy?

What is the relationship between apathy and anhedonia and is this mediated by metacognitive processes such as insight into loss of motivation?

Although apathy and impulsivity describe seemingly opposite behaviours, the two co-occur. What is the mechanistic and computational framework that describes this observation?

Impulsive traits are broad and manifest across many behavioural contexts, but impulse control disorders tend to be isolated/selective. Why does this discrepancy, in the setting of a general neurochemical disturbance, occur?

Central to human motivational symptoms are their subjective and cognitive components. Animal decision-making studies contribute significant physiological and pharmacological knowledge, but how does animal behaviour (e.g., in lever-pressing tasks) map onto human symptoms?

An under-recognised confounder of patient decision-making tasks is that patients with apathy may be worse at task switching, inhibition, planning, and working memory. What influence does executive function have on

value-based decision-making studies, in both motivated and amotivated states?

Key figure

Conceptual relationships between critical factors overlapping between apathy, impulsivity, and decision making

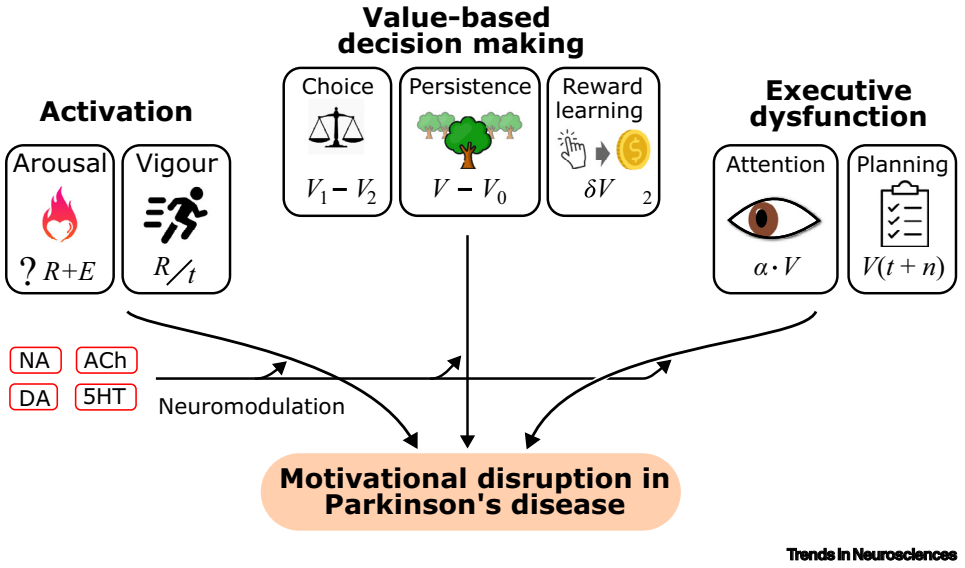

Figure 6. Each factor has a distinct computational framing, summarised in the simplified equations under the terms. R = reward, E = effort, t = time, V = estimated value of an option or state (potential reward discounted by costs), V_0 = environmental value, δV = update in value, αV = attentional gain amplifying value during decision process, $V(t+n)$ = future reward. Neuromodulators make distinct contributions to each cognitive process. Abbreviations: 5HT, serotonin; ACh, acetylcholine; DA, dopamine; NA, noradrenaline.

Looking ahead, identifying which specific mechanism(s) have been impaired in an individual with apathy is an important but significant challenge on the path to effective treatments. The application of computational models to decision-making tasks, collected in large numbers of people with PD across the spectrum of motivation, and combined where appropriate with physiological recordings, may offer the nuanced understanding of behavioural change that is needed to better design and direct therapies. The importance of motivation for overall quality of life means these approaches will also provide important behavioural indices that could serve as endpoints in clinical trials aimed at modifying progression of PD. Integrating measures of cognitive functions such as attention and working memory into decision-making tasks is also crucial to the aforementioned goal, and to better understand the interaction of neuromodulators such as dopamine, acetylcholine, and noradrenaline with apathy and decision making. At the same time, it is important to better delineate the relationship between apathy and impulsivity, and how the overlap between the two relates to neural representations of decision context. And, as an overarching challenge, mapping the knowledge derived from decision-making studies in animals to the subjective and objective elements that comprise human motivational symptoms remains a crucial goal. These are not straightforward questions to answer, but the importance of the problem of apathy for people with PD, combined with the additional insights into normal behaviour this field of research reveals, should be more than sufficient motivation for scientists and clinicians to tackle these crucial questions over the coming years.

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Declaration of interests

The authors have no competing interests to declare.

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