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Updating the role of dopamine in human motivation and apathy

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Apathy is a paradigmatic disorder of motivation, and is encountered across a breadth of neurological and psychiatric disease. Importantly, apathy is not a unitary symptom — rather, it is a syndrome comprising a constellation of impairments across multiple domains of behaviour. Recent work has focused on characterising the distinct neurophysiological mechanisms that give rise to clinical apathy. Although dopamine has long been known to have a central role in complex behaviour, current data indicate that its roles in the learning and valuation of effort and reward may underlie distinct subtypes of motivational impairment. A focus of future work will be to map the involvement of dopamine in motivated decision-making to separate domains of apathy. This will facilitate not only a greater understanding of the neurobiology of motivational disorders, but also the development of targeted, neurobiologically based treatments.

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Apathy — a multifaceted syndrome of impaired motivation

The hallmark of apathy is a reduction in voluntary, goal-directed behaviour. It is a common and debilitating disorder across many neurological and psychiatric conditions, including Parkinson's disease, dementia, stroke, depression and schizophrenia. Importantly, apathy does not represent a single symptom, but a syndrome that consists of impairments across multiple domains of behaviour (Table 1). Even the earliest operational definitions of apathy considered it to comprise 'behavioural,' 'cognitive,' and 'emotional' elements [1], and more recent accounts propose that apathy may manifest as problems with intellectual curiosity, action initiation, self-awareness, emotion, and interest/enthusiasm (Figure 1, right panel) [2,3]. Although such distinctions convey the idea that apathy is multidimensional, the heterogeneous clinical criteria currently being used reflect a lack of nosological and ontological clarity on the condition.

Until recently, the role of dopamine in decision-making has been considered in a largely separate literature, grounded in a strong neurophysiological tradition. This literature has demonstrated that dopamine is unequivocally involved in critical processes underlying motivated behaviour (Figure 1, left panel). Dopamine mediates the incentive salience of a reward [4]; the evaluation of an action's costs and benefits [5]; reward expectation and reinforcement learning [6–8]; and action invigoration [9–14]. Many of these functions are critical for the multiple stages of human decision-making more generally, including the representation of the options on offer; the formation of decision variables that represent the value of these options; the selection of the more preferable option; the programming of relevant motor commands; and the evaluation and learning of action-reward outcomes [15,16].

The contrast between the literatures on apathy and dopamine is stark when considering that current conceptualisations of apathy make few references to its possible underlying neural or computational mechanisms (Figure 1). An important focus in reconciling these two literatures will be to determine how the multifaceted roles of dopamine in motivated decision-making map onto the deficits that characterise clinical apathy in humans [17–20]. Here, I survey the evidence that dopamine deficiency in humans results in symptoms of apathy. I then describe recent approaches to dissect apathy into computationally distinct elements, and consider recent evidence for the dissociability of different components of apathy, for which dopamine might play unique and specific roles. Finally, I discuss the challenges of applying dopamine as a treatment for apathy, and the need to frame it in the context of a wider motivational network.

Dopamine dysfunction is associated with human apathy

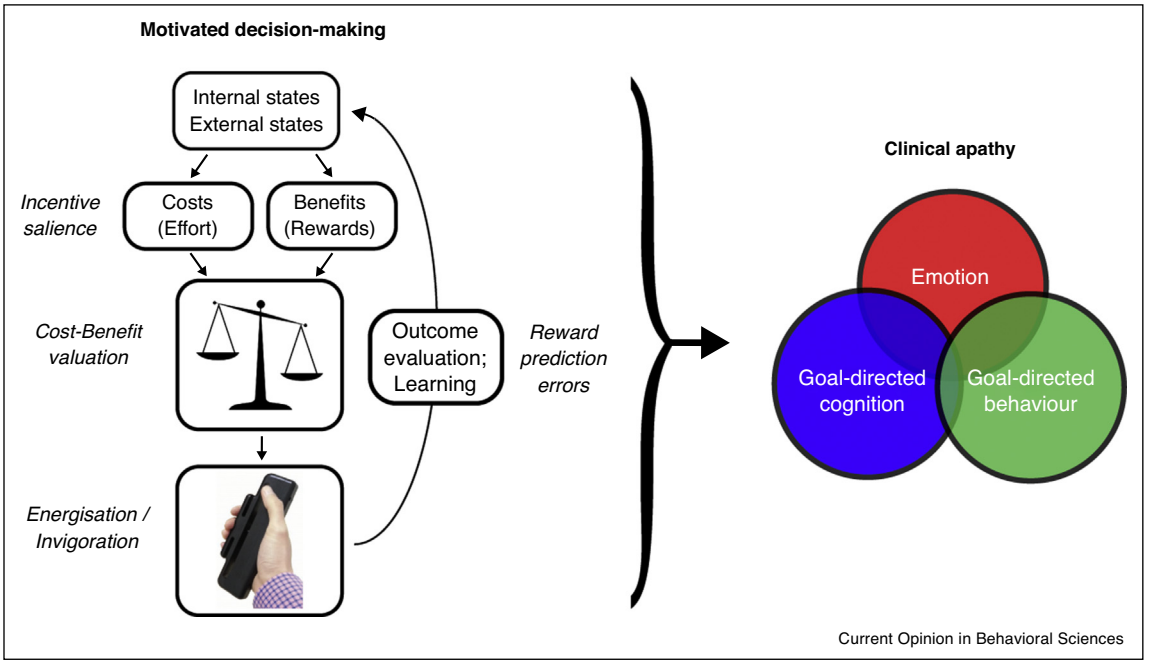
Apathy in humans is often examined in the context of patient models of dopamine deficiency, such as Parkinson's disease (PD) [21]. Apathy is a common feature of PD, with prevalence rates of ~40% [22]. Observational studies reveal a close association between parkinsonian apathy and dopamine deficiency. For example, apathetic symptoms emerge when doses of antiparkinsonian

Table 1

Putative subdomains of the apathetic syndrome. Apathy is usually characterised as a reduction of motivated behaviour, but has been subject to a heterogeneous set of definitions and classifications. Nevertheless, all definitions assume that apathy is comprised of distinct subtypes or subdomains

Author	Year		Proposed components/subdomains		
Marin [1]; Starkstein [73]	1991; 2000	All of:	• Goal-directed overt behaviour • Goal-directed cognition • Emotional concomitants of goal-directed behaviour		
Levy and Dubois [19]	2006		• Emotional-affective • Cognitive • Auto-activation		
Sockeel *et al.* [2]	2006		• Productivity • Interests • Taking initiative	• Novelty-seeking • Voluntary actions • Emotional responses	• Concern • Social life • Self-awareness
Castelli *et al.*, 2007	2007		• Behavioural • Emotional • Motivational		
Robert *et al.* [74]; Mulin *et al.* [58]	2009; 2011	≥2 of:	• Goal-directed behaviour • Goal-directed cognitive activity • Emotion		
Pagonabarraga *et al.* [75]	2015		• Reward deficiency syndrome • Emotional Distress	• Executive function • Auto-activation deficit	
Cathomas *et al.* [76]	2015		• Self-care • Social interaction • Exploration	• Work/education • Recreation	
Ang *et al.* [77]	2017		• Behavioural • Social • Emotional		

Figure 1



The challenge for future research on apathy will be to develop a mechanistic understanding of the distinct and separable neurobiological substrates underlying disorders of motivation. Dopamine is thought to play key roles (italicised) across multiple stages of effort-based decision-making (left panel). A separate clinical literature classifies apathy into putative subdomains of motivational dysfunction (right panel; based on Marin [1] and Starkstein [73]). However, this clinical nosology does not consider its pathophysiology. An imperative for the field will be to bridge the gap between the phenotype of clinical apathy and its underlying neurobiological mechanisms.

medication are reduced [22,23], and improve when they are increased [24]. Furthermore, overall rates of apathy tend to be higher in patients on lower levodopa equivalence doses [25–28]. The symptoms of parkinsonian apathy are thought to arise from abnormalities in dopaminergic signalling. Although the pathological hallmark of PD is neurodegeneration of dopaminergic neurons in the substantia nigra pars compacta, there is growing recognition that the ventral tegmental area is also critically involved [29], with potential downstream effects on the ventral striatum/nucleus accumbens. The link between dopaminergic dysfunction and apathetic behaviour in PD has been supported by neuroimaging studies associating apathy with morphological abnormalities in the nucleus accumbens [30]; reduced striatal dopamine transporter levels (independent of motor disability and depression) [31]; and reduced functional connectivity in frontostriatal pathways [32].

Of course, apathy is also seen in many other disorders, some of which are not typically characterised by dopaminergic deficits (e.g. dementia, stroke, traumatic brain injury). Nevertheless, neuroimaging data have implicated common areas of the mesocorticolimbic pathway in patients with these conditions who are apathetic [33,34]. For example, apathy in stroke, progressive supranuclear palsy, and frontotemporal dementia have all been associated with structural abnormalities in key frontostriatal regions and pathways [33,35,36]. In Alzheimer's disease, apathy has been related to abnormal dopamine transporter levels [37], and hypometabolism in the ventral tegmental area [38]. In schizophrenia, apathy and other negative symptoms have been attributed to a deficit in dopaminergic (D1) transmission in the prefrontal cortex (the 'revised dopamine hypothesis') [39,40]. Together, these data suggest that dysfunctional dopamine transmission within the mesocorticolimbic pathway may drive the development of human apathy across multiple disorders. However, apathy in the vast majority of these studies has been quantified through the use of subjective self-report and questionnaire-based measures (such as those listed in Table 1). Such measures, while clinically convenient, are limited in their ability to provide a mechanistic insight into the components of the apathetic syndrome.

Dissecting subtypes of apathy with effort-based decisions

A common feature across many definitions of apathy is a reduction in goal-directed behaviour (e.g. a loss of self-initiated behaviour, or an inability to sustain behaviour) (Table 1). Recently, research on apathy has experimentally operationalised such impairments as a reduced willingness to engage in high levels of effort in pursuit of potential rewards [41•]. This is based on the idea that effort is aversive, and that organisms aim to minimise the amount of effort required to obtain a reward. This approach has been very fruitful in research on activational aspects of behaviour in non-human animals, and has reliably shown that dopaminergic lesions to corticostriatal pathways reduce the amount of effort an animal is willing to invest in return for rewards [42].

Effort versus reward sensitivity

Human studies using this approach typically require individuals to reveal their preference for the amount of effort they are willing to exert for a given reward, with effort usually operationalised in terms of the force applied to a hand-held dynamometer, or the number of times a button is pressed [3]. By systematically varying both the required effort and the available rewards, several studies have revealed that patients with basal ganglia disease have both heightened sensitivity to effort costs [43,44], as well as lowered sensitivity to potential rewards [45•,46]. Importantly, both the higher effort sensitivity and lower reward sensitivity in apathy appear responsive to treatment with exogenous dopamine [43,45•,46].

The utility of effort-based decision-making paradigms in investigating human apathy is reflected by the large number of disorders in which they have been applied. For example, deficits in effort-based decision-making have been found in PD [43,44], depression [47,48], and schizophrenia [49,50]. The apparent ubiquity of such impairments across a wide range of disorders raises an obvious question: is impaired effort-based decision-making a universal feature of all forms of apathy, independent of the underlying disease process, or does clinical apathy represent the final common pathway of one or more dysfunctional mechanisms? [51].

Dissociable effort and reward sensitivity

To address this question, one focus has been to systematically distinguish effort sensitivity from reward sensitivity in a single task. Emerging data from patients with selective basal ganglia lesions indicate that these two components of effort-based decisions are indeed dissociable [52]. This has been further confirmed by computational models that have parameterised an individual's effort sensitivity independent from their reward sensitivity. Such studies have shown that reward sensitivity in PD is preferentially affected by a dysfunctional mesocorticolimbic pathway, while motor activation/deactivation is driven by the nigrostriatal route [53•]. The dissociability of effort and reward sensitivity suggest that they may be differentially affected by separate disease processes, and give rise to the common clinical manifestation of 'disordered goal-directed behaviour' through separate pathways.

Dissociable cognitive versus physical motivation

A further refinement of this effort-based decision-making approach has been to address how individuals differ in

their motivation to invest different types of effort. Many definitions of apathy draw an intuitive distinction between impairments in goal-directed *behaviour* (i.e. physical activity) versus goal-directed *cognition* (i.e. mental activity). However, the vast majority of studies on effort-based decision-making have focused on the motivation of individuals to invest physical effort for reward. An outstanding question is whether the effect of dopamine on motivation generalises across different domains of effort. Recent studies have begun to compare the neural substrates underlying cognitive and physical effort-based decisions [54], and there is recent cross-species evidence that the subjective valuation of rewards may involve overlapping networks of domain-general and domain-specific areas [55–57]. The existence of domain-specific regions for motivation provides a neurophysiological substrate for the current distinction between 'behavioural' and 'cognitive' subtypes of apathy [58]. However, the overlap in areas that drive domain-general motivation indicates that these two putative subtypes of apathy may in fact arise from dysfunction of similar dopaminergic mechanisms [54].

Dissociable effort-based versus reward-based learning

Dopamine has a long-established role in learning — in particular, reinforcement learning of reward-related values [59]. Much less is known about the role of dopamine in learning about effort costs, even though learning is a critical component of effort and reward valuation. Recently, attention has turned to disentangling the roles of dopamine in the learning of both effort and reward values in apathy. The results of a recent study suggest that effort-based and reward-based learning are encoded in separable dopaminergic pathways. Activity in the dorsomedial prefrontal cortex was closely related to effort learning, as well as to apathy rating scores [60••]. In contrast, activity of the ventral striatum was more involved in reward-learning, and was unrelated to apathy ratings [60••]. This suggests that an action's costs and benefits are learned in parallel dopaminergic pathways, with apathy being more closely related to effort learning and prefrontal cortical activity. This dissociability of effort and reward learning is broadly consistent with data from patients with PD (i.e. with striatal lesions), showing a selective role for dopamine in learning to maximise reward, but not in learning to minimise effort [61•]. How such a dissociation maps onto apathetic behaviour will clearly be a focus of future studies.

Barriers to treatment

Several datasets — from small case series [46] to placebo-controlled trials [62] and larger cross-sectional studies [63] — have reported success in treating apathy with dopaminergic medication. However, the development of more targeted pharmacological interventions will hinge on a more refined understanding of the dynamics of dopamine neurotransmission in all of the above processes [64••,65••]. For example, existing theories propose that fast (phasic) dopamine fluctuations support learning [66,67], while much slower (tonic) dopamine changes are involved in cost–benefit valuations [5]. However, the effect of exogenous dopamine administration on altering tonic versus phasic dopamine responses in humans, and the downstream effect on behaviour, remains unclear [10].

In addition, it will be important to clarify the receptor-specificity of effort-based and reward-based processing. Some have proposed that the variable effect of dopamine replacement on apathetic behaviour in PD may be driven by a difference between levodopa and dopamine, particularly the stimulation of D2/D3 receptors [28,62,63]. The receptor specificity of dopamine to effort-based choice has been much less explored in humans than non-human animals. However, this selectivity has particular translational significance in scenarios in which non-selective dopamine agonism could have deleterious effects on a patient's other symptoms (as might be the case in schizophrenia). Thus, a more nuanced understanding of the role of specific dopamine receptor subtypes in apathy would be critical in future clinical attempts to balance the treatment of a patient's amotivation against the management of their other dopaminergic symptoms — be they motor (as in PD) or non-motor (as in schizophrenia).

Broadening the space — more than dopamine

Although the focus in this review has been on dopamine, it would be overly simplistic to postulate that a single neurotransmitter underpins the breadth of complex behaviours affected in a motivational disorder such as apathy [68]. The incorporation of other neurotransmitter systems into explanatory models of motivation and apathy promise to take the field in interesting directions. A growing body of research suggests that dopamine and serotonin have opposing roles in the learning of actions, as a function of the affective valence of a predicted outcome (a win versus a loss) [69]. More recent computational studies have found that serotonin selectively reduces effort costs, but does not change the weight of monetary incentives [70•]. This interesting counterpoint raises the intriguing suggestion that dopamine and serotonin may play complementary roles in motivation, with dopamine modulating reward sensitivity, and serotonin effort sensitivity. These computational data are consistent with the suggestion that serotonergic loss may underlie some symptoms of parkinsonian apathy [71]. Reconciling these more recent data with established data showing both effort-sensitive and reward-sensitive modulation of motivation in PD may therefore require a broader view of PD as being a disease, not just of dopaminergic dysfunction, but one also involving the serotonergic system (e.g. [72]).

Clinical apathy as a final common pathway of dysfunctional motivation

A key challenge for future research will be to determine how dysfunctional dopaminergic mechanisms map onto the clinical phenotypes of disordered motivation seen in apathetic individuals [17]. The field is now poised to shift towards a more detailed dissection of the components of human apathy, which will be critical in defining the unique deficits that are present across the breadth of neurological and psychiatric diseases. The most powerful approach is likely to combine computational models with pharmacological manipulations of dopamine, as well as in studies of patients with disorders of dopamine dysregulation, such as PD and schizophrenia. Such 'computational phenotyping' [53•] will allow us to understand how and which mechanisms and pathways are affected by specific disease processes. This in turn will be critical to understanding the different subtypes of apathy that are currently poorly clinically distinguished. Revising the current clinical criteria for apathy to reflect a more neurophysiologically based approach is likely to facilitate, not only a greater understanding of the different subtypes of apathy in the clinic, but also the development of more targeted drug treatments for this common and debilitating syndrome.

Conflict of interest statement

Nothing declared.

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