Neuroscience of apathy and anhedonia: a transdiagnostic approach

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Abstract | Apathy and anhedonia are common syndromes of motivation that are associated with a wide range of brain disorders and have no established therapies. Research using animal models suggests that a useful framework for understanding motivated behaviour lies in effort-based decision making for reward. The neurobiological mechanisms underpinning such decisions have now begun to be determined in individuals with apathy or anhedonia, providing an important foundation for developing new treatments. The findings suggest that there might be some shared mechanisms between both syndromes. A transdiagnostic approach that cuts across traditional disease boundaries provides a potentially useful means for understanding these conditions.

Loss of motivation is a common syndrome observed across neurological and psychiatric disorders. In recent years, researchers have identified lack of motivation (also termed amotivation) among substantial proportions of individuals with stroke; traumatic brain injury; common neurodegenerative diseases including Alzheimer’s disease, Parkinson’s disease and vascular dementia; rarer disorders such as frontotemporal dementia and Huntington’s disease; and psychiatric conditions such as major depressive disorder (MDD) and schizophrenia. Several syndromes associated with diminished motivation have been described. Historically, reports of these syndromes arose from diverse medical and psychological experts in the 19th century. Although different terminologies were used for different patient groups — sometimes rather loosely and interchangeably — these phenomena are now recognized to overlap greatly.

In neurological disorders, amotivation is typically categorized as the syndrome of apathy, which itself is defined as diminished motivation for physical, cognitive or emotional activity. In psychiatry, although the term apathy has also been used, amotivation is more often referred to in the context of either anhedonia or negative symptoms. Classically, anhedonia was defined by the French psychologist Ribot as an inability to experience pleasure. However, this definition was later broadened in psychiatric diagnostic criteria to include a motivational component — that is, a loss of interest or pleasure in previously rewarding activities. Recent research suggests that there might be some common mechanisms underlying both apathy and anhedonia.

Findings from studies of behaviour, computational models, neuropharmacological or optogenetic manipulations, brain lesions, deep brain stimulation (DBS) and neuroimaging — in humans and in animal models — have identified the brain systems that are dysfunctional in motivated states. The results implicate disruption of mechanisms underlying the way in which reward is processed by the brain.

Definitions

Although there has been debate, most experts now consider apathy to be a syndrome. One set of criteria for apathy builds on previous conceptualizations and has been validated across neurological and psychiatric conditions. These criteria define apathy as a reduction or loss of motivation compared with an individual’s previous state; associated with decreases in at least two out of three of goal-directed behaviour, cognitive activity or emotion; causing clinically significant impairment in everyday life; but not explained by physical or motor disability, reduced consciousness or drugs. However, this definition might not capture all aspects of apathy. For example, recent research has identified social apathy — reduced interest in interacting with other people as another possible component or dimension of the syndrome.
Some clinicians also use the terms avolition\(^5\) or abulia\(^6\). People with avolition or abulia encounter difficulty in initiating behaviours but can perform the same actions when verbally prompted to do so. Avolition can be a prominent negative symptom of schizophrenia\(^5\). An extreme form of avolition is akinetic mutism, which is characterized by little or no self-generated movement or speech\(^6\).

Anhedonia is defined as consistently and markedly loss of interest or pleasure in social activities, sensory experiences, hobbies or food and drink\(^6\). Fractionation of apathy and anhedonia into components potentially provides a way to examine similarities between the syndromes at a fine-grain level.

Along with depressed mood, anhedonia is one of the cardinal symptoms of MDD. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)\(^4\), patients meet criteria for MDD if they have five or more symptoms, one of which must be either depressed mood or anhedonia. However, anhedonia can occur outside of MDD. For example, it has long been recognized as a negative symptom of schizophrenia, and is increasingly appreciated to be an important component of post-traumatic stress disorder, eating disorders and substance use disorder\(^7\).

Anhedonia and apathy are measured using either questionnaires filled by the patient or caregiver, or a structured interview performed by the clinician (Box 1). The closeness of apathy and anhedonia as syndrome constructs is emphasized by the few studies that have estimated levels of apathy and anhedonia in neurological disorders. Estimates of apathy in neurological disorders vary depending on the scales used and the selection criteria, but some reported mean prevalence rates are shown in the table. Reliable data regarding anhedonia in some of these groups are sparse, largely because studies in neurological disorders focus on apathy. However, in one investigation conducted in Parkinson’s disease, almost all patients who were apathetic were also anhedonic, whereas almost one-third of the sample fulfilled criteria for anhedonia without having apathy\(^8\). Anhedonia is extremely common in depression, with both population-based surveys\(^9\) and DSM-IV field trials\(^10\) suggesting a prevalence of 85–95% in major depressive disorder (MDD), on the basis of responses to a single question. Studies using questionnaires (with cut-offs defined by the authors of the scale) report clinically significant anhedonia in 37% of MDD patients\(^1\). In schizophrenia, anhedonia has been reported to vary in prevalence from 45% when assessed using questionnaires\(^11\) to ~80% using clinical interviews\(^1\). Anhedonia and apathy can occur within the same individual, as reported in both schizophrenia\(^1\) and Parkinson’s disease\(^2\).

Apathy has a severe impact on the quality of life of both the patient and the carer as well as on functional independence and prognosis\(^8\). The severity of anhedonia varies greatly within a patient group and correlates with more severe symptoms, poorer treatment response and low self-reported quality of life in depression\(^12\), and poor functional outcome in schizophrenia\(^13\).

### Table 1: Measurement and prevalence of apathy and anhedonia

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Apathy in population (%)</th>
<th>Refs</th>
<th>Anhedonia in population (%)</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s disease</td>
<td>49</td>
<td>4</td>
<td>61</td>
<td>5</td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>72</td>
<td>6</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>47</td>
<td>10</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td>38</td>
<td>12</td>
<td>37</td>
<td>11</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>40</td>
<td>6</td>
<td>46</td>
<td>7</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>47</td>
<td>14</td>
<td>45</td>
<td>11</td>
</tr>
<tr>
<td>Stroke</td>
<td>36</td>
<td>1</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>61</td>
<td>1</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>65</td>
<td>8</td>
<td>--</td>
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</tr>
</tbody>
</table>

"-" indicates when anhedonia has not been reliably estimated in a patient population.

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Box 1 | Measurement and prevalence of apathy and anhedonia

Clinically, apathy and anhedonia are measured using either self-report questionnaires or structured interviews\(^1,12,13,14\). Popular anhedonia questionnaires\(^15\) include the Scale for Physical Anhedonia and the Scale for Social Anhedonia (which focus on lifetime hedonic responses to specific environmental stimuli), the Snith–Hamilton Pleasure Scale (which is more general and includes less culturally bound questions, rated over recent days) and the Temporal Experience of Pleasure Scale (which attempts to distinguish the hedonic and appetitive components of anhedonia). Several questionnaires for apathy exist, with two commonly used ones being the Apathy Evaluation Scale and the Apathy Scale\(^12,13\).

In interviews, scores are commonly derived using questions from measures such as the Scale for the Assessment of Negative Symptoms in schizophrenia, although such scales usually feature only a small number of items specifically relating to amotivation\(^11\). However, structured interviews specifically focused on apathy (such as the Lille Apathy Rating Scale) and anhedonia (for example, the Clinical Assessment Interview for Negative Symptoms and the Brief Negative Symptom Scale) have been developed\(^14\).

Reviews on the first attempts to apply the diagnostic criteria laid down in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition in real-world settings.

Apathy

Inability to perform self-directed, purposeful activities.

Akinetic mutism

Loss of ability to self-initiate limb movement and speech.

Abulia

Reduced spontaneous verbal, motor, cognitive and emotional behaviours.
examined both in clinical populations. In Parkinson’s disease, for example, some investigators have reported significant positive correlations between scores on apathy and anhedonia scales\(^{30}\). In schizophrenia, apathy and anhedonia usually cluster together as negative symptoms\(^{27-30}\), and the severity of apathy correlates with scores of anhedonia, avolition or asociality\(^{40}\) as well as with global negative symptom scores\(^{41}\). However, some reports also show that anhedonia — at least in terms of inability to experience pleasure — can be dissociable from apathy (for example, in Parkinson’s disease)\(^{42}\).

These findings demonstrate how important it might be to deconstruct apathy and anhedonia into component processes, rather than to consider them as single, monolithic entities. To the best of our knowledge, such an approach, using either behavioural experimental studies or computational modelling, has not hitherto been used to compare mechanisms underlying both apathy and anhedonia within the same individual or patient group (BOX 1).

Aspects of apathy and anhedonia may also be related to two common symptoms: anergia and fatigue. People with anergia complain of feeling sluggish, being drained or lacking strength even without exerting themselves, whereas fatigue refers to tiredness following activity, either physical or mental. It is not uncommon to find patients who articulate lack of motivation in terms of lacking energy or being fatigued. When apathy, anhedonia and fatigue are evaluated concurrently, there are significant positive correlations between all of these symptoms\(^{31}\), for example in Parkinson’s disease\(^{43}\). Furthermore, the Tenth Revision of the International Classification of Diseases (ICD-10) criteria for MDD include fatigue or low energy as a cardinal symptom, in addition to anhedonia and depressed mood.

Anergia and fatigue can also occur in individuals without depression — for example, in systemic illnesses or chronic fatigue syndrome. An important question is whether, in addition to any peripheral muscular factors, there might be central motivational contributions to these symptoms. Similarly, apathy and anhedonia are now recognized to occur not only in the context of clinical diagnoses but also, in milder forms, in the general population, particularly with ageing\(^{44}\). This realization has led some researchers to investigate whether there might be a neurobiological basis to these symptoms in otherwise healthy individuals\(^{45}\), with ageing\(^{47-49}\) or in people at high risk of developing depression\(^{50}\). Across several different studies, in young and old people, both structural and functional brain activity changes have been identified\(^{50-58}\), including in frontal and basal ganglia regions identified in patient groups discussed below (see Brain regions below).

### Behavioural approaches

#### Fluency

The number of examples generated of a verbal category (for example, words beginning with the letter F) or a non-verbal category (for instance, different patterns on a dot array using four straight lines).

#### Anticipation

Once an individual has selected an option, they typically experience motivational arousal (evidenced by physiological measures such as changes in heart rate or pupil dilation) in anticipation of action and/or reward\(^{59}\). For example, people normally show...
Anticipatory pupil dilatation that scales with potential reward magnitude in advance of making speeded movements to obtain reward. This pupil response is blunted in some patients with apathy23 (Fig. 2a,b).

**Action and effort.** The initiation, maintenance and invigoration of action together constitute part of appetitive behaviour — for example, the locomotor approach of an animal to a potentially rewarding experience, such as food. Appetitive behaviour has been referred to as a measure of ‘wanting’ (distinct from ‘liking’; see below)23, although some caution against the use of subjective terms in reference to animal studies.

Tasks used to study appetitive components of behaviour often measure how much physical effort an animal is willing to allocate to obtain a reward. For example, in progressive ratio tasks, the number of lever presses a rat has to make to obtain a set reward progressively increases until the animal reaches its ‘breaking point’ and is no longer willing to exert further effort45. Similarly, in a variation of the T-maze, rodents must decide between scaling a barrier to obtain highly rewarding food and a low-effort, low-reward food option46 (Fig. 2c). In humans, effort allocation can be manipulated using the number of button presses, the speed of response or the amount of force exerted to obtain rewards (Fig. 2d–i). Often, such tasks use choice behaviour as an indication of willingness to exert effort46,48–53.

Fewer studies have examined willingness to allocate cognitive effort. Rodents might, for example, have to choose to opt for a highly demanding attention trial (detect a brief illumination) over a low-demand one (detect a prolonged illumination) to obtain a greater reward44. In humans too, researchers have probed willingness to expend mental effort (in tasks that place high demands on attention or working memory) versus physical effort (squeezing tightly on hand-held dynamometers)44,45. These studies have shown both common and dissociable brain region contributions to effort-based decision making for rewards in the cognitive and physical effort domains44–46,48. One important aspect of effort tasks is that the highly effortful option must be achievable; otherwise, any observed changes in decision making could relate to probability discounting, not effort discounting.

A paradigm commonly used to assess ‘wanting’, originally developed in rodents, is Pavlovian–instrumental transfer (PIT). PIT involves three stages: Pavlovian (passive) conditioning pairing an initially neutral stimulus (such as a tone or light) with a rewarding outcome (food); instrumental (active, choice-based) association between an action (pressing a lever) and the rewarding outcome; and, finally, the PIT phase itself — the presentation of the Pavlovian conditioned stimulus (CS; that is, the tone or light) during instrumental performance — usually during extinction (that is, without delivery of rewarding outcomes). Presentation of the (unrelated) CS causes an invigoration of instrumental responding (known as the PIT effect), and is interpreted as reflecting incentive salience, or wanting47. Human analogues of the PIT task have been developed, with some evidence that the PIT effect is attenuated in individuals with depression48.

**Hedonic impact.** Consummatory behaviour refers to the achievement of a goal — for example, eating food. Some refer to this as the ‘liking’ phase of motivated behaviour46. One probe used to index consummatory
Fig. 2 | Behavioural paradigms for assessing amotivation. a | A speeded saccade for reward task, in which the monetary reward depends on the speed of response. The reward on offer is announced at the beginning of each trial, before the saccade target is presented. b | On this task, participants’ pupils normally dilate more with greater anticipated reward (after the auditory cue announcing maximum reward on offer). Reward sensitivity of the pupils is blunted in individuals with Parkinson’s disease (PD) and apathy compared with individuals with PD but without apathy. Shaded area represents standard error of the mean. c | Rodent T-maze experiments reveal that depletion of dopamine in the nucleus accumbens or lesions of the anterior cingulate cortex shifts rats from a strategy of working hard for large rewards (scaling an obstacle, indicated by dashed line, to obtain the large reward) to opting for a smaller reward that requires far less effort. d | An effort task that requires human participants to select between low or high physical effort options (number of button presses) associated with different levels of reward. e | Effort task in which human participants decide to accept or reject offers in which different levels of reward are available for different levels of physical effort (grip force). The image on the screen displays the reward on offer (depicted as the number of apples on a tree) and the force required to obtain that level of reward (indicated by the height of the yellow line on the tree trunk). f | On this task, the likelihood of accepting offers increases with reward on offer and decreases with increasing effort required. Parts a and b are adapted from REF. Part c is adapted with permission from REF. Part d is adapted with permission from REF. Parts e and f are adapted from REF.
behaviour in animal models is the sucrose preference test: rodents given the choice between water and dilute sucrose solution develop a preference for the latter. Animals that have been exposed to chronic mild stress (a model of depression) show decreased preference for sucrose, taken to indicate reduced hedonic capacity. Direct pleasure from the consummatory phase of behaviour has also been indexed by the facial expressions of rodents and primate in response to sweet versus bitter substances. However, several studies in humans suggest that hedonic aspects of the consummatory phase (measured by self-reported pleasure in response to sweet tastes) may be intact in people with schizophrenia with pronounced negative symptoms or MDD, raising the question of how appropriate decreased liking (as assessed through sucrose preference or facial expression) in rodents is as a model of anhedonia in humans.

Learning. Finally, an important aspect of effort-based decision making for reward is how individuals learn from the outcomes of their actions to guide future selections. This concept is known as reinforcement learning — that is, how rewards or losses associated with a stimulus or an action alter subsequent behaviours through updates to stimulus value. Learning can be assessed by examining how choices change over time in response to feedback. In early work, this was often achieved by analysing performance on early versus late trials in, for example, the Iowa Gambling task, revealing differences between patient groups and healthy volunteers in terms of poorer learning of the most rewarding selections over time. However, the interpretation of such differences is challenging, as several processes could potentially contribute (including option selection, hedonic impact and learning). A fruitful alternative approach to data analysis that has gained popularity in recent years is to use computational modelling.

Computational modelling

Computational models leverage the richness of observed data (for example, patterns of behaviour that evolve on a trial-by-trial basis) to provide insight into which processes are important in driving individual differences. For example, a difficult, partially rewarded perceptual task was developed to examine anhedonia. The task revealed reliable, replicable differences in what the authors call reward responsiveness (which measures the bias towards selecting the stimulus more frequently associated with reward) between control participants and individuals with depression. However, alterations in several processes — including learning, reward valuation or simply perceptual discrimination — could potentially contribute to this reward responsiveness measure.

Application of a computational model (similar to that in Box 3) to a large number of data sets produced

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**Box 2 | Utility of computational modelling of behaviour**

A computational approach can provide useful insights into what may drive observed patterns of behaviour. Computational models have increasingly been applied to tasks assessing motivation and decision making. In contrast to standard (‘descriptive’) data analyses, computational approaches start by creating a generative model that includes the processes thought to be involved in task performance, specified in a mathematically precise form (an example is shown in Box 3). Models usually contain a number of free parameters, each of which governs the influence of a specific process on information processing and behavioural output. Parameters are estimated from the data and can often capture patterns that would not be immediately evident from a descriptive analysis (for example, patterns that evolve over time during learning). The estimated parameters can be used to summarize the data alongside traditional descriptive measures as they can distil large amounts of information and are hypothesized to relate to specific cognitive processes. Uncertainty estimates can also be generated for each parameter at the individual subject level.

**Model fitting**

Model fitting involves adjusting the parameter values in the model until the pattern of output (for example, choices) that it makes matches, as closely as possible, that of the real participant. The estimation process also produces a measure of model fit. Often, several different model architectures will be compared (model selection), with parameters extracted from the winning model. To avoid overfitting, the fit of a model is balanced against its complexity (which is related to the number of free parameters). Parameters across several models can also be averaged, which can be useful if data from different individuals are best fit by different models (although this makes sense only if models are structurally similar).

A crucial process is model checking — that is, testing whether the model faithfully reproduces the observed data — which may, in turn, lead to the construction of a better model. It is also important to check how accurately parameters can be recovered; this involves generating data from the model using known parameters, which should then be estimable. If parameter recovery fails, the model requires revision.

**Limitations of the computational approach**

There are certain limitations of the computational approach to consider. First, although modern desktop computers can quickly implement simple models and estimation methods (for example, maximum likelihood), more complex procedures (such as sampling) can be slow and not very practical. Second, parameters can be interpreted in multiple ways. For example, the inverse temperature parameter (β in Box 3) of the softmax function can be interpreted in terms of consistency, exploration or valuation, limiting the interpretation of such models. Third, even simple models can contain redundant parameters, which can result in poor estimation. Fourth, as with any statistical analysis, larger data sets will tend to favour more complex models. This point limits the utility of model comparison, as which model is favoured will depend in part on the amount of data included in the model. Indeed, some investigators eschew model comparison altogether, advocating a model-checking approach.
a clearer interpretation: symptoms of anhedonia were associated not with differences in incremental learning or perceptual discrimination but instead with blunted expected value of reward at the time of decision (Fig. 1). In a different context, computational modeling of data from a reinforcement learning task in individuals with schizophrenia again revealed an apparent sparing of incremental learning, with the overall level of poor performance predominantly accounted for by impairments of working memory (which can be important in learning tasks owing to the time delay between stimuli and outcomes). Thus, the use of computational models in these studies helped to dissect the different cognitive processes involved in reward tasks, showing that learning per se is apparently spared in anhedonia, and that instead differences in behaviour.
on tests of reward processing are accounted for by other processes.

Computational modelling has also demonstrated that improvements in apathy scores in individuals with Parkinson’s disease who were taking dopaminergic medication were associated with greater reward sensitivity (that is, the expected value of reward) but not with changes in effort sensitivity. Conversely, healthy individuals taking a selective serotonin-reuptake inhibitor produced more effort, which modelling revealed to be due to reduced effort costs, rather than increases in reward sensitivity. Although to date there has been little systematic use of modelling in this field, these examples show how using a computational approach can illuminate how specific cognitive processes map onto different symptom profiles and treatments.

**Brain regions**

Reports of previously well people suddenly developing profound amotivation following strokes or other focal lesions have implicated a set of brain regions that seem to be crucial for motivated behaviour in humans. These include the basal ganglia (particularly ventral aspects including the globus pallidus and ventral striatum (vStr)), parts of the anterior cingulate cortex (ACC) and the ventromedial prefrontal cortex (vmPFC), which is often referred to as medial orbitofrontal cortex (mPFC).

Early experimental DBS studies in people institutionalized for psychiatric disorders reported that they might gain pleasure from self-stimulation of electrodes implanted in the septal region, which included the nucleus accumbens (NAcc) — part of the vStr — and ventral pallidum. However, a more scrutinous assessment suggested that stimulation might in fact have led to patients merely wanting to engage in more pleasurable activities. More recent human DBS studies show that ACC stimulation can induce the expectation of an imminent challenge that the patient feels determined to overcome. Furthermore, DBS of the subgenual ACC was suggested to ameliorate symptoms of depression in some individuals who had been resistant to treatment with drugs, although a larger trial did not find a significant effect of such stimulation.

Findings from many investigations in animals also converge on a pivotal role in motivation of a network of brain regions that includes ventral basal ganglia structures (including the NAcc and ventral pallidum), the ACC, the ventral tegmental area (VTA) and the basolateral amygdala (BLA). The VTA is the source of widespread dopamine (DA) projections to the vStr (known as the mesolimbic DA system); to the ACC and the PFC (the mesocortical DA system); and to the amygdala.

**Integration of reward and effort signals.** Several neuroimaging studies in healthy humans have attempted to examine the basis of cost–benefit decision making when effort is required to obtain rewards (Fig. 1). Activation of the vStr or pallidum varies positively with the magnitude of prospective reward and, in some reports, has been reported to be negatively modulated by prospective effort. In humans, the ACC plays a key role in integrating costs (effort) and benefits (reward) to compute the net value of performing an action.

Investigation of cognitive and physical effort has revealed both common and unique brain-activation patterns. One study found that reward devaluation by both types of effort was represented within a common network including the ACC and other dorsomedial frontal regions, the anterior insula and the dorsolateral PFC. Importantly, activation in these ‘domain-general’ regions also co-varied positively with effort and negatively
with reward, suggesting that these parameters might be integrated within these areas. By contrast, activity within the amygdala seemed to reflect processing of the value of rewards associated specifically with cognitive effort.

**Option selection and option generation.** Intriguingly, when people have to select from reward–effort combinations, the activation of ACC or SMA corresponds to the difference in reward or effort levels of the chosen and unchosen options. This finding suggests that these dorsomedial frontal regions might be important for option selection after the valuation of the potential behavioural options that are presented to an individual (Fig. 1). Which brain regions are involved in self-generated options for behaviour remains to be established, but some data point to a role of the pre-SMA and possibly the dorsolateral prefrontal cortex.

**Brain regions in apathy and anhedonia.** Neuroimaging studies across various human neurodegenerative conditions have revealed that apathy is strongly associated with atrophy of or functional disruption of the dorsal ACC (dACC), vmPFC or OFC, vStr and VTA, as well as brain regions connected to these areas. Intriguingly, work examining neural correlates of anhedonia in patients with depression has implicated a largely convergent network of brain regions that show blunted activation, relative to controls, when performing tasks involving appetitive, cost–benefit decision and summatory or learning phases of reward processing. In depression, activation is reduced in regions including the vStr, caudate, vmPFC or OFC and dACC (although contradictory results were reported in the dACC in different studies).

Although the precise pattern of regions observed to show blunted responses in depression is not identical across studies, some of this inconsistency is attributable to clinical heterogeneity (with frequent reports that the degree of blunting correlates with the severity of anhedonic symptoms) and the use of different paradigms. For example, a recent investigation reported no differences between depressed and non-depressed groups in reward-prediction error signals in the vStr, part of learning from outcomes (Fig. 1), in contrast to earlier findings using different fMRI paradigms.
The results from investigations in adults with depression discussed above are consistent with a large study of motivational processing in a predominantly healthy community sample of adolescents (of whom a minority experienced clinical depression), which identified a robust inverse relationship between VStr activation during the anticipatory phase of reward processing (FIG. 1) and depressive symptoms, especially anhedonia (Fig. 5b), as well as future risk of depression. A similar picture is evident during the anticipatory phase in studies of anhedonic individuals with schizophrenia, although the ubiquitous use of antipsychotic medications, which block DA transmission, complicates their interpretation. A meta-analysis of 33 studies in depression and 24 studies in schizophrenia (with paradigms tapping several of the processes depicted in FIG. 1) concluded that reward-related responses were reliably blunted in the caudate, putamen and ACC in both diagnoses.

**Neuromodulators**

A large literature exists on the effect of pharmacological manipulations of neurotransmitters on motivational processing in animals. Other investigations have correlated motivation with monoamine neurotransmitter release, measured using microdialysis or fast-scan cyclic voltammetry (FSCV) concurrently with behaviour. Some studies have manipulated midbrain monoaminergic neurons directly using optogenetic methods.

**Dopamine in animal studies.** The first evidence for a role of DA in motivation came from findings that deleting DA — using the neurotoxin 6-hydroxydopamine (6-OHDA) — led to robust reductions in instrumental conditioned responding (an aspect of sustaining effort; FIG. 1) that were reversed by amphetamine (which enhances DA signalling). Later, direct microinjections of DA agonists and antagonists into the NAc of rats revealed, respectively, increases and decreases in conditioned reinforcement. Similar manipulations also affect performance in the same direction on PIT and effort expenditure tasks, for example, DA agonists reduce vigour and preference for high-effort–high-reward options, suggesting that DA profoundly influences the decision and action phases of reward processing.

Importantly, hedonic responses during the receipt of primary reward (that is, during the consummatory phase of reward processing; FIG. 1) are not affected by DA in rats but are altered by opiate manipulation. More recent work shows that adenosine A2A receptor antagonists can reverse deficits in effort allocation produced by several interventions (for example, DA receptor antagonists or tetrabenazine, a drug that depletes DA), potentially by acting on adenosine A2A receptors that colocalize with DA D2 receptors in the striatum and NAc.

There is also good evidence that DA is involved in learning (FIG. 1), with an influential study showing that phasic DA neuron firing in the midbrain temporally corresponds to the evolution of reward-prediction errors (BOX 2). This finding has since been confirmed using optogenetic methods and has led to a proposed distinction between the functions of tonic DA signals, which are proposed to play a primary role in encoding action and effort, and phasic DA signals, which are hypothesized to influence reward learning.

However, the dichotomy between tonic and phasic DA has been challenged by FSCV findings. When rats navigate mazes to retrieve rewards, NAc DA signals ramp up slowly as animals come closer to their goals (action and anticipation; FIG. 1), scaling with reward magnitude. These DA ramping signals might represent the estimated expected value of reward, which in turn might be used in cost–benefit decisions to evaluate...
whether it is worth engaging in effortful activity\textsuperscript{129}. Intriguingly, DA release seems to be contingent on action (and therefore effort), not just valuation, because when rats perform a rewarded go/no-go task, DA signals are attenuated when animals must inhibit movement to obtain a reward\textsuperscript{130}.

Together, these findings suggest that the tonic–phasic DA hypothesis might require revision, and that instead a unitary account, in which phasic signals simultaneously influence both valuation and learning, might provide a better explanation for the role of DA in reward processing\textsuperscript{122}—with phasic DA signals before choice affecting valuation and propensity to deploy effort, and those during consummation affecting learning\textsuperscript{120}.

**Dopamine in human studies.** Human psychopharmacology studies have been largely consistent with the evidence linking DA to effort-based decision making for reward in animals\textsuperscript{121}. Dietary depletion of DA precursors, which reduces DA synthesis\textsuperscript{124}, attenuates participants’ sensitivity to rewards during decision making\textsuperscript{125} and also increases punishment learning relative to reward learning\textsuperscript{126}, with some reporting corresponding reductions in reward-elicited blood-oxygen-level-dependent (BOLD) responses in the striatum\textsuperscript{127}. Research using DA receptor antagonists to block transmission has yielded less consistent results, possibly owing to doses used and the actions of these compounds on other monoamine systems and inhibitory autoreceptors\textsuperscript{128}. L-DOPA (L-3,4-dihydroxyphenylalanine; which increases DA synthesis), amphetamine and methylphenidate (which block DA reuptake) and D\textsubscript{2/3} receptor agonists generally increase several of the amine and methylphenidate (which block DA reuptake) and D\textsubscript{2/3} receptor agonists generally increase several of the aspects depicted in \textit{Fig. 1}, including speed\textsuperscript{129} and vigour\textsuperscript{130} of responses (that is, affecting action); effortful\textsuperscript{131} and risky\textsuperscript{132} choices (influencing cost–benefit decision making); reward learning\textsuperscript{133}; and associated reward-related striatal BOLD responses (reviewed in REF.\textsuperscript{123}).

Despite the clear evidence that DA transmission, especially in the striatum, has a central role in controlling motivated behaviour, standard pharmacological treatments for depression do not target the DA system\textsuperscript{132}. To our knowledge, besides a few pilot studies of agomelatine\textsuperscript{134} (an atypical antidepressant that disinhibits DA release through its action on serotonin 5-HT\textsubscript{2c} receptors), there has never been a trial specifically focused on treating anhedonia. However, a D\textsubscript{2/3} receptor agonist, piribedil, was reported to be successful in treating apathy in DBS-treated individuals with Parkinson’s disease who subsequently have their DA drug dose reduced\textsuperscript{134}. Dopaminergic drugs also enhance effort-based decision making in Parkinson’s disease by boosting reward sensitivity\textsuperscript{136,137}. Finally, a cholinesterase inhibitor has also been reported to confer improvement in apathy in Parkinson’s disease, although whether this is via effects on effort-based decision making has not been established\textsuperscript{138}.

Interestingly, ketamine, which antagonizes NMDA receptors and is effective in treatment-resistant depression (in which anhedonia is common)\textsuperscript{139}, has profound facilitatory downstream effects on DA transmission\textsuperscript{140}. Ketamine has also been reported to be effective in ameliorating anhedonia over and above general depressive symptoms, with reductions in anhedonia associated with increases in resting-state metabolism in the vStr and ACC\textsuperscript{141}. Further studies are needed to investigate whether ketamine can improve symptoms of amotivation in disorders besides treatment-resistant depression.

A few studies have linked DA to motivational symptoms in individuals with neurological and psychiatric disorders using positron emission tomography (PET). In depression, striatal D\textsubscript{2/3} receptor binding was negatively correlated with anhedonia\textsuperscript{142}. In Parkinson’s disease\textsuperscript{143} and anhedonic depression\textsuperscript{144}, there is also a negative relationship between striatal DA transporter binding and amotivation, and in cannabis users, apathy is associated with low DA synthesis capacity\textsuperscript{142}. These attenuations of DA function may in part be caused by chronic inflammation\textsuperscript{144}, which is common in disorders in which fatigue, anhedonia and apathy are prominent\textsuperscript{145}.

**Serotonin in animal studies.** The other major neurotransmitter linked to motivation is serotonin (5-HT). A common finding from neurophysiological studies is that there are opponent interactions between 5-HT and DA\textsuperscript{146}. For example, drugs acting at the 5-HT\textsubscript{5c} receptor can modulate DA release from neurons of the mesolimbic and mesocortical pathways. The 5-HT\textsubscript{5c} receptor antagonist SB-242084 increases the number and duration of effortful responses that rats will make for food rewards; this observation could be explained by changes in either the decision-making or action phases of reward processing\textsuperscript{148} (Fig. 1).

One influential computational account—based in part on evidence that 5-HT plays a role in inhibiting action in the face of aversive stimuli\textsuperscript{149} and in learned helplessness\textsuperscript{150} (in which motivational responding is reduced)—has hypothesized that DA signals prediction errors for reward whereas 5-HT signals those for punishment (that is, part of learning\textsuperscript{149}; Fig. 1). More recent theoretical formulations propose a more nuanced picture, suggesting that 5-HT may promote Pavlovian (flexible) inhibitory control (which could be related to either decision making or action)\textsuperscript{151}.

Empirical research has suggested that a simple relationship between 5-HT and aversive processing is an oversimplification\textsuperscript{152}. Recordings made directly from neurons in the dorsal raphe nucleus (DRN), a major source of 5-HT neurons, show that firing is modulated by the size of upcoming reward (related to anticipation; Fig. 1), similar to the pattern observed in DA neurons\textsuperscript{153}, although with considerable heterogeneity among DRN neurons, which are not all serotonergic. Optogenetic stimulation of identified 5-HT DRN neurons results in increased patience for rewards delivered after a cued delay (part of decision making\textsuperscript{152}; Fig. 1). Other optogenetic studies stimulating DRN neurons report that stimulation is reinforcing and elicits a greater propensity to exert effort (again, reflecting part of decision making; Fig. 1). However, this effect is not solely related to 5-HT release as some of the stimulated DRN neurons were glutamatergic\textsuperscript{154}.

**Serotonin in human studies.** Pharmacological manipulations of 5-HT in humans have provided some consistent effects. Dietary depletion of a 5-HT precursor reliably results in reduced behavioural inhibition in the face of potential punishment (that is, disinhibition,
Behavioural activation therapy
A psychological therapy that focuses on activity scheduling to encourage patients to approach activities that they avoid and on analysing processes (for example, rumination) that serve as forms of avoidance.

Cognitive behavioural therapy
A psychological therapy that aims to assist a person to change their thinking and behaviour by practising effective strategies to decrease symptoms and distress.

reflecting increased vigour185; FIG. 1), a conclusion supported by neuroimaging186. Other reports show that 5-HT precursor depletion reduced representation of expected reward value during decision making in a learning task (as assessed using computational modelling)187 and reduced the speed of responding for reward188 (part of action; FIG. 1). Another investigation in healthy volunteers (also discussed in the Computational modelling section above) demonstrated that both acute and chronic administration of a selective serotonin-reuptake inhibitor affected decision making, reducing effort costs but not reward valuation27 (FIG. 1). Notably, apathy in Parkinson's disease has been associated with low 5-HT transporter binding, which some researchers interpret as a measure of neuronal integrity, in vStr and ACC189. However, in general, the role of 5-HT in motivation is far from clear and requires substantial further empirical work.

Summary. Extensive investigations have suggested that the DA and 5-HT systems modulate several aspects of effort-based decision making for rewards. However, the findings do not suggest that there is a simple mapping of each of these neurotransmitter systems to the components identified from behavioural studies (FIG. 1). Rather, the results seem to suggest more complex involvement of these neuromodulators, and very few studies to date have examined their interaction with one another in shaping motivated behaviour. These considerations have implications for development of new therapies for apathy and anhedonia. Given the complexity of each behavioural syndrome — with dissociable component processes and potentially different patterns of behavioural deficit across individuals labelled as having the same syndrome — it seems unlikely that a single drug therapy would be appropriate for all patients.

Conclusions
This Review of diverse sets of data from human and animal model experiments reveals some of the mechanisms that might be involved in the genesis of apathy and anhedonia, and provides a framework for developing potential treatments. To move forward, it seems crucial to establish which underlying brain mechanisms contribute to a syndrome of amotivation, such as apathy or anhedonia, in an individual patient. Using clinical definitions might not be sufficient to capture these (see also REF.24), as different constellations of disrupted mechanisms might occur in different individuals. Moreover, the pattern of deficits need not be disease specific. Hence, future research will need to focus on elucidating the mechanisms that underpin a behavioural syndrome.

As we have seen, anhedonia and apathy are strongly related across different disorders when both have been measured using clinical scales36,37,190. However, there is not a perfect overlap; therefore, the question arises as to which mechanisms might be common to both and which might be unique to each of these syndromes. The development of new questionnaires provides one way to address this question. One of them now attempts to distinguish between anticipatory and consummatory aspects of motivation but has not always been useful in making distinctions between these two processes in clinical groups191. However, it must be borne in mind that these are subjective assessments that do not necessarily provide the granularity required.

Perhaps a better way to establish whether there are any fundamental differences between apathy and anhedonia might be to fractionate behaviour and examine underlying components, such as those delineated in FIG. 1. To improve phenotyping in this way would require a battery of behavioural paradigms, ideally combined with computational modelling (BOXES 2, 3). To investigate whether dysfunction of the same brain regions undermines the disruptions of reward-related behaviour observed across brain disorders would require the application of a core battery of functional imaging tasks across clinical diagnoses.

Although both apathy and anhedonia are clinically debilitating and have a profound impact on quality of life, there have been few attempts to develop pharmacological treatments192. This seems an area ripe for investigation, given the clear clinical need and close correspondence between behavioural tests developed for humans and animal models. The results of pharmacological modulation and stimulation in rodent models have revealed the complexity of neurotransmitter involvement in motivated behaviour. Nevertheless, they provide hope that it might be possible to develop treatments targeted to components of effort-based decision making for reward. Such efforts might be relevant to psychological therapies as well. For example, behaviour activation therapy for depression, which specifically targets goal-directed behaviour, can be as effective as cognitive behavioural therapy191. In addition, several psychosocial interventions, including cognitive-behavioural therapy or exercise therapy, seem to be modestly effective in treating negative symptoms in schizophrenia, although better-controlled studies are required to establish their efficacy192.

The considerations suggest that for further progress in this field, it is essential to understand the mechanisms underlying the ‘surface manifestations’ of apathy and anhedonia — the clinical presentation — and to characterize the phenotype more carefully in individual cases. The ultimate aim would be to use this framework to develop personalized treatments — pharmacological or psychological — for patients suffering from debilitating motivational symptoms.

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23. This study combines empirical findings with computational modeling to pinpoint impaired reward processing in RBD. Brain 153, 2202–2212 (2010).
35. This landmark experimental paper examines the role of DA in appetitive and consummatory reward processing, providing clear evidence that the former, but not the latter, is disrupted by profound DA depletion.
39. This article provides a clear explanation from a computational neuroscience perspective of the different aspects of motivational processing that may underlie depression.
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This pioneering experimental study combines fMRI with simultaneous optogenetic stimulation of both DA and mPFC neurons. Stimulating DA neurons increased (and silencing reduced) vSRT responses and reward-seeking behaviour, which was blunted by mPFC stimulation.

This paper presents a clear account of the links between dopaminergic signaling and reward processing, including how inflammation may result in a decrease in DA transmission, leading to symptoms of amotivation.