

Apathy and Motivation: Biological Basis and Drug Treatment

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Keywords

apathy, motivation, dopamine, treatment, neuropsychiatric, neurodegenerative

Abstract

Apathy is a disabling syndrome associated with poor functional outcomes that is common across a broad range of neurological and psychiatric conditions. Currently, there are no established therapies specifically for the condition, and safe and effective treatments are urgently needed. Advances in the understanding of motivation and goal-directed behavior in humans and animals have shed light on the cognitive and neurobiological mechanisms contributing to apathy, providing an important foundation for the development of new treatments. Here, we review the cognitive components, neural circuitry, and pharmacology of apathy and motivation, highlighting converging evidence of shared transdiagnostic mechanisms. Though no pharmacological treatments have yet been licensed, we summarize trials of existing and novel compounds to date, identifying several promising candidates for clinical use and avenues of future drug development.

Effort-based decision making for reward:

a series of cognitive steps underlying goal-directed decision making/motivation dependent on the potential rewards and effort costs associated with an action

INTRODUCTION

Apathy is a multidimensional syndrome characterized by diminished motivation for engaging in physical, cognitive, emotional, and social activity, which has been described by several conceptual and theoretical frameworks (1–3). The division of apathy into cognitive, behavioral, and emotional subtypes has been supported by observations of patients with neurological disorders (3, 4). Factor analysis of symptom scales also identified a social dimension, though this is poorly captured by most measures (3). Research into apathy has primarily focused on neurological disorders; however, the framework and conceptualization of apathy bear considerable similarity to those of other motivational syndromes observed in psychiatry. For example, negative symptoms in schizophrenia, of which apathy is a component, are also often conceptualized as consisting of cognitive (disorganized or executive symptoms), behavioral, and emotional/affective subdomains (5). A common feature across phenomenological descriptions of the syndrome is impaired volition and goal-directed behavior, such as the loss of self-initiated behavior or of the ability to sustain effort (6). This observation supports a transdiagnostic view that apathy and other motivational syndromes may share some underlying cognitive components (6).

Apathy is now recognized as a common and highly disabling neuropsychiatric syndrome (1–3) that occurs across a wide range of neurological and psychiatric disorders (6, 7), including Alzheimer's disease (clinically significant apathy reported in 49% of patients) (8), frontotemporal dementia (FTD) (72%) (9), Parkinson's disease (40%) (10), stroke (36%) (11), and schizophrenia (47%) (12). It has a severe negative impact on quality of life (13) and is associated with greater disability (7), cognitive decline (14), caregiver stress (15), and mortality (16).

Apathy frequently overlaps with anhedonia, a core symptom of depression, defined as a loss of interest or pleasure in previously rewarding activities (17). Although evidence suggests that these syndromes of motivation might share some underlying mechanisms (17), longitudinal studies of neurodegenerative conditions have demonstrated that apathy is distinct from depression (18). In dementia, apathy is associated with worse clinical outcomes independent of depression (19), and symptoms of apathy, but not depression, increase the risk of progression from mild cognitive impairment to Alzheimer's disease (20).

Focal lesions to several brain regions have been observed to precipitate pathological apathy. These regions include the ventromedial prefrontal cortex (vmPFC), dorsal anterior cingulate cortex (dACC), and basal ganglia, as well as connections between these regions (21). It is now also recognized that neurodegeneration or dysfunction of these frontostriatal circuits may play a key role in the genesis of the syndrome. An intriguing question is whether, despite different underlying pathologies across disorders, the same circuits are affected in apathy across different brain disorders (21).

COGNITIVE MECHANISMS OF MOTIVATION AND APATHY

Recently, research has attempted to experimentally dissect the cognitive components driving disorders of motivation to better understand and characterize the phenotype of apathy and amotivation (6, 21). One such framework is effort-based decision making for reward. This framework is based on the notion that goal-directed decision making/motivation is dependent on the potential rewards and effort costs associated with an action, which has been conceptualized as a series of cognitive processes (see **Figure 1**).

Option Generation

Patients with severe apathy are often able to perform actions when prompted but fail to generate actions of their own volition. One study, in which patients with schizophrenia were asked to

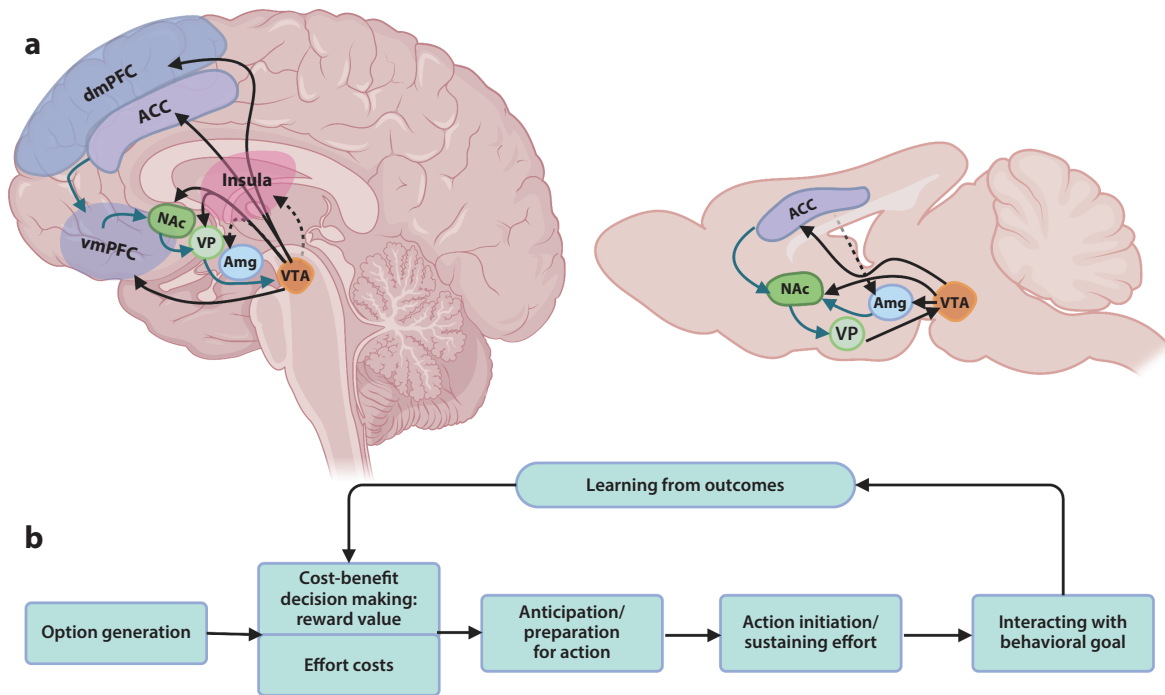


Figure 1

(a) Diagram of the brain regions and anatomical connections implicated in motivation in the human and rodent brain. Dopaminergic projections are indicated by black arrows, and glutamate/GABA projections are indicated by blue arrows. Dashed lines indicate projections to more lateral regions. (b) Cognitive mechanisms underlying effort-based decision making to obtain rewards. Abbreviations: ACC, anterior cingulate cortex; Amg, amygdala; dmPFC, dorsomedial prefrontal cortex; GABA, γ -aminobutyric acid; NAc, nucleus accumbens; VP, ventral pallidum; vmPFC, ventromedial prefrontal cortex; VTA, ventral tegmental area. Figure adapted from images created using BioRender.com.

verbally generate options for action in real-world scenarios, reported that apathy correlated negatively with the number of options generated (22). However, in Parkinson's disease, when participants were asked to draw as many different paths as possible between two points within a fixed time, there was no relationship between the number of options generated and self-reported apathy, although there was a relationship in the healthy participant group (23).

Such option generation tasks are similar to verbal fluency tests of executive function in which participants are asked to generate words for different categories. Verbal fluency impairments have consistently been associated with greater apathy across neurodegenerative diseases (24), in psychosis (25), and in healthy older adults (26), raising the possibility that executive dysfunction may play an important role in causing apathy. Impairments in fluency (quantity produced), flexibility (number of categories), and creativity (uniqueness) have also been reported in FTD (27), emphasizing the potential mechanistic role of option generation driving apathy in conditions in which a dysexecutive syndrome is prominent.

Option Selection and Cost-Benefit Decision Making

Patients with apathy also exhibit impairments in selecting a behavioral action. Option selection depends on the potential costs and benefits of the action and how the decision may affect future available options.

Option generation: the ability to generate potential options for behavior, whether self-generated or externally cued

Reward sensitivity: the degree to which an individual's behavior is motivated by reward-relevant stimuli

Motivational arousal/anticipation: motivational arousal (evidenced by physiological measures such as changes in heart rate or pupil dilation) in anticipation of action and/or reward

Animal studies of effort-based choice utilize tasks that manipulate the amount of reward on offer for different levels of effort. These include the T-maze task, in which animals choose between climbing a barrier to obtain a preferred food in one arm versus consuming a freely available food in the other (28).

Human studies have utilized similar paradigms, asking participants to exert varying levels of effort (for example, grip force) for different magnitudes of reward. Individuals with Parkinson's disease and apathy are less willing to exert effort for low rewards than are motivated patients (29, 30). Another study in Parkinson's disease patients using a cognitive, instead of physical, effort exertion task reported a negative association between apathy and reward sensitivity (31). This suggests that changes in how reward is evaluated in both cognitive and physical effort processing can contribute to apathy (32).

Changes in cost-benefit decision making have also been associated with apathy in other neurological conditions. Patients with cerebral small vessel disease and apathy are also less responsive to low levels of reward (33) and can also be less willing to exert high levels of effort (34). In FTD, apathy may be associated with increased effort aversion, but not reward sensitivity (29). Several studies of patients with schizophrenia have found that apathy, but not other negative symptoms, is associated with decreased willingness to exert effort for reward (35–37). These findings suggest that changes in sensitivity to reward or effort costs could be a transdiagnostic mechanism driving apathy across psychiatric and neurological conditions.

Anticipation

Motivational arousal occurs in anticipation of action and its potential outcome, leading to physiological changes in heart rate or pupillary dilatation. Studies of patients with Parkinson's disease and genetic cerebrovascular disease have demonstrated that apathy is associated with blunted pupillary responses to anticipation of reward (33, 38). Patients with schizophrenia with higher apathy have reduced electrodermal activity, irrespective of reward (39). Accurate anticipatory physiological arousal enables the progression to action initiation and preparation for exertion (40). It is also thought to inform decision making by means of interoception (i.e., the representation of the internal physiological state of the body) (41). Blunted anticipatory physiological reactivity may lead to bidirectional impairment in brain-body signaling and representation of motivational states, thereby contributing to apathy. However, no relationship between interoceptive accuracy and apathy has been identified in either Parkinson's disease or amyotrophic lateral sclerosis (42–44).

Initiating Action and Sustaining Effort

Apathy may also be a consequence of impaired action initiation and sustaining effort, which constitute appetitive behavior and are often interpreted to reflect "wanting." In animals, this is measured by quantifying how much effort an animal is willing to exert to obtain a reward (28), for example, progressively increasing the number of lever presses a rodent has to make for a reward until a breaking point where it gives up (28).

Assessment of appetitive behavior in humans involves measuring the speed of response or amount of effort exerted (45). To date, most studies of apathy and motivational syndromes have focused on the choice to exert effort rather than differences in sustaining effort. Studies of speed of response for reward in Parkinson's disease patients have not shown an association with apathy (38, 46). Likewise, patients with schizophrenia with higher apathy and depressed patients exhibit no reduction in reward-related speeding (47, 48). Though further investigations are needed, these findings do not support the notion that impairments in appetitive behavior contribute to apathy.

Hedonic Response

A theoretical mechanism underlying apathy is reduced hedonic capacity, or the ability to experience pleasure, which would in turn disincentivize future action. In animal models, hedonic capacity is measured by indexing consummatory response (49), for example, interpretation of facial expressions during sugar consumption in primates or rodents (50).

In humans, where hedonic capacity is measured through self-report, evidence to date does not support hedonic impairment as a key mechanism driving disorders of motivation. For example, hedonic responses are intact in patients with a high burden of negative symptoms in schizophrenia (51), and apathy in Parkinson's disease is not associated with consummatory impairment (52).

Learning

Finally, how individuals learn from the outcomes of actions is crucial for guiding future selection of behavioral options and motivation (53). In the reinforcement learning framework, reward prediction errors (RPEs) are thought to drive learning by updating models of association between prospective predictions and outcomes every time an observed outcome deviates from the prediction (54).

In probabilistic reinforcement learning tasks (used in both animals and humans), a series of choices between options associated with high and low probabilities of reward is presented (53). Trials or time taken to establish the initial association with the higher-probability option, and when reward contingencies change, enables the measurement of learning (53). Performance on probabilistic learning tasks in two small studies of apathy in patients with Parkinson's disease did not show a specific impairment in learning, though reinforcement learning is impaired in Parkinson's more broadly (55–57). Similarly, in patients with schizophrenia, no consistent impairments in learning have been found (58), nor an association with motivational deficits (59, 60).

However, further understanding of how learning is integrated with other mechanisms underlying motivation is needed. For example, a recent study revealed that exerting effort facilitates more efficient learning from positive outcomes, a potential mechanism that might contribute to apathy and that warrants further investigation (61).

NEURAL CIRCUITRY OF MOTIVATION AND APATHY

Early studies of the neural circuitry of motivation were largely informed by the association of apathy with specific patterns of neurodegeneration, or the development of profound amotivation following focal lesions (62). For example, akinetic mutism, in which patients are alert but in a state of profound apathy and indifference, can result from lesions to the ACC and subcortical structures, including the ventral striatum (VS) (62–65). In stroke, lesions to the basal ganglia have been most consistently associated with apathy (66).

Although studies examining the association between apathy and lesion location have not always produced reliable findings (66), the association with basal ganglia lesions is consistent with the high prevalence of apathy in disorders with prominent neurodegeneration in this region such as Parkinson's and Huntington's disease (10). In Alzheimer's dementia, greater atrophy of the ACC, basal ganglia (particularly striatum), orbitofrontal cortex (OFC), and anterior insula has been associated with increased apathy, independent of cognitive impairment (63, 67–70). Apathy in FTD also correlates with atrophy of the OFC, again independent of executive dysfunction (71).

Hedonic response: response to the achievement of a goal; some refer to this as the liking phase of motivated behavior

Reinforcement learning: how rewards or losses associated with a stimulus or action alter subsequent behaviors through updates to stimulus value

In schizophrenia, analysis of the association between brain anatomy and negative symptoms has yielded inconsistent results. More severe negative symptoms were correlated with lower gray matter in the vmPFC and striatum (72, 73), but other studies found discrepant results (74, 75).

Deep brain stimulation (DBS) studies have also shed light on the role of brain regions involved in motivation. Stimulation of the ACC in two individuals with epilepsy induced the expectation of a challenge that they were determined to overcome. One of the patients reported during stimulation, “It was more of a positive thing like... push harder to try and get through this” (76, p. 1360). Conversely, apathy can be increased in some Parkinson’s disease patients following subthalamic nucleus DBS therapy compared to the preoperative state (77).

Human and animal studies converge on a network of brain regions that plays a crucial role in motivation (see **Figure 2**). These regions include the VS [nucleus accumbens (NAc) in rodents], ventral pallidum (VP), the ACC and its connections with the basolateral amygdala, vmPFC/OFC, and ventral tegmental area (VTA). The VTA is the source of dopamine projections to the NAc, whereas the substantia nigra supplies dopamine projections to the dorsal striatum. Lesions of the NAc or ACC and optogenetic silencing of neuronal activity in these areas can lead to profound demotivation in animals (78–80).

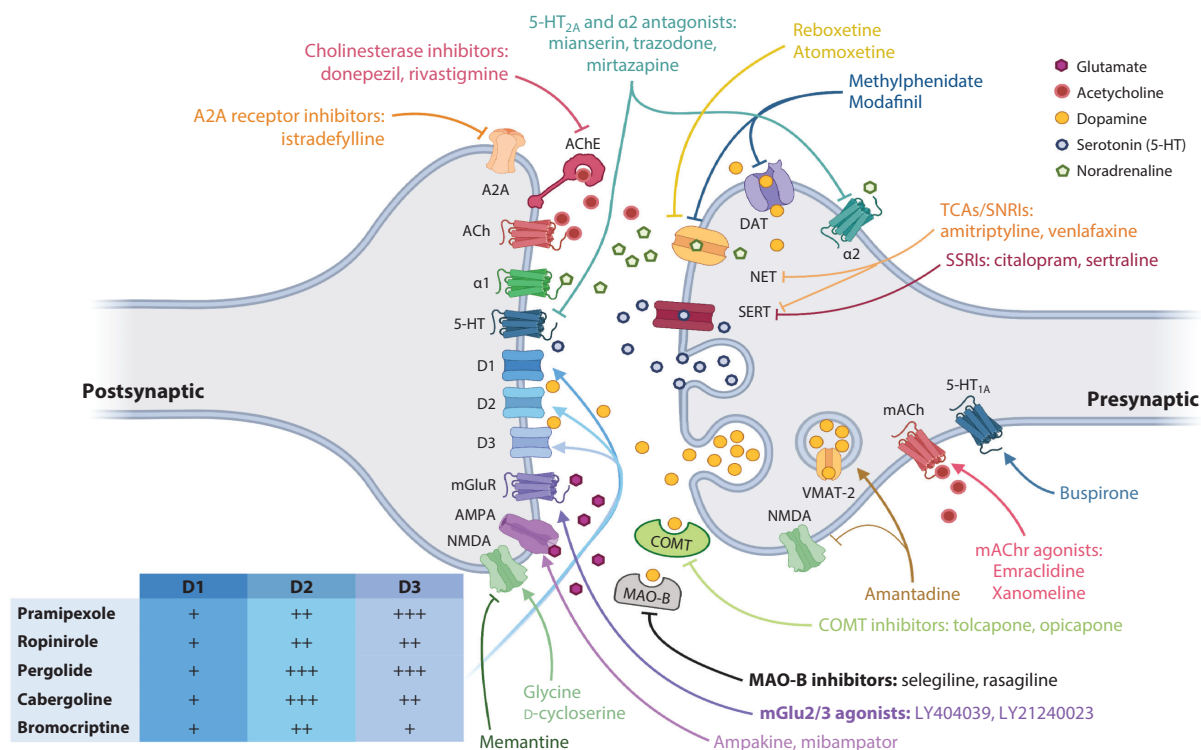


Figure 2

Mechanisms of action of drug candidates tested in randomized controlled trials to treat disorders of motivation. Abbreviations: 5-HT, serotonin (5-HT) receptor; A2A, adenosine 2A; AChE, acetylcholinesterase; AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid ionotropic glutamate receptor; COMT, catechol-*O*-methyltransferase; D, dopamine receptor; DAT, dopamine transporter; (m)ACh, (metabotropic) acetylcholine receptor; MAO-B: monoamine oxidase type B; NET, noradrenaline transporter; mGluR, metabotropic glutamate receptor; SERT, serotonin transporter; SNRI, serotonin and noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; VMAT, vesicular monoamine transporter. Figure adapted from images created using BioRender.com.

NEURAL CIRCUITRY OF EFFORT-BASED DECISION MAKING

Greater understanding of the brain regions implicated in clinical apathy has informed recent advances into the neural circuitry underlying effort-based decision making and led to improved understanding of the neural mechanisms and neuromodulatory systems underlying motivation (21) (**Figure 1**).

Option Generation

Studies using verbal fluency or creative thinking paradigms in healthy participants undergoing functional magnetic resonance imaging (fMRI) have shown that option generation is a function of executive processing and have identified a key role for the PFC (81, 82). Intriguingly, preserved creative thinking in patients with FTD has also been strongly associated with PFC integrity. However, no investigation to date has examined the neural correlates of option generation and their relationship with apathy in clinical populations (27). Unfortunately, no comparable test of option generation in animals exists.

Option Selection and Cost-Benefit Decision Making

Animal studies using intracranial self-stimulation have enabled direct recording of neural activity during cost-benefit decision making and revealed that rodents will choose to exert effort via lever presses to receive stimulation of the VTA. The development of optogenetic methods has revolutionized our understanding of the neural processes and systems involved in reward and effort valuation. An investigation combining optogenetic stimulation of the VTA with fMRI in rodents revealed that stimulation led to increased activity in the striatum and increased reward seeking, whereas VTA inhibition reduced striatal activity and reward seeking (79). The same study reported that stimulation of medial PFC led to reduced striatal response and reward seeking, and it concluded that disrupted frontostriatal circuit synchrony could be a mechanism underlying disorders of motivation (79).

In humans, a meta-analysis of fMRI studies in healthy participants concluded that vmPFC, VS, and VTA are primarily involved in representing and signaling reward valuation, whereas the ACC and anterior insula signal effort costs (83). VS activity increases with the magnitude of prospective reward and is negatively modulated by prospective effort (84). In contrast, ACC activity positively correlates with effort costs and is negatively related to prospective reward value, suggesting that the ACC may play a key role in integrating the costs and benefits of performing an action (85).

In drug-naïve Parkinson's patients with clinically significant apathy, apathy severity correlated negatively with dACC and caudate activity (86). Further, a meta-analysis of fMRI studies investigating the neural correlates of apathy in schizophrenia during reward-processing tasks identified a convergent network of brain regions, including the striatum, ACC, and OFC (87).

Reward Anticipation and Hedonic Responses

Distinct brain regions have been associated with reward anticipation and reward delivery, suggesting that the circuitry underlying motivation may differ from that of hedonic processing (88). A meta-analysis of healthy participants found that VS and insula activity were consistently associated with the anticipation of reward. In contrast, reward delivery was most strongly associated with the activation of ACC/vmPFC bilaterally, extending to the OFC (88). However, other investigations have found overlapping roles of the VS, insula, and OFC in reward anticipation and hedonic response (89).

Option selection and cost-benefit decision making: process of selecting a behavioral option depending on the potential costs and benefits of the action and how the decision may affect future available options

Few studies have investigated how these neural processes correlate with apathy. In one study of patients with schizophrenia, apathy correlated negatively with VS activation during the anticipation, but not receipt, of reward (90).

Reward Learning

RPE signals are known to be encoded in dopaminergic neurons in the substantia nigra and VTA and are broadcast to the VS to mediate reward-related learning (91). Regions involved in reward valuation and effort costs such as the VS and ACC encode information about the outcomes of actions that drive learning (85). However, recent work has suggested that effort and RPEs are encoded in parallel but interconnected brain regions (92). That study reported that effort prediction error signals were expressed in the dorsomedial PFC, and this was associated with apathy rating scores (92). In contrast, RPEs were primarily encoded in the VS and were unrelated to apathy (92).

In summary, the frontostriatal circuits implicated in apathy and motivation (**Figure 1**) center on dopaminergic projections from the VTA to VS with onward projections via the thalamus to PFC regions, specifically the ACC and vmPFC/OFC. Activity in and connectivity between these regions mediate the decision to exert effort, the value of an action, and the willingness to sustain exertion and learn from behaviors, and disruption within these circuits plays a key role in the etiology of apathy (85).

NEUROTRANSMITTERS

Dopamine

The mesolimbic dopamine system has been consistently implicated in the neurochemistry underlying motivation and its disruption in the development of apathy (62).

Dopamine levels, reward processing, and apathy. Tetrabenazine, a vesicular monoamine transport-2 (VMAT-2) inhibitor, depletes striatal dopamine by 75% in the NAc (93). In rodents, depletion of dopamine in the NAc reduces willingness to work, reward response vigor, and effort exertion (62, 94). In effort-related choice tasks such as the T-maze, NAc dopamine depletion consistently shifts choice behavior to selection of the low-effort option (28, 95).

In humans, the study of patients with Parkinson's disease, a model of dopamine deficit, has revealed a robust association between apathy and dopamine depletion (85). Apathy in Parkinson's can often emerge following reduction in medication and is successfully treated with dopamine agonists (10, 96, 97). A robust negative relationship between reduced striatal dopamine transporter (DAT) levels, a measure of presynaptic dopaminergic projection integrity, and motivational symptoms emerges as the disease progresses, independent of depression or motor symptoms (98). In schizophrenia, antipsychotic dopamine antagonists exacerbate motivational deficits and reduce dopaminergic transmission in the PFC, which has been associated with more severe apathy (99). Similarly, in Alzheimer's disease, though not typically considered a disorder of dopamine, lower DAT levels correlate with increased apathy (100). Trials of tetrabenazine treatment for tardive dyskinesia have shown an increased risk of apathy (101). However, further longer-term studies are needed to address important questions about the motivational effects of recently approved tetrabenazine derivative treatments (valbenazine and deutetabenazine) (101).

Parkinson's disease patients exhibit greater impairments in reward processing when off dopaminergic medication compared to when on it (57). However, further dissection of the relative contribution of dopamine transmission in signaling prospective reward and effort costs of an action has revealed distinct effects of apathy and dopamine (30). Apathy in Parkinson's patients

blunts reward sensitivity, whereas dopamine has a general effect in motivating behavior for high-effort, high-reward options (30). The finding that dopamine enhances willingness to exert effort has been replicated using both physical and cognitive effort-based decision-making tasks (31, 102).

A more complex picture has been reported in individuals at risk for psychosis, with dopamine synthesis being negatively associated with VS responses to reward cues, while the same relationship was positive in healthy participants (103). Dopamine state has also been shown to play an important role in option generation in Parkinson's disease. Patients on dopamine medication were able to draw a greater number of different paths between two points than when off of it, independent of motor symptoms (23).

Though manipulation of dopamine transmission appears to be crucial for motivation, it does not regulate hedonic capacity. Rodent reactivity to a pleasurable stimulus after NAc dopamine depletion remains the same as that of controls (62). This finding is consistent with human studies where dopamine blockade using the antagonist amisulpride was associated with impairment in reward anticipation but did not affect hedonic response (104). In contrast, participants receiving naltrexone, an opioid antagonist, did report reduced hedonic capacity during reward delivery (104). This supports the theory that mesolimbic dopamine primarily modulates motivation, whereas the experience of pleasure relies on parallel endogenous opioid systems in partly overlapping brain regions (104, 105).

Clarifying dopamine's role in apathy will also hinge on improved understanding of the dynamics of dopamine neurotransmission underlying motivation. Phasic midbrain dopamine firing encodes RPEs, a finding since confirmed by optogenetic studies (91, 106). Subsequent studies have proposed a distinction between tonic dopamine signals encoding reward valuation and effort and phasic dopamine signals encoding learning. More recent research has suggested a more integrated account of dopamine dynamics. As rodents approach rewards, NAc dopamine signals ramp up and scale with the magnitude of reward (107). This finding suggests that ramping signals may encode estimated expected reward value and influence cost-benefit decision making (107). Spatially and temporally tailored wave-like dopamine patterns of signaling have also been observed and shown to encode learning and prospective demands of a task (108).

Dopamine receptors, reward processing, and apathy. The above findings confirm that disrupted mesolimbic dopaminergic transmission is a key mechanism underlying apathy (85, 109). However, the distribution and function of dopamine receptors differ considerably. A more refined approach has been to clarify the differential role of specific receptors in motivation and apathy (109).

There are five known dopamine receptors (D1–D5), all of which are G protein-coupled receptors that can be grouped into D1-like (D1, D5) or D2-like (D2, D3, D4) classifications based on their transduction properties. Activation of D1-like receptors increases intracellular cyclic adenosine monophosphate (cAMP), which tends to promote synaptic plasticity and increase neuronal excitability, while activation of the D2 family of receptors has the opposite effects (106). This has led to D1-like receptors being conceptualized as excitatory and D2-like receptors as inhibitory (106). However, more recent investigations have revealed that dopamine receptors can exert some of their effects through an array of alternative signaling pathways that may or may not involve cAMP (110). For example, D2/3 receptor activation of the G $\beta\gamma$ protein subunit of G protein can modulate ion channels such as G protein inwardly rectifying potassium channels and calcium channels (L and N types) (110). Brain-derived neurotrophic factor (BDNF) receptors can also be transactivated by D1 and D2 receptors (111), and dopamine binds directly to trace amine-associated receptors, a family of intracellular receptors that can dimerize with dopamine receptors

and modulate dopaminergic activity (112). Therefore, the neuronal effects of dopamine depend on target cell receptors, secondary messenger responses, postsynaptic ion channel activation, and protein expression profiles (110).

D1 and D2 have a dense distribution within the frontotemporal cortices, limbic system, and the striatum (113). In contrast, D3 receptors are expressed more narrowly and distributed primarily within the mesolimbic system, particularly the VS (114). Owing to their expression profile and the effects of their pharmacological modulation, the D1–D3 receptors are believed to play an important role in reward processing and motivation (113). Less is known about the role of D4 and D5, which are distributed more diffusely (114).

A study in rodents using an effort-based decision-making task compared the behavioral effects of D1 agonists and the selective D1/D5 receptor antagonist ecopipam (115). Ecopipam treatment induced effort aversion, shifting choices toward low-effort, low-reward options (115). However, D1 agonist treatment reversed ecopipam's demotivating effects and shifted preference back to the high-effort, high-reward option (115). In humans, the D1 receptor has been proposed to play a central role in motivation and reinforcement learning (113). A recent report concluded that D1 stimulation modulates both motivation and flexible learning of cue-reward associations, improving reward learning (116). A positron emission tomography study using two different radioligands found that striatal D1 and D2 binding were differentially associated with learning from positive and negative outcomes, respectively (16).

Dopamine's role in motivation appears to depend on both receptor and location. Increasing D2 receptor expression in the VS in rats selectively increased motivation for reward (117). However, D2 receptor overexpression in the dorsal striatum was not associated with any behavioral change on motivational tasks (117). In patients with schizophrenia, lower striatal D2 receptor binding was also specifically associated with decreased motivation (118).

The adenosine system is now understood to closely interact with dopamine function, particularly D2 receptors. Adenosine A2A receptors are located in striatal regions, have a similar distribution to D2 receptors, and reverse the effects of D2 agonism (119). Adenosine A2A receptor antagonists are used to treat motor symptoms in Parkinson's disease (120) but have also been associated with increased motivation. For example, asthma patients treated with theophylline (a potent adenosine antagonist) can experience hyperactivity and restlessness, and caffeine's motivational properties are attributed to adenosine antagonism (121). Recent studies have revealed that the motivational effects of the adenosine system are specific to A2A receptor antagonism, act via the D2 receptor, and induce a preference to engage in effort (122, 123).

The strategic distribution of D3 receptors in the VS has concentrated attention on its role in reward processing and motivation. Decreased expression of the D3 receptor and its selective inhibition in the dorsal striatum of rats produced marked motivational deficits, which were reversed by a D3 agonist (124). Another study comparing D1-, D2-, and D3-specific agonists in rescuing motivational deficits induced by lesions to the substantia nigra found that only D3 agonists were effective (125). In postmortem studies of patients with schizophrenia, lower expression of substantia nigra D3 receptors has been associated with greater negative symptom burden (126). Agonism of D3 receptors has already been identified as a potential treatment for apathy in Parkinson's disease and proposed as a therapeutic target for apathy in other disorders (97, 113).

Synaptic clearance mechanisms also mediate dopamine's function and vary across corticostriatal regions (127). For example, in the VS, rapid recycling via DAT predominates (127). In contrast, in the PFC, DAT recycling is minimal and enzymatic degradation by catechol-O-methyltransferase (COMT) is the primary mechanism for clearance, modulating evoked dopamine release measured over minutes (128–130). Reinforcement learning and apathy have both been associated with functional polymorphisms in *COMT* (131, 132).

In summary, dopamine is a key modulator of motivation and a promising target for the treatment of apathy. However, understanding the complex dynamics of dopamine in modulating motivational states is crucial for the development of effective treatments. Due to the variation in metabolism, signaling, and receptor distribution, manipulating dopamine can have paradoxical consequences for distinct cognitive processes, often depending on basal levels of dopamine in different brain regions (133).

Serotonin

There are 15 known serotonin (5-hydroxytryptamine, 5-HT) receptors, and the role of this complex system in motivation remains poorly understood (134). Serotonin modulates the release of other neurotransmitters and is coreleased with dopamine in the VS (135). A consistent finding from early neurophysiological studies of serotonin function is its opponent interaction with dopamine. For example, drugs acting at the 5-HT_{2c} receptor can reduce mesolimbic dopamine release, and 5-HT_{2c} antagonists can mimic dopaminergic function and increase willingness and duration of effort exertion for reward in rats (136, 137). Following these observations, it was hypothesized that 5-HT inhibits action in an aversive context, encoding a punishment prediction error in contrast to dopamine-signaled RPEs (138). However, subsequent recordings from the dorsal raphe nucleus (DRN, one of the main sources of 5-HT neurons) found that firing scaled with the size of prospective reward, while optogenetic stimulation of the DRN increased patience for reward delivery (139, 140). Additionally 5-HT_{1A} agonism increases dopamine release in the PFC (141). This suggests that the interaction between 5-HT and dopamine may be crucial in mediating the temporal dynamics of RPEs that drive reinforcement learning.

In humans, there have been conflicting accounts of 5-HT's role in motivation. Dietary depletion of the 5-HT precursor tryptophan results in reduced response vigor to reward and reduced valuation of expected reward during a learning task (134, 142, 143). Studies administering selective serotonin reuptake inhibitors (SSRIs) have reported reduced effort costs but unchanged reward value (144). This finding would suggest that SSRIs should treat apathy; however, paradoxically, the use of SSRIs has been associated with greater apathy compared to other classes of antidepressants (145).

In summary, it is evident that the complex dynamics and interaction between dopamine and 5-HT play a key role in motivation. However, further empirical work in clinical populations is needed to clarify 5-HT's role in apathy (138).

Noradrenaline

The locus coeruleus (LC) is a small, pigmented nucleus located in the pons and is the primary site of noradrenaline synthesis in the brain (146). Noradrenaline's role in motivation is only just beginning to be understood (146). However, recent positive trials of noradrenergic drugs suggest that this relatively small neuromodulatory system plays a central role in motivation and apathy (147, 148).

Primate studies indicate that LC neurons are activated immediately before initiating an effortful action and correlate with effort production (149). Manipulation of LC activity in monkeys with clonidine, a selective α_2 -agonist known to decrease LC activity, led to a reduced willingness to exert effort (150). LC activity also signals anticipation of action and is closely associated with autonomic arousal and pupil dilation, which are themselves correlated with both physical and mental effort (149, 150).

Neurodegeneration of the LC occurs early in the disease course of Alzheimer's and Parkinson's (151), and greater degeneration of the LC has been associated with increased apathy in patients

with Parkinson's (152). Although, to our knowledge, no studies have examined the effects of adrenoceptor antagonists on apathy, β -blocker therapy in cardiac patients has long been associated with an increased risk of lethargy and fatigue (153). Few studies have investigated the role of noradrenaline in mediating the cognitive components of motivation. However, noradrenaline has been repeatedly associated with exploratory behavior, in other words, deciding to forego a known option in favor of a potentially more rewarding but unknown alternative. Two investigations in healthy participants have shown that the β -adrenergic receptor antagonist propranolol attenuates value-free random exploration (154, 155). This finding suggests that noradrenaline's role in motivation may drive goal-directed behavior for actions with unknown potential rewards.

In summary, while dopamine encodes the cost-benefit trade-off of an action, noradrenaline may signal the anticipatory arousal and allocation of effort needed to overcome action costs and affect exploration (156, 157). Disruption of the noradrenergic system may lead to apathy through imprecise anticipation or effort allocation and supports preliminary evidence that noradrenergic therapies could be promising treatments for apathy (157, 158).

Acetylcholine

Cholinergic interneurons are critical regulators of striatal network activity, and the role of cholinergic dysfunction in Alzheimer's disease, in which apathy is prevalent, has renewed interest in acetylcholine's role in motivation.

Recent evidence suggests that the cholinergic system, which consists of ionotropic nicotinic acetylcholine receptors and G protein-coupled muscarinic acetylcholine receptors (mAChRs), is a powerful modulator of dopamine signaling and, consequently, motivation (159). There are two nicotinic receptor subtypes, N1 and N2, which are primarily subdivided based on their distinct locations; N1 receptors are present at the neuromuscular junction, whereas N2 receptors are located within the peripheral and central nervous system. There are five main subtypes of muscarinic receptors (M1–M5), which are found throughout the nervous system but have distinct, though overlapping, distributions (160). For example, M1, M2, and M4 receptors are abundant in the cortex and striatum, whereas M5 receptors are numerous on dopaminergic neurons (160). Similar to dopamine receptors, each has a diverse array of second messenger responses and effects on ion channels (160). Several studies have shown that mAChRs can bidirectionally modulate dopamine-dependent action (159). Presynaptic M2 and M4 act as autoreceptors on striatal cholinergic interneurons, inhibiting acetylcholine release and modulating local dopamine release (159). Behavioral effects of dopaminergic drugs are enhanced by mAChR antagonists and attenuated by mAChR agonists. For example, administration of mAChR agonists into the rodent NAc reduced reward seeking (161). However, this appears to be receptor dependent as selective blockade of M1 but not M4 enhances reward seeking and rescues antipsychotic-induced amotivation (162).

Despite reducing striatal dopamine release, preliminary trials of emraclidine and xanomeline (M4 mAChR agonists; see **Figure 2**) have shown efficacy in the treatment of negative symptoms in schizophrenia (163, 164). Cholinesterase inhibitors also reduce apathy in Alzheimer's disease, Parkinson's disease, and Lewy body dementia (163, 165). However, to our knowledge, no study to date in humans has examined the effects of manipulating specific cholinergic receptors on reward processing.

Other Neurotransmitters

Glutamate is the most abundant excitatory neurotransmitter in the brain, and GABAergic medium spiny neurons comprise 95% of all cells in the VS, receiving glutamatergic input from the cortex

(166). Dysfunction in glutamate reuptake and recycling can cause excitotoxicity, which has been proposed as a mechanism underlying neurodegenerative disorders (165).

Glutamate's role in apathy is poorly understood; however, one study using proton magnetic resonance spectroscopy in patients with schizophrenia found that reduced ACC glutamate was associated with more negative symptoms (167). In healthy participants, a higher glutamine (a metabolic precursor)-to-glutamate ratio within the VS predicted greater sustained effort exertion and lower perceived effort (168). A metabolic account of glutamate accumulation driving fatigue has recently been proposed. Preference for sooner, low-effort rewards following sustained cognitive effort was associated with greater glutamate accumulation in the lateral PFC (169). The authors concluded that glutamate accumulation makes cortical activation more costly, leading to fatigue and a reduced willingness to exert effort (169). This possible neurometabolic consequence of glutamate accumulation may also provide an explanation of the close association between fatigue and apathy (170).

Neuronal projections from the VTA are typically considered dopaminergic, but the recent discovery of combinatorial neurons that corelease dopamine with GABA has indicated a key role for this neurotransmitter in motivation (171). Mouse studies have shown that VTA GABA-transmitting neurons signal cues predicting the absence of reward (171), and VP GABA neurons are crucial in high-risk motivated behavior, inducing conservative, risk-averse behavior when silenced (172). Stimulation of GABA_A receptors in the VP has also been shown to induce apathy, partly mediated by the depletion of NAc dopamine (173). In patients with epilepsy, the use of antiepileptics that potentiate GABA-mediated inhibitory neurotransmission is associated with increased apathy (174), and a small study of patients with Alzheimer's disease found that increased plasma GABA correlated with higher apathy (175). However, to our knowledge, no studies have examined the effects of GABAergic medication on the cognitive mechanisms underlying apathy.

Recreational cannabis use has long been associated with apathy (176), but the role of the endocannabinoid system in motivation is only just beginning to be understood (176). In rodents, administration of cannabinoid-1 (CB1) receptor agonists into the ACC and OFC induces marked apathy (177), and endogenous CB1 receptor agonists suppress dopaminergic activity in the NAc and reward seeking (178).

In humans, a study of the effects of cannabinoids on effort-based decision making revealed that Δ^9 -tetrahydrocannabinol (THC), a CB1 receptor partial agonist, reduced willingness to exert effort (179). Greater understanding of the precise mechanisms underlying the effects of cannabis on motivation will enable insight into the therapeutic potential of endocannabinoid modulation for apathy.

PHARMACOLOGICAL INTERVENTIONS

Repurposing Existing Treatments

Repurposed drugs have been used in the majority of randomized controlled trials (RCTs) relevant to apathy, most of which examined it as a secondary outcome measure. A summary of double-blind RCTs of pharmacological interventions to treat apathy across schizophrenia, Parkinson's disease, and dementia (**Figures 2 and 3; Supplemental Table 1**) highlights the more promising and disappointing avenues of treatment tested to date.

For example, it appears that modafinil is an ineffective treatment for apathy, as all nine RCTs of modafinil for apathy (eight of which were in schizophrenia) had null findings. Though modafinil is a weak dopamine and noradrenaline reuptake inhibitor (**Figure 2; Table 1**), it has additional histaminergic activity (196), indicating that sufficient concurrent modulation of dopaminergic and noradrenergic systems may be needed for therapeutic efficacy. Similarly, most (9/14) trials of SSRIs

Supplemental Material >

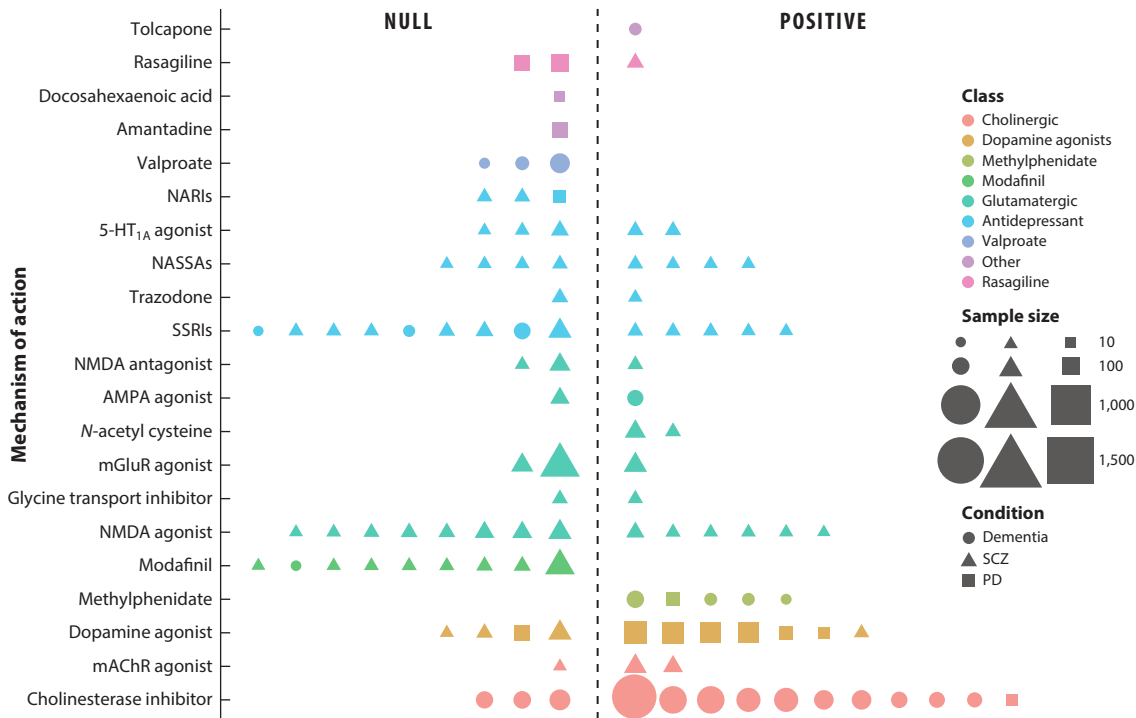


Figure 3

Summary plot of transdiagnostic outcomes of double-blind, randomized, placebo-controlled trials of pharmacological interventions to treat apathy in dementia, SCZ, and PD. Abbreviations: 5-HT, 5-hydroxytryptamine; AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; mAChR, muscarinic acetylcholine receptor; mGluR, metabotropic glutamate receptor; NARI, noradrenaline reuptake inhibitor; NASSA, noradrenaline and specific serotonergic antidepressant; NMDA, *N*-methyl-D-aspartate; PD, Parkinson's disease; SCZ, schizophrenia; SSRI, selective serotonin reuptake inhibitor.

for apathy have shown a lack of efficacy, a finding supported by cohort study data indicating that SSRI treatment can exacerbate apathy (145).

In contrast, trials of methylphenidate suggest that it may be an effective treatment for apathy. All five RCTs reported significant improvements in apathy (in Alzheimer's and Parkinson's diseases). Methylphenidate is a potent noradrenaline and dopamine reuptake inhibitor (**Figure 2**; **Table 1**), and the results of these trials support basic neuroscientific research showing that these systems play a crucial role in the neurobiological mechanisms underlying motivation.

In Parkinson's disease, dopamine agonists also appear to be clinically effective treatments for apathy (6/7 positive trials). However, dopamine agonists have diverse receptor-binding profiles, and there have been no head-to-head trials to date (**Figure 2**) that could inform treatment regimens and shed light on the mechanisms underlying motivation. In contrast to Parkinson's disease, dopamine agonists appear to be ineffective for apathy in schizophrenia (1/4 positive trials), suggesting that different mechanisms may be driving amotivational symptoms; or possibly the concurrent use of antipsychotic medication may negate any therapeutic effect.

Cholinesterase inhibitors are currently utilized for their small but clinically meaningful cognitive benefits in Alzheimer's disease (199). However, most trial findings to date (11/14 positive) also support a therapeutic role for apathy. This finding is intriguing given the limited neuroscientific research into the role of the cholinergic system in motivation compared to other

Table 1 Summary of medications trialed as treatments for apathy and their mechanisms of action

Medication(s)	Clinical indication(s)	Mechanism of action
Tolcapone, opicapone, entacapone	PD	COMT inhibitors: COMT is a catecholamine-degrading enzyme. Enzymatic degradation by COMT is the primary mechanism for synaptic dopamine clearance in the prefrontal cortex. COMT inhibitors increase cortical dopamine by inhibiting this key catabolic pathway either directly within the brain (tolcapone) or peripherally (180).
Rasagiline, selegiline	PD	MAO-B inhibitors: MAO-B inhibition in the brain principally reduces the catabolism of dopamine (181).
Docosahexaenoic acid	NA	Omega-3 long-chain polyunsaturated fatty acid: Lipid-bound docosahexaenoic acid is hypothesized to modulate neurotransmission via modifying cell membrane fluidity (182).
Amantadine	Antiviral, PD	Originally an antiviral agent, amantadine increases striatal dopamine biosynthesis and synaptic release and is a low-affinity noncompetitive antagonist of NMDA receptors (183).
Valproate/valproic acid	Epilepsy, mood stabilizer	A simple branched-chained fatty acid, valproic acid inhibits GABA transaminase from increasing levels in the central nervous system and reducing high-frequency firing of neurons via voltage-gated sodium, potassium, and calcium channel blockade (184).
Atomoxetine, reboxetine	ADHD, mood disorders	NARIs; atomoxetine also inhibits reuptake of dopamine within the prefrontal cortex and is an NMDA receptor antagonist at clinical doses (185).
Buspirone, tandospirone	Dyskinesia, mood disorders	These are 5-HT _{1A} receptor partial agonists, weak 5-HT receptor agonists, and weak antagonists at dopamine D ₂ autoreceptors (186).
Trazodone	Insomnia, mood disorders	Serotonin receptor antagonist and reuptake inhibitor: Trazodone is a SERT inhibitor and 5-HT ₂ receptor antagonist (187). It is also a weak antagonist at α_1 - and α_2 -adrenergic receptors and histamine H ₁ receptors.
Mirtazapine	Mood disorders	This noradrenergic and specific serotonergic antidepressant antagonizes the adrenergic α_2 -autoreceptors and α_2 -heteroreceptors as well as blocks 5-HT ₂ and 5-HT ₃ receptors (188).
Sertraline, citalopram, fluoxetine	Mood disorders	SSRIs: These have high affinity for SERT, inhibiting the reuptake of 5-HT. Most SSRIs also have weak affinity to the noradrenaline transporter (189).
Memantine	AD	NMDA antagonist: Memantine is classified as an open channel blocker because it can enter the NMDA receptor channel, blocking current flow only after channel opening (190).
Ampakine (CX516), mibampator	AD (phase II), SCZ (phase II)	AMPA receptor agonists: Both mibampator and CX516 are positive allosteric modulators of the AMPA receptor and enhance depolarization by prolonging the channel opening in response to glutamate (191).
N-acetyl cysteine	Paracetamol overdose	This is a glutathione precursor that is hypothesized to modulate NMDA receptor activity by decreasing oxidizing agents that can bind to the redox-sensitive NMDA receptor complexes (192).
LY4044039, LY21240023	SCZ (phase II)	These are selective agonists for metabotropic glutamate 2/3 (mGlu2/3) receptors (193).
D-alanine, sarcosine	SCZ (phase II)	These are glycine transport inhibitors that increase the levels of the NMDA receptor agonist glycine (194).

(Continued)

Table 1 (Continued)

Medication(s)	Clinical indication(s)	Mechanism of action
D-serine, D-cycloserine, glycine	SCZ (phase II)	These are glycine site agonists or partial agonists for the NMDA receptor (195).
Modafinil	Sleep disorders	Several mechanisms of action: Modafinil is a modest potency inhibitor of dopamine and noradrenaline transporters, potentiating dopamine and noradrenaline neurotransmission, though in vitro studies suggest this property is weaker than that of methylphenidate (196). In addition, modafinil leads to significantly elevated extracellular dopamine, noradrenaline, 5-HT, glutamate, and histamine levels and decreased GABA levels, particularly in the neocortex (196).
Methylphenidate	ADHD	This is a high-affinity inhibitor of dopamine and NARIs (147).
Pramipexole, ropinirole, aripiprazole (low dose)	PD	These are dopamine agonists with variable affinity for D1, D2, and D3 receptors (96).
Istradefylline	PD	Istradefylline inhibits A2A receptors located in the striatum, preventing A2A receptors from forming heterotetramers with D2 dopamine receptors, therefore potentiating dopamine D2 agonism (197).
Emraclidine, xanomeline	SCZ	mAChR agonists: Presynaptic mAChRs can act as autoreceptors on striatal cholinergic interneurons to inhibit acetylcholine release and modulate local dopamine release (163).
Donepezil, rivastigmine, metrifonate	AD	These are acetylcholinesterase inhibitors that lead to the accumulation of acetylcholine and enhanced stimulation of postsynaptic cholinergic receptors (198).

Abbreviations: A2A, adenosine 2A; AD, Alzheimer's disease; ADHD, attention deficit hyperactivity disorder; AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; COMT, catechol-*O*-methyltransferase; GABA, γ -aminobutyric acid; mAChR, M4 muscarinic receptor; MAO-B, monoamine oxidase type B; NA, not applicable; NARI, noradrenaline reuptake inhibitor; NMDA, *N*-methyl-D-aspartate; PD, Parkinson's disease; SCZ, schizophrenia; SERT, serotonin transporter; SSRI, selective serotonin reuptake inhibitor.

neurotransmitters. Further trials of cholinergic therapies for apathy are needed, particularly for groups such as patients with schizophrenia, where dopaminergic therapies are limited by the risk of exacerbating positive symptoms (hallucinations and delusions). Novel cholinergic agents such as emraclidine (an M4 agonist) have already shown promise in treating negative symptoms and offer more targeted means of modulating the cholinergic system (**Figure 2**).

Novel Treatments

A wide range of glutamatergic therapies have been tested for motivational symptoms in schizophrenia, with largely disappointing results (**Figure 3**). However, recent investigations have shown that ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, has rapid-acting antidepressant effects and specifically improves motivation-related symptoms of depression, particularly anhedonia (200). Anhedonia and apathy might share some underlying cognitive and neural mechanisms (6), and recent evidence suggests that ketamine may reverse motivation-related reward-processing deficits (201) and rectify frontostriatal connectivity (202). No trials have been conducted for apathy to date, but ketamine warrants further investigation as a potential treatment.

Repetitive transcranial magnetic stimulation (rTMS) has shown promise in the treatment of apathy in neurological conditions such as stroke, Parkinson's disease, and mild cognitive impairment (203). Though these have been small trials, targeting different brain regions (the dorsolateral

PFC and supplementary motor area), several studies have used fMRI to guide rTMS target identification for other conditions (204). In the future, utilizing effort-based decision-making tasks while patients undergo fMRI may guide personalized rTMS targets for apathy based on network connectivity, while accounting for anatomical variability.

Up to 15% of Parkinson's patients are candidates for DBS, which is also now used in severe psychiatric conditions, including obsessive compulsive disorder. Though most DBS studies in Parkinson's have reported worsened apathy after subthalamic nucleus DBS, other targets are promising. For example, DBS of the VS in animal studies and in patients with severe depression improves amotivational symptoms, and stimulation of the ACC induces a feeling of determination, highlighting its future potential for patients with Parkinson's disease and apathy or severe, treatment-resistant cases (205).

Effort sensitivity:
the degree to which an individual's behavior is discounted by the effort costs of an action

CONCLUSION

Apathy is a common and disabling syndrome that has poor long-term functional outcomes. Safe and effective treatments for patients with the condition are desperately needed across neuropsychiatric disorders. Conceptualizing apathy as a consequence of disruption to the component parts of motivation (e.g., reward versus effort sensitivity) provides a framework to delineate transdiagnostic or disease-specific mechanisms of apathy and how they relate to complex changes in neurotransmitter systems. Utilizing our rapidly developing understanding of the cognitive and neural mechanisms of motivation from preclinical basic neuroscience studies will be crucial in developing and refining targeted treatments for apathy.

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