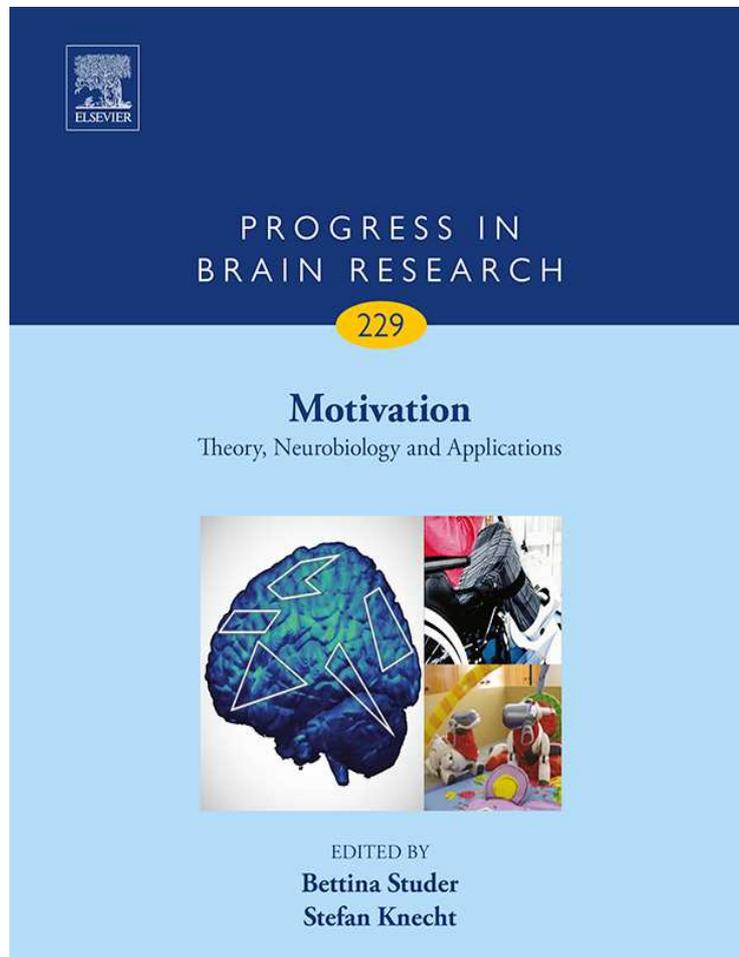


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The role of dopamine in the pathophysiology and treatment of apathy

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Abstract

Disorders of diminished motivation, such as apathy, are common and prevalent across a wide range of medical conditions, including Parkinson's disease, Alzheimer's dementia, stroke, depression, and schizophrenia. Such disorders have a significant impact on morbidity and quality of life, yet their management lacks consensus and remains unsatisfactory. Here, we review laboratory and clinical evidence for the use of dopaminergic therapies in the treatment of apathy. Dopamine is a key neurotransmitter that regulates motivated decision making in humans and other species. A large corpus of evidence suggests that it plays an important role in promoting approach behavior by attributing incentive salience to reward stimuli, and facilitating the overcoming of effort costs. Furthermore, dopaminergic neurons innervate several frontostriatal structures that mediate reward-guided behavior. Based on these findings, there are a priori reasons for considering dopamine in the treatment of disorders of diminished motivation. We highlight key studies that have attempted to use dopamine to manage patients with apathy, and that collectively offer cautious evidence in favor of its efficacy. However, many of these studies are small, unblinded, and uncontrolled, and utilize subjective, questionnaire-based measures of apathy. Given the development of novel paradigms which are able to objectively dissect motivational dysfunction, we are now well positioned to quantify the effect of specific classes of dopaminergic medication on reward- and effort-based decision making in apathy. We anticipate that such paradigms will lay the foundation for future studies to evaluate new and existing treatments for disorders of motivation, using sensitive measures of apathy as primary quantifiable end points.

Keywords

Motivation, Disorders of motivation, Apathy, Dopamine, Decision making, Effort, Reward

1 INTRODUCTION

Apathy is one of several disorders characterized by an impairment in motivation (Table 1). Some have proposed that such disorders lie on a continuum, from apathy on the milder end to akinetic mutism at its most severe (Marin and Wilkosz, 2005). Although the terminology for these disorders has been historically useful, many of these terms were defined on the basis of clinical observations over the last century. As such, they do not account for more contemporary discoveries in the biological sciences that have begun to distinguish different components of motivation. For example, “anhedonia” has been used to refer to multiple components of reward-based behavior, including the emotional experience of reward presentation; the anticipation of pleasurable outcomes; and the consumption of the desired good—however, extensive evidence now shows that these processes are dissociable (Berridge et al., 2009; Markou et al., 2013; Salamone et al., 2007; Smith et al., 2011; Treadway and Zald, 2011).

1.1 WHAT IS APATHY?

One of the earliest contemporary definitions of apathy was that it was characterized by “diminished goal-oriented behavior and cognition, and a diminished emotional connection to goal-directed behavior” (Marin, 1991); and, later, “the absence or lack of emotion, interest, concern, or motivation” (Marin, 1996). Over time, there have been several different conceptualizations of apathy, but a common feature is apathy as a disorder of motivation (Cummings et al., 1994; Levy and Dubois, 2006; Robert et al., 2002; Sockeel et al., 2006; Starkstein and Leentjens, 2008; Stuss et al., 2000). Indeed, one recent set of proposed diagnostic criteria requires a lack of motivation, resulting in significant clinical or functional impairment (Table 2; Mulin et al., 2011). This classification also preserves and elaborates on a feature of the earlier definition, which distinguishes several putative components of apathy, including behavioral, cognitive, and emotional elements. In schizophrenia, apathy is clustered alongside avolition and anergia in the Scale for Assessment of Negative Symptoms (SANS; Andreasen, 1984). For the purposes of this review, we consider diminished motivation to be a core feature of apathy, and we discuss studies which, unless otherwise indicated, have examined patients who have been diagnosed with apathy according to a standard set of diagnostic criteria (see also Chong et al., 2016 and Section 4.3.1 for a description of an apathetic patient involved in one of our tasks).

Table 1 Disorders of Diminished Motivation and Their Putative Definitions

Term	Definition(s)
Abulia	Impaired spontaneity in action and speech, with normal intellectual content, reduced range of movement, mental slowness, decreased attention in the presence of increased distractibility, and apathy (Bhatia and Marsden, 1994; Fisher, 1982).
Akinetic mutism	Lack of self-initiated motor or mental activity, and indifference even to biologically relevant stimuli (pain, hunger, thirst) in the presence of normal alertness (Cairns et al., 1941).
Anergia	Lack of perceived energy (Markou et al., 2013).
Anhedonia	The inability to experience pleasure (Barch and Dowd, 2010; Ribot, 1896).
Apathy	Disorder of motivation characterized by diminished voluntary and goal-directed behavior and cognition (Starkstein and Leentjens, 2008). The most recent working definition subdivides it into behavioral, cognitive, and emotional components (see Table 2). Specific deficits postulated to include intellectual curiosity, action initiation, self-awareness, emotion, and interest/enthusiasm (Cummings et al., 1994; Levy and Dubois, 2006; Marin et al., 1991; Robert et al., 2002; Sockeel et al., 2006; Starkstein and Leentjens, 2008; Stuss et al., 2000).
Autoactivation deficit (or athymhormia, psychic akinesia, reversible inertia)	Deficit in spontaneous activation of mental processing, observed in behavioral, cognitive, or affective domains, which can be totally reversed by external stimulation that activates normal patterns of response (Laplaine and Dubois, 2001). Manifest as lack of self-initiated voluntary behavior (Levy and Dubois, 2006; van Reekum et al., 2005).
Avolition	Reduced ability to initiate and maintain goal-directed behavior (Foussias and Remington, 2010; Kraepelin, 1921).
Fatigue (central)	Lack of physical or mental energy related to abnormalities in motivational mechanisms (Chaudhuri and Behan, 2004).
Psychomotor retardation	Slowing of movement, or generally reduced tendency to engage in motor activity (Jones and Pansa, 1979; Sobin and Sackeim, 1997; Widlocher, 1983).

Table 2 Proposed Diagnostic Criteria for Apathy (Drijgers et al., 2010; Mulin et al., 2011; Robert et al., 2009)

For a diagnosis of Apathy the patient should fulfill criteria A, B, C, and D:

- A. Loss of or diminished motivation in comparison to the patient's previous level of functioning and which is not consistent with his age or culture. These changes in motivation may be reported by the patient himself or by the observations of others.
- B. Presence of at least one symptom in at least two of the three following domains for a period of at least 4 weeks and present most of the time.
- Domain B1—Behavior:* Loss of, or diminished, goal-directed behavior as evidenced by at least one of the following:
- *Initiation symptom:* loss of self-initiated behavior (for example: starting conversation, doing basic tasks of day-to-day living, seeking social activities, communicating choices).
 - *Responsiveness symptom:* loss of environment-stimulated behavior (for example: responding to conversation, participating in social activities).
- Domain B2—Cognition:* Loss of, or diminished, goal-directed cognitive activity as evidenced by at least one of the following:
- *Initiation symptom:* loss of spontaneous ideas and curiosity for routine and new events (ie, challenging tasks, recent news, social opportunities, personal/family and social affairs).
 - *Responsiveness symptom:* loss of environment-stimulated ideas and curiosity for routine and new events (ie, in the person's residence, neighborhood, or community).
- Domain B3—Emotion:* Loss of, or diminished, emotion as evidenced by at least one of the following:
- *Initiation symptom:* loss of spontaneous emotion, observed, or self-reported (for example, subjective feeling of weak or absent emotions, or observation by others of a blunted affect).
 - *Responsiveness symptom:* loss of emotional responsiveness to positive or negative stimuli or events (for example, observer reports of unchanging affect, or of little emotional reaction to exciting events, personal loss, serious illness, emotional-laden news).
- C. These symptoms (A–B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning.
- D. The symptoms (A–B) are not exclusively explained or due to physical disabilities (eg, blindness and loss of hearing), to motor disabilities, to diminished level of consciousness, or to the direct physiological effects of a substance (eg, drug of abuse, a medication).
-

1.2 APATHY IS NOT DEPRESSION

Given the clinical manifestations of apathy, it is somewhat unsurprising that it is often conflated with depression. Indeed, they often overlap behaviorally, and apathy has been shown to be a harbinger of future depression (Starkstein et al., 2006). It is vital to appreciate, however, that apathy and depression are clinically and physiologically distinct entities (Kirsch-Darrow et al., 2006; Marin et al., 1993; Santangelo et al., 2013). Across multiple primary diseases, apathy has been found to be dissociable from other symptoms of depression, such as emotional distress, agitation, vegetative symptoms, suicidal ideation, hopelessness, and heightened sadness (Kirsch-Darrow et al., 2006; Levy et al., 1998; Starkstein et al., 2009). Thus,

even though apathy and depression may share similar surface manifestations, they most likely arise from separate etiologies, which will be important in the development of future treatments tailored to both conditions.

1.3 APATHY IS INDEPENDENT OF COGNITIVE DYSFUNCTION

It is equally important to recognize that apathy does not merely reflect a generalized cognitive impairment. For example, in Parkinson's disease (PD), apathy is an isolated, independent, nonmotor symptom, even after adjusting for the severity of cognitive status and motor symptoms (Dujardin et al., 2014). General measures of attention and cognition (eg, MMSE or IQ) lack sensitivity for detecting apathy and typically show little change in apathetic individuals (Feil et al., 2003).

1.4 APATHY IS COMMON AND DEBILITATING

The exact prevalence of apathy is difficult to estimate, with cited rates being highly variable. For example, estimates of apathy have ranged from 17% to 70% in PD (Aarsland et al., 2009; Leentjens et al., 2008), 29% to 81% in Alzheimer's dementia (AD; Aarsland et al., 2001; Lyketsos et al., 2000; Marin et al., 1994; Migneco et al., 2001), and 10% to 71% in traumatic brain injury (Andersson et al., 1999; Kant et al., 1988). There are potentially several reasons for such variability. Because of variable diagnostic criteria, we lack an objective means to classify apathy, and it has traditionally been underrecognized (Landes et al., 2001). It may be confounded or confused with other phenomena: laziness, oppositional behavior, depression, or general emotional distress. In addition, although "apathy" as a symptom occurs in many diseases—including PD, dementia, schizophrenia, and depression—it tends to be overshadowed by the constellation of other symptoms which define the primary illness. Moreover, apathetic individuals have poor insight into their condition and are unable to advocate for themselves, and may therefore remain a silent population that is difficult to identify, study, and manage.

Nevertheless, the clinical impact of apathy is becoming increasingly well recognized. It is a significant contributor to poor outcome in neurologic and psychiatric populations, independent of depression. Apathy is associated with worsening social and functional impairment; decreased treatment responsiveness or compliance, poor awareness of behavioral and cognitive changes; poorer clinical outcome; and overall poorer quality of life (Boyle et al., 2003; Gerritsen et al., 2005; Mega et al., 1999; Pluck and Brown, 2002; Starkstein et al., 1993, 2001, 2006). Furthermore, it is associated with more rapid cognitive decline (Starkstein et al., 2006) and contributes above and beyond dementia severity in affecting basic activities of daily living (Zawacki et al., 2002). Apart from impacting upon the individual, it also contributes to caregivers' distress; dissatisfaction with caregiving; increased feelings of frustration; and disruptions to family life, which may compound patients' disability (Aarsland et al., 2007; Benoit et al., 1999; Campbell and Duffy, 1997; Kaufer et al., 1998; Lyketsos et al., 2002; van Reekum et al., 2005). Overall, therefore,

apathy imposes high levels of economic, social, and physical burden and distress and frequently leads to earlier institutionalization than for similarly impaired patients without apathy (Moretti et al., 2002).

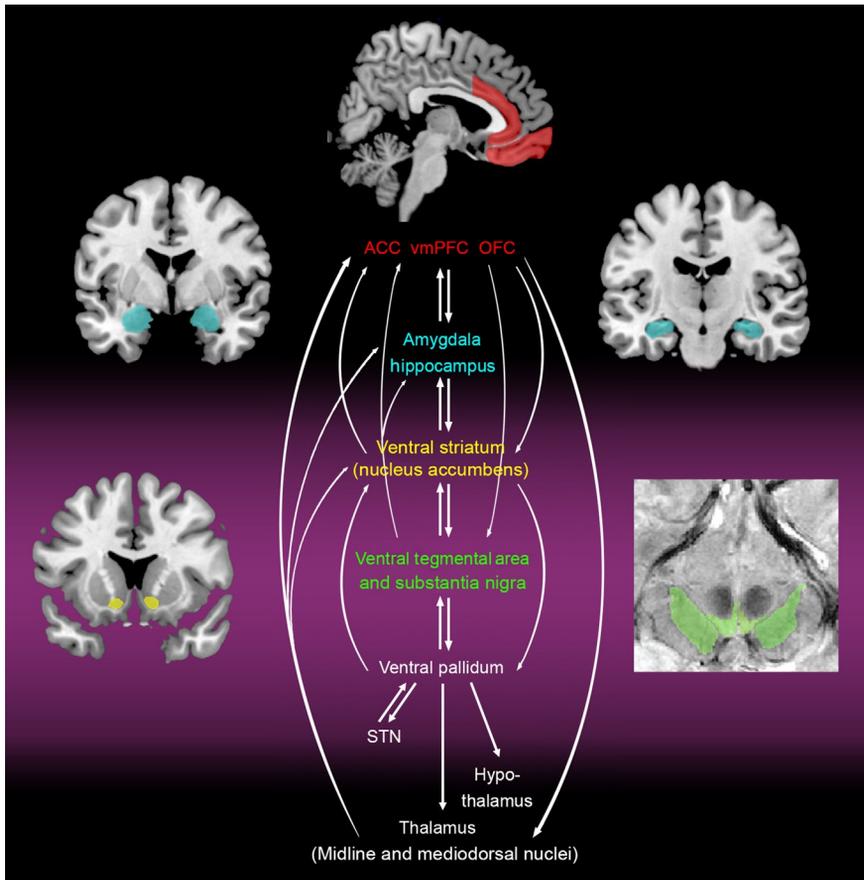
Despite its impact, only recently has apathy become an important subject of scientific enquiry. Treatment of the condition has not been the subject of many large-scale studies, and management strategies vary considerably. In addition to lifestyle and environmental interventions, a vast range of drugs have been used, depending on the patient and their primary disease. Of these treatments, there is a significant volume of preclinical literature supporting the involvement of dopamine in behavioral activation and motivation in nonhuman animals (Salamone and Correa, 2012). Here, therefore, we focus on the potential utility of dopamine as a treatment for apathy. In the following sections, we first consider the causal link between dopaminergic lesions and motivational deficits, before considering various attempts at using dopaminergic drugs to treat apathy in humans.

2 APATHY AS A DISORDER OF DOPAMINERGIC FUNCTION

2.1 DOPAMINERGIC DEFICITS IN NONHUMAN ANIMALS MODULATE REWARD AND EFFORT SENSITIVITY

A key feature of motivated behavior is that it requires one to decide whether to embark on a course of action for a given reward given the associated costs (Chong et al., 2016). Thus, motivation requires an animal to be sensitive to the rewards on offer for its actions (“reward sensitivity”), as well as the costs associated with it, such as the effort required to obtain it (“effort sensitivity”). This cost–benefit computation is thought to be underpinned by a distributed network of brain areas, including the ventral striatum, ventral pallidum, medial prefrontal and anterior cingulate cortices (ACC), and basolateral amygdala (Fig. 1; Farrar et al., 2008; Floresco and Ghods-Sharifi, 2007; Hauber and Sommer, 2009; Walton et al., 2003). The core of this network is composed of reciprocal connections between the basal ganglia and prefrontal cortex, particularly the dopaminergic mesocorticolimbic and nigrostriatal pathways (Levy, 2012).

The mesocorticolimbic dopamine system is considered to be central to the brain’s reward and motivational circuitry (Robbins and Everitt, 2006; Salamone et al., 2006). It projects from the ventral tegmental area of the midbrain to a widespread area of cortical and subcortical regions, including the ventral striatum/nucleus accumbens (NAcc), medial prefrontal areas, the amygdala, and the hippocampus (Fig. 1). The NAcc is a subcortical structure comprising an inner core and outer shell, with the shell being one of the major projection areas of mesolimbic dopamine neurons, which also receives important connections from the hippocampus and amygdala (Sokoloff et al., 2006). Dopamine released in the NAcc is thought to play a central role in effort-based decisions, and some have proposed that the NAcc plays a critical role as a “limbic–motor interface” to translate motivation into action

**FIG. 1**

Simplified schematic of the reward pathway in humans. The core of the mesocorticolimbic system is formed by basal ganglia nuclei (*shaded maroon*). Projections from the dopaminergic midbrain originate from the ventral tegmental area and substantia nigra and project to the ventral striatum (nucleus accumbens; *yellow*), prefrontal cortex (*red*), and limbic and other subcortical structures (amygdala and hippocampus, *blue*). The midsagittal section (*top*) illustrates the anterior cingulate cortex (ACC) superiorly and the ventromedial prefrontal cortex (vmPFC) inferiorly, with the orbitofrontal cortex (OFC) on the ventral surface of the brain. The coronal slices illustrate the amygdala nuclei (*top left, blue*), hippocampal formation (*top right, blue*), and ventral striatum (*bottom left, yellow*). The axial MRI of the midbrain illustrates the substantia nigra laterally and the ventral tegmental area medially (*bottom right, green*; as segmented in a recent 7T MRI study (Eapen et al., 2011)). STN, subthalamic nucleus.

(Mogenson et al., 1980). The prefrontal cortex, in particular ventromedial prefrontal areas and the ACC, is functionally interconnected with basal ganglia and limbic structures through different circuits (Mega and Cummings, 1994) and plays a critical role in reward processing, initiation, planning, and monitoring of goal-directed behavior (Fuster, 2008).

There is extensive evidence that a dopaminergic deficit, or selective lesions to the mesocorticolimbic system, results in less-motivated behavior, which resembles the behavior of patients with apathy. For example, typical studies in rodents require the animal to decide how much effort it is willing to invest for various rewards. Such paradigms may include operant conditioning tasks or dual alternative, effort discounting tasks (Chong et al., 2016). These tasks are able to quantify motivation in terms of the animal's sensitivity to available rewards—that is, how much reward is required to incentivize it to act. They are also able to quantify the animal's sensitivity to effort costs—that is, how much effort it is willing to exert to obtain those rewards. The animal's reward and effort sensitivities can then be compared before and after lesions to the mesocorticolimbic system. Typically, dopamine transmission is disrupted through systemic administration of low doses of dopamine antagonists, or selective dopamine depletion or antagonism (eg, with 6-hydroxy-dopamine, SCC 23390, ecopipam, haloperidol, flupenthixol; Salamone and Correa, 2012).

A vast volume of literature has been built on this approach, and the results from many of these tasks are strikingly similar. The overall pattern is that disrupting dopamine transmission reduces an animal's sensitivity to reward and increases its sensitivity to effort. Thus, it will require greater rewards to incentivize it to act, and it will be willing to invest less effort for given rewards. This is a consistent finding across a range of paradigms and can occur in the context of systemic dopaminergic depletion, disruption of dopaminergic input to the basal ganglia and/or frontal lobes, or from selective antagonism of basal ganglia and cortical dopamine receptors (Cousins and Salamone, 1994; Cummings, 1993; Denk et al., 2005; Farrar et al., 2010; Floresco et al., 2008; Hauber and Sommer, 2009; Mai et al., 2012; Nowend et al., 2001; Nunes et al., 2010, 2013; Pardo et al., 2012; Randall et al., 2012; Salamone and Correa, 2012; Salamone et al., 1991, 1994, 2003, 2007; Schweimer and Hauber, 2006; Sink et al., 2008; Walton et al., 2005). Together, this literature highlights the importance of the reward- and effort-related functions of dopaminergic systems.

2.2 DOPAMINERGIC DEFICITS IN HUMANS LEAD TO APATHY

In humans, apathy and lack of motivation have been reported following dopaminergic dysfunction and lesions to the mesocorticolimbic pathway. The most obvious example of this is patients with PD and Huntington's disease (Craufurd et al., 2001; Pederson et al., 2009), both of which are paradigmatic models of dopaminergic dysfunction. Although PD is characterized as a motor deficit stemming from nigrostriatal dysfunction, it is also associated with significant motivational deficits. For example, in patients with PD, striatal activity after monetary reward is reduced

relative to healthy controls (Künig et al., 2000). Moreover, individuals with PD are willing to invest less effort than controls for low amounts of reward (Chong et al., 2015).

Apathy in PD has been linked to underactivity in the ventral striatum and disruption of basal ganglia circuitry due to midbrain neurodegeneration (Remy et al., 2005). In a study directly comparing PD patients scoring high on apathy vs those scoring low, apathy was associated with decreased responsiveness to monetary gains in an extensive circuit involving the vmPFC, amygdala, striatum, and midbrain (Lawrence et al., 2011). This was thought to be caused by a reduction of dopaminergic afferents to the ventral striatum disrupting normal interactions among the frontal lobe, caudate, anterior cingulate circuits, and basal ganglia (Martínez-Horta et al., 2014). Dysfunction of this mesocorticolimbic dopaminergic pathway is therefore considered to be key to the pathophysiological basis of apathy in PD.

Other striatal lesions outside of PD have also been found to cause a profound apathetic state. For example, apathy occurs following strokes to the basal ganglia (Adam et al., 2012; Schmidt et al., 2008), while apathy, abulia, and akinetic mutism have all been reported following lesions to the globus pallidus, thalamus, and ACC (Oberndorfer et al., 2002; Tengvar et al., 2004).

Intriguingly, apathy in other patient populations also points to dopaminergic dysfunction. For example, although AD is not typically considered a disorder of dopamine, imaging studies have shown significantly decreased D2 receptor density and decreased dopamine reuptake. These findings are most pronounced in structures associated with the nigrostriatal and mesocorticolimbic tracts of AD patients, most notably the striatum (Mitchell et al., 2011). In addition, single-photon emission computed tomography (SPECT) studies in AD have found that apathy correlates with decreased activity in the ACC, and this relationship is independent of cognitive impairment (Craig et al., 1996; Migneco et al., 2001; Robert et al., 2006).

To summarize, data on human apathy are consistent with animal findings implicating central dopaminergic systems in the development of motivational deficits. Disrupting dopaminergic transmission within the mesocorticolimbic circuit is important in modulating reward- and effort-based decisions, which are important components in the pathogenesis of the amotivated, apathetic state (Bardgett et al., 2009; Chelonis et al., 2011; Krack et al., 2003; Ostlund et al., 2011; Salamone et al., 2007; Treadway et al., 2012).

3 DOPAMINE IN TREATING APATHETIC BEHAVIOR IN ANIMALS

The majority of studies implicating dopamine in animal models of motivation are based on dopamine antagonism, either through systemic administration of a dopamine antagonist or selective targeting of striatal or prefrontal structures. Surprisingly, however, relatively less work has been conducted on the effect of dopaminergic augmentation on motivation (Bardgett et al., 2009; Floresco et al.,

2008). Nevertheless, existing data suggest that stimulating the dopaminergic system, either nonselectively or with D1–D3 receptor agonists, can reverse experimentally induced deficits in reward and effort sensitivity.

3.1 NONSPECIFIC EFFECTS OF DOPAMINE

In rodent models of effort-based decision making, dopamine transmission is usually augmented by parenteral administration of *D-amphetamine*, an indirect dopamine agonist that increases synaptic dopaminergic levels. Using a T-maze procedure, animals in one study were required to choose between one arm offering a high reward for high amounts of effort, and another arm offering a low reward for less effort (Bardgett et al., 2009). Rodents that were rendered less motivated by the administration of D1 or D2 receptor antagonists shifted their preferences toward the low-effort/low-reward arm, but, importantly, *D-amphetamine* had the effect of restoring preferences for the higher effort offer (Bardgett et al., 2009). One limitation with *D-amphetamine*, however, is that it increases locomotor activity, and it is possible that restored preferences for the high effort arm could have been due to greater physical capacity (Salomon et al., 2006).

Apart from *D-amphetamine*, *bupropion* has been studied for its effects on inhibiting catecholamine and dopamine reuptake (Dwoskin et al., 2006). *Bupropion* is a drug commonly used in humans as an antidepressant. In rodents, the effect of *bupropion* has been tested with T-maze procedures and operant (fixed or progressive ratio) tasks. The administration of *bupropion* has been consistently found to increase preference for the high-effort/high-reward options, both in otherwise healthy rodents (Randall et al., 2015) and in those that develop effort-related impairments induced by tetrabenazine—a vesicular monoamine transporter (VMAT)-2 inhibitor that acts as a dopamine-depleting agent (Nunes et al., 2013; Randall et al., 2014; Yohn et al., 2015). However, *D-amphetamine* and *bupropion* are both relatively nonselective, and they increase levels of neurotransmitters other than dopamine (eg, serotonin and noradrenaline in the case of *D-amphetamine*).

3.2 RECEPTOR-SPECIFIC EFFECTS

Rather than nonspecifically raise plasma dopamine levels, and to control for the effects on other neurotransmitter systems, a more refined approach has been to target dopamine receptors with agonists that are selective to one or more dopamine receptor subtypes. Currently, there are five known dopamine receptors (D1–D5), which are classified as “D1-like” (D1, D5), or “D2-like” (D2–D4) according to their cellular transduction properties (Civelli, 1995). The distributions of these receptors differ considerably and are thought to reflect their differential roles in motor, cognitive, and limbic functions (Beaulieu and Gainetdinov, 2011; Bentivoglio and Morelli, 2005; Guillin et al., 2001; Weiner et al., 1991). D1 and D2 receptors are densely distributed within the frontotemporal cortices, limbic system, and striatum. The D3 receptor appears strategically distributed within the mesolimbic system, specifically

the ventral striatum (in particular, the shell of the NAcc), midbrain, and pallidum. In contrast, the density of D4 and D5 receptors is much more limited, and their functions in the context of motivational processes remain less well defined (Beaulieu and Gainetdinov, 2011; Meador-Woodruff, 1994).

Given their distribution, D1–D3 receptors are thought to play important roles in regulating affective, reward-related, and motivational processes (Basso et al., 2005; de la Mora et al., 2010; Katz et al., 2006; Newman et al., 2012; Paolo and Galistu, 2012; Short et al., 2006; Sokoloff et al., 2006). For example, using an effort-based decision-making task, a recent study compared the efficacy of selective *D1 agonists* (SKF38393, SKF81297, and A77636) on reversing the effects of ecopipam, a selective D1/D5 receptor antagonist (Yohn et al., 2015a). Each of the D1 agonists administered significantly attenuated the effects of ecopipam, resulting in a shift in animals' preference toward exerting higher effort for higher reward vs exerting less effort for low reward.

Another approach to examine receptor specificity has been to overexpress dopamine D2 receptors, which has led to animals shifting their preference toward higher effort options in effort-based tasks (Trifilieff et al., 2013). In addition, *adenosine A2A antagonists* have been used to investigate motivation in animals based on their functional interaction with dopamine D2 receptors. Adenosine A2A receptors are primarily located in striatal areas, including the neostriatum and NAcc, and specifically reverse the effects of D2 antagonism. Although this interaction has traditionally been used to investigate motor functions related to parkinsonism, it has recently been discovered that adenosine A2A antagonists also affect motivated behavior. Specifically, they reverse the preference shift caused by D2 antagonism in rodents tested on both operant and T-maze choice procedures (Farrar et al., 2010; Mott et al., 2009; Nunes et al., 2010; Pardo et al., 2012; Salamone et al., 2009; Worden et al., 2009). These results implicate D2 receptors in the regulation of motivated behavior.

Following the discovery of D3 receptors, their relatively restricted distribution drew attention to their potential role in reward, particularly in the context of drug addiction (Newman et al., 2012). Indeed, the D3 receptor has been extensively investigated as a potential target to treat substance use disorders (the “D3 Receptor Hypothesis”). In addition to their important role in reward, more recent reports have uncovered their important contribution to effort-based decision making. For example, one study used a progressive ratio schedule to test the relative contributions of D1–D3 receptor stimulation, following dopaminergic cell loss in the substantia nigra pars compacta (SNc; Carnicella et al., 2014). The authors found that only the D3 agonist (PD-128907), but neither the D1 (SKF-38393) nor D2 (sumanirole) agonists, reversed the motivational deficits induced by the SNc dopaminergic lesions. Such effects are not universal (eg, Bardgett et al., 2009). Overall, however, D3 receptors seem to play an important role in the control of motivated behavior, and mediating the beneficial effects of dopamine agonists on the behavioral alterations induced by dopaminergic cell loss. This has led some to propose the D3 receptor as a specific therapeutic target for neuropsychiatric symptoms in several disorders (Sokoloff et al., 2006), including PD (Joyce, 2001; Leentjens et al., 2009).

Taken together, this body of data suggests that dopamine is capable of augmenting motivated behavior in animals, although the distinct role of specific receptor subtypes to this process remains to be further elaborated. Given the causal role that dopaminergic depletion appears to play in altering the animal's sensitivity to reward and effort, it seems intuitive that dopamine supplementation could be used to improve motivational impairments in humans. Next, we review the attempts that have been undertaken in humans to improve apathy by administering exogenous dopamine.

4 DOPAMINE IN THE TREATMENT OF HUMAN APATHY

The treatment of apathy currently lacks consensus, and the choice of pharmacotherapy is based principally on the primary disease. In this context, it is unsurprising that most studies examining the efficacy of dopamine for treatment of apathy come from patients with PD (Table 3; Leentjens et al., 2009). In contrast, dopaminergic drugs have rarely been trialed in conditions such as AD, in which anticholinesterase

Table 3 Dopamine Agonists Commonly Used for the Treatment of Parkinson's Disease

Generic Name	Trade Names	Dopamine Receptor Specificity ^a	Other Receptors
Ergoline derivatives			
Bromocriptine	Parlodel™, Cycloset™	D2 > D3 (>D4 > D5 > D1)	5HT, α_1 , α_2 , β_1 , β_2
Cabergoline	Caberlin™, Cabaser™	D2 > D3 (>D5 > D4 > D1)	5HT, α_1 , α_2
Pergolide	Permax™, Prascend™	D2 > D1	5HT
Nonergoline derivatives			
Pramipexole	Sifrol™, Mirapex™, Mirapexin™	D3 > D2 > D4	5-HT, α_2
Piribedil	Pronoran™, Trivastal™, Trastal™, Trivastan™, Clarium™	D2, D3	α_2
Ropinirole	Requip™, Reprevé™, Ronirol™, Adartrel™	D2, D3, D4	Weak: 5-HT ₂ , α_2
Rotigotine	Neupro™	D3 > D4 > D5 > D2 > D1	5-HT, α_1 , α_2 , β_1 , β_2 , H ₁
Other (antiviral)			
Amantadine	Symmetrel™	Poorly understood. Increases DA release; blocks DA reuptake	NMDA antagonist

^aBold indicates greatest affinity.

inhibitors are the mainstay of treatment (Berman et al., 2012). Similarly, in schizophrenia, antipsychotics are the primary class of drug used to treat apathy, even though the benefits of dopamine agonists on the negative symptoms of schizophrenia have long been recognized (Benkert et al., 1995; Bodkin et al., 2005; Jaskiw and Popli, 2004; Lindenmayer et al., 2013).

Although there are reports of dopamine being used for the treatment of apathy in disorders other than PD (such as stroke, traumatic brain injury, and depression), a significant gap in this literature is the lack of strong evidence in favor of this application (ie, Class I or II Evidence). The majority of reports involve small cohorts of individuals, are open label, and/or have not used apathy as a primary outcome measure. A likely reason for this is the underrecognition of apathy as a problem, and the difficulty in recruiting apathetic individuals for such studies. In addition, the vast majority of studies that attempt to monitor responses to treatment use one or more questionnaire-based tools, which lack the sensitivity to measure more objective metrics of motivation, such as break points or indifference points (Chong et al., 2016). As such, the effect of dopamine on specific components of apathy, such as reward or effort sensitivity, has remained poorly explored.

4.1 NONSELECTIVE DOPAMINE AUGMENTATION IN APATHY

The most direct, and least specific, method of augmenting the concentration of dopamine in humans is to administer *levodopa*—the precursor molecule of dopamine, and the mainstay of treatment for the motor symptoms of PD. One of the earliest studies to show an improvement in apathy on levodopa was conducted in 23 nondemented, nondepressed patients with PD (Czernecki et al., 2002). The main conclusion of this study was that patients were less apathetic when ON medication relative to OFF (mean daily dose 1115 mg), as measured using the Starkstein Apathy Scale.

Alternatively, presynaptic concentrations of dopamine can be increased by inhibiting its metabolism. *Monoamine oxidase-B (MAO-B) inhibitors*, such as selegiline and rasagiline, selectively target the predominant isoform of the MAO enzyme involved in the metabolic breakdown of dopamine in the brain (Fernandez and Chen, 2007). Although most often used in the treatment of PD, they have more recently been used in depression as well. A recent retrospective review of 181 patients with PD found that patients on selegiline or rasagiline were less likely to report apathy than those taking other antiparkinsonian agents (Zahodne et al., 2014). This complements other, much smaller, case series ($n < 5$), suggesting the utility of selegiline in stroke and traumatic brain injury, which came to similar conclusions (Marin et al., 1995; Newburn and Newburn, 2005).

Amantadine has been used to stimulate the release of dopamine and delay dopamine reuptake. However, its precise mechanism of action is not entirely clear, as it also has effects on glutamate, and is a potent NMDA receptor antagonist (Aoki and Sitar, 1988). Most reports of a beneficial effect of amantadine on apathy have involved small cohorts ($n < 6$) and mostly on patients with traumatic brain injury (Kraus and Maki, 1997; van Reekum et al., 1995).

The primary clinical application of levodopa, MAO-B inhibitors, and amantadine is in the treatment of the motor symptoms of PD, but their potent dopaminergic effects render them useful in off-label trials in managing apathetic symptoms. In addition to these drugs, other classes of medication have been trialed which also have potent dopaminergic effects, even though they are not principally utilized for these properties. For example, *methylphenidate* is a stimulant chemically related to amphetamine, which stimulates dopamine release (Seeman and Madras, 2002), and some studies have reported improvement of apathetic symptoms on this drug in AD (Herrmann et al., 2008; Padala et al., 2010). Similarly, *bupropion* (Wellbutrin™) is a catecholamine reuptake inhibitor most commonly prescribed as an antidepressant (Dwoskin et al., 2006). In animals, it significantly shifts preferences toward more effortful, more rewarding offers (see Section 3.1; Randall et al., 2015), and there is a suggestion in humans that it improved apathy in a small case series of patients with depression or organic brain disease, although it was unclear whether this was due to changes in depressive scores (Corcoran et al., 2004).

4.2 RECEPTOR-SPECIFIC DOPAMINE AGONISTS

The beneficial effects of levodopa on apathy may not be exclusively caused by the restoration of function to dopaminergic projections, as levodopa uptake and decarboxylation also occur, for example, in serotonergic neurons (Ng et al., 1971). Therefore, investigators have turned to more selective dopaminergic agonists to isolate the effect on postsynaptic dopamine receptors (Reichmann et al., 2006). One study examined the effect of a single dose of a highly selective D1 agonist (*dihydropyridine*, DAR-0100) on the negative symptoms of schizophrenia (George et al., 2007). This investigation failed to find any significant effects, but given the single dose and the absence of apathy as a primary end point, the utility of sustained D1 agonism specifically on apathy remains unknown. A more commonly encountered drug is *bromocriptine*, an ergot derivative dopamine agonist, and one of the earliest dopamine agonists to be used in the treatment of PD. It acts primarily on the D2 receptor, but is active at all receptor subtypes. Early studies on the use of bromocriptine in apathy were equivocal, and often involved patients concurrently taking other drugs, such as methylphenidate (Marin et al., 1995) or levodopa/benserazide (Debette et al., 2002).

More recently, nonergoline dopaminergic agonists have been developed which are in more common use as treatments for PD. Following the discovery of D3, and later D4 and D5 receptors, attention was drawn to the relatively restricted location of D3 receptors, seemingly related to dopaminergic functions associated with the mesolimbic system (see Section 3.2). Most modern nonergot dopamine agonists predominantly target the D2 and/or D3 receptors (Table 3). For example, *pramipexole* binds preferentially, and with high affinity, to the D3 receptor (Guttman and Jaskolka, 2001), although it also has agonist activity at pre- and postsynaptic receptors belonging to other receptors in the D2-like family (Piercey et al., 1996). *Piribedil* and *ropinirole* are both relatively selective D2/D3 agonists, which do not interfere with the serotonergic system. All of these agents have been reported to have some

success in ameliorating apathy in PD (Czernecki et al., 2008; Oguro et al., 2014; Rektorova et al., 2008; Thobois et al., 2013) as well as in stroke (Kohn et al., 2010). In some of these studies, improvements in apathy might be difficult to disambiguate from accompanying improvement in mood, although they appear not to be correlated (Czernecki et al., 2008).

An informative study was recently conducted with the aim of performing a head-to-head comparison of the neuropsychiatric effects of levodopa, pramipexole, and ropinirole in PD (Pérez-Pérez et al., 2015). This was a large study of 515 nondemented patients, with apathy being one of several outcome measures assessed with the Neuropsychiatric Inventory. The overall conclusion was that both the frequency and severity of apathetic symptoms was less with pramipexole than either ropinirole or levodopa. This may be parsimonious evidence for the efficacy of D3 receptor agonists in the treatment of apathy.

4.3 DISSECTING THE EFFECT OF DOPAMINE ON OBJECTIVE METRICS OF MOTIVATION

In considering the preceding attempts at treating human apathy, an obvious feature of these studies is their heterogeneity, with several classes of dopaminergic drugs having been utilized across a range of disorders with varying efficacy. One of the limitations in understanding the role of dopamine in treating apathy is that apathy appears not to be a singular construct, but comprised of different elements, such as reward and effort sensitivity. However, current questionnaire-based methods are inherently limited in their ability to dissect the mechanisms of disordered motivation, and insufficiently sensitive to quantify or monitor any changes to effort- or reward-based decision making following treatment (Chong et al., 2016). Here, we review recent attempts at quantifying the effects of dopaminergic medication on different components of apathetic behavior.

4.3.1 *Effects of dopamine on reward sensitivity in apathy*

Based on animal data, one component of motivation appears to be impaired reward sensitivity. Consistent with this suggestion was a recent case study we recently reported on a patient (KD) who developed profound apathy following a rare, bilateral stroke affecting the globus pallidus, predominantly its internal components (GPi; Fig. 2A; Adam et al., 2012). Probabilistic diffusion tractography demonstrated that the region of the GPi that was particularly affected was strongly connected to the lateral orbitofrontal cortex and ventromedial prefrontal cortex—two areas which are significantly involved in reward sensitivity. Premorbidly, he was described as exuberant and outgoing, but, after his stroke, he became reticent and reserved. He became disinterested in others, had reduced spontaneity of thought and action, and lost his job. His scores on the Apathy Inventory were in the pathological range on the initiative and interest subscales (8/12, normal ≤ 4) (Robert et al., 2002). Importantly, however, he was not depressed, as reflected in his scores on several depression inventories, which were within the normal range (the Montgomery–Asberg

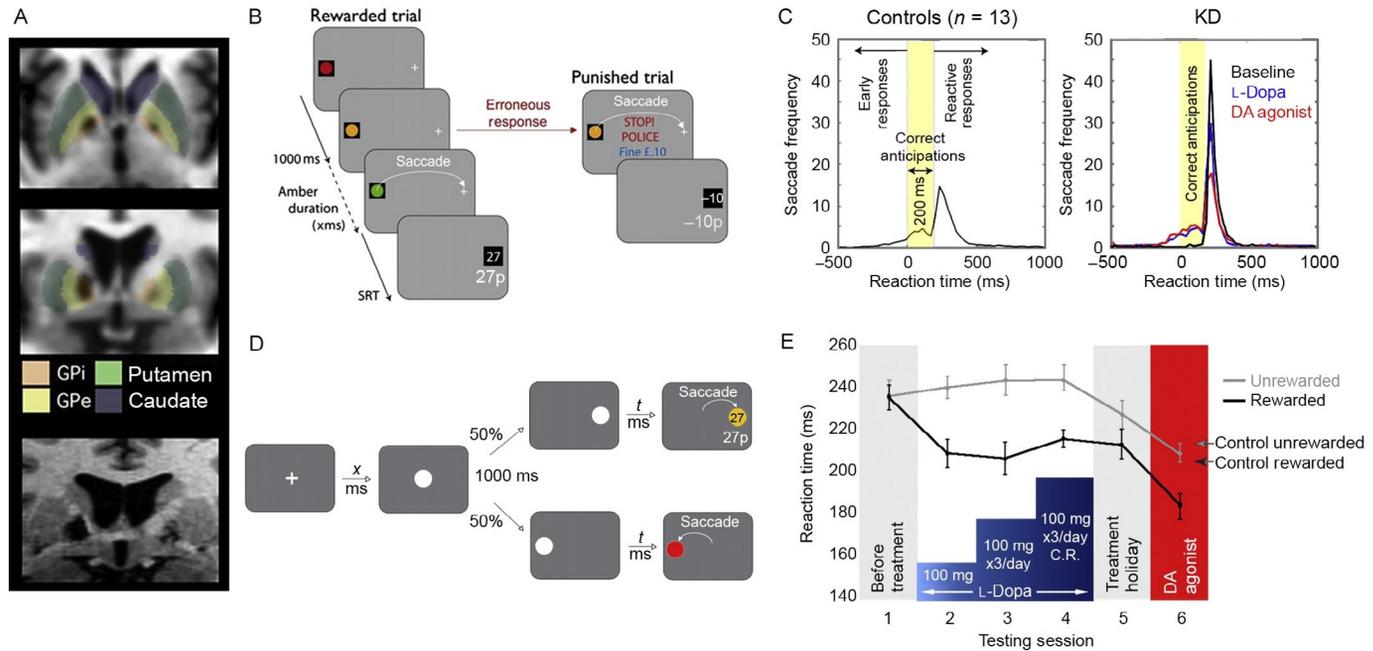


FIG. 2

See legend on opposite page.

FIG. 2

We examined the effects of dopamine on a patient (KD) with apathy caused by selective, bilateral lesions to the globus pallidus (Adam et al., 2012). (A) Sections demonstrating the extent of basal ganglia lesions. KD's GPi lesion was larger on the *left* than on the *right*. The lesions are projected onto boundaries of the GPi (*orange*), GPe (*yellow*), putamen (*green*), and caudate (*purple*). The *bottom left* coronal section is a close up at the level of the anterior commissure. (B) KD participated in two tasks examining reward sensitivity. In the traffic lights task (TLT), participants fixated a *circle* which successively turned *red*, *amber*, and *green*. They were required not to move their eyes until the onset of the green light; otherwise they receive a small, fixed penalty. To maximize reward, participants had to make a saccade to the contralateral target as quickly as possible after green light onset. Amber durations (x) were selected at random from a normal distribution. Reward was calculated with a hyperbolically decaying function with a maximum value of 150 pence (£1.50) at $t=0$. Thus to maximize reward subjects should program an eye movement to coincide with green light onset. However, amber durations were not constant and therefore they either had to take a risk (high reward or punishment) or wait for the green light before programming a saccade (low reward). (C) Traffic lights task (TLT): saccadic distributions. (A) Saccades for age-matched controls ($n=13$) performing the TLT showed two distinct distributions: an early, anticipatory distribution, and a later, reactive one made in response to green light onset. Early responses were divided into errors (saccades before the green light came on) and correct anticipations (saccades with <200 ms latency after the green light). Pretreatment, KD made mostly reactive saccades, and very few anticipatory saccades (*black*). After treatment with L-DOPA 100 mg (Madopar CR 125 mg) three times a day for 12 weeks, there was a dramatic increase in early responding in KD (*blue*). After 12 weeks treatment with a dopamine agonist (ropinirole XL, 4 mg once a day), KD's distribution of saccades looks most similar to that of control subjects (*red*). (D) In the directional saccadic reward task, participants attended a central fixation spot which was extinguished after 1000 ms. They then made a speeded saccade to a target to the *left* or *right* of fixation (equiprobable). One side was rewarded while the other received no reward. The rewarded side (RS) remained constant for an unpredictable number of trials before switching to the other side. (E) Results from the directional saccadic reward task. The control group ($n=12$, *arrows to side*) showed a preference for the rewarded target locations, with significantly shorter SRTs. KD showed no reward preference before treatment (Session 1). In Session 2, he was given a single dose (100 mg) of levodopa which led to a significant reward preference. This was maintained throughout chronic dopaminergic therapy (Sessions 3 Madopar 125 mg three times daily for 4 weeks, Session 4 Madopar Controlled Release 125 mg three times daily for 12 weeks). Following a treatment holiday (4 weeks), this reward preference was absent (Session 5). However, with subsequent treatment on the dopamine agonist ropinirole (1 mg three times a day), there was both a reestablishment of reward preference and significant decrease in latency to both rewarded and unrewarded targets. Error bars are ± 1 SEM (standard error of the mean).

Adapted from Adam, R., Leff, A., Sinha, N., Turner, C., Bays, P., Draganski, B., Husain, M., 2012. Dopamine reverses reward insensitivity in apathy following globus pallidus lesions. *Cortex* 49, 1292–1303.

Depression Rating Scale (Montgomery and Asberg, 1979), the Beck Depression Inventory (Beck et al., 1988), and the Hamilton rating scale for depression (Hamilton, 1960)).

KD's apathy was reflected in his performance on two oculomotor measures of motivation, which were specifically designed to probe reward sensitivity. In one task, the "Traffic Lights Task," KD fixated on a disc at the left or right of the screen, which successively turned red, amber, and green (Fig. 2B). The instant the disc turned green, he was required to make a speeded saccade to a target location on the opposite side of the screen. The faster the saccadic initiation time, the more he was rewarded up to a maximum of £1.50, according to an exponential falloff. Any preemptive saccades initiated prior to the onset of the green disc were penalized by a fixed, small amount (10p). In healthy participants, the distribution of reaction times is bimodal—although most responses are "reactive" and follow the onset of the green disc, a second peak of responses were due to anticipatory responses to the green disc. Up to 45% of responses in healthy controls were such "anticipatory" responses. In contrast, KD showed a unimodal response, with few attempts at initiating early saccades to maximize reward (<10%) (Fig. 2C).

The second task that KD performed was a directional reward-sensitive saccade task (Fig. 2D). This task required him to fixate a central cross and perform speeded saccades to targets to the left or right of fixation. The target locations were equiprobable, but only targets on one side were rewarded as a function of reaction time (with the equivalent exponentially decaying function as in the traffic lights task). The rewarded side was altered, without warning, every 10–14 trials. Reward sensitivity was measured as the difference in saccade reaction times to the rewarded and unrewarded sides. Controls showed a small, but significant, saccade reaction time advantage to the rewarded side. In contrast, however, KD showed no directional difference.

The decision was made to trial KD on dopamine supplementation with levodopa/benserazide (100/25 mg, Madopar™). He undertook both oculomotor tasks immediately prior to commencing his first dose and then 1 h after the administration of his first dose. Strikingly, after only one dose, he showed a significant improvement in his performance on both tasks. On the traffic lights task, he showed a restoration of the normal bimodal distribution seen in healthy controls (Fig. 2C). Similarly, on the directional reward-sensitivity task, KD showed a markedly significant preference for the rewarded side compared to the unrewarded side (211 vs 238 ms; Fig. 2E). Not only were these changes manifest only 1 h following his first dose, but his improvements in both tasks were sustained and continued over the following months while on medication—the proportion of early "anticipatory" responses in the traffic lights task reached a peak at 24 weeks (33.4%), and the advantage of the rewarded side increased in the directional task over the following 12 weeks.

The causal role of levodopa in ameliorating KD's reward sensitivity was demonstrated following a clinical decision to stop the levodopa, and switch him to the dopamine agonist, ropinirole. During the intervening "drug holiday" while KD was off medication, his performance on both oculomotor tasks returned back to pretreatment levels. The percentage of his anticipatory responses on the traffic lights task again

declined back to baseline levels (<10%), and his preference for the rewarded side diminished back to pretreatment levels on the directional reward-sensitive task. However, after he was commenced on ropinirole (4 mg), his performance again improved on both tasks (Fig. 2C and E), to levels that appeared even greater relative to his performance on levodopa.

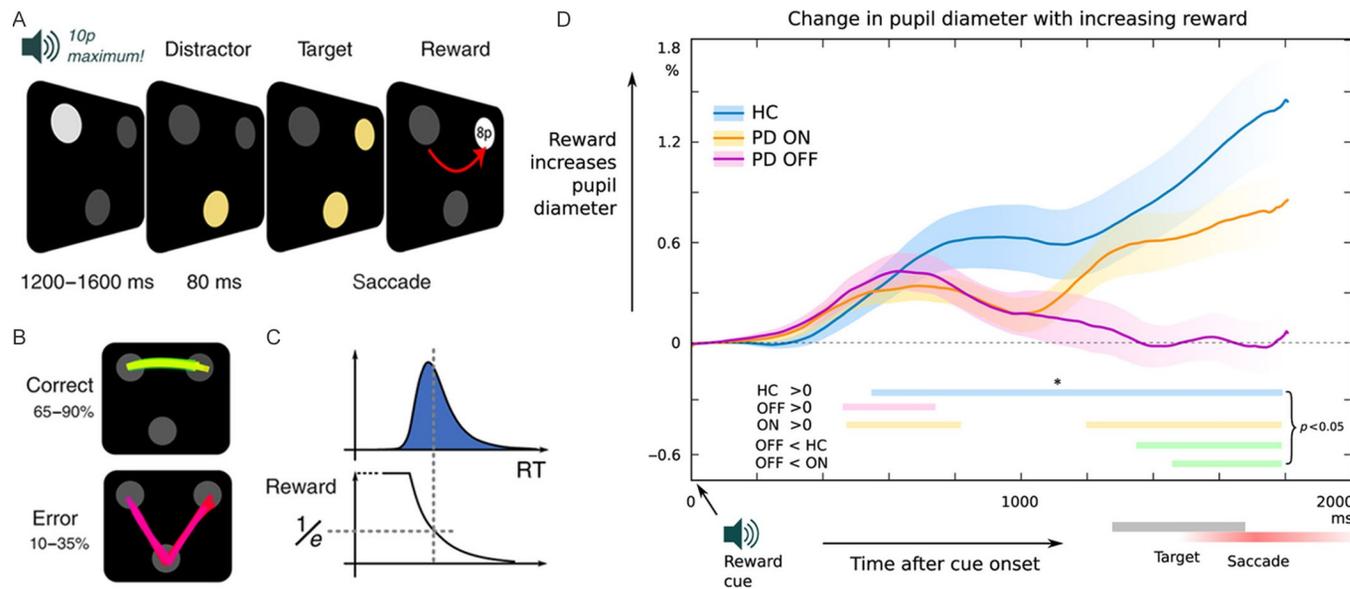
Importantly, the administration of levodopa/benserazide and ropinirole resulted not only in improved performance on the metrics of reward sensitivity but also in functional outcome. KD's clinical apathy improved when indexed against conventional apathy scales (the Apathy Inventory). He was also able to engage in more spontaneous conversation, had improved social interactions, was more interested in day-to-day events, and even managed to secure a job.

This case study demonstrates several points. First, it illustrates the utility of paradigms that can dissect a specific component of apathy—in this case, reward sensitivity—which can then be used as a proxy to measure motivation. Second, it is proof in principle for a strong causal relationship for dopamine in reversing reward insensitivity in a human model of apathy. Third, the restoration of KD's reward sensitivity correlated with clinical and functional improvements, as measured on traditional questionnaire-based measures, suggesting that reward sensitivity is an important component of apathy. Finally, it implies that selective dopamine agonist therapy (in this case with ropinirole) may be advantageous over less-selective dopamine supplementation (with levodopa), which suggests that future research should seek to clarify the differential role of dopamine receptors in the treatment of apathy.

4.3.2 Effects of dopamine on subclinical reward insensitivity

Although apathy represents the clinical manifestation of impaired motivational processes, it is unlikely to be an all-or-nothing phenomenon. Rather, early dysfunction in reward mechanisms may give rise to subtle impairments in motivation, which do not become clinically evident until they disrupt day-to-day function. Thus, another approach to determining the potential role of dopamine in treating apathy is to examine how it modulates subclinical changes in motivation. Indeed, given the evidence showing that lesions to dopaminergic pathways reduce reward sensitivity, one prediction is that all patients with PD should demonstrate varying levels of motivational deficits. However, subtle levels of motivational impairments might be ineffectively captured based on current self-report-based tools.

We have recently developed another oculomotor task that aims to probe subclinical changes in reward sensitivity in patients with PD and to examine the potential role of dopamine in ameliorating such deficits (Fig. 3; Manohar and Husain, 2015; Manohar et al., 2015). In this distractor-avoidance task, participants made a speeded saccade to a target location, while ignoring the presence of a distractor immediately preceding that target (Fig. 3A–C). Crucially, participants were provided with a monetary incentive for their performance. Prior to commencing each trial, an auditory precue was delivered to indicate the maximum reward that was available for an accurate saccade to that location (0, 10, 50p). As a measure of reward sensitivity, we measured autonomic arousal in the form of pupillary dilatation, which has the

**FIG. 3**

Using a novel oculomotor reward sensitivity task, we measured autonomic responses to reward cues (Manohar and Husain, 2015).

(A) Participants fixated an illuminated disc, and received an auditory cue indicating how much reward could be won by making a speeded eye movement (0, 10, 50p). After a variable delay, a saccade had to be made to the second of two other discs that illuminated, one slightly later than the other. (B) Correct saccades were those that went directly to the target, whereas on error trials an initial saccade was made to the distractor. Percentages indicate the range of proportion of correct and error trials over all participants. (C) Reward was numerically displayed at the target, based on speed, and scaled up by the amount on offer on that trial. The value fell off exponentially with increasing response time (measured from distractor onset until gaze arrived at the target), with adaptive time constants that maintained a constant average rate of reward. (D) The effects of reward on pupil size, given by linear regression at each time point. For each participant, the pupil traces were correlated with the incentive on the current trial. The correlation coefficient was plotted as a function of time. Positive values indicate that with higher incentives, the pupil was larger; conversely negative values indicate that reward made the pupil smaller. Comparisons of these coefficients with zero, and with each other, are shown. Reward increased pupil size in all three groups, but controls were significantly more reward sensitive than PD patients when OFF medication (unpaired comparison). Also, PD patients were more reward sensitive when ON compared with when OFF (paired comparison). All statistics are calculated for $p < 0.05$ controlling for familywise error using permutation.

Adapted from Manohar, S.G., Husain, M., 2015. Reduced pupillary reward sensitivity in Parkinson's disease. *NPJ Parkinson's Dis.* 1, 15026.

advantage of being able to disambiguate the effect of dopamine on reward independent from its effects on motor function (Manohar and Husain, 2015).

We tested a group of nondemented, nonapathetic patients with PD over two counterbalanced sessions—ON and OFF their usual dopaminergic medication—and compared their performance to healthy, age-matched controls (Manohar and Husain, 2015). Patients were on either levodopa or a dopamine agonist. As predicted, controls demonstrated greater autonomic arousal in the form of pupillary dilatation to high vs low rewards. In contrast, PD patients OFF medication showed little differential response in their pupillary diameters to increasing reward. Crucially, however, these reward-sensitive pupillary responses were restored toward healthy levels when the identical patients were tested ON their usual medication (Fig. 3D). Together, these findings highlight that the autonomic responses to reward incentives in PD may be blunted, even in nonclinically apathetic patients, and that dopamine is effective in at least partially restoring these deficits.

4.3.3 Effects of dopamine on subclinical effort hypersensitivity

Based on the seminal work in animal studies of motivation, it is clear that motivation can be framed not only as reduced reward sensitivity but also as heightened sensitivity to effort (Chong et al., 2016). In a direct extension of this animal research, several human studies have now demonstrated that dopamine therapy increases the willingness of patients to exert effort for reward (Chong et al., 2015; Porat et al., 2014; Wardle et al., 2011). For example, we recently devised a novel paradigm to investigate the willingness of patients with PD to exert effort for reward, with effort being operationalized as the amount of force delivered to handheld dynamometers (Fig. 4; Chong et al., 2015). Notably none of these patients were clinically apathetic or depressed, as measured using standard clinical questionnaires (the Lille Apathy Rating Scale (Sockeel et al., 2006) and the Depression, Anxiety, and Stress Scales (Lovibond and Lovibond, 1995)).

The task was framed in the form of a game, the goal of which was to gather as many apples as possible from trees in an orchard (Fig. 4A and B). During the experiment, participants were presented with cartoons of apple trees and were instructed to accumulate as many apples as possible based on the combinations of stake and effort that were presented. Potential rewards were indicated by the number of apples on the tree (1, 3, 6, 9, 12, 15). Effort levels were individualized to each participant as a function of their maximum voluntary contraction (MVC) determined at the beginning of each experimental session. Effort requirements varied over six levels, from 60% to 110% MVC, in 10% increments. By referencing the effort levels in each session to each individual's maximum force, we were able to normalize the difficulty of each level across sessions and across individuals.

On each trial, participants had to decide whether they were willing to exert the specified level of effort for the specified stake. If they judged the particular combination of stake and effort to be “not worth it,” they selected the “No” response, and the next trial would commence. If, however, they decided to engage in that trial, they selected the “Yes” option, and began delivering the required amount of force for the

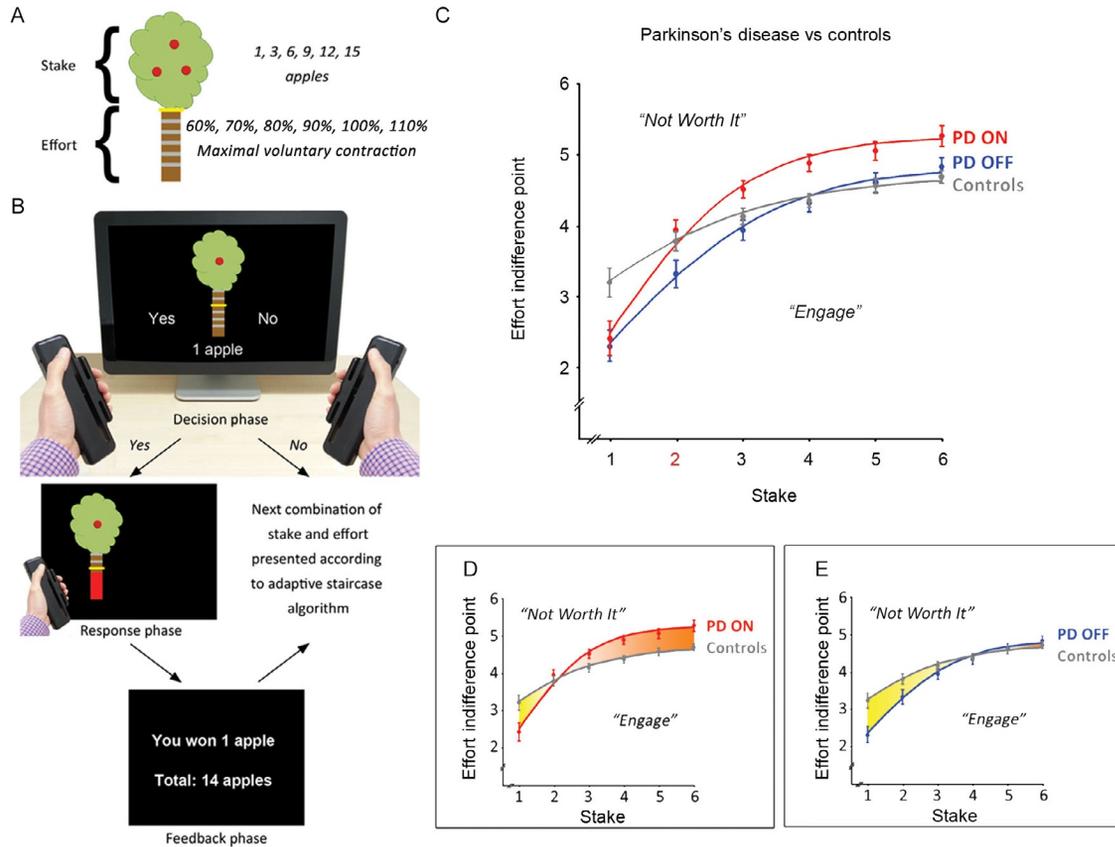


FIG. 4

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apples on offer. By parametrically varying the combinations of effort and reward, and subsequently applying logistic regression techniques, we were able to determine, for each level of reward, the point at which participants accepted and rejected the offer on 50% of occasions—their effort “indifference points” (Bonnelle et al., 2015; Chong et al., 2015). These effort indifference points could then be used as a metric against which to benchmark each patient’s motivation.

To determine the effect of dopaminergic medication on the willingness to exert effort for reward, we tested these patients ON and OFF their usual dopaminergic medication (which may have been either levodopa or a dopamine agonist). We found that, regardless of their medication status, patients with PD were willing to exert less effort when the stakes were low (Fig. 4C–E). This implied a degree of subclinical apathy, but only for the lowest rewards, that was not evident on standard clinical questionnaires. Furthermore, as predicted, patients OFF medication were willing to invest less effort for reward, but crucially this was ameliorated by dopamine, which had the effect of increasing the amount of effort that patients were willing to invest. Interestingly, relative to healthy controls, there was a reward-dependent effect, such that, at higher rewards, patients with PD ON dopaminergic medication

FIG. 4

The Apple Gathering Task (Chong et al., 2015). (A) In a typical trial, stakes were indicated by the number of apples on the tree, while the associated effort was indicated by the height of a *yellow bar* positioned at one of six levels on the tree trunk (as proportions of participants’ MVCs). (B) On each trial, participants decided whether they were willing to exert the specified level of effort for the specified stake. If they judged the particular combination of stake and effort to be “not worth it,” they selected the “No” response. If, however, they decided to engage in that trial, they selected the “Yes” response, and then had to squeeze a handheld dynamometer with a force sufficient to reach the target effort level. Participants received visual feedback of their performance, as indicated by the height of a *red force feedback bar*. To reduce the effect of fatigue, participants were only required to squeeze the dynamometers on 50% of accepted trials. At the conclusion of each trial, participants were provided with feedback on the number of apples gathered. (C) For each participant, we calculated their effort indifference points—the effort level at which the probability of engaging in a trial for a given stake was 50%. Regardless of medication status, patients had significantly lower effort indifference points than controls for the lowest reward. However, for high rewards, effort indifference points were significantly higher for patients when they were ON medication, relative not only to when they were OFF medication, but even compared to healthy controls. Inset: For clarity, PD data are replotted against control performance for patients (D) ON medication and (E) OFF medication. *Shading* denotes effort indifference points being greater for patients than controls (*orange*), or less for patients than controls (*yellow*). Error bars indicate ± 1 SEM.

Adapted from Chong, T.T.-J., Bonnelle, V., Manohar, S., Veromann, K.-R., Muhammed, K., Tofaris, G., Hu, M., Husain, M., 2015. Dopamine enhances willingness to exert effort for reward in Parkinson's disease. Cortex 69, 40–46.

were willing to invest even more effort than their age-matched counterparts. This echoes previous findings in animal studies showing that dopamine augmentation restored motivated behavior.

Other studies using different paradigms have documented similar effects in PD. For example, Porat and colleagues tested nonpathetic patients with PD on a Gain/Loss Effort Task, which is based on the progressive ratio tasks in animals (Chong et al., 2016; Porat et al., 2014). In this task, the authors separately measured the maximum amount of effort that participants are willing to expend to *either* increase monetary gain or avoid/minimize monetary loss. Effort in this paradigm was operationalized as the number of button presses on a keyboard, with the number of presses required to increase gain or avoid loss progressively increased in an exponential progressive ratio schedule.

Interestingly, the authors found a differential effect of dopamine as a function of patients' more affected side. Dopamine did indeed have the effect of increasing patients' willingness to exert effort. However, patients with a more affected right side were more willing to exert effort to maximize gain, whereas those with a more affected left side were more willing to exert effort to avoid loss. This asymmetry might reflect differential hemispheric involvement in PD—previous tracer studies have shown reduced uptake in the nigrostriatal system contralateral to the more affected side (Brooks, 2003; Djaldetti et al., 2006), which is most pronounced in the putamen, but also present in the caudate, ventral striatum, and frontal regions (Jokinen et al., 2009; Marie et al., 1995). These findings raise the suggestion that the effects of dopamine on motivation are sensitive to the nature of the reinforcer (positive or negative), and invite future studies of this distinction.

The effect of dopamine on incentivizing effort-based decisions has also been found in healthy, nonpathetic individuals. For example, the Effort Expenditure for Rewards Task (EEfRT) has been used to examine the effect of *D*-amphetamine on the willingness of healthy individuals to exert effort for reward (Wardle et al., 2011). This task, inspired by the T-maze tasks in rodents (Salamone et al., 2007), requires participants to choose between a high-effort/high-reward offer and a low-effort/low-reward option. The high-effort option requires 100 button presses in 21 s with the nondominant fifth digit, whereas the low-effort option requires 30 button presses with the dominant index finger in 7 s. For each successfully completed trial, the low-effort option was worth \$1.00, whereas the value of the higher effort option was varied between \$1.24 and \$4.30. In the original version of the task, there was also a probabilistic component to the task, in which some trials were more likely to result in a payoff than others (12%, 50%, and 88%).

In this task, the proportion of trials in which participants chose the high-effort/high-reward offer was greater when they were on *D*-amphetamine vs placebo. There appeared to be a dose-dependent effect, such that it was only efficacious at a dose of 20 mg, but not 10 mg, relative to placebo. Further analyses were undertaken using a generalized regression technique (Generalized Estimating Equation modeling), which showed that *D*-amphetamine increased the willingness of volunteers to exert effort for monetary rewards particularly when reward probability was lower,

suggesting a role for increased tolerance for probability costs. Amphetamine sped task performance, but its psychomotor effects did not significantly predict effects on decision making.

Together, although these studies were conducted on individuals without clinical apathy, they demonstrate the utility of dopamine in increasing sensitivity to reward and increasing the willingness of subjects to invest effort. These findings therefore represent proof in principle of the potential utility of dopamine in ameliorating key components of motivated decision making, and therefore apathetic behavior.

5 EXTENDING THIS WORK

5.1 EFFECTS OF DOPAMINE ON METRICS OF MOTIVATION

Salamone and colleagues have long argued that the primary effect of dopamine is to regulate effortful activity, allowing an animal to overcome response costs associated with pursuing valuable stimuli. The recent development of paradigms that are available to objectively quantify and track the progress of motivational disorders should act as an incentive for the development of new treatments and to determine the efficacy of existing drugs. Few of the drugs that have been trialed in the treatment of apathy have been systematically evaluated using sensitive measures of reward- or effort-based decisions, such as those described in the previous section. Based on these paradigms, future trials should focus on examining the effect of dopamine augmentation on modulating specific components of motivated decision making—such as reward or effort sensitivity—in order to relate them more closely to the clinical manifestations of apathy.

More broadly, although altered effort and/or reward sensitivity appears to be a core feature of the apathetic state, they need not be the only features that characterize it. Given the rich history of effort- and reward-based decision making in animals, applying the principles and paradigms developed in the animal literature would seem to be an obvious first step in defining the mechanisms underlying human apathy. However, it is entirely possible that there remain other deficits in decision making or executive function that characterize apathy, but which are yet to be defined. Defining the nature of such deficits would be a useful course for future research, as they may allow us to dissect different subtypes of apathetic behavior, and potentially clarify the distinction between the many terms that have been historically used to describe the phenotype of disordered motivation (Table 1). The dual goal of future research will therefore be to further clarify the role of effort- and reward-based decision making in human apathy, while defining other deficits which may be used to diagnose, monitor, and treat the apathetic state.

5.2 RECEPTOR SPECIFICITY

Clarifying the differential role of specific dopamine receptors to motivation will be integral to future work on developing targeted treatments for human apathy, which aim to maximize the effect on motivational deficits. For example, based on their

distribution within the ventral striatum and other limbic regions of the brain, D3 receptors may be a particularly useful target for the treatment of apathy. Our single case study of ropinirole improving reward sensitivity in an individual with profound apathy would be a proof of principle that D2/D3 receptor agonism is a potentially effective treatment, and it would be useful to extend this to a larger cohort of apathetic individuals using similar paradigms.

5.3 TAILORING DOPAMINE TO SPECIFIC POPULATIONS

It remains unclear whether apathy in many psychiatric and neurological conditions in which it is encountered (eg, AD vs schizophrenia vs PD) represents the same phenotypic manifestation of the identical underlying pathology, or whether the motivational deficits in each of these conditions are subtly different. Such an issue would be important to clarify with more sensitive measures of motivation, as it would dictate the specific therapy that is used in treating these diseases, and in determining at what stage of each disease therapy should be initiated.

At present, treatment options defer to the primary illness. Thus, in PD, dopamine is a parsimonious treatment to manage both the apathetic symptoms as well as the motor manifestations. However, a much more complex management problem is posed by patients with schizophrenia, in which dopamine may potentially worsen psychotic symptoms (Lieberman et al., 1987). Some have proposed that increasing dopamine levels in schizophrenia in conjunction with concurrent dopamine D2 antagonism attenuates this risk, although such reports are largely anecdotal, and no controlled trials have been conducted to verify this (Angrist et al., 1982; Jaskiw and Popli, 2004; Levi-Minzi et al., 1991; Ohmori et al., 1993; Roesch-Ely et al., 2006; van Kammen and Boronow, 1988). In such a situation, clarifying the role of specific receptor subtypes to the pathology of apathy as well as in the pathology of the primary condition is imperative.

In addition to determining or developing the specific drugs to treat apathy, it is also important to clarify the dose-dependent relationship between dopamine and motivation in individual subjects. Several studies suggest that dopamine follows an inverted-U-shaped function, such that there exists an optimal point at which dopamine mediates particular cognitive functions (Cools and D'Esposito, 2011). Administering doses of dopaminergic medication in excess of the optimum may push apathetic individuals to the other end of the motivational spectrum, and potentially result in impulse control disorders commonly encountered in patients on dopamine agonists (Voon et al., 2009). The optimum dose of dopamine replacement in apathy is likely to vary across patients as a complex function of individual factors, such as genetically determined pharmacokinetic and pharmacodynamic effects. An important goal of future work will therefore be to develop methods capable of determining the dose of dopamine therapy that delivers the maximum therapeutic efficacy at the lowest tolerable doses for individual subjects. This is an important clinical issue, given that apathy is common in elderly patients (such as those with dementia), who in general are less tolerant of high doses of medication (Chong and D'Souza, 2013).

5.4 NONPHARMACOLOGICAL MEANS OF INCREASING DOPAMINE

In addition to pharmacological methods of increasing dopamine, several studies have suggested innovative ways to increase dopamine concentrations, involving noninvasive stimulation of the primary motor cortex. For example, transcranial direct current stimulation (tDCS) in rats has shown a 60% increase in dopamine concentration in the ipsilateral striatum (Tanaka et al., 2013), and a recent study in patients with PD has showed that bilateral tDCS over the primary motor cortex (with the cathode placed over the more affected side and anode over the less affected side) resulted in less subjective effort in a manual isometric force production task (Salimpour et al., 2015). In addition, transcranial magnetic stimulation (TMS) over primary motor cortex in PD has been shown to increase serum dopamine levels and result in improved motor performance (Khedr et al., 2007), and stimulation of the primary and supplementary motor areas in healthy individuals has reduced the subjective sense of physical effort (Chong, 2015; Takarada et al., 2014; Zénon et al., 2015). These suggest novel, nonpharmacological ways of increasing dopamine levels to reduce the subjective sense of effort, which may in turn aid those with clinical apathy.

6 CONCLUSION

The development of safe and effective therapies for apathy constitutes a pressing, unmet need. A rational approach to this goal is informed by the study of the components, circuitry and pharmacology of motivated behavior in human and nonhuman animals. Dopamine represents a useful and rational target for the treatment of apathetic symptoms across a wide range of psychiatric and neurological disorders.

The accelerating pace of basic and clinical neuroscience research promises to improve our understanding of apathy and its treatment with dopaminergic medication. Using the paradigms at our disposal, future research should focus on identifying the specific neural circuitry mediating the motivational effects of dopamine agonists and should employ tests of reward- and effort-based decision making to evaluate the utility of specific agonists for the treatment of apathy. Furthermore, by dissecting the phenomenon of motivation into its components (eg, reward vs effort sensitivity), it may be possible to refine targeted treatments tailored to individual populations, as a function of their major apathetic deficit.

Despite the promise of dopaminergic treatments of apathy, further large-scale, controlled clinical trials of potentially useful pharmacologic interventions are essential before any firm recommendations can be made. The growing body of empirical investigations on the neurobiology of apathy will likely prove helpful in providing a sound theoretical basis for the application of currently available treatments, as well as for the development of novel therapeutic interventions, that will ultimately allow us to determine which drugs to administer, and at what doses, for individual subjects to improve their objective deficits in motivated behavior.

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