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REVIEW ARTICLE

Activational and effort-related aspects of motivation: neural mechanisms and implications for psychopathology

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Motivation has been defined as the process that allows organisms to regulate their internal and external environment, and control the probability, proximity and availability of stimuli. As such, motivation is a complex process that is critical for survival, which involves multiple behavioural functions mediated by a number of interacting neural circuits. Classical theories of motivation suggest that there are both directional and activational aspects of motivation, and activational aspects (i.e. speed and vigour of both the instigation and persistence of behaviour) are critical for enabling organisms to overcome work-related obstacles or constraints that separate them from significant stimuli. The present review discusses the role of brain dopamine and related circuits in behavioural activation, exertion of effort in instrumental behaviour, and effort-related decision-making, based upon both animal and human studies. Impairments in behavioural activation and effort-related aspects of motivation are associated with psychiatric symptoms such as anergia, fatigue, lassitude and psychomotor retardation, which cross multiple pathologies, including depression, schizophrenia, and Parkinson's disease. Therefore, this review also attempts to provide an interdisciplinary approach that integrates findings from basic behavioural neuroscience, behavioural economics, clinical neuropsychology, psychiatry, and neurology, to provide a coherent framework for future research and theory in this critical field. Although dopamine systems are a critical part of the brain circuitry regulating behavioural activation, exertion of effort, and effort-related decision-making, mesolimbic dopamine is only one part of a distributed circuitry that includes multiple neurotransmitters and brain areas. Overall, there is a striking similarity between the brain areas involved in behavioural activation and effort-related processes in rodents and in humans. Animal models of effort-related decision-making are highly translatable to humans, and an emerging body of evidence indicates that alterations in effort-based decision-making are evident in several psychiatric and neurological disorders. People with major depression, schizophrenia, and Parkinson's disease show evidence of decision-making biases towards a lower exertion of effort. Translational studies linking research with animal models, human volunteers, and clinical populations are greatly expanding our knowledge about the neural basis of effort-related motivational dysfunction, and it is hoped that this research will ultimately lead to improved treatment for motivational and psychomotor symptoms in psychiatry and neurology.

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On the neural regulation of motivated behaviour: conceptual overview

Motivation has been defined as the process that allows organisms to regulate their internal and external environment, and control the probability, proximity, and availability of stimuli (Salamone, 1992, 2010). Clearly, motivation is a complex process that is critical for survival, and involves multiple behavioural functions mediated by an array of interacting neural circuits. Classical motivation theory has emphasized that there are distinct facets of motivation; for example directional and activational aspects (Duffy, 1963; Cofer and Apley, 1964; Salamone, 1987, 1988, 2010). Thus, behaviour can be directed towards some stimuli (e.g. food, water, sex) and away from others (e.g. painful conditions, predators, stressors). Furthermore, it is generally recognized that motivation has an activational or energetic component. Motivated behaviour is characterized by a high degree of behavioural activation, as demonstrated by the speed, vigour or persistence seen in the instigation and maintenance of instrumental responding (Salamone, 1988, 1992; Salamone and Correa, 2002, 2012; Robbins and Everitt, 2007; Croxson *et al.*, 2009; Kurniawan *et al.*, 2010; Nicola, 2010; McGinty *et al.*, 2013; Floresco, 2015), as well as the induction of a wide variety of activities by the presentation of motivational stimuli (Robbins and Koob, 1980; Salamone, 1988; McCullough and Salamone, 1992). The ability to generate rapid or vigorous responses, and maintain them over time, is a fundamental and highly adaptive feature of motivational processes. Such neurobehavioural mechanisms allow organisms to forage over wide areas, quickly pounce on prey, work with vigour towards a selected goal, and exert effort to overcome obstacles that block access to significant stimuli.

The neural mechanisms mediating directional aspects of motivation, such as the selection of particular foods, water, sodium, or sexual activity, can be quite specific. For example, the brain circuits that instigate the selection of specific foods have neural components that are distinct from those that instigate thirst motivation (Carlson, 2014). Indeed, even thirst motivation is not a unitary construct, because there are different thirst-related signals that impinge upon distinct neural mechanisms (i.e. osmotic versus volemic thirst). However, there is considerable evidence indicating that the brain circuitry regulating activational aspects of motivation can be shared across different classes of stimuli and conditions. One of the key components of the neural circuitry mediating behavioural activation and effort-related processes is the mesolimbic dopamine system (Salamone *et al.*, 1997, 2007, 2012; Salamone and Correa, 2002, 2012; Robbins and Everitt, 2007). Of course, this system, with its target in nucleus accumbens/ventral striatum, is only one part of a broader forebrain circuitry that includes multiple neurotransmitters, brain areas, and pathways (Salamone and Correa, 2012).

Impairments in behavioural activation and effort-related aspects of motivation can result in psychiatric symptoms that span multiple pathologies (Salamone *et al.*, 2006). According to Demyttenaere *et al.* (2005), fatigue/loss of energy is one of the most common of all psychiatric symptoms in general medicine. Motivational/psychomotor symptoms such as retardation, fatigue, lassitude, loss of energy and reduced exertion of effort are critical and debilitating features of major depressive disorder (Stahl, 2002; Demyttenaere *et al.*, 2005; Salamone *et al.*, 2006; Treadway and Zald, 2011; Fava *et al.*, 2014). The severity of such effort-related symptoms in depression is highly correlated with problems in social function, employment, and treatment outcomes (Tylee *et al.*, 1999; Stahl, 2002), and these motivational symptoms are highly resistant to treatment (Stahl, 2002; Nutt *et al.*, 2007; Fava *et al.*, 2014). Many common antidepressants, such as serotonin (5-HT) uptake inhibitors (e.g. fluoxetine and citalopram), are relatively limited in their ability to treat motivational dysfunction, and in some people can induce or exacerbate these symptoms (Padala *et al.*, 2012; Stenman and Lilja, 2013; Fava *et al.*, 2014). Moreover, effort-related motivational symptoms are present in diverse psychiatric and neurological disorders, including bipolar disorder, schizophrenia, parkinsonism, chronic fatigue syndrome and multiple sclerosis (Caligiuri and Ellwanger, 2000; Salamone *et al.*, 2006, 2010; Friedman *et al.*, 2007; Tellez *et al.*, 2008; Chong *et al.*, 2015).

The present review discusses the role of brain dopamine and related circuits in behavioural activation, exertion of effort, and effort-related decision-making, based upon both animal and human studies. Moreover, the clinical significance and neural underpinnings of motivational/psychomotor pathologies such as anergia, fatigue, lassitude and psychomotor retardation are reviewed, and the contribution of animal models to the development of treatments for these symptoms is discussed. This review is intended to provide an interdisciplinary approach that integrates findings from basic behavioural neuroscience, behavioural economics, clinical neuropsychology, psychiatry, and neurology, to provide a coherent framework for future research and theory in this critical field.

Background on the role of dopamine in activational/ effort-related aspects of motivation: animal studies

Considerable evidence from the animal literature indicates that nucleus accumbens dopamine is involved in behavioural activation and energy expenditure (Salamone, 1988, 1992; Salamone and Correa, 2002, 2012; Robbins and Everitt, 2007; Beeler *et al.*, 2012, 2015). Microinjections of stimulants that enhance dopamine transmission into nucleus accumbens can increase locomotor activity (Delfs *et al.*, 1990). Accumbens dopamine depletions or antagonism suppress stimulant-induced and novelty-induced locomotion (Koob *et al.*, 1978; Cousins *et al.*, 1993; Baldo *et al.*, 2002; Correa *et al.*, 2002), and accumbens dopamine participates in sensorimotor gating functions (Koob and Swerdlow, 1988; Swerdlow *et al.*, 1990). Accumbens dopamine is also involved in schedule-induced activity, which is thought to be a model of compulsive behaviour. Periodic non-contingent presentation of small food pellets to food-restricted rats can induce vigorous motor activities, including excessive drinking, wheel running, and locomotion (Staddon and Simmelhag, 1971; Killeen, 1975; Killeen *et al.*, 1978; López-Crespo *et al.*, 2004). Such schedule-induced activities are marked by concomitant increases in accumbens dopamine release (McCullough and Salamone, 1992), and are suppressed by dopamine antagonists and accumbens dopamine depletions (Robbins and Koob, 1980; Wallace *et al.*, 1983; Salamone, 1988; McCullough and Salamone, 1992). Locomotor activity also can be instigated by the presentation of cues associated with sucrose, an effect that is blocked by dopamine antagonism (Salamone *et al.*, 2015*b*).

Accumbens dopamine also regulates instrumental response output. Stimulants that enhance dopamine transmission increase operant responding on schedules that generate low baseline rates of responding, an effect that is diminished by neurotoxic depletion of accumbens dopamine (Robbins *et al.*, 1983). De Jong *et al.* (2015) reported that knockdown of ventral tegmental dopamine D2 autoreceptors, which enhance accumbens dopamine transmission, selectively increased incentive motivation for food and cocaine as measured by progressive ratio responding. Moreover, the effects of dopamine antagonism or depletion interact powerfully with the response requirements of the task (Salamone, 1986; Salamone *et al.*, 2003). One way of varying the response requirements of instrumental behaviour is to vary the ratio requirements of operant schedules (i.e. the number of lever presses required). Caul and Brindle (2001) reported that the dopamine antagonist haloperidol had a substantial effect on progressive ratio performance (i.e. a schedule in which the ratio lever pressing requirement gradually increments) at low doses that had no effect on fixed ratio 1 (FR1) responding. Accumbens dopamine depletions suppress lever pressing on ratio schedules in a manner that is related to the size of the ratio requirement. FR1 responding is only marginally and transiently affected by dopamine depletion, while rats responding on moderate size ratio schedules (FR5, 16, 20) showed modest reductions in response rates, and animals tested on schedules with high ratios (e.g. FR16, 64, 300) were severely impaired (McCullough *et al.*, 1993*a*; Aberman *et al.*, 1998; Aberman and Salamone, 1999; Salamone *et al.*, 2001; Ishiwari *et al.*, 2004). Thus, as described by Salamone and Correa (2002), accumbens dopamine depletions blunt the response-enhancing effects of moderate sized ratio requirements, and also enhance the response-suppressing effects of very large ratio requirements (i.e. they induce 'ratio strain', or 'breaking').

It is reasonable to ask if the dopaminergic manipulations that decrease instrumental behaviour are doing so because they mimic extinction (i.e. non-delivery of reward), impair appetite or generally disrupt primary motivation, alter hedonic reactivity to the primary reward, or make animals particularly sensitive to time requirements such as delays. For many years it was suggested that dopamine is the 'reward transmitter' or the 'pleasure chemical', but as discussed in previous papers, this view has many conceptual and empirical problems (Salamone *et al.*, 1997, 2005, 2007; Salamone and Correa, 2002, 2012; Floresco, 2015). Although it was suggested several decades ago that dopamine antagonism or depletion produced an extinction-like effect, numerous studies have shown a lack of similarity between dopamine antagonism or depletion and the effects of extinction (Tombaugh *et al.*, 1980; Faustman and Fowler, 1981; Salamone, 1986, 1988; McCullough *et al.*, 1993*a*; Salamone *et al.*, 1995, 1997, 2007; Rick *et al.*, 2006; see review by Salamone and Correa, 2002). Across a number of behavioural conditions, the effects of low doses of dopamine antagonists or accumbens dopamine depletions on operant behaviour do not generally resemble the effects of devaluation of food reinforcement or appetite suppressant drugs (Salamone *et al.*, 1991, 2002; Aberman and Salamone, 1999; Sink *et al.*, 2008; Randall *et al.*, 2012, 2014). Although striatal mechanisms are known to be involved in mediating the action/outcome associations that underlie reinforcement learning, this effect is more generally attributed to neostriatal (i.e. dorsal striatal) mechanisms rather than nucleus accumbens (i.e. ventral striatum; Corbit *et al.*, 2001; Yin *et al.*, 2008; Belin *et al.*, 2009; Corbit and Janak, 2010; Lex and Hauber, 2010; Salamone and Correa, 2012). Furthermore, alteration of dopamine transmission with drugs, dopamine depletions, or genetic manipulations does not alter hedonic reactivity to sucrose (Berridge and Robinson, 1998, 2003; Sederholm *et al.*, 2002; Peciña *et al.*, 2003; Berridge, 2007; Smith *et al.*, 2011; Berridge and Kringelbach, 2015; Pardo *et al.*, 2015; see the distinction between 'liking' and 'wanting')

Thus, although low doses of dopamine antagonists and nucleus accumbens dopamine depletions impair many features of behavioural activation and instrumental responding (e.g. response rate, responding on high ratio schedules, see also studies of Pavlovian-to-Instrumental transfer, including Wyvell and Berridge, 2000; Parkinson *et al.*, 2002; Dalley *et al.*, 2005; Lex and Hauber, 2008, 2010; Yin *et al.*, 2008; Corbit and Balleine, 2011), there also are many fundamental features of appetitive motivation that are left intact after these manipulations. Such findings are not unique to food reinforcement; they also are seen when water (Horvitz *et al.*, 1993), sex (Hull *et al.*, 1991), social play behaviour (Achterberg *et al.*, 2016), and maternal behaviour (Pereira and Ferreira, 2006, 2015) are used as the motivational stimulus. Moreover, mesolimbic dopamine is known to be involved in aversive motivation and responsiveness to stress (McCullough *et al.*, 1993*b*; Salamone, 1994; Tidey and Miczek, 1996; Anstrom and Woodward, 2005; Anstrom *et al.*, 2009; Fernando *et al.*, 2014). Thus, the effects of dopamine antagonists and accumbens dopamine depletions are not accurately described as being broad or general effects on 'reward', hedonia, reinforcement, or motivation; instead, they are selective and dissociative in nature, substantially affecting some aspects of appetitive and aversive motivation, while leaving others intact (Salamone *et al.*, 2005; Floresco, 2015). Behavioural responses that are most sensitive to interference with accumbens dopamine transmission tend to be vigorous activities, including instrumental behaviours, which are elicited and supported by conditioned stimuli (Salamone and Correa, 2012). Thus, mesolimbic dopamine participates in functions akin to the 'anticipation-invigoration' mechanism proposed by Cofer and Apley (1964) in their treatise on incentive motivation. In a sense, the integrity of mesolimbic dopamine transmission enables organisms to transcend the psychological distance that separates them from motivationally relevant stimuli (Salamone and Correa, 2012).

Consistent with these ideas, prolonged dopamine signalling in response to distal cues during maze learning has been suggested to provide a sustained motivational drive that maintains instrumental behaviour (Howe *et al.*, 2013). More recently, Hamid *et al.* (2016) studied fast cyclic voltammetry responses of rats responding on distinct phases of a flexible decision-making task. They reported that phasic dopamine responses increased as animals progressed towards the increasing likelihood of reinforcement, and thus represented a temporally discounted estimate of future reinforcement. These dopamine signals were correlated with important features of behavioural output, such as response latencies, and it was suggested that mesolimbic dopamine helps to translate estimates of reinforcer availability into decisions to work for reward. Thus, mesolimbic dopamine release could be used as a motivational signal, which regulates motivational excitement and the decision of whether or not to engage in effortful activity (Hamid *et al.*, 2016).

Nucleus accumbens dopamine and the forebrain circuitry regulating effort-related decision-making in animals

It was suggested years ago that studies of cost/benefit decision-making involving work-related response costs could shed light on the behavioural functions of mesolimbic dopamine (Salamone, 1987, 1991, 1992). Organisms in their natural environment make effort-based decisions and allocate behavioural resources into goal-directed actions based on assessments of work-related response costs and motivational value or preference. This type of function is critical for animals foraging in the wild (see 'Optimal foraging theory' section; Krebs, 1977), but also can be adapted to experimental procedures in laboratories. Thus, ideas about how animals allocate their behavioural resources in choice situations eventually led to the development of procedures that study effort-related choice behaviour (also known as effort-related or effort-based decision-making). Effort-related decision-making is typically studied using tasks that offer a choice between high effort instrumental actions leading to more highly valued reinforcers versus an alternative low effort/low reward option.

One such procedure involves an operant task that offers a choice between FR5 lever pressing to obtain a relatively preferred food (high carbohydrate pellets), versus approaching and consuming a concurrently available but less preferred food (standard laboratory chow; Salamone *et al.*, 1991). Under baseline or control conditions, rats typically eat only small amounts of chow, and get most of their food by lever pressing on the FR5 schedule. However, low doses of dopamine antagonists and depletions or antagonism of accumbens dopamine dramatically shift choice behaviour, decreasing the tendency to work for food by lever pressing, but substantially increasing chow intake (Salamone *et al.*, 1991, 2002; Koch *et al.*, 2000; Nowend *et al.*, 2001; Sink *et al.*, 2008; Farrar *et al.*, 2010). Thus, despite the reduced lever pressing produced by impaired dopamine transmission, rats show a compensatory reallocation of behaviour and select a new path to an alternative food source. The use of this task as a measure of effort-related choice behaviour has been validated in several ways. In contrast to the effects of impaired dopamine transmission, pre-feeding to devalue food reinforcement reduced both lever pressing and chow intake (Salamone *et al.*, 1991). Drug treatments that produced the shift in choice behaviour did not alter food intake or preference in free-feeding choice tests (Salamone *et al.*, 1991; Koch *et al.*, 2000; Farrar *et al.*, 2008; Nunes *et al.*, 2013*a*, *b*; Pardo *et al.*, 2015). Increasing the lever pressing work requirement with larger ratios shifts response allocation from lever pressing to chow intake, indicating that

these procedures are sensitive to work requirements (Salamone *et al.*, 1997; Randall *et al.*, 2012). Unlike the effects of dopamine antagonism or depletion, appetite suppressants such as fenfluramine and cannabinoid CB1 antagonists do not increase chow intake at doses that suppress lever pressing (Salamone *et al.*, 2002; Sink *et al.*, 2008; Randall *et al.*, 2012, 2014). Thus, dopamine antagonism or depletion do not simply reduce appetite for food or primary food motivation (Salamone and Correa, 2002, 2009, 2012).

Another task that has been used to assess effort-related decision-making is the T-maze barrier choice procedure (Salamone *et al.*, 1994*a*). There are two choice arms of the maze, which can have different reinforcement densities (e.g. four versus two food pellets, or four versus zero), and to provide an effort-related challenge, a vertical barrier is placed in the arm with the higher density of reinforcement. Low doses of dopamine antagonists and accumbens dopamine depletions shift choice behaviour and bias animals towards the low effort alternative, decreasing selection of the high reward/high cost arm with the barrier, but increasing selection of the low reward with no barrier (Salamone *et al.*, 1994; Cousins *et al.*, 1996; Denk *et al.*, 2005; Mott *et al.*, 2009; Mai *et al.*, 2012; Pardo *et al.*, 2012). When there is no barrier in the arm with the high reward density, or when there is a barrier in both arms of the maze, dopamine antagonism and accumbens dopamine depletions do not alter response choice (Salamone *et al.*, 1994; Pardo *et al.*, 2012). Also, when the barrier arm contains four reinforcement pellets but the other arm contains none, rats with impaired accumbens dopamine transmission still choose the high density arm, climb the barrier, and consume all the food pellets (Cousins *et al.*, 1996; Yohn *et al.*, 2015*b*).

Discounting tasks are often used in decision-making research. With these tasks, conditions related to reinforcement such as delay and probability are systematically varied within a test session, and the animal is offered a variety of choices with different trade-offs. Effort discounting tasks have been developed in the last few years. Bardgett *et al.* (2009) showed that D1 or D2 antagonism reduced selection of the high effort arm with the barrier using a discounting procedure based upon the T-maze barrier task. In contrast, administration of amphetamine, which increases dopamine transmission, biased rats towards selection of the high effort arm. Floresco and colleagues (Floresco *et al.*, 2008; Hosking *et al.*, 2015) have developed effort-discounting procedures based on alterations in the ratio requirements (number of lever presses) to obtain reinforcements. Dopamine antagonism has been shown to bias selection towards the lower ratio option. In addition, inactivation of nucleus accumbens core neurons by local blockade of $GABA_{A/B}$ receptors also reduced selection of the higher effort alternative (Ghods-Sharifi and Floresco, 2010).

A test that combines features of the FR5/chow feeding choice task and effort discounting procedures is the progressive ratio (PROG)/chow feeding concurrent choice task. With this task, rats can lever press on a PROG schedule reinforced by preferred high-carbohydrate food pellets, or alternatively approach and consume the less-preferred lab chow that is concurrently available. If a rat receives no reinforcer for 2 min, the lever pressing component becomes inactivated, and eventually all rats reach a break point and switch to chow. The dopamine antagonists haloperidol, eticlopride and ecopipam decreased PROG lever pressing, but did not decrease levels of chow intake (Randall *et al.*, 2012, 2014*a*). Moreover, the effects of dopamine antagonism or depletion differed markedly from those of appetite-related manipulations such as prefeeding and cannabinoid CB1 receptor antagonists or inverse agonists, all of which decreased both PROG lever pressing and chow intake. Performance on the PROG/chow feeding choice task is highly variable; some rats lever press very little and have high levels of chow intake (low responders), while others lever press much more and consume only small amounts of chow (high responders). Immunocytochemical analysis of the signal transduction protein pDARPP-32(Thr34) (i.e. DARPP-32 phosphorylated at the threonine 34 residue), which is involved in dopamine-related signalling, revealed that there was significantly higher expression of pDARPP-32(Thr34) in accumbens core in high responders compared to low responders (Randall *et al.*, 2012).

It is clear that dopamine antagonism and accumbens dopamine depletions cause animals to reallocate their instrumental response selection based on the response requirements of the task, and select lower cost alternatives (Salamone *et al.*, 2007, 2012; Salamone and Correa, 2012). Furthermore, dopamine transmission appears to exert a bidirectional influence over response output in tasks involving effort-related choice behaviour (Bardgett *et al.*, 2009). Dopamine transporter (DAT, encoded by *Slc6a3*) knockdown mice showed increased lever pressing and decreased chow intake compared to wild-type mice (Cagniard *et al.*, 2006). Trifilieff *et al.* (2013) reported that selective overexpression of D2 receptors in the nucleus accumbens of adult mice also led to an increase in selection of high effort alternatives in choice tasks.

It is important to consider that there appear to be multiple dimensions of effort (Westbrook and Braver, 2015). Hosking *et al.* (2015) compared the effects of the dopamine antagonists on a ratio discounting task that assesses physical effort versus a cognitive effort discounting task. While dopamine antagonism altered decision-making based upon physical effort, it had no effect on discounting based upon cognitive effort (difficulty of a discrimination task). Also, effort-related challenges presented by different force requirements may not be regulated in the same way as those presented by tasks involving repeated responding, such as that seen in ratio schedules. Ishiwari *et al.* (2004) studied the effect of accumbens dopamine depletions on lever pressing tasks that involved different force or ratio requirements, and reported that the effects of dopamine

depletions interacted strongly with the ratio requirements, but not with the force requirements. This is consistent with studies from Fowler *et al.* (1986), who observed that dopamine antagonism affected the temporal aspects of responding more than the 'force domain'. Another important consideration is that selection of high-effort alternatives on decision-making tasks appears to be somewhat dissociable from other measures of behavioural activation, such as response speed (Wardle *et al.*, 2011; Yohn *et al.*, 2015*a*, *b*).

Considerable evidence indicates that the effects of dopamine antagonism and accumbens dopamine depletions on ratio lever pressing output and effort-based decision-making are not simply due to an interaction with the effects of reinforcement intermittency or delay. Rats responding on conventional variable interval (VI) schedules (e.g. VI 30, 60 or 120 s) were not affected by accumbens dopamine depletions that substantially suppressed responding when a ratio requirement (FR5 or 10) was attached to the same interval requirements (Correa *et al.*, 2002; Mingote *et al.*, 2005). Although interference with dopamine transmission alters performance on progressive ratio schedules, it did not affect performance on a progressive interval schedule (Wakabayashi *et al.*, 2004). These observations are consistent with reports indicating that accumbens dopamine depletions failed to disrupt delay discounting (Winstanley *et al.*, 2005). Moreover, the effects of systemic dopamine antagonism on ratio discounting do not depend simply on delay-related actions; Floresco *et al.* (2008) demonstrated that dopamine antagonism produced a bias towards the low ratio option in rats tested on a ratio discounting task even when an 'equivalent delay' procedure was used that controlled for the time to complete the ratio components. Although inactivation of nucleus accumbens core by blockade of GABA receptors reduced selection of the higher effort alternative (Ghods-Sharifi and Floresco, 2010), this same manipulation was actually reported to increase delay discounting (i.e. increase selection of the long delay option; Moschak and Mitchell, 2014).

In addition to the empirical studies reviewed above, various computational approaches have been developed to account for the role of mesolimbic dopamine in effort-related processes. Niv *et al.* (2007) developed a model that focused upon the role of mesolimbic dopamine in regulating instrumental response vigour. Phillips *et al.* (2007) provided a simple mathematical framework for how dopamine modulates cost/benefit decisions and provides an opportunistic drive that regulates the threshold cost expenditure for obtaining rewards. Collins and Frank (2014) also described a model that is useful for characterizing the effects of dopamine depletions on ratio lever press performance and choice incentives involved in effort-based choice.

Several other transmitters and neuromodulators in addition to dopamine, across multiple brain areas, interact to regulate effort-related functions. Dopamine D2 and adenosine A_{2A} receptors are co-localized on striatal medium spiny neurons and interact with each other, and systemic or local intra-accumbens core injections of adenosine A_{2A} antagonists can reverse the effort-related effects of dopamine antagonists and restore near-normal patterns of behaviour (Farrar *et al.*, 2007, 2010; Mott *et al.*, 2009; Salamone *et al.*, 2009; Worden *et al.*, 2009; Nunes *et al.*, 2010; Pardo *et al.*, 2012; Santerre *et al.*, 2012). Conversely, intra-accumbens injections of adenosine A_{2A} agonists can induce effects on effort-related choice that resemble those resulting from dopamine antagonism or depletion (Font *et al.*, 2008; Mingote *et al.*, 2008). Systemic administration of the adenosine A_{2A} antagonist MSX-3 to rats increased work output on the lever pressing component of the PROG/chow feeding choice procedure (Randall *et al.*, 2012). Intra-accumbens injections of the muscarinic agonist pilocarpine altered effort-related choice, decreasing selection of the high effort option, which is consistent with previous studies indicating that striatal dopamine and acetylcholine interact (Nunes *et al.*, 2013*a*). Activity of locus coeruleus norepinephrine neurons is correlated with exertion of effort in monkeys responding on a force grip task (Varazzani *et al.*, 2015). A number of papers have shown that there is a distributed neural circuitry that regulates effort-based decision-making, which includes basolateral amygdala, prefrontal/anterior cingulate cortex, and ventral pallidal GABA in addition to nucleus accumbens; this has been confirmed in studies using 'disconnection methods' that involve combined contralateral manipulation of two different parts of the circuit (Salamone *et al.*, 1994, 1997, 2007; Walton *et al.*, 2003; Floresco and Ghods-Sharifi, 2007; Farrar *et al.*, 2008; Mingote *et al.*, 2008; Hauber and Sommer, 2009; see Fig. 1).

Animal models of effort-related motivational impairments in psychopathology, and implications for treatment

Because of the importance of effort-related dysfunctions in psychopathology (see discussion in the sections below), animal tests of effort-based decision-making have recently been used to develop formal models of motivational symptoms. The rodent tasks described above have been studied for their sensitivity to some of the conditions associated with depression, and also for assessment of potential and well-known therapeutic agents. Reduced selection of high effort choices in rodents can be induced by several conditions associated with depression, including stress (Shafiei *et al.*, 2012), injections of the proinflammatory cytokine interleukin 1β (IL1β, encoded by *Il1b*; Nunes *et al.*, 2014), and administration of tetrabenazine (TBZ). In rats tested on the FR5/chow feeding choice task, injections of low doses of IL1β shifted effort-related choice, decreasing lever pressing and increasing chow intake at doses that did not change

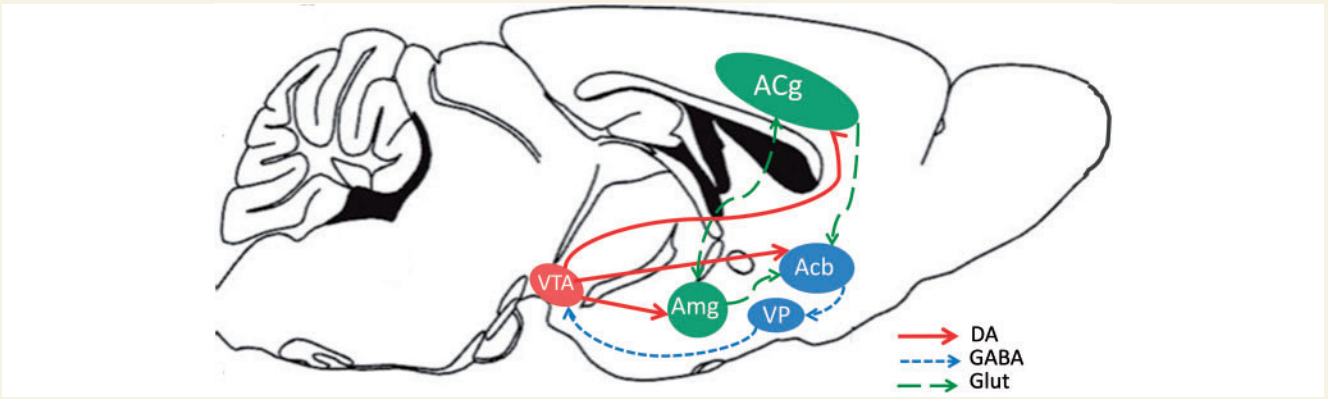

Figure 1 Schematic showing anatomical connections in the rodent brain between structures involved in effort-related choice behaviour. Acb = nucleus accumbens; ACg = anterior cingulate gyrus; Amg = amygdala; DA = dopamine; GABA = gamma aminobutyric acid; Glut = glutamate; VP = ventral pallidum; VTA = ventral tegmental area.

food preference or induce fever. These effects of IL1β were reversed by co-administration of the adenosine A_{2A} receptor antagonist MSX-3 (Nunes *et al.*, 2014).

Several recent studies have focused on the effort-related effects of TBZ. TBZ inhibits VMAT-2 (i.e. vesicular monoamine transporter type 2, encoded by *Slc18a2*), which results in reduced vesicular storage and depletion of monoamines. The greatest effects of TBZ at low doses have been reported to be on dopamine in the striatal complex, which is substantially depleted relative to norepinephrine and 5-HT (Pettibone *et al.*, 1984; Tanra *et al.*, 1995). Originally developed as a reserpine-type antipsychotic, TBZ has been approved for use as a treatment for Huntington's disease and other movement disorders, but its major side effects include depressive symptoms (Frank, 2009, 2010; Guay, 2010; Chen *et al.*, 2012). Like reserpine, TBZ has been used in studies involving classical animal models of depression (Preskorn *et al.*, 1984; Kent *et al.*, 1986; Wang *et al.*, 2010). Low doses of TBZ that decreased accumbens dopamine release and dopamine-related signal transduction altered effort-related choice behaviour as assessed by concurrent lever pressing/chow feeding choice procedures (Nunes *et al.*, 2013*b*; Randall *et al.*, 2014). The doses of TBZ that decreased selection of FR or PROG lever pressing did not alter preference for high carbohydrate pellets (the reinforcer for the high effort option) versus chow intake (Nunes *et al.*, 2013*b*), and did not produce effects similar to reinforcer devaluation by prefeeding, or appetite suppressant drugs (Randall *et al.*, 2012, 2014). The shift from lever pressing to chow intake was also produced by local infusions of the TBZ into nucleus accumbens core, but not overlying medial dorsal striatum (Nunes *et al.*, 2013*b*). A version of the concurrent lever pressing/chow intake task was recently developed, in which different sucrose concentrations were used as the reinforcer (Pardo *et al.*, 2015). TBZ shifted choice behaviour by reducing lever pressing for the strongly preferred higher concentration of sucrose, and increasing selection of the low concentration of sucrose that was obtained with low effort (i.e. drinking with no lever pressing requirement). The same doses of TBZ that produced this shift had no effect on sucrose preference or hedonic taste reactivity (Pardo *et al.*, 2015). Low doses of TBZ (0.25–0.75 mg/kg) altered effort-related decision-making in rats tested on the T-maze barrier task, but did not affect arm selection when there was no barrier in the maze, or when the arm with the barrier had four reinforcement pellets but the other arm had no pellets (Yohn *et al.*, 2015*a*, *b*). This pattern of results demonstrates that TBZ did not reduce selection of the high effort alternative because it was impairing sensitivity to reinforcement density, preference for four pellets versus two, discrimination of left versus right, or reference memory, or because of an inability to climb the barrier or an absolute ceiling level of barrier crossings (Yohn *et al.*, 2015*a*).

An important feature of animal models is their utility for studies of drug development, which includes validation with known therapeutic agents as well as the assessment of novel compounds or strategies. Recently, several drugs have been tested for their ability to reverse deficits in effort-related decision-making. Adenosine A_{2A} antagonists produce antiparkinsonian effects in animal models and human clinical studies, and one of them, istradefylline, is used clinically in Japan. Recent case reports indicate that fatigue in some parkinsonian patients can be alleviated by treatment with istradefylline (Nomoto *et al.*, 2014). Furthermore, A_{2A} antagonists have been shown to induce antidepressant-like effects in rodents, as assessed by classical behavioural models (Hodgson *et al.*, 2009; Hanff *et al.*, 2010; Yamada *et al.*, 2013, 2014). The adenosine A_{2A} antagonist MSX-3 has been shown to reverse the effort-related effects of TBZ in rats tested on several different procedures (Nunes *et al.*, 2013*b*; Randall *et al.*, 2014; Yohn *et al.*, 2015*a*). Adenosine A_{2A} receptors are co-localized with dopamine D2 family receptors on enkephalin-positive medium spiny neurons in both neostriatum and accumbens (Rosin *et al.*, 1998; Svenningson *et al.*, 1999). Adenosine A_{2A} and dopamine D2 receptors can form heteromeric complexes, and they converge onto the same

c-AMP/protein kinase A signal transduction cascade (Ferré *et al.*, 2008; Santerre *et al.*, 2012). A dose of 0.75 mg/kg TBZ reduced dopamine-related signal transduction mediated by D1 and D2 receptors (e.g. changes in cFos and expression of multiple forms of pDARPP-32), and MSX-3 significantly attenuated the cellular effects of TBZ related to D2 signalling (Nunes *et al.*, 2013*b*). Thus, adenosine A_{2A} antagonists appear to be acting on enkephalin-positive neurons that contain D2 receptors and form part of the ventral striatopallidal pathway (Mingote *et al.*, 2008; Farrar *et al.*, 2010; Santerre *et al.*, 2012; Nunes *et al.*, 2013*b*).

Catecholamine uptake inhibitors are reported to be moderately efficacious for treating psychomotor retardation and fatigue symptoms of depression (Fabre *et al.*, 1983; Rampello *et al.*, 1991; Pae *et al.*, 2007; Cooper *et al.*, 2014), and can be more effective than 5-HT uptake blockers for treating motivational dysfunction in depressed patients (Papakostas *et al.*, 2006; Cooper *et al.*, 2014). Bupropion (Wellbutrin®) is a catecholamine uptake inhibitor, which has been shown to occupy dopamine transporters in humans at doses that are clinically useful for treating depression (Learned-Coughlin *et al.*, 2003), and to elevate extracellular dopamine and norepinephrine in rats as measured by microdialysis (Hudson *et al.*, 2012; Randall *et al.*, 2015). In rats tested on the T-maze barrier choice task, bupropion fully reversed the effects of TBZ, increasing selection of the barrier arm in TBZ-treated rats (Yohn *et al.*, 2015*a*). Bupropion also reversed the effects of TBZ in rats tested on the FR5/chow feeding choice (Nunes *et al.*, 2013*b*) and PROG/chow feeding choice tasks (Randall *et al.*, 2014). In the absence of TBZ, bupropion increased PROG output in rats responding on the PROG/chow feeding choice task, at doses that increased extracellular dopamine and DARPP-32 expression in nucleus accumbens core (Randall *et al.*, 2015). Because bupropion is known to act as an antidepressant in humans, these results serve to validate the hypothesis that tests of effort-related choice behaviour can be used to assess the effort-related motivational effects of well-known or putative therapeutic agents. Moreover, these results are consistent with studies showing that PROG choice lever pressing output was increased by the novel dopamine uptake inhibitor MRZ-9547 (Sommer *et al.*, 2014), and that amphetamine increased selection of the high effort alternative in humans responding on an effort-related decision-making task (Wardle *et al.*, 2011).

Recent studies have focused on the effects of monoamine uptake inhibitors with different patterns of selectivity for their ability to reverse the effects of TBZ (Yohn *et al.*, 2016*b*). The selective dopamine transport inhibitor GBR12909 also reversed the effects of TBZ of FR5/chow feeding choice performance. However, the norepinephrine uptake inhibitor desipramine and the 5-HT uptake inhibitor fluoxetine both failed to reverse the effects of TBZ. Moreover, higher doses of fluoxetine and desipramine, when administered alone or in combination with TBZ, led to further behavioural impairments (Yohn *et al.*, 2016*b*). These studies demonstrate that drugs acting on dopamine transmission appear to be relatively effective at reversing the effort-related effects of TBZ and enhancing work-related behavioural output, which is consistent with recent studies demonstrating that the amphetamine prodrug lisdexamfetamine reverses the effort-related effects of TBZ, while the 5-HT uptake blocker s-citalopram did not (Yohn *et al.*, 2016*a*). Recent research from our laboratory has shown that methylphenidate and modifinil, which both block dopamine uptake and have been used to treat motivational dysfunction in humans (Stotz *et al.*, 1999; Lam *et al.*, 2007), also can reverse the effects of TBZ in rats tested on the FR5/chow feeding choice task (Fig. 2). These findings are consistent with the hypothesis that augmentation of dopamine transmission may be an effective treatment strategy for the amelioration of effort-related psychiatric symptoms in humans.

Tasks involving effort-related decision-making also have been used to model negative symptoms of schizophrenia. Although local overexpression of dopamine D2 receptors in adult rodents leads to increased behavioural activation and effort expenditure (Trifilieff *et al.*, 2013), several studies have shown that overexpression of D2 receptors in striatal medium spiny neurons throughout development leads to the opposite effect (i.e. a reduction of behavioural activation and exertion of effort in motivated behaviour; Ward *et al.*, 2012). D2 overexpressing mice show attenuated PROG responding (Drew *et al.*, 2007; Simpson *et al.*, 2011), and reduced selection of the high effort alternative in a test of effort-based choice (Ward *et al.*, 2012). Nevertheless, they do not show alterations in hedonic reactivity to food rewards, or changes in food preference or intake. Thus, it has been hypothesized that the effort-related impairments in D2 receptor overexpressing mice could be useful for modelling some of the negative symptoms of schizophrenia (Simpson *et al.*, 2011; Markou *et al.*, 2013).

Translational studies of effort-related decision-making in non-pathological human subjects

In 2009, Treadway, Zald and colleagues (Treadway *et al.*, 2009) developed the Effort-Expenditure for Rewards Task (EEfRT) to extend work on effort-related decision-making to humans. People are given a choice on each trial between a difficult (high effort) choice and an easy (low effort) option. The more difficult choice required the subject to make 100 button presses using the non-dominant little finger within 21 s, while the easy choice required 30 button presses with the index finger of the dominant

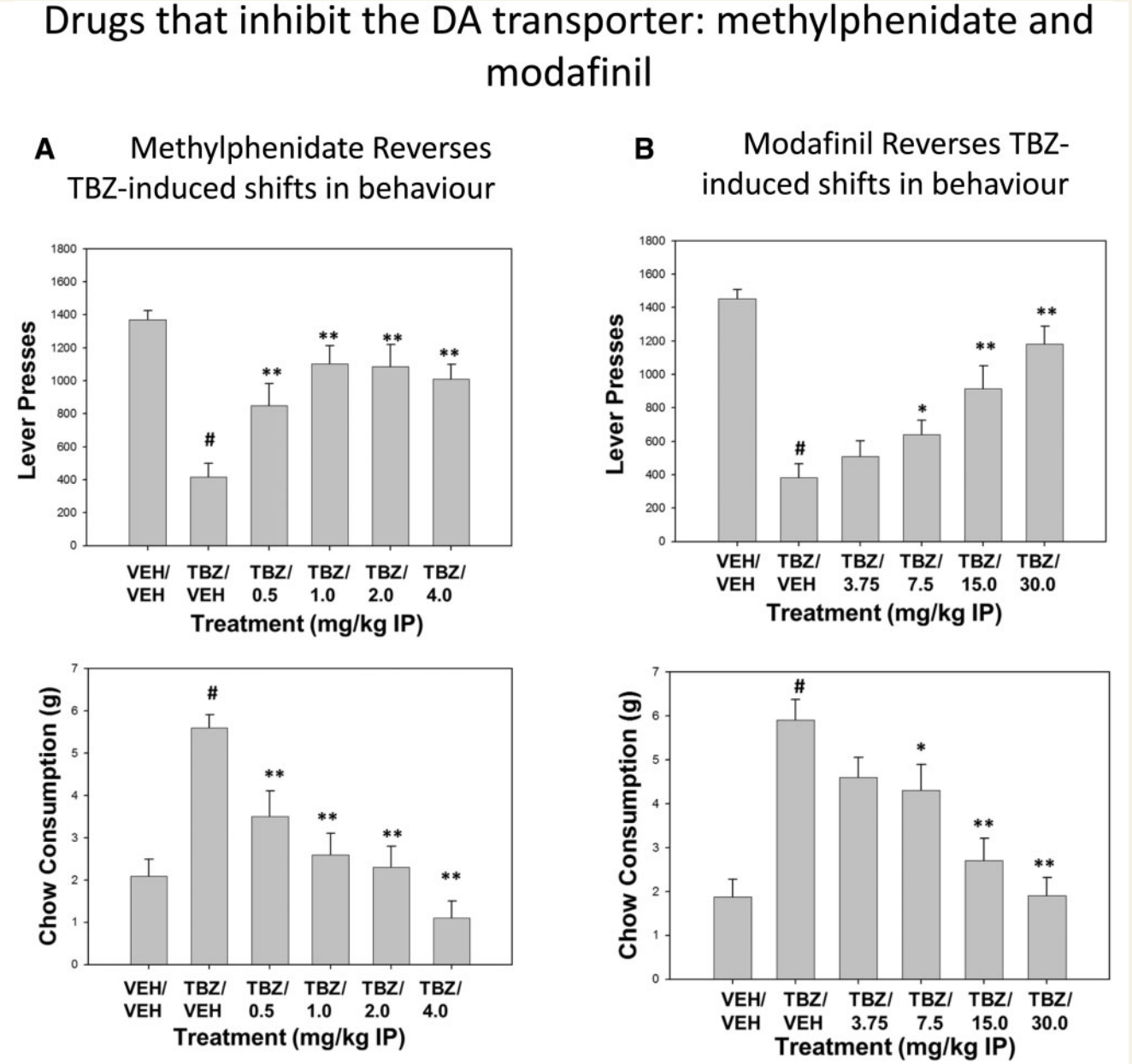

Figure 2 Ability of methylphenidate and modafinil to reverse the effects of TBZ in rats responding on the concurrent FR5/chow choice task. All rats (adult male, Sprague-Dawley rats, Harlan Sprague-Dawley) were trained as described in Yohn *et al.* (2016*a*), and tested in 30-min sessions. Rats were tested 5 days/week, and drug testing was conducted 1 day each week, with a randomized order of drug treatments. (**A**) Methylphenidate. Rats (n = 12) received intraperitoneal (IP) injections of vehicle or 0.75 mg/kg of TBZ 90 min prior to testing, and also received intraperitoneal injections of vehicle or methylphenidate 45 min prior to testing. *Top*: Mean [± standard error of the mean (SEM)] number of lever presses. There was an overall significant effect of drug treatment on lever pressing [$F(5,55) = 14.7$, $P < 0.001$]. Planned comparisons showed that TBZ significantly decreased lever pressing compared to vehicle ($^{\#}P < 0.05$), and that all doses of methylphenidate plus TBZ significantly increased lever pressing relative to TBZ plus vehicle ($^{**}P < 0.01$). *Bottom*: Mean (±SEM) gram quantity of chow intake. There was an overall significant effect of drug treatment on chow intake [$F(5,55) = 19.6$, $P < 0.001$]. Planned comparisons showed that TBZ significantly increased chow consumption relative to vehicle ($^{\#}P < 0.05$), and that all doses of methylphenidate plus TBZ significantly decreased chow intake relative to TBZ plus vehicle ($^{**}P < 0.01$). (**B**) Modafinil. Rats (n = 12) received intraperitoneal injections of vehicle or 0.75 mg/kg of TBZ 90 min prior to testing, and intraperitoneal injections of either vehicle or modafinil 30 min prior to testing. *Top*: Mean (±SEM) number of lever presses. There was an overall significant effect of drug treatment on lever pressing [$F(5,55) = 21.0$, $P < 0.001$]. Planned comparisons showed that TBZ significantly decreased lever pressing compared to vehicle ($^{\#}P < 0.05$), and that the 7.5–30.0 mg/kg doses of modafinil plus TBZ significantly increased lever pressing relative to TBZ plus vehicle ($^{*}P < 0.05$; $^{**}P < 0.01$). *Bottom*: Mean (±SEM) gram quantity of chow intake. There was an overall significant effect of drug treatment on chow intake [$F(5,55) = 14.1$, $P < 0.001$]. Planned comparisons showed that TBZ significantly increased chow consumption relative to vehicle ($^{\#}P < 0.05$), and that the 7.5–30.0 mg/kg doses of modafinil plus TBZ significantly increased lever pressing relative to TBZ plus vehicle ($^{*}P < 0.05$; $^{**}P < 0.01$). Results are from the unpublished thesis of Augustyna Gojol, University of Connecticut, 2015.

hand within 7 s. Monetary reward was kept constant for the easy task ($1.00), while for the hard task, people could earn more money ($1.24–$4.30). Moreover, reward probability can be varied across trials. This task has been used in several studies over the last few years, including research involving both non-pathological subjects and people with various psychiatric disorders. An initial study examined the effects of d-amphetamine, which enhances dopamine transmission by stimulating release and blocking uptake of dopamine (Wardle *et al.*, 2011). Healthy human volunteers were assessed using the EEfRT task. Over three sessions, subjects received treatments with either placebo, 10 mg or 20 mg d-amphetamine under counterbalanced double-blind conditions. As predicted, amphetamine enhanced willingness to exert effort, increasing selection of the high-effort option. This effect was particularly strong when reward probability was relatively low. However, amphetamine did not alter the effect of reward magnitude on willingness to exert effort.

In another study (Treadway *et al.*, 2012*a*), healthy human volunteers went through a dual-scan PET imaging protocol with ^{18}F-fallypride and d-amphetamine to measure dopamine transmission, and were separately tested on the EEfRT task. Individual differences in dopamine transmission in the left striatum and ventromedial prefrontal cortex were correlated with the willingness to expend greater effort for larger rewards, especially when reward probability was low. Furthermore, variability in dopamine responses in the bilateral insula was negatively correlated with willingness to expend effort for rewards, which is consistent with evidence indicating that this brain area is involved in the processing of response costs. These results emphasize the role of dopamine signalling in striatal and prefrontal areas in humans as a key neurochemical component of the mechanisms underlying individual differences in cost/benefit decision-making, and are consistent with animal research on individual differences in effort-related processes (Randall *et al.*, 2012).

Several other imaging papers have focused on the relation between neural activity and mental or physical effort in humans. Some evidence indicates that ventral striatal functional MRI activity can reflect responsiveness to reward discounted by the amount of effort that is required. Botvinick *et al.* (2009) found that nucleus accumbens functional MRI activity was less strongly activated following a high-demand mental effort task compared to a low demand one. Croxson *et al.* (2009) tested subjects who were scanned while they performed a series of effortful actions to obtain access to secondary reinforcement. Subjects were presented with one of eight different visual cues at the beginning of each trial, which they had previously learned would signal how much effort the course of action would require, and how much reward could be expected upon completion. Cue-evoked functional MRI activity in the ventral striatum and midbrain signalled the expected amount of reward discounted by the amount of effort to be invested. Activity in dorsal anterior cingulate cortex also reflected the interaction between expected reward and effort costs. However, ventral striatal functional MRI responses also seem to be somewhat context-dependent, and increased activity seen during some tasks can reflect increases in response to the effort that is involved in performing the task. Evidence also indicates that fast phasic dopamine signals as measured by voltammetry and electrophysiology also are context-dependent, and signal different things depending upon the context of the behavioural conditions being studied (Hollon *et al.*, 2014; Marinelli and McCutcheon, 2014; Hamid *et al.*, 2016). Schmidt *et al.* (2012) observed that ventral striatum functional MRI blood oxygen level-dependent (BOLD) activity was related to anticipation of reward and exertion of mental and physical effort, but not to receipt of the monetary reward. Another functional MRI study by Kurniawan *et al.* (2013) reported that the supplementary motor cortex, anterior cingulate cortex, and striatum showed higher BOLD responses during anticipation of high effort, and that striatal signals during anticipation were more directly related to anticipated effort rather than expected valence. Furthermore, functional MRI activity in nucleus accumbens was shown to predict high exertion of effort in people performing an instrumental motivation task (Kroemer *et al.*, 2014).

Psychopathological symptoms related to impairments in activational and effort-related aspects of motivation

Impairments in behavioural activation and effort-related processes can manifest themselves as pathological symptoms that are seen across multiple psychiatric and neurological disorders. Fatigue/loss of energy is one of the most common of all psychiatric symptoms in general medicine (Demyttenaere *et al.*, 2005). Effort-related motivational/psychomotor symptoms are present in diverse conditions, including major depression, bipolar disorder, schizophrenia, parkinsonism, organic brain disease, immune or inflammatory challenge, chronic fatigue syndrome and multiple sclerosis (Caligiuri and Ellwanger, 2000; Salamone *et al.*, 2006, 2010; Friedman *et al.*, 2007; Tellez *et al.*, 2008; Clarke *et al.*, 2011; Barch *et al.*, 2014, 2015; Wolf *et al.*, 2014; Chong *et al.*, 2015; Johnson *et al.*, 2015). The neural bases of effort-related dysfunctions in humans are still being characterized, nevertheless, considerable evidence implicates central dopamine, basal ganglia, and related corticolimbic circuitry (Rogers *et al.*, 1987; Brown and Gershon, 1993; Hickie *et al.*, 1999; Caligiuri and Ellwanger, 2000; Brody *et al.*, 2001; Schmidt

et al., 2001; Volkow *et al.*, 2001; Salamone *et al.*, 2006, 2007; Tellez *et al.*, 2008; Treadway and Zald, 2011).

One of the disorders that is commonly accompanied by motivational dysfunction is major depression. In addition to being marked by emotional and cognitive symptoms, the majority of depressed patients demonstrate effort-related motivational symptoms, including psychomotor retardation, anergia, lassitude, and fatigue (Stahl, 2002; Demyttenaere *et al.*, 2005; Salamone *et al.*, 2006; Treadway and Zald, 2011; Fava *et al.*, 2014; Gorwood *et al.*, 2014). Lack of self-reported energy is related to low mood in people with bipolar disorder (Johnson *et al.*, 2015), and in depressed people is the symptom that is most strongly correlated with the impairments in social function and work-related factors such as days in bed, days of lost work, and low work productivity (Tylee *et al.*, 1999; Stahl, 2002). Depressed people show reductions in locomotor activity that are related to signs of clinical improvement (Todder *et al.*, 2009). In a factor analytic study of patients with major depression, Gullion and Rush (1998) identified a 'lack of energy' factor (i.e. problems with energy/fatigability, psychomotor retardation, inability to work), which was the factor that loaded most strongly onto a second order general depression factor.

Treatment of motivational dysfunction in depressed people is more problematic than treatment of mood or anxiety symptoms. Many common antidepressants, including 5-HT transport (SERT) inhibitors such as fluoxetine, are relatively ineffective for treating motivational dysfunction, and in fact have been reported to induce or exacerbate these symptoms in some patients (Nutt *et al.*, 2007; Targum and Fava, 2011; Padala *et al.*, 2012; Stenman and Lilja, 2013; Fava *et al.*, 2014; Rothschild *et al.*, 2014). SERT inhibitors appear to be better at treating anxiety-related symptoms as opposed to motivational symptoms (Papakostas *et al.*, 2008). Bell *et al.* (2013) reported that individual differences in behavioural traits can differentiate between depressed patients that are more responsive to fluoxetine (people with mood problems, irritability, and rumination) versus the catecholamine uptake blocker bupropion (i.e. motivated, achievement-oriented, active, exercise-oriented people). Catecholamine uptake inhibitors such as bupropion have been reported to improve fatigue or anergic symptoms (Rampello *et al.*, 1991; Papakostas *et al.*, 2006; Pae *et al.*, 2007; Cooper *et al.*, 2014).

Although motivational/psychomotor symptoms are most often measured by rating scales or subscales on various tests, recent studies with objective measures have shown that depressed patients also show reduced effort exertion and alterations in effort-based decision-making (Clery-Melin *et al.*, 2011; Treadway *et al.*, 2012*b*; Yang *et al.*, 2014). Clery-Melin *et al.* (2011) reported that patients with depression exerted less effort (i.e. lower force output involving hand grip) compared to control subjects on a task in which monetary incentives were used. Interestingly, the depressed patients had increased ratings of their perceived effort when the high monetary incentive was used, whereas control subjects showed a decrease. Treadway *et al.* (2012*b*) reported that patients with major depression showed reduced selection of the high effort choice on the EEfRT task compared to control subjects, particularly when reward probability was high, and therefore control-level performance was at its highest. Yang *et al.* (2014) used the same task, and also observed that patients diagnosed with major depression, as well as those with subsyndromal depression, showed reduced selection of the high effort alternative. In a subsequent paper, these authors observed diminished caudate responsiveness after presentation of high reward magnitudes in depressed patients who showed reduced high effort selection on the EEfRT task (Yang *et al.*, 2015).

Motivational symptoms also are widely reported in schizophrenic patients. Although schizophrenia is typically considered to be a 'thought disorder', with cardinal positive symptoms such as hallucinations and delusions, schizophrenics also display a host of other impairments, including memory dysfunctions and negative symptoms such as avolition and amotivation (Gard *et al.*, 2009; Barch and Dowd, 2010; Fervaha *et al.*, 2013, 2015; Markou *et al.*, 2013; Davis *et al.*, 2014; Foussias *et al.*, 2015; Tsapakis *et al.*, 2015). Research by Gard *et al.* (2014) indicated that schizophrenic patients have fundamental problems with engagement in effortful behaviour that are not dependent upon difficulties with experiencing pleasure or setting pleasure-based goals. Gold *et al.* (2013) reported that schizophrenics showed reduced selection of high-effort alternatives on a novel decision-making task, and this initial observation has been followed by a recent wave of papers demonstrating that people with schizophrenia show 'effort shyness'; i.e. reduced selection of high-effort options in objective tests of effort-based decision-making (Barch *et al.*, 2014, 2015; Hartmann *et al.*, 2015; Gold *et al.*, 2015; Green *et al.*, 2015; Horan *et al.*, 2015; Reddy *et al.*, 2015*a*, *b*; Treadway *et al.*, 2015). In a recent review, Reddy *et al.* (2015*a*) surveyed a group of tasks that assessed cognitive, perceptual and physical effort for their suitability in assessing motivational impairments in schizophrenics. The EEfRT task showed good reliability and utility with repeated measures, while a force-grip task yielded large differences between patient and control groups (Reddy *et al.*, 2015*a*). Horan *et al.* (2015) assessed the same tasks for their external validity and correlates, and reported that performance on the effort-based tasks generally showed small/medium correlations with clinical ratings of life functions, negative symptoms, and motivation.

Parkinson's disease is a movement disorder characterized by degeneration of nigrostriatal dopamine neurons, additional neuropathologies, and motor symptoms such as akinesia, bradykinesia, rigidity and tremor. Nevertheless, patients with Parkinson's disease also demonstrate depressive symptoms and motivational dysfunctions that typically are labelled as fatigue in the literature (Friedman *et al.*, 2007). Fatigue symptoms in parkinsonian patients are characterized by subjective reports of a lack of energy (i.e. 'my

battery runs down' or 'my energy bubble just bursts'; Friedman *et al.*, 2007), and reduced selection of high-effort activities (Elbers *et al.*, 2009). Shore *et al.* (2011) studied appetitive motivation in parkinsonian patients using food reinforcement and presentation of food-related cues. While control subjects show marked behavioural activation in response to food-associated cues, parkinsonian patients showed the opposite effect (i.e. reduced response rates). In addition, Aarts *et al.* (2012) reported that parkinsonian patients showed a reduced capacity to repeat performance of the current task-set under conditions of high reinforcement.

Recent reports also have examined the exertion of effort in parkinsonian patients. Porat *et al.* (2014) studied patients with asymmetrical dopamine loss for their ability to exert effort to maximize monetary gains and minimize losses, using a progressive ratio schedule. Patients with relatively greater dopamine impairments in the left hemisphere, when tested OFF medication, showed greater approach deficits (i.e. less effort to increase gain than to avoid loss). In contrast, the opposite pattern of effort expenditure was demonstrated by patients with greater right hemisphere dopamine deficits. If patients performed the same task while medicated, there was increased willingness to expend effort. Chong *et al.* (2015) studied effort-related decision-making in patients with idiopathic Parkinson's disease. They developed a novel paradigm in which subjects decided whether or not they were willing to squeeze a hand-held dynamometer at varying levels of force for different magnitudes of reward. For each subject, the effort level at which the probability of accepting a reward was 50% (i.e. the effort 'indifference point') was determined. Parkinsonian patients were tested during both the ON and OFF phases of their dopaminergic medication effect, and their performance on the task was compared to that of age-matched controls. None of the patients was clinically apathetic as defined by the Lille Apathy Rating Scale. Regardless of medication status, parkinsonian patients chose to engage in less effort than controls for the lowest level of reward. Interestingly, dopamine transmission had a motivating effect on the choice behaviour of the patients; more effort was exerted by patients when they were in the ON medication state relative to the OFF state. Importantly, the effort-related effects of medication were not related to general improvements in motor function. Thus, Chong *et al.* (2015) suggested that deficits in motivational decision-making are present in patients with Parkinson's disease, and that enhancement of dopamine transmission acts to eliminate motivational deficits by promoting the allocation of effortful responding.

Pro-inflammatory cytokines also have been implicated in the fatigue-related symptoms seen in patients with infectious or inflammatory disease (Dantzer *et al.*, 2008; Harboe *et al.*, 2009; Miller and Norman Cousins Lecture, 2009), multiple sclerosis (Lapierre and Hum, 2007), Parkinson's disease (Katsarou *et al.*, 2007), and major depression (Dantzer *et al.*, 2008; Dantzer, 2009; Miller and Norman Cousins Lecture, 2009; Piser, 2010). Cytokines such as interleukin-1 (IL1) mediate a set of behavioural signs known as 'sickness behaviour' (Kent *et al.*, 1992); these include depressed activity, loss of interest or motivation, and lack of body-care activities. Initially linked to infectious diseases, research on cytokines has been extended to studies of neurological and psychiatric disorders, including investigations related to fatigue, anergia, and depression (Smith, 1991; Dantzer *et al.*, 2008; Miller and Norman Cousins Lecture, 2009). Peripheral cytokines can act on macrophage-like cells in the choroid plexus and circumventricular organs, which induces synthesis of cytokines that diffuse into brain tissue (Dantzer, 2009). Also, peripheral cytokines act on afferent branches of cranial nerves, instigating the central production of cytokines by microglia (Dantzer, 2009). Cytokines are involved in the fatigue-related symptoms seen in patients with infectious or inflammatory disease (Dantzer *et al.*, 2008; Harboe *et al.*, 2009; Miller and Norman Cousins Lecture, 2009), multiple sclerosis (Lapierre and Hum, 2007), and Parkinson's disease (Katsarou *et al.*, 2007). Considerable evidence indicates that cytokines are involved in effort-related symptoms such as psychomotor slowing, anergia and fatigue in patients with major depression (Raison *et al.*, 2006; Dantzer *et al.*, 2008; Miller and Norman Cousins Lecture, 2009). Patients with depression have been reported to have increased levels of pro-inflammatory cytokines, including IL6, and IL1β (Smith, 1991; Raison *et al.*, 2006; van den Biggelaar *et al.*, 2007; Dantzer *et al.*, 2008; Dowlati *et al.*, 2010; Hiles *et al.*, 2012). High levels of IL1β in depressed patients were predictive of a lack of therapeutic response to the antidepressants nortriptyline and escitalopram (Cattaneo *et al.*, 2013). Cytokines such as IL2 and interferon-α (IFNα) have been shown to induce depression with associated psychomotor slowing and fatigue in patients who were given this treatment to boost their immune system (Dantzer *et al.*, 2008, 2012; Majer *et al.*, 2008; Lotrich, 2009). Fatigue and loss of energy was reported to be the most common symptom induced by IFNα although depressed mood was reported by some patients (30–60%), fatigue and loss of energy occurred in 80% of patients receiving treatment with IFNα (Miller and Norman Cousins Lecture, 2009). Moreover, patients that received IFNα treatment, when compared to healthy people with major depression, showed less agitation and suicidal ideation, but significantly greater psychomotor slowing (Capuron *et al.*, 2009). Emerging evidence has implicated prefrontal cortex, basal ganglia and limbic system in mediating the impact of cytokines on depressive symptoms (Capuron *et al.*, 2005; Dantzer *et al.*, 2008; Majer *et al.*, 2008; Miller and Norman Cousins Lecture, 2009; Felger *et al.*, 2013). IFNα-induced increases in glucose metabolism in basal ganglia areas, including nucleus accumbens, were correlated with the development of psychomotor slowing and fatigue (Capuron *et al.*, 2005, 2007; Miller and Norman Cousins Lecture, 2009).

Despite the fact that depression, schizophrenia and Parkinson's disease are distinct disorders with unique sets of behavioural and neural pathologies, it is important to consider that there may be some overlap in terms of the neural mechanisms involved in the motivational dysfunctions that are seen. The research domain criterion (RDoC) initiative offered by the US National Institute of Mental Health (Cuthbert and Insel, 2013) has promoted the idea that scientists and clinicians should study the neural circuits that mediate specific symptoms in addition to focusing on traditional diagnostic categories. This idea is potentially important for understanding the circuitry underlying motivational/psychomotor pathologies, such as effort-related dysfunction (Salamone and Correa, 2012; Barch *et al.*, 2015). For several years, it has been suggested that there is overlap between some of the psychomotor symptoms of depression and parkinsonism (Caligiuri and Ellwanger, 2000; Rogers *et al.*, 2000). It has been suggested that dopamine systems and related frontostriatal circuits could be involved in psychomotor and motivational symptoms that are seen across multiple neurological and psychiatric disorders (Salamone *et al.*, 2006, 2015*a*; Winograd-Gurvich *et al.*, 2006). Moreover, drugs that augment dopamine transmission have been reported to have positive effects on motivational or psychomotor functions. Brown and Gershon (1993) reported that L-DOPA was not an effective antidepressant in a broad sense, but it did improve psychomotor function in depressed patients. Beierholm *et al.* (2013) reported that L-DOPA enhanced response vigour in healthy human volunteers. Methylphenidate can attenuate fatigue and apathy in patients with Parkinson's disease (Friedman *et al.*, 2007; Devos *et al.*, 2013) and major depression (Rizvi *et al.*, 2014). Stotz *et al.* (1999) reported that amphetamine and methylphenidate increased self-reported energy and psychomotor activity in depressed patients within hours after administration. Although level or type of antipsychotic medication has not been found to be a strong correlate of impairments in effort-related decision-making in schizophrenics (Green *et al.*, 2015), administration of antipsychotic dopamine antagonists to normal subjects has been shown to induce negative symptoms (Artaloytia *et al.*, 2006). A PET study of raclopride binding potential in striatum reported that lower baseline dopamine D2 receptor transmission in ventral striatum of unmedicated schizophrenic patients was associated with more severe negative symptoms such as apathy and social withdrawal (Kegeles *et al.*, 2010).

Complications in assessing effort-related dysfunctions in psychopathology

As is the case with the animal research reviewed above, interpretation of the significance of effort-related symptoms associated with pathological states should be considered in the context of other possible dysfunctions in motivational or affective processes (Gold *et al.*, 2015). For example, it is reasonable to ask if the bias towards low effort options seen in people with depression, schizophrenia or Parkinson's disease is simply dependent upon reduced in-the-moment hedonic reactivity to primary rewards. Sienkiewicz-Jarosz *et al.* (2013) reported that patients with Parkinson's disease did not differ from control subjects in terms of pleasantness ratings of gustatory and olfactory stimuli, or intensity ratings of higher concentrations of sucrose. Gard *et al.* (2007) developed a self-report trait measure of anticipatory versus consummatory pleasure, and observed that schizophrenics showed impairments in anticipatory but not consummatory aspects of pleasure. However, Hartmann *et al.* (2015) reported that anticipatory pleasure for monetary reward could not totally explain the alterations in effort-related decision-making seen in schizophrenic patients. In a recent review by Barch *et al.* (2015), it was noted that there are consistent reports in the literature of intact in-the-moment hedonic (i.e. 'liking') in schizophrenics. Surprisingly, hedonic ratings of sweet tastes and odour stimuli in depressed patients generally do not differ from those of control subjects (Amsterdam *et al.*, 1987; Berlin *et al.*, 1998; Clepce *et al.*, 2010; Dichter *et al.*, 2010; Treadway and Zald, 2011; Pizzagalli, 2014; Barch *et al.*, 2015) (this observation suggests a lack of validity in the use of sucrose intake or preference as an animal model of anhedonia in depression; see also Pardo *et al.*, 2015). Moreover, the severity of depressive symptoms in a non-clinical sample was not correlated with hedonic ratings of various types of tastes (Scinska *et al.*, 2004). Nevertheless, there is considerable evidence of impairments in positively reinforced instrumental behaviour and anticipatory aspects of motivation and affect in depressed patients and schizophrenics (Dichter, 2010; Treadway and Zald, 2011; Pizzagalli, 2014; Barch *et al.*, 2015). At this point, it is not clear which specific psychological processes underlie the alterations in effort-related aspects of motivation that are observed in various patient populations. These effects could reflect changes in behavioural activation or aspects of reward processing, as well as cognitive or affective functions related to reward anticipation or the impact of delayed reinforcement, and in fact could differ across disorders, and between specific individuals.

Part of the difficulty in interpreting the functional significance of effort-related dysfunction in psychopathology lies in the imprecise nature of the concepts and vocabulary that are used. The term 'reward', when used to denote a neurobehavioural process, is so ill-defined, and so variably used, as to be almost meaningless (Salamone *et al.*, 2005; Salamone and Correa, 2012, 2013). Moreover, it is clear that mesolimbic dopamine is involved in aversive motivation and stress (Salamone, 1994; Salamone *et al.*, 1997, 2007, 2015*b*). For these reasons, as well as the evident complexity of the actual behavioural functions of

mesolimbic dopamine (Salamone and Correa, 2012; Salamone *et al.*, 2015*b*), it is problematic to label mesolimbic dopamine as the 'reward system' or nucleus accumbens as the 'reward centre' or 'pleasure centre' of the brain. In that case, one cannot label an imaging response from the ventral midbrain or ventral striatum induced by presentation of a primary reinforcer as representing a hedonic response, simply because that response is occurring in the 'reward system'.

There are similar problems with the clinical use of the term 'anhedonia' (Treadway and Zald, 2011; Markou *et al.*, 2013). According to its original psychiatric definition, anhedonia referred to an inability to experience pleasure (Ribot, 1896). However, through many years, the use of the term has evolved to include a heterogeneous and at times ambiguous mixture of functions that are dissociable from each other (Dichter, 2010; Treadway and Zald, 2011). Thus, it now has to be explained in detail that there are types of anhedonia that are 'motivational' in nature, and not necessarily marked by reduced hedonic response to primary rewards (Treadway and Zald, 2011). Furthermore, labelling effort-related dysfunctions as a type of anhedonia implies the primacy of an emotional component in the impairment, while diminishing and obscuring the role of processes involving aspects of motivation such as behavioural activation and action instigation, as well as cognitive functions involved in estimating or predicting future events. Though it can be suggested that effort-based impairments are related to trait measures of anticipatory pleasure, it is not clear that anticipatory pleasure self-reported on an inventory is precisely the same thing as 'pleasure during anticipation' (i.e. the affective state that is directly experienced during anticipation or instrumental responding). Moreover, years of study of affective processes have emphasized the important distinction between emotional valence and arousal (Gerber *et al.*, 2008). As a result, it is not clear if people suffering from problems with anticipatory pleasure are basing their self-report on blunted positive valence or their perception of their own diminished arousal or intensity. Also, while it is often suggested that affect causes motivation, why cannot the opposite also be true? Perhaps affective states in part reflect the experience of being motivated. Another consideration is that the relation between terms such as anergia, fatigue, lassitude, amotivation, apathy, and psychomotor retardation remains uncertain (Clarke *et al.*, 2011), and it is unclear how these are related to empirically measured alterations in effort-based choice. These terminological points are not trivial; scientific and clinical terms and definitions are tools that are every bit as important as any device or technique (Salamone and Correa, 2012). Thus, despite the great progress that has been made, continued research will be necessary to develop and refine the measures and concepts that are used to characterize different aspects of appetitive motivation in clinical populations.

Importance of behavioural economic concepts for understanding effort-based choice

One of the most powerful ways of characterizing instrumental behaviour has been the use of terms and concepts from behavioural economics. For example, the use of the term 'value' has skyrocketed in both the basic neuroscience and clinical literatures, and investigators widely use terms such as reinforcement value, valuation, devaluation, discounted value, etc. Other economic concepts, such as cost/benefit analysis, preference, utility, substitution, demand, and elasticity also are frequently used. Much of the initial impetus for this came from researchers studying the experimental analysis of behaviour, and economic concepts have been particularly important in this area (Bickel *et al.*, 1995; Hursh and Winger, 1995; Madden *et al.*, 2000, 2007). However, economic terms and concepts are also now readily seen in the basic and clinical neuroscience literatures. Economic terms are so readily applicable to the study of complex behaviour because economics is not really about money; it is about choice. The main subject of the present review, effort-related choice behaviour, thus lends itself to this type of analysis.

A full review of behavioural economic concepts is beyond the scope of the present paper. Nevertheless, there are some fundamental points that can be raised, which shed light on the basic and clinical research described above. Based on an economic analysis, a reinforcer is a good or commodity, and the instrumental behaviour is essentially labour that is bartered for access to the reinforcer. The response requirement is therefore the price that needs to be paid, in terms of the labour performed. Thus, the results of some behavioural experiments can be analysed as a demand curve (Hursh and Winger, 1995), which plots response output as a function of price (response costs; *x*-axis) versus the amount of reinforcer obtained (*y*-axis). As accumbens dopamine depletions have little effect when the response cost is low, but substantial effects with increasing response requirement, it can be said that accumbens dopamine depletions increase elasticity of demand (Fig. 3; Aberman and Salamone, 1999; Salamone *et al.*, 2009, 2012). In other words, dopamine depletions decrease the willingness to pay higher prices, in terms of response costs (i.e. costs involving physical effort), for food reinforcement. Demand analysis also has been an effective tool for characterizing the role that various neural systems play in regulating drug seeking and taking (Hursh and Winger, 1995; Heyman, 2000; Madden and Kalman, 2010; Heinz *et al.*, 2012; Bentzley *et al.*, 2013, 2014; Bentzley and Aston-Jones, 2015).

In the lever pressing/chow feeding procedures described above, an additional factor is added, because animals are

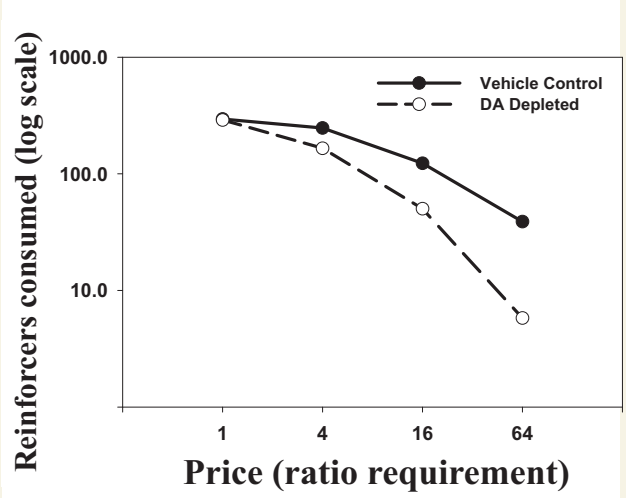

Figure 3 The effect of increasing price, shown as ratio requirement, on the number of operant pellets consumed in rats with accumbens dopamine depletions compared to rats in the vehicle control group. These results are based on data from Aberman and Salamone (1999). The data are represented as a demand curve, calculated from the mean number of reinforcement pellets consumed (shown on a log scale) as a function of price (ratio requirement). Although comparable levels of consumption in dopamine (DA)-depleted and control groups were seen with the FR1 schedule, dopamine-depleted rats showed markedly reduced consumption relative to the control group at higher ratio levels.

given a low-cost substitute, in the form of the concurrently available chow. Economic decisions can be powerfully affected by the availability of substitutes; a person who cannot afford or is unwilling to pay for an expensive car can purchase a cheaper alternative. In the case of the lever pressing/chow feeding choice procedures described above, the presence of the concurrent chow acts to pull animals away from lever pressing, and as higher costs are applied (i.e. higher FR or PROG requirements), the animals decrease lever pressing and increase chow intake (Salamone *et al.*, 1997; Randall *et al.*, 2012). This effect is accentuated by interference with accumbens dopamine transmission, and animals shift from lever pressing to chow intake, as described above.

Given these findings, the question of whether or not a manipulation such as interference with dopamine transmission affects the reinforcement value of the primary reinforcer (e.g. food) is a complex one. For example, research on response/reinforcement matching offers various methods for measuring reinforcement value (Heyman *et al.*, 1987). In these experiments animals match relative responding to the relative value (e.g. magnitude, density or rate) of reinforcement across multiple alternatives. However, as described in detail previously (Williams, 1988; Salamone *et al.*, 1997, 2012), reinforcement value as measured by the matching equations is not strictly speaking a measure of the reinforcement value of food *per se*; rather, it is a measure of the relative value of the whole activity of lever pressing for, obtaining, and consuming the food. In a matching analysis, Aparicio (2007) reported that the dopamine antagonist haloperidol did not alter the discrimination between reinforcement rich versus reinforcement poor levers, but did affect response bias. According to work by Baum and Rachlin (1969), the relative reinforcement value of activities can be measured by the relative allocation of time between alternatives. In that case, studies using the FR5/chow feeding choice procedure indicate that dopamine antagonism or depletion would be decreasing the relative value of lever pressing for the preferred food, but actually increasing the relative value of chow intake. These findings hardly yield a clear picture of the effect of dopaminergic manipulations on the value of the food itself. This picture is further complicated by papers demonstrating that the doses of dopamine antagonists or the mesolimbic dopamine depletions that produce alterations in effort-related choice do not change hedonic reactivity to the primary reinforcer, consumption of the reinforcers, or preference between the different sources of food reinforcement in free-feeding tests (Salamone *et al.*, 1991; Berridge *et al.*, 2007; Nunes *et al.*, 2013*b*; Pardo *et al.*, 2015; Yohn *et al.*, 2015*a*). Thus, even if reinforcement value is empirically defined as how much an organism will pay for a commodity (i.e. 'essential value', Hursh and Silberberg, 2008), it appears that interference with dopamine transmission dissociates 'willingness to pay' from preference and utility (i.e. the total satisfaction or benefit received from consuming a good). What types of conditions could generate this dissociation? Although behavioural processes may appear to be associated with each other under baseline or control conditions, they can be dissociated by brain manipulations or pathologies (Salamone and Correa, 2002; Berridge and Robinson, 2003; Salamone *et al.*, 2007). Thus, there is something about the processes that are measured by willingness to pay that appear to be particularly sensitive to dopaminergic manipulations. One possible economic concept related to the role of dopamine could be 'purchasing power', which in economic terms refers to the available monetary resources that enable a person to make cost-related choices. It is possible that interference with dopamine transmission, by reducing the activating effects of motivational stimuli, constrains the behavioural resources available for investing time and effort in lever pressing for a reinforcer such as food, which leads to a re-allocation of behavioural resources when the response costs are high (Salamone *et al.*, 2016). Such an effect is nevertheless dissociable from an action on preference or hedonic reactivity when costs are low.

Although the discussion in this section has focused on the effects of dopaminergic manipulations in animals, the principles being highlighted are of equal importance in assessing human studies, including the types of imaging experiments and clinical research described above (Shenhav *et al.*, 2013). Under pathological conditions, one cannot assume that empirically derived measures

of reinforcement value equal preference, hedonia or satisfaction. Brain manipulations and pathological states are capable of parsing complex processes into dissociable components, and this provides another reason why caution should be exercised in the use of language to describe those impairments.

Conclusions

In summary, converging lines of evidence ranging from classical studies of motivation to contemporary research in basic and clinical neuroscience emphasize the importance of behavioural activation and effort-related aspects of motivation. Dopamine systems are a critical part of the brain circuitry regulating behavioural activation, exertion of effort, and effort-related decision-making. Interference with mesolimbic dopamine transmission biases animals towards selection of low effort options, but these effects are not dependent upon interference with the primary or unconditioned reinforcing effects of stimuli such as food. Doses of dopamine antagonists or mesolimbic dopamine depletions that reduce selection of high effort alternatives do not change hedonic reactivity to the primary reinforcer, consumption of the reinforcers, or preference between the different sources of food reinforcement in free-feeding tests (Salamone *et al.*, 1991, 2007; Berridge *et al.*, 2007; Salamone and Correa, 2012; Nunes *et al.*, 2013*b*; Pardo *et al.*, 2015; Yohn *et al.*, 2015*a*). In addition to mesolimbic dopamine, effort-related functions engage a distributed neural circuitry that includes multiple neurotransmitters across basal ganglia, limbic and cortical areas. Moreover, there is a striking similarity between the brain areas involved in behavioural activation and effort-related processes in rodents and in humans. An emerging body of evidence indicates that alterations in effort-based decision-making are evident in several psychiatric and neurological disorders. While depression, schizophrenia and parkinsonism are marked by reduced selection of high effort alternatives, autistic adults show the opposite effect (Damiano *et al.*, 2012), and it will be important to conduct further investigations of effort-related functions in people with bipolar disorder (Johnson *et al.*, 2012; Whitton *et al.*, 2015). Formal animal models of effort-related dysfunction have been developed, which are not necessarily functioning as models of a particular disorder, but rather are focused upon specific symptom dimensions and circuits that span multiple disorders, in line with the RDoC initiative described above. Translational studies linking research with animal models, human volunteers, and clinical populations is already beginning to revolutionize the understanding of the neural basis of effort-related motivational dysfunction, and it is hoped that this research will ultimately lead to improved treatment for motivational and psychomotor symptoms in psychiatry and neurology.

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