



# Translational approaches to evaluating motivation in laboratory rodents: conventional and touchscreen-based procedures

Benjamin U Phillips<sup>1,5</sup>, Laura Lopez-Cruz<sup>1,5</sup>,  
Jonathan Hailwood<sup>1</sup>, Christopher J Heath<sup>2,6</sup>,  
Lisa M Saksida<sup>1,3,4,6</sup> and Timothy J Bussey<sup>1,3,4,6</sup>

Several neuropsychiatric and neurodegenerative disorders are characterised by motivational impairments manifested as lack of behavioural activation or energy resulting in significant functional impairment. Given the clinical significance of these symptoms, the study of motivation in preclinical research has recently intensified. This review briefly summarises the tasks that have been implemented for the evaluation of motivation in different species, emphasising the recent use of touchscreen-based rodent testing systems. This methodology has been widely used in the evaluation of multiple cognitive domains emphasising their translational value and flexibility. Recently touchscreen-based versions of classical tasks for the evaluation of motivation have been or are currently being developed and validated, thus facilitating translation from animal to human research and promoting their implementation in clinical contexts.

## Addresses

<sup>1</sup> Department of Psychology and MRC/Wellcome Trust Behavioural and Clinical Neuroscience Institute, University of Cambridge, Downing Street, Cambridge CB2 3EB, UK

<sup>2</sup> School of Life, Health and Chemical Sciences, The Open University, Walton Hall, Milton Keynes MK7 6AA, UK

<sup>3</sup> Molecular Medicine Research Laboratories, Robarts Research Institute & Department of Physiology and Pharmacology, Schulich School of Medicine & Dentistry, Western University, London, ON, Canada

<sup>4</sup> The Brain and Mind Institute, Western University, London, ON, Canada

Corresponding author: Lopez-Cruz, Laura ([l1522@cam.ac.uk](mailto:l1522@cam.ac.uk))

<sup>5</sup> Joint first author.

<sup>6</sup> Joint senior author.

**Current Opinion in Behavioral Sciences** 2018, **22**:21–27

This review comes from a themed issue on **Apathy and motivation**

Edited by **Christopher Pryce** and **Masud Husain**

<https://doi.org/10.1016/j.cobeha.2017.12.008>

2352-1546/© 2017 Published by Elsevier Ltd.

## Introduction

Motivation is typically defined as the set of adaptive processes by which organisms orient and initiate

behaviour towards or away from salient internal and environmental stimuli [1<sup>\*\*</sup>,2]. It is complex and multifaceted, encompassing directional, activation and effort-related components [1<sup>\*\*</sup>,3]. To successfully adapt to the environment, organisms must direct and activate appropriate behaviour in response to significant stimuli and assign a suitable degree of effort based on work-related assessments, preferences or motivational value. These abilities are disrupted in a wide range of mental illnesses, including depression, dementia, Huntington's Disease, Parkinson's Disease and schizophrenia [4–7].

Clinically, deficits in motivation are typically termed apathy or anergia, which encompass loss or diminishment of goal-directed behaviour and/or cognitive activity [8] and lack of behavioural activation with consequent impairments in important areas of function [9]. These symptoms result in profound functional disability for patients, reduced quality of life for them and their caregivers and can lead to earlier institutionalisation [10]. Despite the highly deleterious nature of these symptoms, there are few targeted therapeutics available for ameliorating them.

To better address this issue, a greater understanding of the neurobiological mechanisms underlying motivation and how these are disrupted in various disease states will be required. The development and optimisation of procedures to assess motivation in preclinical disease models will therefore be of substantial benefit. Ensuring these procedures have high levels of translational validity is also essential to maximise the likelihood of successful delivery of promising therapeutics to the clinic.

Rodent touchscreen-based tests offer a number of advantages including similarity with computerised cognitive assessments increasingly used clinically [11<sup>\*\*</sup>] and are versatile pre-clinical tools for the assessment of motivation in rodent models [12<sup>\*\*</sup>,13]. In this review we discuss methods for the study of motivation in laboratory rodents and recent developments of tests instantiated in the touchscreen apparatus. Implications for the translation of results obtained in rodents towards the development of therapeutics directed at ameliorating apathy are discussed.

## Current methods for studying motivation in animals

Effort-based decision-making and tasks requiring sustained vigorous responding are the most common tools for evaluating motivation in animals [2]. Performance impairments are considered to mirror the apathy observed in various patient groups [1\*\*,2,14]. These studies have frequently focused on the mesolimbic dopamine (DA) system as a key component in the neural circuitry that regulates behavioural activation, effort allocation and the ability of organisms to overcome work-related response challenges [14,15]. This maps well on to the sub-construct of 'willingness to work' that has been characterised in the RDoc framework as a major factor in 'approach motivation' [16], thus emphasising the importance of identifying the neural substrates of these transdiagnostic dimensions across species.

One widely used procedure is the Progressive Ratio (PR) task [17], which assesses motivation by measuring the ability of an animal to maintain responding in order to obtain a reinforcer in the face of increasing response requirements. PR is typically performed in operant chambers in which animals are required to press a lever or enter a nose poke to get a valuable reward [18,19]. This task measures the maximum number of responses that animals are willing to emit to obtain the reinforcer, known as the 'breakpoint'. Although PR has been widely used in rodents and non-human primates [20,21], more recent studies of motivation have used Effort-Related Choice (ERC) tasks that require animals to choose between high effort actions such as repeated lever pressing on a variety of ratio schedules leading to highly valued reinforcers (e.g. sweet pellets, sucrose solution or exercise) versus an alternative low effort/low reward value option (e.g. freely available standard laboratory food) [18,22–25].

A valuable addition to the range of tasks that is typically performed in operant chambers is the effort discounting (ED) task which was originally developed for rats and has been recently adapted for mice [26,27]. In ED, subjects are offered a choice between two instrumental responses (e.g. lever-press) one of which yields a larger magnitude reinforcer. Over the course of a session, the response requirement for the large reward gradually increases, whereas only a single response is needed to obtain the smaller one [28]. Together with the delay discounting task (DD), in which a gradually increasing delay is associated with the large reward option, ED has helped to identify various brain areas and neurochemical mechanisms involved in the regulation of effort or delay related processes during decision making [27,29].

Mazes have been also used to study effort-based decision making in rodents. One example is the T-maze barrier task that was first designed for rats and adapted for mice [30,31]. In this task, the two choice arms of a T-maze

contain different amounts of reinforcer (e.g. one versus two sucrose pellets) and provide a work-related challenge with a vertical barrier placed across the arm with the higher reward density [23,30,31]. A more recent development is a novel T-maze based task in which animals choose between exercising in a running wheel or eating freely available sweet pellets [25]. Running requires effort expenditure but also has reinforcing properties that enable it to be used as the reward for the 'high effort' option in the context of effort-based decision making [25].

ERC tasks, unlike PR, provide a better understanding of activation and directional components of motivation [1\*\*]. Although both tasks are sensitive to the same manipulations (e.g. DA receptor antagonists or DA depletion) [12\*\*,23,25,27,32], ERC tasks evaluate whether a given manipulation affects the primary properties of the reinforcer. For example, a manipulation that decreases PR breakpoint, when evaluated in ERC may not result in a generalised decrease in operant output but instead causes the reallocation of behavioural resources from the more effortful but preferred reward option to the less preferred but less effortful option available in these tasks. Such behavioural shift is consistent with the manipulation affecting effort-related outcomes (such as willingness to work) without affecting other processes such as 'reward valuation' [1\*\*,30].

## Translating animal motivational assessments to humans

Given its clinical significance [33], the quantitative assessment of motivation in humans is increasingly important. Such behaviours have traditionally been assessed via questionnaire-based measures, aimed at assessing pathological disruptions in motivation. These include either subsets of inventories [34] or specific scales [35,36]. However, in addition to limitations associated with such assessments such as recall bias, linking these to assessments used in experimental animals such as PR and ERC is problematic [37\*]. As a result, a number of research groups have suggested the use of behavioural measures of specific constructs such as reward anticipation [38] and effort exertion [5] and a few have achieved successful translation of some of the preclinical assays. For example, PR has been adapted for use in humans and although several different versions exist [39–41], all assess the ability to maintain responding for a (monetary) reward under increasing work requirements. As in rodent PR, responding consists of a cognitively non-demanding task, such as selecting the largest number [41] or repeatedly pressing a button [39] with breakpoint being the primary outcome measure.

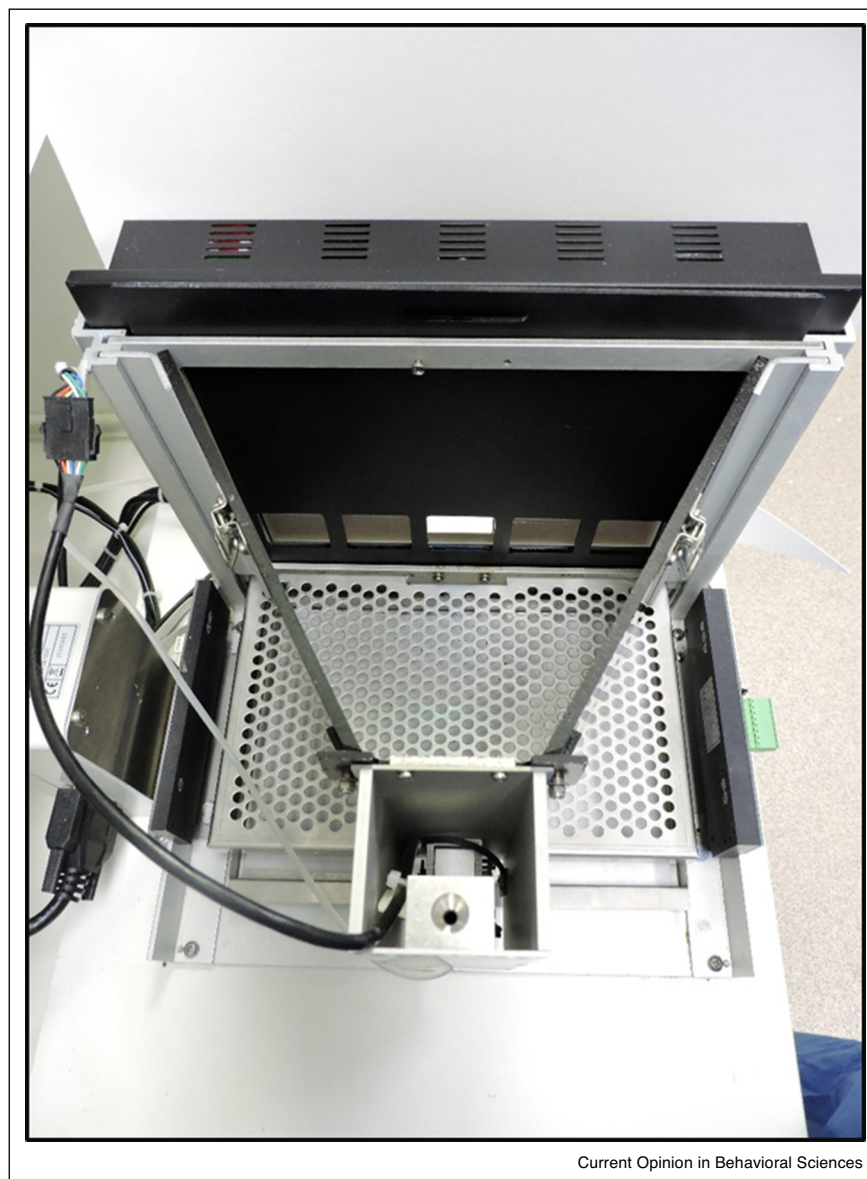
As discussed previously, ERC assays have been widely used in preclinical settings. Treadway and colleagues have developed a human analogue of ERC known as the Effort-Expenditure for Rewards Task (EEfRT)

[42,43]. Like ERC, EEfRT allows subjects to choose between a high-effort high-reward and a low-effort low-reward option. Effort is manipulated by requiring subjects to complete a number of button presses within a given period of time. Several EEfRT studies have replicated rodent ERC findings. For example, administration of amphetamine in animals and humans can increase selection of the high effort-high reward option [27,44]. Furthermore, the results of a positron emission tomography (PET) study in humans highlighted the role of dopaminergic activity within the ventral striatum in high-effort choice selection in EEfRT which mirrors the effects of

dopamine depletion in equivalent structures in animals performing ERC [45,46].

Together, these studies highlight how certain constructs related to motivation can be assessed using paradigms adapted in species-specific ways. It may be possible, however, to further increase the success of cross species translation through the use of automated touchscreen operant systems. Although non-touchscreen based ERC tasks have been successfully back translated from animal to human research [42], the development of new touchscreen-based motivational tasks in both humans

Figure 1



Current Opinion in Behavioral Sciences

Standard mouse Bussey Saksida touchscreen chambers (Campden Instruments Ltd., Loughborough, UK). View from the top. Surrounding sound attenuating chamber not shown.

and rodents with a high degree of similarity between them could facilitate the comparison of results obtained across species. In addition, back and forward translation has already been demonstrated with touchscreen-based tasks focused on cognitive abilities [11\*\*,47\*\*,48].

### Touchscreen-based tasks as a new tool for evaluating motivation in different species

Until recently, the majority of research using touchscreen-equipped systems (see Figure 1) has focused on cognitive domains such as attention, memory and executive function [49–51].

The substantial translational potential of touchscreen-delivered assessment in humans and animals is exemplified by a series of studies of the gene *Dlg2*. Specifically, cognitive assessment of humans using the touchscreen-based CANTAB system and evaluation of mice using analogous rodent touchscreen tasks yielded similar cross-species performance profiles in groups with *Dlg2* mutations [50]. Importantly, subsequent use of an identical version of the touchscreen paired associates learning (PAL) task to evaluate humans and mice with *Dlg2* mutations also yielded a performance profile common between species [47\*\*,49].

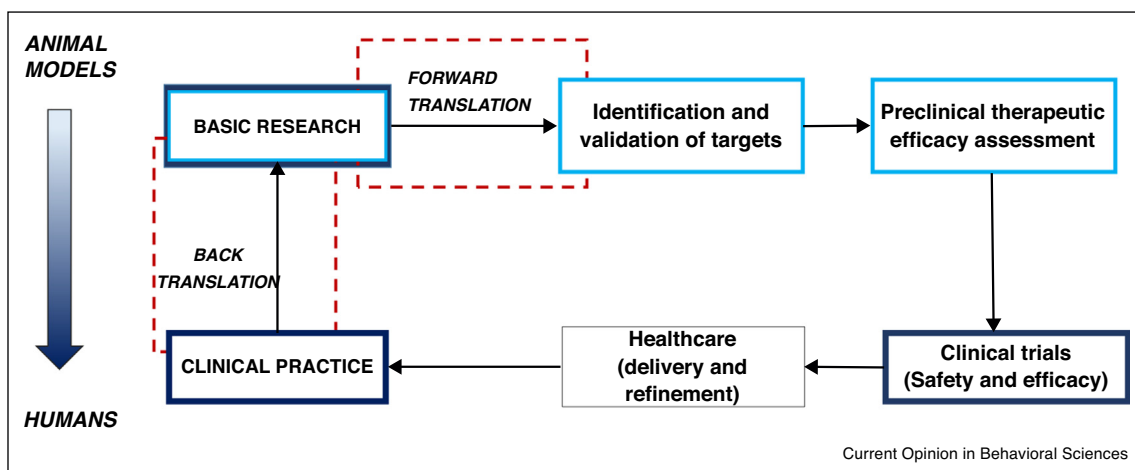
To capitalise on this translational potential, a number of touchscreen-based assays targeting motivation including PR, ERC and ED have been validated for use in mice [12\*\*,52, Lopez-Cruz *et al.*, unpublished], rats [Hailwood *et al.*, unpublished] and non-human primates [52,53]. Additionally, a human touchscreen PR task has been developed as part of the EMOTICOM affective cognition assessment battery [54]. The EMOTICOM PR, like other human versions, consists of completing a simple

task under increasing response requirements for monetary reward. This version of PR, therefore, can be considered analogous to the preclinical touchscreen version and generates the same profile of outcome measures, including breakpoint, running rate and post reinforcement pause [12\*\*]. Tasks that feature objective and quantitative measures between species represent an improved approach to measuring similar underlying cognitive processes as has been demonstrated in previous studies [47\*\*].

The EMOTICOM battery also contains DD task. Although DD is often used as a test for the assessment of impulsive decision-making in rodents, it is also used in combination with ED as a measure of how much time animals are willing to wait for a larger/more preferred reinforcer and therefore can provide insight into motivational state. A DD variant has been recently adapted and validated for mice in the touchscreen apparatus [Phillips *et al.*, 2017, unpublished] providing another opportunity for translation between the human and rodent assessment platforms.

The development and validation of tasks to assess motivation, effort and effort-associated decision making in rodents using touchscreen-equipped systems [12\*\*,13,55] enables the inherent advantages of this methodology to be applied to research areas beyond investigation of the well-established cognitive domains for which this manipulum is widely used [49,56,57]. Given the exclusion of explicitly aversive stimuli from touchscreen-delivered tasks, and the consistent testing environment, it is possible to integrate a variety of different tasks into a unified assessment battery [49] that can be used to evaluate multiple psychological constructs in the same animal.

Figure 2



Idealised work flow of therapeutic development. Stages in which touchscreens can be used are highlighted (light blue: rodents; dark blue: humans).

The integration of motivation and effort-related tasks into batteries consisting of cognitive assessments will substantially enhance data yields and enable detailed studies of the interaction between motivation, effort and cognitive performance in the same individual in the same apparatus. This approach will eliminate issues related to between-subject designs impeding efforts to correlate performance across tasks and any potential confounds associated with the use of different apparatus to evaluate different constructs, consistent with the 3Rs principles of reduction and refinement [58].

## Conclusions

Although much development remains to be completed, forward-translation and back-translation between pre-clinical models and clinical populations, facilitated by the use of analogous interspecies touchscreen-based assays, has the potential to provide substantial insight into the neurobiological underpinnings of apathy, offer a powerful platform for therapeutic screening and provide a quantitative read-out of behaviour unconfounded by observer/recall bias to complement more subjective measures obtained via clinical questionnaire-based instruments (see Figure 2).

## Conflict of interest statement

Nothing declared.

## Acknowledgements

The present research was supported by an NC3Rs project grant (NC/N001451/1) awarded to CJH, LMS and TJB. BUP is supported by a Medical Research Council PhD studentship. JH was supported by a Medical Research Council CASE studentship. TJB and LMS consult for Campden Instruments, Ltd.

## References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Salamone JD, Yohn SE, López-Cruz L, San Miguel N, Correa M: **••** **Activational and effort-related aspects of motivation: neural mechanisms and implications for psychopathology.** *Brain* 2016, **139**:1325-1347.
- This review discusses the role of dopamine and other related circuits in behavioural activation and effort-related processes. It is essential to better understand the neural substrates associated with motivational symptoms present in several psychopathologies.
2. Markou A, Salamone JD, Bussey TJ, Mar AC, Brunner D, Gilmour G, Balsam P: **Measuring reinforcement learning and motivation constructs in experimental animals: relevance to the negative symptoms of schizophrenia.** *Neurosci Biobehav Rev* 2013, **37**:2149-2165.
3. Salamone JD, Correa M: **The mysterious motivational functions of mesolimbic dopamine.** *Neuron* 2012, **76**:470-485.
4. Whitton AE, Treadway MT, Pizzagalli DA: **Reward processing dysfunction in major depression, bipolar disorder and schizophrenia.** *Curr Opin Psychiatry* 2015, **28**:7-12.
5. Chong TT-J, Bonnelle V, Manohar S, Veromann K-R, Muhammed K, Tofaris GK, Hu M, Husain M: **Dopamine enhances willingness to exert effort for reward in Parkinson's disease.** *Cortex* 2015, **69**:40-46.
6. Ter Keurst A, Tuerlings JHAM, Bertholet EA, Wijnen HW: **[Apathetic geriatric patient benefits from methylphenidate].** *Ned Tijdschr Geneesk* 2017, **161**:D1903.
7. Gelderblom H, Wüstenberg T, McLean T, Mütze L, Fischer W, Saft C, Hoffmann R, Süßmuth S, Schlattmann P, van Duijn E et al.: **Bupropion for the treatment of apathy in Huntington's disease: a multicenter, randomised, double-blind, placebo-controlled, prospective crossover trial.** *PLOS ONE* 2017, **12**:e0173872.
8. Marin RS: **Apathy: a neuropsychiatric syndrome.** *J Neuropsychiatry Clin Neurosci* 1991, **3**:243-254.
9. Robert P, Onyike CU, Leentjens AFG, Dujardin K, Aalten P, Starkstein S, Verhey FRJ, Yessavage J, Clement JP, Drapier D et al.: **Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders.** *Eur Psychiatry* 2009, **24**:98-104.
10. Ornstein K, Gaugler JE: **The problem with "problem behaviors": a systematic review of the association between individual patient behavioral and psychological symptoms and caregiver depression and burden within the dementia patient-caregiver dyad.** *Int Psychogeriatr* 2012, **24**:1536-1552.
11. Hvoslef-Eide M, Nilsson SRO, Saksida LM, Bussey TJ: **Cognitive •• translation using the rodent touchscreen testing approach.** *Curr Top Behav Neurosci* 2016, **28**:423-447.
- This review suggests the use of touchscreen-based systems as translational tools for evaluating cognitive processes. It summarizes some examples of successful cross-species translation.
12. Heath CJ, Bussey TJ, Saksida LM: **Motivational assessment of •• mice using the touchscreen operant testing system: effects of dopaminergic drugs.** *Psychopharmacology (Berl)* 2015, **232**:4043-4057.
- First study to show that motivation and effort-related decision making can be measured in rodents using touchscreen-based systems.
13. Heath CJ, Phillips BU, Bussey TJ, Saksida LM: **Measuring motivation and reward-related decision making in the rodent operant touchscreen system.** *Curr Protoc Neurosci* 2016, **74**:8.34.1-20.
14. Salamone JD, Correa M, Yohn S, Lopez Cruz L, San Miguel N, Alatorre L: **The pharmacology of effort-related choice behavior: dopamine, depression, and individual differences.** *Behav Process* 2016, **127**:3-17.
15. Hart EE, Izquierdo A: **Basolateral amygdala supports the maintenance of value and effortful choice of a preferred option.** *Eur J Neurosci* 2017, **45**:388-397.
16. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, Sanislow C, Wang P: **Research domain criteria (RDoC): toward a new classification framework for research on mental disorders.** *Am J Psychiatry* 2010, **167**:748-751.
17. Hodos W: **Progressive ratio as a measure of reward strength.** *Science* 1961, **134**:943-944.
18. Wong A, Dogra VR, Reichelt AC: **High-sucrose diets in male rats disrupt aspects of decision making tasks, motivation and spatial memory, but not impulsivity measured by operant delay-discounting.** *Behav Brain Res* 2017, **327**:144-154.
19. De Jong JW, Roelofs TJM, Mol FMU, Hillen AEJ, Meijboom KE, Luijendijk MCM, van der Eerden HAM, Garner KM, Vanderschuren LJM, Adan RAH: **Reducing ventral tegmental dopamine D2 receptor expression selectively boosts incentive motivation.** *Neuropsychopharmacology* 2015, **40**:2085-2095.
20. Poland RS, Bull C, Syed WA, Bowers MS: **Rodent brain microinjection to study molecular substrates of motivated behavior.** *J Vis Exp* 2015 <http://dx.doi.org/10.3791/53018>.
21. Rodriguez JS, Morris SM, Hotchkiss CE, Doerge DR, Allen RR, Mattison DR, Paule MG: **The effects of chronic methylphenidate administration on operant test battery performance in juvenile rhesus monkeys.** *Neurotoxicol Teratol* 2010, **32**:142-151.
22. Yohn SE, Errante EE, Rosenbloom-Snow A, Somerville M, Rowland M, Tokarski K, Zafar N, Correa M, Salamone JD: **Blockade of uptake for dopamine, but not norepinephrine or 5-HT, increases selection of high effort instrumental activity: implications for treatment of effort-related motivational**

- symptoms in psychopathology.** *Neuropharmacology* 2016, **109**:270-280.
23. Yohn SE, Thompson C, Randall PA, Lee CA, Müller CE, Baqi Y, Correa M, Salamone JD: **The VMAT-2 inhibitor tetrabenazine alters effort-related decision making as measured by the T-maze barrier choice task: reversal with the adenosine A2A antagonist MSX-3 and the catecholamine uptake blocker bupropion.** *Psychopharmacology (Berl)* 2015, **232**:1313-1323.
  24. Bryce CA, Floresco SB: **Perturbations in effort-related decision-making driven by acute stress and corticotropin-releasing factor.** *Neuropsychopharmacology* 2016, **41**:2147-2159.
  25. Correa M, Pardo M, Bayarri P, López-Cruz L, San Miguel N, Valverde O, Ledent C, Salamone JD: **Choosing voluntary exercise over sucrose consumption depends upon dopamine transmission: effects of haloperidol in wild type and adenosine A<sub>2</sub>AKO mice.** *Psychopharmacology (Berl)* 2016, **233**:393-404.
  26. Robles CF, Johnson AW: **Disruptions in effort-based decision-making and consummatory behavior following antagonism of the dopamine D2 receptor.** *Behav Brain Res* 2017, **320**:431-439.
  27. Floresco SB, Tse MTL, Ghods-Sharifi S: **Dopaminergic and glutamatergic regulation of effort- and delay-based decision making.** *Neuropsychopharmacology* 2008, **33**:1966-1979.
  28. Floresco SB, St Onge JR, Ghods-Sharifi S, Winstanley CA: **Cortico-limbic-striatal circuits subserving different forms of cost-benefit decision making.** *Cogn Affect Behav Neurosci* 2008, **8**:375-389.
  29. Massar SAA, Libedinsky C, Weiyan C, Huettel SA, Chee MWL: **Separate and overlapping brain areas encode subjective value during delay and effort discounting.** *Neuroimage* 2015, **120**:104-113.
  30. Salamone JD, Cousins MS, Bucher S: **Anhedonia or anergia? Effects of haloperidol and nucleus accumbens dopamine depletion on instrumental response selection in a T-maze cost/benefit procedure.** *Behav Brain Res* 1994, **65**:221-229.
  31. Pardo M, Lopez-Cruz L, Valverde O, Ledent C, Baqi Y, Müller CE, Salamone JD, Correa M: **Adenosine A2A receptor antagonism and genetic deletion attenuate the effects of dopamine D2 antagonism on effort-based decision making in mice.** *Neuropharmacology* 2012, **62**:2068-2077.
  32. Randall PA, Lee CA, Nunes EJ, Yohn SE, Nowak V, Khan B, Shah P, Pandit S, Vemuri VK, Makriyannis A *et al.*: **The VMAT-2 inhibitor tetrabenazine affects effort-related decision making in a progressive ratio/chow feeding choice task: reversal with antidepressant drugs.** *PLOS ONE* 2014, **9**:e99320.
  33. Lanctôt KL, Agüera-Ortiz L, Brodaty H, Francis PT, Geda YE, Ismail Z, Marshall GA, Mortby ME, Onyike CU, Padala PR *et al.*: **Apathy associated with neurocognitive disorders: recent progress and future directions.** *Alzheimers Dement* 2017, **13**:84-100.
  34. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J: **The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia.** *Neurology* 1994, **44**:2308-2314.
  35. Radakovic R, Abrahams S: **Developing a new apathy measurement scale: Dimensional Apathy Scale.** *Psychiatry Res* 2014, **219**:658-663.
  36. Fervaha G, Takeuchi H, Fousias G, Hahn MK, Agid O, Remington G: **Achievement motivation in early schizophrenia: relationship with symptoms, cognition and functional outcome.** *Early Interv Psychiatry* 2017 <http://dx.doi.org/10.1111/eip.12405>.
  37. Young JW, Markou A: **Translational rodent paradigms to investigate neuromechanisms underlying behaviors relevant to amotivation and altered reward processing in schizophrenia.** *Schizophr Bull* 2015, **41**:1024-1034.
- A translational approach for studying negative symptoms in schizophrenia is presented. This review provides a translational approach identifying tasks that can be used to assess reward/motivational deficits in both humans and animal models.
38. Arrondo G, Segarra N, Metastasio A, Ziauddeen H, Spencer J, Reinders NR, Dudas RB, Robbins TW, Fletcher PC, Murray GK: **Reduction in ventral striatal activity when anticipating a reward in depression and schizophrenia: a replicated cross-diagnostic finding.** *Front Psychol* 2015, **6**:1280.
  39. Strauss GP, Whearty KM, Morra LF, Sullivan SK, Ossenfort KL, Frost KH: **Avolition in schizophrenia is associated with reduced willingness to expend effort for reward on a Progressive Ratio task.** *Schizophr Res* 2016, **170**:198-204.
  40. Bland AR, Roiser JP, Mehta MA, Schei T, Boland H, Campbell-Meiklejohn DK, Emsley RA, Munafò MR, Penton-Voak IS, Seara-Cardoso A *et al.*: **EMOTICOM: a neuropsychological test battery to evaluate emotion, motivation, impulsivity, and social cognition.** *Front Behav Neurosci* 2016, **10**:25.
  41. Wolf DH, Satterthwaite TD, Kantrowitz JJ, Katchmar N, Vandekar L, Elliott MA, Ruparel K: **Amotivation in schizophrenia: integrated assessment with behavioral, clinical, and imaging measures.** *Schizophr Bull* 2014, **40**:1328-1337.
  42. Treadway MT, Buckholtz JW, Schwartzman AN, Lambert WE, Zald DH: **Worth the "EEfRT"? The effort expenditure for rewards task as an objective measure of motivation and anhedonia.** *PLoS ONE* 2009, **4**:e6598.
- A novel task for evaluation of effort-based decision making in humans is presented for the first time in this study. The EEfRT task showed to be sensitive to motivational impairments in humans.
43. Lasselin J, Treadway MT, Lacourt TE, Soop A, Olsson MJ, Karshikoff B, Paues-Göransson S, Axelsson J, Dantzer R, Lekander M: **Lipopolysaccharide alters motivated behavior in a monetary reward task: a randomized trial.** *Neuropsychopharmacology* 2017, **42**:801-810.
  44. Wardle MC, Treadway MT, Mayo LM, Zald DH, de Wit H: **Amping up effort: effects of d-amphetamine on human effort-based decision-making.** *J Neurosci* 2011, **31**:16597-16602.
  45. Treadway MT, Buckholtz JW, Cowan RL, Woodward ND, Li R, Ansari MS, Baldwin RM, Schwartzman AN, Kessler RM, Zald DH: **Dopaminergic mechanisms of individual differences in human effort-based decision-making.** *J Neurosci* 2012, **32**:6170-6176.
  46. Salamone JD, Steinpreis RE, McCullough LD, Smith P, Grebel D, Mahan K: **Haloperidol and nucleus accumbens dopamine depletion suppress lever pressing for food but increase free food consumption in a novel food choice procedure.** *Psychopharmacology (Berl)* 1991, **104**:515-521.
  47. Nithianantharajah J, McKeachie AG, Stewart TJ, Johnstone M, Blackwood DH, St Clair D, Grant SGN, Bussey TJ, Saksida LM: **Bridging the translational divide: identical cognitive touchscreen testing in mice and humans carrying mutations in a disease-relevant homologous gene.** *Sci Rep* 2015, **5**:14613.
- This study offers the first example of using the identical touchscreen-based cognitive test to access rodents and humans carrying disease related genetic mutations.
48. Nithianantharajah J, Komiyama NH, McKeachie A, Johnstone M, Blackwood DH, St Clair D, Emes RD, van de Lagemaat LN, Saksida LM, Bussey TJ *et al.*: **Synaptic scaffold evolution generated components of vertebrate cognitive complexity.** *Nat Neurosci* 2013, **16**:16-24.
  49. Horner AE, Heath CJ, Hvoslef-Eide M, Kent BA, Kim CH, Nilsson SRO, Alsjö J, Oomen CA, Holmes A, Saksida LM *et al.*: **The touchscreen operant platform for testing learning and memory in rats and mice.** *Nat Protoc* 2013, **8**:1961-1984.
  50. Nithianantharajah J, Grant SGN: **Cognitive components in mice and humans: combining genetics and touchscreens for medical translation.** *Neurobiol Learn Mem* 2013, **105**:13-19.
  51. Bussey TJ, Padain TL, Skillings EA, Winters BD, Morton AJ, Saksida LM: **The touchscreen cognitive testing method for rodents: how to get the best out of your rat.** *Learn Mem* 2008, **15**:516-523.
  52. Kangas BD, Bergman J, Coyle JT: **Touchscreen assays of learning, response inhibition, and motivation in the marmoset (*Callithrix jacchus*).** *Anim Cogn* 2016, **19**:673-677.
  53. Weed MR, Taffe MA, Polis I, Roberts AC, Robbins TW, Koob GF, Bloom FE, Gold LH: **Performance norms for a rhesus monkey**

- neuropsychological testing battery: acquisition and long-term performance.** *Brain Res Cogn Brain Res* 1999, **8**:185-201.
54. Robbins TW, James M, Owen AM, Sahakian BJ, McInnes L, Rabbitt P: **Cambridge Neuropsychological Test Automated Battery (CANTAB): a factor analytic study of a large sample of normal elderly volunteers.** *Dementia* 1994, **5**:266-281.
55. Phillips BU, Heath CJ, Ossowska Z, Bussey TJ, Saksida LM: **Optimisation of cognitive performance in rodent operant (touchscreen) testing: evaluation and effects of reinforcer strength.** *Learn Behav* 2017 <http://dx.doi.org/10.3758/s13420-017-0260-7>.
56. Mar AC, Horner AE, Nilsson SRO, Alsiö J, Kent BA, Kim CH, Holmes A, Saksida LM, Bussey TJ: **The touchscreen operant platform for assessing executive function in rats and mice.** *Nat Protoc* 2013, **8**:1985-2005.
57. Oomen CA, Hvoslef-Eide M, Kofink D, Preusser F, Mar AC, Saksida LM, Bussey TJ: **A novel 2- and 3-choice touchscreen-based continuous trial-unique nonmatching-to-location task (cTUNL) sensitive to functional differences between dentate gyrus and CA3 subregions of the hippocampus.** *Psychopharmacology (Berl)* 2015, **232**:3921-3933.
58. Burden N, Chapman K, Sewell F, Robinson V: **Pioneering better science through the 3Rs: an introduction to the national centre for the replacement, refinement, and reduction of animals in research (NC3Rs).** *J Am Assoc Lab Anim Sci* 2015, **54**:198-208.