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

Journal Item

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

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Abstract

A number of neuropsychiatric and neurodegenerative disorders are characterized by motivational impairments manifested as lack of behavioural activation, interest 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 successfully implemented for the evaluation of motivation in different species, emphasizing the recent use of touchscreen-based rodent testing systems. The touchscreen methodology has been widely used in the evaluation of multiple cognitive domains emphasizing 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.

Key words: Effort, apathy, anergia, decision making, translational studies, depression, mood

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**,2]. It is complex and multifaceted, encompassing directional, activational and effort-related components [1,3]. 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**] and are versatile pre-clinical tools for the assessment of motivation in rodent models [12**,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 behavioral 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 in 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 vs. 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 activational 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 generalized decrease in operant output but instead causes the reallocation of behavioral resources from the more effortful but preferred reward option to the less preferred but less effortful option available in these tasks. Such behavioral 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 behaviors 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 behavioral 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 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 capitalize 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 manipulandum 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. 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- 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 behavior unconfounded by observer/recall bias to complement more subjective measures obtained via clinical questionnaire-based instruments (see Figure 2).

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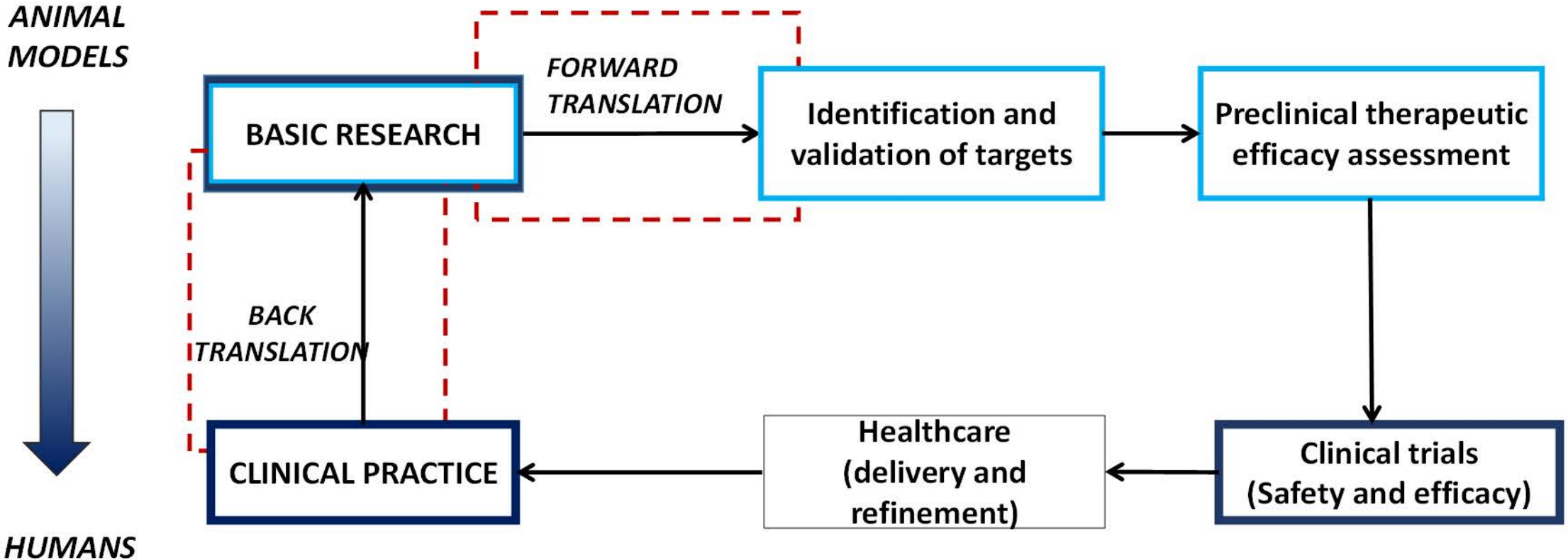
FIGURE CAPTIONS

Figure 1. Standard mouse Bussey Saksida touchscreen chambers (Campden Instruments Ltd, Loughborough, UK). View from the top. Surrounding sound attenuating chamber not shown.

Figure 2. Idealised work flow of therapeutic development. Stages in which touchscreens can be used are highlighted (Light blue: Rodents – Dark blue: Humans).


ANIMAL MODELS
HUMANS
BASIC RESEARCH
FORWARD TRANSLATION
Identification and validation of targets
Preclinical therapeutic efficacy assessment
BACK TRANSLATION
CLINICAL PRACTICE
Healthcare (delivery and refinement)
Clinical trials (Safety and efficacy)